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Synthesis and structure/NMDA receptor affinity relationships of 1-substituted tetrahydro-3-benzazepines

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Abstract—A novel synthesis of 1-substituted tetrahydro-1*H*-3-benzazepines **4** is described. Starting with (2-bromophenyl)acetaldehyde acetal **5**, the nitrostyrene **9** was prepared in three steps allowing the addition of various nucleophiles to yield the nitroacetals **10**. The one-pot Zn/HCl reductive cyclization of the nitroacetals **10** provided the 3-benzazepines **4**, which were investigated for their affinity to the phencyclidine binding site of the NMDA receptor. A one-atomic spacer between the 3-benzazepine system and the phenyl residue in position 1 seems to be favorable for high NMDA receptor binding. In this series the benzazepine **4l** substituted with the conformationally restricted and H-bond accepting acetanilide substituent in position 1 displays the highest NMDA receptor affinity ($K_i = 89$ nM).
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1. Introduction

(*S*)-Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS). It operates through ionotropic (iGlu) and metabotropic glutamate receptors (mGlu).[1] The best-characterized excitatory amino acid receptor is the NMDA receptor, which is selectively activated by *N*-methyl-D-aspartate and is highly sensitive to Mg^{2+}-ions, which have been shown to block the NMDA receptor in a voltage dependent manner.[2,3]

The physiological activation of the NMDA receptor is important for the development of neurons and thus for processes like learning and memory.[4,5] However, an overstimulation of the NMDA receptor by an uncontrolled release of (*S*)-glutamate is involved in a number of acute and chronic neurodegenerative disorders. In particular, the excitotoxic processes, which are caused by cerebral ischemia (stroke), epilepsy and trauma (brain injury), are based on massive influx of Ca^{2+}-ions through the NMDA receptor associated ion channel. The participation of the NMDA receptor in the development of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis[6] and alcohol dependency has been discussed. Therefore, the NMDA receptor represents an interesting target for the therapeutic intervention of these neurological diseases.[1,2]

Our interest has been focused on the phencyclidine — (PCP) binding site, which is located within the NMDA receptor associated ion channel. Ligands interacting with the PCP binding site block the influx of Ca^{2+}-ions and therefore function as NMDA receptor antagonists.[1,3]

The tetracyclic MK-801 (**1**) represents a non-competitive NMDA receptor antagonist, binding with high affinity ($K_i = 1.26$ nM)[7] at the PCP-binding site of the NMDA receptor. The formal cleavage of the C_{9a}/C_{10}-bond of MK-801 results in tetrahydroisoquinolines **2**, which also interact with the PCP-binding site (see Fig. 1).[8–10] Extension of the imino bridge of **1** leads to the constitutional isomer **3**,[11,12] which also binds with high affinity at the PCP-binding site of the NMDA receptor. In a previous investigation we have shown that the ring opened (cleavage of the C_{9a}/C_{10}-bond) analogue of **3**, the racemic 1-phenyl-tetrahydro-3-benzazepine **4a**, exhibits considerable interaction with the NMDA receptor.[13]

In order to investigate the structure–affinity relationships within the 3-benzazepine class of NMDA receptor antagonists we developed a new method for the synth-

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esis of tetrahydro-3-benzazepines with various substituents in position 1. Herein, synthesis and NMDA receptor binding of various 3-benzazepines are described and structure–affinity relationships are discussed.

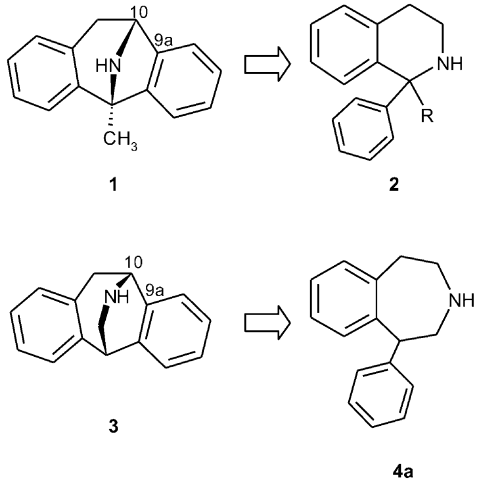


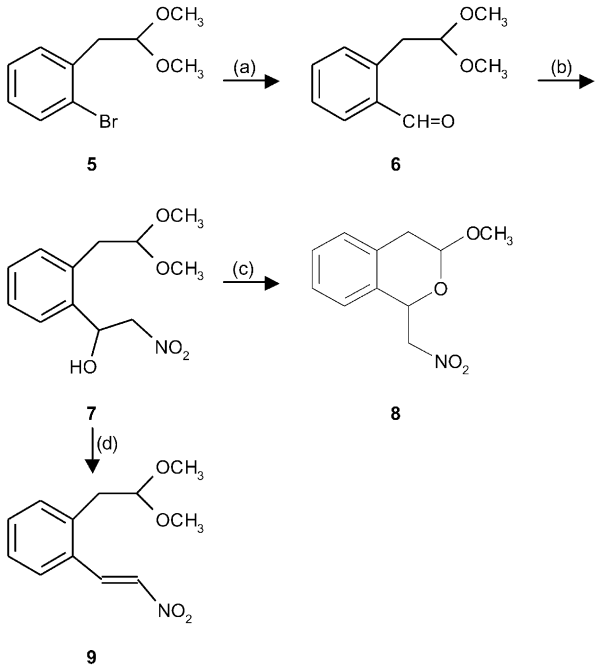
Figure 1.

2. Chemistry

According to our plan the *Michael addition* of various nucleophiles to the β-nitrostyrene **9** should provide nitroacetals **10**, which should be reductively cyclized to yield 1-substituted 3-benzazepines **4**.

The synthesis of the required β-nitrostyrene **9** was started with the (2-bromophenyl)acetaldehyde acetal **5** (see Scheme 1).[14] Bromine/lithium exchange with *n*-butyllithium at −78 °C generated an aryllithium intermediate, which was trapped with dimethylformamide or *N*-methylformanilide to furnish the homophthalaldehyde monoacetal **6**.[14] The addition of nitromethane to the aldehyde **6** (*Henry reaction*[15]) proceeded in the presence of KOH to give the nitroaldol product **7** in 79% yield. Reaction of the nitroaldol **7** with *p*-toluenesulfonic acid in methanol did not provide the β-nitrostyrene **9**. Instead of dehydration an intramolecular transacetalization occurred and the 1-nitromethyl-2-benzopyran **8** could be isolated in 40% yield. However, the dehydration of **7** was successful with methanesulfonyl chloride and an excess of triethylamine at low temperature, yielding 79% of the β-nitrostyrene **9**.

At first the addition of various phenyl nucleophiles to the β-nitrostyrene **9** was investigated (see Table 1). Phenyllithium reacted only in the solvent THF to give the addition product **10a**. After performing the same reaction in the solvent Et_2O the addition product **10a** could not be detected. Addition of $CuBr{\cdot}S(CH_3)_2$ (0.5 equivalents) to phenyllithium improved the yield of **10a**. Depending on the solvent the yield rose to 40% (THF) and 56% (Et_2O), respectively. A considerable effect of the solvent was observed using the Grignard reagent PhMgBr. Whereas addition of PhMgBr in Et_2O resulted in the best yield of **10a** (64%, entry 6) no product was found after reaction in the solvent THF. The addition of one equivalent of CuI to the Grignard reagent



Scheme 1. (a) *n*-BuLi, THF, −78 °C; then DMF, ref 14. (b) CH_3NO_2, KOH, CH_3OH, H_2O, 7 h, 0 °C, 79%. (c) *p*-$TolSO_3H$, CH_3OH, 16 h. rt, 40%. (d) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 8 h, 0 °C, 79%.

PhMgBr and the subsequent reaction with the β-nitrostyrene **9** provided the same yields of **10a** in both solvents THF and Et_2O (44%, entry 7 and 42%, entry 8).

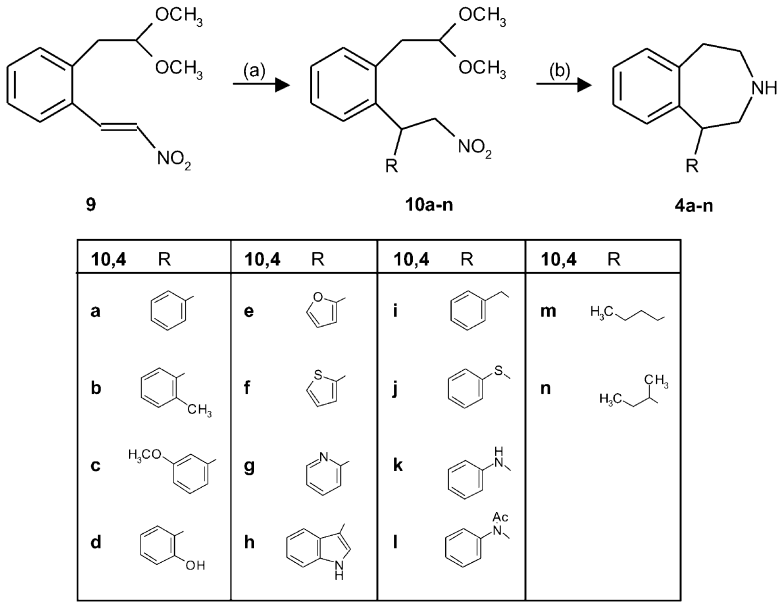
Table 1. Addition of various phenyl nucleophiles Ph-Nu to the β-nitrostyrene **9**

Entry	Ph-Nu	Solvent	Yield (%) of **10a**
1	PhLi	THF	17
2	PhLi	Et_2O	0
3	PhLi/$CuBr{\cdot}S(CH_3)_2$[a]	THF	40
4	PhLi/$CuBr{\cdot}S(CH_3)_2$[a]	Et_2O	56
5	PhMgBr	THF	0
6	PhMgBr	Et_2O	64
7	PhMgBr/CuI[b]	THF	44
8	PhMgBr/CuI[b]	Et_2O	42

[a] PhLi: CuBr $S(CH_3)_2$ = 2:1.
[b] PhMgBr: CuI = 1:1.

Based on these results various nucleophiles were added to the β-nitrostyrene **9** (see Scheme 2). The added nucleophiles are classified in four types: 1. phenyl und substituted phenyl nucleophiles; 2. heteroaryl nucleophiles; 3. phenyl-X nucleophiles (X = CH_2, S, NR); 4. alkyl nucleophiles.

2-Bromotoluene and 3-bromoanisol were used for the synthesis of **10b** and **c**, bearing substituted phenyl residues in β-position. In both cases the Grignard reagent prepared from the corresponding bromobenzene and Mg in Et_2O gave only low yields of the addition products **10b** (31%) and **c** (38%), respectively. However, addition of the aryllithium derivatives in THF, which were generated in situ by Br/Li-exchange, led to the addition products **10b** and **c** in 63% and 46% yield, respectively. The relatively low yields of the Grignard addition products may be due to the sluggish formation

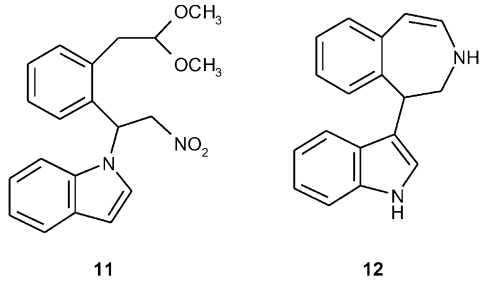


Scheme 2. (a) Various nucleophiles, for details see text. (b) Zn, HCl, THF, reflux.

of substituted aryl Grignard reagents. The hydroxyphenyl substituted nitroacetal **10d** was synthesised by adding sodium phenolate, which was generated by deprotonation of phenol with NaH in THF.

Furan and thiophene were deprotonated in position 2 with *n*-BuLi at −78 °C and subsequently added to β-nitrostyrene **9**, providing the addition products **10e** and **10f** in 81% and 79% yield, respectively. 2-Pyridyllithium was generated by Br/Li-exchange of 2-bromopyridine and reacted with β-nitrostyrene **9**, yielding the pyridyl addition product **10g**. After deprotonation with NaH indole was added to the β-nitrostyrene **9**. Purification of the reaction products by flash chromatography furnished the indol-3-yl derivative **10h** in 94% yield and a small amount of the regioisomeric indol-1-yl derivative **11** (4.8%, see Scheme 3).

The distance between the added phenyl residue and the 3-benzazepine nucleus was extended by introduction of a spacer group (CH_2, S, NR). This spacer group was expected to improve the orientation of the phenyl residue towards the receptor protein. For this purpose benzylmagnesium bromide was added to the β-nitrostyrene **9** in the presence and absence of CuI (1 equivalent, solvent Et_2O). Both reactions led to the same yield (63%) of the benzyl addition product **10i**. The addition



Scheme 3.

of thiophenol and aniline was catalyzed by triethylamine yielding 93% and 86% of the addition products **10j** and **k**, respectively. After deprotonation with NaH acetanilide was added successfully (**10l**: 60%).

The alkyl substituted products **10m** and **n** were obtained by adding the commercially available *n*-butyllithium and *s*-butyllithium, respectively. When *s*-butyllithium was added, two stereogenic centers were established. Therefore, two sets of signals in a ratio of 1:1 were seen in the ^{1}H NMR spectrum representing the two formed diastereomers of **10n**.

Next, the nitroacetals **10** were to be transformed into the tetrahydro-3-benzazepines **4**. The single steps of the overall transformation are as follows: (i) reduction of the nitro group, (ii) hydrolysis of the acetal moiety, (iii) condensation of the generated primary amine and the aldehyde to give an imine/enamine and finally, (iv) a further reduction. In order to perform and optimize these single steps a great number of experiments was carried out. However, it was found that the one-pot procedure using Zn dust and diluted HCl[13] was generally applicable and gave the best overall yields of the 3-benzazepines **4** (30–67%). The reason for the relatively low yield of the 2-pyridyl-3-benzazepine **4g** (25%) is the instability of the 2-pyridyl addition product **10g**. In spite of several attempts the 3-benzazepine **4k** derived from the aniline addition product **10k** could not be isolated. Most probably the secondary amine is responsible for side reactions of **10k**/**4k**. This presumption was confirmed by isolating 2-[2-(anilinomethyl)phenyl]acetaldehyde dimethyl acetal after $LiAlH_4$ reduction of **10k**, which results from nitromethane elimination and reduction. The standard reduction of the 3-indolyl derivative **10h** using 10 equivalents of Zn and HCl stopped at the enamine stage **12** (see Scheme 3). Increasing the Zn and HCl amounts from 10 to 80 equivalents and prolonging the reaction time to 96 h did not lead to

completion of the transformation, and the enamine **12** was still the main product. Thus, the products were separated and purified by flash chromatography to yield the desired tetrahydro-3-benzazepine **4h** (28%) and the enamine **12** (41%).

3. Receptor binding studies

The affinity of the 1-substituted tetrahydro-3-benzazepines **4a–n** and reference compounds for the phencyclidine-binding site of the NMDA-receptor was determined in competition experiments with the radioligand [^{3}H]-(+)-MK-801 (**1**). In the assay pig brain cortex preparations were used as receptor material. Non-specific binding was determined in the presence of a large excess of non-tritiated (+)-MK-801 (**1**).[7,16]

The NMDA-receptor affinities of the 3-benzazepines **4** and three reference compounds are summarized in Table 2. In accordance with the literature[13] moderate NMDA-receptor affinity was found for the 1-phenyl-3-benzazepine **4a** ($K_i = 8.74$ μM). The *o*-tolyl-derivative **4b** displays 4-fold enhanced NMDA-receptor affinity. A similar trend was observed with 1-substituted tetrahydroisoquinolines.[17]

The introduction of electron rich phenyl (**4c**, **d**) or hetaryl substituents (**4e**, **f**, **h**) in position 1 of the 3-benzazepines 4 leads to reduced NMDA-receptor affinity. Even the electron poor 2-pyridyl derivative **4g** does not significantly exceed the NMDA-receptor affinity of the phenyl derivative **4a**.

The affinities of the 1-alkyl substituted 3-benzazepines **4m** and **n** for the PCP-binding site of the NMDA receptor are very low. However, the K_i-value (11.0 μM) of the *s*-butyl derivative **4n** is in the same range as the K_i-values of 3-benzazepines with aromatic residues in position 1 (e.g., **4a**).

Surprisingly, a considerable improvement of the NMDA receptor affinity was obtained by introducing a one-atomic spacer between the 3-benzazepine heterocycle and the phenyl residue in position 1. The benzyl and the phenylsulfanyl derivatives **4i** and **j** exhibit similar affinities with K_i-values in the range of 1 μM. The highest affinity in this series of NMDA antagonists was found for the acetanilide **4l**, which is about 100 times more potent than the 1-phenyl derivative **4a**. The K_i-value of the acetanilide **4l** ($K_i = 89$ nM) indicates NMDA receptor affinity in the range of the prototypical NMDA antagonists phencyclidine and (*S*)-ketamine (see Table 2). The high affinity of **4l** may be due to the charge distribution and the capability of the acetamide moiety to take part in the formation of H-bonds.

4. Conclusion

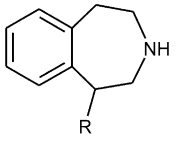
The novel synthesis of tetrahydro-3-benzazepines by *Michael addition* and reductive cyclization allows the introduction of various substituents in position 1 of the 3-benzazepine heterocycle. Ligands with a one-atomic spacer between the 3-benzazepine heterocycle and the phenyl residue in position 1 display most promising NMDA receptor affinity. In particular, the acetanilide **4l** with the H-bond accepting amide substructure attains the NMDA receptor affinity of prototypical NMDA antagonists (e.g., (*S*)-ketamine).

5. Experimental

5.1. Chemistry, 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 (tlc): Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc):[18] 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 SMP 2 (Stuart Scientific), uncorrected. Elemental analyses: Elemental Analyzer 240 (Perkin–Elmer) and Vario EL (Elementaranalysesysteme GmbH). MS: MAT 312, MAT 8200, MAT 44, and TSQ 7000 (Finnigan); EI = electron

Table 2. Affinities of the 3-benzazepines **4** for the phencyclidine-binding site of the NMDA-receptor



4a-n

Compd.	R	K_i ± SEM [μM]	Compd.	R	K_i ± SEM [μM]
4a	C_6H_5	8.74 ± 2.06	**4i**	C_6H_5-CH_2	1.05 ± 0.21
4b	2-CH_3-C_6H_4	2.17 ± 0.43	**4j**	C_6H_5-S	1.40 ± 0.18
4c	3-MeO-C_6H_4	5.61 ± 1.63	**4l**	C_6H_5-NAc	0.089 ± 0.017
4d	2-HO-C_6H_4	> 100	**4m**	*n*-Bu	16.1 ± 4.63
4e	2-Furyl	15.9 ± 2.63	**4n**	*s*-Bu	11.0 ± 2.53
4f	2-Thienyl	21.7 ± 5.38	Dexoxadrol		0.019 ± 0.0025
4g	2-Pyridyl	6.85 ± 1.37	Phencyclidine		0.028 ± 0.0046
4h	Indol-3-yl	24.4 ± 5.66	(*S*)-Ketamine		0.108 ± 0.012

impact, CI = chemical ionization. High resolution MS (HR-MS): MAT 8200 (Finnigan). IR: IR spectrophotometer 1605 FT-IR (Perkin–Elmer). ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz): Unity 300 FT NMR spectrometer (Varian), δ in ppm related to tetramethylsilane, coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and ^{1}H NMR signals were supported by 2D NMR techniques.

5.2. (±)-2-[2-(1-Hydroxy-2-nitroethyl)phenyl]acetaldehyde dimethyl acetal (7)

At 0 °C nitromethane (2.02 mL, 37.1 mmol) was added to **6**[14] (720 mg, 3.71 mmol). Then a solution of KOH (292 mg, 5.22 mmol) in a mixture of CH_3OH/H_2O 1:1 (1.5 mL) was added and the mixture was stirred for 7 h at 0 °C. A saturated solution of NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (5×10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Colorless oil, yield 749.4 mg (79%). $C_{12}H_{17}NO_5$ (255.3) calcd C 56.5H 6.71 N 5.49 found C 56.4H 6.75 N 5.39. IR (film): $\tilde{\nu}$ [cm^{-1}] = 3414, 2836, 1553, 1376, 765. ^{1}H NMR ($CDCl_3$): δ = 3.05 (d, J = 5.3 Hz, 2H, ArCH_2CH(OCH$_3$)$_2$), 3.33 (s, 6H, ArCH$_2$CH(OCH_3)$_2$), 4.47 (t, J = 5.3 Hz, 1H, ArCH$_2$CH(OCH$_3$)$_2$), 4.61 (dd, J = 13.0/3.5 Hz, 1H, ArCH(OH)CH_2NO$_2$), 4.69 (dd, J = 13.0/9.2 Hz, 1H, ArCH(OH)CH_2NO$_2$), 5.72 (dd, J = 9.2/3.5 Hz, 1H, ArCH(OH)CH$_2$NO$_2$), 7.20–7.30 (m, 3H, 4-H$_{arom.}$, 5-H$_{arom.}$, 6-H$_{arom.}$), 7.39 (dd, J = 6.1/1.2 Hz, 1H, 3-H$_{arom.}$). A signal for the OH-proton was not observed.

5.3. (±)-3-Methoxy-1-(nitromethyl)-3,4-dihydro-1*H*-2-benzopyran (8)

A solution of *p*-toluenesulfonic acid (5 mg, 26 μmol) in CH_3OH (2 mL) was slowly added to a cooled solution of **7** (30 mg, 117 μmol) in CH_3OH (4 mL) and the mixture was stirred for 16 h at rt. After addition of a saturated solution of $NaHCO_3$ the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), concentrated in vacuo and the residue (77.7 mg) was purified by fc (1 cm, petroleum ether/ethyl acetate 80:20, fractions 5 mL, R_f = 0.42). Pale yellow oil, yield 10.5 mg (40%). $C_{11}H_{13}NO_4$ (223.3). — IR (film): $\tilde{\nu}$ [cm^{-1}] = 2838, 1558, 1380, 1129, 1059. — ^{1}H NMR ($CDCl_3$): δ = 3.52 (s, 3H, OCH_3), 4.66 (dd, J = 12.7/9.8 Hz, 1H, ArCH_2CH(OCH$_3$)OR), 4.77 (d, J = 6.8 Hz, 2H, CH_2NO$_2$), 4.86 (dd, J = 12.7/2.9 Hz, 1H, ArCH_2CH(OCH$_3$)OR), 5.58 (dd, J = 9.8/2.9 Hz, 1H, ArCH$_2$CH(OCH$_3$)OR), 5.67 (t, J = 6.6 Hz, 1H, ArCH(OR)CH$_2$NO$_2$), 7.04 (td, J = 6.8/1.9 Hz, 1H, 7-H$_{arom.}$), 7.16 (td, J = 6.4/2.4 Hz, 1H, 6-H$_{arom.}$), 7.23 (dd, J = 7.3/1.9 Hz, 1H, 5-H$_{arom.}$), 7.23 (dd, J = 6.4/2.4 Hz, 1H, 8-H$_{arom.}$).

5.4. (*E*)-2-[2-(2-Nitrovinyl)phenyl]acetaldehyde dimethyl acetal (9)

The nitroaldol **7** (480 mg, 1.88 mmol) was dissolved in CH_2Cl_2 (15 mL) and the solution was cooled to −50 °C. Then, methanesulfonyl chloride (175 μL, 2.19 mmol) and Et_3N (607 μL, 4.38 mmol) were added and the mixture was stirred for 8 h at 0 °C. A saturated solution of NH_4Cl (15 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (5×10 mL), the organic layer was dried ($MgSO_4$), concentrated in vacuo and the residue (551.4 mg) was purified by fc (3 cm, petroleum ether/ethyl acetate 80:20, fractions 10 mL, R_f = 0.37). Pale yellow oil, which solidifies upon standing in the refrigerator, yield 351.5 mg (79%). $C_{12}H_{15}NO_4$ (237.3) calcd C 60.8H 6.37 N 5.90 found C 60.6H 6.28 N 5.78. IR (film): $\tilde{\nu}$ [cm^{-1}] = 2854, 2835, 1601, 1558, 1342. ^{1}H NMR ($CDCl_3$): δ = 3.07 (d, J = 5.3 Hz, 2H, ArCH_2CH(OCH$_3$)$_2$), 3.34 (s, 6H, ArCH$_2$CH(OCH_3)$_2$), 4.46 (t, J = 5.3 Hz, 1H, ArCH$_2$CH(OCH$_3$)$_2$), 7.30 (td, J = 7.3/1.3 Hz, 1H, 5-H$_{arom.}$), 7.33 (d, J = 7.6 Hz, 1H, 6-H$_{arom.}$), 7.43 (td, J = 7.6/1.3 Hz, 1H, 4-H$_{arom.}$), 7.50 (d, J = 13.6 Hz, 1H, ArCH=CHNO$_2$), 7.53 (d, J = 7.8 Hz, 1H, 3-H$_{arom.}$), 8.43 (d, J = 13.4 Hz, 1H, ArCH=CHNO$_2$).

5.5. (±)-2-[2-(2-Nitro-1-phenylethyl)phenyl]acetaldehyde dimethyl acetal (10a)[13]

A solution of bromobenzene (220 μL, 2.11 mmol) in Et_2O (5 mL) was added to Mg (52 mg, 2.11 mmol). The mixture was heated to reflux for 10 min. Then, the mixture was cooled (0 °C) and a solution of **9** (100 mg, 422 μmol) in Et_2O (5 mL) was added and the mixture was stirred for 18 h at rt. Subsequently, a saturated solution of NH_4Cl (10 mL) was added, the Et_2O layer was separated and the aqueous layer was extracted with Et_2O (4×10 mL). The combined Et_2O layers were dried ($MgSO_4$) and concentrated in vacuo to yield a residue (182.8 mg), which was purified by fc (2 cm, petroleum ether/ethyl acetate 90:10, fractions 5 mL, R_f = 0.22). Pale yellow oil, yield 85.0 mg (64%). $C_{18}H_{21}NO_4$ (315.4). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2864, 1603, 1551, 1378. ^{1}H NMR ($CDCl_3$): δ = 2.92 (dd, J = 14.3/5.1 Hz, 1H, ArCH_2CH(OCH$_3$)$_2$), 3.07 (dd, J = 14.3/5.9 Hz, 1H, ArCH_2CH(OCH$_3$)$_2$), 3.30 (s, 3H, ArCH$_2$CH(OCH_3)$_2$), 3.33 (s, 3H, ArCH$_2$CH(OCH_3)$_2$), 4.41 (t, J = 5.3 Hz, 1H, ArCH$_2$CH(OCH$_3$)$_2$), 4.94 (dd, J = 13.0/8.2 Hz, 1H, ArCH(Ar)CH_2NO$_2$), 4.99 (dd, J = 13.0/7.9 Hz, 1H, ArCH(Ar)CH_2NO$_2$), 5.50 (t, J = 7.9 Hz, 1H, ArCH(Ar)CH$_2$NO$_2$), 7.23–7.39 (m, 7H, 5-H$_{arom.}$, 6-H$_{arom.}$ and 2-H$_{phenyl}$ to 6-H$_{phenyl}$), 7.46 (td, J = 7.3/1.4 Hz, 1H, 4-H$_{arom.}$), 7.62 (dd, J = 8.4/1.5 Hz, 1H, 3-H$_{arom.}$).

5.6. (±)-2-{2-[1-(2-Methylphenyl)-2-nitroethyl]phenyl}-acetaldehyde dimethyl acetal (10b)

A solution of 2-bromotoluene (254 μL, 2.11 mmol) in THF (10 mL) was cooled to −78 °C and subsequently a solution of *n*-BuLi in *n*-hexane (1.6 M, 1.32 mL, 2.11 mmol) was added. After 20 min a solution of **9** (100 mg, 421 μmol) in THF (3 mL) was added and the mixture was stirred at −78 °C for 7.5 h. Then, a saturated solution of NH_4Cl (10 mL) was added, the Et_2O layer was separated and the aqueous layer was extracted with Et_2O (4×10 mL). The combined Et_2O layers were dried ($MgSO_4$) and concentrated in vacuo to give a residue (201.4 mg) which was purified by fc (2 cm, petroleum ether/ethyl acetate 90:10, fractions 20 mL, R_f = 0.21). Pale yellow oil, yield 86.9 mg (63%). $C_{19}H_{23}NO_4$ (329.4) calcd C 69.3H 7.04 N 4.25 found C 69.5H 7.05 N 3.93.

MS (CI (Iso), 240 eV): $m/z = 329$ (M^+). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2833, 1601, 1551, 1374. ^1H NMR ($CDCl_3$): $\delta = 2.42$ (s, 3H, ArCH_3), 2.82 (dd, $J = 14.2/4.4$ Hz, 1H, ArCH_2CH(OCH_3)$_2$), 2.98 (dd, $J = 14.0/6.4$ Hz, 1H, ArCH_2CH(OCH_3)$_2$), 3.29 (s, 3H, ArCH$_2$CH(OCH_3)$_2$), 3.30 (s, 3H, ArCH$_2$CH(OCH_3)$_2$), 4.39 (dd, $J = 6.4/4.3$ Hz, 1H, ArCH$_2$CH(OCH_3)$_2$), 4.77 (dd, $J = 13.6/7.5$ Hz, 1H, ArCH(Ar)CH_2NO$_2$), 5.02 (dd, $J = 13.6/8.5$ Hz, 1H, ArCH(Ar)CH_2NO$_2$), 5.50 (t, $J = 7.9$ Hz, 1H, ArCH(Ar)-CH$_2$NO$_2$), 7.04–7.29 (m, 8H 3-H$_{arom.}$ To 6-H$_{arom.}$ and 3-H$_{tolyl}$ to 6-H$_{tolyl}$).

5.7. (±)-2-{2-[1-(3-Methoxyphenyl)-2-nitroethyl]phenyl}-acetaldehyde dimethyl acetal (10c)

At −78 °C n-BuLi (1.32 mL, 2.11 mmol, 1.6 M in *n*-hexane) was slowly added to a solution of 3-bromoanisol (266 μL, 2.11 mmol) in THF (10 mL). After 15 min a solution of **9** (100 mg, 421 μmol) in THF (3 mL) was added and the mixture was stirred for 7 h at −78 °C. Then, a saturated solution of NH_4Cl (10 mL) was added, the mixture was extracted with Et_2O (4×10 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (135.4 mg) was purified by fc (1 cm, petroleum ether/ethyl acetate 80:20, fractions 5 mL, $R_f = 0.24$). Pale yellow oil, yield 67.4 mg (46%). $C_{19}H_{23}NO_5$ (345.4) calcd C 66.1H 6.71 N 4.06 found C 66.5H 6.68 N 3.60. MS (CI (NH_3), 240 eV): $m/z = 363$ ($M^+ + NH_4^+$), 332 ($M^+ + NH_4^+$-OCH_3), 301 ($M^+ + NH_4^+$–(OCH_3)$_2$), 270 ($M^+ + NH_4^+$-(OCH_3)$_3$). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2835, 1600, 1553, 1375. ^1H NMR ($CDCl_3$): $\delta = 2.91$ (dd, $J = 14.2/5.0$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.06 (dd, $J = 14.2/6.0$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.31 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 3.33 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 3.76 (s, 3H, Ar–OCH_3), 4.41 (t, $J = 5.3$ Hz, 1H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.92 (dd, $J = 13.1/8.2$ Hz, 1H, Ar–CH(Ar)–CH_2–NO$_2$), 4.97 (dd, $J = 13.1/7.9$ Hz, 1H, Ar–CH(Ar)–CH_2–NO$_2$), 5.34 (t, $J = 8.1$ Hz, 1H, Ar–CH(Ar)–CH$_2$–NO$_2$), 6.42 (dd, $J = 6.7/2.1$ Hz, 1H, 6-H$_{anisol}$), 6.76 (dd, $J = 7.0/2.4$ Hz, 1H, 4-H$_{anisol}$), 6.82 (td, $J = 7.6/1.2$ Hz, 1H, 5-H$_{anisol}$), 7.13 (t, $J = 8.4$ Hz, 1H, 5-H$_{arom.}$), 7.20–7.29 (m, 4H, 2-H$_{anisol}$, 3-H$_{arom.}$ to 4-H$_{arom.}$ and 6-H$_{arom.}$).

5.8. (±)-2-{2-[1-(2-Hydroxyphenyl)-2-nitroethyl]phenyl}-acetaldehyde dimethyl acetal (10d)

At 0 °C a solution of phenol (596 mg, 6.3 mmol) in THF (5 mL) was added to a mixture of NaH (252 mg, 6.3 mmol, 60% dispersion in oil) in THF (15 mL). Then a solution of **9** (300 mg, 1.26 mmol) in THF (5 mL) was slowly added and the mixture was stirred for 6 h at rt. Then, a saturated solution of NH_4Cl (20 mL) was added, the mixture was extracted with Et_2O (4×10 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (943.8 mg) was purified by fc (3 cm, petroleum ether/ethyl acetate 80:20, fractions 20 mL, $R_f = 0.29$). Colorless oil, yield 150.7 mg (36%). $C_{18}H_{21}NO_5$ (331.4) calcd C 65.2H 6.39 N 4.23 found C 64.2H 6.71 N 3.66. MS (70 eV): $m/z = 331$ (M^+), 300 (M^+-OCH_3), 283 (M^+–OCH_3–OH). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3322, 2836, 1599, 1551, 1373. ^1H NMR ($CDCl_3$): $\delta = 2.99$ (dd, $J = 14.3/5.0$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.11 (dd, $J = 14.1/6.0$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.31 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 3.38 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.52 (dd, $J = 6.0/4.9$ Hz, 1H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.78 (dd, $J = 13.4/7.5$ Hz, 1H, Ar–CH(Ar)–CH_2–NO$_2$), 5.00 (dd, $J = 13.3/8.5$ Hz, 1H, Ar–CH(Ar)–CH_2–NO$_2$), 5.56 (t, $J = 8.0$ Hz, 1H, Ar–CH(Ar)–CH$_2$–NO$_2$), 6.27 (s, 1H, Ar–OH), 6.79 (dd, $J = 8.1/1.3$ Hz, 1H, 3-H$_{phenol}$), 6.87 (td, $J = 7.5/1.1$ Hz, 1H, 5-H$_{phenol}$), 7.08 (dd, $J = 7.7/1.5$ Hz, 1H, 6-H$_{phenol}$), 7.11–7.26 (m, 5H, 3-H$_{arom.}$ to 6-H$_{arom.}$ and 4-H$_{phenol}$).

5.9. (±)-2-{2-[1-(Furan-2-yl)-2-nitroethyl]phenyl}acetaldehyde dimethyl acetal (10e)

At −78 °C furan (153 μL, 2.11 mmol) was added to a solution of *n*-BuLi (1.32 mL, 2.11 mmol, 1.6 M in *n*-hexane) in Et_2O (10 mL). The mixture was stirred for 15 min at −78 °C and for 60 min at rt. Then, a solution of **9** (100 mg, 421 μmol) in Et_2O (5 mL) was added and the mixture was stirred for additional 7 h at −78 °C. Then, a saturated solution of NH_4Cl (10 mL) was added, the mixture was extracted with Et_2O (4×10 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (133.6 mg) was purified by fc (1 cm, petroleum ether/ethyl acetate 80:20, fractions 5 mL, $R_f = 0.33$). Pale yellow oil, yield 103.8 mg (81%). $C_{16}H_{19}NO_5$ (305.3) calcd C 62.9H 6.27 N 4.59 found C 62.4H 6.25 N 4.50. MS (CI (NH_3), 240 eV): $m/z = 323$ ($M + NH_4^+$), 292 ($M + NH_4^+$–OCH_3), 277 ($M + NH_4^+$–OCH_3–CH_3), 261 ($M + NH_4^+$–(OCH_3)$_2$). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2832, 1554, 1341, 754. ^1H NMR ($CDCl_3$): $\delta = 3.03$ (dd, $J = 13.9/5.0$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.09 (dd, $J = 13.9/5.3$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.32 (s, 3H, Ar-CH(OCH_3)$_2$), 3.33 (s, 3H, Ar–CH(OCH_3)$_2$), 4.50 (t, $J = 5.3$ Hz, 1H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.82 (dd, $J = 13.1/6.7$ Hz, 1H, Ar–CH(Fur.)–CH_2–NO$_2$), 4.99 (dd, $J = 13.1/8.5$ Hz, 1H, Ar–CH(Fur.)–CH_2–NO$_2$), 5.38 (dd, $J = 8.5/7.0$ Hz, 1H, Ar–CH(Fur.)-CH$_2$-NO$_2$), 6.06 (td, $J = 3.4/0.9$ Hz, 1H, 3-H$_{fur.}$), 6.28 (dd, $J = 3.1/1.8$ Hz, 1H, 4-H$_{fur.}$), 7.21–7.28 (m, 4H, 3-H$_{arom.}$ to 6-H$_{arom.}$), 7.33 (dd, $J = 1.8/0.9$ Hz, 1H, 5-H$_{fur.}$).

5.10. (±)-2-{2-[2-Nitro-1-(thiophen-2-yl)ethyl]phenyl}-acetaldehyde dimethyl acetal (10f)

At −78 °C thiophene (3.36 mL, 42.2 mmol) was added to a solution of *n*-BuLi (26.4 mL, 42.2 mmol, 1.6 M in *n*-hexane) in Et_2O (100 mL). The mixture was stirred for 110 min at −78 °C to rt. Then, a solution of **9** (2.0 g, 8.42 mmol) in Et_2O (5 mL) was added and the mixture was stirred for 6 h at −78 °C to −60 °C. Then, a saturated solution of NH_4Cl (100 mL) was added, the mixture was extracted with Et_2O (4×50 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (3.35 g) was purified by fc (6 cm, petroleum ether/ethyl acetate 80:20, fractions 20 mL, $R_f = 0.42$). Pale yellow oil, yield 2.14 g (79%). $C_{16}H_{19}NO_4S$ (321.4) calcd C 59.8H 5.96 N 4.36 found C 60.3H 6.05 N 4.14. MS (ESI, 3.8 kV): $m/z = 344$ ($M^+ + Na$), 321 (M^+). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2832, 1556, 1434, 1377. ^1H NMR ($CDCl_3$): $\delta = 2.98$ (dd, $J = 14.4/5.4$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.05 (dd, $J = 14.4/5.8$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.30 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 3.31

(s, 3H, Ar–CH_2–CH(OCH_3)$_2$), 4.44 (t, J = 5.4 Hz, 1H, Ar–CH_2–C*H*(OCH_3)$_2$), 4.91 (dd, J = 13.0/7.7 Hz, 1H, Ar–CH(Thioph.)–C*H*$_2$–NO_2), 4.96 (dd, J = 12.9/8.2 Hz, 1H, Ar–CH(Thioph.)–C*H*$_2$–NO_2), 5.58 (t, J = 7.9 Hz, 1H, Ar–C*H*(Thioph.)–CH_2–NO_2), 6.87 (dd, J = 3.7/1.1 Hz, 1H, 3-$H_{thioph.}$), 6.91 (dd, J = 5.0/3.5 Hz, 1H, 4-$H_{thioph.}$), 7.18 (dd, J = 3.7/1.2 Hz, 1H, 5-$H_{thioph.}$), 7.25–7.28 (m, 4H, 3-$H_{arom.}$ to 6-$H_{arom.}$).

5.11. (±)-2-{2-[2-Nitro-1-(pyridin-2-yl)ethyl]phenyl}acetaldehyde dimethyl acetal (10g)

At −78 °C *n*-BuLi (2.68 mL, 4.11 mmol, 1.6 M in *n*-hexane) was added to a solution of 2-bromopyridine (402 μL, 4.11 mmol) in THF (20 mL). After stirring for 20 min at −78 °C a solution of **9** (230 mg, 0.97 mmol) in THF (5 mL) was added and the mixture was stirred at −78 °C for 7.5 h. Then, a saturated solution of NH_4Cl (20 mL) was added, the mixture was extracted with Et_2O (4×10 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (331.1 mg) was purified by fc (3 cm, petroleum ether/ethyl acetate 90:10, fractions 20 mL, R_f = 0.19). Colorless oil, yield (143.4 mg, 47%). $C_{17}H_{20}N_2O_4$ (316.4). IR (film): $\tilde{\nu}$ [cm^{-1}] = 1551, 1436, 1374. ^{1}H NMR ($CDCl_3$): δ = 3.11 (dd, J = 14.2/5.3 Hz, 1H, Ar–C*H*$_2$–CH(OCH_3)$_2$), 3.17 (dd, J = 14.2/5.3 Hz, 1H, Ar–C*H*$_2$–CH(OCH_3)$_2$), 3.36 (s, 3H, Ar–CH_2–CH(OC*H*$_3$)$_2$), 3.37 (s, 3H, Ar–CH_2–CH(OC*H*$_3$)$_2$), 4.56 (t, J = 5.3 Hz, 1H, Ar–CH_2–C*H*(OCH_3)$_2$), 4.76 (dd, J = 11.9/4.0 Hz, 1H, Ar–CH(Pyr.)–C*H*$_2$-NO_2), 5.47 (dd, J = 9.2/4.0 Hz, 1H, Ar–C*H*(Pyr.)–CH_2–NO_2), 5.53 (dd, J = 12.0/9.3 Hz, 1H, Ar–CH(Pyr.)–C*H*$_2$–NO_2), 7.10 (d, J = 8.5 Hz, 1H, 3-$H_{arom.}$), 7.14 (dd, J = 5.0/1.4 Hz, 1H, 3-$H_{pyr.}$), 7.17–7.22 (m, 3H, 4-$H_{arom.}$, 5-$H_{arom.}$ and 5-$H_{pyr.}$), 7.27 (dd, J = 6.7/1.8 Hz, 1H, 6-$H_{arom.}$), 7.55 (td, J = 7.6/1.8 Hz, 1H, 4-$H_{pyr.}$), 8.55 (dd, J = 4.9/1.0 Hz, 1H, 6-$H_{pyr.}$).

5.12. (±)-2-{2-[1-(Indol-3-yl)-2-nitroethyl]phenyl}acetaldehyde dimethyl acetal (10h) and(±)-2-{2-[1-(Indol-1-yl)-2-nitroethyl]phenyl}acetaldehyde dimethyl acetal (11)

At 0 °C a solution of indole (738 mg, 6.3 mmol) in THF (3 mL) was added to a suspension of NaH (252 mg, 6.3 mmol, 60% dispersion in oil) in THF (10 mL) and the mixture was stirred for 10 min at 0 °C Then, a solution of **9** (300 mg, 1.26 mmol) in THF (5 mL) was added and the mixture was stirred for 7 h at 0 °C to rt. Then, a saturated solution of NH_4Cl (15 mL) was added, the mixture was extracted with Et_2O (4×10 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (1.46 g) was purified by fc (4 cm, petroleum ether/ethyl acetate 85:15, fractions 20 mL).

11 (R_f = 0.17): Colorless oil, yield (21.5 mg, 4.8%). $C_{20}H_{22}N_2O_4$ (354.4). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2851, 1598, 1551, 1368. ^{1}H NMR ($CDCl_3$): δ = 2.84 (dd, J = 14.2/3.8 Hz, 1H, Ar–C*H*$_2$–CH(OCH_3)$_2$), 3.02 (dd, J = 14.6/6.7 Hz, 1H, Ar–C*H*$_2$–CH(OCH_3)$_2$), 3.23 (s, 3H, Ar–CH_2–CH(OC*H*$_3$)$_2$), 3.31 (s, 3H, Ar–CH_2–CH(OC*H*$_3$)$_2$), 4.28 (dd, J = 6.8/3.8 Hz, 1H, Ar–CH_2–C*H*(OCH_3)$_2$), 5.10 (dd, J = 13.3/8.4 Hz, 1H, Ar–CH(Ind.)–C*H*$_2$–NO_2), 5.20 (dd, J = 13.3/6.6 Hz, 1H, Ar–CH(Ind.)–C*H*$_2$–NO_2), 6.54 (d, J = 3.4 Hz, 1H, 3-$H_{Ind.}$), 6.94 (dd, J = 8.2/6.7 Hz, 1H, Ar–C*H*(Ind.)–CH_2–NO_2), 7.05 (d, J = 3.6 Hz, 1H, 2-$H_{Ind.}$), 7.09 (td, J = 7.5/1.9 Hz, 1H, 5-$H_{Ind.}$), 7.13 (td, J = 7.5/0.8 Hz, 1H, 6-$H_{Ind.}$), 7.23 (dd, J = 7.6/1.1 Hz, 1H, 3-$H_{arom.}$), 7.26–7.32 (m, 3H, 4-$H_{arom.}$ to 6-$H_{arom.}$), 7.54 (dd, J = 7.9/0.9 Hz, 1H, 7-$H_{Ind.}$), 7.61 (dd, J = 7.6/0.9 Hz, 1H, 4-$H_{Ind.}$).

10h (R_f = 0.16): Colorless oil, yield 422.1 mg (94%). $C_{20}H_{22}N_2O_4$ (354.4) calcd C 67.8H 6.26 N 7.90 found C 68.2H 6.52 N 7.52. MS (EI/CI, 70 eV): m/z = 354 (M^+), 323 (M^+–OCH_3), 308 (M^+–OCH_3–CH_3), 292 (M^+ 2×(OCH_3)). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3417, 2854, 1603, 1556, 1377. ^{1}H NMR ($CDCl_3$): δ = 3.07 (dd, J = 14.3/5.2 Hz, 1H, Ar–C*H*$_2$–CH(OCH_3)$_2$), 3.15 (dd, J = 14.0/5.8 Hz, 1H, Ar–C*H*$_2$–CH(OCH_3)$_2$), 3.29 (s, 3H, Ar–CH_2–CH(OC*H*$_3$)$_2$), 3.34 (s, 3H, Ar–CH_2–CH(OC*H*$_3$)$_2$), 4.52 (t, J = 5.3 Hz, 1H, Ar–CH_2–C*H*(OCH_3)$_2$), 4.99 (dd, J = 13.1/8.1 Hz, 1H, Ar–CH(Ind.)–C*H*$_2$–NO_2), 5.03 (dd, J = 13.0/7.8 Hz, 1H, Ar–CH(Ind.)–C*H*$_2$–NO_2), 5.62 (t, J = 7.9 Hz, 1H, Ar–C*H*(Ind.)–CH_2–NO_2), 6.87 (dd, J = 2.4/0.6 Hz, 1H, 2-$H_{Ind.}$), 7.09 (td, J = 7.0/0.9 Hz, 1H, 5-$H_{Ind.}$), 7.17 (dd, J = 7.6/1.2 Hz, 1H, 3-$H_{arom.}$), 7.23 (td, J = 7.0/2.2 Hz, 2H, 4-$H_{arom.}$ and 5-$H_{arom.}$), 7.29–7.33 (m, 3H, 6-$H_{arom.}$, 6-$H_{Ind.}$ and 7-$H_{Ind.}$), 7.52 (dd, J = 7.9/0.6 Hz, 1H, 4-$H_{Ind.}$), 8.21 (br, 1H, N-$H_{Ind.}$).

5.13. (±)-2-[2-(1-Nitro-3-phenylpropan-2-yl)phenyl]acetaldehyde dimethyl acetal (10i)

At rt a solution of benzyl bromide (3.0 mL, 25.3 mmol) in Et_2O (10 mL) was added to Mg (614 mg, 25.3 mmol) and the mixture was heated to reflux for 10 min The mixture was cooled to 0 °C and a solution of **9** (2.0 g, 8.42 mmol) in Et_2O (10 mL) was added. After stirring for 16 h at rt a saturated solution of NH_4Cl (20 mL) was added, the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (4.63 g) was purified by fc (5 cm, petroleum ether/ethyl acetate 90:10, fractions 30 mL, R_f = 0.22). Pale yellow oil, yield 1,75 g (63%). $C_{19}H_{23}NO_4$ (329.4). MS (EI, 70 eV): m/z = 329 (M^+), 298 (M^+-OCH_3). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2851, 2837, 1559, 1343. ^{1}H NMR ($CDCl_3$): δ = 2.79 (dd, J = 14.1/5.4 Hz, 1H, Ar–C*H*$_2$–CH(OCH_3)$_2$), 2.91 (dd, J = 13.5/7.8 Hz, 1H, Ar–CH(CH_2–NO_2)–C*H*$_2$–Ar), 2.92 (dd, J = 14.2/5.7 Hz, 1H, Ar–C*H*$_2$–CH(OCH_3)$_2$), 3.04 (dd, J = 13.8/7.3 Hz, 1H, Ar–CH(CH_2–NO_2)–C*H*$_2$–Ar), 3.31 (s, 3H, Ar–CH_2–CH(OC*H*$_3$)$_2$), 3.32 (s, 3H, Ar–CH_2–CH(OC*H*$_3$)$_2$), 4.22 (quint, J = 7.6 Hz, 1H, Ar–C*H*(CH_2–NO_2)–CH_2–Ar), 4.30 (t, J = 5.5 Hz, 1H, Ar–CH_2–C*H*(OCH_3)$_2$), 4.54 (dd, J = 12.7/6.9 Hz, 1H, Ar–CH(Bn)–C*H*$_2$–NO_2), 4.61 (dd, J = 12.5/8.3 Hz, 1H, Ar–CH(Bn)–C*H*$_2$–NO_2), 7.11 (dd, J = 7.6/1.5 Hz, 2H, 2-$H_{bn.}$ and 6-$H_{bn.}$), 7.19–7.29 (m, 7H, 3-$H_{arom.}$ to 6-$H_{arom.}$ and 3-$H_{bn.}$ to 5-$H_{bn.}$).

5.14. (±)-2-{2-[2-Nitro-1-(phenylsulfanyl)ethyl]phenyl}acetaldehyde dimethyl acetal (10j)

A solution of **9** (230 mg, 969 μmol), thiophenol (105 μL, 1.02 mmol) and NEt_3 (24 μL, 194 μmol) in THF (8 mL) was stirred for 2 h at rt and for 2 h at 66 °C. The mixture was concentrated in vacuo and the residue (343.1 mg) was purified by fc (2 cm, petroleum ether/ethyl

acetate 90:10, fractions 5 mL, $R_f = 0.30$). Pale yellow oil, yield 311.6 mg (93%). $C_{18}H_{21}NO_4S$ (347.4) calcd C 62.2H 6.09 N 4.03 found C 62.3H 6.06 N 4.17. MS (EI, 70 eV): $m/z = 347$ (M^+), 316 (M^+-OCH_3), 270 (M^+–OCH_3–NO_2). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2853, 2831, 1556, 1341. ^1H NMR ($CDCl_3$): δ = 3.04 (dd, $J = 14.4/5.4$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.12 (dd, $J = 14.2/5.6$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.36 (s, 6H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.57 (t, $J = 5.5$ Hz, 1H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.70 (dd, $J = 13.1/6.5$ Hz, 1H, Ar–CH(SPh)–CH_2–NO_2), 4.96 (dd, $J = 13.2/9.3$ Hz, 1H, Ar–CH(SPh)–CH_2–NO_2), 5.36 (dd, $J = 9.3/6.4$ Hz, 1H, Ar–CH(SPh)–CH_2–NO_2), 7.16–7.35 (m, 7H, 3-$H_{arom.}$ to 6-$H_{arom.}$, 2-H_{SPh}, 4-H_{SPh} and 6-H_{SPh}), 7.42 (dd, $J = 6.7/2.1$ Hz, 2H, 3-H_{SPh} and 5-H_{SPh}).

5.15. (±)-2-[2-(1-Anilino-2-nitroethyl)phenyl]acetaldehyde dimethyl acetal (10k)

At 0 °C aniline (42 μL, 464 mmol) and NEt_3 (11 μL, 885 μmol) were added to a solution of **9** (100 mg, 421 μmol) in THF (4 mL) and the mixture was stirred for 2 h at rt and for 2 h at 66 °C. The solvent was evaporated in vacuo and the residue (185.5 mg) was purified by fc (2 cm, petroleum ether/ethyl acetate 90:10, fractions 5 mL, $R_f = 0.19$). Pale yellow oil, yield 120.1 mg (86%). $C_{18}H_{22}N_2O_4$ (330.4) calcd C 65.4H 6.71 N 8.48 found C 64.7H 6.68 N 8.22. IR (film): $\tilde{\nu}$ [cm^{-1}] = 2856, 2831, 1558, 1342. ^1H NMR ($CDCl_3$): δ = 3.07 (dd, $J = 14.3/5.2$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.11 (dd, $J = 14.4/5.7$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.33 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 3.34 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.38 (br, 1H, Ar–CH(NH–Ar)–CH_2–NO_2), 4.57 (t, $J = 5.4$ Hz, 1H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.64 (dd, $J = 12.3/8.3$ Hz, 1H, Ar–CH(NH–Ar)–CH_2–NO_2), 4.82 (dd, $J = 12.4/5.2$ Hz, 1H, Ar–CH(NH–Ar)–CH_2–NO_2), 5.56 (dd, $J = 8.2/5.2$ Hz, 1H, Ar–CH(NH–Ar)–CH_2–NO_2), 6.62 (dd, $J = 7.6/0.9$ Hz, 2H, 2-$H_{aniline}$ and 6-$H_{aniline}$), 6.73 (td, $J = 7.3/0.9$ Hz, 1H, 4-$H_{aniline}$), 7.15 (dd, $J = 7.3/1.2$ Hz, 2H, 3-$H_{aniline}$ and 5-$H_{aniline}$), 7.22–7.30 (m, 3H, 3-$H_{arom.}$ to 5-$H_{arom.}$), 7.42 (dd, $J = 6.1/2.1$ Hz, 1H, 6-$H_{arom.}$).

5.16. (±)-*N*-{1-[2-(2,2-Dimethoxyethyl)phenyl]-2-nitroethyl}-*N*-phenylacetamide (10l)

At 0 °C a solution of acetanilide (568 mg, 4.2 mmol) in THF (3 mL) was added to a suspension of NaH (168 mg, 4.2 mmol, 60% dispersion in oil) in THF (15 mL). After 10 min a solution of **9** (200 mg, 0.84 mmol) in THF (3 mL) was added and the mixture was stirred for 8 h at 0–5 °C. Then, a saturated solution of NH_4Cl (20 mL) was added, the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (793.0 mg) was purified by fc (3 cm, petroleum ether/ethyl acetate 60:40, fractions 20 mL, $R_f = 0.32$). Pale yellow oil, yield 233.1 mg (60%). $C_{20}H_{24}N_2O_5$ (372.4). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2849, 2832, 1689, 1559, 1344. ^1H NMR ($CDCl_3$): δ = 1.75 (s, 3H, NR_2–CO–CH_3), 2.89 (dd, $J = 14.2/5.0$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.25 (dd, $J = 14.2/5.6$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.34 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 3.35 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.52 (t, $J = 5.3$ Hz, 1H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.68 (dd, $J = 12.4/5.3$ Hz, 1H, Ar–CH(N(Ac)–Ar)–CH_2–NO_2), 5.19 (dd, $J = 12.4/9.6$ Hz, 1H, Ar–CH(N(Ac)–Ar)–CH_2–NO_2), 6.53 (dd, $J = 7.9/0.9$ Hz, 1H, 4-$H_{anilide}$), 6.94 (td, $J = 7.6/1.6$ Hz, 2H, 3-$H_{anilide}$ and 5-$H_{anilide}$), 7.01 (dd, $J = 9.7/5.5$ Hz, 1H, Ar–CH(N(Ac)–Ar)–CH_2–NO_2), 7.21 (td, $J = 7.5/1.2$ Hz, 2H, 2-$H_{anilide}$ and 6-$H_{anilide}$), 7.25–7.35 (m, 4H, 3-$H_{arom.}$ to 6-$H_{arom.}$), 7.91 (br, 1H, –NH(Ac)–Ar). ^{13}C NMR ($CDCl_3$): δ = 23.3 (1 C, CO–CH_3), 36.3 (1 C, Ar–CH_2–CH(OCH_3)$_2$), 53.2 (1 C, Ar–CHR–CH_2–NO_2), 53.5 (1 C, Ar–CH$_2$–CH(OCH_3)$_2$), 54.1 (1 C, Ar–CH$_2$–CH(OCH_3)$_2$), 75.5 (1 C, Ar–CHR–CH_2–NO_2), 105.3 (1 C, Ar–CH$_2$–CH(OCH_3)$_2$), 126.3 (1 C, $CH_{arom.}$), 127.6 (1 C, $CH_{arom.}$), 128.5 (1 C, $CH_{arom.}$), 128.7 (2 C, $CH_{arom.}$), 129.4 (2 C, $CH_{arom.}$), 130.2 (1 C, $CH_{arom.}$), 131.5 (1 C, $CH_{arom.}$), 134.0 (1 C, $C_{arom.}$), 136.4 (1 C, $C_{arom.}$), 138.9 (1 C, $C_{arom.}$), 170.6 (1 C, –CO–CH_3).

5.17. (±)-2-[2-(1-Nitrohexan-2-yl)phenyl]acetaldehyde dimethyl acetal (10m)

At −78 °C *n*-BuLi (1.2 mL 1.92 mmol, 1.6 M in *n*-hexane) was added to a solution of **9** (200 mg, 0.84 mmol) in THF (20 mL) and the mixture was stirred for 6 h at −78 °C. Then, a saturated solution of NH_4Cl (20 mL) was added, the mixture was extracted with Et_2O (4×10 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (238.1 mg) was purified by fc (2 cm, petroleum ether/ethyl acetate 90:10, fractions 10 mL, $R_f = 0.23$). Pale yellow oil, yield 154.9 mg (62%). $C_{16}H_{25}NO_4$ (295.4 g/mol) calcd C 65.1H 8.53 N 4.74 found C 65.1H 8.50 N 4.47. MS (ESI, 3.8 kV): $m/z = 318$ ($M^+ + Na$), 303 ($M^+ + Na$–CH_3), 287 ($M^+ + Na$–OCH_3). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3050, 2857, 2836, 1557, 1340. ^1H NMR ($CDCl_3$): δ = 0.83 (t, $J = 7.1$ Hz, 3H, Ar–CH(CH$_2$–NO_2)–(CH$_2$)$_3$–CH_3), 1.08–1.32 (m, 4H, Ar–CH(CH$_2$–NO_2)–CH$_2$–(CH_2)$_2$–CH$_3$), 1.64–1.72 (m, 2H, Ar–CH(CH$_2$–NO_2)–CH_2–(CH$_2$)$_2$–CH$_3$), 2.97 (dd, $J = 14.0/5.5$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.04 (dd, $J = 14.1/5.6$ Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.35 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 3.36 (s, 3H, Ar–CH$_2$–CH(OCH_3)$_2$), 3.88 (quint, $J = 7.4$ Hz, 1H, Ar–CH(^{n}Bu)–CH_2–NO_2), 4.49 (dd, $J = 12.0/7.8$ Hz, 1H, Ar–CH(^{n}Bu)–CH_2–NO_2), 4.51 (t, $J = 5.5$ Hz, 1H, Ar–CH$_2$–CH(OCH_3)$_2$), 4.55 (dd, $J = 12.1/7.2$ Hz, 1H, Ar–CH(^{n}Bu)–CH_2–NO_2), 7.15–7.28 (m, 4H, 3-$H_{arom.}$ to 6-$H_{arom.}$).

5.18. (±)-2-{2-[(2*RS*,3*RS*) and (2*RS*,3*SR*)-3-Methyl-1-nitropentan-2-yl]phenyl}acetaldehyde dimethyl acetal (10n)

At −78 °C a solution of **9** (300 mg, 1.26 mmol) in THF (3 mL) was added to a solution of *s*-BuLi (1.2 mL, 1.56 mmol, 1.3 M in cyclohexane) in THF (20 mL) and the mixture was stirred for 8 h at −78 °C. Then, a saturated solution of NH_4Cl (20 mL) was added, the mixture was extracted with Et_2O (4×10 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (321.3 mg) was purified by fc (3 cm, petroleum ether/ethyl acetate 90:10, fractions 20 mL, $R_f = 0.24$). Pale yellow oil, yield 155.5 mg (42%). $C_{16}H_{25}NO_4$ (295.4) calcd C 65.1H 8.53 N 4.74 found C 65.4H 8.40 N 4.87. MS (CI (NH_3), 240 eV): $m/z = 313$ ($M^+ + NH_4^+$), 282

($M^+ + NH_4^+ - OCH_3$), 251 ($M^+ + NH_4^+ - (OCH_3)_2$). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2832, 1552, 1378. ^1H NMR ($CDCl_3$): δ = 0.81 (d, *J* = 6.7 Hz, 3×0.5H, Ar–CH(CH_2–NO_2)–CH(CH_3)–CH_2–CH_3), 0.87 (t, *J* = 7.3 Hz, 3×0.5H, Ar–CH(CH_2–NO_2)–CH(CH_3)–CH_2–CH_3), 0.93 (t, *J* = 7.3 Hz, 3×0.5H, Ar–CH(CH_2-NO_2)–CH(CH_3)–CH_2–CH_3), 0.98 (d, *J* = 6.7 Hz, 3×0.5H, Ar–CH(CH_2–NO_2)–CH(CH_3)–CH_2–CH_3), 1.02–1.24 (m, 1H, Ar–CH(CH_2–NO_2)–CH(CH_3)–CH_2–CH_3), 1.55–1.83 (m, 2H, Ar–CH(CH_2–NO_2)–CH(CH_3)–CH_2–CH_3), 2.91 (dd, *J* = 14.3/5.8 Hz, 0.5H, Ar–CH_2–CH(OCH_3)$_2$), 2.93 (dd, *J* = 14.3/6.2 Hz, 0.5H, Ar–CH_2–CH(OCH_3)$_2$), 3.05 (dd, *J* = 14.5/5.0 Hz, 1H, Ar–CH_2–CH(OCH_3)$_2$), 3.33 (s, 3H, Ar-CH_2-CH(OCH_3)$_2$), 3.36 (s, 3H, Ar–CH_2–CH(OCH_3)$_2$), 3.75–3.84 (m, 1H, Ar–CH(^{s}Bu)–CH_2–NO_2), 4.51 (dd, *J* = 6.0/5.0 Hz, 0.5H, Ar–CH_2–CH(OCH_3)$_2$), 4.53 (dd, *J* = 6.0/5.0 Hz, 0.5H, Ar–CH_2–CH(OCH_3)$_2$), 4.63 (dd, *J* = 12.5/8.9 Hz, 0.5H, Ar–CH(^{s}Bu)–CH_2–NO_2), 4.66 (dd, *J* = 12.5/8.9 Hz, 0.5H, Ar–CH(^{s}Bu)–CH_2–NO_2), 4.73 (dd, *J* = 12.5/5.8 Hz, 0.5H, Ar–CH(^{s}Bu)–CH_2–NO_2), 4.76 (dd, *J* = 12.5/5.8 Hz, 0.5H, Ar–CH(^{s}Bu)–CH_2–NO_2), 7.13–7.27 (m, 4H, 3-$H_{arom.}$ to 6-$H_{arom.}$). The ratio of diastereomers is 50:50.

5.19. (±)-1-Phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4a)[13]

A mixture of **10a** (190 mg, 602 μmol), Zn dust (394 mg, 6.0 mmol), 1 N HCl (6.0 mL 6.0 mmol) and THF (15 mL) was heated to reflux for 5 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (124.3 mg) was purified by fc (1 cm, CH_2Cl_2/CH_3OH 80:10, fractions 3 mL, R_f = 0.22). Pale yellow oil, yield 90.4 mg (67%). Spectroscopic data are given in ref [13]

5.20. (±)-1-(2-Methylphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4b)

A mixture of **10b** (160 mg, 486 μmol), Zn dust (318 mg, 4.8 mmol), 1 N HCl (4.8 mL 4.8 mmol) and THF (10 mL) was heated to reflux for 14 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (120.7 mg) was purified by fc (1 cm, CH_2Cl_2/CH_3OH 80:10, fractions 3 mL, R_f = 0.17). Pale yellow oil, yield 74.1 mg (64.2%). $C_{17}H_{19}N$ (237.3) calcd C 86.0H 8.07 N 5.90 found C 85.0H 7.88 N 5.51. MS (EI, 70 eV): *m*/*z* = 237 (M^+), 222 (M^+–CH_3), 208 (M^+–CH_2NH), 194 (M–$(CH_2)_2NH$), 180 (M–$(CH_2)_2NHCH_2$). HR–MS calcd 237.1517 found 237.1517. IR (film): $\tilde{\nu}$ [cm^{-1}] = 3316, 1486. ^1H NMR ($CDCl_3$): δ = 2.20 (s, 3H, Ar–CH_3), 2.53 (br, 1H, R_2N–*H*), 2.80–2.99 (m, 2H, Ar–CH_2–CH_2–NHR), 3.20–3.27 (m, 2H, Ar–CH_2–CH_2–NHR), 3.31 (dd, *J* = 12.8/8.5, 1H, Ar–CH(Ar)–CH_2–NHR), 3.54 (dd, *J* = 12.8/1.5 Hz, 1H, Ar–CH(Ar)–CH_2–NHR), 4.53 (dd, *J* = 8.9/1.5 Hz, 1H, Ar–CH(Ar)–CH_2–NHR), 6.47 (d, *J* = 7.6 Hz, 1H, 9-$H_{arom.}$), 7.00 (td, *J* = 7.5/1.4 Hz, 1H, 7-$H_{arom.}$), 7.11 (td, *J* = 7.2/1.1 Hz, 1H, 8-$H_{arom.}$), 7.17 (dd, *J* = 5.8/1.2 Hz, 1H, 6-H_{tolyl}), 7.22–7.31 (m, 4H, 6-$H_{arom.}$ and 3-H_{tolyl} to 5-H_{tolyl}).

5.21. (±)-1-(3-Methoxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4c)

A mixture of **10c** (220 mg, 637 μmol), Zn dust (418 mg, 6.4 mmol) 1 N HCl (6.4 mL, 6.4 mmol) and THF (10 mL) was heated to reflux for 10 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (133.1 mg) was purified by fc (1 cm, CH_2Cl_2/CH_3OH 80:10, fractions 5 mL, R_f = 0.15). Pale yellow oil, yield 122.5 mg (60%). $C_{17}H_{19}NO$ (253.3) calcd C 80.6H 7.56 N 5.53 found C 79.9H 7.67 N 5.47. MS (EI, 70 eV): *m*/*z* = 253 (M^+), 238 (M^+–CH_3), 222 (M^+–OCH_3), 210 (M^+–$(CH_2)_2NH$), 180 (M^+–OCH_3–$(CH_2)_2NH$). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3438, 1488. ^1H NMR ($CDCl_3$): δ = 2.24 (s, 1H, R_2N-*H*), 2.90–2.94 (m, 2H, Ar–CH_2–CH_2–NHR), 2.99–3.02 (m, 2H, Ar–CH_2–CH_2–NHR), 3.36 (dd, *J* = 13.7/2.1 Hz, 1H, Ar–CH(Ar)–CH_2–NHR), 3.57 (dd, *J* = 13.7/7.0 Hz, 1H, Ar–CH(Ar)–CH_2–NHR), 3.78 (s, 3H, Ar–OCH_3), 4.27 (dd, *J* = 7.3/1.5 Hz, 1H, Ar–CH(Ar)–CH_2–NHR), 6.70 (t, *J* = 1.7 Hz, 1H, 2-H_{anisol}), 6.75 (d, *J* = 7.6 Hz, 1H, 9-$H_{arom.}$), 6.81 (dd, *J* = 8.2/2.4 Hz, 1H, 4-H_{anisol}), 6.91 (d, *J* = 7.0 Hz, 1H, 6-$H_{arom.}$), 7.09–7.17 (m, 3H, 6-H_{anisol}, 7-$H_{arom.}$ and 8-$H_{arom.}$), 7.28 (t, *J* = 8.0 Hz, 1H, 5-H_{anisol}).

5.22. (±)-1-(2-Hydroxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4d)

A mixture of **10d** (150 mg, 453 μmol), Zn dust (294 mg, 4.5 mmol), 1 N HCl (4.5 mL 4.5 mmol) and THF (20 mL) was heated to reflux for 5 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (115.5 mg) was purified by fc (1 cm, CH_2Cl_2/CH_3OH 80:10, fractions 5 mL, R_f = 0.15). Pale yellow oil, yield 38.9 mg (36%). $C_{16}H_{16}NO$ (239.3) calcd C 80.3H 7.16 N 5.85 found C 79.0H 6.76 N 5.49. MS (EI/CI, 70 eV): *m*/*z* = 239 (M^+), 222 (M^+–OH), 210 (M^+–CH_2NH), 196 (M^+–$(CH_2)_2NH$). HR–MS: calcd 239.1311 found 239.1310. IR (film): $\tilde{\nu}$ [cm^{-1}] = 3737, 3371, 1451. ^1H NMR ($CDCl_3$): δ = 2.72 (s, 1H, R_2N-*H*), 2.85–2.93 (m, 2H, Ar–CH_2-CH_2-NHR), 3.13–3.22 (m, 1H, Ar–CH_2–CH_2–NHR), 3.31 (dd, *J* = 12.8/2.4 Hz, 1H, Ar–CH(Ar)–CH_2–NHR), 3.35-3.43 (m, 1H, Ar–CH_2–CH_2–NHR), 3.64 (dd, *J* = 13.0/4.7 Hz, 1H, Ar–CH(Ar)–CH_2–NHR), 4.44 (dd, *J* = 4.4/2.6 Hz, 1H, Ar–CH(Ar)–CH_2–NHR), 6.31 (br, 1H, Ar–O*H*), 6.70 (td, *J* = 7.3/1.1 Hz, 1H, 4-H_{phenol}), 6.87 (dd, *J* = 8.5/1.2 Hz, 1H, 6-Hphenol), 7.06 (dd, *J* = 7.0/0.9 Hz, 1H, 9-$H_{arom.}$), 7.14 (dd, *J* = 7.0/0.9 Hz, 1H, 6-$H_{arom.}$), 7.16–7.44 (m, 4H, 7-$H_{arom.}$, 8-$H_{arom.}$, 3-H_{phenol} and 5-H_{phenol}).

5.23. (±)-1-(Furan-2-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4e)

A mixture of **10e** (95 mg, 324 μmol), Zn dust (209 mg, 3.2 mmol), 1 N HCl (3.2 mL 3.2 mmol) and THF (10 mL) was heated to reflux for 6 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (50.3 mg) was pur-

ified by fc (1 cm, CH_2Cl_2/CH_3OH 80:10, fractions 3 mL, $R_f = 0.16$). Pale yellow oil, yield 40.9 mg (30%). $C_{14}H_{15}NO$ (213.3). MS (EI/CI, 70 eV): $m/z = 213$ (M^+), 198 (M^+–NH), 170 (M^+–$(CH_2)_2NH$). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3326, 1472. ^1H NMR ($CDCl_3$): δ = 1.99 (br, 1H, R_2N–*H*), 2.81 (dt, *J* = 10.0/2.9 Hz, 1H, Ar–C*H*$_2$–CH_2–NHR), 2.85 (dt, *J* = 10.0/2.0 Hz, 1H, Ar–C*H*$_2$–CH_2–NHR), 3.00 (dt, *J* = 9.5/2.6 Hz, 1H, Ar–CH_2–C*H*$_2$–NHR), 3.09 (dt, *J* = 9.2/2.3 Hz, 1H, Ar–CH_2–C*H*$_2$–NHR), 3.21 (dd, *J* = 14.0/2.1 Hz, 1H, Ar–CH(Fur.)–C*H*$_2$–NHR), 3.63 (dd, *J* = 13.9/6.0 Hz, 1H, Ar-CH(Fur.)–C*H*$_2$–NHR), 4.22 (dd, *J* = 5.8/1.8 Hz, 1H, Ar-C*H*(Fur.)–CH_2–NHR), 5.86 (dd, *J* = 3.1/0.9 Hz, 1H, 3-$H_{fur.}$), 6.33 (dd, *J* = 3.1/1.8 Hz, 1H, 4-$H_{fur.}$), 7.00 (dd, *J* = 6.4/2.1 Hz, 1H, 9-$H_{arom.}$), 7.11–7.21 (m, 3H, 6-$H_{arom.}$ to 8-$H_{arom.}$), 7.42 (dd, *J* = 1.8/0.8 Hz, 1H, 5-$H_{fur.}$).

5.24. (±)-1-(Thiophen-2-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4f)

A mixture of **10f** (117 mg, 364 μmol), Zn dust (235 mg, 3.6 mmol), 1 N HCl (3.6 mL 3.6 mmol) and THF (10 mL) was heated to reflux for 12 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (66.8 mg) was purified by fc (1 cm, CH_2Cl_2/CH_3OH 80:10, fractions 3 mL, $R_f = 0.21$). Pale yellow oil, yield 46.9 mg (56%). $C_{14}H_{15}NS$ (229.4) calcd C 73.3H 6.59 N 6.11 S 13.38 found C 73.1H 6.82 N 6.13 S 13.28. MS (EI, 70 eV): $m/z = 229$ (M^+), 200 (M^+–CH_2NH), 186 (M^+–$(CH_2)_2NH$). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3401, 1453. ^1H NMR ($CDCl_3$): δ = 2.19 (br, 1H, R_2N–*H*), 2.72–2.91 (m, 2H, Ar–C*H*$_2$–CH_2–NHR), 2.94 (dt, *J* = 13.4/3.1 Hz, 1H, Ar–CH_2–C*H*$_2$–NHR), 3.14 (dt, *J* = 13.7/3.0 Hz, 1H, Ar–CH_2–C*H*$_2$–NHR), 3.34 (dd, *J* = 14.0/2.1 Hz, 1H, Ar-CH(Thioph.)–C*H*$_2$–NHR), 3.61 (dd, *J* = 14.2/5.6 Hz, 1H, Ar–CH(Thioph.)–C*H*$_2$–NHR), 4.38 (dd, *J* = 5.2/1.5 Hz, 1H, Ar–C*H*(Thioph.)–CH_2–NHR), 6.62 (dd, *J* = 3.7/1.2 Hz, 1H, 3-$H_{thioph.}$), 6.96 (dd, *J* = 5.0/3.5 Hz, 1H, 4-$H_{thioph.}$), 7.10 (dd, *J* = 6.7/2.4 Hz, 1H, 9-$H_{arom.}$), 7.13–7.23 (m, 3H, 6-$H_{arom.}$ to 8-$H_{arom.}$), 7.22 (dd, *J* = 5.2/1.2 Hz, 1H, 5-$H_{thioph.}$).

5.25. (±)-1-(Pyridin-2-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4g)

A mixture of **10g** (140 mg, 443 μmol), Zn dust (289 mg, 4.4 mmol), 1 N HCl (4.4 mL 4.4 mmol) and THF (10 mL) was heated to reflux for 12 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (121.9 mg) was purified by fc (1 cm, CH_2Cl_2/CH_3OH 80:10, fractions 5 mL, $R_f = 0.16$). Pale yellow oil, yield 34,6 mg (25%). $C_{15}H_{16}N_2$ (224.3). MS (EI/CI, 70 eV): $m/z = 224$ (M^+), 209 (M^+–NH), 181 (M^+–$(CH_2)_2NH$). HR–MS: calcd 223.1236 found 223.1235. IR (film): $\tilde{\nu}$ [cm^{-1}] = 3346, 1469. ^1H NMR ($CDCl_3$): δ = 2.76 (dt, *J* = 8.5/4.5 Hz, 1H, Ar–C*H*$_2$–CH_2–NHR), 2.93 (dt, *J* = 8.8/3.9 Hz, 1H, Ar–C*H*$_2$–CH_2–NHR), 3.12 (t, *J* = 4.1 Hz, 1H, Ar–CH_2–C*H*$_2$–NHR), 3.17 (t, *J* = 4.3 Hz, 1H, Ar–CH_2–C*H*$_2$–NHR), 3.21 (br, 1H, R_2N–*H*), 3.29 (dd, *J* = 13.9/2.0 Hz, 1H, Ar–CH(Pyr.)–C*H*$_2$–NHR), 4.00 (dd, *J* = 13.9/5.6 Hz, 1H, Ar–CH(Pyr.)–C*H*$_2$–NHR), 4.30 (dd, *J* = 5.8/1.5 Hz, 1H, Ar–C*H*(Pyr.)–CH_2–NHR), 6.91 (d, *J* = 7.9 Hz, 1H, 9-$H_{arom.}$), 7.04 (dd, *J* = 5.8/2.7 Hz, 1H, 3-$H_{pyr.}$), 7.10–7.19 (m, 4H, 6-$H_{arom.}$ to 8-$H_{arom.}$ and 5-$H_{pyr.}$), 7.56 (td, *J* = 7.8/1.8 Hz, 1H, 4-$H_{pyr.}$), 8.63 (dd, *J* = 4.9/0.8 Hz, 1H, 6-$H_{pyr.}$).

5.26. (±)-1-(Indol-3-yl)-2,3-dihydro-1*H*-3-benzazepine (12) and (±)-1-(Indol-3-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4h)

A mixture of **10h** (320 mg, 903 μmol), Zn dust (1.18 g, 18.0 mmol), 1 N HCl (18 mL 18 mmol) and THF (25 mL) was heated to reflux for 14 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (298.0 mg) was purified by fc (2 cm, CH_2Cl_2/CH_3OH 80:10, fractions 5 mL).

12 ($R_f = 0.28$): Pale yellow solid, yield 96.3 mg (41%). $C_{18}H_{16}N_2$ (260.3) calcd C 83.0H 6.19 N 10.76 found C 81.5H 6.24 N 10.42. MS (EI, 70 eV): $m/z = 260$ (M^+), 230 (M^+–HCH_2NH), 219 (M^+–$(CH)_2NH$). HR–MS: calcd 260.1313 found 260.1313. IR (film): $\tilde{\nu}$ [cm^{-1}] = 3453, 1586, 1556. ^1H NMR ($CDCl_3$): δ = 2.87 (d, *J* = 7.6 Hz, 2H, Ar–CH(Ind)–C*H*$_2$-NHR), 3.45 (s, 1H, R_2N-*H*), 4.35 (t, *J* = 7.7 Hz, 1H, Ar–C*H*(Ind)–CH_2–NHR), 6.65 (d, *J* = 11.6 Hz, 1H, Ar–C*H*=CH–NHR), 6.83 (d, *J* = 11.6 Hz, 1H, Ar–CH=C*H*-NHR), 7.11 (dd, *J* = 7.0/1.5 Hz, 1H, 9-$H_{arom.}$), 7.14 (d, *J* = 2.6 Hz, 1H, 2-$H_{Ind.}$), 7.17 (dd, *J* = 7.0/1.5 Hz, 1H, 6-$H_{arom.}$), 7.20-7.27 (m, 2H, 7-$H_{arom.}$ and 8-$H_{arom.}$), 7.31–7.34 (m, 3H, 5-$H_{Ind.}$ to 7-$H_{Ind.}$), 7.73 (dd, *J* = 6.4/2.1 Hz, 1H, 4-$H_{Ind.}$), 8.49 (br, 1H, N-$H_{Ind.}$). ^{13}C NMR ($CDCl_3$): δ = 35.0 (1 C, Ar–CH(Ind.)–*C*H_2–NR_2), 65.2 (1 C, Ar-*C*H(Ind.)–CH_2–NR_2), 111.4 (1 C, Ar–*C*H=CH–NR_2), 122.7 (1 C, $CH_{arom.}$), 126.5 (1 C, $CH_{arom.}$), 127.0 (1 C, $CH_{arom.}$), 127.3 (1 C, $CH_{arom.}$), 127.6 (1 C, $CH_{arom.}$), 128.1 (1 C, $CH_{arom.}$), 128.2 (1 C, Ar–CH=*C*H–NR_2), 128.5 (1 C, $CH_{arom.}$), 128.9 (1 C, $CH_{arom.}$), 129.8 (1 C, $CH_{arom.}$), 136.5 (1 C, $C_{arom.}$), 140.4 (1 C, $C_{arom.}$), 140.9 (1 C, $C_{arom.}$), 141.3 (1 C, $C_{arom.}$), 143.4 (1 C, $C_{arom.}$).

4h ($R_f = 0.25$): Pale yellow oil, yield 66.4 mg (28%). $C_{18}H_{18}N_2$ (262.4). MS (EI, 70 eV): $m/z = 262$ (M^+), 247 (M^+–NH), 232 (M^+–HCH_2NH), 218 (M^+–$H(CH_2)_2NH$). HR–MS: calcd 262.1467 found 262.1470. IR (film): $\tilde{\nu}$ [cm^{-1}] = 3278, 1605. ^1H NMR ($CDCl_3$): δ = 2.79 (br, 1H, R_2N-*H*), 2.83–2.86 (m, 2H, Ar–C*H*$_2$–CH_2-NHR), 2.98–3.02 (m, 2H, Ar–CH_2–C*H*$_2$–NHR), 3.37 (dd, *J* = 13.7/2.1 Hz, 1H, Ar–CH(Ind.)–C*H*$_2$–NHR), 3.68 (dd, *J* = 13.7/7.0 Hz, 1H, Ar–CH(Ind.)–C*H*$_2$–NHR), 4.54 (dd, *J* = 7.3/1.8 Hz, 1H, Ar–C*H*(Ind.)-CH_2–NHR), 7.02 (dd, *J* = 7.0/0.9 Hz, 1H, 9-$H_{arom.}$), 7.06 (dd, *J* = 7.0/0.9 Hz, 1H, 6-$H_{arom.}$), 7.09 (d, *J* = 2.7 Hz, 1H, 2-$H_{Ind.}$), 7.15-7.29 (m, 4H, 7-$H_{arom.}$, 8-$H_{arom.}$, 5-$H_{Ind.}$ and 6-$H_{Ind.}$), 7.34 (d, *J* = 8.2 Hz, 1H, 7-$H_{Ind.}$), 7.45 (d, *J* = 7.6 Hz, 1H, 4-$H_{Ind.}$), 8.86 (br, 1H, N-$H_{Ind.}$). ^{13}C NMR ($CDCl_3$): δ = 35.1 (1 C, Ar–CH(Ind.)–*C*H_2–NR_2), 41.6 (1 C, Ar–*C*H_2–CH_2–NR_2), 54.3 (1 C, Ar–

CH_2–CH_2–NR_2), 65.2 (1 C, Ar-*C*H(Ind.)-CH_2-NR_2), 126.5 (1 C, $CH_{arom.}$), 127.0 (1 C, $CH_{arom.}$), 127.6 (1 C, $CH_{arom.}$), 128.5 (1 C, $CH_{arom.}$), 128.5 (1 C, $CH_{arom.}$), 129.8 (1 C, $CH_{arom.}$), 128.2 (1 C, $CH_{arom.}$), 128.5 (1 C, $CH_{arom.}$), 128.9 (1 C, $CH_{arom.}$), 136.5 (1 C, $C_{arom.}$), 138.0 (1 C, $C_{arom.}$), 140.4 (1 C, $C_{arom.}$), 140.9 (1 C, $C_{arom.}$), 143.4 (1 C, $C_{arom.}$).

5.27. (±)-1-Benzyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4i)

A mixture of **10i** (85 mg, 258 μmol), Zn dust (169 mg, 2.6 mmol), 1 N HCl (2.6 mL 2.6 mmol) and THF (10 mL) was heated to reflux for 4 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (59.2 mg) was purified by fc (1 cm, CH_2Cl_2/CH_3OH 80:10, fractions 3 mL, R_f = 0.17). Pale yellow oil, yield 19.1 mg (31%). $C_{17}H_{19}N$ (237.3). MS (EI, 70 eV): m/z = 237 (M^+), 222 (M^+–NH), 194 (M^+–$(CH_2)_2NH$). HR–MS: calcd 237.1517 found 237.1517. IR (film): $\tilde{\nu}$ [cm^{-1}] = 3341, 1492. ^1H NMR ($CDCl_3$): δ = 2.05 (br, 1H, R_2N-*H*), 2.76-2.97 (m, 4H, Ar–C*H*$_2$–C*H*$_2$–NHR), 3.07–3.28 (m, 5H, Ar–C*H*(C*H*$_2$–Ar)–C*H*$_2$–NHR), 7.00 (dd, J = 6.1/1.8 Hz, 1H, 9-$H_{arom.}$), 7.05–7.29 (m, 8H, 2-$H_{bn.}$ to 6-$H_{bn.}$ and 6-$H_{arom.}$ to 8-$H_{arom.}$).

5.28. (±)-1-(Phenylsulfanyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4j)

A mixture of **10j** (115 mg, 331 μmol), Zn dust (216 mg, 3.3 mmol), 1 N HCl (3.3 mL 3.3 mmol) and THF (10 mL) was heated to reflux for 4 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (73.5 mg) was purified by fc (1 cm, CH_2Cl_2/CH_3OH 80:10, fractions 3 mL, R_f = 0.37). Pale yellow oil, yield 35.1 mg (42%). $C_{16}H_{17}NS$ (255.4) calcd C 75.3H 6.71 N 5.48 S 12.56 found C 75.1H 6.69 N 5.37 S 12.40. MS (EI, 70 eV): m/z = 255 (M^+), 150 ($C_6H_5SCH_2CH_2N$). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3342, 1478. ^1H NMR ($CDCl_3$): δ = 2.20 (br, 1H, R_2N-*H*), 2.70-2.80 (m, 2H, Ar–C*H*$_2$–CH$_2$–NHR), 3.17 (dd, J = 13.9/1.7 Hz, 1H, Ar–CH(SPh)–C*H*$_2$–NHR), 3.33 (ddd, J = 13.7/5.5/2.2 Hz, 1H, Ar–CH$_2$–C*H*$_2$–NHR), 3.40 (dd, J = 13.9/5.0 Hz, 1H, Ar–CH(SPh)–C*H*$_2$–NHR), 3.61 (ddd, J = 14.3/11.4/2.3 Hz, 1H, Ar–CH$_2$–C*H*$_2$–NHR), 4.32 (dd, J = 4.9/1.8 Hz, 1H, Ar–C*H*(SPh)–CH$_2$–NHR), 6.90 (dd, J = 7.0/0.9 Hz, 1H, 9-$H_{arom.}$), 7.01 (tt, J = 6.7/0.9 Hz, 1H, 4-H_{SPh}), 7.12 (dd, J = 6.1/1.2 Hz, 2H, 2-H_{SPH} and 6-H_{SPh}), 7.24 (td, J = 6.7/1.2 Hz, 2H, 3-H_{SPh} and 5-H_{SPh}), 7.25 (dd, J = 6.9/1.2 Hz, 1H, 6-$H_{arom.}$), 7.32–7.37 (m, 2H, 7-$H_{arom.}$ and 8-$H_{arom.}$).

5.29. (±)-*N*-Phenyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-yl)acetamide (4l)

A mixture of **10l** (185 mg, 497 μmol), Zn dust (327 mg, 5.0 mmol), 1 N HCl (5.0 mL 5.0 mmol) and THF (15 mL) was heated to reflux for 5 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (170.9 mg) was purified by fc (2 cm, CH_2Cl_2/CH_3OH 80:10, fractions 3 mL, R_f = 0.31). Pale yellow oil, yield 55.6 mg (40%). $C_{18}H_{20}N_2$ (280.4). MS (EI, 70 eV): m/z = 280 (M^+), 237 (M^+–CH_3CO), 208 (M^+–CH_3CO–CH_2NH), 194 (M^+–CH_3CO–$(CH_2)_2NH$). HR–MS: calcd 280.1577 found 280.1575. IR (film): $\tilde{\nu}$ [cm^{-1}] = 3342, 1649, 1495. ^1H NMR ($CDCl_3$): δ = 1.89 (s, 3H, R_2N–CO–C*H*$_3$), 2.26 (br, 1H, R_2N-*H*), 2.36 (dt, J = 9.1/4.6 Hz, 1H, Ar–C*H*$_2$–CH$_2$–NHR), 2.52 (dt, J = 9.6/4.7 Hz, 1H, Ar-C*H*$_2$-CH$_2$-NHR), 2.80–2.96 (m, 2H, Ar–CH$_2$–C*H*$_2$–NHR), 3.23 (dd, J = 13.7/5.2 Hz, 1H, Ar–CH(N(Ac)–Ar)–C*H*$_2$–NHR), 3.33 (dd, J = 13.9/5.3 Hz, 1H, Ar–CH(N(Ac)–Ar)–C*H*$_2$–NHR), 5.77 (t, J = 5.5 Hz, 1H, Ar–C*H*(N(Ac)–Ar)–CH$_2$–NHR), 6.98 (d, J = 7.0 Hz, 2H, 2-$H_{anilide}$ and 6-$H_{anilide}$), 7.00 (t, J = 7.3 Hz, 1H, 4-$H_{anilide}$), 7.17 (t, J = 7.3 Hz, 2H, 3-$H_{anilide}$ and 5-$H_{anilide}$), 7.24 (dd, J = 7.0/0.9 Hz, 1H, 6-$H_{arom.}$), 7.26–7.30 (td, J = 7.8/1.8 Hz, 2H, 7-$H_{arom.}$ and 8-$H_{arom.}$), 7.43 (d, J = 7.3 Hz, 1H, 9-$H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 23.4 (1 C, *C*H$_3$–CO–NR_2), 36.8 (1 C, Ar–*C*H$_2$–CH$_2$–NHR), 47.3 (1 C, Ar–CH$_2$–*C*H$_2$–NHR), 50.0 (1 C, Ar–CH(NR_2)–*C*H$_2$–NHR), 64.0 (1 C, Ar–*C*H(NR_2)–CH$_2$–NHR), 126.6 (1 C, $CH_{arom.}$), 127.4 (1 C, $CH_{arom.}$), 128.0 (1 C, $CH_{arom.}$), 129.2 (2 C, $CH_{arom.}$), 129.3 (2 C, $CH_{arom.}$), 129.8 (1 C, $CH_{arom.}$), 130.0 (1 C, $CH_{arom.}$), 138.7 (1 C, $C_{arom.}$), 139.5 (1 C, $C_{arom.}$), 141.8 (1 C, $C_{arom.}$), 170.2 (1 C, CH_3–*C*O–NR_2).

5.29.1. (±)-1-(Butan-1-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4m). A mixture of **10m** (195 mg, 660 μmol), Zn dust (432 mg, 6.6 mmol), 1 N HCl (6.6 mL 6.6 mmol) and THF (20 mL) was heated to reflux for 5 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (109.4 mg) was purified by fc (2 cm, CH_2Cl_2/CH_3OH 80:10, fractions 5 mL, R_f = 0.21). Pale yellow oil, yield 77.3 mg (58%). $C_{14}H_{21}N$ (203.3). MS (EI, 70 eV): m/z = 203 (M^+), 188 (M^+–CH_3), 174 (M^+-CH_2CH_3), 160 (M^+–$(CH_2)_2CH_3$), 146 (M^+-$(CH_2)_3CH_3$). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3302, 1549. ^1H NMR ($CDCl_3$): δ = 0.90 (t, J = 7.0 Hz, 3H, Azep.$(CH_2)_3$–C*H*$_3$), 1.20-1.40 (m, 4H, Azep.CH_2–(C*H*$_2$)$_2$–CH_3), 1.67–1.89 (m, 2H, Azep.C*H*$_2$–$(CH_2)_3$–H), 2.23 (br, 1H, R_2N-*H*), 2.77–2.87 (m, 4H, Ar–(C*H*$_2$)$_2$–NHR), 3.02 (d, J = 3.7 Hz, 2H, Ar–CH(^{n}Bu)–C*H*$_2$–NHR), 3.06–3.17 (m, 1H, Ar–C*H*(^{n}Bu)–CH$_2$–NHR), 7.06–7.19 (m, 4H, 6-$H_{arom.}$ to 9-$H_{arom.}$).

5.30. (±)-1-(Butan-2-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4n)

A mixture of **10n** (108 mg, 366 μmol), Zn dust (242 mg, 3.7 mmol), 1 N HCl (3.7 mL 3.7 mmol) and THF (12 mL) was heated to reflux for 5 h. After addition of 2 N NaOH (pH 9–11) the mixture was extracted with Et_2O (4×20 mL), the Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue (51.6 mg) was purified by fc (1 cm, CH_2Cl_2/CH_3OH 80:10, fractions 5 mL, R_f = 0.23). Pale yellow oil, yield 39.7 mg (53%). $C_{14}H_{21}N$ (203.3). MS (EI, 70 eV): m/z = 203 (M), 174

($M–CH_2CH_3$), 146 ($M^+–CH(CH_3)CH_2CH_3$). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3303, 1549. ^1H NMR ($CDCl_3$): $\delta = 0.68$ (d, $J = 6.7$ Hz, 3×0.5H, Azep.CH(CH_3)–CH_2–CH_3), 0.79 (t, $J = 7.2$ Hz, 3×0.5H, Azep.CH(CH_3)–CH_2–CH_3), 0.96 (t, $J = 7.3$ Hz, 3×0.5H, Azep.CH(CH_3)–CH_2–CH_3), 1.04 (d, $J = 6.7$ Hz, 3×0.5H, Azep.CH(CH_3)–CH_2–CH_3), 1.20 (qd, $J = 6.8/1.5$ Hz, 0.5H, Azep.CH(CH_3)–CH_2–CH_3), 1.23 (qd, $J = 7.2/2.7$ Hz, 0.5H, Azep.CH(CH_3)–CH_2–CH_3), 1.72 (qd, $J = 6.9/3.0$ Hz, 0.5H, Azep.CH(CH_3)–CH_2–CH_3), 1.79 (qd, $J = 7.0/3.2$ Hz, 0.5H, Azep.CH(CH_3)–CH_2–CH_3), 2.14–2.29 (m, 1H, Azep.CH(CH_3)–CH_2–CH_3), 2.40–2.43 (m, 0.5H, Ar–CH(^{s}Bu)–CH_2–NHR), 2.44–2.47 (m, 0.5H, Ar–CH(^{s}Bu)–CH_2–NHR), 2.50 (br, 1H, R_2N-H), 2.65–2.77 (m, 2H, Ar–CH_2–CH_2–NHR), 2.90 (dd, $J = 13.7/5.1$, 1H, Ar–CH(^{s}Bu)–CH_2–NHR), 3.16–3.30 (m, 2H, Ar–CH_2–CH_2–NHR), 3.35 (dd, $J = 13.5/2.7$ Hz, 1H, Ar–CH(^{s}Bu)–CH_2–NHR), 7.00–7.23 (m, 4H, 6-$H_{arom.}$ to 9-$H_{arom.}$). The ratio of diastereomers is 50:50.

6. Receptor binding studies

6.1. General

Teflon-glass-homogenizer: Potter®S (B. Braun Biotech International). Rotor/stator homogenizer: Ultraturrax® T25 basic (Ika Labortechnik). Centrifuge: High speed refrigerating centrifuge model J2-HS (Beckman). Filter: Whatman glass fiber filters GF/C presoaked in 1% polyethylenimine (in water) for 3 h at 4 °C before use. Filtration was performed with a Brandel 24-well cell harvester. Scintillation cocktail: Rotiszint eco plus (Roth). Liquid scintillation analyzer: Tri-Carb 2100 TR (Canberra Packard), counting efficiency 66%. All experiments were carried out in triplicate. IC_{50}-values were determined from competition experiments with at least 6 concentrations of test compounds and were calculated with the curve-fitting program GraphPad Prism® 3.0 (GraphPad Software) by nonlinear regression analysis. K_i-values were calculated according to Cheng and Prusoff;[19] K_D ((+)-MK-801) = 2.26 nM. For compounds with high affinity (low K_i-values) mean values ± SEM from at least three independent experiments are given.

6.2. Investigation of the affinity for the phencyclidine binding site of the NMDA receptor[7,16]

[^{3}H]-(+)-MK-801 binding to pig brain cortex membrane preparations was performed according to standard radioligand binding assays, which were slightly modified as described below.

Preparation of the receptor material: Fresh pig cortex was homogenized with a potter (500 rpm, 10 up-and-down strokes) in 10 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1000 *g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 10,000 *g* for 20 min at 4 °C. The pellet was resuspended in buffer (5 mM Tris acetate with 1 mM EDTA, pH 7.5) with an Ultraturrax (8000 rpm) and centrifuged at 20,000 *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[20] using bovine serum albumin as standard, and subsequently the preparation was frozen (−83 °C) in 5 mL portions of about 1 mg protein/mL.

Performance of the assay: The test was performed with the radioligand [^{3}H]-(+)-MK-801 (832.5 GBq/mmol; NEN™ Life Science Products). 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 buffer (5 mM Tris-acetate, 1 mM EDTA, pH 7.5) in a total volume of 500 µL for 90 min at 25 °C. The incubation was terminated by rapid filtration through presoaked Whatman GF/C filters (1% polyethylenimine in water for 3 h at 4 °C) using a cell harvester. After washing four times with 2 mL of cold buffer 3 mL of scintillation cocktail were added to the filters. After at least 8 h bound radioactivity trapped on the filters was counted in a liquid scintillation analyzer. The nonspecific binding was determined with 10 µM (+)-MK-801.

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