Stereoselective synthesis and structure–affinity relationships of bicyclic κ receptor agonists†

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Reductive amination of the bicyclic ketone **4** led diastereoselectively to *endo*-configured amines, which were transformed into the amides **7–10**. The synthesis of the diastereomers **25** with an *exo*-configured amino moiety at position 6 was only successful after deactivation of both N-atoms of the 1,4-diazabicyclo[3.3.1]nonane system. The *N*-1-oxide **19** with an *N*-4-tosyl moiety was the crucial intermediate, which allows S_N2 substitution with NaN_3 under inversion of the configuration at position 6. Whereas the *endo*-configured pyrrolidine **7a** (**WMS-1302**) revealed a κ receptor affinity of 73 nM, the *exo*-configured diastereomer **25a** was almost inactive at the κ receptor ($K_i > 1$ μM). Replacement of the 3,4-dichlorophenylacetyl residue by other acyl and sulfonyl residues showed that it is essential for high κ affinity. The κ receptor affinities of the conformationally constrained pyrrolidines **7a** and **25a** were correlated with the dihedral angle N(pyrrolidine)–C–C–N(acetamide). A systematic conformational analysis of the potent but flexible κ agonist **2** showed that a dihedral angle of 168° (as in **25a**) is energetically more disfavored than a dihedral angle of 58° (**7a**). However, even the conformation with a dihedral angle of 58° does not represent an energy minimum, which might explain the reduced κ affinity of **7a**.

Introduction

The clinically used strong analgesics interact with the three classical opioid receptors, which are termed μ, κ and δ receptors. Whereas activation of all three opioid receptor subtypes leads to strong analgesia, the side effect profiles associated with the three subtypes differ considerably. In view of their side effect profile, κ agonists are of particular interest, because, in contrast to μ agonists, they cause minimal physical dependence, respiratory depression and inhibition of gastrointestinal motility. In addition to their analgesic effects in *in vivo* models, κ agonists have been shown to be potent neuroprotective and antihyperalgesic agents. However, sedation, dysphoria and strong diuresis are the most severe side effects associated with the application of κ agonists.[1]

All three subtypes have already been cloned.[2] However, X-ray crystal structures of the G-protein coupled membrane-bound receptors showing the exact three dimensional orientation of the ligand binding sites are not yet available. Therefore, for the development of novel selective κ agonists, lead compounds with high κ affinity were selected.

Most of the described κ agonists can be subdivided into four compound classes:[1] peptides (*e.g.* the physiological agonist Dynorphine A[1,3]), benzomorphans (*e.g.* ethylketocyclazocine[1,3]), arylacetamides (*e.g.* the prototypical κ agonist U-50 488[4]) and the non-basic natural product salvinorin A.[5,6] Monoacylated ethylenediamines derived from the prototypical κ agonist U-50 488 are of particular interest for this project.

During the last few years, potent κ agonists have been described, which are derived from the lead compound U-50 488, including annulated compounds,[7,8] simplified ligands,[9,10] as well as heterocyclic analogues like 2-(aminomethyl)piperidines[11,12] and 2-(aminomethyl)piperazines.[13–15] The (2*R*)-configured 2-(aminomethyl)piperazine **1** (GR-89 696) belongs to the most active κ agonists with an IC_{50}-value of 0.018 nM[13–15] ($K_i = 0.36$ nM,[16] Fig. 1). Very recently, we have shown that the κ receptor affinity of **1** was exceeded by the (*S*,*S*)-configured pyrrolidinylethyl derivative **2** ($K_i = 0.31$ nM), bearing an additional CH_3-moiety at the C-2 side chain.[16,17] In both compounds, the κ affinity is strongly dependent on the stereochemistry; in Fig. 1 the most active stereoisomers are shown.

The 1,4-diacylated piperazine system of **1** and **2** represents a rather rigid substructure. However, the axially oriented substituent in position 2[17] can rotate without hindrance around the indicated axial bond. In order to investigate the preferred orientation (bioactive conformation) of the pharmacophoric pyrrolidine moiety of **1** and **2**, conformationally constrained κ receptor agonists were designed. Herein, we report on the stereoselective synthesis and pharmacological evaluation of bicyclic κ receptor agonists of type **3**. The 1,4-diazabicyclo[3.3.1]nonane system of **3** results upon connection of the methyl residue of **2** with the second piperazine N-atom. The orientation of the basic amino group in position 6 can be adjusted by the stereochemistry.

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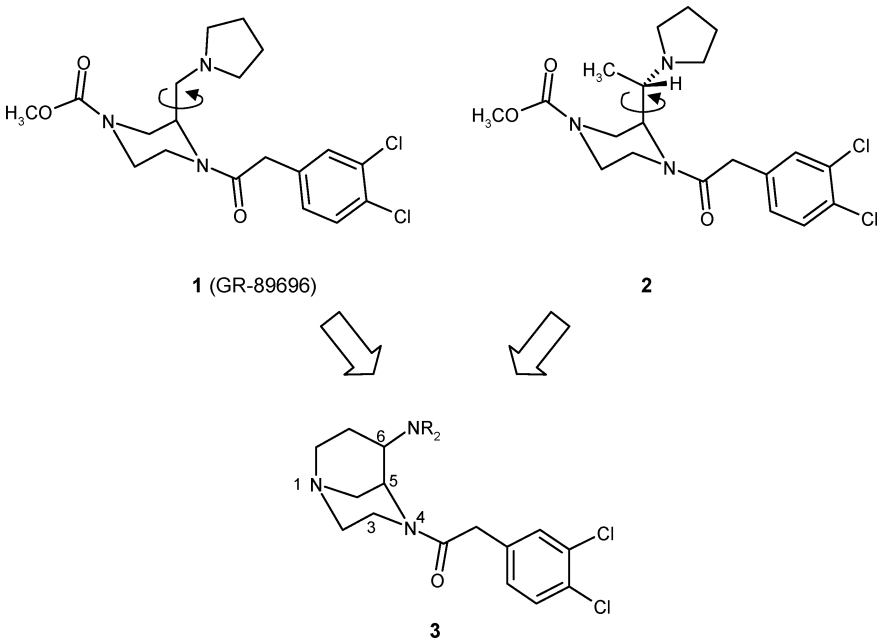


Fig. 1 Design of conformationally constrained κ agonists **3**, with a defined dihedral angle between the two pharmacophoric elements: pyrroline and phenylacetamide.

Results and discussion

Chemistry

The synthesis of the first series of κ agonists started with the bicyclic ketone **4**, which has been prepared in four reaction steps from ethyl piperazine-2-carboxylate.[18] Reductive amination of ketone **4** with pyrrolidine and $NaBH(OAc)_3$[19] provided diastereoselectively the *endo*-configured pyrrolidine **5a** in 59% yield. The corresponding dimethylamine **5c** was prepared in the same manner (38% yield). Unfortunately, the diethylamine **5b**, as a ring-opened pyrrolidine analogue, was not available by direct reductive amination of ketone **4** with the secondary amine diethylamine. Therefore, the diethylamine **5b** was prepared stepwise. First, reductive amination of ketone **4** with the primary amine ethylamine and $NaBH(OAc)_3$ led to the ethylamine **5d**, which was reductively alkylated with acetaldehyde and $NaBH(OAc)_3$ to afford the tertiary amine **5b** (Scheme 1).

Hydrogenolytic removal of the *N*-benzyl protecting group of **5a–c** provided the secondary amines **6a–c**, which were directly acylated, without purification, using 3,4-dichlorophenylacetic acid in the presence of dicyclohexylcarbodiimide (DCC), to form the desired dichlorophenylacetamides **7a–c**.

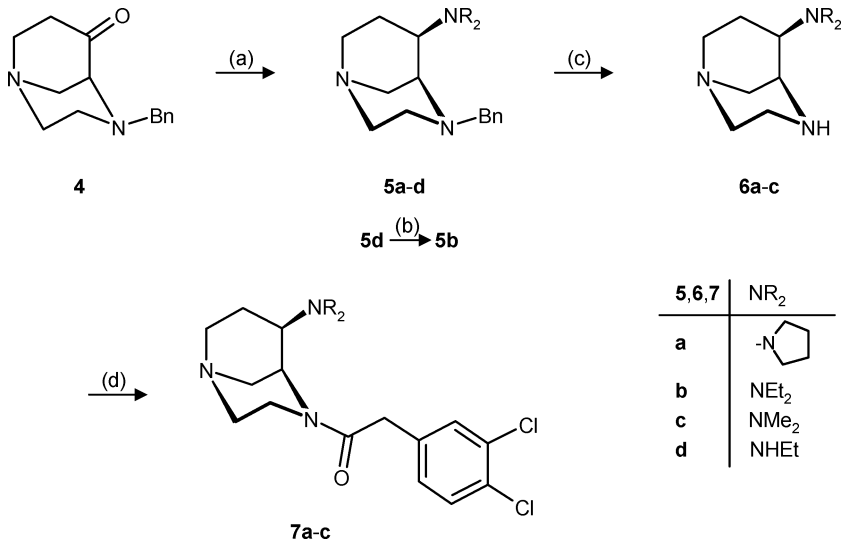
In order to prove the *endo*-configuration of the final products **7** unequivocally, an X-ray crystal structure analysis was performed. For this purpose, pyrrolidine **7a** was recrystallized from a mixture of diethyl ether and acetonitrile to obtain colorless crystals which were suitable for X-ray crystal structure analysis (Fig. 2). The X-ray crystal structure clearly shows the *endo*-configuration of the pyrrolidine substituent at position 6. Both six-membered heterocycles adopt the chair conformation and, moreover, the dihedral angle between the pyrrolidine N-atom and the acetamide N-atom could be determined to be 58.3° (see the Discussion of the dihedral angle section).

In addition to the relative configuration of the final products, the X-ray crystal structure also proves the reaction path of the reductive amination. The reducing agent $NaBH(OAc)_3$ can only attack the intermediate iminium ion from the *exo*-face, whereas the *endo*-face is shielded by the larger bridge.

Although it is known from the literature that the dichlorophenylacetyl residue is optimal for binding at κ receptors,[1] it was replaced by some similar residues (Scheme 2). Thus, the *N*-benzyl moiety of pyrrolidine **5a** was removed hydrogenolytically to form the secondary amine **6a**, which was directly converted into the phenylacetyl (**8a**), benzoyl (**9a**) and tosyl (**10a**) derivatives. The diethylamine **10b** with an *N*-tosyl group was also prepared by treatment of the benzyl derivative **5b** with H_2, Pd/C and subsequent tosylation.

For the synthesis of the diastereomeric amines with *exo*-orientation of the amino group, ketone **4** should be reduced diastereomerically and the resulting *endo*-alcohol should be transformed into *exo*-amines by an inversion reaction. Indeed, reduction of ketone **4** with $LiBH_4$ in THF provided exclusively the *endo*-alcohol **11** in 91% yield (Scheme 3). However, all attempts to activate the OH-moiety with mesyl chloride or tosyl chloride, even at low temperature, led to very fast decomposition of the alcohol **11**. Also, the direct reaction of **11** in a Mitsunobu inversion[20] (PPh_3, diisopropyl azodicarboxylate (DIAD)) using different N-nucleophiles, like succinimide, phthalimide and $Zn(N_3)_2 \cdot (pyridine)_2$ complex,[21] failed due to fast decomposition. Moreover, it was shown that alcohol **11** itself was also very unstable. Storage in the refrigerator at 0 °C under N_2 for three days led to a dark coloration of the compound and additional peaks in the HPLC.

In order to stabilize alcohol **11**, the *N*-benzyl group should be replaced by an *N*-tosyl moiety. Unfortunately, the direct synthesis of the sulfonamide **14** failed since the Dieckmann condensation of the tosyl-protected piperazine derivative did not give the



Scheme 1 The synthesized compounds are racemates; only one enantiomer is shown in this and the following schemes. Reagents and reaction conditions: (a) R_2NH, $NaBH(OAc)_3$, THF, rt, **5a**: 59%; **5c**: 38%; **5d**: 47%. (b) $CH_3CH{=}O$, $NaBH(OAc)_3$, THF, 2 h, rt, 64%. (c) H_2, Pd/C, CH_3OH, rt. (d) 3,4-Dichlorophenylacetic acid, DCC, CH_2Cl_2, rt, **7a**: 47%; **7b**: 70%; **7c**: 53%.

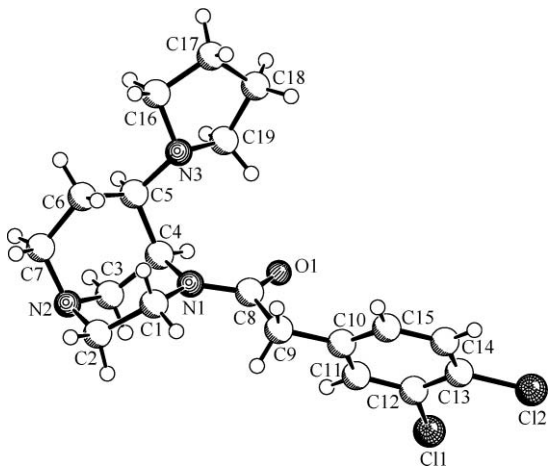
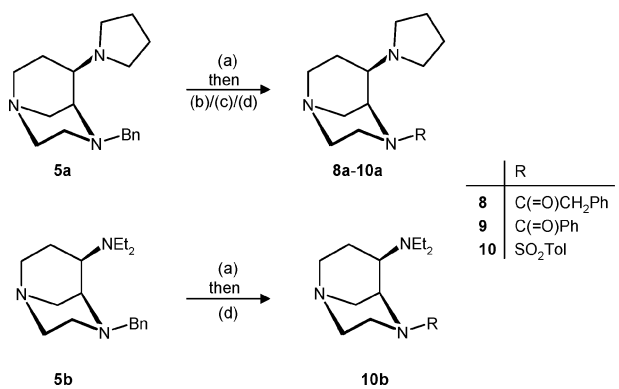


Fig. 2 X-Ray crystal structure of **7a**, proving the *endo*-configuration of the pyrrolidine substituent.



Scheme 2 Reagents and reaction conditions: (a) H_2, Pd/C, CH_3OH, rt. (b) Phenylacetic acid, DCC, CH_2Cl_2, rt, 78%. (c) Benzoyl chloride, NEt_3, CH_2Cl_2, rt, 48%. (d) Tosyl chloride, NEt_3, CH_2Cl_2, rt, **10a**: 35%; **10b**: 80%.

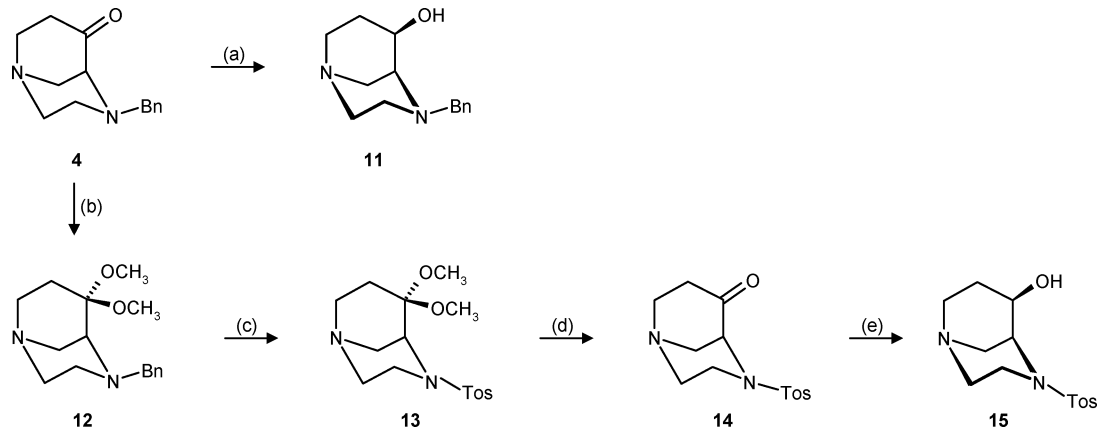
corresponding bicyclic product.[18] Therefore, an exchange of the *N*-protecting group was performed. First, ketone **4** was protected as dimethyl acetal **12**. Hydrogenolytic removal of the *N*-benzyl group and subsequent reaction with tosyl chloride provided the sulfonamide **13**, which was hydrolyzed with dilute HCl to form the *N*-tosyl-protected ketone **14**. Reduction of **14** with $NaBH_4$ in methanol provided diastereomerically the *endo*-configured alcohol **15** in 91% yield. In contrast to **11**, alcohol **15** with the *N*-tosyl protecting group was considerably more stable, and could be stored at 0 °C for several months without decomposition.

Furthermore, alcohol **15** could be reacted with mesyl chloride and tosyl chloride to obtain the rather stable mesylate **16** and tosylate **17** in 83 and 70% yields, respectively (Scheme 4).

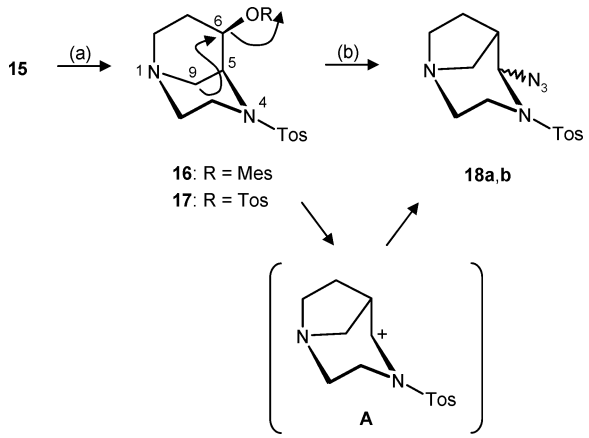
Treatment of the *endo*-mesylate **16** with NaN_3 in DMF at 80 °C led to two new products, whose mass spectra were in agreement with the calculated molecular weights. Careful analysis of the ^1H and ^{13}C NMR spectra, however, revealed that the diastereomeric azides **18** had been formed instead of the desired *exo*-azide **21**. Variation of the reaction conditions during the nucleophilic substitution of mesylate **16**, starting with tosylate **17**, and even the direct substitution of alcohol **15** *via* a Mitsunobu inversion (PPh_3, DIAD, $Zn(N_3)_2{\cdot}(pyridine)_2$ complex), always led to the rearranged azides **18**.

This transformation is explained by a rearrangement of mesylate **16**, which is outlined in Scheme 4. The rearrangement is driven by the exact antiperiplanar orientation of the C-9–C-5 bond and the C–O bond of the leaving group. The nitrogen atom at position 1, with its free electron pair, supports this rearrangement, and the nitrogen atom of the sulfonamide at position 4 stabilizes the intermediate carbenium ion **A**, which is finally trapped by the azide nucleophile. The intermediate carbenium ion **A** also explains nicely the formation of two diastereomeric azides **18a** and **18b**, since the planar carbenium ion **A** can be attacked from both sides.

After elucidation of this process, we postulated that a similar rearrangement is the reason for the instability of alcohol **11**.



Scheme 3 Reagents and reaction conditions: (a) $LiBH_4$, THF, –20 °C, 91%. (b) CH_3OH, $HC(OCH_3)_3$, *p*-TosOH, reflux, 79%. (c) H_2, Pd/C, CH_3OH, rt, then tosyl chloride, NEt_3, CH_2Cl_2, rt, 80%. (d) 2 M HCl, H_2O, reflux, 93%. (e) $NaBH_4$, CH_3OH, 0 °C, 91%.



Scheme 4 Reagents and reaction conditions: (a) Mesyl chloride or tosyl chloride, NEt_3, CH_2Cl_2, rt, **16**: 83%; **17**: 70%. (b) NaN_3, DMF, 80 °C, **18a**: 22%; **18b**: 32%.

Compared to the carbenium ion **A**, the analogous carbenium ion formed from the *N*-benzyl-protected alcohol **11** is much better stabilized by the *N*-benzyl moiety than the *N*-sulfonyl derivative **A**. Therefore, its formation, together with subsequent uncontrolled transformations, is generally favored.

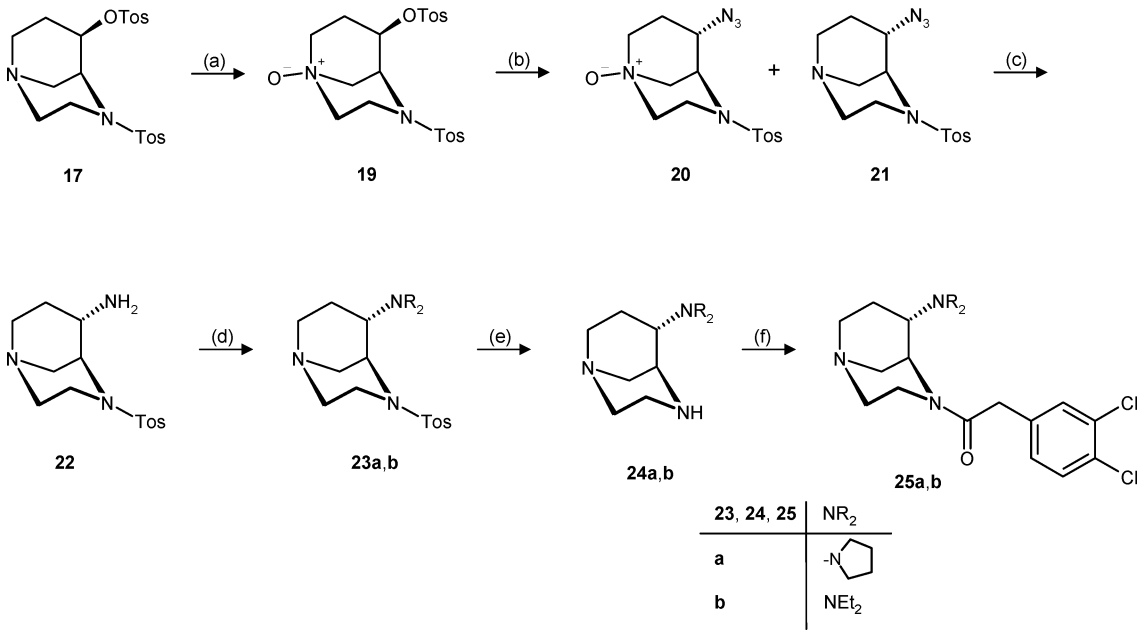
The observation that the reduction of the electron donating properties of N-4 (compare the stability of alcohols **11** and **15**) leads to an at least slightly reduced rearrangement tendency stimulated the idea to reduce the electron donating activity of N-1 as well, in order to suppress the unwanted rearrangement reaction completely. For this purpose, the *N*-oxide **19** was prepared by oxidation of tosylate **17** with *m*-chloroperbenzoic acid (MCPBA, Scheme 5).[22] Indeed, the S_N2 substitution of tosylate **19**, bearing electron withdrawing groups at both N-atoms, with NaN_3 in DMF at 150 °C successfully gave the *exo*-configured azides **20** and **21**. Whereas azide **21** was isolated in 46% yield as the main product, the *N*-oxide **20** could not be separated completely from the starting tosylate **19**. Performing this substitution reaction with microwave irradiation resulted in a considerable reduction of the reaction time from 20 h to 15 min. Obviously, during heating of the reaction mixture in DMF to 150 °C with an excess of NaN_3, reduction of the *N*-oxide **20** occurred, directly forming azide **21** with a tertiary amino group. However, this side reaction is not detrimental, as in the next reaction step the azide moiety was reduced with H_2 in the presence of Pd/C. Under these reaction conditions, both functional groups, the *N*-oxide and the azide, were reduced and, therefore, a mixture of **20** and **21** containing small amounts of the starting *N*-oxide **19** was usually employed for this reaction step (Scheme 5).

Hydrogenation of the mixture of azides **20** and **21** yielded the primary amine **22**, which was reductively alkylated without further purification. Reductive amination is the preferred method in this reaction step, since alkyl halides react very fast with the bridgehead tertiary amine to form quaternary ammonium ions. For the synthesis of the diethylamine **23b**, an excess of acetaldehyde in the presence of $NaBH(OAc)_3$ was used. However, succinaldehyde, which was required for the synthesis of the pyrrolidine moiety, was not commercially available. Therefore, succinaldehyde was generated *in situ* upon hydrolysis of 2,5-dimethoxytetrahydrofuran with dilute HCl.[23] This procedure provided the *exo*-configured pyrrolidine **23a** in 36% yield, starting from the *N*-oxide **19**.

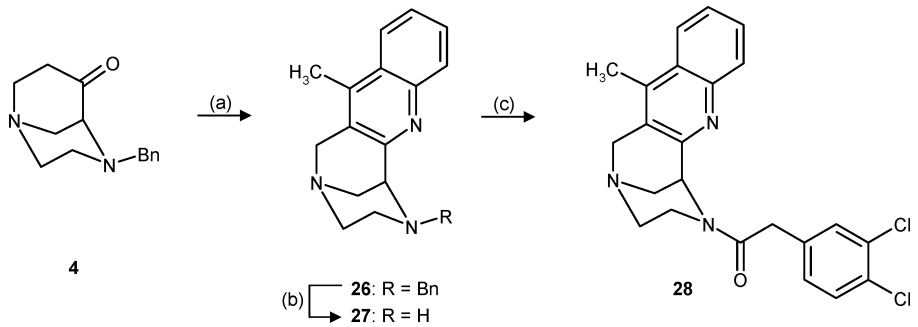
In order to finalize the synthesis of the dichlorophenylacetamides **25**, the tosyl protecting group was cleaved with Mg in refluxing methanol. The resulting secondary amines **24a** and **24b** were subsequently acylated with dichlorophenylacetyl chloride and NEt_3, to give the *exo*-configured bicyclic amines **25a** and **25b** in 31% and 45% yield, respectively.

To broaden the structure–κ receptor affinity relationships, the tertiary amine (*e.g.* pyrrolidine) at position 6 was replaced by N-containing substituents with modified basicity. For this purpose N-heterocycles were annulated to the bicyclic framework. In particular, the weakly basic quinoline **28** and the non-basic indole **31** were envisaged, synthesized and pharmacologically evaluated. The key step in the synthesis of the weakly basic quinoline **28** was a Friedländer quinoline synthesis[24] of the bicyclic ketone **4** with 2-aminoacetophenone in boiling glacial acetic acid to give the quinoline **26** in 73% yield (Scheme 6.) Hydrogenolytic removal of the *N*-benzyl group led to the secondary amine **27**, and attachment of the pharmacophoric dichlorophenylacetyl residue was performed by coupling with dichlorophenylacetic acid and DCC.

A Fischer indole synthesis[25] of the bicyclic ketone **4** with *p*-methoxyphenylhydrazine in the presence of HCl provided the



Scheme 5 Reagents and reaction conditions: (a) MCPBA, K_2CO_3, CH_2Cl_2, 73%. (b) NaN_3, DMF, 80 °C, **21**: 46%. (c) H_2, Pd/C, CH_3OH, rt. (d) Succinaldehyde or $CH_3CH{=}O$, $NaBH(OAc)_3$, THF, rt, **23a**: 36%; **23b**: 29%. (e) Mg, CH_3OH, reflux. (f) 3,4-Dichlorophenylacetyl chloride, NEt_3, CH_2Cl_2, rt, **25a**: 25%; **25b**: 45%.



Scheme 6 Reagents and reaction conditions: (a) *o*-Aminoacetophenone, HOAc, reflux, 73%. (b) NH_4HCO_2, Pd/C, CH_3OH, reflux, 89%. (c) 3,4-Dichlorophenylacetic acid, DCC, CH_2Cl_2, rt, 74%.

indole **29**. After hydrogenolytic cleavage of the *N*-benzyl group, the resulting secondary amine **30** was acylated with dichlorophenylacetic acid and DCC to give indole **31** in 54% yield. (Scheme 7) In contrast to the other phenylacetamides, the indole N-atom of **31** does not possess basic properties.

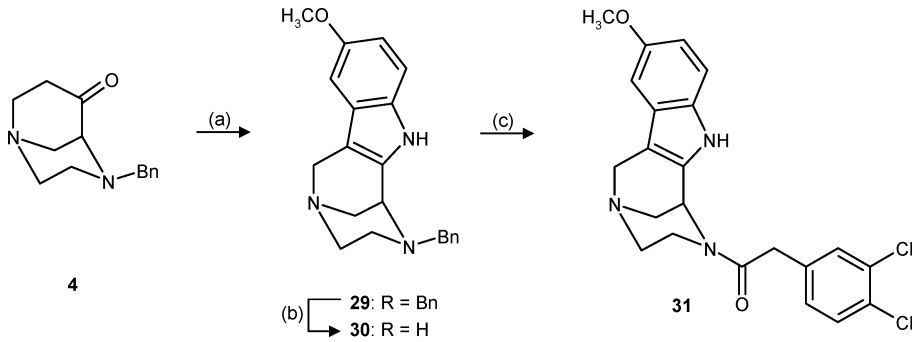
Receptor binding studies

The κ receptor affinity of the bicyclic amines was determined in competition experiments with the radioligand [^{3}H]-U-69 593. In the assay, membrane preparations of guinea pig brains were used as receptor material. The non-specific binding was determined in the presence of a large excess of non-tritiated U-69 593 (10 μM).[16]

In Table 1, the κ receptor affinities of the synthesized amines, together with the κ affinities of some reference compounds, are summarized. In our assay, the pyrrolidine derivative **7a** has a K_i-value of 73 nM. Whereas replacement of the pyrrolidine ring by a dimethylamino group (**7c**) did not influence the κ receptor affinity, the corresponding diethylamine shows a considerably reduced κ affinity. This result is not surprising, since the two ethyl residues on the N-atom can never adopt the same conformation as the pyrrolidine ring due to repulsion of the terminal methyl groups.

The data in Table 1 clearly show that the 3,4-dichlorophenylacetyl residue and the *endo*-configuration are essential for a strong interaction with the binding site of the κ receptor. Exchange of this residue for a phenylacetyl (**8a**), benzoyl (**9a**) or tosyl residue (**10a**, **10b**) led to almost complete loss of the κ receptor affinity. The change of the configuration from *endo*-configured amines **7** to *exo*-configured amines **25** also led to inactive compounds. The quinoline and indole annulated bicyclic compounds **28** and **31** did not interact significantly with the κ receptor. It is assumed that the reduced (quinoline **28**) or eliminated (indole **31**) basicity together with the planar geometry around the N-atom are responsible for the reduced κ receptor affinity.

In addition to the κ receptor affinity, the affinity of the bicyclic amines towards the other two classical opioid receptors, μ and δ, as well as to the historically related σ_1, σ_2 and NMDA receptors were investigated in receptor binding studies with radioligands. At a concentration of 1 μM the test compounds did not compete



Scheme 7 Reagents and reaction conditions: (a) *p*-Methoxyphenylhydrazine HCl, EtOH, HCl, reflux, 28%. (b) H_2, Pd/C, CH_3OH, rt. (c) 3,4-Dichlorophenylacetic acid, DCC, CH_2Cl_2, rt, 54%.

Table 1 κ Receptor affinities of the bicyclic compounds

Compound	κ Affinity [^{3}H]-U-69 593 $K_i \pm$ SEM/nM[a]
7a (WMS-1302)	73 ± 9.1
7b	361 ± 65
7c	65 ± 4.0
8a	0%[b]
9a	0%[b]
10a	0%[b]
10b	0%[b]
23a	0%[b]
23b	0%[b]
25a	0%[b]
25b	0%[b]
28	16%[b]
31	1%[b]
2[16]	0.31 ± 0.1
U-50 488	0.31 ± 0.1
U-69 593	0.97 ± 0.4
Naloxone	7.3 ± 0.4

[a] The K_i-values were determined in three independent experiments ($n = 3$) unless otherwise noted. [b] Percent inhibition at a concentration of 1 μM of the test compound.

significantly with the radioligands. Therefore the IC_{50}-values are at least higher than 1 μM. This result indicates that the *endo*-configured pyrrolidine, **7a** and its dimethylamine analogue **7c**, are selective κ agonists with minimal affinity to the investigated receptor systems.

Discussion of the dihedral angle

Compared with the lead compound **2**, the most potent κ agonist of this series, the *endo*-configured pyrrolidine **7a** (**WMS-1302**), is about 200-fold less active (see Table 1). The reduction of the κ receptor affinity may be due to (1) the additional basic bridgehead N-atom in position 1 of the bicyclic system and/or (2) the fixation of the pyrrolidine ring in an unfavorable orientation.

In addition to the basic pyrrolidine system, the known κ agonists with an ethylenediamine substructure generally do not have a further basic N-atom. Usually, additional N-atoms present in potential κ agonists are supplied with propionyl or methoxycarbonyl moieties.[13–16] However, very recently we have demonstrated that an additional basic N-atom is indeed tolerated by the κ receptor protein. In the quinoxaline compound class of κ agonists, secondary amines as well as methyl and benzyl amines even exceed the corresponding propionyl and methoxycarbonyl derivatives with respect to κ receptor affinity.[26] Therefore, we assume that the additional basic N-atom of **7a** is at least not exclusively responsible for the reduced κ affinity.

In Fig. 3, the dihedral angles (N(pyrrolidine)–C–C–N(acetamide)) of the diastereomeric pyrrolidines **7a** and **25a** are compared. The dihedral angle of the energetically most favored conformer (MOE) of the almost inactive *exo*-configured pyrrolidine **25a** is 168° (Fig. 3). Originally, we were very interested in this stereoisomer, since **25a** is directly obtained by connecting the free methyl group with the carbamate N-atom of the very potent flexible κ agonist **2** (see Fig. 1).

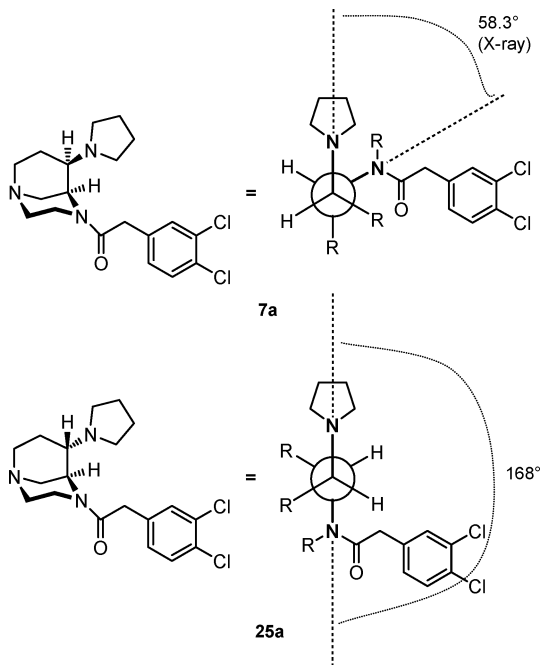


Fig. 3 Dihedral angles of the diastereomeric pyrrolidines **7a** and **25a**.

A systematic conformational analysis of N-protonated **2** was performed by rotation of the pyrrolidinylethyl residue in 10° intervals around the axially oriented C–C-bond (Fig. 4). Subsequently, the resulting conformations were energy minimized without changing the crucial dihedral angle N–C–C–N. The energy profile in Fig. 5 shows that a dihedral angle of 168° is energetically disfavored. Therefore, the potent κ agonist **2** probably does not adopt a conformation similar to **25a** at the κ receptor.

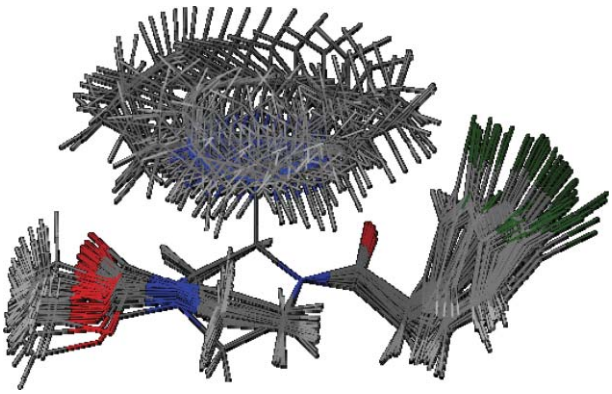


Fig. 4 Superposition of the energy minimized conformations resulting upon 10° rotation of the axially oriented pyrrolidinylethyl moiety of **2**.

According to the X-ray crystal structure of the *endo*-configured pyrrolidine **7a** (**WMS-1302**), both six-membered heterocycles adopt the chair conformation, which results in a dihedral angle of 58.3° (Fig. 3). Since the X-ray crystal structure is an energetically favored conformation, at least in the solid state, it is possible that **7a** reacts in this conformation with the κ receptor protein. In comparison with the *exo*-diastereomer **25a**, the κ affinity of **7a** is increased, but reduced compared with the κ affinity of **2**. So we assume that the dihedral angle of 58° is closer to the dihedral angle of the bioactive conformation of **2**, but still is not optimal. This assumption is supported by the energy profile of **2** depicted in Fig. 5, which reveals that the dihedral angle of 58° is close to the energy minimum of 70°, but still differs slightly from it.

Conclusion

Starting from the very potent but flexible κ agonist **2**, the conformationally constrained stereoisomeric bicyclic amines **7** and **25** have been synthesized. Compared with the lead compound **2** (K_i = 0.31 nM), the κ affinity of the *endo*-configured pyrrolidine **7a** (**WMS-1302**) and the *exo*-configured pyrrolidine **25a** is considerably reduced (K_i = 73 nM, K_i > 1 μM). It is assumed that the relative orientation of the pharmacophoric elements, the pyrrolidine ring and the dichlorophenylacetamide, determines the interaction of the bicyclic ligands with the κ receptor. Whereas a dihedral angle of 168° (**25a**) is not tolerated by the κ receptor, the dihedral angle of 58° of **7a** is closer to the bioactive conformation of **2**. The systematic conformational analysis of **2** revealed that the dihedral angle of 58° is energetically favored compared to 168°, but still differs from an energy minimum. This fact might explain the reduced κ receptor affinity of the bicyclic pyrrolidine **7a**.

Experimental

General chemistry

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (tlc): silica gel 60 F_{254} plates (Merck). Flash

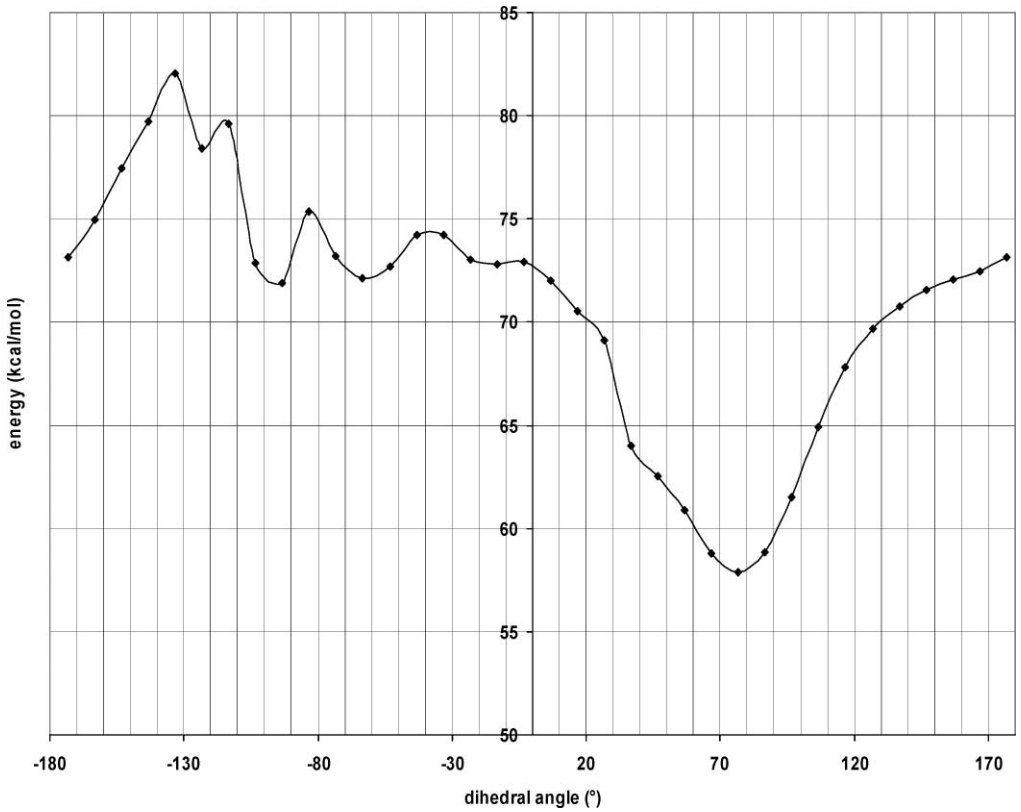


Fig. 5 Energy profile resulting upon rotation of compound **2** with a proton at the pyrrolidine N-atom around the axially oriented C–C bond at position 3 (compare to Fig. 1).

chromatography (fc): silica gel 60, 40–64 µm (Merck); parentheses include: diameter of the column, height of SiO_2 column, fraction size, eluent, R_f value. Melting point: melting point apparatus SMP 3 (Stuart Scientific), uncorrected. MS: MAT GCQ (Thermo-Finnigan); EI = electron impact, ESI = electrospray ionization. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury-400BB spectrometer (Varian); δ in ppm relative to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. HPLC method 1: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 µm), 250-4 mm; flow rate: 1.00 mL/min; injection volume: 5.0 µL; detection at λ = 210 nm; solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid: gradient elution: (A%): 0 min: 90%, 4 min: 90%, 29 min: 0%, 31 min: 0%, 31.5 min: 90%, 40 min: 90%. HPLC method 2: Equipment: pump: HPLC pump 64 (Knauer); UV-Detector: Variable Wavelength Monitor (Knauer); data acquisition: D-2500 Chromato-Integrator (Merck Hitachi); injection volume: 20.0 µL; stop time: 2 × t_R; A: column: LiChroCART® 250-4 with Superspher® 100 RP-18; solvent: methanol/water = 75:25 + 0.1% triethylamine; flow rate: 0.6 mL/min; detection: wavelength: 235 nm; B: column: LiChroCART® 250-4 with Superspher® 100 RP-18; solvent: acetonitrile/water = 70:30 + 0.1% triethylamine; flow rate: 1.0 mL/min; detection: wavelength: 254 nm; C: column: phenomenex Gemini 5 µm C18 100A, 250–21.2 mm; solvent: methanol/water = 50:50 + 0.1% triethylamine; flow rate: 0.8 mL/min; detection: wavelength: 235 nm.

(1*RS*,5*SR*,6*RS*)-4-Benzyl-6-(pyrrolidin-1-yl)-1,4-diazabicyclo-[3.3.1]nonane (5a). Under N_2 atmosphere $NaBH(OAc)_3$ (318 mg, 1.5 mmol) was added to a solution of **4** (230 mg, 1.0 mmol) and pyrrolidine (90 µL, 1.1 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 14 h, then a saturated $NaHCO_3$ solution (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 + 1% dimethylethylamine, R_f = 0.29) to afford 168 mg (59%) of **5a** as a pale yellow oil. $C_{18}H_{27}N_3$ (M_r = 285.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.67–1.76 (m, 5H, 7-H and $N(CH_2CH_2)_2$), 2.09–2.28 (m, 2H, 7-H and 6-H), 2.40–2.52 (m, 5H, 1H of 2-H or 3-H and $N(CH_2CH_2)_2$), 2.66 (d, J = 13.3 Hz, 1H, 9-H), 2.75–2.82 (m, 1H, 2-H or 3-H), 2.84 (s, 1H, 5-H), 3.03–3.09 (m, 2H, 8-H), 3.13–3.22 (m, 1H, 2-H or 3-H), 3.27–3.40 (m, 2H, 9-H and 1H of 2-H or 3-H), 4.00 (d, J = 14.1 Hz, 1H, $PhCH_2N$), 4.08 (d, J = 14.1 Hz, 1H, $PhCH_2N$), 7.17–7.37 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): δ [ppm] = 23.2 (2C, $N(CH_2CH_2)_2$), 29.2 (1C, C-7), 46.8 (1C, C-2 or C-3), 50.8 (1C, C-2 or C-3), 51.5 (1C, C-9), 51.7 (1C, C-5), 52.0 (1C, C-8), 52.2 (2C, $N(CH_2CH_2)_2$), 60.2 (1C, $PhCH_2N$), 68.4 (1C, C-6), 127.0 (1C, $C\text{-}4_{phenyl}$), 128.4 (2C, $C\text{-}3_{phenyl}$), 128.9 (2C, $C\text{-}2_{phenyl}$), 140.6 (1C, $C\text{-}1_{phenyl}$). IR (neat): ṽ [cm^{-1}] = 697 and 668 (m, arom. out of plane). MS (EI): *m*/*z* [%] = 285 (M, 100), 194 (M–$PhCH_2$, 13), 91 ($PhCH_2$, 31).

(1*RS*,5*SR*,6*RS*)-4-Benzyl-*N*,*N*-diethyl-1,4-diazabicyclo-[3.3.1]nonan-6-amine (5b). Under N_2 atmosphere $NaBH(OAc)_3$ (380 mg, 1.8 mmol) was added to a solution of **5d** (240 mg, 0.9 mmol) and acetaldehyde (100 µL, 1.8 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 16 h, then a saturated $NaHCO_3$ solution (30 mL) was added and the mixture extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 + 1% NH_3, R_f = 0.20) to afford 165 mg (64%) of **5b** as a colourless oil. $C_{18}H_{29}N_3$ (M_r = 287.5). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.96 (t, J = 7.0 Hz, 6H, $N(CH_2CH_3)_2$, 1.60–1.69 (m, 1H, 7-H), 2.18–2.32 (m, 1H, 7-H or 6-H), 2.37–2.45 (m, 1H, 7-H or 6-H), 2.58 (d, J = 13.3 Hz, 1H, 9-H), 2.61–2.67 (m, 1H, 2-H or 3-H), 2.68–2.81 (m, 5H, 1H of 2-H or 3-H and $N(CH_2CH_3)_2$, 2.90 (s, 1H, 5-H), 2.92–3.07 (m, 3H, 2× 8-H and 1H of 2-H or 3-H), 3.27–3.39 (m, 2H, 9-H and 1H of 2-H or 3-H), 3.90 (d, J = 14.1 Hz, 1H, $PhCH_2N$), 3.99 (d, J = 14.1 Hz, 1H, $PhCH_2N$), 7.19–7.37 (m, 5H, arom. H). IR (neat): ṽ [cm^{-1}] = 735 and 700 (m, arom. out of plane). MS (EI): *m*/*z* [%]: 287 (M, 55), 91 ($PhCH_2$, 86).

(1*RS*,5*SR*,6*RS*)-4-Benzyl-*N*,*N*-dimethyl-1,4-diazabicyclo-[3.3.1]nonan-6-amine (5c). Under N_2 atmosphere $NaBH(OAc)_3$ (318 mg, 1.5 mmol) was added to a solution of **4** (230 mg, 1.0 mmol), dimethylamine (2.5 mL of a 2 M solution in THF, 5.0 mmol) and acetic acid (60 µL, 1.0 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 14 h, then a saturated $NaHCO_3$ solution (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 + 1% triethylamine, R_f = 0.23) to afford 97 mg (38%) of **5c** as a pale yellow oil. $C_{16}H_{25}N_3$ (M_r = 259.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.70–1.81 (m, 1H, 7-H), 2.03–2.15 (m, 2H, 7-H and 6-H), 2.19 (s, 6H, $N(CH_3)_2$), 2.44 (ddd, J = 13.3/5.5/3.1 Hz, 1H, 2-H or 3-H), 2.55 (d, J = 13.3 Hz, 1H, 9-H), 2.68–2.76 (m, 1H, 2-H or 3-H), 2.85 (s, 1H, 5-H), 2.98–3.19 (m, 3H, 2× 8-H and 1H of 2-H or 3-H), 3.31–3.43 (m, 2H, 9-H and 1H of 2-H or 3-H), 3.98 (d, J = 14.1 Hz, 1H, $PhCH_2N$), 4.02 (d, J = 14.1 Hz, 1H, $PhCH_2N$), 7.17–7.38 (m, 5H, arom. H). IR (neat): ṽ [cm^{-1}] = 701 and 648 (m, arom. out of plane). MS (EI): *m*/*z* [%] = 259 (M, 100), 91 ($PhCH_2$, 50).

(1*RS*,5*SR*,6*RS*)-4-Benzyl-*N*-ethyl-1,4-diazabicyclo[3.3.1]-nonan-6-amine (5d). Under N_2 atmosphere $NaBH(OAc)_3$ (636 mg, 3.0 mmol) was added to a solution of **4** (460 mg, 2.0 mmol) and ethylamine-HCl (245 mg, 3.0 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for 36 h, then a saturated $NaHCO_3$ solution (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (∅ = 3 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 + 1% NH_3, R_f = 0.17) to afford 242 mg (47%) of **5d** as a pale yellow oil. $C_{16}H_{25}N_3$ (M_r = 259.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.06 (t, J = 7.0 Hz, 3H, $NHCH_2CH_3$), 1.67–1.93 (m, 3H, 2H of 7-H or 6-H and $NHCH_2CH_3$), 2.39–2.47 (m, 1H, 7-H or 6-H), 2.53 (d, J = 13.3 Hz, 1H, 9-H), 2.55–2.62 (m, 2H, $NHCH_2CH_3$), 2.66 (ddd, J = 11.7/6.3/3.1 Hz, 1H, 2-H or 3-H), 2.69–2.77 (m, 1H, 2-H or 3-H), 2.82 (s, 1H, 5-H), 2.90–2.99 (m, 3H, 2× 8-H and 1H of 2-H or 3-H), 3.26–3.35 (m, 1H, 2-H or 3-H), 3.38 (d, J = 13.3 Hz, 1H, 9-H), 3.88 (d, J = 14.1 Hz, 1H, $PhCH_2N$), 3.93 (d, J = 14.1 Hz, 1H, $PhCH_2N$), 7.19–7.35 (m, 5H, arom. H). IR (neat): ṽ

[cm^{-1}] = 3300 (br w, N-H), 737 and 695 (m, arom. out of plane). MS (EI): *m/z* [%] = 259 (M, 55), 168 (M–PhCH$_2$, 5), 91 (PhCH$_2$, 82).

2-(3,4-Dichlorophenyl)-1-[(1*RS*,5*SR*,6*RS*)-6-(pyrrolidin-1-yl)-1,4-diazabicyclo[3.3.1]nonan-4-yl]ethanone (7a). A solution of **5a** (135 mg, 0.47 mmol) containing 10% Pd/C (15 mg) in anhydrous methanol (10 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The crude product was dissolved in CH_2Cl_2 (15 mL). Then, DCC (146 mg, 0.71 mmol) and 3,4-dichlorophenylacetic acid (146 mg, 0.71 mmol) were added. After 3 h the reaction mixture was washed with 1 M NaOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 with 1% NH_3, R_f = 0.51) to afford 84 mg (47%) of **7a** as a colourless oil, which gave a colourless solid (mp 144 °C) upon standing in the fridge. $C_{19}H_{25}Cl_2N_3O$ (M_r = 382.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.66–1.83 (m, 6H, 2× 7-H and 4× N(CH$_2$CH_2)$_2$), 2.27–2.37 (m, 0.85H, 6-H), 2.40–2.49 (m, 2H, N(CH_2CH$_2$)$_2$), 2.51–2.58 (m, 0.15H, 6-H), 2.65–2.78 (m, 2H, N(CH_2CH$_2$)$_2$), 2.83–2.94 (m, 2H, NCH_2), 2.97–3.22 (m, 4.15H, NCH_2), 3.28 (dd, J = 13.3/6.3 Hz, 0.85H, NCH_2), 3.54 (td, J = 13.3/4.7 Hz, 0.85H, NCH_2), 3.68 (d, J = 15.7 Hz, 0.85H, COCH_2Ar), 3.72–3.83 (m, 0.45H, 0.15× 5-H and 0.30× COCH_2Ar), 3.77 (d, J = 15.7 Hz, 0.85H, COCH_2Ar), 4.09–4.15 (m, 0.15H, NCH_2), 4.73 (s broad, 0.85H, 5-H), 7.05 (dd, J = 7.8/2.4 Hz, 0.15H, 6′-H$_{dichlorophenyl}$), 7.15 (dd, J = 7.8/2.4 Hz, 0.85H, 6′-H$_{dichlorophenyl}$), 7.30 (d, J = 2.4 Hz, 0.15H, 2′-H$_{dichlorophenyl}$), 7.34 (d, J = 7.8 Hz, 1H, 5′-H$_{dichlorophenyl}$), 7.44 (d, J = 2.3 Hz, 0.85H, 2′-H$_{dichlorophenyl}$). Ratio of rotational isomers 85:15. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1632 (s, C=O), 881 and 821 (w, arom. out of plane). MS (EI): *m/z* [%] = 381 (M, 2× ^{35}Cl, 100), 383 (M, ^{35}Cl/^{37}Cl, 63), 385 (M, 2× ^{37}Cl, 9). HPLC (Method 1): t_R = 14.7 min, purity 98.9%. X-ray crystal structure analysis:[27–30] see the ESI.†

2-(3,4-Dichlorophenyl)-1-[(1*RS*,5*SR*,6*RS*)-6-(diethylamino)-1,4-diazabicyclo[3.3.1]nonan-4-yl]ethanone (7b). A solution of **5b** (150 mg, 0.52 mmol) containing 10% Pd/C (15 mg) in anhydrous methanol (10 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The crude product was dissolved in CH_2Cl_2 (15 mL). Then DCC (206 mg, 1.0 mmol) and 3,4-dichlorophenylacetic acid (205 mg, 1.0 mmol) were added. After 3 h the reaction mixture was washed with 1 M NaOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 with 1% NH_3, R_f = 0.44) to afford 140 mg (70%) of **7b** as a colourless oil, which gave a colourless solid (mp 147 °C) upon standing in the fridge. $C_{19}H_{27}Cl_2N_3O$ (M_r = 384.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.88–0.97 (m, 6× 0.42H, N(CH$_2$CH_3)$_2$), 1.02 (t, J = 7.0 Hz, 6× 0.58H, N(CH$_2$CH_3)$_2$), 1.63–1.77 (m, 2H, 7-H), 1.96–2.10 (m, 0.58H, 6-H), 2.47–2.67 (m, 4H, N(CH_2CH$_3$)$_2$), 2.78–3.25 (m, 7H, 6.58× NCH_2 and 0.42× 6-H), 3.34 (dd, J = 13.3/6.3 Hz, 0.42H, NCH_2), 3.51–3.73 (m, 1.84H, 0.42× NCH_2, 0.84× COCH_2Ar and 0.58× 5-H), 3.83 (d, J = 15.7 Hz, 0.58H, COCH_2Ar), 4.06 (d, J = 15.7 Hz, 0.58H, COCH_2Ar), 4.07–4.11 (m, 0.58H, NCH_2), 4.79 (s broad, 0.42H, 5-H), 7.05 (dd, J = 7.8/2.3 Hz, 0.58H, 6′-H$_{dichlorophenyl}$), 7.14 (dd, J = 7.8/2.3 Hz, 0.42H, 6′-H$_{dichlorophenyl}$), 7.30 (d, J = 2.3 Hz, 0.58H, 2′-H$_{dichlorophenyl}$), 7.35 (dd, J = 7.8/2.3 Hz, 1H, 5′-H$_{dichlorophenyl}$), 7.39 (d, J = 2.3 Hz, 0.42H, 2′-H$_{dichlorophenyl}$). Ratio of rotational isomers 42:58. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1634 (s, C=O), 881 and 822 (w, arom. out of plane). MS (EI): *m/z* [%] = 383 (M, 2× ^{35}Cl, 97), 385 (M, ^{35}Cl/^{37}Cl, 60), 387 (M, 2× ^{37}Cl, 9). HPLC (Method 1): t_R = 13.9 min, purity 96.5%.

2-(3,4-Dichlorophenyl)-1-[(1*RS*,5*SR*,6*RS*)-6-(dimethylamino)-1,4-diazabicyclo[3.3.1]nonan-4-yl]ethanone (7c). A mixture of **5c** (90 mg, 0.35 mmol), 10% Pd/C (10 mg) and anhydrous methanol (10 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The crude product was dissolved in CH_2Cl_2 (15 mL). Then, DCC (103 mg, 0.50 mmol) and 3,4-dichlorophenylacetic acid (102 mg, 0.50 mmol) were added. After 3 h the reaction mixture was washed with 1 M NaOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 with 1% NH_3, R_f = 0.42) to afford 66 mg (53%) of **7c** as a colourless oil, which gave a colourless solid (mp 95 °C) upon standing in the fridge. $C_{17}H_{23}Cl_2N_3O$ (M_r = 356.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.66–1.75 (m, 1H, 7-H), 1.77–1.85 (m, 1H, 7-H), 2.19–2.25 (m, 0.76H, 6-H), 2.27 (m, 6× 0.24H, N(CH_3)$_2$), 2.30 (m, 6× 0.76H, N(CH_3)$_2$), 2.64–2.70 (m, 0.24H, 6-H), 2.81–2.92 (m, 2H, NCH_2), 2.97–3.22 (m, 4.24H, NCH_2), 3.33 (dd, J = 13.3/6.3 Hz, 0.76H, NCH_2), 3.54 (td, J = 13.3/4.7 Hz, 0.76H, NCH_2), 3.67 (d, J = 15.7 Hz, 0.76H, COCH_2Ar), 3.74 (d, J = 15.7 Hz, 0.76H, COCH_2Ar), 3.78 (s broad, 0.24H, 5-H), 3.81 (d, J = 15.7 Hz, 0.24H, COCH_2Ar), 3.90 (d, J = 15.7 Hz, 0.24H, COCH_2Ar), 4.06–4.11 (m, 0.24H, NCH_2), 4.81 (s broad, 0.76H, 5-H), 7.06 (dd, J = 7.8/2.3 Hz, 0.24H, 6′-H$_{dichlorophenyl}$), 7.11 (dd, J = 7.8/2.3 Hz, 0.76H, 6′-H$_{dichlorophenyl}$), 7.32 (d, J = 2.3 Hz, 0.24H, 2′-H$_{dichlorophenyl}$), 7.35 (d broad, J = 7.8 Hz, 1H, 5′-H$_{dichlorophenyl}$), 7.44 (d, J = 2.3 Hz, 0.76H, 2′-H$_{dichlorophenyl}$). Ratio of rotational isomers 76:24. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1631 (s, C=O), 874 and 811 (w, arom. out of plane). MS (ESI): *m/z* [%] = 356 (MH, 2× ^{35}Cl, 100), 358 (MH, ^{35}Cl/^{37}Cl, 60), 360 (MH, 2× ^{37}Cl, 9). HPLC (Method 1): t_R = 13.9 min, purity 97.2%.

(1*RS*,5*SR*,6*RS*)-4-Benzyl-1,4-diazabicyclo[3.3.1]nonan-6-ol (11). Under N_2 atmosphere lithium borohydride (2 M solution in THF, 4.0 mL, 8.0 mmol) was added slowly to a solution of **4** (461 mg, 2.0 mmol) in dry methanol (15 mL) at –20 °C. After 1 h the reaction mixture was acidified by addition of 1 M aq. HCl. The resulting mixture was warmed to rt and stirred for 2 h. Then, saturated $NaHCO_3$ solution was added (pH 8–9) and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (∅ = 3 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 + 1% NEt_3, R_f = 0.32) to afford 422 mg (91%) of **11** as a colourless oil. $C_{14}H_{20}N_2O$ (M_r = 232.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.83–2.02 (m, 2H, 7-H), 2.42–2.53 (m, 2H, NCH_2), 2.57 (s broad, 1H, O*H*), 2.72 (dtd, J = 14.1/5.5/1.6 Hz, 1H, NCH_2), 2.79 (s broad, 1H, 5-H),

2.86–3.00 (m, 3H, NCH_2), 3.30 (ddd, J = 13.3/8.6/6.3 Hz, 1H, NCH_2), 2.75 (dt, J = 14.1/2.3 Hz, 1H, NCH_2), 3.71 (s broad, 1H, 6-H), 3.90 (d, J = 14.1 Hz, 1H, PhCH_2N), 3.96 (d, J = 14.1 Hz, 1H, PhCH_2N), 7.20–7.33 (m, 5H, arom. H). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3317 (m br, O-H), 739 and 696(m, arom. out of plane). MS (EI): *m/z* [%] = 232 (M, 100), 141 (M–PhCH$_2$, 97), 91 (PhCH$_2$, 45).

4-Tosyl-1,4-diazabicyclo[3.3.1]nonan-6-one (14). A solution of **13** (930 mg, 2.5 mmol) was heated to reflux in 2 M aqueous HCl (50 mL) under N_2 atmosphere. After 14 h the reaction mixture was cooled to room temperature, made alkaline with KOH solution and extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography [∅ = 3 cm, V = 10 mL, CH_2Cl_2/MeOH 9.5/0.5 → 9/1, R_f = 0.55 (CH_2Cl_2/MeOH 9/1)] to afford 685 mg (93%) of **14** as a colourless solid, mp 129 °C. $C_{14}H_{18}N_2O_3S$ (M_r = 294.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.94–2.05 (m, 1H, 7-H), 2.17–2.25 (m, 1H, 7-H), 2.39 (s, 3H, ArCH_3), 3.00 (d, J = 14.1 Hz, 1H, 9-H), 3.05–3.14 (m, 4H, NCH_2), 3.34–3.47 (m, 2H, NCH_2), 3.52–3.59 (m, 1H, NCH_2), 4.11 (s, 1H, 5-H), 7.27 (d, J = 8.6 Hz, 2H, 3′-H$_{tosylate}$, 5′-H$_{tosylate}$), 7.60 (d, J = 8.6 Hz, 2H, 2′-H$_{tosylate}$, 6′-H$_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1715 (s, C=O), 1160 (s, S=O), 809 (m, arom. out of plane). MS (EI): *m/z* [%] = 294 (M, 9), 139 (M–SO$_2$C$_6$H$_4$CH$_3$, 100). HPLC (Method 1): t_R = 11.5 min, purity 99.9%.

(1*RS*,5*SR*,6*RS*)-4-Tosyl-1,4-diazabicyclo[3.3.1]nonan-6-ol (15). Under N_2 atmosphere, sodium borohydride (330 mg, 8.7 mmol) was added in small portions to an ice-cooled solution of **14** (642 mg, 2.2 mmol) in dry methanol (50 mL). After 1 h at 0 °C the reaction was terminated by addition of 1 M aq. HCl. The resulting mixture was warmed to rt and stirred for an additional 0.5 h. Then, saturated $NaHCO_3$ solution was added (pH 8–9) and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography [∅ = 3 cm, V = 10 mL, CH_2Cl_2/MeOH 9.5/0.5 → 9/1, R_f = 0.39 (CH_2Cl_2/MeOH 9/1)] to afford 589 mg (91%) of **15** as a colourless solid, mp 159 °C. $C_{14}H_{20}N_2O_3S$ (M_r = 296.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.70–1.82 (m, 1H, 7-H), 1.87–1.95 (m, 1H, 7-H), 2.41 (s, 3H, ArCH_3), 2.68 (d, J = 14.1 Hz, 1H, 9-H), 2.77–2.83 (m, 1H, NCH_2), 2.84–3.10 (m, 4H, NCH_2), 3.29 (ddd, J = 13.3/7.0/3.1 Hz, 1H, NCH_2), 3.43–3.55 (m, 1H, NCH_2), 3.76–3.85 (m, 2H, 5-H, 6-H), 7.30 (d, J = 8.6 Hz, 2H, 3′-H$_{tosylate}$, 5′-H$_{tosylate}$), 7.71 (d, J = 8.6 Hz, 2H, 2′-H$_{tosylate}$, 6′-H$_{tosylate}$). The signal for the proton of the OH group could not be detected. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3200 (br w, O-H), 1153 (s, S=O), 822 (m, arom. out of plane). MS (EI): *m/z* [%] = 296 (M, 19), 141 (M–SO$_2$C$_6$H$_4$CH$_3$, 100). HPLC (Method 1): t_R = 11.6 min, purity 99.1%.

(1*RS*,5*RS*,6*SR*)-1-Oxy-4-tosyl-1,4-diazabicyclo[3.3.1]nonan-6-yl toluene-4-sulfonate (19). Under N_2 atmosphere, 3-chloroperoxybenzoic acid (70%, 130 mg, 0.53 mmol) was added to an ice-cooled mixture of **17** (217 mg, 0.48 mmol) and K_2CO_3 (166 mg, 1.20 mmol) in CH_2Cl_2 (20 mL). After 1 h at 0 °C, water was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography [∅ = 2 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 with 1% NH_3, R_f = 0.22 (CH_2Cl_2/MeOH 9/1 with 1% NH_3)] to afford 164 mg (73%) of **19** as a colourless solid, mp 162 °C. $C_{21}H_{26}N_2O_6S_2$ (M_r = 466.6). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.23–2.39 (m, 2H, 7-H), 2.42 (s, 3H, ArCH_3), 2.45 (s, 3H, ArCH_3), 3.07–3.15 (m, 1H, 9-H), 3.19–3.31 (m, 1H, 2-H or 3-H), 3.34 (d, J = 13.3 Hz, 1H, 9-H), 3.43–3.58 (m, 2H, 1× 8-H and 1H of 2-H or 3-H), 3.62–3.70 (m, 1H, 8-H), 3.72–3.83 (m, 1H, 2-H or 3-H), 3.93 (dd, J = 14.9/7.0 Hz, 1H, 2-H or 3-H), 4.61 (s, 1H, 5-H), 4.67–4.76 (m, 1H, 6-H), 7.30 (d, J = 8.6 Hz, 2H, 3′-H$_{tosylate}$, 5′-H$_{tosylate}$), 7.36 (d, J = 8.6 Hz, 2H, 3′-H$_{tosylate}$, 5′-H$_{tosylate}$), 7.70 (d, J = 8.6 Hz, 2H, 2′-H$_{tosylate}$, 6′-H$_{tosylate}$), 7.84 (d, J = 8.6 Hz, 2H, 2′-H$_{tosylate}$, 6′-H$_{tosylate}$). ^{13}C NMR ($CDCl_3$): δ [ppm] = 21.8, 22.0 (2C, Ar*C*H$_3$), 28.9 (1C, C-7), 42.0 (1C, C-2 or C-3), 53.0 (1C, C-5), 66.4 (1C, C-2 or C-3), 66.6 (1C, C-8), 66.8 (1C, C-9), 73.1 (1C, C-6), 127.4 (2C, C-2$_{tosylate}$, C-6$_{tosylate}$), 128.4 (2C, C-2$_{tosylate}$, C-6$_{tosylate}$), 130.3 (2C, C-3$_{tosylate}$, C-5$_{tosylate}$), 130.5 (2C, C-3$_{tosylate}$, C-5$_{tosylate}$), 132.9 (1C, C-1$_{tosylate}$), 136.3 (1C, C-1$_{tosylate}$), 144.8 (1C, C-4$_{tosylate}$), 145.8 (1C, C-4$_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1343 (s, N-O), 1157 (s, S=O), 812 (m, arom. out of plane). MS (ESI): *m/z* [%] = 467 (M + H, 23), 489 (M + Na, 24), 933 (2M + H, 100). HPLC (Method 1): t_R = 18.8 min, purity 98.2%.

(1*RS*,5*SR*,6*SR*)-6-Azido-4-(4-methylphenylsulfonyl)-1,4-diazabicyclo[3.3.1]nonane (21). Under N_2 atmosphere, a mixture of **19** (233 mg, 0.5 mmol) and sodium azide (325 mg, 5.0 mmol) in dry DMF (10 mL) was heated to 80 °C. Since a conversion was not observed after 16 h, the reaction mixture was heated to 150 °C. After additional 20 h the reaction mixture was cooled to rt, diluted with 2 M NaOH and extracted with small portions of ethyl acetate (6×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (∅ = 3 cm, V = 10 mL, CH_2Cl_2/MeOH 9.5/0.5, R_f = 0.35) to afford 74 mg (46%) of **21** as a colourless oil. $C_{14}H_{19}N_5O_2S$ (M_r = 321.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.56 (dd, J = 15.2/4.2 Hz, 1H, 7-H), 2.10–2.22 (m, 1H, 7-H), 2.42 (s, 3H, ArCH_3), 2.64 (d, J = 14.2 Hz, 1H, 9-H), 2.75 (dd, J = 14.7/6.3 Hz, 1H, 8-H), 2.95–3.06 (m, 1H, 2-H or 3-H), 3.09–3.25 (m, 4H, 2× 2-H or 3-H, 1× 8-H and 1× 9-H), 3.42–3.54 (m, 2H, 1× 2-H or 3-H and 6-H), 4.04 (s broad, 1H, 5-H), 7.31 (d, J = 7.9 Hz, 2H, 3′-H$_{tosylate}$, 5′-H$_{tosylate}$), 7.68 (d, J = 7.9 Hz, 2H, 2′-H$_{tosylate}$, 6′-H$_{tosylate}$). ^{13}C NMR ($CDCl_3$): δ [ppm] = 21.8 (1C, Ar*C*H$_3$), 24.9 (1C, C-7), 40.7 (1C, C-2 or C-3), 46.6 (1C, C-9), 47.9 (1C, C-8), 48.0 (1C, C-6), 49.8 (1C, C-2 or C-3), 59.1 (1C, C-5), 127.4 (2C, C-2$_{tosylate}$, C-6$_{tosylate}$), 130.1 (2C, C-3$_{tosylate}$, C-5$_{tosylate}$), 135.9 (1C, C-1$_{tosylate}$), 144.0 (1C, C-4$_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2094 (s, N=N=N), 1159 (s, S=O), 815 (m, arom. out of plane). MS (ESI): *m/z* [%] = 322 (MH, 27), 665 (M + Na, 100). HPLC (Method 1): t_R = 15.7 min, purity 95.5%.

(1*RS*,5*SR*,6*SR*)-6-(Pyrrolidin-1-yl)-4-(4-methylphenylsulfonyl)-1,4-diazabicyclo[3.3.1]nonan-6-amine (23a). A mixture of **19** (513 mg, 1.1 mmol) and sodium azide (143 mg, 2.2 mmol) in dry DMF (3 mL) was heated by microwave irradiation in a sealed microwave reaction vial (300 W max. power, 150 °C max. temperature, 3.0 bar max. pressure, time program 5-10-5 min, cooling on). Then, the reaction mixture was diluted with 2 N NaOH and extracted with small portions of ethyl acetate (6×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The crude product was dissolved in anhydrous MeOH (15 mL), 10% Pd/C (30 mg) was added and the resulting slurry was stirred under an atmosphere of

hydrogen at room temperature for 2 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The crude product was dissolved in THF (15 mL), and, under N_2 atmosphere, $NaBH(OAc)_3$ (630 mg, 3.0 mmol) and succinaldehyde (172 mg, 2.0 mmol, obtained as described in ref. 23 upon hydrolysis of 2,5-dimethoxytetrahydrofuran) were added. The reaction mixture was stirred at room temperature for 16 h. Then, 0.1 M NaOH was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (∅ = 3 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1, $R_f = 0.28$) to afford 137 mg (36%) of **23a** as a colourless oil. $C_{18}H_{27}N_3O_2S$ ($M_r = 349.5$). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.60 (d broad, J = 15.7 Hz, 1H, 7-H), 1.71–1.80 (m, 4H, $N(CH_2CH_2)_2$), 1.94–2.06 (m, 1H, 7-H), 2.41 (s, 3H, $ArCH_3$), 2.48–2.68 (m, 7H, 6-H, 1× 8-H, 1× 9-H and $N(CH_2CH_2)_2$), 2.94–3.03 (m, 1H, 1× 2-H or 3-H), 3.13–3.28 (m, 3H, 2× 2-H or 3-H and 1× 8-H), 3.44 (d, J = 13.3 Hz, 1H, 9-H), 3.49–3.58 (m, 1H, 1× 2-H or 3-H), 3.70 (s broad, 1H, 5-H), 7.29 (d, J = 7.8 Hz, 2H, 3′-$H_{tosylate}$, 5′-$H_{tosylate}$), 7.68 (d, J = 7.8 Hz, 2H, 2′-$H_{tosylate}$, 6′-$H_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1157 (s, S=O), 815 (m, arom. out of plane). MS (ESI): *m*/*z* [%] = 350 (MH, 100). HPLC (Method 1): t_R = 11.4 min, purity 96.6%.

(1*RS*,5*SR*,6*SR*)-*N*,*N*-Diethyl-4-(4-methylphenylsulfonyl)-1,4-diazabicyclo[3.3.1]nonan-6-amine (23b). A mixture of **19** (233 mg, 0.5 mmol) and sodium azide (325 mg, 5.0 mmol) in dry DMF (3 mL) was heated by microwave irradiation in a sealed microwave reaction vial (300 W max. power, 150 °C max. temperature, 3.0 bar max. pressure, time program 5-10-5 min, cooling on). Then, the reaction mixture was diluted with 2 M NaOH and extracted with small portions of ethyl acetate (6×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The crude product was dissolved in anhydrous MeOH (10 mL), 10% Pd/C (15 mg) was added and the resulting slurry was stirred under an atmosphere of hydrogen at room temperature for 1 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The crude product was dissolved in THF (10 mL), and, under N_2 atmosphere, $NaBH(OAc)_3$ (160 mg, 0.75 mmol) and acetaldehyde (43 µL, 0.75 mmol) were added. The reaction mixture was stirred at room temperature for 16 h. Then 0.1 M NaOH was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1, $R_f = 0.32$) to afford 51 mg (29%) of **23b** as a pale yellow oil. $C_{18}H_{29}N_3O_2S$ ($M_r = 351.5$). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.96 (t, J = 7.0 Hz, 6H, $N(CH_2CH_3)_2$, 1.58 (dd, J = 15.7/2.4 Hz, 1H, 7-H), 1.86–1.98 (m, 1H, 7-H), 2.41 (s, 3H, $ArCH_3$), 2.56 (d, J = 13.3 H, 1H, 9-H), 2.63–2.69 (m, 1H, 8-H), 2.64 (q, J = 7.0 Hz, 4H, $N(CH_2CH_3)_2$, 2.89–2.98 (m, 2H, 1× 2-H or 3-H and 6-H), 3.09–3.25 (m, 3H, 2× 2-H or 3-H and 1× 8-H), 3.37 (d, J = 13.3 Hz, 1H, 9-H), 3.46–3.55 (m, 1H, 1× 2-H or 3-H), 3.64 (s broad, 1H, 5-H), 7.28 (d, J = 7.8 Hz, 2H, 3′-$H_{tosylate}$, 5′-$H_{tosylate}$), 7.68 (d, J = 7.8 Hz, 2H, 2′-$H_{tosylate}$, 6′-$H_{tosylate}$). ^{13}C NMR ($CDCl_3$): δ [ppm] = 11.8 (2C, NCH_2CH_3), 21.8 (1C, $ArCH_3$), 23.2 (1C, C-7), 40.4 (1C, C-2 or C-3), 43.2 (2C, NCH_2CH_3), 46.9 (1C, C-9), 48.4 (1C, C-5), 48.8 (1C, C-8), 50.5 (1C, C-2 or C-3), 57.9 (1C, C-6), 127.4 (2C, C-2$_{tosylate}$, C-6$_{tosylate}$), 129.9 (2C, C-3$_{tosylate}$, C-5$_{tosylate}$), 136.8 (1C, C-1$_{tosylate}$), 143.5 (1C, C-4$_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1157 (s, S=O), 814 (m, arom. out of plane). MS (ESI): *m*/*z* [%] = 352 (MH, 100). HPLC (Method 1): t_R = 11.4 min, purity 96.6%.

2-(3,4-Dichlorophenyl)-1-[(1*RS*,5*SR*,6*SR*)-6-(pyrrolidin-1-yl)-1,4-diazabicyclo[3.3.1]non-4-yl]ethanone (25a). Magnesium (turnings, 90 mg, 3.75 mmol) was added to a solution of **23a** (130 mg, 0.37 mmol) in MeOH (10 mL), and the mixture was heated to reflux. After 2 h, additional magnesium (turnings, 90 mg, 3.75 mmol) was added, and the mixture was again heated to reflux for 2 h and cooled to rt. Then HCl (gas) was bubbled through the reaction mixture until the insoluble material had dissolved. The resulting solution was concentrated *in vacuo*. The residue was dispersed in CH_2Cl_2 (15 mL) and 3,4-dichlorophenylacetyl chloride (827 mg, 3.7 mmol) and triethylamine (1.0 mL, 7.2 mmol) were added. After 16 h at rt the reaction mixture was washed with 1 M NaOH. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (∅ = 3 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 with 1% NH_3, $R_f = 0.25$) to afford 35 mg (25%) of **25a** as a colourless oil. $C_{19}H_{25}Cl_2N_3O$ ($M_r = 382.3$). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.64–1.83 (m, 5H, 1× 7-H and 4× $N(CH_2CH_2)_2$), 1.86–1.99 (m, 1H, 1× 7-H), 2.43–2.49 (m, 1H, 6-H), 2.52–2.61 (m, 2.9H, $N(CH_2CH_2)_2$), 2.62–2.72 (m, 2.55H, 1.1× $N(CH_2CH_2)_2$, 0.45× 8-H and 1× 9-H), 2.78 (dd, J = 14.1/5.5 Hz, 0.55H, 8-H), 3.02 (dd, J = 14.1/6.5 Hz, 0.55H, 2-H or 3-H), 3.09 (dd, J = 14.3/7.0 Hz, 0.45H, 2-H or 3-H), 3.21–3.46 (m, 3H, 2× 2-H or 3-H and 1× 8-H), 3.53–3.62 (m, 3H, 0.55× 2-H or 3-H, 0.45× 5-H, 1× 9-H, 1× $COCH_2Ar$), 3.68–3.73 (m, 1H, $COCH_2Ar$), 3.86 (dd, J = 14.3/7.0 Hz, 0.45H, 2-H or 3-H), 4.36 (s broad, 0.55H, 5-H), 7.04–7.08 (m, 1H, 6′-$H_{dichlorophenyl}$), 7.32 (d broad, J = 2.0 Hz, 1H, 2′-$H_{dichlorophenyl}$), 7.36 (d, J = 8.3 Hz, 0.45H, 5′-$H_{dichlorophenyl}$), 7.37 (d, J = 8.3 Hz, 0.55H, 5′-$H_{dichlorophenyl}$). Ratio of rotational isomers 55:45. ^{13}C NMR ($CDCl_3$): δ [ppm] = 23.5 (0.9 C, $N(CH_2CH_2)_2$), 23.6 (1.1C, $N(CH_2CH_2)_2$), 26.1 (0.45C, C-7), 26.5 (0.55C, C-7), 39.1 (0.45C, $COCH_2Ar$), 39.8 (0.45C, C-2 or C-3), 40.2 (0.55C $COCH_2Ar$), 42.0 (0.55C, C-2 or C-3), 44.7 (0.55C, C-5), 46.9 (0.55C, C-9), 47.4 (0.45C, C-9), 47.6 (0.45C, C-8), 47.7 (0.55C, C-8), 47.8 (0.45C, C-5), 49.9 (0.45C, C-2 or C-3), 50.0 (0.55C, C-2 or C-3), 51.9 (1.1C, $N(CH_2CH_2)_2$), 52.0 (0.9C, $N(CH_2CH_2)_2$), 61.5 (0.55C, C-6), 64.0 (0.45C, C-6), 128.3 (0.45C, C-6$_{phenyl}$), 128.6 (0.55C, C-6$_{phenyl}$), 130.4 (0.45C, C-5$_{phenyl}$), 130.5 (0.55C, C-5$_{phenyl}$), 130.8 (0.45C, C-2$_{phenyl}$), 130.9 (0.45C, C-4$_{phenyl}$), 131.0 (0.55C, C-4$_{phenyl}$), 131.1 (0.55C, C-2$_{phenyl}$), 132.5 (1C, C-3$_{phenyl}$), 135.0 (0.55C, C-1$_{phenyl}$), 135.3 (0.45C, C-1$_{phenyl}$), 170.3 (0.55C, $COCH_2Ar$), 170.4 (0.45C, $COCH_2Ar$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1634 (s, C=O), 877 and 824 (w, arom. out of plane). MS (EI): *m*/*z* [%] = 381 (M, 2× ^{35}Cl, 100), 383 (M, ^{35}Cl/^{37}Cl, 65), 385 (M, 2× ^{37}Cl, 11). HPLC (Method 1): t_R = 13.6 min, purity 97.5%.

2-(3,4-Dichlorophenyl)-1-[(1*RS*,5*SR*,6*SR*)-6-(diethylamino)-1,4-diazabicyclo[3.3.1]nonan-4-yl]ethanone (25b). Magnesium (turnings, 30 mg, 1.25 mmol) was added to a solution of **23b** (40 mg, 0.11 mmol) in MeOH (10 mL), and the mixture was heated to reflux. After 2 h, additional magnesium (turnings, 30 mg, 1.25 mmol) was added, and the mixture was again heated to reflux for 2 h and cooled to rt. Then, HCl (gas) was bubbled through

the reaction mixture until the insoluble material had dissolved. The resulting solution was concentrated *in vacuo*. The residue was dispersed in CH_2Cl_2 (10 mL) and 3,4-dichlorophenylacetyl chloride (246 mg, 1.1 mmol) and triethylamine (310 µL, 2.2 mmol) were added. After 16 h at rt the reaction mixture was washed with 1 M NaOH. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 with 1% NH_3, R_f = 0.31) to afford 19 mg (45%) of **25b** as a colourless oil. $C_{19}H_{27}Cl_2N_3O$ (M_r = 384.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.96 (t, J = 7.0 Hz, 3.6H, $N(CH_2CH_3)_2$), 0.99 (t, J = 7.0 Hz, 2.4H, $N(CH_2CH_3)_2$), 1.63–1.93 (m, 2H, 7-H), 2.55–2.83 (m, 7H, 4× $N(CH_2CH_3)_2$, 6-H, 1× 9-H, 1× 8-H), 2.94–3.04 (m, 1H, 2-H or 3-H), 3.11–3.36 (m, 3H, 2× 2-H or 3-H and 1× 8-H), 3.39–3.76 (m, 4H, 0.6× 2-H or 3-H, 0.4× 5-H, 1× 9-H, $COCH_2Ar$), 3.90 (dd, J = 14.5/6.2 Hz, 0.4H, 2-H or 3-H), 4.29 (s broad, 0.6H, 5-H), 7.03–7.09 (m, 1H, 6′-$H_{dichlorophenyl}$), 7.32 (d broad, J = 2.0 Hz, 1H, 2′-$H_{dichlorophenyl}$), 7.36 (d, J = 8.3 Hz, 0.4H, 5′-$H_{dichlorophenyl}$), 7.37 (d, J = 8.3 Hz, 0.6H, 5′-$H_{dichlorophenyl}$), Ratio of rotational isomers 60:40. IR (neat): ṽ [cm^{-1}] = 1636 (s, C=O), 870 and 824 (w, arom. out of plane). MS (EI): *m/z* [%] = 383 (M, 2× ^{35}Cl, 100), 385 (M, ^{35}Cl/^{37}Cl, 53), 387 (M, 2× ^{37}Cl, 8). HPLC (Method 1): t_R = 14.1 min, purity 95.6%.

5-[2-(3,4-Dichlorophenyl)acetyl]-12-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-[1,4]diazocino[6,7-b]quinoline (28). A solution of **27** (130 mg, 0.55 mmol), 3,4-dichlorophenylacetic acid (169 mg, 0.83 mmol) and DCC (170 mg, 0.83 mmol) in CH_2Cl_2 (20 mL) was stirred at rt for 14 h. Then, the reaction mixture was washed with a saturated solution of $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography [∅ = 3 cm, l = 15 cm, V = 15 mL, CH_2Cl_2/MeOH 9.5/0.5, R_f = 0.56 (CH_2Cl_2/MeOH 9/1)] to afford 173 mg (74%) of **28** as a colourless solid, mp 108 °C. $C_{23}H_{21}Cl_2N_3O$ (M_r = 426.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.46–2.55 (m, 0.78H, NCH_2), 2.53 (s, 3× 0.22H, CH_3), 2.56 (s, 3× 0.78H, CH_3), 2.80–2.86 (m, 0.22H, NCH_2), 2.90–2.97 (m, 0.22H, NCH_2), 3.05–3.13 (m, 1H, NCH_2), 3.18–3.48 (m, 3H, NCH_2), 3.63 (d, J = 15.7 Hz, 0.22H, $COCH_2Ar$), 3.68 (d, J = 15.7 Hz, 0.22H, $COCH_2Ar$), 4.06–4.19 (m, 2.56H, 1× 1-H, 0.78× $COCH_2Ar$, 0.78× NCH_2), 4.37 (d, J = 15.7 Hz, 0.78H, $COCH_2Ar$), 4.44 (d, J = 18.0 Hz, 1H, 1-H), 5.03 (s broad, 0.78H, 6-H), 5.96 (s broad, 0.22H, 6-H), 7.04 (dd, J = 8.6/2.3 Hz, 0.22H, 6′-$H_{dichlorophenyl}$), 7.18–7.28 (m, 1.22H, 0.78× 6′-$H_{dichlorophenyl}$, 0.22× 2′-$H_{dichlorophenyl}$ and 0.22× 5′-$H_{dichlorophenyl}$), 7.41 (d, J = 7.8 Hz, 0.78H, 2′-$H_{dichlorophenyl}$), 7.50–7.59 (m, 1.78, 1× 10-H and 0.78× 5′-$H_{dichlorophenyl}$), 7.63 - 7.71 (m, 1H, 9-H), 7.95–8.04 (m, 1.78H, 1× 11-H and 0.78× 8-H), 8.10–8.15 (m, 0.22H, 8-H). Ratio of rotational isomers 78:22. IR (neat): ṽ [cm^{-1}] = 1634 (s, C=O), 1499 (m, C=C), 756 and 737 (m, arom. out of plane). MS (ESI): *m/z* [%] = 426 (MH, 2× ^{35}Cl, 86), 428 (MH, ^{35}Cl/^{37}Cl, 55), 873 (2M + Na, 4× ^{35}Cl, 81), 875 (2M + Na, 3×^{35}Cl/1×^{37}Cl, 100), 877 (2M + Na, 2×^{35}Cl/2×^{37}Cl, 48). HPLC (Method 1): t_R = 18.9 min, purity 97.6%.

5-[(3,4-Dichlorophenyl)acetyl]-10-methoxy-2,3,4,5,6,7-hexahydro-2,6-methano-1*H*-[1,4]diazocino[6,7-b]indole (31). A solution of **29** (80 mg, 0.24 mmol) containing 10% Pd/C (10 mg) in anhydrous methanol (10 mL) was stirred under an atmosphere of hydrogen at room temperature for 4 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The crude product (**30**) was dissolved in CH_2Cl_2 (10 mL), then DCC (74 mg, 0.36 mmol) and 3,4-dichlorophenylacetic acid (74 mg, 0.36 mmol) were added. After 3 h, 1M NaOH was added to the reaction mixture, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9.5/0.5, R_f = 0.20) to afford 54 mg (54%) of **31** as a colourless solid, mp 221 °C. $C_{22}H_{21}Cl_2N_3O_2$ (M_r = 430.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.94–3.02 (m, 1H, NCH_2), 3.03–3.12 (m, 1H, NCH_2), 3.18–3.37 (m, 4H, NCH_2), 3.50 (d, J = 15.7 Hz, 1H, 1-H), 3.59 (d, J = 15.7 Hz, 1H, 1-H), 3.81 (s, 3× 0.12H, OCH_3), 3.81 (s, 3× 0.88H, OCH_3), 3.93 (d, J = 16.4 Hz, 0.88H, $COCH_2Ar$), 3.95 (d, J = 16.4 Hz, 0.12H, $COCH_2Ar$), 4.37 (d, J = 16.4 Hz, 0.12H, $COCH_2Ar$), 3.41 (d, J = 16.4 Hz, 0.88H, $COCH_2Ar$), 4.64 (s broad, 0.12H, 6-H), 5.55 (s broad, 0.88H, 6-H), 6.84 (dd, J = 9.4/2.3 Hz, 1H, 9-H), 6.87 (d, J = 2.3 Hz, 1H, 11-H), 7.05 (dd, J = 8.6/1.6 Hz, 0.88H, 6′-$H_{dichlorophenyl}$), 7.15 (d broad, J = 8.6 Hz, 0.12H, 6′-$H_{dichlorophenyl}$), 7.18–7.32 (m, 3H, 8-H, 5′-$H_{dichlorophenyl}$ and 2′-$H_{dichlorophenyl}$), 8.35 (s broad, 1H, N*H*). Ratio of rotational isomers 88:12. IR (neat): ṽ [cm^{-1}] = 3205 (m broad, N-H), 1632 (s, C=O), 786, 777 and 740 (m, arom. out of plane). MS (EI): *m/z* [%] = 429 (M, 2× ^{35}Cl, 30), 431 (M, ^{35}Cl/^{37}Cl, 16), 433 (M, 2× ^{37}Cl, 3). HPLC (Method 1): t_R = 19.4 min, purity 98.5%.

Receptor binding studies

Materials and general procedures. Guinea pig brains were commercially available (Harlan-Winkelmann, Germany). Homogenizer: Elvehjem Potter (B. Braun Biotech International). Centrifuge: high-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Finnigan). Filter: Printed Filtermat Type B (Perkin Elmer), pre-soaked in 0.5% aqueous polyethylenimine for 2 h at rt before use. The filtration was carried out with a MicroBeta FilterMate-96 Harvester (Perkin Elmer). The scintillation analysis was performed using Meltilex (Type 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 rt, the scintillation was measured using a MicroBeta Trilux scintillation analyzer (Perkin Elmer). The counting efficiency was 20%.

Membrane preparation for the κ assay (modified according to ref. 16). 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 23 500 × *g* for 20 min at 4 °C. The pellet was resuspended in 5–6 volumes of buffer (50 mM TRIS, pH 7.4), and centrifuged again at 23 500 × *g* (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5–6 volumes of buffer, the protein concentration was determined according to the method of Bradford[31], using bovine serum albumin as the standard, and subsequently the preparation was frozen (–80 °C) in 1.5 mL portions containing about 1.5 mg protein mL^{-1}.

Performing of the κ assay (modified according to ref. 16). The test was performed with the radioligand [^{3}H]-U-69 593 (55 Ci mmol^{-1}, Amersham, Little Chalfont, UK). The thawed membrane preparation (about 75 µg of the protein) was incubated with various concentrations of test compounds, 1 nM [^{3}H]-U-69'593, and TRIS-$MgCl_2$-buffer (50 mM, 8 mM $MgCl_2$, pH 7.4) in a total volume of 200 µL for 150 min at 37 °C. The incubation was terminated by rapid filtration through the pre-soaked filtermats using a 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 unlabelled U-69 593. The K_d-value of U-69 593 is 0.69 nM.[32]

Membrane preparation for the µ assay (modified according to ref. 16). 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 23 500 × *g* for 20 min at 4 °C. The pellet was resuspended in 5–6 volumes of buffer (50 mM TRIS, pH 7.4), and centrifuged again at 23 500 × *g* (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5–6 volumes of buffer, the protein concentration was determined according to the method of Bradford[31] using bovine serum albumin as the standard, and subsequently the preparation was frozen (–80 °C) in 1.5 mL portions containing about 1.5 mg protein mL^{-1}.

Performing of the µ assay (modified according to ref. 16). The test was performed with the radioligand [^{3}H]-DAMGO (51 Ci mmol^{-1}, Perkin Elmer LAS). The thawed membrane preparation (about 75 µg of the protein) was incubated with various concentrations of test compounds, 3 nM [^{3}H]-DAMGO, and TRIS-$MgCl_2$-PMSF-Buffer (50 mM, 8 mM $MgCl_2$, pH 7.4) in a total volume of 200 µL for 150 min at 37 °C. The incubation was terminated by rapid filtration through the pre-soaked filtermats using a 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 unlabelled Naloxon. The K_d-value of DAMGO is 0.57 nM.[33]

Further assays. The details of the δ, σ_1, σ_2 and NMDA assays are given in the following references: δ assay,[34] σ_1 assay,[35] σ_2 assay,[35] and affinity towards the phencyclidine binding site of the NMDA receptor.[36]

Data analysis. All experiments were carried out in triplicate 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.[37] The K_i-values are given as mean values ± SEM from three independent experiments.

Molecular modelling. The conformational analysis was performed with force field MMFF94x of the Molecular Modelling Program MOE (molecular operating environment), version 2008.10 (Chemical Computing Group AG).

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