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Forcing the phenyl moiety into the axial position by embedding the 2-phenyl-1,3-dioxane system in a tricyclic benzomorphan scaffold: design, synthesis and biological evaluation

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The relative configuration and the substitution pattern control the interaction of 2-(2-phenyl1,3-dioxan-4-yl) ethan-1-amines with σ_1 receptors or the PCP binding site of NMDA receptors. In order to investigate the influence of the orientation of the phenyl moiety in 2-position on the receptor interaction, the 2-phenyl-1,3-dioxane system was embedded in a tricyclic benzomorphan scaffold (**3**) fixing the phenyl moiety in an axial orientation relative to the 1,3-dioxane ring. The key step of the synthesis of tricyclic amines **3** was the addition of lithiated 2-methylbenzamide **7** at pentanone **6** to afford the tertiary alcohol **8**. Lactone formation (**9**), DIBAH reduction (**10**) and intramolecular transacetalization led to the tricyclic alcohol **11**, which was converted into a series of twelve primary, secondary and tertiary amines **3a–m**. Although the primary amine **3a** is structurally related to the potent PCP antagonist **2a**, it did not interact with the PCP binding site of the NMDA receptor. The missing ethyl moiety and/or an unfavorable orientation of the phenyl moiety might be responsible for the lost PCP affinity of **3a**. As observed for the flexible 1,3-dioxanes **1b** and **2b**, introduction of a benzyl moiety at the amino group resulted in high σ_1 receptor affinity of **3b**. In accordance with σ_1 pharmacophore models, two small or two large substituents at the amino moiety were less tolerated by the σ_1 receptor, whereas an additional small methyl moiety increased the σ_1 affinity of **3h** and **3j**. With respect to σ_1 receptor affinity and selectivity over the σ_2 subtype, the methylated cyclohexylmethylamine **3j** ($K_i(\sigma_1)$ = 6.4 nM, 9-fold selectivity) represents the most promising ligand. The highest ligand-lipophilicity efficiency (LLE) was obtained for the secondary cyclohexylmethylamine **3d** (LLE = 6.7). However, the highest metabolic stability (phase I metabolism) was determined for the benzylamine **3b** (89% intact after incubation for 90 min).

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1. Introduction

This project deals with target hopping, *i.e.*, a switch from open channel blockers of *N*-methyl-D-aspartate (NMDA) receptors to σ_1 receptor ligands.

The heterotetrameric NMDA receptor belongs to the class of ligand-gated ion channels. The pore of the NMDA receptor contains binding sites for Mg^{2+} ions and phencyclidine (1-(1-phenylcyclohexyl)piperidine, PCP, Fig. 1).[1–3] Addressing the PCP binding site with ligands leads to inhibition of the ion flux through the open channel.[1–3] NMDA receptor inhibitors interacting with the PCP binding site are termed open-channel blockers, as the ion channel has to be opened by the agonists glutamate and glycine before the ligands can enter the channel pore and reach their binding site. Very potent open-channel blockers, such as phencyclidine, MK-801, and dexoxadrol (Fig. 1)[1–3] are associated with desired analgesic and anesthetic activity, but also with strong undesired psychotomimetic and hallucinogenic effects. However, some low affinity open-channel blockers are clinically used as dissociative anesthetic (ketamine) and antitussive (dextromethorphan) as well as for the treatment of Parkinson's (amantadine) and Alzheimer's disease (memantine).[1–3] The structure of the NMDA receptor has been solved by X-ray crystal structure analysis.[4,5]

The σ_1 receptor is a chaperone predominantly located in the membrane of the endoplasmic reticulum controlling Ca^{2+} flux. It is involved in neurodegenerative and neuropsychiatric diseases such as schizophrenia, depression and addiction as well as Alzheimer's diseases. Moreover, inhibition of the σ_1 receptor can be exploited for the treatment of neuropathic pain and cancer.[6–8] In the forced swimming test, σ_1 receptor knock-out mice showed a depression-like behavior.[9,10] In 2016, the σ_1 receptor was crystallized for the first time exhibiting an

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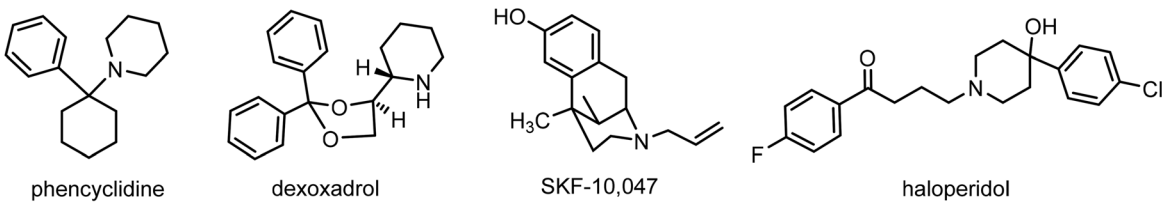


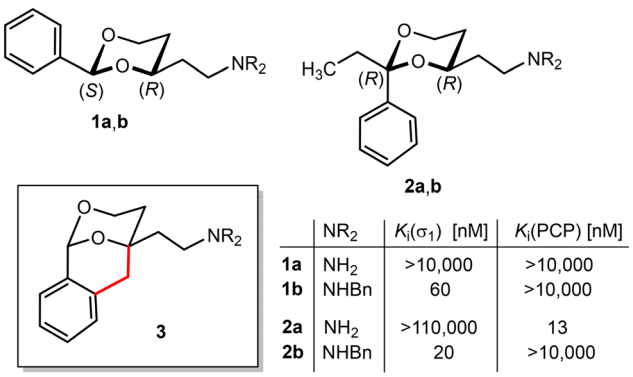
Fig. 1 Prototypical ligands interacting with the PCP binding site of the NMDA receptor and/or with σ receptors.

unexpected structure with only one transmembrane helix.[11] Two years later, structures of the σ_1 receptor in complex with prototypical ligands haloperidol and (+)-pentazocine were reported.[12]

σ receptors and the PCP binding site of NMDA receptors are historically related. After refuting the hypothesis that the σ receptor is an opioid receptor subtype,[13] it was postulated that the PCP binding site and the σ receptor are identical.[14] This hypothesis arose from the observation that prototypical open channel blockers of the NMDA receptor, *e.g.*, phencyclidine, interacted with high affinity with σ receptors as well. Moreover, prototypical σ ligands such as racemic SKF-10 047 (*rac-N*-allylnormetazocine, Fig. 1) could also inhibit the NMDA receptor by interacting with the PCP binding site.[14] However, identification of ligands inhibiting selectively the NMDA receptor by interaction with the PCP binding site without addressing the σ receptor (*e.g.*, dexoxadrol) and ligands interacting selectively with σ_1 receptors but not with the PCP binding site (*e.g.*, haloperidol, Fig. 1) led to a clear differentiation of σ receptors and the PCP binding site. Moreover, the distribution patterns of both proteins in the central nervous system are quite different.[15]

The confusion regarding binding affinity of benzomorphans originated from their absolute configuration: dextrorotatory (*S*,*S*,*S*)-configured *N*-allyl-normetazocine ((+)-SKF-10 047) shows high affinity towards the σ_1 receptor subtype, whereas the levorotatory (*R*,*R*,*R*)-configured enantiomer (−)-SKF-10 047 inhibits the NMDA receptor associated cation channel. Small *N*-substituents (*e.g.*, H or CH_3) of (*R*,*R*,*R*)-(−)-benzomorphans increase the PCP binding affinity and decrease the affinity towards opioid receptors.[16]

Derived from the PCP ligands dexoxadrol and etoxadrol 2,4-disubstituted 1,3-dioxanes **1** and **2** have been developed.[17,18] Depending on the substitution pattern and the orientation of the phenyl moiety in 2-position, **1** and **2** showed high affinity and selectivity either for the σ_1 receptor or the PCP binding site of the NMDA receptor. Whereas the benzaldehyde-derived primary amine **1a** did neither interact with σ_1 receptors nor the PCP binding site, the analogous benzylamine **1b** revealed high σ_1 receptor affinity and selectivity (>170-fold) over the PCP binding site. The propiophenone-derived 1,3-dioxane **2a** with a primary amino moiety showed strong interaction with the PCP binding site and high selectivity over the σ_1 receptor (>750-fold). Introduction of a benzyl moiety at the primary amine of **2a** led to the secondary amine **2b** with high σ_1 receptor affinity and high selectivity over the PCP binding site (>500-fold)[17] (Fig. 2).



	NR_2	$K_i(\sigma_1)$ [nM]	K_i(PCP) [nM]
1a	NH_2	>10,000	>10,000
1b	NHBn	60	>10,000
2a	NH_2	>110,000	13
2b	NHBn	20	>10,000

Fig. 2 Design of conformationally restricted 1,3-dioxanes **3** with the phenyl ring fixed in axial orientation.

Herein, we report the synthesis and biological evaluation of conformationally restricted analogs of **1** and **2**, in which the 2-phenyl-1,3-dioxane system is embedded in a tricyclic benzomorphan scaffold. In the tricyclic acetals **3** the phenyl moiety in "2-position" of the 1,3-dioxane ring is forced to adopt the axial orientation. This axial orientation of the phenyl moiety is not possible for benzaldehyde-derived acetals **1**, since the phenyl moiety always adopts the equatorial orientation due to thermodynamic reasons. On the other hand, the "axial orientation" (related to the 1,3-dioxane ring) of the phenyl ring in tricyclic compounds **3** corresponds to the axial orientation in the propiophenone-derived 1,3-dioxanes **2**. However, the ethyl moiety at the acetalic center of **2** is missing in the tricyclic acetals **3**. The conformationally restricted acetals **3** should provide relationships between structural modifications and affinity towards σ receptors and NMDA receptors. In particular, insights should be gained about the relevance of the orientation of the phenyl moiety and the presence of an additional ethyl substituent in 2-position of the 1,3-dioxane ring. Variation of the substituents at the amnio moiety should further broaden this SAR study.

2. Results and discussion

2.1. Synthesis

The synthesis of the conformationally restricted 1,3-dioxanes **3** started with pentane-1,3,5-triol (**4**).[19] The primary alcoholic groups of **4** were selectively protected by the *tert*-butyldimethylsilyl (TBS) protective group to afford the bis-silyl ether **5**.

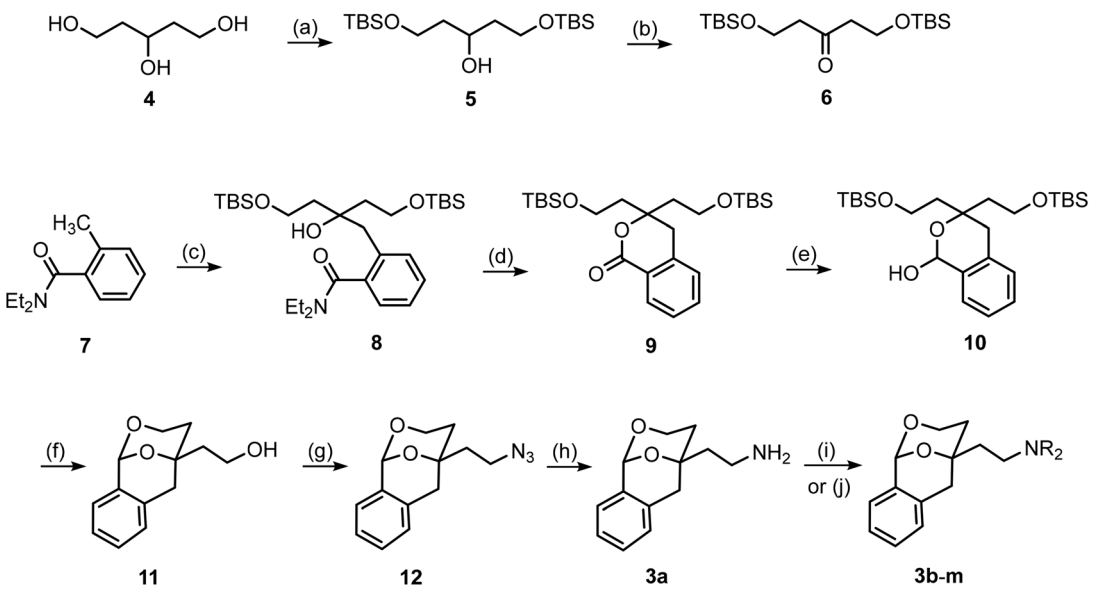
Subsequently, the remaining secondary alcohol **5** was oxidized with Dess Martin Periodinane (DMP)[20] to give the ketone **6** in 97% yield as key intermediate of this synthesis (Scheme 1).

The next step, *i.e.*, the nucleophilic addition of 2-methylbenzamide **7** to the ketone **6** represents the key step of the synthesis. For this purpose, benzamide **7** was deprotonated with *sec*-BuLi at the CH_3 moiety and the resulting methyllithium species reacted with the ketone **6** to provide the tertiary alcohol **8** in 92% yield. Heating of the hydroxy amide **8** without solvent at 186 °C for 16 h led to the δ-lactone **9**, which was reduced with diisobutylaluminum hydride (DIBAH)[21] to provide the cyclic hemi acetal **10** in 94% yield. Treatment of the hemi acetal **10** with diluted HCl led to cleavage of both silyl ethers, but only one primary alcohol could react with the hemi acetal to form the tricyclic acetal **11**. During this reaction step, the symmetry of the molecules was lost leading to chiral compounds (Scheme 1).

After establishment of the tricyclic system **11**, the remaining primary alcohol was converted into various amines **3**. At first, a Mitsunobu reaction with $Zn(N_3)_2{\cdot}2$ pyridine in the presence of PPh_3 and diisopropyl azodicarboxylate (DIAD) transformed the primary alcohol **11** into azide **12**, which was reduced with H_2 and Pd/C to afford the primary amine **3a**. Finally, reductive alkylation of the primary amine **3a** with aldehydes and $NaBH(OAc)_3$[22] provided secondary and tertiary amines **3b–m**. Stoichiometric amounts of aldehyde led to secondary amines (*e.g.;* **3d**, **3f**, **3g**), intermediate amounts of benzaldehyde provided a mixture of secondary and tertiary amines **3b** and **3c**, whereas an excess of aldehyde completely alkylated the primary amine **3a** affording tertiary amines **3e**, **3k** nd **3l**. The piperidine ring of **3m** was established by reductive alkylation of the primary amine **3a** with glutaraldehyde and $NaBH(OAc)_3$.[22] Reductive methylation with formaldehyde and $NaBH(OAc)_3$ converted the secondary amines **3b** and **3d** into tertiary methylamines **3h** and **3j**, respectively.

2.2. Receptor affinity

The affinity of the amines **3a–m** towards the PCP binding site of the NMDA receptor and towards σ_1 and σ_2 receptors was determined in radioligand receptor binding studies. In the PCP assay, pig brain cortex was used as receptor material and [^{3}H](+)-MK-801 as radioligand.[17,23] [^{3}H](+)-pentazocine and [^{3}H]di-*o*-tolylguanidine served as radioligands and guinea pig brain and rat liver as receptor material in the σ_1 and σ_2 receptor assay, respectively.[24,25] The recorded affinities of amines **3**



3	NR_2
b	NHBn
c	NBn_2
d	$NHCH_2C_6H_{11}$
e	$N(CH_2C_6H_{11})_2$
f	$NHCH_2C_6H_4$(4-F)
g	$NHCH_2CH_2CH_2Ph$

3	NR_2	
h	$N(CH_3)Bn$	(k) ← 3b
j	$N(CH_3)CH_2C_6H_{11}$	(k) ← 3d
k	$N(CH_3)_2$	
l	$N(C_4H_9)_2$	
m		

Scheme 1 Synthesis of conformationally restricted 1,3-dioxanes **3** with axially oriented phenyl moiety in "2-position". Reagents and reaction conditions: (a) TBS-Cl, imidazole, DMF, rt, 6 h, 71%. (b) Dess Martin Periodinane (DMP), CH_2Cl_2, rt, 4.5 h, 97%. (c) *sec*-BuLi, THF, −78 °C, 1.5 h; then addition of ketone **6**, −50 °C, 2.5 h, 92%. (d) Neat, 186 °C, 16 h, 82%. (e) DIBAH, CH_2Cl_2, −78 °C, 70 min, 93%. (f) HCl, THF, rt, 16 h, 99%. (g) $Zn(M_3)_2{\cdot}2$ pyridine, PPh_3, DIAD, THF, rt, 19 h, 64%. (h) H_2 (balloon), Pd/C, EtOAc, rt, 16 h, 75%. (i) RCH═O, $NaBH(OAc)_3$, CH_2Cl_2, rt. (j) O═$HCCH_2CH_2CH_2CH$═O, $NaBH(OAc)_3$, CH_2Cl_2, rt, 18 h, 32%. (k) Formalin, $NaBH(OAc)_3$, CH_2Cl_2, rt, 18 h, 97% (**3h**), 87% (**3j**).

are summarized in Table 1 together with the K_i values of some reference compounds.

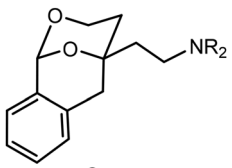
The primary amine **3a** did not show high affinity for the PCP binding site of the NMDA receptor. The structurally related lead compound **2a** exhibited a strong interaction with the PCP binding site of the NMDA receptor (K_i = 13 nM, see Fig. 1). Both compounds **2a** and **3a** are primary amines with an axially oriented phenyl moiety in 2-position of the 1,3-dioxane ring. However, **2a** has an additional ethyl moiety in 2-position of the 1,3-dioxane ring, which is not present in the tricyclic amine **3a**. The missing ethyl moiety or the slightly different orientation of the axially oriented phenyl moiety in 2-postion of the 1,3-dioxnae ring might be responsible for the complete loss of PCP affinity of primary amine **3a**.

Introduction of various substituents at the amino moiety did not lead to PCP affinity of **3b–m**. This observation is in good accordance with literature describing the highest PCP affinity for primary amines for these types of ligands.[17]

In agreement with literature (see Fig. 1), the primary amine **3a** did not bind at σ_1 and σ_2 receptors. However, as shown for the lead compounds **1b** and **2b**, the introduction of a benzyl moiety increased the σ_1 affinity of **3b** (K_i = 69 nM) considerably. A cyclohexylmethyl moiety instead of the benzyl moiety increased the σ_1 affinity to 15 nM (**3d**). A further increase of the σ_1 affinity could be obtained by methylation of the secondary amines **3b** and **3d**: the analogous methylamines **3h** (K_i = 15 nM) and **3j** (K_i = 6.4 nM) revealed the highest σ_1 affinity of this class of compounds. Two large (**3c**, **3e**) or two small substituents (**3k**. **3m**) at the amino moiety did not lead to high σ_1 affinity. A larger alkyl chain between the N-atom and the terminal phenyl moiety reduced the σ_1 affinity of the phenylpropyl derivative **3g** (K_i = 242 nM).

The secondary amines **3b**, **3d**, and **3f** show very similar affinities towards both σ_1 and σ_2 receptors. However, selectivity for the σ_1 receptor was gained by introduction of an additional CH_3 moiety at the amino group. The methylated benzylamine **3h** and the methylated cyclohexylmethylamine **3j** displayed 9-fold selectivity for the σ_1 receptor over the σ_2 subtype.

Table 1 PCP, σ_1 and σ_2 receptor affinities of tricyclic amines **3** and reference compounds



3a-m

Entry	Compd	NR_2	$K_i \pm SEM^{a,b}$ (nM) PCP	σ_1	σ_2
1	**3a**	NH_2	>1000	>1000	>1000
2	**3b**	NHBn	>1000	69 ± 9	60 ± 23
3	**3c**	NBn_2	>1000	>1000	>1000
4	**3d**	$NHCH_2C_6H_{11}$	>1000	15 ± 4	26 ± 16
5	**3e**	$N(CH_2C_6H_{11})_2$	>1000	280	375
6	**3f**	$NHCH_2C_6H_4$(4-F)	>1000	47 ± 29	30 ± 11
7	**3g**	$NHCH_2CH_2CH_2Ph$	>1000	242	62 ± 8
8	**3h**	$N(CH_3)Bn$	>1000	15 ± 3	137
9	**3j**	$N(CH_3)CH_2C_6H_{11}$	>1000	6.4 ± 2.0	55 ± 11
10	**3k**	$N(CH_3)_2$	>1000	>1000	>1000
11	**3l**	$N(C_4H_9)_2$	>1000	3410	298
12	**3m**	$N(CH_2)_5$	>1000	766	381
13	Dexoxadrol		25 ± 4	—	—
14	Phencyclidine		59 ± 12	—	—
15	(+)-Pentazocine		—	5.7 ± 2.2	—
16	Haloperidol		—	6.3 ± 1.6	78 ± 2.3
17	Di-*o*-tolylguanidine		—	89 ± 29	58 ± 18

[a] K_i values represent the mean of at least three independent experiments. [b] For ligands with low affinity, the K_i value was determined only once.

2.3. Physicochemical and pharmacokinetic properties of selected ligands

In order to get an idea about the lipophilicity of the tricyclic compounds, the log $D_{7.4}$ value of selected ligands was determined using the micro-shake flask method.[26,27] In brief, the compounds were distributed between *n*-octanol and MOPS buffer pH 7.4 layers and the amount of the compound in the buffer layer was determined by LC-MS.

The recorded log $D_{7.4}$ values are summarized in Table 2. The benzylamine **3b** and the cyclohexylmethylamine **3d** show the same log $D_{7.4}$ value of 1.1. The additional methyl moiety at the amino group of **3j** increased the log $D_{7.4}$ value by approx. one log unit. The amount of the primary amine **3a** in the aqueous layer was higher than its amount in the *n*-octanol layer leading to a negative log $D_{7.4}$ value of −1.9 (Table 2).

The recorded log $D_{7.4}$ values were used to calculate the ligand-lipophilicity efficiency (LLE), which modulates the biological activity of a ligand by its lipophilicity (LLE = $-\log K_i - \log D_{7.4}$).[28,29] Due to its increased σ_1 affinity, the LLE value of the cyclohexylmethyl derivative **3d** (LLE = 6.7) is higher than the LLE value of the benzyl derivative **3b** (LLE = 6.1). However, the increased σ_1 affinity of the methylated derivative **3j** is compensated by its increased lipophilicity resulting in a reduced LLE value of 6.2. The LLE value for the primary amine **3a** was not calculated, since **3a** did not show any interactions with the σ_1 receptor even at a concentration of 1 μM (Table 2).

The plasma protein binding of the amines **3a**, **3b**, **3d** and **3j** was determined by high performance affinity chromatography (HPAC) using a stationary phase coated with human serum albumin. The retention time correlates with the affinity towards human serum albumin, which represents the main component of human blood.[30,31] The plasma protein binding of the secondary amines **3b** and **3d** and the tertiary amine **3j** is very similar (75–78%). However, the very polar primary amine **3a** exhibited a considerably lower binding to human serum albumin of 42% (Table 2).

In order to investigate the phase I metabolic stability, selected amines were incubated with mouse liver microsomes and NADPH at 37 °C for 90 min. The amount of the residual parent compound was determined by LC-MS.[26,32] The benzylamine **3b** revealed high metabolic stability, since 89% of the parent compound were intact after 90 min. The cyclohexylmethylamines **3d** and **3j** were faster metabolized and only 32% and 45% remained unchanged after 90 min, respectively.

Table 2 Physicochemical and pharmacokinetic properties including ligand-lipophilicity efficiency (LLE) of selected σ_1 ligands

Compd	NR_2	$-\log K_i(\sigma_1)$	$\log D_{7.4}$ ± SD (n = 3)	LLE[a]	Plasma protein binding[b]	Metabolic stability ± SD (n = 3)[c]
3a	NH_2	<6	−1.9[d]		42 ± 0.2	87 ± 4
3b	NHBn	7.2	1.1 ± 0.04	6.1	75 ± 1	89 ± 6
3d	$NHCH_2C_6H_{11}$	7.8	1.1 ± 0.05	6.7	77 ± 1	32 ± 4
3j	$N(CH_3)CH_2C_6H_{11}$	8.2	2.0 ± 0.1	6.2	78 ± 1	45 ± 4
Imipramine[e]						14 ± 1

[a] LLE (ligand-lipophilicity efficiency) = $-\log K_i - \log D_{7.4}$. [b] Interaction with human serum albumin was recorded by HPAC analysis. [c] Amount (in %) of parent compound after incubation with mouse liver microsomes and NADPH for 90 min. [d] Mean of two values. [e] Imipramine was used as reference compound to prove the activity of the microsomes and NADPH in the metabolic experiments.

3. Conclusion

The 1,3-dioxane **2a** bearing an axially oriented phenyl moiety at 2-position and a primary amino moiety at the ethyl substituent in 4-position showed high affinity towards the PCP binding sit of the NMDA receptor (K_i = 13 nM), but no affinity at σ_1 and σ_2 receptors (Fig. 1). Although structurally related to **2a**, the conformationally restricted 1,3-dioxane **3a** with a primary amino moiety at the ethyl substituent did not interact with the PCP binding site. We hypothesize that the missing 2-ethyl moiety of **2a** and/or an unfavorable orientation of the conformationally restricted phenyl moiety are the reason for the reduced PCP affinity of the primary amine **3a**.

Independent of the orientation of the phenyl moiety in 2-position, both 1,3-dioxanes **1b** and **2b** with a benzylamino moiety displayed high σ_1 affinity (Fig. 1). The same effect was observed for the benzylamine **3b** showing also high σ_1 affinity (K_i = 69 nM).

The results obtained for this novel class of σ_1 ligands correlate well with pharmacophore models for σ_1 receptor ligands. According to these models, potent σ_1 ligands should contain a central amino moiety substituted with two lipophilic substituents.[33–35] The introduction of an additional large substituent at the amino group as in **3c** and **3e** led to considerably reduced σ_1 affinity. On the other hand, two small substituents at the amino moiety (*e.g.*, compounds **3k**, **3l**, **3m**) are not sufficient to bind with high affinity at σ_1 receptors. However, a small methyl moiety in addition to the large benzyl or cyclohexylmethyl moiety at the amino group resulted in increased σ_1 affinity of **3h** and **3j**.

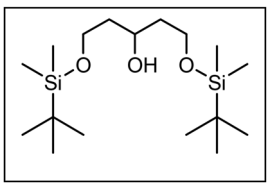
The highest σ_1 affinity was observed for the cyclohexylmethyl substituted amines **3d** (K_i = 15 nM) and **3j** (K_i = 6.4 nM). Due to their low lipophilicity ($\log D_{7.4}$ = 1.1 and 2.0, respectively), both compounds exhibit high LLE values of 6.7 and 6.2, respectively. However, in the presence of mouse liver microsomes and NMDPH (phase I metabolism), both amines **3d** and **3j** were rapidly metabolized. In contrast, the less potent benzylamine **3b** ($K_i(\sigma_1)$ = 69 nM, LLE = 6.1) revealed high metabolic stability as 89% of the parent compound remained unchanged upon incubation with liver microsomes and NADPH over 90 min.

In conclusion, the methylated cyclohexylmethylamine **3j** showed the highest σ_1 affinity (K_i = 6.4 nM) and the highest selectivity over the σ_2 subtype (9-fold). The secondary cyclohexylmethylamine **3d** exhibited the highest LLE value (6.7) and the benzylamine **3b** was the metabolically most stable σ_1 ligand of this series (89% intact after 90 min).

4. Experimental

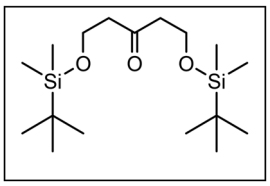
4.1. Synthetic procedures

4.1.1. 1,5-Bis(*tert*-butyldimethylsilyloxy)pentan-3-ol (5).



Pentane-1,3,5-triol[19] (**4**, 3 g, 25 mmol), *tert*-butyldimethylsilyl chloride (7.5 g, 50 mmol) and imidazole (10.2 g, 150 mmol) were dissolved in DMF (30 mL) in a Schlenk flask under N_2 atmosphere. The reaction mixture was stirred at rt for 6 h. After addition of water (50 mL) the organic layer was extracted with ethyl acetate (4 × 50 mL). The organic layer was then washed with brine (100 mL), dried (Na_2SO_4), concentrated *in vacuo* and the residue was purified by fc (∅ = 8 cm, h = 19.5 cm, ethyl acetate : cyclohexane = 0.2 : 9.8, V = 65 mL, R_f = 0.08 (ethyl acetate : cyclohexane = 0.4 : 9.6)). Colorless oil, yield 6.1 g (71%). $C_{17}H_{40}O_3Si_2$ (348.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.07 (s, 12H, 2 × Si(CH_3)$_2$), 0.89 (s, 18H, 2 × SiC(CH_3)$_3$), 1.63–1.75 (m, 4H, CH_2CH_2OSi), 3.65 (d, J = 2.3 Hz, 1H, O*H*), 3.76–3.87 (m, 4H, CH_2OSi), 3.95–4.02 (m, 1H, C*H*). IR: ν [cm^{-1}] = 3524 (b, ν, O–H), 2954 (w, ν, C–H, alkyl). MS (EI): m/z = 349 $[M + H]^+$. Elemental analysis: calcd C 58.56, H 11.56; found C 58.54, H 11.80.

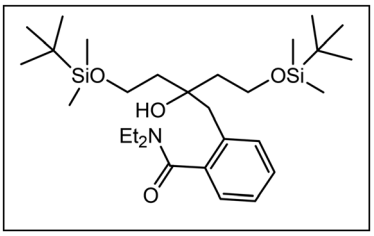
4.1.2. 1,5-Bis(*tert*-butyldimethylsilyloxy)pentan-3-one (6).



Under N_2 atmosphere, a solution of alcohol **5** (2.2 g, 6.4 mmol) in CH_2Cl_2 (90 mL) was added to a solution of Dess Martin Periodinane (3.3 g, 7.7 mmol) in CH_2Cl_2 (75 mL). The

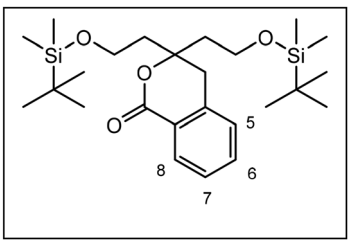
reaction mixture was stirred for 4.5 h at rt. Et_2O (150 mL) and 1 M NaOH (63 mL) were added and the mixture was stirred for another 15 min. The Et_2O layer was separated and washed with NaOH (100 mL) and water (100 mL) followed by extraction of the combined aqueous layers with Et_2O (4 × 200 mL). Finally, the organic layer was dried (Na_2SO_4), the solvent was removed *in vacuo* and the residue was purified by fc (∅ = 6 cm, *h* = 15.5 cm, ethyl acetate : cyclohexane = 0.3 : 9.7, *V* = 30 mL, R_f = 0.17). Colorless oil, yield 2.2 g (97%). $C_{17}H_{38}O_3Si_2$ (346.2). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.05 (s, 12H, 2 × Si(CH_3)$_2$), 0.87 (s, 18H, 2 × SiC(CH_3)$_3$), 2.65 (t, *J* = 6.4 Hz, 4H, CH_2CH_2OSi), 3.88 (t, *J* = 6.4 Hz, 4H, CH_2OSi). IR: ν [cm^{-1}] = 2955, 2857 (w, ν, C–H, alkyl), 1715 (s, ν, C=O). MS (EI): *m*/*z* = 347 $[M + H]^+$, 289 $[M - C(CH_3)_3]^+$. Elemental analysis: calcd C 58.90, H 11.05; found C 59.28, H 11.34.

4.1.3. 2-{4-(*tert*-Butyldimethylsilyloxy)-2-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2-hydroxybutan-1-yl}-*N*,*N*-diethylbenzamide (8).



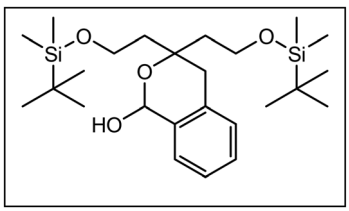
Under N_2 atmosphere diethylamide **7** (368 mg, 1.92 mmol) was dissolved in abs. THF (125 mL) and cooled down to −78 °C. Then, 1.3 M *sec*-butyllithium in cyclohexane/hexane = 92 : 8 (2.0 mL, 2.12 mmol) was added dropwise to the solution and the color changed from colorless to orange. After 1.5 h ketone **6** (1.0 g, 2.9 mmol) dissolved in THF (5 mL) was added using a syringe pump over 10 min. The reaction mixture turned yellow and was allowed to warm to −50 °C during 2.5 h. Water (50 mL) was added at −50 °C and after addition of brine (50 mL), the aqueous layer was extracted with chloroform (4 × 100 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (∅ = 6 cm, *h* = 21 cm, ethyl acetate : cyclohexane = 2 : 8, *V* = 10 mL, R_f = 0.42). Colorless oil, yield 949 mg (92%). $C_{29}H_{55}NO_4Si_2$ (537.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.05 (s, 12H, 2 × Si(CH_3)$_2$), 0.88 (s, 18H, 2 × SiC(CH_3)$_3$), 1.04 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.26 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.56–1.80 (m, 4H, CH_2CH_2OSi), 2.55–2.74 (m, 1H, CH_2OSi), 2.86–3.05 (m, 1H, CH_2OSi), 3.09–3.14 (m, 2H, CH_2CH_3), 3.31–3.51 (m, 1H, CH_2OSi), 3.58–3.75 (m, 1H, CH_2OSi), 3.76–3.92 (m, 4H, CH_2CH_3 and CH_2Ph), 4.79 (s, 1H, O*H*), 7.16 (dd, *J* = 7.6/1.4 Hz, 1H, C$H_{arom.}$), 7.22 (td, *J* = 7.5/1.3 Hz, 1H, C$H_{arom.}$), 7.31 (td, *J* = 7.6/1.6 Hz, 1H, C$H_{arom.}$), 7.53 (dd, *J* = 7.7/0.9 Hz, 1H, C$H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ [ppm] = −5.2 (6C, Si(CH_3)$_3$), 13.0 (1C, CH_2CH_3), 14.1 (1C, CH_2CH_3), 26.1 (6C, SiC(CH_3)$_3$), 39.3 (2C, OCH_2CH_2), 41.6 (1C, OCH_2), 43.0 (1C, OCH_2), 43.3 (1C, CH_2CH_3), 60.1 (1C, CH_2Ph), 60.2 (1C, CH_2CH_3), 73.5 (1C, *C*q), 125.7 (1C, *C*H$_{arom}$), 126.1 (1C, *C*H$_{arom}$), 128.4 (1C, *C*H$_{arom}$), 132.2 (1C, *C*H$_{arom}$), 135.3 (1C, *C*q$_{arom}$), 137.5 (1C, *C*q$_{arom}$), 172.0 (1C, *C*=O). IR: ν [cm^{-1}] = 2951 (s, ν, C–H, alkyl), 1613 (s, ν, C=O), 772 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{29}H_{55}NO_4Si_2H$ [M + H] 538.3742, found 538.3754. HPLC: Compound **8** was not stable during HPLC analysis.

4.1.4. 3,3-Bis-[2-(*tert*-butyldimethylsilyloxy)ethyl]-3,4-dihydro-2-benzopyran-1-one (9).



Diethylamide **8** (1.0 g, 1.93 mmol) was heated in a silicone bath to 186 °C overnight. The residue was purified by fc (∅ = 4 cm, *h* = 17.5 cm, ethyl acetate : cyclohexane = 5 : 95, *V* = 20 mL, R_f = 0.6). Colorless oil, yield 736 mg (82%). $C_{25}H_{44}O_4Si_2$ (464.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.02, 0.03 (2s, 12H, Si(CH_3)$_2$), 0.87 (s, 18H, SiC(CH_3)$_3$), 2.00 (t, *J* = 6.5 Hz, 4H, CH_2CH_2OSi), 3.21 (s, 2H, ArCH_2), 3.79 (td, *J* = 6.4/1.8 Hz, 4H, CH_2OSi), 7.19 (d, *J* = 7.5 Hz, 1H, 5-CH_{arom}), 7.36 (td, *J* = 7.7/1.1 Hz, 1H, 7-CH_{arom}), 7.52 (td, *J* = 7.5/1.4 Hz, 1H, 6-CH_{arom}), 8.07 (dd, *J* = 7.7/1.1 Hz, 1H, 8-CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = −5.3 (2C, Si(CH_3)$_2$), −5.3 (2C, Si(CH_3)$_2$), 18.4 (2C, *C*(CH$_3$)$_3$), 26.1 (6C, SiC(CH_3)$_3$), 36.9 (1C, CH_2Ph), 40.3 (2C, CH_2CH_2OSi), 58.9 (2C, CH_2OSi), 84.0 (1C, *C*-3), 125.2 (1C, *C*H$_{arom}$), 127.5 (1C, *C*H$_{arom}$), 128.3 (1C, *C*H$_{arom}$), 130.0 (1C, *C*H$_{arom}$), 134.0 (1C, *C*q$_{arom}$), 138.5 (1C, *C*q$_{arom}$), 165.1 (1C, *C*=O). IR: ν [cm^{-1}] = 2951 (s, ν, C–H, alkyl), 1720 (s, ν, C=O), 752 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{25}H_{44}O_4Si_2H$ [M + H] 465.2864, found 465.2848, calcd for $C_{25}H_{44}O_4Si_2$ − C(CH$_3$)$_3$ + H [M − C(CH$_3$) + H] 407.2074, found 407.2051. Purity (HPLC): 97.1%, t_R = 28.81 min.

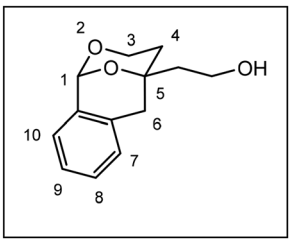
4.1.5. 3,3-Bis[2-(*tert*-butyldimethylsilyloxy)ethyl]-3,4-dihydro-1*H*-2-benzopyran-1-ol (10).



Lactone **9** was dissolved in CH_2Cl_2 (33 mL) and cooled down to −78 °C. 1M DIBAH solution in toluene (1.7 mL, 1.7 mmol) was added and the reaction mixture was stirred at −78 °C for 1 h and 10 min. After addition of saturated $NaHCO_3$ solution (20 mL) at −78 °C and brine (10 mL), the aqueous layer was extracted with chloroform (4 × 25 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (∅ = 4 cm, *h* = 20 cm, ethyl acetate : cyclohexane = 5 : 95, *V* = 20 mL, R_f = 0.33 (ethyl acetate : cyclohexane = 1.9)). Colorless oil, yield 598 mg (93%). $C_{25}H_{46}O_4Si_2$ (466.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.017, 0.021,

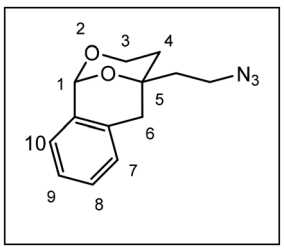
0.027, 0.030 (4s, 12H, Si(CH_3)$_2$), 0.87, 0.88 (2s, 18H, SiC(CH_3)$_3$), 1.80 (t, J = 7.3 Hz, 2H, CH_2CH$_2$OSi), 1.92 (t, J = 6.6 Hz, 1H, CH_2CH$_2$OSi), 1.93 (t, J = 6.9 Hz, 1H, CH_2CH$_2$OSi), 2.80 (d, J = 15.8 Hz, 1H, CH_2Ph), 2.99 (d, J = 15.8 Hz, 1H, CH_2Ph), 3.74 (t, J = 7.0 Hz, 2H, CH_2OSi), 3.76 (t, J = 6.8 Hz, 2H, CH_2OSi), 5.52 (s, 1H, CH), 7.06–7.08 (m, 1H, CH_{arom}), 7.16–7.18 (m, 1H, CH_{arom}), 7.21–7.26 (m, 2H, CH_{arom}). IR: ν [cm^{-1}] = 3406 (b, ν, O–H), 2951 (s, ν, C–H, alkyl), 748 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{25}H_{46}O_4Si_2$ − OH [M − OH] 449.2947, found 449.2950. HPLC: Compound **10** was not stable during HPLC analysis.

4.1.6. 2-(1,5-Epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl) ethan-1-ol (11).



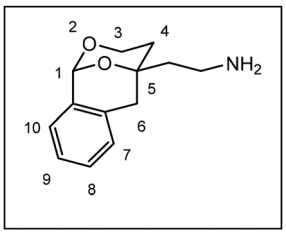
Lactol **10** (1.3 g, 2.8 mmol) was dissolved in abs. THF (104 mL) and acidified with 1M HCl (pH 1, 11 mL). The reaction mixture was stirred overnight at rt. After removing the THF *in vacuo*, brine (25 mL) was added and the aqueous layer was extracted with chloroform (4 × 50 mL). The residue was dried (Na_2SO_4) and purified by fc (⌀ = 8 cm, h = 18 cm, ethyl acetate : cyclohexane = 1 : 1–>6 : 4, V = 65 mL, R_f = 0.28). Colorless oil, yield 613 mg (99%). $C_{13}H_{16}O_3$ (220.1). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.49 (d broad, J = 13.3 Hz, 1H, 4-H$_{eq}$), 1.92 (td, J = 5.7/2.8 Hz, 2H, CH_2CH$_2$OH), 2.30–2.39 (m, 1H, 4-H$_{ax}$), 2.76 (d, J = 17.5 Hz, 1H, CH_2Ph), 3.23 (d, J = 17.5 Hz, 1H, CH_2Ph), 3.66–3.70 (m, 2H, 3-H$_{ax}$ and 3-H$_{eq}$), 3.91 (ddd, J = 6.4/5.3/1.4 Hz, 2H, CH_2OH), 5.94 (s, 1H, 1-H), 7.14 (d, J = 7.6 Hz, 1H, CH_{arom}), 7.17 (dd, J = 7.5/1.5 Hz, 1H, CH_{arom}), 7.24 (t, J = 11.1 Hz, 1H, CH_{arom}), 7.30 (td, J = 7.4/1.6 Hz, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 36.6 (1C, *C*-4), 36.8 (1C, *C*-6), 45.0 (1C, CH_2CH$_2$OH), 57.0 (1C, *C*-3), 58.9 (1C, CH_2OH), 72.8 (1C, *C*-5), 94.2 (1C, *C*-1), 126.6 (1C, CH_{arom}), 126.6 (1C, CH_{arom}), 127.3 (1C, CH_{arom}), 128.7 (1C, CH_{arom}), 131.9 (1C, Cq_{arom}), 135.0 (1C, Cq_{arom}). IR: ν [cm^{-1}] = 3406 (b, ν, O–H), 2943 (s, ν, C–H, alkyl), 764 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{13}H_{16}O_3$H [M + H] 221.1172, found 221.1201. Purity (HPLC): 99.7%, t_R = 13.65 min.

4.1.7. 5-(2-Azidoethyl)-1,5-epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocine (12).



Alcohol **11** (649 mg, 2.94 mmol) was dissolved in dry THF (49 mL). Then Zn(N$_3$)$_2$·2 pyridine (907 mg, 2.94 mmol), PPh$_3$ (1.5 g, 5.9 mmol) and THF (31 mL) were added. DIAD (1.2 mL, 5.9 mmol) was added dropwise and the reaction mixture was stirred at rt for 19 h. After addition of 1 M NaOH (50 mL) and brine (25 mL), the aqueous layer was extracted with ethyl acetate (4 × 50 mL). The organic layer was dried (Na_2SO_4) and after evaporation of the solvent the residue was purified by fc (⌀ = 8 cm, h = 17.5 cm, ethyl acetate : cyclohexane = 4 : 6, V = 65 mL, R_f = 0.74 (cyclohexane : ethyl acetate = 6 : 4)). Colorless oil, yield 702 mg (97%). $C_{13}H_{15}N_3O_2$ (245.1). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.53 (d, J = 13.4 Hz, 1H, 4-H$_{eq}$), 1.94 (td, J = 7.1/0.9 Hz, 2H, CH_2CH$_2$N$_3$), 2.15–2.24 (m, 1H, 4-H$_{ax}$), 2.78 (d, J = 17.4 Hz, 1H, CH_2Ph), 3.12 (d, J = 17.4 Hz, 1H, CH_2Ph), 3.50 (t, J = 7.4 Hz, 2H, CH_2N$_3$), 3.60–3.70 (m, 2H, 3-H$_{ax}$ and 3-H$_{eq}$), 5.93 (s, 1H, 1-H), 7.13 (d, J = 7.4 Hz, 1H, CH_{arom}), 7.17 (dd, J = 7.5/1.3 Hz, 1H, CH_{arom}), 7.24 (t, J = 7.4 Hz, 1H, CH_{arom}), 7.29 (td, J = 7.4/1.6 Hz, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 36.46 (1C, *C*-4), 36.51 (1C, *C*-6), 42.3 (1C, CH_2CH$_2$N$_3$), 46.1 (1C, CH_2N$_3$), 56.9 (1C, *C*-3), 70.5 (1C, *C*-5), 94.4 (1C, *C*-1), 126.7 (2C, CH_{arom}), 127.3 (1C, CH_{arom}), 128.7 (1C, CH_{arom}), 132.0 (1C, Cq_{arom}), 134.7 (1C, Cq_{arom}). IR: ν [cm^{-1}] = 2951 (s, ν, C–H, alkyl), 2091 (s, ν, N═N═N), 1103 (s, δ, C–O), 764 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{13}H_{15}N_3O_2$ − N_2 + H [M − N_2 + H] 218.1181, found 218.1161. Purity (HPLC): 97.3%, t_R = 19.11 min.

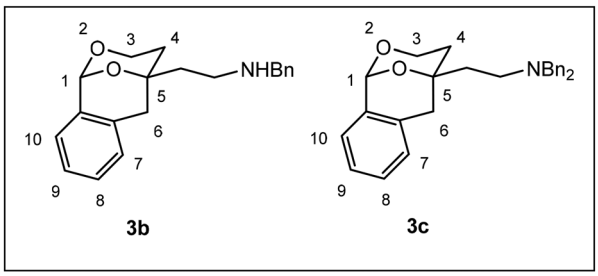
4.1.8. 2-(1,5-Epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl) ethan-1-amine (3a).



Azide **12** (702 mg, 2.86 mmol) was dissolved in ethyl acetate (27 mL) and Pd/C (112 mg, 16%) was added. The mixture was stirred under a H_2 atmosphere (1 atm) overnight. It was filtered through Celite®, the filtrate was concentrated *in vacuo* and the residue was purified by fc (⌀ = 4.5 cm, h = 18 cm, methanol : CH_2Cl_2 : NH_3 = 50 : 50 : 1, V = 20 mL, R_f = 0.28 (ethyl acetate: methanol = 8 : 2)). Colorless oil, yield 472 mg (75%). $C_{13}H_{17}NO_2$ (219.1). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.50 (d, J = 13.3 Hz, 1H, 4-H$_{eq}$), 1.81 (t, J = 7.8 Hz, 2H, CH_2CH$_2$NH$_2$), 2.17–2.25 (m, 1H, 4-H$_{ax}$), 2.74 (d, J = 17.4 Hz, 1H, CH_2Ph), 2.90 (t, J = 7.5 Hz, 2H, CH_2NH$_2$), 3.12 (d, J = 17.4 Hz, 1H, CH_2Ph), 3.59–3.69 (m, 2H, 3-H$_{ax}$ and 3-H$_{eq}$), 5.92 (s, 1H, 1-H), 7.12 (d, J = 7.4 Hz, 1H, CH_{arom}), 7.17 (dd, J = 7.4/1.3 Hz, 1H, CH_{arom}), 7.22 (t, J = 7.3 Hz, 1H, CH_{arom}), 7.28 (td, J = 7.4/1.7 Hz, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 36.6 (1C, *C*-4), 36.7 (1C, *C*-6), 36.8 (1C, CH_2CH$_2$NH$_2$), 47.8 (1C, CH_2NH$_2$), 57.7 (1C, *C*-3), 71.3 (1C, *C*-5), 94.4 (1C, *C*-1), 126.5 (1C, CH_{arom}), 126.6 (1C, CH_{arom}), 127.3 (1C, CH_{arom}), 128.6 (1C, CH_{arom}), 132.3 (1C, Cq_{arom}), 135.2 (1C, Cq_{arom}). IR: ν [cm^{-1}] = 3364 (b, ν, N–H), 2940 (s, ν, C–H, alkyl), 764 (s, δ, 1,2-disubst. aryl). MS (APCI):

calcd for $C_{13}H_{17}NO_2$ + H [M + H] 220.1332, found 220.1312. Purity (HPLC): 99.9%, t_R = 10.18 min.

4.1.9. *N*-Benzyl-2-(1,5-epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)ethan-1-amine (3b) and *N*,*N*-dibenzyl-2-(1,5-epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)ethan-1-amine (3c).



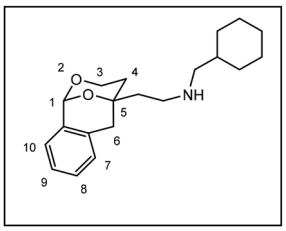
NEt_3 (40 mg, 0.39 mmol) was added to a solution of **3a**-HCl (50 mg, 0.20 mmol) in CH_2Cl_2 (6 mL) to obtain the free primary amine. Then, benzaldehyde (30 μL, 0.29 mmol) and $NaBH(OAc)_3$ (83 mg, 0.39 mmol) were added. The reaction mixture was stirred overnight at rt. After addition of a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), the aqueous layer was extracted with chloroform (4 × 20 mL). Finally, the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (∅ = 1.5 cm, *h* = 13.0 cm, methanol : CH_2Cl_2 : NH_3 = 4 : 96.9 : 0.1, *V* = 5 mL). The fraction with the R_f = 0.55 of the first fc purification was purified by another fc (∅ = 1.5 cm, *h* = 15 cm, cyclohexane : ethyl acetate : *N*,*N*-dimethylethylamine = 94 : 6 : 0.1, *V* = 5 mL).

Compound **3b** (R_f = 0.33 (methanol : ethyl acetate = 2 : 8)): colorless oil, yield 9 mg (16%). $C_{20}H_{23}NO_2$ (309.2). ^{1}H NMR ($CDCl_3$): *δ* [ppm] = 1.49 (d, *J* = 13.3 Hz, 1H, 4-H_{eq}), 1.80 (s broad, 1H, N*H*), 1.88 (t, *J* = 7.9 Hz, 2H, CH_2CH$_2$NH), 2.16–2.24 (m, 1H, 4-H_{ax}), 2.74 (d, *J* = 17.5 Hz, 1H, 6-H), 2.84 (t, *J* = 7.4 Hz, 2H, CH_2NH), 3.12 (d, *J* = 17.5 Hz, 1H, 6-H), 3.60–3.66 (m, 2H, 3-H_{ax} and 3-H_{eq}), 3.82 (s, 2H, CH_2Ph), 5.93 (s, 1H, 1-H), 7.11 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.17 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.21–7.33 (m, 7H, CH_{arom}).

^{13}C NMR ($CDCl_3$): *δ* [ppm] = 36.6 (1C, *C*-4), 36.7 (1C, *C*-6), 43.8 (1C, *C*H$_2$CH$_2$NH), 43.8 (1C, CH_2NH), 54.3 (1C, *C*H$_2$Ph), 57.1 (1C, *C*-3), 71.4 (1C, *C*-5), 94.4 (1C, *C*-1), 126.5 (1C, *C*H$_{arom}$), 126.6 (1C, *C*H$_{arom}$), 127.1 (2C, *C*H$_{arom}$), 127.3 (1C, *C*H$_{arom}$), 128.3 (2C, *C*H$_{arom}$), 128.6 (2C, *C*H$_{arom}$), 132.2 (1C, *C*q$_{arom}$), 135.2 (1C, *Cq*$_{arom}$), 140.2 (1C, *C*q$_{arom}$). IR: *ν* [cm^{-1}] = 3329 (w, *ν*, N–H), 3028 (s, *ν*, C–H, aryl), 2932 (s, *ν*, C–H, alkyl), 1605 (s, *ν*, C═C, aryl), 764 (s, *δ*, 1,2-disubst. aryl). MS (APCI): calcd for $C_{20}H_{23}NO_2H$ [M + H] 310.1802, found 310.1802. Purity (HPLC): 99.5%, t_R = 15.90 min.

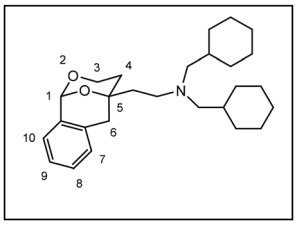
Compound **3c** (R_f = 0.55 (methanol : ethyl acetate = 2 : 8)): colorless oil, yield 35 mg (45%). $C_{27}H_{29}NO_2$ (399.2). ^{1}H NMR ($CDCl_3$): *δ* [ppm] = 1.29 (d, *J* = 13.6 Hz, 1H, 4-H_{eq}), 1.79 (ddd, *J* = 9.1/6.5/2.6 Hz, 2H, CH_2CH$_2$N), 1.94 (td, *J* = 12.4/7.2 Hz, 1H, 4-H_{ax}), 2.47 (d, *J* = 17.2 Hz, 1H, 6-H), 2.49–2.53 (m, 2H, CH_2N), 2.85 (d, *J* = 17.5 Hz, 1H, 6-H), 3.40–3.54 (m, 6H, CH_2Ph and 3-H_{ax} and 3-H_{eq}), 5.77 (s, 1H, 1-H), 6.92 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.03 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.07–7.16 (m, 4H, CH_{arom}), 7.20 (t, *J* = 7.4 Hz, 4H, CH_{arom}), 7.27 (d, *J* = 7.1 Hz, 4H, CH_{arom}). ^{13}C NMR ($CDCl_3$): *δ* [ppm] = 36.3 (1C, *C*-6), 36.6 (1C, *C*-4), 41.1 (1C, *C*H$_2$CH$_2$N), 47.1 (1C, CH_2N), 57.0 (2C, *C*H$_2$Ph), 58.4 (1C, *C*-3), 71.2 (1C, *C*-5), 94.3 (1C, *C*-1), 126.4 (1C, *C*H$_{arom}$), 126.6 (1C, *C*H$_{arom}$), 127.0 (1C, *C*H$_{arom}$), 127.3 (1C, *C*H$_{arom}$), 128.3 (4C, *C*H$_{arom}$), 128.5 (2C, *C*H$_{arom}$), 129.0 (4C, *C*H$_{arom}$), 132.3 (1C, *C*q$_{arom}$), 135.2 (1C, *C*q$_{arom}$), 139.7 (2C, *C*q$_{arom}$). IR: *ν* [cm^{-1}] = 3059 (s, *ν*, C–H, aryl), 2936 (s, *ν*, C–H, alkyl), 1601 (s, *ν*, C═C, aryl), 733 (s, *δ*, 1,2-disubst. aryl). MS (APCI): calcd for $C_{27}H_{29}NO_2H$ [M + H] 400.2271, found 400.2223; calcd for $C_{27}H_{29}NO_2$ − CH_2Ph [M − CH_2Ph] 308.1651, found 308.1649. Purity (HPLC): 98.6%, t_R = 19.61 min.

4.1.10. *N*-(Cyclohexylmethyl)-2-(1,5-epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)ethan-1-amine (3d).



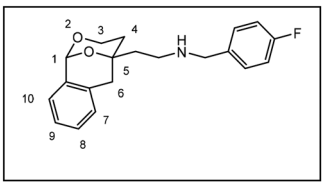
Cyclohexanecarbaldehyde (45 μL, 0.37 mmol) and $NaBH(OAc)_3$ (158 mg, 0.74 mmol) were added to a solution of the primary amine **3a** (82 mg, 0.37 mmol) in CH_2Cl_2 (11.5 mL). The reaction mixture was stirred for 18 h at rt. After addition of a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), the aqueous layer was extracted with chloroform (4 × 20 mL). Finally, the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (∅ = 3 cm, *h* = 1.5 cm, methanol : CH_2Cl_2 : NH_3 = 20 : 80 : 0.1, *V* = 10 mL, R_f = 0.13 (methanol : ethyl acetate = 20 : 80)). Colorless oil, yield 41 mg (35%). $C_{20}H_{29}NO_2$ (315.2). ^{1}H NMR ($CDCl_3$): *δ* [ppm] = 0.85–0.94 (m, 2H, CH(CH_2)$_5$), 1.12–1.28 (m, 3H, CH(CH_2)$_5$), 1.49 (d, *J* = 13.2 Hz, 1H, 4-H_{eq}), 1.64–1.75 (m, 5H, CH(CH_2)$_5$), 1.86 (t, *J* = 7.8 Hz, 2H, CH_2CH$_2$N), 2.17–2.24 (m, 2H, 4-H_{ax}, C*H*(CH$_2$)$_5$), 2.47 (d, *J* = 6.6 Hz, 2H, CH_2CH(CH$_2$)$_5$), 2.74 (d, *J* = 17.5 Hz, 1H, 6-H), 2.79 (t, *J* = 7.4 Hz, 2H, CH_2N), 3.12 (d, *J* = 17.5 Hz, 1H, 6-H), 3.62–3.69 (m, 2H, 3-H_{ax} and 3-H_{eq}), 5.91 (s, 1H, 1-H), 7.11 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.16 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.21 (t, *J* = 7.2 Hz, 1H, CH_{arom}), 7.27 (td, *J* = 7.4/1.6 Hz, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): *δ* [ppm] = 26.1 (2C, CH(*C*H$_2$)$_5$), 26.7 (2C, CH(*C*H$_2$)$_5$), 31.5 (1C, CH(*C*H$_2$)$_5$), 36.6 (1C, *C*-4), 36.7 (1C, *C*-6), 37.8 (1C, *C*H(CH$_2$)$_5$), 43.7 (1C, *C*H$_2$CH$_2$NH), 44.4 (1C, *C*H$_2$NH), 56.9 (1C, *C*H$_2$CH(CH$_2$)$_5$), 57.0 (1C, *C*-3), 71.3 (1C, *C*-5), 94.4 (1C, *C*-1), 126.5 (1C, *C*H$_{arom}$), 126.6 (1C, *C*H$_{arom}$), 127.3 (1C, *C*H$_{arom}$), 128.6 (1C, *C*H$_{arom}$), 132.2 (1C, *C*q$_{arom}$), 135.2 (1C, *Cq*$_{arom}$). IR: *ν* [cm^{-1}] = 2920 (s, *ν*, C–H, alkyl), 1103 (s, *δ*, C–O), 764 (s, *δ*, 1,2-disubst. aryl). MS (APCI): calcd for $C_{20}H_{29}NO_2H$ [M + H] 316.2271, found 316.2234; calcd for $C_{20}H_{29}NO_2$ − Cy [M − Cy] 232.1338, found 232.1306. Purity (HPLC): 95.6%, t_R = 17.15 min.

4.1.11. *N*,*N*-Bis(cyclohexylmethyl)-2-(1,5-epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)ethan-1-amine (3e).



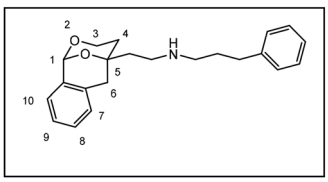
NEt_3 (40 mg, 0.39 mmol) was added to a solution of **3a**·HCl (50 mg, 0.20 mmol) in CH_2Cl_2 (6 mL) to obtain the free primary amine. Then, cyclohexanecarbaldehyde (36 μL, 0.29 mmol) and $NaBH(OAc)_3$ (83 mg, 0.39 mmol) were added. The reaction mixture was stirred for 18 h at rt. After addition of a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), the aqueous layer was extracted with chloroform (4 × 15 mL). Finally, the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (⌀ = 1.5 cm, *h* = 13 cm, ethyl acetate : cyclohexane : *N*,*N*-dimethylethylamine = 6 : 94 : 0.1, *V* = 5 mL, R_f = 0.34 (methanol : ethyl acetate = 20 : 80)). Colorless oil, yield 41 mg (51%). $C_{27}H_{41}NO_2$ (411.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.77–0.85 (m, 5H, CH(CH_2)$_5$), 1.13–2.25 (m, 6H, CH(CH_2)$_5$), 1.38 (s broad, 2H, C*H*(CH_2)$_5$), 1.51 (d, *J* = 13.3 Hz, 1H, 4-H_{eq}), 1.67–1.80 (m, 11H, CH(CH_2)$_5$), 2.10–2.21 (m, 5H, CH_2CH_2N, $CH_2CH(CH_2)_5$, 4-H_{ax}), 2.49 (d, *J* = 7.8 Hz, 2H, CH_2N), 2.73 (d, *J* = 17.5 Hz, 1H, 6-H), 3.16 (d, *J* = 17.5 Hz, 1H, 6-H), 3.62–3.65 (m, 2H, 3-H_{ax} and 3-H_{eq}), 5.93 (s, 1H, 1-H), 7.12 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.17 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.21 (t, *J* = 6.9 Hz, 1H, CH_{arom}), 7.27 (td, *J* = 7.4/1.6 Hz, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 26.4 (4C, CH(CH_2)$_5$), 27.1 (2C, CH(CH_2)$_5$), 32.1 (4C, CH(CH_2)$_5$), 36.4 (2C, *C*H(CH_2)$_5$), 36.6 (1C, *C*-6), 36.8 (1C, *C*-4), 41.4 (1C, CH_2CH_2N), 48.9 (1C, CH_2N), 57.1 (1C, *C*-3), 62.7 (2C, $CH_2CH(CH_2)_5$), 71.2 (1C, *C*-5), 94.4 (1C, *C*-1), 126.4 (1C, CH_{arom}), 126.6 (1C, CH_{arom}), 127.3 (1C, CH_{arom}), 128.5 (1C, CH_{arom}), 132.4 (1C, Cq_{arom}), 135.4 (1C, Cq_{arom}). IR: ν [cm^{-1}] = 2920 (s, ν, C–H, alkyl), 1103 (s, δ, C–O), 764 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{27}H_{41}NO_2H$ [M + H] 412.3210, found 412.3201. Purity (HPLC): 96.1%, t_R = 22.02 min.

4.1.12. 2-(1,5-Epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)-*N*-(4-fluorobenzyl)ethan-1-amine (3f).



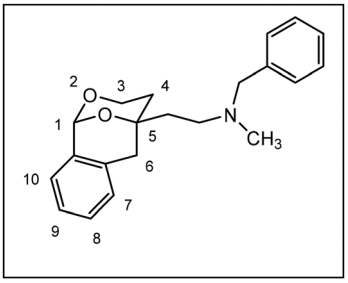
4-Fluorobenzaldehyde (30 μL, 0.28 mmol) and $NaBH(OAc)_3$ (119 mg, 0.56 mmol) were added to a solution of the primary amine **3a** (62 mg, 0.28 mmol) in CH_2Cl_2 (8.5 mL). The reaction mixture was stirred for 18 h at rt. After addition of a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), the aqueous layer was extracted with chloroform (4 × 20 mL). Finally, the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (⌀ = 2 cm, *h* = 20 cm, methanol : CH_2Cl_2 : NH_3 = 5 : 95 : 0.1, *V* = 10 mL, R_f = 0.46 (methanol : ethyl acetate = 20 : 80)). Colorless oil, yield 50 mg (55%). $C_{20}H_{22}FNO_2$ (327.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.46 (d, *J* = 13.2 Hz, 1H, 4-H_{eq}), 1.84 (t, *J* = 8.0 Hz, 2H, CH_2CH_2N), 1.84 (s broad, 1H, N*H*), 2.13–2.22 (m, 1H, 4-H_{ax}), 2.71 (d, *J* = 17.5 Hz, 1H, 6-H), 2.80 (t, *J* = 7.4 Hz, 2H, CH_2N), 3.09 (d, *J* = 17.5 Hz, 1H, 6-H), 3.57–3.66 (m, 2H, 3-H_{ax} and 3-H_{eq}), 3.75 (s, 2H, CH_2Ph), 5.90 (s, 1H, 1-H), 6.96 (t, *J* = 8.8 Hz, 2H, CH_{arom}), 7.09 (d, *J* = 7.5 Hz, 1H, CH_{arom}), 7.14 (dd, *J* = 7.5/1.2 Hz, 1H, CH_{arom}), 7.20 (t, *J* = 7.0 Hz, 1H, CH_{arom}), 7.24–7.28 (m, 3H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 36.7 (1C, *C*-4), 36.7 (1C, *C*-6), 43.8 (2C, CH_2CH_2N), 53.6 (1C, CH_2Ph), 57.1 (1C, *C*-3), 71.4 (1C, *C*-5), 94.4 (1C, *C*-1), 115.3 (1C, CH_{arom}), 115.5 (1C, CH_{arom}), 126.6 (1C, CH_{arom}), 126.7 (1C, CH_{arom}), 127.4 (1C, CH_{arom}), 128.7 (1C, CH_{arom}), 129.8 (1C, CH_{arom}), 129.9 (1C, CH_{arom}), 132.3 (1C, Cq_{arom}), 135.2 (1C, Cq_{arom}), 160.9 (1C, Cq_{arom}), 163.2 (1C, Cq_{arom}). IR: ν [cm^{-1}] = 3333 (b, ν, N–H), 2932 (s, ν, C–H, alkyl), 1601 (s, ν, C═C, aryl), 1099 (s, δ, C–O), 764 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{20}H_{22}FNO_2H$ [M + H] 328.1707, found 328.1731. Purity (HPLC): 99.3%, t_R = 16.25 min.

4.1.13. 2-(1,5-Epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)-*N*-(3-phenylpropyl)ethan-1-amine (3g).



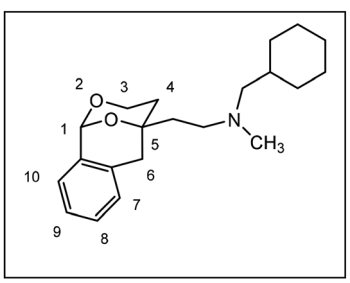
3-Phenylpropionaldehyde (37 μL, 0.28 mmol) and $NaBH(OAc)_3$ (119 mg, 0.56 mmol) were added to a solution of the primary amine **3a** (62 mg, 0.28 mmol) in CH_2Cl_2 (8.5 mL). The reaction mixture was stirred for 18 h at rt. After addition of a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), the aqueous layer was extracted with chloroform (4 × 20 mL). Finally, the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (⌀ = 2 cm, *h* = 20 cm, methanol : CH_2Cl_2 : NH_3 = 5 : 95 : 0.1–>10 : 90 : 0.1, *V* = 10 mL, R_f = 0.19 (methanol : ethyl acetate = 20 : 80)). Colorless oil, yield 44 mg (46%). $C_{22}H_{27}NO_2$ (337.5). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.50 (d, *J* = 13.4 Hz, 1H, 4-H_{eq}), 2.02–2.10 (m, 4H, CH_2CH_2N and CH_2CH_2Ph), 2.20–2.28 (m, 1H, 4-H_{ax}), 2.74 (t, *J* = 8.0 Hz, 2H, $CH_2CH_2CH_2$Ph), 2.78 (d, *J* = 17.7 Hz, 1H, 6-H), 2.88 (t, *J* = 7.2 Hz, 2H, $NCH_2CH_2CH_2$Ph), 3.03 (t, *J* = 7.5 Hz, 2H, CH_2N), 3.17 (d, *J* = 17.5 Hz, 1H, 6-H), 3.64–3.70 (m, 2H, 3-H_{ax} and 3-H_{eq}), 4.64 (s broad, 1H, N*H*), 5.97 (s, 1H, 1-H), 7.16–7.37 (m, 9H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 29.9 (1C, CH_2CH_2Ph), 33.3 (1C, CH_2Ph), 36.4 (1C, *C*-4), 36.5 (1C, *C*-6), 41.5 (1C, CH_2CH_2N), 43.8 (1C, CH_2N), 48.8 (1C, CH_2N), 56.9 (1C, *C*-3), 71.0 (1C, *C*-5), 94.3 (1C, *C*-1), 126.2 (1C, CH_{arom}), 126.6 (1C, CH_{arom}), 126.6 (1C, CH_{arom}), 127.3 (1C, CH_{arom}), 128.5 (2C, CH_{arom}), 128.6 (2C, CH_{arom}), 128.7 (1C, CH_{arom}), 131.9 (1C, Cq_{arom}), 134.8 (1C, Cq_{arom}), 141.2 (1C, Cq_{arom}). IR: ν [cm^{-1}] = 3329 (s, ν, N–H), 2932 (s, ν, C–H, alkyl), 1605 (s, ν, C═C, aryl), 1099 (s, δ, C–O), 737 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{22}H_{27}NO_2H$ [M + H] 338.2115, found 338.2127; calcd for $C_{22}H_{27}NO_2$ − $CH_2CH_2CH_2Ph$ [M − $CH_2CH_2CH_2Ph$] 218.1181, found 218.1178. Purity (HPLC): 98.2%, t_R = 17.69 min.

4.1.14. *N*-Benzyl-2-(1,5-epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)-*N*-methylethan-1-amine (3h).



Formalin solution (37%, 114 μL, 4.10 mmol) and $NaBH(OAc)_3$ (130 mg, 0.62 mmol) were added to a solution of the benzylamine **3b** (63 mg, 0.21 mmol) in CH_2Cl_2 (7 mL). The reaction mixture was stirred for 18 h at rt. After addition of a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), the aqueous layer was extracted with chloroform (4 × 20 mL). Finally, the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (∅ = 1.5 cm, *h* = 15 cm, methanol : CH_2Cl_2 : NH_3 = 5 : 95 : 0.1, *V* = 10 mL, R_f = 0.62 (methanol : ethyl acetate = 3 : 7)). Colorless oil, yield 64 mg (97%). $C_{21}H_{25}NO_2$ (323.2). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.52 (d, *J* = 13.3 Hz, 1H, 4-H_{eq}), 1.89 (dd, *J* = 8.9/6.6 Hz, 2H, CH_2CH$_2$N), 2.13–2.19 (m, 1H, 4-H_{ax}), 2.23 (s, 3H, CH_3), 2.58 (td, *J* = 7.0/3.0 Hz, 2H, CH_2N), 2.73 (d, *J* = 17.5 Hz, 1H, 6-H), 3.10 (d, *J* = 17.5 Hz, 1H, 6-H), 3.52 (s, 2H, CH_2*Ph*), 3.57–3.65 (m, 2H, 3-H_{ax} and 3-H_{eq}), 5.93 (s, 1H, 1-H), 7.10 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.17 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.20–7.36 (m, 7H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 36.6 (1C, *C*-4), 36.7 (1C, *C*-6), 41.6 (1C, CH_2CH_2N), 42.4 (1C, NCH_3), 51.3 (1C, CH_2N), 57.1 (1C, *C*-3), 62.5 (1C, CH_2Ph), 71.2 (1C, *C*-5), 94.4 (1C, *C*-1), 126.5 (1C, CH_{arom}), 126.6 (1C, CH_{arom}), 127.1 (1C, CH_{arom}), 127.3 (1C, CH_{arom}), 128.4 (2C, CH_{arom}), 128.5 (1C, CH_{arom}), 129.2 (2C, CH_{arom}), 132.3 (1C, Cq_{arom}), 135.3 (1C, Cq_{arom}), 139.1 (1C, Cq_{arom}). IR: ν [cm^{-1}] = 3024 (s, ν, C–H, aryl), 2951 (s, ν, C–H, alkyl), 1604 (s, ν, C=C, aryl), 1134 (s, δ, C–O), 764 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{21}H_{25}NO_2H$ [M + H] 324.1958, found 324.1938; calcd for $C_{21}H_{25}NO_2$ − Bn [M − Bn] 232.1338, found 323.1306; calcd for $C_{21}H_{25}NO_2$ − $CH_2CH_2N(CH_3)$(Bn) [M − $CH_2CH_2N(CH_3)$(Bn)] 175.0759, found 175.0753. Purity (HPLC): 99.5%, t_R = 16.50 min.

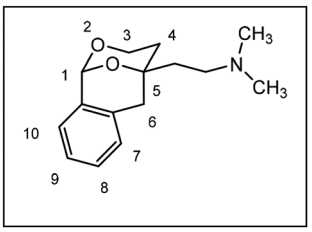
4.1.15. *N*-(Cyclohexylmethyl)-2-(1,5-epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)-*N*-methylethan-1-amine (3j).



Formalin solution (37%, 52 μL, 1.88 mmol) and $NaBH(OAc)_3$ (60 mg, 0.28 mmol) were added to a solution of the cyclohexylmethylamine **3d** (30 mg, 0.09 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 18 h at rt. After addition of a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), the aqueous layer was extracted with chloroform (4 × 20 mL). Finally, the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (∅ = 1.5 cm, *h* = 17 cm, methanol : CH_2Cl_2 : NH_3 = 5 : 95 : 0.1, *V* = 10 mL, R_f = 0.25 (methanol : ethyl acetate = 20 : 80)). Colorless oil, yield 27 mg (87%). $C_{21}H_{31}NO_2$ (329.2). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.86–0.90 (m, 2H, CH(CH_2)$_5$), 1.10–1.25 (m, 3H, CH(CH_2)$_5$), 1.45–1.50 (m, 1H, CH(CH$_2$)$_5$), 1.54 (d, *J* = 8.0 Hz, 1H, 4-H_{eq}), 1.64–1.72 (m, 3H, CH(CH_2)$_5$), 1.75–1.79 (m, 2H, CH(CH_2)$_5$), 1.82–1.86 (m, 2H, CH_2CH$_2$N), 2.14–2.22 (m, 3H, CH_2CH(CH$_2$)$_5$ and 4-H_{ax}), 2.25 (s, 3H, CH_3), 2.52–2.55 (m, 2H, CH_2N), 2.76 (d, *J* = 17.5 Hz, 1H, 6-H), 3.14 (d, *J* = 17.5 Hz, 1H, 6-H), 3.59–3.68 (m, 2H, 3-H_{ax} and 3-H_{eq}), 5.92 (s, 1H, 1-H), 7.12 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.16 (d, *J* = 7.4 Hz, 1H, CH_{arom}), 7.22 (t, *J* = 7.2 Hz, 1H, CH_{arom}), 7.27 (td, *J* = 7.3/1.6 Hz, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 26.2 (2C, CH(*C*H$_2$)$_5$), 26.9 (2C, CH(*C*H$_2$)$_5$), 32.0 (1C, CH(*C*H$_2$)$_5$), 35.8 (1C, *C*H(CH$_2$)$_5$), 36.6 (1C, *C*-6), 36.7 (1C, *C*-4), 41.0 (1C, *C*H$_2$CH$_2$N), 43.1 (1C, *C*H$_2$N), 52.2 (1C, N*C*H$_3$), 57.1 (1C, *C*-3), 65.1 (1C, *C*H$_2$CH(CH$_2$)$_5$), 71.2 (1C, *C*-5), 94.4 (1C, *C*-1), 126.5 (1C, *C*H$_{arom}$), 126.6 (1C, *C*H$_{arom}$), 127.3 (1C, *C*H$_{arom}$), 128.5 (1C, *C*H$_{arom}$), 132.3 (1C, *C*q$_{arom}$), 135.3 (1C, *C*q$_{arom}$).

IR: ν [cm^{-1}] = 2920 (s, ν, C–H, alkyl), 1103 (s, δ, C–O), 764 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{21}H_{31}NO_2H$ [M + H] 330.2540, found 330.2504; calcd for $C_{21}H_{31}NO_2$ − CH_2Cy [M − CH_2Cy] 232.1338, found 232.1391. Purity (HPLC): 99.2%, t_R = 17.98 min.

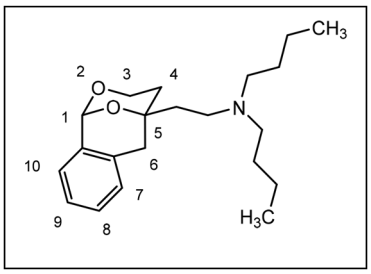
4.1.16. 2-(1,5-Epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)-*N*,*N*-dimethylethan-1-amine (3k).



NEt_3 (100 μL, 145 mg, 0.72 mmol) was added to a suspension of **3a**-HCl (62 mg, 0.24 mmol) in CH_2Cl_2 (7 mL) to obtain the free primary amine **3a**. Then, formalin solution (37%, 133 μL, 4.83 mmol) and $NaBH(OAc)_3$ (154 mg, 0.72 mmol) were added. The reaction mixture was stirred overnight at rt. Saturated $NaHCO_3$ solution (10 mL) and brine (10 mL) were added and the aqueous layer was extracted with chloroform (4 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (∅ = 2 cm, *h* = 15.5 cm, methanol : CH_2Cl_2 : NH_3 = 10 : 90 : 1, *V* = 10 mL, R_f = 0.13 (methanol : ethyl acetate = 2 : 8)). Yellow oil, yield 30 mg (50%). $C_{15}H_{21}NO_2$ (247.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.53 (d, *J* = 8.0 Hz, 1H, 4-H_{eq}), 1.81–1.85 (m, 2H, CH_2CH$_2$N), 2.14–2.22 (m, 1H, 4-H_{ax}), 2.27 (m, 6H, N(CH_3)$_2$), 2.46 (t, *J* = 7.5 Hz, 2H, CH_2N), 2.76 (d, *J* = 17.4 Hz, 1H, 6-H), 3.11 (d, *J* = 17.5 Hz, 1H, 6-H), 3.58–3.65 (m, 2H, 3-H_{ax} and

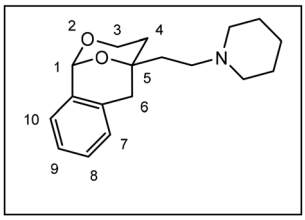
3-H$_{eq}$), 5.92 (s, 1H, 1-H), 7.11 (d, J = 7.4 Hz, 1H, CH_{arom}), 7.16 (dd, J = 7.5/1.4 Hz, 1H, CH_{arom}), 7.21 (t, J = 7.1 Hz, 1H, CH_{arom}), 7.27 (td, J = 7.4/1.6 Hz, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 36.6 (1C, *C*-6), 36.6 (1C, *C*-4), 41.8 (1C, CH_2CH_2N), 45.6 (2C, N(CH_3)$_2$), 53.5 (1C, CH_2N), 57.0 (1C, *C*-3), 71.0 (1C, *C*-5), 94.4 (1C, *C*-1), 126.5 (1C, CH_{arom}), 126.6 (1C, CH_{arom}), 127.3 (1C, CH_{arom}), 128.6 (1C, CH_{arom}), 132.3 (1C, Cq_{arom}), 135.1 (1C, Cq_{arom}). IR: ν [cm^{-1}] = 2947 (s, ν, C–H, alkyl), 1103 (s, δ, C–O), 764 (s, δ, 1,2-disubst. aryl). MS (APCI): calcd for $C_{15}H_{21}NO_2$ + H [M + H] 248.1645, found 248.1666. Purity (HPLC): 99.0%, t_R = 12.09 min.

4.1.17. *N*,*N*-Dibutyl-2-(1,5-epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)ethan-1-amine (3l).



Butyraldehyde (33 µL, 0.36 mmol) and NaBH(OAc)$_3$ (154 mg, 0.73 mmol) were added to a solution of the primary amine **3a** (80 mg, 0.36 mmol) in CH_2Cl_2 (11 mL). The reaction mixture was stirred for 18 h at rt. After addition of a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), the aqueous layer was extracted with $CHCl_3$ (4 × 10 mL). Finally, the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (∅ = 2 cm, h = 17 cm, methanol : CH_2Cl_2 : NH_3 = 10 : 90 : 0.1, V = 10 mL, R_f = 0.43 (methanol : ethyl acetate = 20 : 80)). Colorless oil, yield 8 mg (7%). $C_{21}H_{33}NO_2$ (331.5). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.94 (t, J = 7.3 Hz, 6H, $NCH_2CH_2CH_2CH_3$), 1.29–1.39 (m, 4H, $NCH_2CH_2CH_2CH_3$), 1.53–1.60 (m, 5H, $NCH_2CH_2CH_2CH_3$, 4-H$_{eq}$), 1.94–1.97 (m, 2H, CH_2CH_2N), 2.13–2.22 (m, 1H, 4-H$_{ax}$), 2.59–2.74 (m, 4H, $NCH_2CH_2CH_2CH_3$), 2.79 (d, J = 17.7 Hz, 1H, 6-H), 2.81–2.94 (m, 2H, CH_2N), 3.13 (d, J = 17.7 Hz, 1H, 6-H), 3.63–3.66 (m, 2H, 3-H$_{ax}$ and 3-H$_{eq}$), 5.91 (s, 1H, 1-*H*), 7.13 (d, J = 7.5 Hz, 1H, CH_{arom}), 7.17 (dd, J = 7.4/1.1 Hz, 1H, CH_{arom}), 7.23 (t, J = 7.2 Hz, 1H, CH_{arom}), 7.29 (td, J = 7.5/1.6 Hz, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 14.0 (2C, $NCH_2CH_2CH_2CH_3$), 20.7 (2C, $NCH_2CH_2CH_2CH_3$), 27.6 (2C, $NCH_2CH_2CH_2CH_3$), 36.4 (1C, *C*-6), 36.7 (1C, *C*-4), 40.0 (1C, CH_2CH_2N), 47.8 (1C, CH_2N), 53.3 (2C, $NCH_2CH_2CH_2CH_3$), 57.0 (1C, *C*-3), 70.9 (1C, *C*-5), 94.4 (1C, *C*-1), 126.60 (1C, CH_{arom}), 126.63 (1C, CH_{arom}), 127.4 (1C, CH_{arom}), 128.7 (1C, CH_{arom}), 132.1 (1C, Cq_{arom}), 134.9 (1C, Cq_{arom}). IR: ν [cm^{-1}] = 2955 (s, C–H), 1609 (s, C–C$_{arom}$), 1103 (s, C–O), 764 (s, 1,2-disubst. benzene). MS (APCI): calcd for $C_{21}H_{33}NO_2H$ [M + H] 332.2584, found 332.2598; calcd for $C_{21}H_{33}NO_2$ − butyl [M − butyl] 274.1807, found 274.1806. Purity (HPLC): 96.3%, t_R = 18.18 min.

4.1.18. 1-[2-(1,5-Epoxy-3,4,5,6-tetrahydro-1*H*-2-benzoxocin-5-yl)ethyl]piperidine (3m).



NEt$_3$ (90 µL, 0.65 mmol) was added to a solution of **3a**-HCl (83 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) to obtain the free primary amine **3a**. Then, glutaraldehyde (31 µL, 0.33 mmol) and NaBH(OAc)$_3$ (138 mg, 0.65 mmol) were added. The reaction mixture was stirred for 18 h at rt. After addition of a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), the aqueous layer was extracted with $CHCl_3$ (4 × 10 mL). Finally, the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by fc (∅ = 2 cm, h = 18 cm, methanol : CH_2Cl_2 : NH_3 = 10 : 90 : 0.1, V = 10 mL, R_f = 0.17 (methanol : ethyl acetate = 20 : 80)). Colorless oil, yield 30 mg (32%). $C_{18}H_{25}NO_2$ (287.2). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.52–1.56 (m, 3H, 4-H$_{eq}$, 4-CH_2 pip), 1.77–1.85 (m, 4H, 3-CH_2, 5-CH_2 pip), 2.05–2.21 (m, 3H, 4-H$_{ax}$, CH_2CH_2N), 2.62–2.86 (m, 6H, CH_2N, 2-CH_2, 6-CH_2 pip), 2.79 (d, J = 17.8 Hz, 1H, 6-H), 3.13 (d, J = 17.8 Hz, 1H, 6-H), 3.62–3.65 (m, 2H, 3-H$_{ax}$ and 3-H$_{eq}$), 5.89 (s, 1H, 1-H), 7.11–7.16 (m, 2H, CH_{arom}), 7.21 (t, J = 7.1 Hz, 1H, CH_{arom}), 7.28 (td, J = 7.4/1.6 Hz, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ [ppm] = 23.4 (1C, *C*-4 pip), 24.4 (2C, *C*-3, *C*-5 pip), 36.3 (1C, *C*-6), 36.7 (1C, *C*-4), 38.7 (1C, CH_2CH_2N), 52.8 (1C, CH_2N), 54.3 (2C, *C*-2, *C*-6 pip), 56.9 (1C, *C*-3), 70.7 (1C, *C*-5), 94.4 (1C, *C*-1), 126.6 (2C, CH_{arom}), 127.4 (1C, CH_{arom}), 128.7 (1C, CH_{arom}), 132.0 (1C, Cq_{arom}), 134.8 (1C, Cq_{arom}). IR: ν [cm^{-1}] = 2932 (s, C–H), 1099 (s, C–O), 764 (s, 1,2-disubst. benzene). MS (APCI): calcd for $C_{18}H_{25}NO_2H$ [M + H] 288.1958, found 288.1981. Purity (HPLC): 97.4%, t_R = 13.89 min.

4.2. Receptor binding studies

4.2.1. σ_1 receptor assay.[24,25] The assay was performed with the radioligand [^{3}H]-(+)-pentazocine (22.0 Ci mmol^{-1}; Perkin Elmer). Guinea pig brains were commercially available (Envigo, Horst, Netherlands). The thawed membrane preparation of guinea pig brain (about 100 µg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-pentazocine, and TRIS buffer (50 mM, pH 7.4) at 37 °C. The non-specific binding was determined with 10 µM unlabeled (+)-pentazocine.

4.2.2. Further assays to record receptor affinity. The assays to determine the affinity towards σ_2 receptors,[24,25] and towards the PCP binding site of NMDA receptors,[17,23] were conducted as reported in literature. Details of the receptor binding studies are given in the SI.

4.3. Determination of log $D_{7.4}$ values, plasma protein binding and metabolic stability *in vitro*

log $D_{7.4}$ values were recorded using the micro shake flask method reported in ref. 26 and 27. Plasma protein binding

was recorded by HPAC.[30,31] Metabolic stability was determined by incubation with mouse liver microsomes.[26,32] Details are given in the SI.

Conflicts of interest

The authors declare no conflict of interest.

Abbreviations

DIAD	Diisopropyl azodicarboxylate
DIBAH	Diisobutylaluminum hydride
DMP	Dess-Martin-Periodinane
HPAC	High performance affinity chromatography
LLE	Ligand-lipophilicity efficiency
LC-MS	Liquid chromatography combined with mass spectrometry
MOPS	3-Morpholinopropanesulfonic acid
NADPH	Nicotinamide adenine dinucleotide phosphate
NMDA	*N*-Methyl-D-aspartate
NMR	Nuclear magnetic resonance
PCP	1-(1-Phenylcyclohexyl)piperidine (phencyclidine)
SEM	Standard error of the mean
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran

Data availability

All data will be made available on request to the corresponding author of this manuscript.

Supplementary information (SI): general synthetic methods, the method to determine the purity of the compounds, details of the receptor binding studies including the assays for σ_1 and σ_2 receptor affinity as well as the assay to determine the affinity towards the PCP binding site of the NMDA receptor. Experimental details to determine $\log D_{7.4}$ values, plasma protein binding and metabolic stability are given. Moreover, ^{1}H and ^{13}C NMR spectra as well as HPLC traces for all test compounds. See DOI: https://doi.org/10.1039/d6ob00129g.

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