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Structure–affinity relationship studies of non-competitive NMDA receptor antagonists derived from dexoxadrol and etoxadrol

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Dedicated to Prof. Dr. h.c. F. Eiden on the occasion of his 80th birthday.

Abstract—The synthesis and NMDA receptor affinity of ring and side-chain homologues of etoxadrol and dexoxadrol are described. For the regioselective synthesis of etoxadrol homologues, the regioisomeric 4-azidobutanediols (±)-**9** and (±)-**14** were employed. A synthesis of the enantiomerically pure azidobutanediols (*S*)-, (*R*)-**9** and (*S*)-, (*R*)-**14** was developed and the homochiral building blocks were used for the synthesis of enantiomerically pure etoxadrol and dexoxadrol homologues. The affinity of the racemic and enantiomerically pure primary amines toward the phencyclidine binding site of the NMDA receptor was investigated in receptor binding studies with tritium labeled [^{3}H]-(+)-MK-801 as radioligand. Benzaldehyde derivatives (±)-**12a**, (±)-**13a**, and (±)-**16a** bearing a proton at the acetalic position do not interact significantly with the NMDA receptor. An enantioselective NMDA receptor binding was observed for the *trans*-configured 2-(2-ethyl-2-phenyl-1,3-dioxolan-4-yl)ethanamine **13b**, the (2-ethyl-2-phenyl-1,3-dioxan-4-yl)methanamine **16b**, and the (2,2-diphenyl-1,3-dioxan-4-yl)methanamine **16c**. The NMDA receptor affinity of these compounds resides almost exclusively in the (*S*)-configured enantiomers (2*S*,4*S*)-**13b**, (2*S*,4*S*)-**16b**, and (4*S*)-**16c**. The lowest K_i-value in this series was found for the (2*S*,4*S*)-configured 1,3-dioxolane (2*S*,4*S*)-**13b** (K_i = 69 nM), which is in the range of the K_i-value of the lead compounds etoxadrol and dexoxadrol, indicating that the 2-aminoethyl and the piperidin-2-yl substituents lead to similar NMDA receptor interactions.

1. Introduction

The physiological activity of the excitatory amino acid neurotransmitter (*S*)-glutamate is communicated by interaction with ionotropic (NMDA, AMPA, and kainate) and metabotropic receptors (mGluR1–mGluR8).[1] Among these receptors, the NMDA receptor, which is selectively activated by *N*-methyl-D-aspartate (NMDA), is best characterized. The NMDA receptor is highly sensitive to Mg^{2+}-ions, which have been shown to block the ion channel of the NMDA receptor in a voltage-dependent manner.[2,3]

Cloning of the subunits of the ionotropic glutamate receptors resulted in six different NMDA receptor subunits, which are termed NR1, NR2A-D, and NR3A. Additionally, several splice variants have been identified. Whether a functional NMDA receptor consists of four or five subunits still remains to be elucidated. Although the precise subunit composition of the NMDA receptor complex is still unclear, it is well established that a functional ion channel is formed by a heteromeric arrangement of at least one NR1 subunit and one NR2 subunit.[1,4,5]

The physiological activation of the NMDA receptor is important for the development of neurons and thus associated with processes, such as learning and memory. However, an overactivation of the NMDA receptor leads to an increased influx of Ca^{2+}-ions into neurons, resulting in damage of the neuronal cells (excitotoxicity). Therefore, compounds blocking the excessive influx of Ca^{2+}-ions into neurons are of major interest as neuroprotective agents, which may be used for the therapy of cerebral ischemia (stroke), epilepsy, and trauma (brain injury). Moreover, permanent increased activation of NMDA receptors has been discussed to be involved in the development of chronic neurodegenerative disorders,

Keywords: Non-competitive NMDA receptor antagonists; Enantiomerically pure azidobutanediols; 1,3-Dioxolanes; 1,3-Dioxanes; Stereoselective receptor binding.
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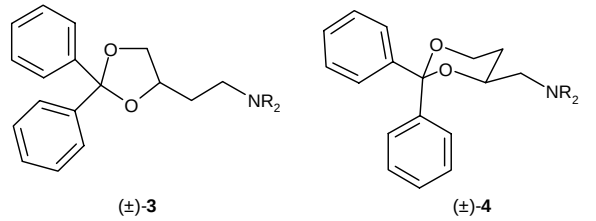
for example, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and alcohol dependency. Altogether, the NMDA receptor represents an interesting target for the development of novel drugs for the therapy of neurological disorders.[1,6]

The opening of the NMDA receptor-associated cation channel is controlled by various ligands interacting with different binding sites at the receptor. The receptor comprises binding sites for glutamate, glycine, polyamines, Zn^{2+}, Mg^{2+}, H^+, and phencyclidine (PCP).[3] Our interest has been focused on the PCP binding site that is located within the cation channel. Compounds interacting with the PCP binding site work as non-competitive NMDA receptor antagonists by blocking the cation channel and inhibiting the influx of Ca^{2+}-ions.

In 1966, the 1,3-dioxolane derivative **1** (dexoxadrol, Fig. 1) was synthesized and pharmacologically evaluated as a local anesthetic and general anesthetic drug.[7,8] During clinical evaluation, it became obvious that non-tolerable side effects (retrograde amnesia, psychotomimetic effects) are associated with the application of dexoxadrol. These observations have led to termination of clinical development. After the 'PCP receptor' has been postulated as a target system for phencyclidine and related compounds, it was shown that dexoxadrol binds with high affinity toward this receptor. Later on, it became clear that the PCP receptor is not a unique receptor but a binding site within the NMDA receptor-associated ion channel.[9]

There are only few studies concerning the relationship between the structure of dexoxadrol analogues and their NMDA receptor affinity.[9,10] Etoxadrol (**2**, Fig. 1) represents an analogue with a similar NMDA receptor affinity.[11] The last detailed structure–affinity relationship study with dexoxadrol and its analogues has been described by Thurkauf et al. in 1992.[9] This is surprising since the lead structures dexoxadrol and etoxadrol represent chemically very interesting compounds with two or three stereogenic centers and two heterocyclic systems (1,3-dioxolane, piperidine) allowing numerous structural modifications.

Recently, we have described a structure NMDA receptor affinity study of novel dexoxadrol homologues (±)-**3** and (±)-**4** with various amino substituents NR_2 (Fig. 2). In both series (±)-**3** and (±)-**4**, the benzophenone acetal substructure was conserved and the piperidine ring was replaced by an amino moiety. Whereas in compound (±)-**3**, the distance between the basic amino group and the 1,3-dioxolane ring was extended by one carbon atom (side-chain homologue of dexoxadrol), in compound (±)-**4** the oxygen heterocycle was extended to a six-membered 1,3-dioxane (ring homologue of dexoxadrol). It was found that in both series of homologues the primary amines ($NR_2 = NH_2$) possess the highest affinity toward the PCP binding site of the NMDA receptor. Introduction of a secondary or a tertiary amino substituent into (±)-**3** and (±)-**4** led to a decreased receptor affinity of the ligands.[12]



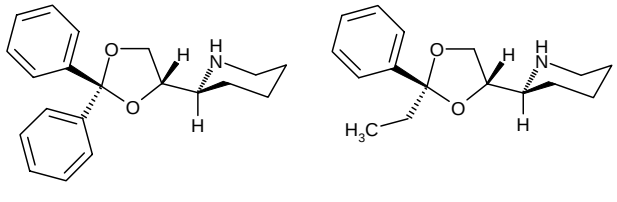
(±)-**3** (±)-**4**

Figure 2. Dexoxadrol homologues with various amino substituents.

In this communication, we describe the synthesis of analogues of **3** and **4** with various substituents at position 2 of the oxygen-containing heterocycles. In particular, we are interested in propiophenone acetals, which are similar to the NMDA receptor antagonist etoxadrol (**2**), and in benzaldehyde acetals bearing only one carbon substituent at the acetalic position. Different substituents in position 2 result in an additional center of chirality. Therefore, the influence of the configuration of novel 1,3-dioxolanes and 1,3-dioxanes on the NMDA receptor affinity is a special aspect of this report.

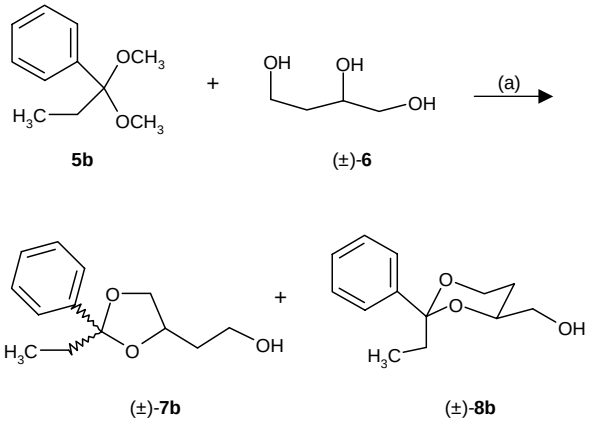
2. Chemistry

At first, the synthesis of the etoxadrol homologues **12b**, **13b**, and **16b** was planned to proceed in analogy with the synthesis of the dexoxadrol homologues **3** and **4** by condensation of propiophenone dimethyl acetal (**5b**)[13] with racemic butane-1,2,4-triol (±)-**6**, which led to a mixture of regioisomeric and diastereomeric acetals (±)-**7b** and (±)-**8b** (Scheme 1). In contrast to the transacetalization of benzophenone dimethyl acetal, the regioselectivity



1 (dexoxadrol) **2** (etoxadrol)

Figure 1. Structures of the lead compounds dexoxadrol and etoxadrol.



5b (±)-**6**

(±)-**7b** (±)-**8b**

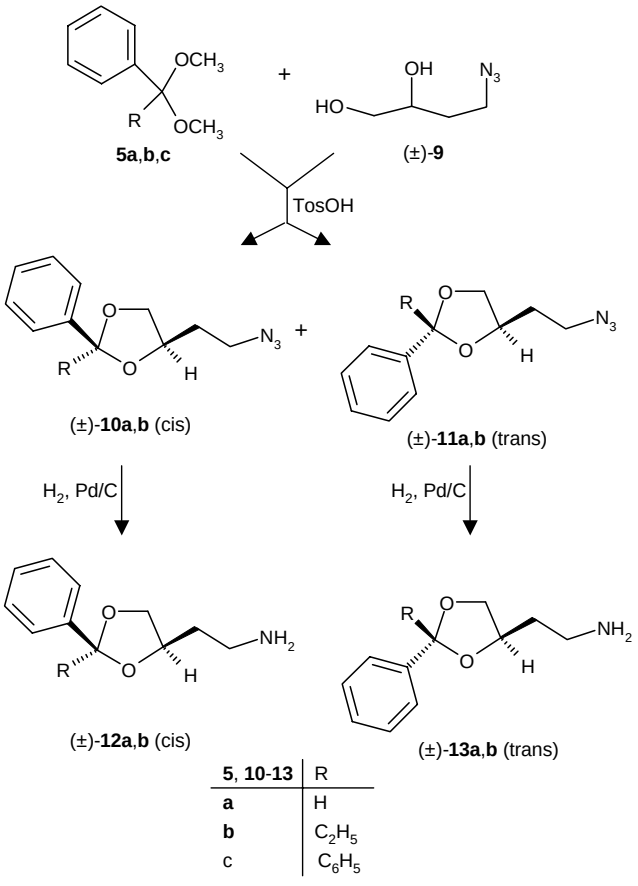
Scheme 1. Reaction conditions: (a) see Table 1.

Table 1. Regio- and diastereoselectivity during the transacetalization of propiophenone dimethyl acetal (**5b**) with butane-1,2,4-triol (±)-**6**

Entry	Temperature (°C)	Time (h)	Ratio **7b**:**8b**	Ratio *cis*-**7b**:*trans*-**7b**	Total yield (%)
1	20	1.5	78:22	48:52	69
2	20	24	79:21	51:49	73
3	66	3	80:20	57:43	81
4	66	24	88:12	35:65	64

of this transformation was only slightly influenced by the reaction conditions. At room temperature, the 1,3-dioxolanes (±)-**7b** and the 1,3-dioxane (±)-**8b** were formed in the ratio 78:22 (Table 1, entry 1), whereas heating of the reaction mixture to 66 °C for 24 h led to the regioisomers (±)-**7b** and (±)-**8b** in a ratio of 88:12 (Table 1, entry 4). In addition to the low control of regioselectivity, the chromatographic separation of the regioisomeric acetals (±)-**7b** and (±)-**8b** was very difficult and provided the desired alcohols (±)-**7b** and (±)-**8b** in only moderate yield. Therefore, an alternate synthesis was performed.

Recently, we have described the selective synthesis of the regioisomeric azidobutanediols (±)-**9** and (±)-**14**.[14] These building blocks were employed for the selective construction of the five- and six-membered acetals **12**, **13**, and **16**. Transacetalization of propiophenone dimethyl acetal (**5b**) with 4-azidobutane-1,2-diol (±)-**9** afforded the *cis*- and *trans*-configured 1,3-dioxolanes (±)-**10b** and (±)-**11b** in the ratio 1:1 (Scheme 2). The diastereomeric dioxolanes were separated by flash chromatography and subsequently reduced by H_2 and Pd/C to provide the *cis*- and *trans*-configured primary amines (±)-**12b** and (±)-**13b**. (The stereodescriptors *cis* and *trans* define the relative configuration of the phenyl and aminoethyl substituents.)

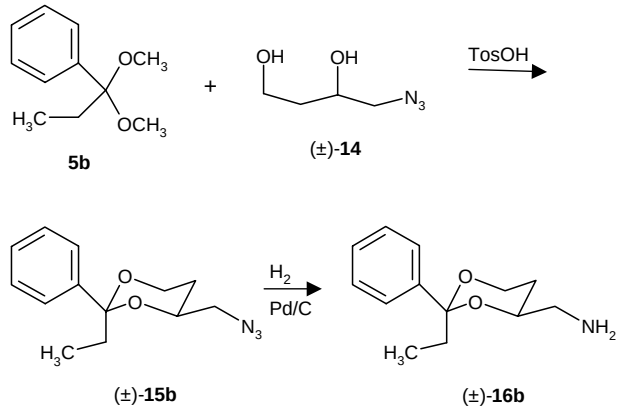


Scheme 2.

The relative configuration of the azides (±)-**10b** and (±)-**11b** was determined by NOE experiments. Saturation of the signal at 0.90 ppm (CH_2CH_3) of the *trans*-configured diastereomer (±)-**11b** led to an increased signal at 1.6 ppm ($CH_2CH_2N_3$), indicating a *cis*-relationship of these substituents. On the other hand, saturation of the same signal (0.90 ppm, CH_2CH_3) of the *cis*-configured diastereomer (±)-**10b** did not influence the signal intensity of the $CH_2CH_2N_3$-side chain.

The regioisomeric 4-azidobutane-1,3-diol (±)-**14** reacted with the dimethyl acetal **5b** stereoselectively to give exclusively the *cis*-configured 1,3-dioxane (±)-**15b** (Scheme 3). Catalytic hydrogenation of the azide moiety led to the primary amine (±)-**16b**. The *cis*-configuration of the azide (±)-**15b** was shown by a positive NOE between the axially arranged ethyl residue in position 2 and the axially oriented protons in 4- and 6-position.

For the purpose of comparison, the benzaldehyde derived 1,3-dioxolanes (±)-**12a**, (±)-**13a** and 1,3-dioxanes (±)-**16a** bearing a phenyl residue and a proton in position 2 were prepared and evaluated for their NMDA-receptor affinity. Thus, transacetalization of benzaldehyde dimethyl acetal (**5a**) with 4-azidobutane-1,2-diol (±)-**9** yielded the *cis*- and *trans*-configured 1,3-dioxolanes (±)-**10a** and (±)-**11a** in a ratio of 58:42 (see Scheme 2). The diastereomeric 1,3-dioxolanes (±)-**10a** and (±)-**11a** were separated by flash chromatography and the purified products were reduced with H_2 and Pd/C to afford



Scheme 3.

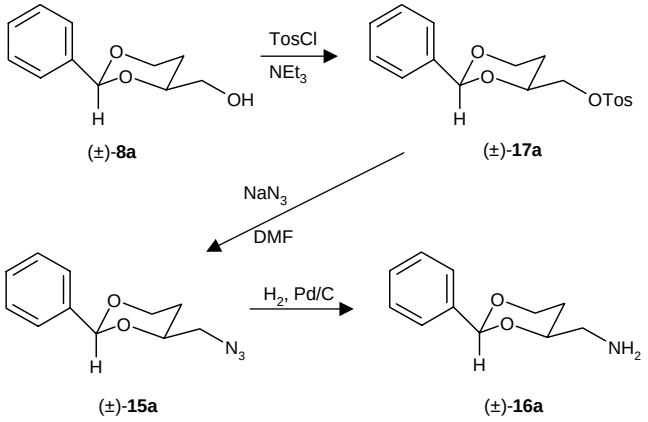
the *cis*- and *trans*-configured primary amines (±)-**12a** and (±)-**13a**. A positive NOE between the protons in position 2 and 4 proves the *cis*-configuration of the azide (±)-**10a**, whereas a positive NOE between 2-H and the $CH_2CH_2N_3$-moiety demonstrates the *trans*-configuration of (±)-**11a**.

Noteworthy, acetalization of benzaldehyde and transacetalization of benzaldehyde dimethyl acetal with butane-1,2,4-triol (**6**) predominantly lead to the six-membered acetal (±)-**8a**.[15,16] Therefore, the synthesis of the five-membered acetals **10a**–**13a** from benzaldehyde derivatives employing the azidobutanediol strategy is of particular interest.

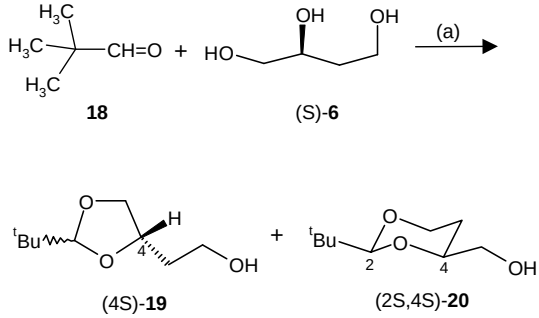
The (1,3-dioxan-4-yl)methanol (±)-**8a**[15,16] was employed for the synthesis of the primary amine (±)-**16a** (Scheme 4). The reaction of the alcohol (±)-**8a** with *p*-toluenesulfonyl chloride provided the tosylate (±)-**17a**, which was substituted with NaN_3 to give the azide (±)-**15a**. Subsequent hydrogenation using the catalyst Pd/C afforded the primary amine (±)-**16a**.

The receptor binding studies have demonstrated moderate to high NMDA receptor affinity of the racemic 1,3-dioxolanes and 1,3-dioxanes derived from benzophenone (R = Ph, **c**-series) and propiophenone (R = Et, **b**-series) (see Table 2). Therefore, we envisaged the synthesis of the corresponding enantiomerically pure derivatives. For this purpose, the regioisomeric 4-azidobutanediols **9** and **14** were synthesized in an enantiomerically pure form.

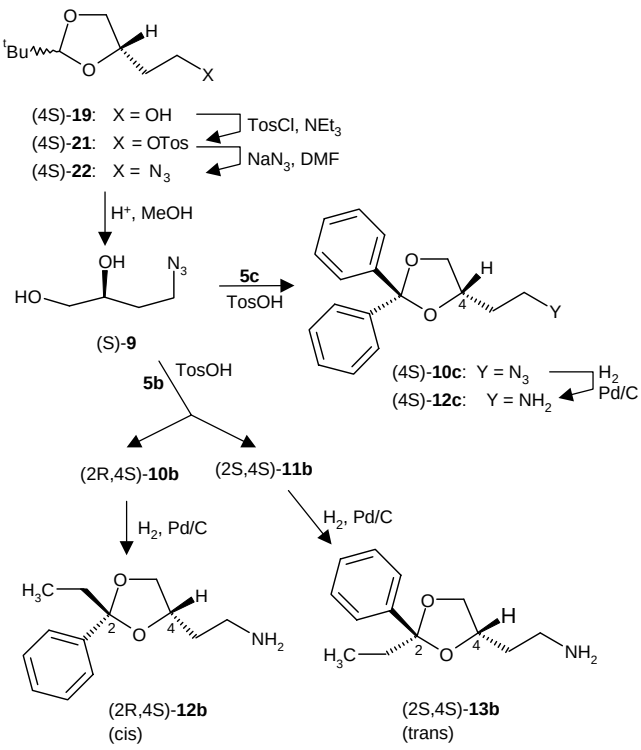
The synthesis of the enantiomerically pure azidobutanediols **9** and **14**, and their transformation into the target compounds are outlined in Schemes 5–7 for the (*S*)-configured enantiomers and follow the same route as the synthesis of the corresponding racemates.[14] Commercially available (*S*)-butane-1,2,4-triol (*S*)-**6** was condensed with pivalaldehyde **18** to afford the regioisomeric acetals (4*S*)-**19** and (2*S*,4*S*)-**20** (Scheme 5). The ratio of these acetals was controlled by the reaction conditions. Refluxing of a THF solution for 70 h yielded predominantly the thermodynamically more stable 1,3-dioxane (2*S*,4*S*)-**20** ((4*S*)-**19**/(2*S*,4*S*)-**20** = 24:76),



Scheme 4.



Scheme 5. Reagents and conditions: (a) *p*-toluenesulfonic acid, THF, 66 °C, 4 h, yields: (4*S*)-**19**: 45%; (2*S*,4*S*)-**20**: 31%.

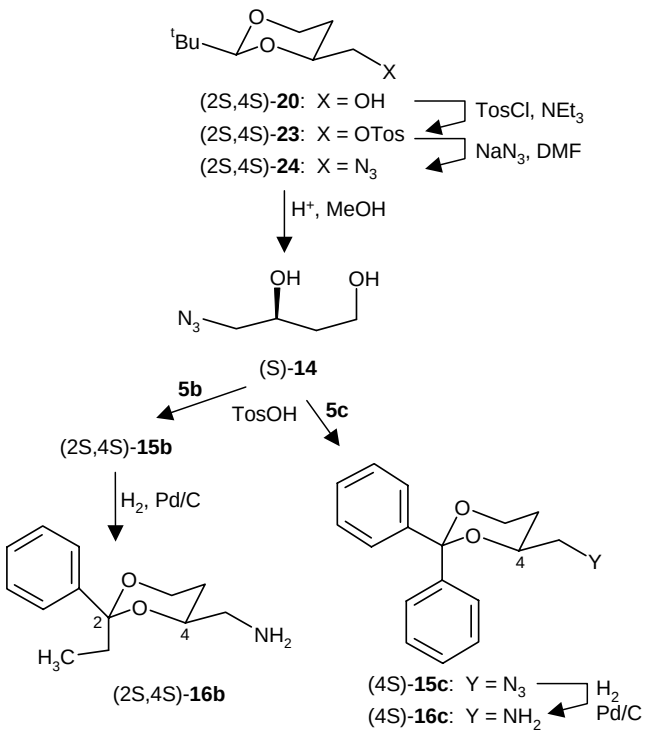


Scheme 6.

whereas under kinetic control (29 h, 20 °C) the five-membered 1,3-dioxolane (4*S*)-**19** predominated ((4*S*)-**19**/(2*S*,4*S*)-**20** = 70:30).

The regioisomers (4*S*)-**19** and (2*S*,4*S*)-**20** were separated by flash chromatography and transformed into the (*S*)-configured azidobutanediols (*S*)-**9** and (*S*)-**14** via the tosylates (4*S*)-**21**, (2*S*,4*S*)-**23** and azides (4*S*)-**22**, (2*S*,4*S*)-**24** (Schemes 6 and 7). The cleavage of the pivalaldehyde acetals (4*S*)-**22** and (2*S*,4*S*)-**24** was performed in methanol in the presence of the strongly acidic ion exchange resin Amberlyst® 15. After separation of the ion exchange resin by filtration, evaporation under reduced pressure removed all volatile components including pivalaldehyde dimethyl acetal, providing the azidobutanediols (*S*)-**9** and (*S*)-**14** in high yield and purity.

As described for the racemates, the (*S*)-configured azidobutanediols (*S*)-**9** and (*S*)-**14** were transformed into



Scheme 7.

enantiomerically pure 1,3-dioxolanes (2*R*,4*S*)-**12b**, (2*S*,4*S*)-**13b**, (4*S*)-**12c** (Scheme 6), and 1,3-dioxanes (2*S*,4*S*)-**16b** and (4*S*)-**16c** (Scheme 7). In the same manner, the enantiomers were prepared using the (*R*)-configured azidobutanediols (*R*)-**9** and (*R*)-**14** as chiral building blocks.

3. Receptor binding studies

The affinity of the racemic and enantiomerically pure primary amines toward the PCP binding site of the NMDA receptor was determined in competition experiments with the radioligand [^{3}H]-(+)-MK-801, which binds to this site with high affinity and selectivity. In the assay, membrane receptor preparations from pig brain cortex were used. Non-specific binding was determined by saturation of the specific binding sites with a large excess of non-tritiated (+)-MK-801.[17,18]

There are several compounds interacting both with the phencyclidine binding site of the NMDA receptor and with σ receptors. Therefore, in the past the enigmatic σ receptor had been regarded to be identical with the phencyclidine binding site of the NMDA receptor.[19] This hypothesis was disproved by further investigations demonstrating the σ receptor to be a unique receptor.[20,21] The cross-reactivity of ligands with both receptor types prompted us to investigate the σ_1 receptor affinity of the enantiomerically pure compounds in addition to their NMDA receptor affinity.

In the σ_1 assay, homogenates of guinea pig brain preparations were used as receptor material. The σ_1 selective ligand [^{3}H]-(+)-pentazocine was employed as radioligand, and the non-specific binding was determined by saturation of the specific binding sites with a large excess of haloperidol.[22]

4. Results and discussion

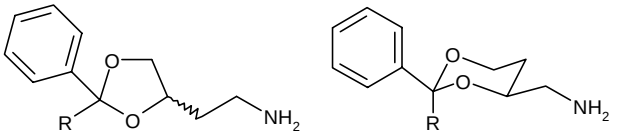
The affinities of the racemic primary amines containing various substituents at the acetalic position (H, C_2H_5, and C_6H_5) toward the PCP binding site of the NMDA receptor are given in Table 2.

It is obvious that the interaction of the benzaldehyde derivatives (±)-**12a**, (±)-**13a**, and (±)-**16a** (R = H) with the PCP binding site of the NMDA receptor is very low. This observation is in accordance with literature report, that indicate high NMDA receptor affinity only for ligands substituted with a phenyl and a second voluminous group (e.g., C_6H_5, C_2H_5) at the acetalic position.

High affinity was obtained with ligands bearing an ethyl substituent at the acetalic position. In the 1,3-dioxane series the ethyl derivative (±)-**16b** is about three times more active than the diphenyl derivative (±)-**16c**. In the five membered series, the NMDA receptor affinity is strongly dependent on the stereochemistry. Whereas the K_i-value of the *cis*-configured 1,3-dioxolane (±)-**12b** (K_i = 6030 nM) is higher than the that of the corresponding diphenyl derivative (±)-**12c** (K_i = 3380 nM), the *trans*-configured 1,3-dioxolane (±)-**13b** displays a 30-fold increase of NMDA receptor affinity (K_i = 118 nM). A similar result had been obtained with etoxadrol (**2**) stereoisomers. Transformation of etoxadrol with a *trans*-orientation of piperidinyl and phenyl residues in the 1,3-dioxolane ring into 2′-epi-etoxadrol with a *cis*-relationship of the corresponding substituents resulted in a 35-fold loss in NMDA receptor affinity.[11]

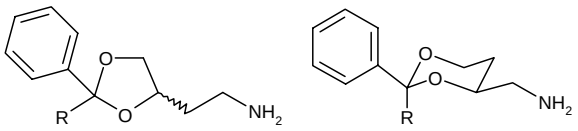
The promising NMDA receptor affinities of some racemic primary amines led to the synthesis and pharmacological evaluation of the corresponding enantiomerically pure compounds. In Table 3, the results of the NMDA

Table 2. NMDA receptor affinity of racemic dioxolanes and dioxanes



Compound	Ring size	R	K_i ± SEM (nM) n = 3
(±)-**12a**	5	H (*cis*)	>100,000 (n = 1)
(±)-**13a**	5	H (*trans*)	>100,000 (n = 1)
(±)-**12b**	5	C_2H_5 (*cis*)	6030 ± 1130
(±)-**13b**	5	C_2H_5 (*trans*)	118 ± 2
(±)-**12c**	5	C_6H_5	3380 ± 290
(±)-**16a**	6	H	>10,000 (n = 1)
(±)-**16b**	6	C_2H_5	449 ± 8
(±)-**16c**	6	C_6H_5	1450 ± 90
Dexoxadrol (**1**)			23.3 ± 3.4
Etoxadrol (**2**)			19.8 ± 2.0

Table 3. NMDA receptor affinity of enantiomerically pure dioxolanes and dioxanes



Compound	Ring size	R	K_i ± SEM (nM) $n = 3$
(±)-**12b**	5	C_2H_5 (*cis*)	6030 ± 1130
(2*R*,4*S*)-**12b**	5	C_2H_5 (*cis*)	5950 ± 610
(2*S*,4*R*)-**12b**	5	C_2H_5 (*cis*)	5000 ± 260
(±)-**13b**	5	C_2H_5 (*trans*)	118 ± 2
(2*S*,4*S*)-**13b**	5	C_2H_5 (*trans*)	69 ± 7
(2*R*,4*R*)-**13b**	5	C_2H_5 (*trans*)	1190 ± 70
(±)-**12c**	5	C_6H_5	3380 ± 290
(4*S*)-**12c**	5	C_6H_5	3260 ± 150
(4*R*)-**12c**	5	C_6H_5	3190 ± 130
(±)-**16b**	6	C_2H_5	449 ± 8
(2*S*,4*S*)-**16b**	6	C_2H_5	257 ± 12
(2*R*,4*R*)-**16b**	6	C_2H_5	3420 ± 200
(±)-**16c**	6	C_6H_5	1450 ± 90
(4*S*)-**16c**	6	C_6H_5	717 ± 42
(4*R*)-**16c**	6	C_6H_5	5840 ± 530
Dexoxadrol (**1**)			23.3 ± 3.4
Etoxadrol (**2**)			19.8 ± 2.0

receptor affinity studies with enantiomerically pure ligands are given.

Table 3 shows that the enantiomers of the *cis*-configured 1,3-dioxolane **12b** and the diphenyl substituted 1,3-dioxolane **12c** are almost equally potent at the PCP binding site of the NMDA receptor. Their K_i-values do not differ significantly from those of the racemates. On the other hand, the *trans*-configured 1,3-dioxolane **13b** and the 1,3-dioxanes **16b** and **16c** display strong enantioselective NMDA receptor binding (factor 8–17). Their NMDA receptor affinity resides almost exclusively in the (*S*)-configured enantiomers (2*S*,4*S*)-**13b**, (2*S*,4*S*)-**16b**, and (4*S*)-**16c**.

In the six-membered series, the ethyl derivative (2*S*,4*S*)-**16b** (K_i = 257 nM) is about three times more active than the corresponding diphenyl derivative (4*S*)-**16c** (K_i = 717 nM). The most active compound in this series with the highest enantioselectivity of the NMDA receptor binding (factor 17) is the (*S*,*S*)-configured phenylethyl-1,3-dioxolane (2*S*,4*S*)-**13b**. The corresponding binding curves of the racemate and the enantiomers of **13b** are shown in Figure. 3. Its NMDA receptor affinity (K_i = 69 nM) is almost in the range of the NMDA receptor affinity of the lead compounds dexoxadrol and etoxadrol.

The stereochemistry of the high affinity primary amine (2*S*,4*S*)-**13b** is in accordance with the three-dimensional structure of the lead compound etoxadrol ((*S*,*S*,*S*)-configuration). Moreover, a similar enantioselective NMDA receptor binding has been shown for etoxadrol: The (*R*,*R*,*R*)-configured etoxadrol enantiomer displays about 25-fold lower NMDA receptor affinity than the (*S*,*S*,*S*)-configured enantiomer.[11] Recently, a pharmacophore model for non-competitive NMDA receptor antagonists has been proposed.[26] In principle, (2*S*,4*S*)-**13b** fits well to the characteristic features of this model (see Fig. 4).

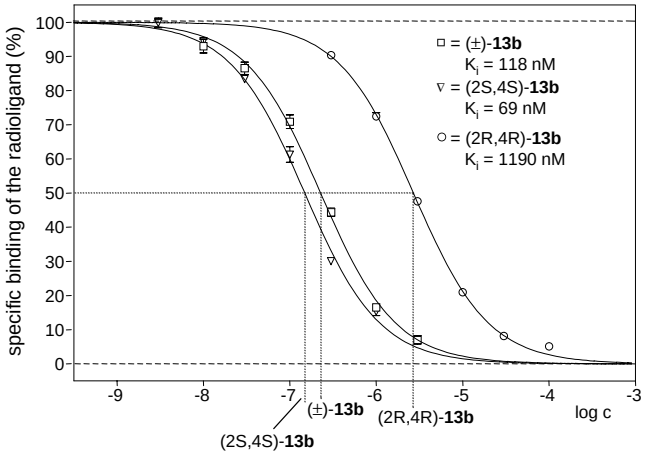


Figure 3. Comparison of the competition curves of racemic dioxolane (±)-**13b** and its enantiomers (2*S*,4*S*)-**13b** and (2*R*,4*R*)-**13b**.

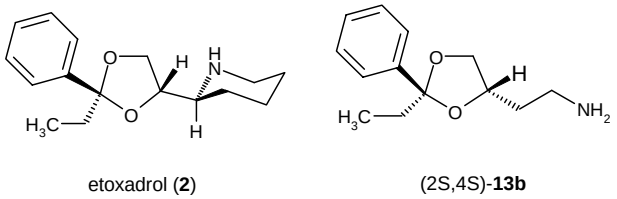


Figure 4. Comparison of the three-dimensional structure of (2*S*,4*S*)-**13b** with etoxadrol (**2**).

To determine the σ_1 receptor affinity of the enantiomerically pure primary amines, a screening with a concentration of 10 μM was carried out. At this concentration, the inhibition of the radioligand binding was less than 35%, indicating an IC_{50}-value higher than 10 μM. Thus, the σ_1 receptor affinity of the described primary amines is very low. In particular, the high affinity NMDA receptor antagonists (2*S*,4*S*)-**13b** and (2*S*,4*S*)-**16b** exhibit high selectivity against σ_1 receptors.

5. Conclusion

Herein, we have shown that homologization of the oxygen heterocycle or the distance amine–oxygen heterocycle of the lead structures dexoxadrol and etoxadrol provides novel non-competitive NMDA receptor antagonists (PCP binding site) binding in the high nanomolar range. The relative and absolute configuration of the novel ligands considerably influence the NMDA receptor binding. The NMDA receptor affinity of (2*S*,4*S*)-**13b** is in the same range as the NMDA receptor affinity of etoxadrol. This result indicates that the 2-aminoethyl substituent and the piperidin-2-yl moiety cause similar interactions with the NMDA receptor.

6. Experimental

6.1. Chemistry, general

Thin-layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc)[23]: Silica gel 60, 0.040–0.063 mm (Merck); parentheses include: Diameter of the column [cm], eluent, fraction size [mL], R_f. Melting points: Melting point apparatus SMP 2 (Stuart Scientific), uncorrected. Optical rotation: Polarimeter 241 (Perkin Elmer); 1.0 dm tube; concentration *c* [g/100 mL]; temperature is given. Elemental analyses: Vario EL (Elementaranalysesysteme GmbH). The purity of all target compounds was shown by elemental analyses, which agree with the calculated values within ±0.4 %. MS: MAT 312, MAT 8200, MAT 44, and TSQ 7000 (Finnigan); EI, electron impact; CI, chemical ionization. High resolution MS (HRMS): MAT 8200 (Finnigan). IR: IR spectrophotometer 1605 FT-IR (Perkin-Elmer); (br, broad; m, medium; s, strong). ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz): Unity 300 FT NMR spectrometer (Varian), δ in ppm related to tetramethylsilane, coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and ^{1}H NMR signals were supported by 2D NMR techniques.

6.2. Propiophenone dimethyl acetal (5b)[13]

A solution of propiophenone (13.3 mL, 100 mmol), *p*-toluenesulfonic acid monohydrate (0.951 g, 5 mmol), and trimethyl orthoformate (110 mL, 1.0 mol) in methanol (200 mL) was heated to reflux for 24 h. A part of the solvent was evaporated in vacuo, Et_2O (250 mL) was added to the residue (ca. 50 mL), and the mixture was washed with a saturated solution of $NaHCO_3$ (250 mL). After drying ($MgSO_4$), the organic layer was concentrated in vacuo and the residue was purified by fc (8 cm, petroleum ether/ethyl acetate 19:1, 35 mL, R_f = 0.30). Colorless oil, yield 13.9 g (77%). ^{1}H NMR ($CDCl_3$): δ (ppm) CH_3 = 0.60 (t, *J* = 7.5 Hz, 3H, CH_3), 1.92 (q, *J* = 7.3 Hz, 2H, CH_2–), 3.17 (s, 6H, OCH_3), 7.25–7.38 (m, 3 H, arom. H, *m*- and *p*-position), 7.44–7.48 (m, 2H, arom. H, *o*-position). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2972, 2941 (m, ν_{CH}), 2829 (m, $\nu_{CH(OCH_3)}$), 1051 (s, ν_{CO}), 760, 702 (s, γ_{aryl}).

6.3. *rac*-2-(2-Ethyl-2-phenyl-1,3-dioxolan-4-yl)ethan-1-ol ((±)-7b) and *rac*-(2-ethyl-2-phenyl-1,3-dioxan-4-yl)methanol ((±)-8b)

Propiophenone dimethyl acetal (**5b**, 1.80 g, 10.0 mmol), racemic butanetriol (±-**6**, 1.06 g, 10 mmol), and Na_2SO_4 (ca. 1 g) were dissolved and suspended in THF (50 mL). Then, a solution of *p*-toluenesulfonic acid in THF (0.025 mol/L, 20.0 mL) was added and the mixture was heated to reflux for 3 h. It was decanted, Et_2O (50 mL) was added, and the mixture was washed with a saturated solution of $NaHCO_3$ (100 mL), dried ($MgSO_4$), and concentrated in vacuo. A ^{1}H NMR spectrum was recorded and the residue was purified by fc (6 cm, petroleum ether/ethyl acetate = 7: 3, fractions 35 mL).

(±)-**7b** (R_f = 0.28): Colorless oil, yield 0.847 g (38%). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.86 (t, *J* = 7.5 Hz, 3× 0.57H, CH_2CH_3), 0.89 (t, *J* = 7.5 Hz, 3× 0.43H, CH_2CH_3), 1.60–1.74 (m, 2× 0.57H, CH_2CH_2OH), 1.82 (br s, 1H, OH), 1.75–1.98 (m, 2× 0.43H, CH_2CH_2OH), 1.88 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 3.41 (dd, *J* = 8.5/8.2 Hz, 0.57H, 5-H), 3.65 (dd, *J* = 7.6/6.7 Hz, 0.43H, 5-H), 3.76 (dt, *J* = 11.3/5.8 Hz, 0.57H, CH_2CH_2OH), 3.80 (dt, *J* = 11.3/6.0 Hz, 0.57H, CH_2CH_2OH), 3.83 (t, *J* = 5.8 Hz, 2× 0.43H, CH_2CH_2OH), 3.90 (dd, *J* = 7.6/7.0 Hz, 0.43H, 5-H), 4.11 (tdd, *J* = 7.0/6.7/4.7 Hz, 0.43H, 4-H), 4.18 (dd, *J* = 8.2/5.8 Hz, 0.57H, 5-H), 4.34 (dddd, *J* = 8.5/7.9/5.8/4.9 Hz, 0.57H, 4-H), 7.25–7.37 (m, 3H, arom. H in *m*- and *p*-position), 7.41–7.46 (m, 2H, arom. H in *o*-position).

(±)-**8b** (R_f = 0.23): Colorless oil, yield 0.245 g (11%). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.82 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.21 (dtd, *J* = 12.8/2.4/1.5 Hz, 1H, 5-H_{eq}), 1.76 (q, *J* = 7.4 Hz, 2H, CH_2CH_3), 1.79 (br s, 1H, OH), 1.77–1.85 (m, 1H, 5-H_{ax}), 3.58 (dd, *J* = 11.6/6.1 Hz, 1H, CH_2OH), 3.65 (dd, *J* = 11.6/3.7 Hz, 1H, CH_2OH), 3.79 (ddd, *J* = 12.5/11.4/2.4 Hz, 1H, 6-H_{ax}), 3.81–3.90 (m, 1H, 4-H_{ax}), 3.90 (ddd, *J* = 11.4/5.5/1.5 Hz, 1H, 6-H_{eq}), 7.26–7.34 (m, 1H, arom. H in *p*-position), 7.34–7.45 (m, 4H, arom. H in *o*- and *m*-position).

6.4. (−)-(2*S*)-4-Azidobutane-1,2-diol ((*S*)-9)[14]

A mixture of azide (4*S*)-**22** (0.20 g, 1.0 mmol), Amberlyst® 15 (100 mg), and methanol (10 mL) was heated to reflux for 4 h. It was filtered and the solvent together with pivalaldehyde dimethyl acetal was evaporated in vacuo. Further transformations of (*S*)-**9** were performed without purification. Colorless oil, yield 0.13 g (100%). $[\alpha]_{589}^{22}$ −22.0 (*c* 0.74, CH_2Cl_2).

6.5. (+)-(2*R*)-4-Azidobutane-1,2-diol ((*R*)-9)[14]

As described for (*S*)-**9**, the azide (4*R*)-**22** (0.20 g, 1.0 mmol) was reacted with Amberlyst® 15 (100 mg), and methanol (10 mL) to afford the azidobutanediol (*R*)-**9**. Colorless oil, yield 0.13 g (100%). $[\alpha]_{589}^{22}$ +19.8 (*c* 0.77, CH_2Cl_2).

6.6. *rac-cis*-4-(2-Azidoethyl)-2-phenyl-1,3-dioxolane ((±)-10a) and *rac-trans*-4-(2-azidoethyl)-2-phenyl-1,3-dioxolane ((±)-11a)

As described for the racemates (±)-**10b/11b**, benzaldehyde dimethyl acetal (**5a**, 0.76 g, 5.0 mmol) and racemic 4-azidobutane-1,2-diol (±)-**9** (0.328 g, 2.5 mmol) were reacted at room temperature for 20 h. After decantation and extraction, the residue was purified twice by fc (3 cm, petroleum ether/ethyl acetate = 19:1, fractions 5 mL).

(±)-**10a** (*cis*, R_f = 0.10): Colorless oil, yield 84.4 mg (15%). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.91 (dtd, *J* = 14.0/7.3/4.9 Hz, 1H, $CH_2CH_2N_3$), 1.97 (ddt, *J* = 14.0/7.6/6.4 Hz, 1H, $CH_2CH_2N_3$), 3.48 (ddd, *J* = 12.5/7.9/6.7 Hz, 1H, $CH_2CH_2N_3$), 3.53 (ddd, *J* = 12.5/6.7/6.1 Hz, 1H, $CH_2CH_2N_3$), 3.77 (dd, *J* = 7.8/6.1 Hz, 1H, 5-H), 4.16 (dd, *J* = 7.8/6.7 Hz, 1H, 5-H), 4.34 (dddd, *J* = 7.6/6.7/6.1/4.9 Hz, 1H, 4-H), 5.82 (s, 1H, 2-H),

7.37–7.42 (m, 3H, arom. H in *m*- and *p*-position), 7.46–7.50 (m, 2H, arom. H in *o*-position).

(±)-**11a** (*trans*, $R_f = 0.12$): Colorless oil, yield 75.6 mg (14%). MS (EI): *m/z* (%) = 219 (M, 1.6), 105 (PhCO, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.84 (dddd, J = 14.0/7.9/7.3/4.3 Hz, 1H, $CH_2CH_2N_3$), 1.98 (dddd, J = 14.0/8.2/6.4/5.5 Hz, 1H, $CH_2CH_2N_3$), 3.49 (ddd, J = 12.5/7.9/6.4 Hz, 1H, $CH_2CH_2N_3$), 3.55 (ddd, J = 12.5/7.3/5.5 Hz, 1H, $CH_2CH_2N_3$), 3.67 (dd, J = 7.3/6.1 Hz, 1H, 5-H), 4.32 (dd, J = 7.3/6.7 Hz, 1H, 5-H), 4.34 (dddd, J = 8.2/6.7/6.1/4.3 Hz, 1H, 4-H), 5.94 (s, 1H, 2-H), 7.36–7.42 (m, 3H, arom. H in *m*- and *p*-position), 7.45–7.50 (m, 2H, arom. H in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2927 (m, ν_{-CH_2-}), 2880 (m, $\nu_{-CH<}$), 2097 (s, ν_{N_3}).

6.7. *rac-cis*-4-(2-Azidoethyl)-2-ethyl-2-phenyl-1,3-dioxolane ((±)-10b) and *rac-trans*-4-(2-azidoethyl)-2-ethyl-2-phenyl-1,3-dioxolane ((±)-11b)

Na_2SO_4 (ca. 1 g) was added to a solution of racemic azidobutanediol (±)-**9**[14] (0.33 g, 2.5 mmol) and propiophenone dimethyl acetal (**5b**, 0.45 g, 2.5 mmol) in THF (20 mL), and then a solution of *p*-toluenesulfonic acid in THF (5.0 mL, 0.025 mol/L) was added and the mixture was heated to reflux for 8 h. It was decanted, Et_2O (25 mL) was added, and the organic layer was washed with a saturated solution of $NaHCO_3$ (25 mL) and water (25 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by fc (3 cm, petroleum ether/CH_2Cl_2 = 3:2, fractions 3 mL).

(±)-**10b** (*cis*, $R_f = 0.16$): Colorless oil, yield 54.4 mg (8.8%). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.84 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.64 (q, J = 6.7 Hz, 2H, $CH_2CH_2N_3$), 1.86 (q, J = 7.3 Hz, 2H, CH_2CH_3), 3.38 (t, J = 7.9 Hz, 1H, 5-H), 3.41 (t, J = 6.7 Hz, 2H, $CH_2CH_2N_3$), 4.18 (dd, J = 7.9/6.1 Hz, 1H, 5-H), 4.26 (dtd, J = 7.9/6.7/6.1 Hz, 1H, 4-H), 7.24–7.36 (m, 3H, arom. H in *m*- and *p*-position), 7.41–7.47 (m, 2H, arom. H in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2095 (s, ν_{N_3}).

(±)-**11b** (*trans*, $R_f = 0.14$): Colorless oil, yield 80.4 mg (13%). MS (CI): *m/z* (%) = 248 (MH, 52), 220 (MH–N_2, 87), 86 ($OCH_2CH(CH_2)_2N$ + H, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.88 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.83 (dtd, J = 13.7/7.5/4.9 Hz, 1H, $CH_2CH_2N_3$), 1.88 (q, J = 7.5 Hz, 2H, CH_2CH_3), 1.91 (dddd, J = 13.7/7.9/6.6/5.8 Hz, 1H, $CH_2CH_2N_3$), 3.44 (ddd, J = 12.5/7.6/6.6 Hz, 1H, $CH_2CH_2N_3$), 3.49 (ddd, J = 12.5/7.3/5.8 Hz, 1H, $CH_2CH_2N_3$), 3.61 (dd, J = 7.9/6.1 Hz, 1H, 5-H), 3.86 (dd, J = 7.9/7.0 Hz, 1H, 5-H), 4.00 (dddd, J = 7.9/7.0/6.1/4.9 Hz, 1H, 4-H), 7.25–7.36 (m, 3H, arom. H in *m*- and *p*-position), 7.40–7.45 (m, 2H, arom. H in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2098 (s, ν_{N_3}).

6.8. (+)-(2*R*,4*S*)-4-(2-Azidoethyl)-2-ethyl-2-phenyl-1,3-dioxolane ((2*R*,4*S*)-10b) and (−)-(2*S*,4*S*)-4-(2-azidoethyl)-2-ethyl-2-phenyl-1,3-dioxolane ((2*S*,4*S*)-11b)

Propiophenone dimethyl acetal (**5b**, 0.18 g, 1.0 mmol) and (*S*)-configured azidobutanediol (*S*)-**9** (0.13 g, 1.0 mmol) were reacted, worked up and the products were isolated, as described for the racemates **10b/11b**. For the isolation of pure products, repetitive chromatographic separations were necessary.

(2*R*,4*S*)-**10b** (*cis*, $R_f = 0.11$, petroleum ether/CH_2Cl_2 = 4:1): Colorless oil, yield 54.2 mg (22%). $[\alpha]_{589}^{23}$ +13.6 (*c* 0.78, CH_2Cl_2).

(2*S*,4*S*)-**11b** (*trans*, $R_f = 0.10$, petroleum ether/CH_2Cl_2 = 4:1): Colorless oil, yield 74.7 mg (30%). $[\alpha]_{589}^{23}$ − 41.3 (*c* 0.68, CH_2Cl_2).

6.9. (−)-(2*S*,4*R*)-4-(2-Azidoethyl)-2-ethyl-2-phenyl-1,3-dioxolane ((2*S*,4*R*)-10b) and (+)-(2*R*,4*R*)-4-(2-azidoethyl)-2-ethyl-2-phenyl-1,3-dioxolane ((2*R*,4*R*)-11b)

Propiophenone dimethyl acetal (**5b**, 0.18 g, 1.0 mmol) and (*R*)-**9** (0.13 g, 1.0 mmol) were reacted, worked up and the products were isolated, as described for the racemates **10b/11b**. For the isolation of the pure products, repetitive chromatographic separations were necessary.

(2*S*,4*R*)-**10b** (*cis*, $R_f = 0.11$, petroleum ether/CH_2Cl_2 = 4:1): Colorless oil, yield 34.1 mg (14%). $[\alpha]_{589}^{24}$ −12.5 (*c* 0.71, CH_2Cl_2).

(2*R*,4*R*)-**11b** (*trans*, $R_f = 0.10$, petroleum ether/CH_2Cl_2 = 4:1): Colorless oil, yield 62.6 mg (25%). $[\alpha]_{589}^{24}$ +38.5 (*c* 0.74, CH_2Cl_2).

6.10. (−)-(4*S*)-4-(2-Azidoethyl)-2,2-diphenyl-1,3-dioxolane ((4*S*)-10c)

As described for the racemates (±)-**10b/11b**, the (*S*)-configured 4-azidobutanediol (*S*)-**9** (0.131 g, 1.0 mmol) was heated to reflux with benzophenone dimethyl acetal (**5c**, 0.228 g, 1.0 mmol) in THF (10 mL) for 3.5 h. Purification by fc (4 cm, petroleum ether/ethyl acetate = 77:3, fractions 10 mL, $R_f = 0.17$) provided a colorless oil, yield 0.158 g (54%). $[\alpha]_{589}^{23}$ −9.34 (*c* 1.15, CH_2Cl_2). MS (EI): *m/z* (%) = 295 (M, 1.1), 218 (M–Ph, 62), 105 (PhCO, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.85 (dtd, J = 14.0/7.6/4.6 Hz, 1H, $CH_2CH_2N_3$), 1.94 (ddt, J = 14.0/7.9/6.1 Hz, 1H, $CH_2CH_2N_3$), 3.50 (br t, J = 6.9 Hz, 2H, $CH_2CH_2N_3$), 3.75 (dd, J = 7.9/6.7 Hz, 1H, 5-H), 4.15 (dd, J = 7.9/6.7 Hz, 1H, 5-H), 4.29 (dtd, J = 7.9/6.7/4.6 Hz, 1H, 4-H), 7.27–7.38 (m, 6H, arom. H in *m*- and *p*-position), 7.47–7.55 (m, 4H, arom. H in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2943 (m, ν_{-CH_2-}), 2882 (m, $\nu_{-CH<}$), 2097 (s, ν_{N_3}), 1089 (s, ν_{CO}), 756, 703 (s, γ_{aryl}).

6.11. (+)-(4*R*)-4-(2-Azidoethyl)-2,2-diphenyl-1,3-dioxolane ((4*R*)-10c)

As described for the racemates (±)-**10b/11b**, the (*R*)-configured 4-azidobutanediol (*R*)-**9** (65.6 mg, 0.50 mmol) was heated to reflux with benzophenone dimethyl acetal (**5c**, 0.228 g, 1.0 mmol) in THF (7 mL) for 3.5 h. Purification by fc (3 cm, petroleum ether/ethyl acetate 39:1, fractions 10 mL, $R_f = 0.12$) gave a colorless oil, yield 87.7 mg (59%). $[\alpha]_{589}^{24}$ +8.70 (*c* 0.97, CH_2Cl_2).

6.12. *rac-cis*-2-(2-Phenyl-1,3-dioxolan-4-yl)ethan-1-amine ((±)-12a)

As described for the racemic amine (±)-**12b**, the racemic azide (±)-**10a** (28.5 mg, 0.13 mmol) was hydrogenated to yield (±)-**12a**. Colorless oil, yield 18.4 mg (73%). MS (CI): *m/z* (%) = 194 (MH, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.39 (br s, 2H, NH_2), 1.78 (dtd, J = 13.7/7.2/4.9 Hz, 1H, $CH_2CH_2NH_2$), 1.87 (ddt, J = 13.7/7.6/6.7 Hz, 1H, $CH_2CH_2NH_2$), 2.86 (dt, J = 12.5/7.0 Hz, 1H, $CH_2CH_2NH_2$), 2.92 (ddd, J = 12.5/7.3/6.4 Hz, 1H, $CH_2CH_2NH_2$), 3.70 (dd, J = 7.6/7.0 Hz, 1H, 5-H), 4.12 (dd, J = 7.6/6.7 Hz, 1H, 5-H), 4.31 (dddd, J = 7.6/7.0/6.7/4.9 Hz, 1H, 4-H), 5.79 (s, 1H, 2-H), 7.34–7.39 (m, 3H, arom. H in *m*- and *p*-position), 7.45–7.49 (m, 2H, arom. H in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3392 (m, ν_{NH}), 2928, 2884 (m, ν_{CH}), (193.25) HR-MS: Calcd. for M−H 192.1025. Found: 192.1025.

6.13. *rac-cis*-2-(2-Ethyl-2-phenyl-1,3-dioxolan-4-yl)ethan-1-amine (±)-(12b)

Racemic azide (±)-**10b** (22.3 mg, 0.09 mmol) was dissolved in THF (5 mL), Pd/C (5 %, 2.2 mg) was added, and the suspension was stirred under a H_2 atmosphere (1 bar) at room temperature for 90 min. The mixture was filtered through Celite® and the filtrate was concentrated in vacuo. Colorless oil, yield 17.9 mg (90%). MS (CI): *m/z* (%) = 222 (MH, 100), 88 (O–CH_2–CH–$(CH_2)_2$– NH_2 + H, 38). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.88 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.45 (br s, 2H, NH_2), 1.70 (dtd, J = 13.7/7.0/4.9 Hz, 1H, $CH_2CH_2NH_2$), 1.82 (dq, J = 13.7/7.0 Hz, 1H, $CH_2CH_2NH_2$), 1.88 (q, J = 7.3 Hz, 2H, CH_2CH_3), 2.82 (dt, J = 12.5/7.0 Hz, 1H, $CH_2CH_2NH_2$), 2.88 (dt, J = 12.5/7.0 Hz, 1H, $CH_2CH_2NH_2$), 3.58 (t, J = 7.0 Hz, 1H, 5-H), 3.87 (t, J = 7.0 Hz, 1H, 5-H), 3.99 (qd, J = 7.0/4.9 Hz, 1H, 4-H), 7.26–7.35 (m, 3H, arom. H in *m*- and *p*-position), 7.40–7.44 (m, 2H, arom. H in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3368 (m, ν_{NH}), 2938, 2878 (s, ν_{CH}). HR-MS: Calcd 221.1416. Found: 221.1416.

6.14. (+)-2-[(2*R*,4*S*)-2-Ethyl-2-phenyl-1,3-dioxolan-4-yl]ethan-1-amine ((2*R*,4*S*)-12b)

As described for the racemic amine (±)-**12b**, the azide (2*R*,4*S*)-**10b** (27.2 mg, 0.11 mmol) was hydrogenated to yield (2*R*,4*S*)-**12b**. Colorless oil, yield 21.6 mg (89%). $[\alpha]_{589}^{20}$ +20.6 (*c* 1.03, CH_2Cl_2).

6.15. (−)-2-[(2*S*,4*R*)-2-Ethyl-2-phenyl-1,3-dioxolan-4-yl]ethan-1-amine ((2*S*,4*R*)-12b)

As described for the racemic amine (±)-**12b**, the azide (2*S*,4*R*)-**10b** (19.8 mg, 0.08 mmol) was hydrogenated to yield (2*S*,4*R*)-**12b**. Colorless oil, yield 17.7 mg (100%). $[\alpha]_{589}^{20}$ −17.4 (*c* 0.85, CH_2Cl_2).

6.16. (−)-(4*S*)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)ethan-1-amine ((4*S*)-12c)

As described for the racemic amine (±)-**12b**, the azide (4*S*)-**10c** (47.3 mg, 0.16 mmol) was hydrogenated to yield (4*S*)-**12c**. Colorless oil, yield 41.7 mg (97%). $[\alpha]_{589}^{20}$ −2.15 (*c* 1.74, CH_2Cl_2).

6.17. (+)-(4*R*)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)ethan-1-amine ((4*R*)-12c)

As described for the racemic amine (±)-**12b**, the azide (4*R*)-**10c** (32.5 mg, 0.11 mmol) was hydrogenated to yield (*R*)-**12c**. Colorless oil, yield 30.0 mg (100%). $[\alpha]_{589}^{20}$ +2.08 (*c* 1.35, CH_2Cl_2).

6.18. *rac-trans*-2-(2-Phenyl-1,3-dioxolan-4-yl)ethan-1-amine ((±)-13a)

As described for the racemic amine (±)-**12b**, the racemic azide (±)-**11a** (24.1 mg, 0.11 mmol) was hydrogenated to yield (±)-**13a**. Colorless oil, yield 13.3 mg (63%). MS (CI): *m/z* (%) = 194 (MH, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.44 (br s, 2H, NH_2), 1.69 (dtd, J = 13.7/7.0/4.3 Hz, 1H, $CH_2CH_2NH_2$), 1.87 (dddd, J = 13.7/8.2/7.0/6.4 Hz, 1H, $CH_2CH_2NH_2$), 2.85 (dt, J = 12.5/7.0 Hz, 1H, $CH_2CH_2NH_2$), 2.93 (ddd, J = 12.5/7.3/6.4 Hz, 1H, $CH_2CH_2NH_2$), 3.63 (dd, J = 7.3/6.4 Hz, 1H, 5-H), 4.27 (dd, J = 7.3/6.4 Hz, 1H, 5-H), 4.32 (dtd, J = 8.2/6.4/4.3 Hz, 1H, 4-H), 5.92 (s, 1H, 2-H), 7.34–7.39 (m, 3H, arom. H in *m*- and *p*-position), 7.44–7.48 (m, 2H, arom. H in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3389 (m, ν_{NH}), 2924, 2876 (m, ν_{CH}). HR-MS: Calcd for M−H 192.1025. Found: 192.1025.

6.19. *rac-trans*-2-(2-Ethyl-2-phenyl-1,3-dioxolan-4-yl)ethan-1-amine ((±)13b)

As described for the racemic amine (±)-**12b**, the azide (±)-**11b** (24.7 mg, 0.10 mmol) was hydrogenated to yield racemic (±)-**13b**. Colorless oil, yield 19.9 mg (90%). MS (CI): *m/z* (%) = 222 (MH, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.85 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.42 (br s, 2H, NH_2), 1.48 (dtd, J = 13.7/7.2/4.9 Hz, 1H, $CH_2CH_2NH_2$), 1.61 (dddd, J = 13.7/7.9/7.0/6.4 Hz, 1H, $CH_2CH_2NH_2$), 1.86 (q, J = 7.3 Hz, 2H, CH_2CH_3), 2.77 (dt, J = 12.5/7.0 Hz, 1H, $CH_2CH_2NH_2$), 2.84 (ddd, J = 12.5/7.5/6.4 Hz, 1H, $CH_2CH_2NH_2$), 3.35 (t, J = 8.2 Hz, 1H, 5-H), 4.14 (dd, J = 8.2/6.1 Hz, 1H, 5-H), 4.25 (tdd, J = 8.1/6.1/4.9 Hz, 1H, 4-H), 7.25–7.34 (m, 3H, arom. H in *m*- and *p*-position), 7.43–7.47 (m, 2H, arom. H in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3368 (m, ν_{NH}), 2974, 2938, 2877 (s, each, ν_{CH}). HR-MS: Calcd 221.1416. Found: 221.1420.

6.20. (−)-2-[(2*S*,4*S*)-2-Ethyl-2-phenyl-1,3-dioxolan-4-yl]ethan-1-amine ((2*S*,4*S*)-13b)

As described for the racemic amine (±)-**12b**, the azide (2*S*,4*S*)-**11b** (24.7 mg, 0.10 mmol) was hydrogenated to yield (2*S*,4*S*)-**13b**. Colorless oil, yield 21.0 mg (95%). $[\alpha]_{589}^{20}$ −15.0 (*c* 1.01, CH_2Cl_2).

6.21. (+)-2-[(2*R*,4*R*)-2-Ethyl-2-phenyl-1,3-dioxolan-4-yl]ethan-1-amine ((2*R*,4*R*)-13b)

As described for the racemic amine (±)-**12b**, the azide (2*R*,4*R*)-**11b** (24.7 mg, 0.10 mmol) was hydrogenated

to yield (2*R*,4*R*)-**13b**. Colorless oil, yield 21.5 mg (97%). $[\alpha]_{589}^{20}$ +13.9 (*c* 1.00, CH_2Cl_2).

6.22. (+)-(3*S*)-4-Azidobutane-1,3-diol ((*S*)-14)[14]

A mixture of azide (2*S*,4*S*)-**24** (0.128 g, 0.64 mmol), Amberlyst® 15 (60 mg), and methanol (5 mL) was heated to reflux for 4 h. It was filtered and the solvent together with pivalaldehyde dimethyl acetal was evaporated in vacuo. Further transformations of (*S*)-**14** were performed without purification. Colorless oil, yield 69 mg (82%). $[\alpha]_{589}^{21}$ +3.24 (*c* 0.68, CH_2Cl_2).

6.23. (−)-(3*R*)-4-Azidobutane-1,3-diol ((*R*)-14)[14]

A mixture of azide (2*R*,4*R*)-**24** (0.169 g, 0.85 mmol), Amberlyst® 15 (85 mg) and methanol (8 mL) was heated to reflux for 4 h. It was filtered and the solvent together with pivalaldehyde dimethyl acetal was evaporated in vacuo. Further transformations of (*R*)-**14** were performed without purification. Colorless oil, yield 102 mg (92%). $[\alpha]_{589}^{23}$ −3.12 (*c* 0.80, CH_2Cl_2).

6.24. *rac-cis*-4-(Azidomethyl)-2-phenyl-1,3-dioxane ((±)-15a)

A solution of (±)-**17a** (0.348 g, 1.0 mmol) and NaN_3 (0.650 g, 10 mmol) in DMF (20 mL) was heated at 100 °C for 2.5 h. The mixture was concentrated in vacuo (≈10 mbar, 60 °C), the residue was suspended in Et_2O (20 mL), and the Et_2O-layer was washed with a saturated solution of $NaHCO_3$ (10 mL) and water (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Colorless oil, yield 0.210 g (96%). MS (EI): *m/z* (%) = 219 (M, 3.1). 163 (M−CH_2N_3, 88), ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.46 (dtd, *J* = 13.1/2.4/1.5 Hz, 1H, 5-H_{eq}), 1.87 (dddd, *J* = 13.1/12.2/11.6/5.2 Hz, 1H, 5-H_{ax}), 3.22 (dd, *J* = 12.8/4.0 Hz, 1H, CH_2N_3), 3.37 (dd, *J* = 12.8/6.7 Hz, 1H, CH_2N_3), 3.93 (ddd, *J* = 12.2/11.6/2.4 Hz, 1H, 6-H_{ax}), 4.03 (dddd, *J* = 11.6/6.7/4.0/2.4 Hz, 1H, 4-H_{ax}), 4.25 (ddd, *J* = 11.6/5.2/1.5 Hz, 1H, 6-H_{eq}), 5.49 (s, 1H, 2-H_{ax}), 7.26–7.33 (m, 3H, arom. H in *m*- and *p*-position), 7.42–7.46 (m, 2H, arom. H in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2965, 2925 (m, ν_{-CH_2-}), 2099 (s, ν_{N_3}), 1107, 1024 (s, ν_{CO}), 755, 700 (m, γ_{aryl}).

6.25. *rac-cis*-4-(Azidomethyl)-2-ethyl-2-phenyl-1,3-dioxane ((±)-15b)

Na_2SO_4 (ca. 1 g) was added to a solution of racemic azidodiol (±)-**14**[14] (0.262 g, 2.0 mmol) and propiophenone dimethyl acetal (**5b**, 0.361 g, 2.0 mmol) in THF (20 mL), then a solution of *p*-toluenesulfonic acid in THF (5.0 mL, 0.02 mol/L) was added and the mixture was heated to reflux for 4 h. The solvent was evaporated in vacuo, Et_2O (30 mL) was added to the residue, the mixture was decanted, and the Et_2O layer was washed with a saturated solution of $NaHCO_3$ (2× 10 mL) and water (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by fc (4 cm, petroleum ether/ethyl acetate = 77:3, fractions 10 mL, R_f = 0.16). Colorless oil, yield 0.250 g (51%). MS (CI): *m/z* (%) = 248 (MH, 12), 220 (MH−N_2, 97). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.84 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 1.26 (dtd, *J* = 12.8/2.4/1.5 Hz, 1H, 5-H_{eq}), 1.76 (dq, *J* = 13.7/7.6 Hz, 1H, CH_2CH_3), 1.81 (qd, *J* = 12.2/5.2 Hz, 1H, 5-H_{ax}), 1.82 (dq, *J* = 13.7/7.6 Hz, 1H, CH_2CH_3), 3.17 (dd, *J* = 12.8/3.4 Hz, 1H, CH_2N_3), 3.35 (dd, *J* = 12.8/7.3 Hz, 1H, CH_2N_3), 3.81 (ddd, *J* = 12.5/11.3/2.4 Hz, 1H, 6-H_{ax}), 3.93 (ddd, *J* = 11.3/5.2/1.5 Hz, 1H, 6-H_{eq}), 3.95 (dddd, *J* = 12.2/7.3/3.4/2.4 Hz, 1H, 4-H_{ax}), 7.29–7.36 (m, 1H, arom. H in *p*-position), 7.40–7.43 (m, 4H, arom. H in *o*- and *m*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2971, 2931, 2875 (m, ν_{CH}), 2099 (s, ν_{N_3}).

6.26. (−)-(2*S*,4*S*)-4-(Azidomethyl)-2-ethyl-2-phenyl-1,3-dioxane ((2*S*,4*S*)-15b)

As described for the racemate (±)-**15b**, (*S*)-azidobutanetriol (*S*)-**14** (65.6 mg, 0.50 mmol) was reacted with propiophenone dimethyl acetal (**5b**, 0.27 g, 1.5 mmol) to yield (2*S*,4*S*)-**15b**. Colorless oil, yield 40.3 mg (33%). $[\alpha]_{589}^{23}$ −106.3 (*c* 0.73, CH_2Cl_2).

6.27. (+)-(2*R*,4*R*)-4-(Azidomethyl)-2-ethyl-2-phenyl-1,3-dioxane ((2*R*,4*R*)-15b)

As described for the racemate (±)-**15b**, (*R*)-azidobutanetriol (*R*)-**14** (65.6 mg, 0.50 mmol) was reacted with propiophenone dimethyl acetal (**5b**, 90.1 mg, 0.5 mmol) to yield (2*R*,4*R*)-**15b**. Colorless oil, yield 41.3 mg (33%). $[\alpha]_{589}^{24}$ +98.5 (*c* 0.74, CH_2Cl_2).

6.28. (−)-(4*S*)-4-(Azidomethyl)-2,2-diphenyl-1,3-dioxane ((4*S*)-15c)

As described for the racemates (±)-**10b/11b**, the (*S*)-configured 4-azidobutanediol (*S*)-**14** (43.3 mg, 0.33 mmol) was heated to reflux with benzophenone dimethyl acetal (**5c**, 75.3 mg, 0.33 mmol) in THF (5 mL) for 7 h. Purification by fc (3 cm, petroleum ether/ethyl acetate = 19:1, fractions 10 mL, R_f = 0.15) afforded a colorless solid, mp 101 °C, yield 64.8 mg (67%). $[\alpha]_{589}^{23}$ −71.3 (*c* 0.95, CH_2Cl_2). MS (EI): *m/z* (%) = 295 (M, 13), 239 (M−CH_2N_3, 50), 218 (M− Ph, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.38 (dtd, *J* = 12.8/2.4/1.8 Hz, 1H, 5-H_{eq}), 1.94 (dtd, *J* = 12.8/11.6/5.8 Hz, 1H, 5-H_{ax}), 3.21 (dd, *J* = 12.8/3.4 Hz, 1H, CH_2N_3), 3.50 (dd, *J* = 12.8/7.6 Hz, 1H, CH_2N_3), 4.06 (td, *J* = 11.6/2.4 Hz, 1H, 6-H_{ax}), 4.12 (ddd, *J* = 11.6/5.8/1.8 Hz, 1H, 6-H_{eq}), 4.18 (dddd, *J* = 11.6/7.6/3.4/2.4 Hz, 1H, 4-H_{ax}), 7.16–7.32 (m, 4H, arom. H in *m*-position), 7.38–7.44 (m, 2H, arom. H in *p*-position), 7.53–7.59 (m, 4H, arom. H in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2967 (m, ν_{-CH_2-}), 2879 (m, $\nu_{-CH<}$), 2095 (s, ν_{N_3}), 1102 (s, ν_{CO}), 749, 704 (s, γ_{aryl}).

6.29. (+)-(4*R*)-4-(Azidomethyl)-2,2-diphenyl-1,3-dioxane ((4*R*)-15c)

As described for the racemates (±)-**10b/11b**, the (*R*)-configured 4-azidobutanediol (*R*)-**14** (323 mg, 0.25 mmol) was heated to reflux with benzophenone dimethyl acetal (**5c**, 57 mg, 0.50 mmol) in THF (5 mL) for 7 h. Colorless solid, mp 100 °C, yield 52.2 mg (71%). $[\alpha]_{589}^{23}$ +68.1 (*c* 0.72, CH_2Cl_2).

6.30. *rac-cis*-1-(2-Phenyl-1,3-dioxan-4-yl)methanamine ((±)-16a)

As described for the racemic amine (±)-**12b**, the racemic azide (±)-**15a** (46.0 mg, 0.21 mmol) was hydrogenated in THF (5 nL) for 2 h to yield (±)-**16a**. Colorless oil, yield 37.7 mg (93%). MS (CI): *m/z* (%) = 194 (MH^+, 91). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.44 (br s, 2H, NH_2), 1.48 (dtd, J = 13.1/2.4/1.5 Hz, 1H, 5-H_{eq}), 1.85 (dtd, J = 13.1/11.6/5.2 Hz, 1H, 5-H_{ax}), 2.81 (dd, J = 13.3/4.3 Hz, 1H, CH_2NH$_2$), 2.88 (dd, J = 13.3/7.0 Hz, 1H, CH_2NH$_2$), 3.85 (dddd, J = 11.3/7.0/4.3/2.4 Hz, 1H, 4-H_{ax}), 3.97 (ddd, J = 12.2/11.3/2.4 Hz, 1H, 6-H_{ax}), 4.29 (ddd, J = 11.3/5.2/1.5 Hz, 1H, 6-H_{eq}), 5.53 (s, 1H, 2-H_{ax}), 7.30–7.40 (m, 3H, arom. *H* in *m*- and *p*-position), 7.48–7.52 (m, 2H, arom. *H* in *o*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3373 (m, ν_{NH}), 2922, 2857 (m, ν_{CH}), 1593 (m, δ_{NH}). HR-MS: Calcd 193.1103. Found: 193.1102.

6.31. *rac-cis*-1-(2-Ethyl-2-phenyl-1,3-dioxan-4-yl)methanamine ((±)-16b)

As described for the racemic amine (±)-**12b**, the racemic azide (±)-**15b** (32.2 mg, 0.13 mmol) was hydrogenated to yield racemic (±)-**16b**. Colorless oil, yield 26.9 mg (94%). MS (CI): *m/z* (%) = 222 (MH, 57). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.82 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.24 (dtd, J = 12.8/2.7/1.5 Hz, 1H, 5-H_{eq}), 1.43 (br s, 2H, NH_2), 1.74 (tdd, J = 12.8/11.6/5.5 Hz, 1H, 5-H_{ax}), 1.76 (q, J = 7.5 Hz, 2H, CH_2CH_3), 2.74 (dd, J = 13.1/4.1 Hz, 1H, CH_2NH_2), 2.80 (dd, J = 13.1/6.7 Hz, 1H, CH_2NH_2), 3.70 (dddd, J = 11.6/6.7/4.1/2.7 Hz, 1H, 4-H_{ax}), 3.79 (ddd, J = 12.5/11.3/2.7 Hz, 1H, 6-H_{ax}), 3.90 (ddd, J = 11.3/5.5/1.5 Hz, 1H, 6-H_{eq}), 7.27–7.32 (m, 1H, arom. H in *p*-position), 7.38–7.40 (m, 4H, arom. H in *o*- and *m*-position). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3378 (m, ν_{NH}), 2938, 2873 (s, ν_{CH}). HR-MS: Calcd 221.1416. Found: 221.1416.

6.32. (−)-1-[(2*S*,4*S*)-2-Ethyl-2-phenyl-1,3-dioxan-4-yl]methanamine ((2*S*,4*S*)-16b)

As described for the racemic amine (±)-**12b**, the azide (2*S*,4*S*)-**15b** (24.7 mg, 0.10 mmol) was hydrogenated to yield (2*S*,4*S*)-**16b**. Colorless oil, yield 20.8 mg (94%). $[\alpha]_{589}^{20}$ −20.9 (*c* 0.90, CH_2Cl_2).

6.33. (+)-1-[(2*R*,4*R*)-2-Ethyl-2-phenyl-1,3-dioxan-4-yl]methanamine ((2*R*,4*R*)-16b)

As described for the racemic amine (±)-**12b**, the azide (2*R*,4*R*)-**15b** (24.7 mg, 0.10 mmol) was hydrogenated to yield (2*R*,4*R*)-**16b**. Colorless oil, yield 21.0 mg (95%). $[\alpha]_{589}^{20}$ +19.0 (*c* 0.88, CH_2Cl_2).

6.34. (−)-(4*S*)-1-(2,2-Diphenyl-1,3-dioxan-4-yl)methanamine ((4*S*)-16c)

As described for the racemic amine (±)-**12b**, the azide (4*S*)-**15c** (29.5 mg, 0.10 mmol) was hydrogenated to yield (4*S*)-**16c**. Colorless oil, yield 25.7 mg (96%). $[\alpha]_{589}^{20}$ −7.12 (*c* 1.11, CH_2Cl_2).

6.35. (+)-(4*R*)-1-(2,2-Diphenyl-1,3-dioxan-4-yl)methanamine ((4*R*)-16c)

As described for the racemic amine (±)-**12b**, the azide (4*R*)-**15c** (29.5 mg, 0.10 mmol) was hydrogenated to yield (4*R*)-**16c**. Colorless oil, yield 28.0 mg (100%). $[\alpha]_{589}^{20}$ +6.88 (*c* 0.89, CH_2Cl_2).

6.36. *rac-cis*-[(2-Phenyl-1,3-dioxan-4-yl)methyl]tosylate ((±)-17a)

A cold solution of *p*-toluenesulfonyl chloride (1.907 g, 10.0 mmol) in CH_2Cl_2 (10 mL) was added to a cold solution of (±)-**8a**[15,16] (0.971 g, 5 mmol) and NEt_3 (0.84 mL, 6 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred for 48 h at 4 °C. The solvent was evaporated in vacuo and the residue was purified by fc (6 cm, petroleum ether/ethyl acetate = 7:3, fractions 35 mL, R_f = 0.30). Colorless solid, mp 69–74 °C, yield 1.608 g (92%). MS (EI): *m/z* (%) = 348 (M, 51), 163 (M−CH_2OTos, 35). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.55 (dtd, J = 13.4/2.4/1.2 Hz, 1H, 5-H_{eq}), 1.81 (dddd, J = 13.4/12.2/11.0/5.2 Hz, 1H, 5-H_{ax}), 2.42 (s, 3H, PhCH_3), 3.94 (ddd, J = 12.2/11.6/2.7 Hz, 1H, 6-H_{ax}), 4.10 (dd, J = 10.1/6.4 Hz, 1H, CH_2OTos), 4.12 (m, 1H, 4-H_{ax}), 4.14 (dd, J = 10.1/4.0 Hz, 1H, CH_2OTos), 4.28 (ddd, J = 11.6/5.2/1.2 Hz, 1H, 6-H_{eq}), 5.46 (s, 1H, 2-H_{ax}), 7.28 (d, J = 8.5 Hz, 2H, arom. *H*-3, *H*-5$_{PhCH3}$), 7.32–7.36 (m, 3H, arom. *H* in *m*- and *p*-position), 7.37–7.42 (m, 2H, arom. H in *o*-position), 7.79 (d, J = 8.5 Hz, 2H, arom. *H*-2, *H*-6$_{PhCH3}$). IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2962 (m, ν_{-CH_2-}), 2861 (m, $\nu_{-CH<}$).

6.37. (+)-(2*S*,4*S*)/(2*R*,4*S*)-2-(2-*tert*-Butyl-1,3-dioxolan-4-yl)ethan-1-ol ((4*S*)-19) and (+)-(2*S*,4*S*)-(2-*tert*-Butyl-1,3-dioxan-4-yl)methanol ((2*S*,4*S*)-20)

A solution of *p*-toluenesulfonic acid monohydrate (0.10 mol/L, 5.0 mL in THF) was added to a solution of pivalaldehyde (**18**, 1.72 g, 20 mmol) and (*S*)-butane-1,2,4-triol ((*S*)-**6**, 1.06 g, 10 mmol) in THF (45 mL) and the mixture was heated to reflux for 4 h. After the addition of $NaHCO_3$, the mixture was concentrated in vacuo. The residue was suspended in ethyl acetate (40 mL), filtered, and the filtrate was washed with a saturated solution of $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue ((4*S*)-**19**/(2*S*,4*S*)-**20** = 63:37) was purified by fc (8 cm, petroleum ether/ethyl acetate = 7:3, fractions 20 mL).

(2*S*,4*S*)-**20**; (R_f = 0.29): Colorless oil, yield 0.535 g (31%). $[\alpha]_{589}^{23}$ +8.61 (*c* 1.05, CH_2Cl_2).

(4*S*)-**19** (R_f = 0.20): Colorless oil, yield 0.784 g (45%). $[\alpha]_{589}^{23}$ +3.42 (*c* 1.00, CH_2Cl_2). (2*S*,4*S*)-**19**/(2*R*,4*S*)-**19** = 20:80.

6.38. (−)-(2*R*,4*R*)/(2*S*,4*R*)-2-(2-*tert*-Butyl-1,3-dioxolan-4-yl)ethan-1-ol ((4*R*)-19) and (−)-(4*R*)-(2-*tert*-Butyl-1,3-dioxan-4-yl)methanol ((2*R*,4*R*)-20)

The preparation of (4*R*)-**19** and (2*R*,4*R*)-**20** was performed as described above for the enantiomers using (*R*)-butane-1,2,4-triol ((*R*)-**6**, 1.06 g, 10.0 mmol).

(2*R*,4*R*)-**20** (R_f = 0.29): Colorless oil, yield 0.486 g (28%). $[\alpha]_{589}^{23}$ −7.80 (*c* 0.80, CH_2Cl_2).

(4*R*)-**19** (R_f = 0.20): Colorless oil, yield 0.808 g (46%). $[\alpha]_{589}^{23}$ −2.71 (*c* 1.04, CH_2Cl_2). (2*R*,4*R*)-**19**/(2*S*,4*R*)-**19** = 22:78.

6.39. (−)-[(2*S*,4*S*)/(2*R*,4*S*)-2-(2-*tert*-Butyl-1,3-dioxolan-4-yl)ethyl]tosylate ((4*S*)-21)

A cold solution of *p*-toluenesulfonyl chloride (2.48 g, 13 mmol) in CH_2Cl_2 (50 mL) was added to a cold solution of (4*S*)-**19** (1.13 g, 6.5 mmol, (2*S*,4*S*)-**19**/(2*R*,4*S*)-**19** = 20:80) and NEt_3 (1.1 mL, 7.8 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred for 48 h at 4 °C. The solvent was evaporated in vacuo and the residue was purified by fc (8 cm, petroleum ether/ethyl acetate = 7:3, fractions 35 mL, R_f = 0.30). Colorless solid, mp 69–74 °C, yield 1.9 g (89%). (2*S*,4*S*)-**21**/(2*R*,4*S*)-**21** = 20:80. $[\alpha]_{589}^{26}$ −18.2 (*c* 1.12, CH_2Cl_2).

6.40. (+)-[(2*R*,4*R*)/(2*S*,4*R*)-2-(2-*tert*-Butyl-1,3-dioxolan-4-yl)ethyl]tosylate ((4*R*)-21)

As described for (4*S*)-**21**, the dioxolane (4*R*)-**19** (0.66 g, 3.8 mmol, (2*R*,4*R*)-**19**/(2*S*,4*R*)-**19** = 22:78) was reacted with *p*-toluenesulfonyl chloride (1.45 g, 7.6 mmol) and triethylamine (0.64 mL, 4.6 mmol) in CH_2Cl_2 (40 mL) to give the tosylate (4*R*)-**21**. Colorless solid, mp 70–74 °C, yield 0.91 g (73%). [(2*R*,4*R*)-**21**/(2*S*,4*R*)-**21** = 19:81. $[\alpha]_{589}^{26}$ +13.2 (*c* 1.00, CH_2Cl_2).

6.41. (−)-(2*S*,4*S*)/(2*R*,4*S*)-4-(2-Azidoethyl)-2-*tert*-butyl-1,3-dioxolane ((4*S*)-22)

As described for the racemic azide (±)-**15a**, the enantiomerically pure tosylate (4*S*)-**21** (1.64 g, 5.0 mmol, (2*S*,4*S*)-**21**/(2*R*,4*S*)-**21** = 20:80) was reacted with NaN_3 (3.25 g, 50 mmol) in DMF (50 mL) to yield (4*S*)-**22** after work-up. Colorless oil, yield 0.88 g (88%). (2*S*,4*S*)-**22**/(2*R*,4*S*)-**22** = 20:80. $[\alpha]_{589}^{22}$ −20.4 (*c* 0.71, CH_2Cl_2).

6.42. (+)-(2*R*,4*R*)/(2*S*,4*R*)-4-(2-Azidoethyl)-2-*tert*-butyl-1,3-dioxolane ((4*R*)-22)

As described for the racemic azide (±)-**15a**, the enantiomerically pure tosylate (4*R*)-**21** (0.755 g, 2.3 mmol, (2*R*,4*R*)-**21**/(2*S*,4*R*)-**21** = 19:81) was reacted with NaN_3 (1.495 g, 23 mmol) in DMF (35 mL) to yield (4*R*)-**22** after work-up. Colorless oil, yield 0.35 g (77%). (2*R*,4*R*)-**22**/(2*S*,4*R*)-**22** = 21:79. $[\alpha]_{589}^{22}$ +17.1 (*c* 0.75, CH_2Cl_2).

6.43. (+)-[(2*S*,4*S*)-(2-*tert*-Butyl-1,3-dioxan-4-yl)methyl]tosylate ((2*S*,4*S*)-23)

As described for (4*S*-**21**, the dioxane (2*S*,4*S*)-**20** (0.70 g, 4.0 mmol) was reacted with *p*-toluenesulfonyl chloride (1.53 g, 8.0 mmol) and triethylamine (0.67 mL, 4.8 mmol) in CH_2Cl_2 (40 mL) to give the tosylate (2*S*,4*S*)-**23**. Colorless solid, mp 62–64 °C, yield 0.794 g (61%). $[\alpha]_{589}^{26}$ +0.58 (*c* 1.04, CH_2Cl_2).

6.44. (−)-[(2*R*,4*R*)-(2-*tert*-Butyl-1,3-dioxan-4-yl)methyl]-tosylate ((2*R*,4*R*)-23)

As described for (4*S*)-**21**, the dioxane (2*R*,4*R*)-**20** (0.44 g, 2.3 mmol) was reacted with *p*-toluenesulfonyl chloride (0.88 g, 4.6 mmol) and triethylamine (0.39 mL, 2.8 mmol) in CH_2Cl_2 (30 mL) to give the tosylate (2*R*,4*R*)-**23**. Colorless solid, mp 62–64 °C, yield 0.592 g (78%) $[\alpha]_{589}^{26}$ −0.48 (*c* 1.04, CH_2Cl_2).

6.45. (−)-[(2*S*,4*S*)-4-(Azidomethyl)-2-*tert*-butyl-1,3-dioxane ((2*S*,4*S*)-24)

As described for the racemic azide (±)-**15a**, the enantiomerically pure tosylate (2*S*,4*S*)-**23** (0.624 g, 1.9 mmol) was reacted with NaN_3 (1.235 g, 19 mmol) in DMF (30 mL) to yield (2*S*,4*S*)-**24** after work-up. Colorless oil, yield 0.276 g (73%). $[\alpha]_{589}^{22}$ −25.5 (*c* 0.53, CH_2Cl_2).

6.46. (+)-[(2*R*,4*R*)-4-(Azidomethyl)-2-*tert*-butyl-1,3-dioxane ((2*R*,4*R*)-24)]

As described for the racemic azide (±)-**15a**, the enantiomerically pure tosylate (2*R*,4*R*)-**23** (0.460 g, 1.4 mmol) was reacted with NaN_3 (0.910 g, 14 mmol) in DMF (25 mL) to yield (2*R*,4*R*)-**24** after work-up. Colorless oil, yield 0.186 g (67%). $[\alpha]_{589}^{22}$ +23.5 (*c* 0.52, CH_2Cl_2).

7. Receptor binding studies

7.1. General

Homogenizer: Potter®S (B. Braun Biotech International). Ultraturrax: Euroturrax® T20 (Ika Labortechnik). Centrifuge: High-speed cooling centrifuge model J2-HS (Beckman). Filter: Whatman glass fiber filters GF/B and GF/C, presoaked in 1% (NMDA assay) or 0.5% (σ_1 assay) polyethylenimine (in water) for 2 h at 4 °C before use. Filtration was performed with a Brandel 24-well cell harvester. Scintillation cocktail: Rotiscint Eco Plus (Roth). Liquid scintillation analyzer: TriCarb 2100 TR (Canberra Packard), counting efficiency 65%. All experiments were carried out in triplicate. IC_{50}-values were determined in competition experiments with at least six concentrations of test compounds and were calculated with the program GraphPad Prism® 3.0 (GraphPad Software) by non-linear regression analysis. K_i-values were calculated according to Cheng and Prusoff.[24] The K_i-values are given as mean value ± SEM from three independent experiments.

7.2. Investigation of the affinity to the phencyclidine binding site of the NMDA receptor[12]

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

7.3. Preparation of the tissue

Fresh pig brain cortex was homogenized with a potter (500 rpm, 10 up-and-down strokes) in 10 volumes of

cold 0.32 M sucrose. The suspension was centrifuged at 1000*g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 10,000*g* for 20 min at 4 °C. The pellet was resuspended in buffer (5 mM Tris–acetate with 1 mM EDTA, pH 7.5) with an Ultraturrax (8000 rpm) and centrifuged at 20,000*g* (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford[25] using bovine serum albumin as standard, and subsequently the preparation was frozen (−83 °C) in 5 mL portions of about 1 mg protein/mL.

7.4. Performance of the assay

The test was performed with the radioligand [^{3}H]-(+)-MK-801 (832.5 GBq/mmol; NEN^{TM} Life Science Products). The thawed membrane preparation (about 100 μg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-MK-801, and buffer (5 mM Tris–acetate, 1 mM EDTA, pH 7.5) in a total volume of 500 μL for 90 min at 25 °C. The incubation was terminated by rapid filtration through presoaked Whatman GF/C filters using a cell harvester. After washing four times with 2 mL of cold buffer, 3 mL of scintillation cocktail was added to the filters. After at least 8 h, bound radioactivity trapped on the filters was counted in a liquid scintillation analyzer. Non-specific binding was determined with 10 μM (+)-MK-801.

7.5. Investigation of the σ_1 receptor affinity[22]

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

7.6. Membrane preparation

Thawed guinea pig brains (Dunkin Hartley, Harlan-Sera-Lab) were homogenized with an ultraturrax (8000 rpm) in 10 volumes of cold 0.32 M sucrose. The homogenate was centrifuged at 1000*g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 22,000*g* for 20 min at 4 °C. The pellet was resuspended in 10 volumes of buffer (50 mM Tris–HCl, pH 7.4) with an ultraturrax (8000 rpm), incubated for 30 min at 25 °C, and centrifuged at 22,000*g* (20 min, 4 °C). The pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford[25] using bovine serum albumin as standard, and subsequently the preparation was frozen (−83 °C) in 5 mL portions of about 2 mg protein/mL.

7.7. Performance of the σ_1 assay

The test was performed with the radioligand [ring-1,3-^{3}H]-(+)-pentazocine (1036 GBq/mmol; NEN^{TM} Life Science Products). The thawed membrane preparation (about 150 μg of the protein) was incubated with various concentrations of test compounds, 3 nM [^{3}H]-(+)-pentazocine and buffer (50 mM Tris–HCl, pH 7.4), in a total volume of 500 μL for 150 min at 37 °C. The incubation was terminated by rapid filtration through presoaked Whatman GF/B filters using a cell harvester. After washing four times with 2 mL of cold buffer, 3 mL of scintillation cocktail was added to the filters. After at least 8 h, bound radioactivity trapped on the filters was counted in a liquid scintillation analyzer. Non-specific binding was determined with 10 μM haloperidol.

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