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Synthesis and SAR studies of chiral non-racemic dexoxadrol analogues as uncompetitive NMDA receptor antagonists

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ABSTRACT

A series of chiral non-racemic dexoxadrol analogues with various substituents in position 4 of the piperidine ring was synthesized and pharmacologically evaluated. Only the enantiomers having (*S*)-configuration at the 2-position of the piperidine ring and 4-position of the dioxolane ring were considered. Key steps in the synthesis were an imino-Diels–Alder reaction of enantiomerically pure imine (*S*)-**13**, which had been obtained from D-mannitol, with Danishefsky's Diene **14** and the replacement of the *p*-methoxybenzyl protective group with a Cbz-group. It was shown that (*S*,*S*)-configuration of the ring junction (position 2 of the piperidine ring and position 4 of the dioxolane ring) and axial orientation of the C-4-substituent ((4*S*)-configuration) are crucial for high NMDA receptor affinity. 2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidines with a hydroxy moiety ((*S*,*S*,*S*)-**5**, K_i = 28 nM), a fluorine atom ((*S*,*S*,*S*)-**6**, WMS-2539, K_i = 7 nM) and two fluorine atoms ((*S*,*S*)-**7**, K_i = 48 nM) in position 4 represent the most potent NMDA antagonists with high selectivity against σ_1 and σ_2 receptors and the polyamine binding site of the NMDA receptor. The NMDA receptor affinities of the new ligands were correlated with their electrostatic potentials, calculated gas phase proton affinities (negative enthalpies of deprotonation) and dipole moments. According to these calculations decreasing proton affinity and increasing dipole moment are correlated with decreasing NMDA receptor affinity.

1. Introduction

The NMDA (*N*-methyl-D-aspartate) receptor is a ligand gated ion channel, which is activated physiologically by the neurotransmitter (*S*)-glutamate and controls the influx of cations (Na^+, Ca^{2+}) into neurons.[1] The physiological activation of the NMDA receptor is crucial for processes like long term potentiation and synaptic plasticity, which are considered to be the cellular correlates of memory and learning.[2,3] However, overactivation of the NMDA receptor leads to excessive influx of Ca^{2+}-ions into neurons which results in neuronal cell damage up to neuronal cell death (excitotoxicity).[4] Disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, HIV-associated dementia, multiple sclerosis, amyotrophic lateral sclerosis, and neuropathic pain share a common pathway to neuronal damage, that is, due to the overstimulation of glutamate receptors, especially of the NMDA subtype.[5] Acute disorders like stroke, central nervous system trauma and seizures also manifest a component of excitotoxicity. NMDA receptor antagonists are therefore of potential therapeutic value in a number of acute and chronic neurological disorders.

Our interest has been focused on the phencyclidine (PCP, **1**) binding site, which is located within the cation channel pore. Compounds interacting with the PCP binding site act as uncompetitive NMDA receptor antagonists by blocking the cation channel and inhibiting the influx of cations, in particular of Ca^{2+}-ions. Up to now, memantine (**2b**, Fig. 1) is the only NMDA receptor antagonist with moderate NMDA receptor affinity (K_i = 1.2 μM), which is clinically used for the treatment of severe Alzheimer's disease.[6,7] The favorable off rate kinetics of memantine prevents its accumulation in the ion channel leading to minimal adverse side effects.[8,9] Parkinson's disease can be treated with the didemethyl derivative amantadine (**2a**), which also represents a moderate uncompetitive NMDA receptor antagonist.

In contrast to amantadine (**2a**) and memantine (**2b**), the enantiomerically pure piperidine derivative dexoxadrol (*S*,*S*)-**3** binds with high affinity (K_i = 11 nM) at the PCP binding site within the NMDA receptor associated cation channel. Dexoxadrol was originally synthesized by Hardie et al. in the 1960s and revealed local anesthetic, spasmolytic, and central nervous system activity.[10] Later phencyclidine like dissociative anesthetic activities were found.[11] Unfortunately, clinical trials of dexoxadrol had to be stopped because of the psychotomimetic side effects. Since the severe side effects of dexoxadrol are attributed to its high NMDA receptor affinity and unfavorable kinetic properties, novel analogues

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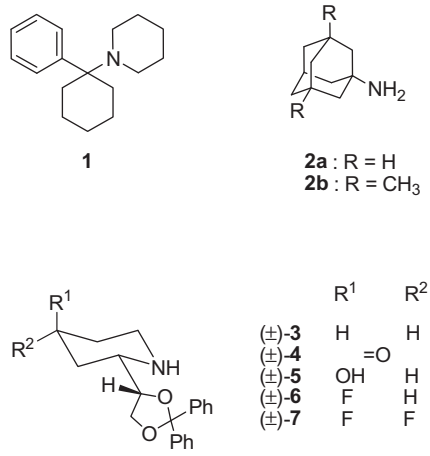


Figure 1. Structures of some important NMDA receptor antagonists: phencyclidine (PCP, **1**); amantadine (**2a**); memantine (**2b**); dioxadrol ((±)-**3**); racemic 4-oxodioxadrol ((±)-**4**), racemic 4-hydroxydioxadrol ((±)-**5**), racemic 4-fluorodioxadrol ((±)-**6**), racemic 4,4-difluorodioxadrol ((±)-**7**). Dexoxadrol is the (*S*,*S*)-enantiomer (*S*,*S*)-**3** of racemic dioxadrol (±)-**3**.

with moderate affinities should display the desired pharmacological effects with an improved side effect profile.

Some derivatives of dexoxadrol have been synthesized in order to get more insight into the structure–affinity relationships within this compound class.[12–15] Recently we have reported on the synthesis of racemic dioxadrol derivatives bearing various substituents (NR_2, OR, =O, F) in position 4 of the piperidine ring.[16–18] It was shown that *like*-configuration (*RS*/*RS*) of the ring junction, that is, the same configuration of the 2-position of the piperidine ring and 4-position of the dioxolane ring, and axial orientation of the C-4-substituent (also *RS*-configuration) are crucial for high NMDA receptor affinity. In particular, 4-oxo [(±)-**4**], 4-hydroxy [(±)-**5**], 4-fluoro [(±)-**6**], and 4,4-difluoro [(±)-**7**] derivatives of dioxadrol [(±)-**3**] with the same configuration at all centers of chirality reveal promising NMDA receptor affinity of 470, 44, 27, and 81 nM, respectively.[16–18] The affinities of these compounds (±)-**4**–(±)-**7** are in an interesting range between the affinities of enantiomerically pure dexoxadrol [(*S*,*S*)-**3**] and memantine (**2b**).

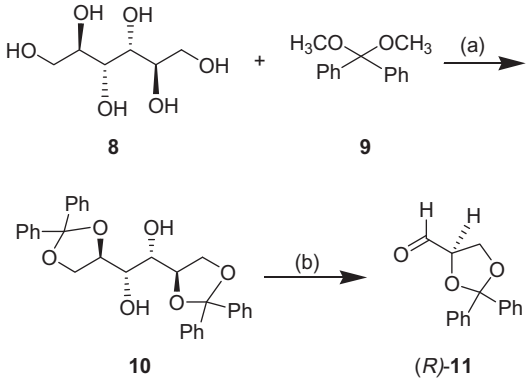
It is well known that the three dimensional structure (absolute configuration) of a chiral molecule plays an important role for its interaction with enantiomerically pure receptor proteins. Therefore, the NMDA receptor affinity of the eutomers of the racemic dioxadrol derivatives (±)-**4**–(±)-**7** should be investigated.

Herein we report on a chiral pool synthesis of the (*S*,(*S*),*S*)-configured eutomers of racemic piperidines (±)-**4**–(±)-**7**, via an imino-Diels–Alder reaction as key step. Moreover, the novel synthetic strategy is extended to the stereoselective synthesis of enantiomerically pure dexoxadrol (*S*,*S*)-**3**.

2. Synthesis

For the chiral pool synthesis of (*S*,*S*)-configured dexoxadrol derivatives the (*R*)-configured aldehyde (*R*)-**11** was required. Conversion of the aldehyde (*R*)-**11** into imines or amines changed the stereodescriptor of the chiral center from (*R*) to (*S*) according to the formalism of the CIP rules.

The synthesis of (*R*)-**11** started with C_2-symmetric D-mannitol (**8**). At first the hexaol **8** was transformed into the double ketal **10** upon reaction with benzophenone dimethyl ketal (**9**) in the presence of $SnCl_2$. The reaction provided the desired diol **10** as the major product, which was isolated in 56% yield. The diol **10** was cleaved with lead tetraacetate at 0 °C to obtain two equivalents of aldehyde (*R*)-**11** in 95% yield (Scheme 1).[19]

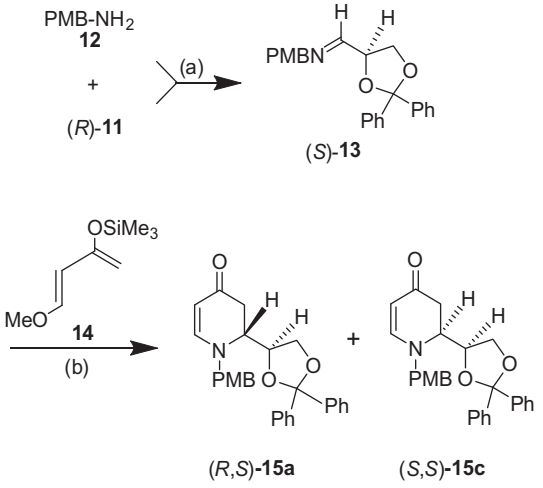


Scheme 1. Synthesis of enantiomerically pure aldehyde (*R*)-**11**. Reagents and conditions: (a) $SnCl_2$, dimethoxyethane, 14 h, reflux, 56% and (b) $Pb(OAc)_4$, CH_2Cl_2, 30 min, 0 °C, 95%.

The second center of chirality at 2-position of the piperidine ring of **15** was established during the imino-Diels–Alder reaction. The desired diastereomer was (*S*,*S*)-**15c** having (*S*)-configuration at both centers of chirality.

First it was planned to control the diastereoselectivity of this key transformation by exploiting the chirality of the aldehyde (*R*)-**11**. In order to investigate the effect of the chirality of (*R*)-**11** on the diastereoselectivity of the imino-Diels–Alder reaction, the aldehyde (*R*)-**11** was converted into imine (*S*)-**13** by condensation with *p*-methoxybenzylamine (PMB-NH_2) (Scheme 2). The imino-Diels–Alder reaction[20] between imine (*S*)-**13** and Danishefsky's diene **14**[21,22] was carried out using different reaction conditions. Different Lewis acid catalysts ($Yb(OTf)_3$, $BF_3{\cdot}OEt_2$), different solvents (THF, CH_2Cl_2) as well as different reaction temperatures (0 °C, −78 °C) were investigated. However, all these transformations took place without diastereoselectivity (43:57–52:48, Table 1, entries 1–5). The ratio of the diastereomers was determined by HPLC analysis of the crude products. The compounds were identified by comparing the retention times with those of the racemic products.[17]

In order to improve the yield of (*S*,*S*)-configured piperidine derivatives enantiomerically pure amines were used as additional chiral auxiliaries for the imine formation and the subsequent imino-Diels–Alder reaction. Enantiomerically pure 1-phenylethylamines (*R*)-**16** and (*S*)-**16** were selected as chiral auxiliaries, since



Scheme 2. Synthesis of dihydropyridones (*R*,*S*)-**15a** and (*S*,*S*)-**15c**. Reagents and conditions: (a) $CH(OMe)_3$, rt, 14 h and (b) reaction conditions see Table 1.

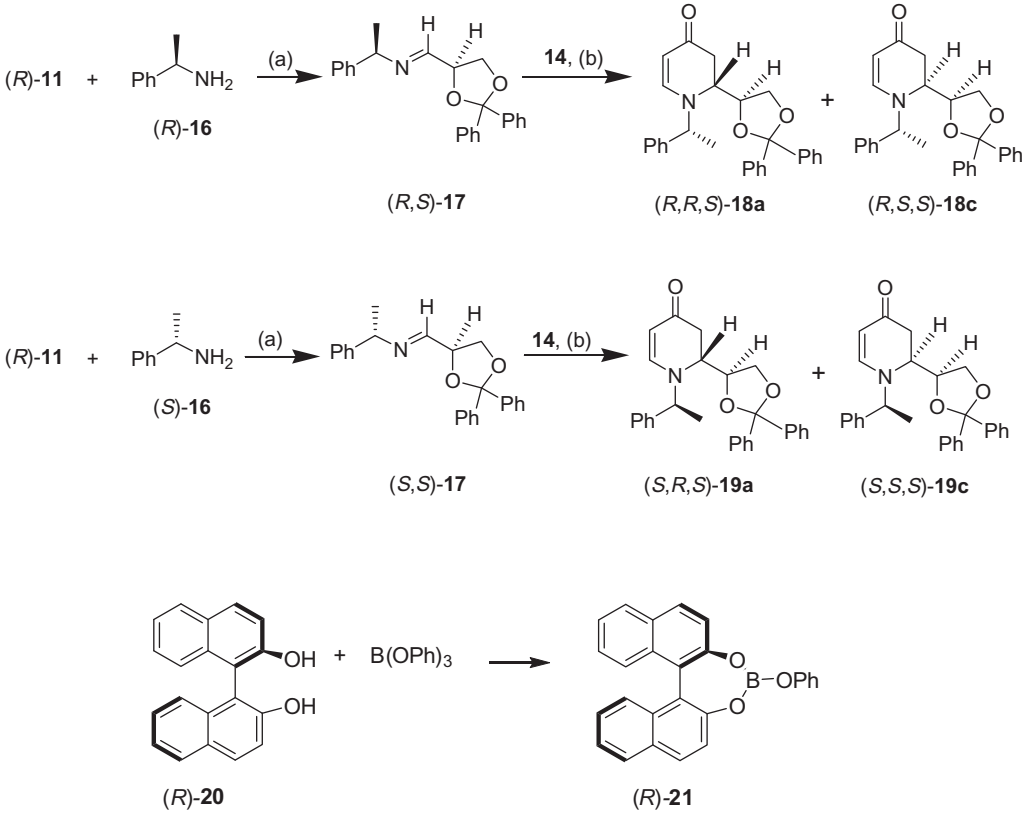
Table 1
Diastereoselectivity in the imino-Diels–Alder reaction under different reaction conditions: in all the cases the diene **14** was added to the imines **13** or **17** at the given temperature and stirred for 4 h at the same temperature followed by warming up to rt overnight

Entry	Solvent	RNH_2	Catalyst (equiv)	Temperature (°C)	Yield (%)	2*R*:2*S*
1	THF	**12**	$Yb(OTf)_3$ (0.2)	0	75	43:57
2	THF	**12**	$Yb(OTf)_3$ (0.2)	−78	75	43:57
3	CH_2Cl_2	**12**	$Yb(OTf)_3$ (0.2)	−78	0	—
4	CH_2Cl_2	**12**	$BF_3{\cdot}OEt_2$ (1.0)	−78	72	52:48
5	CH_2Cl_2	**12**	$BF_3{\cdot}OEt_2$ (0.5)	−78	70	52:48
6	CH_2Cl_2	(*R*)-**16**	$ZnCl_2$ (1.5)	−78	70	70:30
7	CH_2Cl_2	(*R*)-**16**	$BF_3{\cdot}OEt_2$ (1.5)	−78	65	77:23
8	CH_2Cl_2	(*R*)-**16**	$BF_3{\cdot}OEt_2$ (0.5)	−78	67	77:23
9	THF	(*R*)-**16**	$BF_3{\cdot}OEt_2$ (1.5)	−78	75	52:48
10	CH_2Cl_2	(*S*)-**16**	$BF_3{\cdot}OEt_2$ (1.5)	−78	78	88:12
11	THF	(*S*)-**16**	$BF_3{\cdot}OEt_2$ (1.5)	−78	60	67:33
12	CH_2Cl_2	**12**	(*S*)-**21** (0.5)	−78	66	54:46
13	CH_2Cl_2	**12**	(*S*)-**21** (1.0)	−78	65	54:46
14	CH_2Cl_2	**12**	(*R*)-**21** (0.5)	−78	0	—
15	CH_2Cl_2	**12**	(*R*)-**21** (1.0)	−78	0	—
16	CH_2Cl_2	(*R*)-**16**	(*S*)-**21** (0.5)	−78	23	62:38
17	CH_2Cl_2	(*R*)-**16**	(*R*)-**21** (0.5)	−78	0	—
18	CH_2Cl_2	(*S*)-**16**	(*S*)-**21** (0.5)	−78	0	—
19	CH_2Cl_2	(*S*)-**16**	(*R*)-**21** (0.5)	−78	0	—

The yields are the combined yields of both diastereomers. The diastereoselectivity was measured by HPLC. The ratio 2*R*:2*S* refers to the ratio of the diastereomers having (*R*) and (*S*) configuration at the 2-position of the dihydropyridine ring.

the 1-phenylethyl moiety could be easily removed by hydrogenolysis. Moreover, the use of enantiomerically pure 1-phenylethylamines as chiral auxiliaries has been reported to provide high diastereoselectivities during imino-Diels–Alder reactions.[23]

Thus, aldehyde (*R*)-**11** was reacted with (*R*)-**16** and (*S*)-**16** and the resulting imines (*R*,*S*)-**17** and (*S*,*S*)-**17** were employed for the imino-Diels–Alder reaction (Scheme 3). The Lewis acids $ZnCl_2$ and $BF_3{\cdot}OEt_2$ were used in the solvents CH_2Cl_2 and THF. Generally the transformations in CH_2Cl_2 gave higher diastereoselectivities than the reactions in THF. (Table 1, entries 6–11) $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C led to the highest diastereoselectivities of 77:23 ((*R*,*R*,*S*)-**18a**/(*R*,*S*,*S*)-**18c**, Table 1, entries 7 and 8) and 88:12 ((*S*,*R*,*S*)-**19a**/(*S*,*S*,*S*)-**19c**, Table 1, entry 10) employing the diastereomeric imines (*R*,*S*)-**17** and (*S*,*S*)-**17**, respectively. However, both imines (*R*,*S*)-**17** and (*S*,*S*)-**17** led predominantly to the cycloaddition products (*R*,*R*,*S*)-**18a** and (*S*,*R*,*S*)-**19a** with the undesired (*R*)-configuration in position 2 of the dihydropyridine ring. In order to determine the absolute configuration and hence the diastereoselectivities, the



Scheme 3. Investigation of the diastereoselectivity of the imino-Diels–Alder reaction using chiral 1-phenylethylamine and chiral Lewis acids. Reagents and conditions: (a) $CH(OMe)_3$, rt, 14 h and (b) reaction conditions see Table 1.

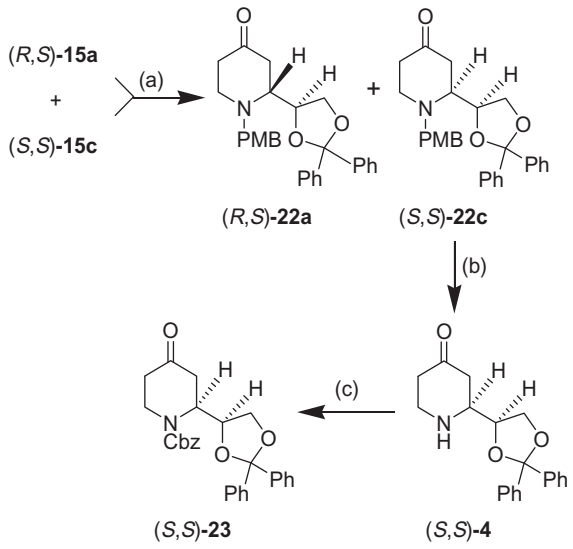
double bond of the dihydropyridones **18** and **19** was reduced selectively with $LiEt_3BH$ and $BF_3{\cdot}OEt_2$ and the 1-phenylethyl group was cleaved by hydrogenolysis leading to the piperidones (*R*,*S*)-**4** and (*S*,*S*)-**4** (compare Scheme 4).

Since the chiral auxiliary approach did not lead to the desired (*S*,*S*)-configured diastereomer in high yields, the use of chiral Lewis acids was envisaged. It has been shown that the Lewis acids (*R*)-**21** and (*S*)-**21** afford high enantioselectivities in similar imino-Diels–Alder reactions.[23] The chiral Lewis acids (*R*)-**21** and (*S*)-**21** were generated in situ by reaction of chiral binaphthols (*R*)-**20** and (*S*)-**20** with triphenyl borate $B(OPh)_3$ (Scheme 3).[23]

First the effect of the chiral Lewis acids (*R*)-**21** and (*S*)-**21** on the diastereoselectivity of the imino-Diels–Alder reaction of the PMB-derived imine (*S*)-**13** was investigated. It was found that the Lewis acid (*S*)-**21** led to the cycloaddition products (*R*,*S*)-**15a** and (*S*,*S*)-**15c** indicating catalytic activity. However, the diastereomers were produced in almost 1:1 ratio, that is, without diastereoselectivity. (Table 1, entries 12 and 13) On the other hand the enantiomeric Lewis acid (*R*)-**21** was not able to catalyze the cycloaddition at all. (Table 1, entries 14 and 15).

Reduced conversion was also observed, when the chiral Lewis acids (*R*)-**21** and (*S*)-**21** were used for the imino-Diels–Alder reaction of phenylethylamine derived imines (*R*,*S*)-**17** and (*S*,*S*)-**17**. Whereas, the reaction of (*R*,*S*)-**17** in the presence of the chiral Lewis acid (*S*)-**21** led to 23% yield of the cycloaddition products with poor diastereoselectivity, the other possible combinations of chiral Lewis acid and imine did not yield any products. (Table 1, entries 16–19) Obviously most combinations of chiral Lewis acid (**21**) and chiral auxiliary (phenylethylamine) are mismatched pairs.

In conclusion, the influence of the chiral substrate (*S*)-**13**, the chiral auxiliary phenylethylamine (**16**) and the chiral Lewis acid **21** on the diastereoselectivity of the imino-Diels–Alder reaction has been investigated. The highest diastereoselectivity was achieved using the imine (*S*,*S*)-**17**, which favored the formation of the product (*S*,*R*,*S*)-**19a** with (2*R*)-configuration of the dihydropyridine ring (88:12, Table 1, entry 10). $Yb(OTf)_3$ in THF led to a slight preference of (*S*,*S*)-**15c** with the desired (2*S*)-configuration (57:43, Table 1, entries 1 and 2). Therefore this mixture (*S*,*S*)-**15c** and (*R*,*S*)-**15a** (57:43) was used for the synthesis of dexoxadrol analogues with different residues in 4-position of the piperidine ring.



Scheme 4. Separation of diastereomers and replacement of the PMB-protective group with the Cbz-protective group. Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, THF, −78 °C, 30 min, then $LiEt_3BH$, −78 °C, 2 h, 35% ((*R*,*S*)-**22a**), 52% ((*S*,*S*)-**22c**); (b) H_2, Pd/C 10%, MeOH, 16 h, rt, 85%; (c) $PhCH_2OCOCl$, NEt_3, THF, 1 h, rt, 90%.

The mixture **15a**/**15c** (43:57) was reduced with $LiEt_3BH$ and $BF_3{\cdot}OEt_2$ to obtain the piperidones (*R*,*S*)-**22a** and (*S*,*S*)-**22c**. Separation by flash chromatography provided the pure diastereomeric piperidones (*R*,*S*)-**22a** and (*S*,*S*)-**22c** in 35% and 52% yield, respectively. Hydrogenolytic removal of the PMB-group of (*S*,*S*)-**22c** using H_2 and Pd/C afforded enantiomerically pure 4-oxodexoxadrol (*S*,*S*)-**4**, which was acylated with benzyl chloroformate (Cbz-Cl) in the presence of triethylamine to give the Cbz-protected piperidone (*S*,*S*)-**23** (Scheme 4).

The Cbz-protected piperidone (*S*,*S*)-**23** was reduced with $NaBH_4$ in MeOH at 0 °C to afford the alcohols (*S*,*R*,*S*)-**24c** and (*S*,*S*,*S*)-**24d** in the ratio 1:1 (Scheme 4).[24] Since both diastereomeric alcohols (*S*,*R*,*S*)-**24c** and (*S*,*S*,*S*)-**24d** were required for further transformations an improvement of the diastereoselectivity was not taken into account. In order to obtain the potential eutomer of the potent racemic alcohol (±)-**5** the Cbz-group of (*S*,*S*,*S*)-**24d** was hydrogenolytically removed and the enantiomerically pure alcohol (*S*,*S*,*S*)-**5** was isolated in 90% yield.

Reaction of the alcohol (*S*,*R*,*S*)-**24c** with diethylaminosulfur trifluoride (DAST) at −78 °C in CH_2Cl_2 for 3 h provided the inverted monofluoride (*S*,*S*,*S*)-**25d** and the regioisomeric alkenes (*S*,*S*)-**26c** and (*S*,*S*)-**26d**. Flash chromatography led to isolation of (*S*,*S*,*S*)-**25d** in 31% yield and of a mixture of alkenes (*S*,*S*)-**26c** and (*S*,*S*)-**26d** in 55% yield. The Cbz-group of (*S*,*S*,*S*)-**25d** was removed upon hydrogenolysis to obtain 4-fluorodexoxadrol (*S*,*S*,*S*)-**6** in 85% yield. Removal of the Cbz-group of the regioisomeric alkenes (*S*,*S*)-**26c** and (*S*,*S*)-**26d** also led to hydrogenation of the double bond affording dexoxadrol, that is, (*S*,*S*)-**3**, in 90% yield (Scheme 5).

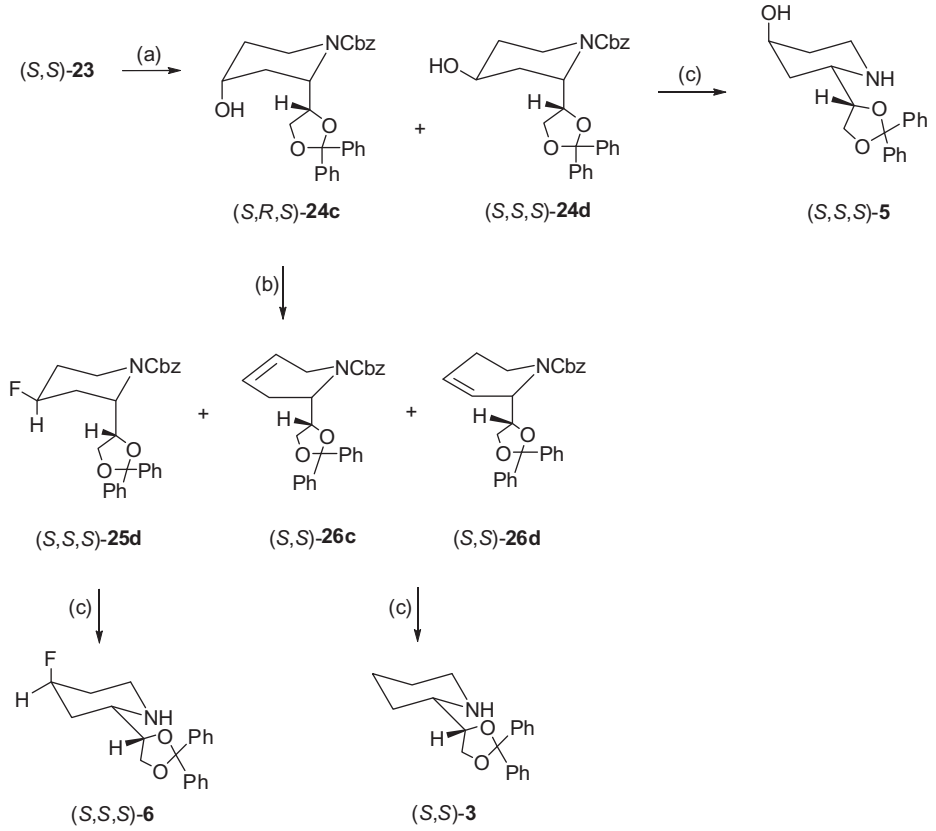
The Cbz-protected piperidone (*S*,*S*)-**23** was converted with DAST[25] at room temperature into the difluoro derivative (*S*,*S*)-**27c**. The Cbz-group of (*S*,*S*)-**27c** was then cleaved by hydrogenolysis to obtain the 4,4-difluorodexoxadrol (*S*,*S*)-**7** in 63% yield from (*S*,*S*)-**23** (Scheme 6).

The relative configuration of the prepared compounds was determined by comparing their ^1H NMR spectra with those of the corresponding racemic mixtures.[17,18] Since the absolute (*S*)-configuration of C-4 of the dioxolane ring is known from the synthesis starting with enantiomerically pure D-mannitol, the absolute configuration at 2- and 4-position of the piperidine ring is also (*S*).

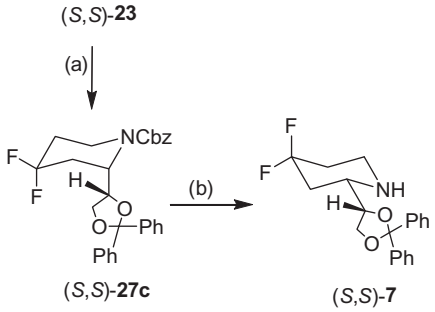
Careful analysis of the ^1H NMR spectra showed an interesting flip of the piperidine ring similar to their racemic counterparts.[17,18] Whereas, the piperidine ring of derivatives with a proton (e.g., **3**–**7**) or a PMB-group (e.g., **22**) attached to the N-atom adopts the $^1C_4$-conformation the corresponding Cbz-derivatives (e.g., **23**–**27**) exist in the $^1C_4$-conformation (compare Schemes 5 and 6). Due to allylic strain[26,27] the *N*-acyl-residue of **23**–**27** forces the substituent in 2-position to adopt an axial orientation, which is only possible after changing the piperidine ring conformation.

In order to determine the enantiomeric purity of the optically active dexoxadrol derivatives a chiral HPLC analysis method was set up using a Daicel Chiralpak AD-H column as chiral selector. For the analysis, piperidone **4** was selected since it represents one of the key intermediates to obtain the dexoxadrol derivatives **3** and **5**–**7**.

For the method development the racemic mixture (±)-**4** was analyzed. The enantiomers were separated using an isocratic method with the solvent system isohexane/ethanol = 93:7 (chiral HPLC method C). HPLC analysis of the ketone (*S*,*S*)-**4**, which had been prepared by imino-Diels–Alder reaction of imine (*S*)-**13** with Danishefsky's diene **14** showed the presence of a small amount of the enantiomer (*R*,*R*)-**4**. (Fig. 2) Integration of the peaks gave a ratio of (*S*,*S*)-**4**/(*R*,*R*)-**4** of 91:9. Racemization may have taken place at the stage of aldehyde (*R*)-**11** or imine (*S*)-**13** upon enolate formation with basic *p*-methoxybenzylamine.



Scheme 5. Synthesis of 4-hydroxydexoxadrol (*S*,*S*,*S*)-**5** and 4-fluorodexoxadrol (*S*,*S*,*S*)-**6**. Reagents and conditions: (a) $NaBH_4$, MeOH, 1 h, 0 °C, 45% ((*S*,*R*,*S*)-**24c**), 48% ((*S*,*S*,*S*)-**24d**); (b) DAST, CH_2Cl_2, 3 h, −78 °C, 31% ((*S*,*S*,*S*)-**25d**), 55% ((*S*,*S*)-**26c**) and ((*S*,*S*)-**26d**); (c) H_2, Pd/C 10%, MeOH, 4 h, rt, 90% ((*S*,*R*,*S*)-**5**), 85% ((*S*,*S*,*S*)-**6**), 90% ((*S*,*S*)-**3**).



Scheme 6. Synthesis of 4,4-difluorodexoxadrol (*S*,*S*)-**7**. Reagents and conditions: (a) DAST, CH_2Cl_2, 16 h, rt, 70% and (b) H_2, Pd/C 10%, MeOH, 4 h, rt, 90%.

In order to find out whether further racemization had taken place during the subsequent reactions, a method for the separation of difluorodexoxadrol enantiomers (*S*,*S*)-**7** and (*R*,*R*)-**7** was set up using racemic difluorodioxadrol (±)-**7** (chiral HPLC method D). After obtaining a separation of the enantiomers (*S*,*S*)-**7** and (*R*,*R*)-**7**, the product (*S*,*S*)-**7** from the enantioselective synthesis was analyzed. The HPLC chromatogram of the difluorodexoxadrol derivative (*S*,*S*)-**7** showed the presence of the enantiomer (*R*,*R*)-**7** in the same ratio ((*S*,*S*)-**7**/(*R*,*R*)-**7** = 91:9). (Fig. 2) Therefore it can be concluded that further racemization during later reaction steps of the synthesis had not taken place.

3. Receptor affinities

The affinities of the novel dexoxadrol analogues (*S*,(*S*),*S*)-**3**–**7** to the PCP binding site of the NMDA receptor were determined in competition experiments using the potent and selective radioligand [^{3}H]-(+)-MK-801. A membrane preparation from pig brain cortex was employed as receptor material.[28,29] The competition curves with six compound concentrations were recorded three times and the resulting K_i-values with SEM are given in Table 2. For purpose of comparison the affinities of the corresponding racemic mixtures are also given in Table 2. The NMDA receptor affinity of dexoxadrol (*S*,*S*)-**3**, which was also synthesized within this project, was tested and compared with the affinity of commercially available dexoxadrol (*S*,*S*)-**3**.

The data in Table 2 demonstrate that the prepared non-racemic ligands are more potent than the racemic mixtures. This result clearly indicates that the eutomers of the active compounds have been synthesized. Since the non-racemic compounds are almost twice as potent as the corresponding racemates, it can be concluded that the distomers with (*R*,(*R*),*R*)-configuration have very low affinity towards the PCP binding site of the NMDA receptor.

The most potent compound in this series is the monofluoro derivative (*S*,*S*,*S*)-**6** with a K_i-value of 7.5 nM, which even exceeds the NMDA receptor affinity of the lead compound dexoxadrol. However, all of the synthesized compounds are of great interest, since compounds with moderate NMDA receptor affinity should produce a reduced side effect profile (compare Section 1).

As expected the NMDA receptor affinity of dexoxadrol (*S*,*S*)-**3** synthesized within this project is identical with the affinity of commercially available dexoxadrol.

Since the racemic mixtures (±)-**3**–(±)-**7** are very selective against σ_1 (K_i-values >800 nM) and σ_2 receptors (K_i-values >1000 nM) as well as the ifenprodil binding site of the NMDA receptor (K_i-values >1000 nM),[17,18] it can be concluded that the synthesized eutomers (*S*,(*S*),*S*)-**3**–**7** also do not interact with these receptor systems.

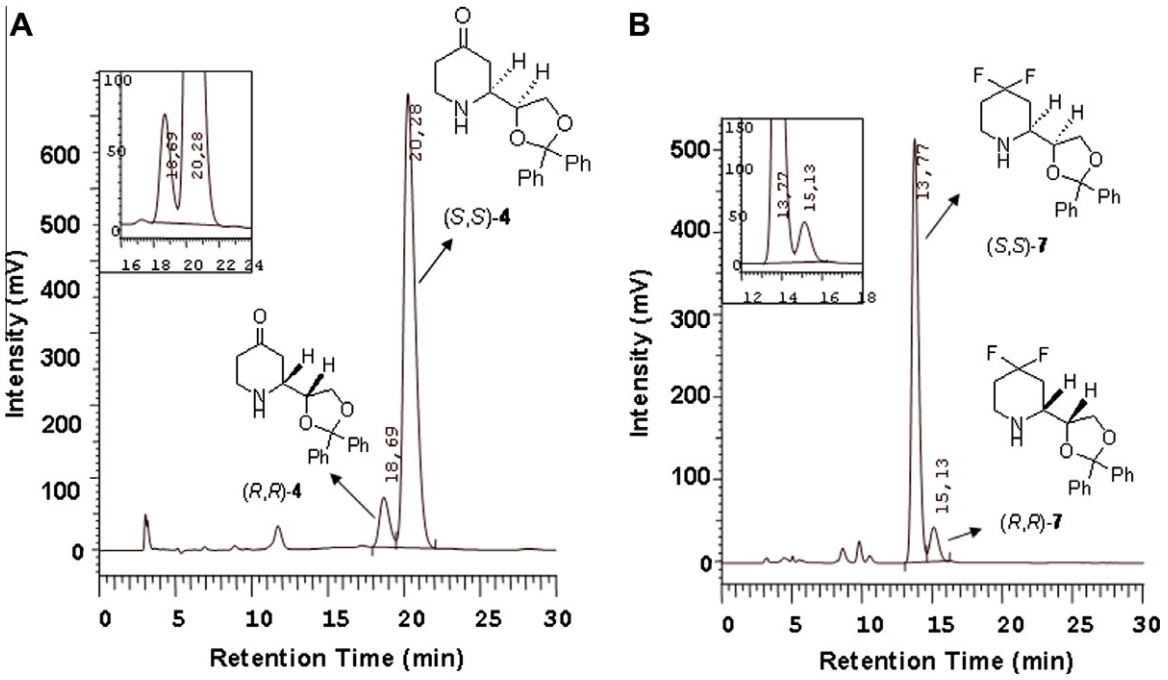
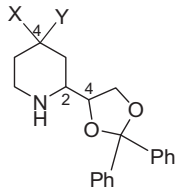


Figure 2. (A) HPLC of compound (*S*,*S*)-**4**: Daicel Chiralpak AD-H 250 × 4.6 mm, 1.00 mL/min isohexane/ethanol 93:7, λ = 210 nm, resolution = 1.24. (B) HPLC of compound (*S*,*S*)-**7**: Daicel Chiralpak AD-H 250 × 4.6 mm, 1.00 mL/min isohexane/ethanol 99.25:0.75, λ = 210 nm, resolution = 1.36.

Table 2
Affinities of racemic and non-racemic dexoxadrol derivatives to the phencyclidine binding site of the NMDA receptor



4-CXY	Compd	K_i ± SEM (nM) (n = 3) NMDA (PCP) ([^{3}H]-(+)-MK-801)	Compd	K_i ± SEM (nM) (n = 3) NMDA (PCP) ([^{3}H]-(+)-MK-801)
CH_2	(±)-**3**	20 ± 4.8 (n = 6)	(*S*,*S*)-**3**	10.9 ± 0.2
C=O	(±)-**4**	470 ± 173	(*S*,*S*)-**4**	355 ± 34
CHOH	(±)-**5**	44 ± 13	(*S*,*S*,*S*)-**5**	28 ± 4.0
CHF	(±)-**6**	27 ± 3.1	(*S*,*S*,*S*)-**6**	7.5 ± 0.45
CF_2	(±)-**7**	81 ± 17	(*S*,*S*)-**7**	48 ± 6.2
		—	Dexoxadrol[a]	11.4 ± 0.3

Unless otherwise noted all data are from three independent experiments (n = 3).
[a] Commercially available dexoxadrol.

4. Theoretical considerations

4.1. Geometry optimization of the molecules

In order to learn more about the chemical properties of the high affinity NMDA receptor antagonists, a conformational search of (*S*,*S*)-**3** was performed using density functional theory (DFT). At first complete geometry optimizations were performed using the DFT-Method B3LYP/6-31G(d) as implemented in the program series GAUSSIAN 03.[30] Special care was applied on the search of the global minima, both with respect to the possible conformations of the five-membered ring and to the orientation of the piperidyl subunit relative to the dioxolane moiety. These geometries were then used for complete optimizations using the DFT-functional B97-D[31] and the basis set def2-TZVP[32] applying the program TURBOMOLE 6.0.[33] This latter method is expected to give very reliable results, especially with regard to dispersion interaction and π–π-interactions. Calculations of the respective N-protonated species were used to determine the gas phase proton affinity of the receptor antagonists on both theoretical levels (the B3LYP/6-31G(d) energies are corrected for zero point energy (ZPE)). The energetically most favored conformation of (*S*,*S*)-**3** is shown in Figure 3. This conformation has been used as template for the conformations of the derivatives with various substituents in position 4 of the piperidine ring ((*S*,*S*)-**4**, (*S*,*S*,*S*)-**5**, (*S*,*S*,*S*)-**6**, (*S*,*S*)-**7**). In all cases, the envelop conformation of the dioxolane ring showed the lowest relative energy of all possibilities studied (Fig. 3).

4.2. Electrostatic potential at the surface of the molecules

Based on the energetically most favored conformations the electrostatic potential at the surface of the molecules has been calculated using density functional theory B3LYP/6-31G(d). The color code indicates electron rich areas (repulsive for negative charge) in red and electron deficient areas (attractive for negative charge) in blue. Figure 4 clearly indicates that the monofluoro derivative (*S*,*S*,*S*)-**6** presents one small electron rich area and the difluoro derivative (*S*,*S*)-**7** presents two electron rich areas for interactions with the NMDA receptor surface. The alcohol (*S*,*S*,*S*)-**5**, which is also very potent, has also an electron rich area, the proton at the OH moiety is the positive region. The low affinity of the carbonyl derivative (*S*,*S*)-**4** may be explained by the very high (or too high) electron density around the 4-position of the piperidine moiety. Additionally the orientation of the dark red area is different from the pale red areas of the fluorine derivatives (*S*,*S*)-**7** and (*S*,*S*,*S*)-**6**.

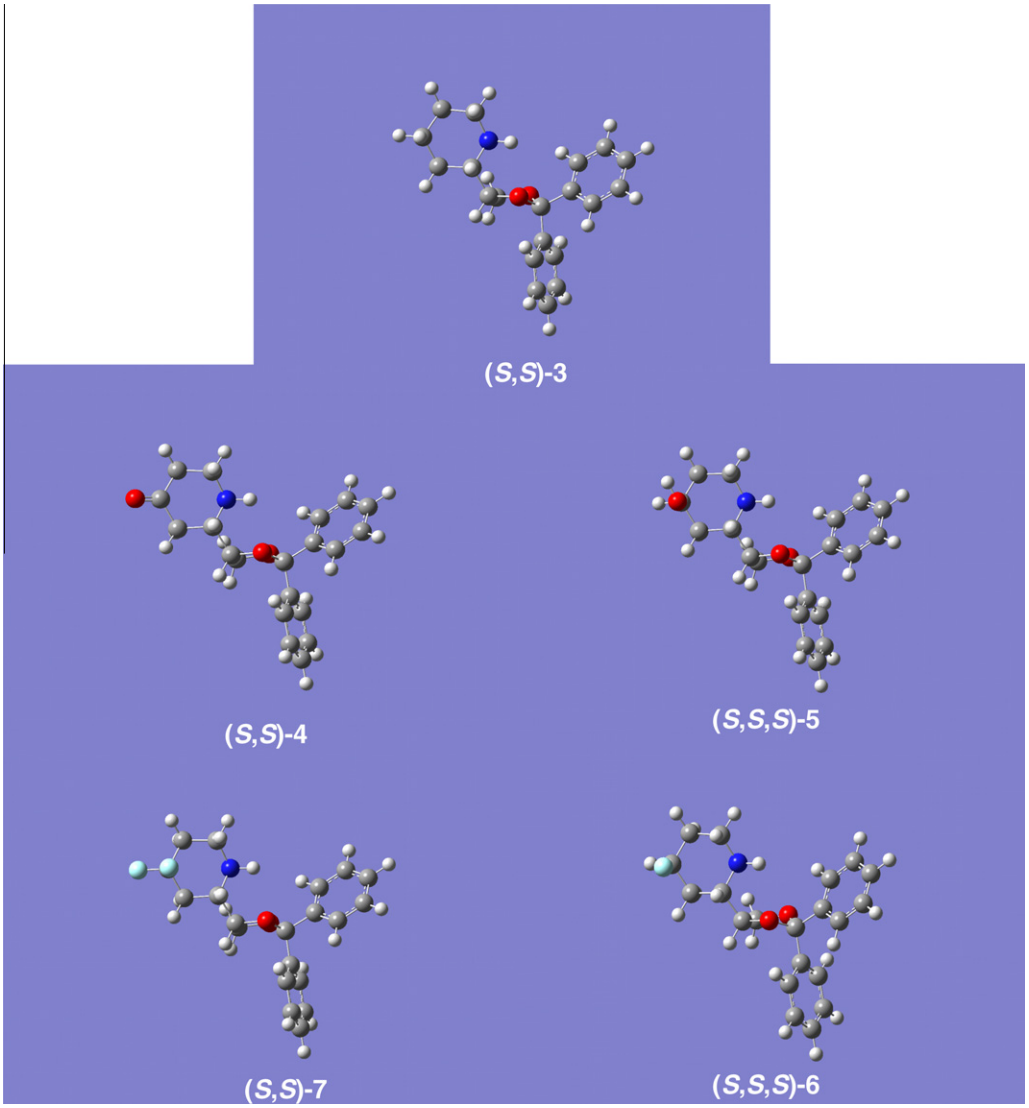


Figure 3. Energetically most favored conformations of the potent NMDA receptor antagonists (*S*,(*S*),*S*)-**3**–**7**. The dioxolane ring adopts the envelop conformation.

4.3. Correlation of the NMDA receptor affinity with proton affinity and the dipole moment of the compounds

The proton affinity and the dipole moment of the dexoxadrol derivatives were considered to explain the trend in the NMDA receptor affinity. The proton affinities and the dipole moments are summarized in Table 3.

As a correlate for the basicity (change in free energy associated with deprotonation) the gas phase proton affinity (change in enthalpy) of the NMDA receptor antagonists has been calculated (Table 3). Compared to (*S*,*S*)-**3**, an axially oriented hydroxy group ((*S*,*S*,*S*)-**5**)) led to a slight increase of the proton affinity of the dexoxadrol analogues. On the other hand, introduction of one strongly electronegative fluorine atom ((*S*,*S*,*S*)-**6**) reduced the proton affinity by approximately two pK_a-unit (according to the thermodynamic equilibrium equation a decrease of proton affinity by 1.34 kcal/mol is at room temperature approximately equivalent to decrease of pK_a by one unit). The largest reduction of the proton affinity is caused by the carbonyl moiety of (*S*,*S*)-**4** and the two electronegative fluorine atoms of (*S*,*S*)-**7**. It could be possible that the very strong reduction of the proton affinity of (*S*,*S*)-**4** and (*S*,*S*)-**7** contributes to the reduced NMDA receptor affinity.

As a further property the dipole moment of the dexoxadrol analogues has been calculated (Table 3). As expected, the dipole moment strongly depends on the particular conformation, especially for the OH derivative (*S*,*S*)-**4**. Compared with the dipole moment of the lead compound (*S*,*S*)-**3** without a substituent in 4-position of the piperidine ring, the dipole moment of the very potent NMDA antagonist (*S*,*S*,*S*)-**6** is slightly reduced and the dipole moments of the less potent compounds (*S*,*S*,*S*)-**5** and (*S*,*S*)-**7** are slightly increased. Ketone (*S*,*S*)-**4** having a large calculated dipole moment shows low NMDA receptor affinity. These data lead to the idea that a reduced dipole moment ((*S*,*S*,*S*)-**6**, (*S*,*S*)-**3**) increases the NMDA receptor affinity and a large dipole moment ((*S*,*S*)-**4**) decreases the NMDA affinity.

In conclusion it can be speculated that basicity and dipole moment play a crucial role for NMDA receptor affinity, since the most potent ligand of this study, the monofluoro derivative (*S*,*S*,*S*)-**6**, has a dipole moment and proton affinity very close to the lead compound dexoxadrol (*S*,*S*)-**3**.

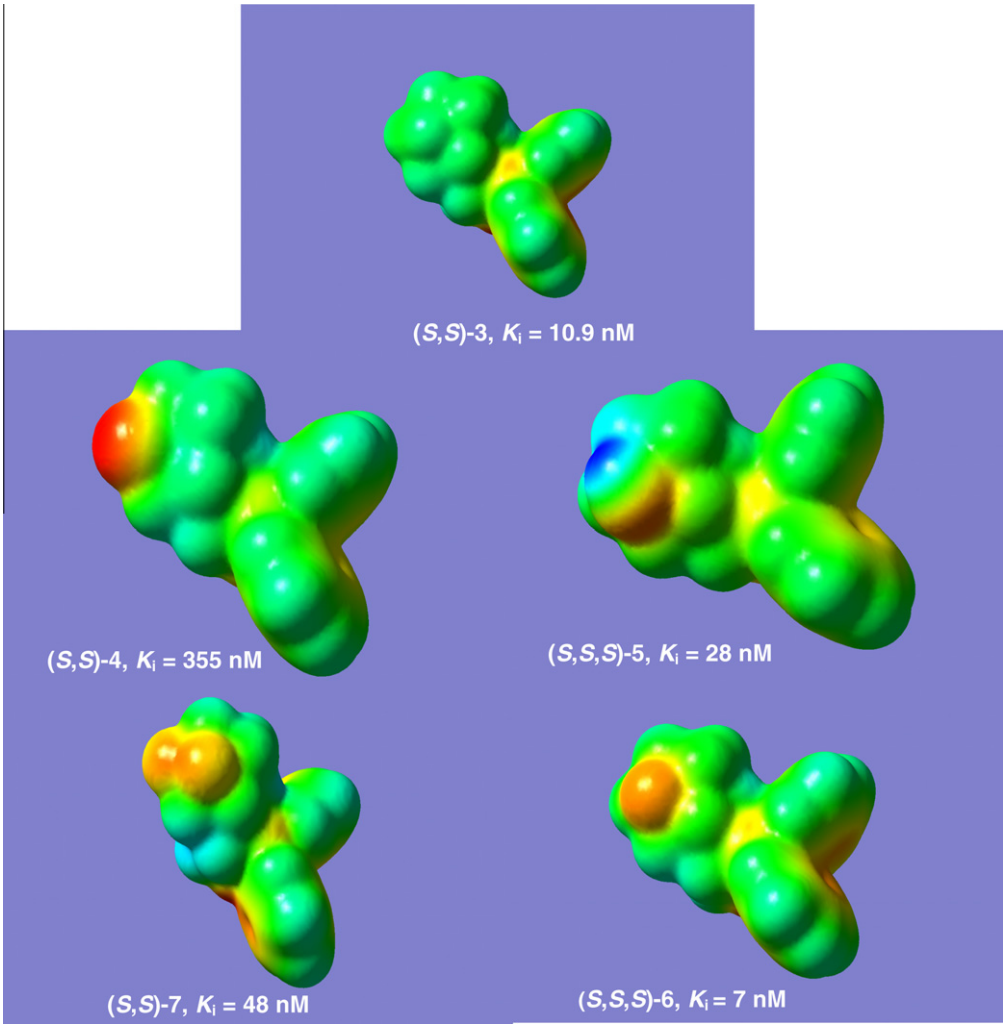


Figure 4. Electrostatic potential at the surface of the energetically most favored conformations of the potent NMDA receptor antagonists (*S*,(*S*),*S*)-**3**–**7**, calculated using density functional theory. Red color indicates electron rich areas (repulsive for negative charge); blue color indicates electron deficient areas (attractive for negative charge).

Table 3
Correlation of NMDA receptor affinity with calculated gas phase proton affinities and dipole moments

Compd	K_i[a] (nM)	Gas phase proton affinity (kcal/mol)		Dipole moment (Debye)
		B3LYP/6-31G(d) (incl. ZPE)	B97-D/def2-TZVP	B3LYP/6-31G(d)
(*S*,*S*)-**3** (CH_2)	10.9	−240.09	−251.78	1.2261
(*S*,*S*)-**4** (C=O)	355	−231.05	−242.46	2.4139
(*S*,*S*,*S*)-**5** (CHOH)	28	−241.38	−252.23	1.6364
(*S*,*S*,*S*)-**6** (CHF)	7.5	−237.54	−248.77	1.1362
(*S*,*S*)-**7** (CF_2)	48	−232.94	−243.96	1.4609

The gas phase proton affinities were calculated using the DFT-Method B3LYP/6-31G(d) as implemented in the program series GAUSSIAN 03 where the energies are corrected for zero point energy (ZPE). In a second calculation the DFT-functional B97-Dand applying the basis set def2-TZVP within the program TURBOMOLE 6.0 was used.

[a] NMDA receptor affinity determined with the radioligand [^{3}H]-(+)-MK-801 (see Table 1).

5. Conclusion

Herein the first stereoselective synthesis of chiral non-racemic dexoxadrol (*S*,*S*)-**3** and analogues with various substituents in 4-position is presented. Whereas, the ketone (*S*,*S*)-**4** shows moderate affinity towards the PCP binding site of the NMDA receptor, the difluoro derivative (*S*,*S*)-**7** (K_i = 48 nM) and the alcohol (*S*,*S*,*S*)-**5** (K_i = 28 nM) are potent and the monofluoro derivative (*S*,*S*,*S*)-**6** (K_i = 7.5 nM) is a very potent NMDA receptor antagonist. The enantiomerically enriched ligands display higher NMDA receptor affinities than the racemic mixtures, which proves that the eutomers have been synthesized. The enantiomers are about twice as active as the racemic mixtures indicating that the distomers are almost inactive, which results in high eudismic ratios. The NMDA receptor affinity of the new ligands was correlated with their electrostatic potential, proton affinity and dipole moment. The calculations showed decreasing NMDA receptor affinity with decreasing proton affinity and increasing dipole moment.

6. Experimental

6.1. Chemistry general

Unless otherwise noted, moisture and oxygen sensitive reactions were conducted in dry glassware (Schlenk flask sealed with a rubber septum) under N_2 (dried with phosphorous pentoxide (Granusic® A, Baker)). Thin layer chromatography (tlc): Silica gel 60 F254 plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column (cm), length of the stationary phase (cm), eluent, fraction size (mL) and retention factor R_f. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz, 300 MHz, 600 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (300 MHz, 600 MHz) spectra were recorded on a Unity Mercury Plus 400 (400 MHz) NMR spectrometer (Varian), Brucker AV 300 (300 MHz), and Varian Unity Plus 600 (600 MHz) operating at 23 °C. High temperature NMR was recorded in Unity Mercury Plus 400 (400 MHz) NMR spectrometer (Varian) at 100 °C. Chemical shifts δ are reported in parts per million (ppm) against the reference compound tetramethylsilane and calculated using the chemical shift of the signal of the residual non-deuterated solvent, for ^{19}F NMR spectroscopy chemical shifts δ are reported in parts per million (ppm) against the reference compound $CFCl_3$ and calculated using the chemical shift of the signal of the solvent. High temperature ^{1}H NMR spectra were recorded using $C_6D_5NO_2$ as solvent. MS: HRMS (ESI): Finnigan MAT 4200s, Brucker Daltonics Micro Tof and Waters Micromass Quatro LCZ, peaks are given in m/z (% of basis peak). EI, electron impact, MAT GCQ (Thermo-Finnigan). HPLC: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 μm); LiChroCART® 250–4 mm cartridge; flow rate: 1.0 mL/min; injection volume: 5.0 μL; detection at λ = 210 nm; method A: solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid: gradient elution: (A%): 0–4 min: 90%, 4–29 min: gradient from 90% to 0%, 29–31 min: 0%, 31–31.5 min: 0–90%, 31.5–40 min: 90%; method B: solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: methanol with 0.05% (v/v) trifluoroacetic acid: gradient elution: (A%): 0–1 min: 80%, 1–22 min: gradient from 80% to 0%, 22–30 min: 0%, 30–31.5 min: 0–80%, 31.5–40 min: 80%. The purity of all test compounds was greater than 95%, which was determined by one of the given HPLC methods. Chiral HPLC: UV detector: L-7400; pump: L-6200A; Column: Daicel Chiralpak AD-H (5 μM) 250–4.6 mm; Precolumn: Daicel Chiralpak AD-H (5 μM) 10–4 mm; Injection volume: 20.0 μL; flow rate: 1.0 mL/min; detection at λ = 210 nm; method C: solvent: isohexane/ethanol = 93: 7, method D: solvent: isohexane/ethanol = 99.25: 0.75. Polarimetry: the optical rotation α (°) was determined with a Polarimeter P-2000 (Jasco). The wavelength of the light used was 589 nm. The temperature, the concentration c (g/100 mL) and the solvent are given in bracket. The specific rotation $[\alpha]_\lambda$ was calculated, its unit (° mL dm^{-1} g^{-1}) is omitted.

6.2. General Procedure A: removal of the PMB- and Cbz-protective group

The Cbz-protected piperidine was dissolved in MeOH (6 mL), Pd/C (10%) was added and the suspension was stirred under H_2 atmosphere (balloon) at rt 16 h (for PMB-group) and 4 h (for Cbz-group). The reaction mixture was filtered through Celite®, which was rinsed with MeOH and the filtrate was evaporated to dryness. The product was purified by fc (2 cm, 12 cm, EtOAc/MeOH/$NEtMe_2$ = 94:5:1, 10 mL).

6.3. (1*S*,2*S*)-1,2-Bis[(*R*)-2,2-diphenyl-1,3-dioxolan-4-yl)]ethane-1,2-diol (10)[19]

A mixture of D-mannitol (**8**, 2.0 g, 10.1 mmol), benzophenone dimethyl acetal (**9**),[34] 5.01 g, 21.9 mmol) and $SnCl_2$ (0.025 g, 0.13 mmol) in freshly distilled dimethoxyethane (50 mL) was heated at reflux until all solid was dissolved (~14 h). Solvent was evaporated and the product was purified by fc (4 cm, 20 cm, petroleum ether/EtOAc = 7:3, 20 mL, R_f = 0.38): colorless solid, yield 1.18 g (56%). IR (neat): ν (cm^{-1}) = 1199/1075 (s, C–O–C). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.54 (d, J = 6.3 Hz, 2H, 2 × OH), 3.92 (t, J = 5.9 Hz, 2H, 2 × CHOH), 4.02–4.09 (m, 4H, 2 × OCH_2), 4.28 (q, J = 6.3 Hz, 2H, 2 × OCH), 7.29–7.38 (m, 12H, Ph), 7.46–7.53 (m, 8H, Ph). ^{13}C NMR ($CDCl_3$): δ = 67.2 (2 × CHOH), 71.3 (2 × OCH_2), 77.3 (2 × OCH), 110.0 (2 × OCO), 125.9 (Ph), 126.2 (Ph), 128.3 (Ph), 128.4 (Ph), 128.5 (Ph), 128.6 (Ph), 141.8 (Ph), 142.2 (Ph). HRMS: calcd for $C_{32}H_{30}O_6H$ 511.2115, found 511.2115. HPLC (method B): purity 94%, t_R = 23.0 min. $[\alpha]_{589}$ = +63.6 (25 °C, c 0.11, CH_2Cl_2). The specific rotation $[\alpha]_{589}$ is not given in the literature.

6.4. (*R*)-2,2-Diphenyl-1,3-dioxolane-4-carbaldehyde ((*R*)-11)[19]

Compound **10** (0.3074 g, 0.6 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled down to 0 °C. Then $Pb(OAc)_4$ (0.401 g, 0.9 mmol) was added. The mixture was stirred at 0 °C for 30 min. The reaction mixture was filtered through Celite®, which was rinsed with CH_2Cl_2 and the filtrate was evaporated in vacuo to dryness. The product was purified by fc (2 cm, 12 cm, petroleum ether/EtOAc = 8:2, 10 mL, R_f = 0.45): colorless oil, yield 0.29 g (95%). $[\alpha]_{589}$ = +5.7 (26 °C, c 0.23, CH_2Cl_2). The specific rotation $[\alpha]_{589}$ is not given in the literature.

6.5. (2*R*) and (2*S*)-1-(4-Methoxybenzyl)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl)]-2,3-dihydropyridin-4(1*H*)-one ((*R*,*S*)-15a and (*S*,*S*)-15c)

The aldehyde (*R*)-**11** (1.574 g, 6.2 mmol) was dissolved in trimethyl orthoformate (8 mL), 4-methoxybenzylamine (PMB-NH_2 **12**, 0.8 mL, 6.2 mmol) was added and the solution was stirred overnight at rt. The mixture was evaporated to dryness, the obtained yellow oil ((*S*)-**13**) was dissolved in THF (15 mL) and the resulting solution was cooled down to 0 °C. Then a solution of $Yb(OTf)_3$ (768 mg, 1.24 mmol) in THF (5 mL) was added and the mixture was stirred at 0 °C for 15 min. Then, Danishefsky's diene **14** (2.20 mL, 11.3 mmol) was added and the mixture was stirred for another 4 h at 0 °C before the reaction mixture was allowed to warm to rt overnight. A saturated solution of $NaHCO_3$ and EtOAc were added, the organic layer was separated, the aqueous layer was extracted twice with EtOAc, the organic layer was dried (K_2CO_3) filtered and concentrated in vacuo. The residue was purified by fc (4 cm, 12 cm, cyclohexane: EtOAc = 1:1, 20 mL, R_f = 0.20). Yellow oil, yield 2.02 g (75%). IR (neat): ν (cm^{-1}) = 1637 (m, C=O), 1579 (s, C=C), 1071 (m, C–O–C). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.97 (d, J = 16.9 Hz, 0.43 H, 3^x-H), 2.48 (dd, J = 16.9/2.8 Hz, 0.57 H, 3^o-H), 2.68 (dd, J = 16.9/7.9 Hz, 0.57 H, 3^o-H), 2.73 (dd, J = 16.9/7.3 Hz, 0.43 H, 3^x-H), 3.45–3.49 (m, 0.43 H, 2^x-H), 3.71 (dd, J = 8.6/5.9 Hz, 0.43 H, $OCH_2{}^x$), 3.77–3.79 (m, 0.57 H, $OCH_2{}^\circ$), 3.80 (s, 3 × 0.57 H, $OCH_3{}^\circ$), 3.81 (s, 3 × 0.43 H, $OCH_3{}^x$), 3.99 (dd, J = 8.3/6.9 Hz, 0.57 H, $OCH_2{}^\circ$), 4.04 (dd, J = 8.6/6.7 Hz, 0.43 H, $OCH_2{}^x$),4.05–4.09 (m, 0.57 H, OCH^o), 4.29 (d, J = 14.9 Hz, 0.57 H, $PhCH_2{}^\circ$), 4.30–4.34 (m, 0.57 H, 2^o-H), 4.41 (d, J = 14.9 Hz, 0.57 H, $PhCH_2{}^\circ$), 4.44 (d, J = 14.7 Hz, 0.43 H, $PhCH_2{}^x$), 4.65 (d, J = 14.9 Hz, 0.43 H, $PhCH_2{}^x$), 4.82 (dt, J = 9.8/6.3 Hz, 0.43 H, OCH^x), 4.94 (d, J = 7.5 Hz, 1H, 5^x-H + 5^o-H), 6.85–6.89 (m, 3H, 2 × Ph + 6^x-H + 6^o-H), 7.02–7.15 (m, 3H, Ph), 7.26–7.34 (m, 5H, Ph), 7.47–7.52 (m, 4H, Ph). The ratio of (*R*,*S*)-**15a**/(*S*,*S*)-**15c** = 43:57;

° = index for the major diastereomer (*S*,*S*)-**15c**; x = index for the minor diastereomer (*R*,*S*)-**15a**. ^{13}C NMR ($CDCl_3$): δ (ppm) = 36.7 (C-3°), 37.3 (C-3^x), 55.2 (C-2°), 56.1 (C-2^x), 58.2 (OC^oH_3, OC^xH_3), 58.7 (PhC^oH_2), 59.4 (PhC^xH_2), 66.7 (OC^oH_2), 66.8 (OC^xH_2), 74.1 (OC^oH, OC^xH), 96.8 (C5^x), 98.5 (C5°), 109.4 (OC°O), 110.5 (OC^xO), 114.2/114.3/125.6/125.8/125.9/126.0/128.0/128.1/128.2/128.3/128.5/128.7/128.9/141.6/141.8/141.9 (PhC), 152.6 (C-6^x), 153.2 (C-6°), 159.4/159.5 (PhC), 188.7 (C-4^x), 189.5 (C-4°). HRMS: calcd for $C_{28}H_{27}NO_4H$ 442.2018, found 442.2013. HPLC (method A): purity 40% (*R*,*S*)-**15a**, t_R = 22.0 min, 53%, (*S*,*S*)-**15c**, t_R = 21.5 min, together 93%.

6.6. (2*R*)-2-[(4*S*)-2,2-Diphenyl-1,3-dioxolan-4-yl]-1-[(1*R*)-1-phenylethyl]-2,3-dihydropyridin-4(1*H*)-one ((*R*,*R*,*S*)-18a) and (2*S*)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]-1-[(1*R*)-1-phenylethyl]-2,3-dihydropyridin-4(1*H*)-one ((*R*,*S*,*S*)-18c)

The aldehyde (*R*)-**11** (0.143 g, 0.56 mmol) was dissolved in trimethyl orthoformate (5 mL), (*R*)-1-phenylethylamine (0.1 mL, 0.56 mmol) was added and the solution was stirred overnight at rt. The mixture was concentrated in vacuo, the obtained yellow residue ((*R*,*S*)-**17**) was dissolved in CH_2Cl_2 (2 mL) and the resulting solution was cooled down to −78 °C. Then $BF_3{\cdot}OEt_2$ (0.10 mL, 0.84 mmol) was added and the mixture was stirred at −78 °C for 15 min. Then, Danishefsky's diene **14** (0.16 mL, 0.84 mmol) was added and the mixture was stirred for another 4 h at −78 °C before the reaction mixture was allowed to warm to rt overnight. A saturated solution of $NaHCO_3$ and EtOAc were added, the organic layer was separated, the aqueous layer was extracted twice with EtOAc, the organic layer was dried (K_2CO_3), filtered and concentrated in vacuo. The residue was purified by fc (2 cm, 12 cm, petroleum ether/EtOAc = 1:1, 20 mL).

Compound (*R*,*R*,*S*)-**18a** (R_f = 0.18): pale yellow oil, yield 0.126 g (53%). IR (neat): ν (cm^{-1}) = 1637 (m, C=O), 1572 (s, C=C), 1207/1072 (m, C–O–C). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.56 (d, J = 6.9 Hz, 3H, CH_3), 1.92 (d broad, J = 17.0 Hz, 1H, 3-H), 2.71 (dd, J = 17.0/7.1 Hz, 1H, 3-H), 3.36–3.41 (m, 1H, 2-H), 3.72 (dd, J = 8.7/5.3 Hz, 1H, OCH_2), 4.01 (dd, J = 8.7/6.6 Hz, 1H, OCH_2), 4.70 (q, J = 6.9 Hz, 1H, CHPh), 4.81 (ddd, J = 9.9/6.5/5.4 Hz, 1H, OCH), 5.04 (d, J = 7.5 Hz, 1H, 5-H), 7.02 (d, J = 7.5 Hz, 1H, 6-H), 7.27–7.53 (m, 15H, Ph). HRMS: calcd for $C_{28}H_{27}NO_3Na$ 448.1883, found 448.1880. $[\alpha]_{589}$ = +197 (22 °C, c 0.37, CH_2Cl_2). HPLC (Method A): purity 87%, t_R = 22.3 min.

Compound (*R*,*S*,*S*)-**18c** (R_f = 0.11): pale yellow oil, yield 33.0 mg (14%). IR (neat): ν (cm^{-1}) = 1637 (m, C=O), 1572 (s, C=C), 1207/1072 (m, C–O–C). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.62 (d, J = 6.8 Hz, 3H, CH_3), 2.60 (dd, J = 16.7/1.6 Hz, 1H, 3-H), 2.77 (dd, J = 16.7/7.5 Hz, 1H, 3-H), 3.92–3.98 (m, 2H, 2-H + OCH_2), 4.05 (dd, J = 8.7/6.5 Hz, 1H, OCH_2), 4.37 (q, J = 6.5 Hz, 1H, CHPh), 4.68 (q, J = 6.8 Hz, 1H, OCH), 4.90 (d, J = 7.6 Hz, 1H, 5-H), 6.75 (d, J = 7.7 Hz, 1H, 6-H), 7.15–7.54 (m, 15H, Ph). HRMS: calcd for $C_{28}H_{27}NO_3Na$ 448.1883, found 448.1891. $[\alpha]_{589}$ = −18 (21 °C, c 0.24, CH_2Cl_2). HPLC (Method A): purity 92%, t_R = 21.4 min.

6.7. (2*R*)-2-[(4*S*)-2,2-Diphenyl-1,3-dioxolan-4-yl]-1-[(1*S*)-1-phenylethyl]-2,3-dihydropyridin-4(1*H*)-one ((*S*,*R*,*S*)-19a) and (2*S*)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]-1-[(1*S*)-1-phenylethyl)]-2,3-dihydropyridin-4(1*H*)-one ((*S*,*S*,*S*)-19c)

The aldehyde (*R*)-**11** (91.4 mg, 0.36 mmol) was dissolved in trimethyl orthoformate (5 mL), (*S*)-1-phenylethylamine (0.06 mL, 0.36 mmol) was added and the solution was stirred overnight at rt. The mixture was concentrated in vacuo, the obtained yellow oil ((*S*,*S*)-**17**) was dissolved in CH_2Cl_2 (2 mL) and the resulting solution was cooled down to −78 °C. Then $BF_3{\cdot}OEt_2$ (0.07 mL, 0.53 mmol) was added and the mixture was stirred at −78 °C for 15 min. Then, Danishefsky's diene **14** (0.10 mL, 0.53 mmol) was added and the mixture was stirred for another 4 h at −78 °C before the reaction mixture was allowed to warm to rt overnight. A saturated solution of $NaHCO_3$ and EtOAc were added, the organic layer was separated, the aqueous layer was extracted twice with EtOAc, the organic layer was dried (K_2CO_3), filtered and concentrated in vacuo. The residue was purified by fc (2 cm, 12 cm, petroleum ether/EtOAc = 1:1, 20 mL).

Compound (*S*,*R*,*S*)-**19a** (R_f = 0.15): pale yellow oil, yield 0.106 g (69%). IR (neat): ν (cm^{-1}) = 1637 (m, C=O), 1575 (s, C=C), 1204/1084 (m, C–O–C). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.53 (d, J = 6.9 Hz, 3H, CH_3), 1.98 (d broad, J = 16.9 Hz, 1H, 3-H), 2.78 (dd, J = 16.9/7.3 Hz, 1H, 3-H), 3.66–3.74 (m, 2H, 2-H + OCH_2), 4.06 (dd, J = 8.3/6.7 Hz, 1H, OCH_2), 4.69 (dt, J = 9.4/6.8 Hz, 1H, OCH), 4.74 (d, J = 7.6 Hz, 1H, 5-H), 4.84 (q, J = 6.9 Hz, 1H, CHPh), 6.66 (d, J = 7.5 Hz, 1H, 6-H), 7.17–7.35 (m, 9H, Ph), 7.40–7.45 (m, 6H, Ph). HRMS: calcd for $C_{28}H_{27}NO_3Na$ 448.1883, found 448.1887. $[\alpha]_{589}$ = +49.3 (23.0 °C, c 1.61, CH_2Cl_2). HPLC (Method A): purity 98%, t_R = 21.7 min.

Compound (*S*,*S*,*S*)-**19c** (R_f = 0.20): pale yellow oil, yield 17.0 mg (10%). IR (neat): ν (cm^{-1}) = 1638 (m, C=O), 1576 (s, C=C), 1206/1087 (m, C–O–C). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.24 (d, J = 7.0 Hz, 3H, CH_3), 2.27 (d broad, J = 16.9 Hz, 1H, 3-H), 2.56 (dd, J = 16.8/8.3 Hz, 1H, 3-H), 3.69 (dd, J = 7.1/5.5 Hz, 1H, 2-H), 3.90 (dd, J = 8.3/7.1 Hz, 1H, OCH_2), 4.00 (dd, J = 8.3/6.3 Hz, 1H, OCH_2), 4.21 (q, J = 6.5 Hz, 1H, OCH), 4.57 (q, J = 7.0 Hz, 1H, CHPh), 4.96 (d, J = 7.6 Hz, 1H, 5-H), 7.09–7.11 (m, 2H, 6-H + Ph), 7.18–7.30 (m, 10H, Ph), 7.40–7.45 (m, 4H, Ph). HRMS: calcd for $C_{28}H_{27}NO_3Na$ 448.1883, found 448.1882. $[\alpha]_{589}$ = −192 (22.5 °C, c 0.85, CH_2Cl_2). HPLC (Method A): purity 93%, t_R = 22.6 min.

6.8. (2*R*)-1-(4-Methoxybenzyl)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]piperidin-4-one ((*R*,*S*)-22a) and (2*S*)-1-(4-methoxybenzyl)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]piperidin-4-one ((*S*,*S*)-22c)

Under N_2 a mixture of (*R*,*S*)-**15a** and (*S*,*S*)-**15c** (43:57, 1.16 g, 2.6 mmol) was dissolved in THF (10 mL) and the solution was cooled down to −78 °C, $BF_3{\cdot}OEt_2$ (0.67 mL, 5.3 mmol) was added slowly and the solution was stirred for 30 min at −78 °C. Then a 1 M solution of $LiEt_3BH$ in THF (5.30 mL, 5.3 mmol) was added slowly and the reaction mixture was stirred for 2 h at −78 °C. Afterwards a saturated solution of $NaHCO_3$ and EtOAc were added and the reaction mixture was warmed to rt. Then further EtOAc was added, the organic layer was separated, the aqueous layer was extracted twice with EtOAc, the organic layer was dried (K_2CO_3) filtered and concentrated in vacuo. The residue was purified by fc (4 cm, 20 cm, petroleum ether/EtOAc = 85:15, 20 mL).

Compound (*R*,*S*)-**22a** (R_f = 0.16): pale yellow oil, yield 0.433 g (37%). IR (neat): ν (cm^{-1}) = 1714 (s, C=O), 1205(s)/1070 (s, –C–O–C–). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.21 (ddd, J = 14.7/5.0/1.3 Hz, 1H, 5-H), 2.26–2.33 (m, 1H, 5-H), 2.40–2.47 (m, 1H, 3-H), 2.66 (ddd, J = 14.8/5.9/0.9 Hz, 1H, 3-H), 2.78–2.84 (m, 1H, 6-H), 3.17 (ddd, J = 12.9/8.3/4.7 Hz, 1H, 6-H), 3.31 (q, J = 5.6 Hz, 1H, 2-H), 3.82 (s, 3H, OCH_3), 3.85 (d, J = 13.4 Hz, 1H, $PhCH_2$), 3.94 (t, J = 7.6 Hz, 1H, OCH_2), 4.05 (d, J = 13.4 Hz, 1H, CH_2Ph), 4.07 (dd, J = 7.8/7.0 Hz, 1H, OCH_2), 4.37 (q, J = 7.2 Hz, 1H, OCH), 6.87–6.89 (m, 2H, Ph), 7.25–7.37 (m, 8H, Ph), 7.48–7.55 (m, 4H, Ph). HRMS: calcd for $C_{28}H_{29}NO_4H$ 444.2169, found 444.2164. EI (70 eV): m/z (rel. int.) = 443 (M^+, 2), 366 (M-Ph, 2), 218 (M-diphenyldioxolanyl, 10), 121 ($CH_2C_6H_4OCH_3$, 100), 77 (Ph, 18). $[\alpha]_{589}$ (82% ee) = +6.4 (24 °C, c 0.44, CH_2Cl_2). HPLC (method A): purity 95%, t_R = 18.0 min.

Compound (*S*,*S*)-**22c** (R_f = 0.11): pale yellow oil, yield 0.632 g (54%). IR (neat): ν (cm^{-1}) = 1709 (s, C=O), 1450 (m, C–H), 1205 (s)/1069 (s, C–O–C). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.30 (dt, J = 15.1/3.8 Hz, 1H, 5-H), 2.51 (ddd, J = 15.4/9.5/6.1 Hz, 1H, 5-H), 2.64 (dd,

J = 14.9/5.9 Hz, 1H, 3-H), 2.71 (ddd, J = 14.8/4.0/1.2 Hz, 1H, 3-H), 2.96 (dt, J = 10.8/5.1 Hz, 1H, 6-H), 3.11–3.20 (m, 2H, 2-H + 6-H), 3.81 (s, 5H, OCH_3, CH_2Ph), 3.88 (dd, J = 8.0/7.0 Hz, 1H, OCH_2) 4.08 (dd, J = 8.1/7.1, 1H, OCH_2), 4.30 (q, J = 6.8 Hz, 1H, OCH), 6.87–6.89 (m, 2H, Ph), 7.23–7.37 (m, 8H, Ph), 7.43–7.45 (m, 2H, Ph), 7.52–7.54 (m, 2H, Ph). HRMS: calcd for $C_{28}H_{29}NO_4H$ 444.2169, found 444.2173. EI (70 eV): m/z (rel. int.) = 443.2 (M^+, 2), 218 (M-diphenyldioxolanyl, 12), 121($CH_2C_6H_4OCH_3$, 100), 77 (Ph, 18). $[\alpha]_{589}$ (82% ee) = +15 (23 °C, c 1.04, CH_2Cl_2). HPLC (method A): purity 97%, t_R = 18.8 min.

6.9. (2*S*)-2-[(4*S*)-2,2-Diphenyl-1,3-dioxolan-4-yl]piperidin-4-one ((*S*,*S*)-4)

According to General Procedure A (*S*,*S*)-**22c** (0.40 g, 0.90 mmol) was dissolved in methanol (5 mL) and Pd/C (10%, 40 mg) was added. The product was purified by fc. Compound (*S*,*S*)-**4** (R_f = 0.31): colorless solid, mp 116 °C, yield 0.25 g (83%). IR (neat): ν (cm^{-1}) = 1713 (s, C=O), 1205/1067 (s, C–O–C). ^1H NMR ($CDCl_3$): δ (ppm) = 1.70 (s broad, 1H, NH), 2.10 (dd, J = 13.8/11.9 Hz, 1H, 3-H), 2.24–2.35 (m, 2H, 5-H), 2.39 (dd, 12.3/9.5 Hz, 1H, 3-H), 2.80 (td, J = 12.1/4.5 Hz, 1H, 6-H), 3.04 (dt, J = 11.7/3.5 HZ, 1H, 6-H), 3.32 (ddd, J = 12.4/6.2/2.5 Hz, 1H, 2-H), 3.91 (t, J = 7.4 Hz, 1H, OCH_2), 4.04–4.14 (m, 2H, OCH_2 + OCH), 7.19–7.29 (m, 6H, Ph), 7.39–7.46 (m, 4H, Ph). HRMS: calcd for $C_{20}H_{21}NO_3H$ 324.1519, found 324.1525. $[\alpha]_{589}$ (82% ee) = +28 (23 °C, c 0.26, CH_2Cl_2). HPLC (method A): purity 93%, t_R = 15.53 min.

6.10. Benzyl (2*S*)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]-4-oxopiperidine-1-carboxylate ((*S*,*S*)-23)

Under N_2 the piperidone (*S*,*S*)-**4** (245 mg, 0.76 mmol) was dissolved in THF (3 mL) and $PhCH_2OCOCl$ (0.16 mL, 1.14 mmol) was added followed by NEt_3 (0.16 mL, 1.14 mmol). The reaction mixture was stirred at rt for 1 h. Then a saturated solution of $NaHCO_3$ and EtOAc were added. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The organic layer was dried (K_2CO_3) filtered and concentrated in vacuo. The residue was purified by fc (3 cm, 12 cm, petroleum ether/EtOAc = 7:3, 10 mL, R_f = 0.21). Colorless oil, yield 0.313 g (90%). IR (neat): ν (cm^{-1}) = 1697 (s, C=O/Cbz C=O), 1206 (s)/1082 (s, C–O–C). ^1H NMR ($C_6D_5NO_2$, 100 °C): δ (ppm) = 2.03–2.17 (m, 1H, 3-H), 2.12 (ddd, J = 16.3/6.6/3.0 Hz, 1H, 5-H), 2.23 (ddd, J = 15.7/7.2/2.8 Hz, 1H, 5-H), 2.45 (dt, J = 15.8/2.8 Hz, 1H, 6-H), 3.18–3.26 (m, 1H, 3-H), 3.61 (ddd, J = 15.0/8.5/3.5 Hz, 1H, 6-H), 3.64–3.67 (m, 1H, 2-H), 3.93–4.04 (m, 2H, OCH_2Ph), 4.31–4.36 (m,1H, OCH), 4.77 (dd, J = 12.6/2.8 Hz, 1H, OCH_2), 4.82 (dd, J = 12.6/3.0 Hz, 1H, OCH_2), 6.81–7.63 (m, 15H, Ph). HRMS: calcd for $C_{28}H_{27}NO_5Na$ 480.1787, found 480.1781. $[\alpha]_{589}$ (82% ee) = −29 (23 °C, c 0.48, CH_2Cl_2). HPLC (method A): purity 99%, t_R = 21.9 min.

6.11. Benzyl (2*S*,4*R*)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]-4-hydroxypiperidine-1-carboxylate ((*S*,*R*,*S*)-24c) and benzyl (2*S*,4*S*)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]-4-hydroxypiperidine-1-carboxylate ((*S*,*S*,*S*)-24d)

A solution of the Cbz-protected ketone (*S*,*S*)-**23** (0.19 g, 0.4 mmol) in methanol (2 mL) was cooled down to 0 °C under N_2 atmosphere. Then $NaBH_4$ (15 mg, 0.4 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h. Water and EtOAc were added, the organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried (K_2CO_3) filtered and concentrated in vacuo. The diastereomeric alcohols (*S*,*R*,*S*)-**24c** and (*S*,*S*,*S*)-**24d** were separated by fc (2 cm, 15 cm, petroleum ether/EtOAc = 7:3, 10 mL).

Compound (*S*,*R*,*S*)-**24c** (R_f = 0.26): colorless oil, yield 83 mg (45%). IR (neat): ν (cm^{-1}) = 1671 (s, Cbz C=O), 1201(s)/1049 (s, C–O–C). ^1H NMR ($CDCl_3$): δ (ppm) = 1.19 (s broad, 2H, 3-H), 1.65–1.56 (m, 3H, 5-H + OH), 2.12 (d broad, J = 15.0 Hz, 1H, 6-H), 3.06–3.37 (m, 1H, 6-H), 3.87–3.91 (m broad, 3H, 2-H + $2OCH_2$), 4.07 (s, 1H, 4-H), 4.13–4.77 (m, 1H, OCH), 5.00–5.07 (m, 2H, OCH_2Ph), 6.90–7.69 (m, 15H, Ph). HRMS: calcd for $C_{28}H_{29}NO_5Na$ 482.1938, found 482.1935. $[\alpha]_{589}$ (82% ee) = +5.7 (24 °C, c 1.5, CH_2Cl_2). HPLC (method A): purity 98%, t_R = 22.4 min.

Compound (*S*,*S*,*S*)-**24d** (R_f = 0.16): colorless oil, yield 88 mg (48%). IR (neat): ν (cm^{-1}) = 1671 (s, Cbz C=O), 1201 (s)/1049 (s, C–O–C). ^1H NMR ($CDCl_3$): δ (ppm) = 1.15–1.23 (m, 3H, 3-H + 5-H), 1.83 (s broad, 1H, OH), 2.33 (d broad, J = 10.8 Hz, 1H, 5-H), 2.69–3.07 (m, 1H, 6-H), 3.89 (s broad, 2H, 6-H + 2-H), 3.95–4.05 (m, 1H, 4-H), 4.05–4.19 (m, 1H, OCH_2), 4.19–4.27 (m, 1H, OCH_2), 4.28–4.52 (m, 1H, OCH), 5.03 (s broad, 2H, OCH_2Ph), 6.94–7.79 (m, 15H, Ph). HRMS: calcd for $C_{28}H_{29}NO_5Na$ 482.1938, found 482.1930. $[\alpha]_{589}$ (82% ee) = −7.4 (24 °C, c 0.35, CH_2Cl_2). HPLC (method A): purity 95%, t_R = 21.9 min.

6.12. (2*S*,4*S*)-2-[(4*S*)-2,2-Diphenyl-1,3-dioxolan-4-yl]piperidin-4-ol ((*S*,*S*,*S*)-5)

According to General Procedure A (*S*,*S*,*S*)-**24d** (72 mg, 0.16 mmol) was dissolved in methanol (5 mL) and Pd/C (10%, 7.0 mg) was added. The product was purified by fc. Compound (*S*,*S*,*S*)-**5** (R_f = 0.09): colorless solid, yield 47 mg (90%). IR (neat): ν (cm^{-1}) = 1066 (s, C–O–C), 698 (s, O–H). ^1H NMR ($CDCl_3$): δ (ppm) = 1.40 (ddd, J = 11.9/9.0/2.5 Hz, 1H, 3-H), 1.56 (bs, 2H, NH + OH), 1.60–1.71 (m, 2H, 3-H, 5-H), 1.74 (ddd, J = 8.1/5.4/3.2 Hz, 1H, 2-H), 2.84 (ddd, J = 12.2/4.4/3.0 Hz, 1H, 5-H), 3.02 (td, J = 12.0/3.6 Hz, 1H, 6-H), 3.26 (ddd, J = 11.7/4.1/2.8 Hz, 1H, 6-H), 3.93 (t, J = 7.1 Hz, 1H, OCH_2), 4.05 (td, J = 6.5/4.6 Hz, 1H, OCH), 4.12 (t, J = 7.0 Hz, 1H, OCH_2), 4.20 (quint, J = 3.1 Hz, 1H, 4-H), 7.26–7.36 (m, 7H, Ph), 7.46–7.54 (m, 3H, Ph). HRMS: calcd for $C_{20}H_{23}NO_3H$ 326.1751, found 326.1747. $[\alpha]_{589}$ (82% ee) = +20 (23 °C, c 0.61, CH_2Cl_2). HPLC (method A): purity 97%, t_R = 16.1 min.

6.13. Benzyl (2*S*,4*S*)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]-4-fluoropiperidine-1-carboxylate ((*S*,*S*,*S*)-25d) and benzyl (2*S*)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate ((*S*,*S*)-26c) and benzyl (2*S*)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]-1,2,5,6-tetrahydropyridine-1-carboxylate ((*S*,*S*)-26d)

Under N_2 the alcohol (*S*,*R*,*S*)-**24c** (76 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (2 mL), cooled down to −78 °C and diethylaminosulfur trifluoride (DAST, 0.02 mL, 0.16 mmol) was added and the mixture was stirred at −78 °C for 3 h. Then, water and CH_2Cl_2 were added and the mixture was warmed to rt. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by fc (2 cm, 12 cm, petroleum ether/EtOAc = 9: 1, 10 mL).

Compound (*S*,*S*,*S*)-**25d** (R_f = 0.32): colorless oil, yield 23 mg (31%). IR (neat): ν (cm^{-1}) = 1698 (s, Cbz C=O), 1205 (s, C–O–C). ^1H NMR ($C_6D_5NO_2$, 100 °C): δ (ppm) = 1.13–1.35 (m, 2H, 3-H + 5-H), 1.58 (s broad, 1H, 3-H), 1.60–1.65 (m, 1H, 5-H), 2.07–2.14 (m, 1H, 6-H), 2.68–2.75 (m, 1H, 6-H), 3.60–3.63(m, 1H, 2-H), 3.84–3.87 (m,1H, OCH_2), 3.99–4.05 (m, 1H, OCH), 4.17 (broad s, 1H, OCH_2), 4.62 (dtt, J = 49.0/10.0/4.9 Hz, 1H, 4-H), 4.71–4.82 (m, 2H, OCH_2Ph), 6.81–7.64 (m, 15H, Ph). HRMS: calcd for $C_{20}H_{28}FNO_4Na$ 484.1900, found 484.1889. $[\alpha]_{589}$ (82% ee) = −6.5 (22 °C, c 0.35, CH_2Cl_2). HPLC (method A): purity 94%, t_R = 24.1 min.

Compounds (*S*,*S*)-**26c** and (*S*,*S*)-**26d** (R_f = 0.43): colorless oil, yield 41 mg (55%). IR (neat): ν (cm^{-1}) = 1698 (s, Cbz C=O), 1205

(s, C–O–C). ^{1}H NMR ($C_6D_5NO_2$, 100 °C): δ (ppm) = 1.07 (d broad, J = 15.7 Hz, 0.7H, 3°-H), 1.28–1.37 (m, 0.7H, 3°-H), 1.49 (ddd, J = 17.4/5.9/2.9 Hz, 0.3H, 5^x-H), 1.76 (d broad, J = 17.6 Hz, 0.3 H, 5^x-H), 2.23–2.30 (m, 0.7H, 6°-H), 2.75 (d broad, J = 18.0 Hz, 0.3H, 6^x-H), 3.16–3.25 (m, 1H, 6°-H + 6^x-H), 3.38–3.42 (m, 1H, 2°-H + 2^x-H), 3.52 (ddd, J = 8.7/7.2/2.9 Hz, 0.7H, OCH_2°), 3.60 (ddd, J = 12.5/6.3/3.3 Hz, 0.3H, OCH_2^x), 3.67 (m broad, 0.7H, OCH°), 3.73–3.76 (m, 0.3H, OCH^x), 3.81 (m broad, 1H, $OCH_2^\circ + OCH_2^x$), 4.33–4.41 (m, 2H, OCH_2Ph), 4.81 (d broad, J = 10.8 Hz, 0.3H, 3^{x}H), 4.91–4.95 (m, 0.3H, 4^{x}H), 5.03–5.12 (m, 1.4H, 4°H + 5°H), 6.42–7.24 (m, 15H, Ph). The ratio of (*S*,*S*)-**26c**/(*S*,*S*)-**26d** = 7:3; ° = index for the major regioisomer (*S*,*S*)-**26c**, x = index for the minor regioisomer (*S*,*S*)-**26d**. HRMS: calcd for $C_{28}H_{27}NO_4Na$ 464.1832, found 464.1836.HRMS: calcd for $C_{28}H_{27}NO_4Na$ 464.1832, found 464.1836. HPLC (method A): purity 95%, t_R = 24.5 min.

6.14. (2*S*,4*S*)-2-[(4*S*)-2,2-Diphenyl-1,3-dioxolan-4-yl]-4-fluoropiperidine ((*S*,*S*,*S*)-6, WMS-2539)

According to General Procedure A (*S*,*S*,*S*)-**25d** (12 mg, 0.02 mmol) was dissolved in methanol (5 mL) and Pd/C (10%, 2.0 mg) was added. The product was purified by fc. Compound (*S*,*S*,*S*)-**6** (R_f = 0.67): colorless oil, yield 6.6 mg (85%). IR (neat): ν (cm^{-1}) = 1067 (s, C–O–C). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.36 (dddd, J = 43.9/13.6/12.1/2.2 Hz, 1H, 3-H_{ax}), 1.53–1.73 (m, 2H, 5-H + NH), 1.87–1.95 (m, 1H, 3-H), 1.96–2.05 (m, 1H, 5-H), 2.90 (ddd, J = 12.2/5.3/1.9 Hz, 1H, 2-H), 2.99 (td, J = 12.4/2.8 Hz, 1H, 6-H), 3.24 (dt, J = 12.2/3.3 Hz, 1H, 6-H), 3.94 (t, J = 6.5 Hz, 1H, OCH_2), 4.04–4.12 (m, 2H, OCH_2 + OCH), 4.97 (dquint, J = 47.9/2.7 Hz, 1H, 4-H), 7.27–7.36 (m, 5H, Ph), 7.47–7.54 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ (ppm) = 31.2 (d, J = 20.4 Hz, C-3), 33.0 (d, J = 20.4 Hz, C-5), 40.6 (C-6), 52.0 (C-2), 65.7 (OCH_2), 79.2 (OCH), 87.4 (d, J = 168.3 Hz, C-4), 109.7 (OCO), 126.0 (Ph-C).126.2 (Ph-C), 128.0 (Ph-C), 128.1 (Ph-C), 128.2 (Ph-C), 128.3 (Ph-C), 141.8 (Ph-C), 142.0 (Ph-C). ^{19}F NMR (300 MHz, $CDCl_3$): δ (ppm) = −184.80 (dtt, J = 47.8/44.2/11.3 Hz, 4-F). HRMS: calcd for $C_{20}H_{22}FNO_2H$ 328.1713, found 328.1707. $[\alpha]_{589}$ (82% ee) = +8.2 (22 °C, c 0.13, CH_2Cl_2). HPLC (method A): purity 96%, t_R = 16.0 min.

6.15. (2*S*)-2-[(4*S*)-2,2-Diphenyl-1,3-dioxolan-4-yl]piperidine ((*S*,*S*)-3, dexoxadrol)

According to General Procedure A the mixture of (*S*,*S*)-**26c** and (*S*,*S*)-**26d** (41 mg, 0.09 mmol) was dissolved in methanol (5 mL) and Pd/C (10%, 4.0 mg) was added. The product was purified by fc. Compound (*S*,*S*)-**3** (R_f = 0.46). Colorless oil, yield 25 mg (90%). IR (neat): ν (cm^{-1}) = 1066 (s, C–O–C). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.01 (qd, J = 12.3/3.7 Hz, 1H, 3-H_{ax}), 1.18–1.26 (m, 1H, 4-H), 1.33 (qt, J = 12.3/3.7 Hz, 1H, 5-H_{ax}), 1.50 (d broad, J = 12.8 Hz, 1H, 5-H), 1.61 (d broad, J = 13.6 Hz, 1H, 3-H), 1.72 (d broad, J = 14.2 Hz, 1H, 4-H), 1.90 (s, 1H, NH), 2.51 (td, J = 11.7/2.8 Hz, 1H, 6-H), 2.75 (ddd, J = 11.3/4.3/2.5 Hz, 1H, 2-H), 2.97(d broad, J = 11.9 Hz, 1H, 6-H), 3.86 (t, J = 7.2 Hz, 1H, OCH_2), 3.96 (td, J = 6.6/4.5 Hz, 1H, OCH), 4.06 (t, J = 6.9 Hz, 1H, OCH_2), 7.17–7.27 (m, 5H, Ph), 7.39–7.46 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ = 24.7 (C-4), 26.6 (C-5), 28.8 (C-3), 46.9 (C-6), 58.2 (C-2), 66.2 (OCH_2), 79.9 (OCH), 109.7 (OCO), 126.4 (Ph-C).126.5 (Ph-C), 128.2 (Ph-C), 128.3 (Ph-C), 128.4 (Ph-C), 128.5 (Ph-C), 142.2 (Ph-C), 142.5 (Ph-C). HRMS: calcd for $C_{20}H_{23}NO_2H$ 310.1807, found 310.1803. $[\alpha]_{589}$ (82% ee) = +30 (23 °C, c 0.42, CH_2Cl_2). HPLC (method A): purity 99%, t_R = 17.7 min.

6.16. Benzyl (2*S*)-2-[(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]-4,4-difluoropiperidine-1-carboxylate ((*S*,*S*)-27c)

Under N_2 the ketone (*S*,*S*)-**23** (90 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (2 mL). Then, diethylaminosulfur trifluoride (DAST, 0.05 mL, 0.40 mmol) was added and the mixture was stirred at rt overnight. Then, water and CH_2Cl_2 were added, the organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by fc (2 cm, 12 cm, petroleum ether/EtOAc = 9:1, 10 mL, R_f = 0.30). Colorless oil, yield 65 mg (70%). IR (neat): ν (cm^{-1}) = 1698 (s, Cbz C=O), 1203 (s, C–O–C). ^{1}H NMR ($C_6D_5NO_2$, 100 °C): δ (ppm) = 1.43–1.64 (m, 4H, 3-H + 5-H), 2.22–2.30 (m, 1H, 6-H), 2.68–2.76 (m, 1H, 6-H), 3.59–3.63 (m, 1H, 2-H), 3.69 (dd, J = 8.0/4.4 Hz, 1H, OCH_2), 3.87 (ddd, J = 8.0/5.1/2.4 Hz 1H, OCH), 4.16 (s broad, 1H, OCH_2) 4.72–4.80 (m, 2H, OCH_2Ph), 6.82–6.92 (m, 9H, Ph), 7.14–7.16 (m, 6H, Ph). HRMS: calcd for $C_{28}H_{27}F_2NO_4Na$ 502.1806, found 502.1800. $[\alpha]_{589}$ (82% ee) = −2.2 (24 °C, c 0.21, CH_2Cl_2). HPLC (method A): purity 98%, t_R = 23.6 min.

6.17. (2*S*)-2-[(4*S*)-2,2-Diphenyl-1,3-dioxolan-4-yl]-4,4-difluoropiperidine ((*S*,*S*)-7)

According to General Procedure A (*S*,*S*)-**27c** (55 mg, 0.11 mmol) was dissolved in methanol (5 mL) and Pd/C (10%, 5.0 mg) was added. The product was purified by fc. Compound (*S*,*S*)-**7** (R_f = 0.30): colorless oil, yield 34.2 mg (90%). IR (neat): ν (cm^{-1}) = 1205 (s, C–O–C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 1.50 (dtd, J = 33.8/12.6/3.8 Hz, 1H, 3-H_{ax}), 1.69–1.83 (m, 2 H, 5-H + NH), 1.98–2.05 (m, 1H, 5-H), 2.12–2.19 (m, 1H, 3-H), 2.78 (td, J = 12.7/2.9 Hz, 1H, 6-H), 3.02–3.05 (m, 1H, 2-H), 3.14 (ddt, J = 12.6/5.3/2.2 Hz, 1H, 6-H), 3.93–3.98 (m, 1H, OCH_2), 4.08–4.13 (m, 2H, OCH_2 + OCH), 7.25–7.35 (m, 6H, Ph), 7.45–7.54 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) = 34.8 (dd, J = 24.0/20.5 Hz, C-5), 36.6 (dd, J = 24.2/21.4 Hz, C-3), 42.3 (d, J = 10.1 Hz, C-6), 55.2 (d, J = 9.6 Hz, C-2), 65.9 (OCH_2), 78.3 (OCH), 109.9 (OCO), 122.3 (dd, J = 244.5/239.2 Hz, C-4), 125.9 (Ph-C), 126.1 (Ph-C), 128.1 (Ph-C), 128.2 (Ph-C), 128.3 (Ph-C), 141.6 (Ph-C), 141.8 (Ph-C). ^{19}F NMR ($CDCl_3$, 600 MHz): δ (ppm) = −101.5 (dtt, J = 236.2/34.2/11.5 Hz, 1F, 4-F), −87.7 (d, J = 236.3 Hz, 1F, 4-F). HRMS: calcd for $C_{20}H_{21}F_2NO_2H$ 346.1619, found 346.1613. $[\alpha]_{589}$ (82% ee) = +22 (22.1 °C, c 0.44, CH_2Cl_2). HPLC (method A): purity 98%, t_R = 18.3 min.

7. Receptor binding studies

7.1. Materials and general procedures

Pig brains were a donation of the local slaughterhouse (Coesfeld, Germany). The guinea pig brains and rat livers were commercially available (Harlan-Winkelmann, Borchen, Germany). Homogenizer: Elvehjem Potter (B. Braun Biotech International, Melsungen, Germany). Centrifuge: High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Fisher Scientific, Langenselbold, Germany). Filter: Printed Filtermat Typ A and B (Perkin–Elmer LAS, Rodgau-Jügesheim, Germany), presoaked in 0.5% aqueous polyethylenimine for 2 h at room temperature before use. The filtration was carried out with a MicroBeta FilterMate-96 Harvester (Perkin–Elmer). The scintillation analysis was performed using Meltilex (Typ A or B) solid scintillator (Perkin–Elmer) and a MicroBeta Trilux scintillation analyzer (Perkin–Elmer). The overall counting efficiency was 20%. All experiments were carried out in triplicates using standard 96-well-multiplates (Diagonal, Muenster, Germany). The IC_{50}-values were determined in competition experiments with at least six concentrations of the test compounds and were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. The K_i-values were calculated according to the formula of Cheng and Prusoff.[35] The K_i-values are given as mean value ± SEM from three independent experiments.

7.2. Determination of the affinity to the phencyclidine binding site of the NMDA receptor, modified according to Ref. 29

7.2.1. Preparation of the tissue

Fresh pig brain cortex was homogenized with the potter (500–800 rpm, 10 up-and-down strokes) in six volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200*g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 23,500*g* for 20 min at 4 °C. The pellet was resuspended in 5–6 volumes of TRIS/EDTA-buffer (5 mM/1 mM, pH 7.5) and centrifuged again at 31,000*g* (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5-6 volumes of buffer, the protein concentration was determined according to the method of Bradford[36] using bovine serum albumin as standard, and subsequently the preparation was frozen (−80 °C) in 1.5 mL portions containing about 0.8 mg protein/mL.

7.2.2. Performance of the assay

The test was performed with the radioligand [^{3}H]-(+)-MK-801 (22.0 Ci/mmol; Perkin–Elmer). The thawed membrane preparation (about 100 μg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-MK-801, and TRIS/EDTA-buffer (5 mM/1 mM, pH 7.5) in a total volume of 200 μL for 150 min at rt. The incubation was terminated by rapid filtration through the presoaked filtermats using a cell harvester. After washing each well five times with 300 μL of water, the filtermats were dried at 95 °C. Subsequently, the solid scintillator was placed on the filtermat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at rt. The bound radioactivity trapped on the filters was counted in the scintillation analyzer. The non-specific binding was determined with 10 μM unlabeled (+)-MK-801. The K_d-value of (+)-MK-801 is 2.26 nM.[37]

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