Available online at www.sciencedirect.com
SCIENCE DIRECT
Bioorganic & Medicinal Chemistry 14 (2006) 5955–5962
Bioorganic & Medicinal Chemistry

Synthesis and NMDA-receptor affinity of 4-oxo-dexoxadrol derivatives

Michael Sax,[a] Kirstin Ebert,[a] Dirk Schepmann,[a] Birgit Wibbeling[b] and Bernhard Wünsch[a,*]

[a]*Institut für Pharmazeutische und Medizinische Chemie, Westfälische Wilhelms-Universität Münster, Hittorfstr. 58-62, D-48149 Münster, Germany*
[b]*Institut für Organische Chemie, Westfälische Wilhelms-Universität Münster, Corrensstr. 40, D-48149 Münster, Germany*

Received 1 February 2006; revised 4 May 2006; accepted 15 May 2006
Available online 5 June 2006

Abstract—A synthesis of novel dexoxadrol analogues is described, which allows modifications of the piperidine substructure. The key step of the synthesis is a hetero Diels–Alder reaction of the imine **12** with Danishefsky's diene **6**. After separation of the diastereomeric piperidones **14a** and **14b**, the relative configuration of the unlike configured piperidone **15b** was determined by X-ray crystal structure analysis. In receptor binding studies the like configured secondary amine **15a** (racemate) showed considerable affinity toward the phencyclidine binding site of the NMDA receptor (K_i = 470 nM).

1. Introduction

Diseases with age as a major risk factor are becoming more and more threatening for the older population. Such is the case for neurodegenerative disorders like Parkinson's disease (PD) and Alzheimer's disease (AD), which are caused by the degeneration of dopaminergic and cholinergic neurons, respectively. Unfortunately, the possibilities for the treatment of these diseases are rather poor because up to now the therapeutic gold standard is compensation of the decreased neurotransmitter level. This is usually achieved by giving levodopa as a dopamine precursor (PD) and acetylcholinesterase inhibitors (AD) to prevent degradation of the neurotransmitter acetylcholine, which leads to higher neurotransmitter concentrations in the synaptic cleft. These treatments do lead to higher efficacy of the remaining intact neurons, but the result is merely a symptomatic therapy. Unfortunately, the treatments do not prevent nor reduce the progression of neurodegeneration. Therefore, great efforts have been undertaken to develop drugs which meet this impairment.[1]

With regard to Alzheimer's disease, NMDA receptor antagonists have neuroprotective potential by protecting neurons from excessive pathological calcium influx, which leads to damage of neurons and finally to neuronal cell death. Up to now, memantine (**1a**) is the only NMDA receptor antagonist with moderate NMDA receptor affinity (K_i = 1.2 μM) which has been introduced for the treatment of severe Alzheimer's disease.[1,2] The particular advantage of memantine is the fast off-rate kinetic preventing the drug from accumulating in the ion channel. Therefore, memantine enters the open channel preferentially when it is pathologically activated for long periods of time. The physiological neurotransmission is not disturbed by memantine resulting in minimal adverse effects.[1] Parkinson's disease is treated with the NMDA receptor antagonists amantadine (**1b**) and budipine (1-*tert*-butyl-4,4-diphenylpiperidine) displaying also moderate NMDA receptor affinity (Fig. 1).

In contrast to memantine, the piperidine derivative dexoxadrol (**2**) binds with high affinity (K_i = 39 nM) at the phencyclidine binding site within the NMDA receptor-associated cation channel. Dexoxadrol (**2**) was synthesized by Hardie et al. in the 1960s and revealed local anesthetic, spasmolytic, and central nervous system activity.[3a] Later, phencyclidine-like (**3**) dissociative anesthetic activities were found.[4] Unfortunately, clinical trials of **2** had to be stopped because of the

Keywords: NMDA receptor antagonists; 4-Oxo-dexoxadrol; Hetero Diels–Alder reaction; X-ray crystal structure; Piperidines 2-substituted.
* Corresponding author. Tel.: +49 0251 83 33311; fax: +49 0251 83 32144; e-mail: wuensch@uni-muenster.de

0968-0896/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2006.05.020

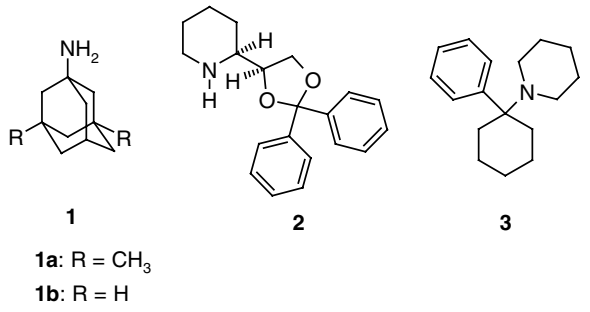


Figure 1. Structures of some important NMDA receptor antagonists: **1a**, memantine; **1b**, amantadine; **2**, dexoxadrol; **3**, phencyclidine (PCP).

psychotomimetic side effects. However, many derivatives of **2** have been synthesized since then in order to get more insight into the structure–affinity relationships within this substance class.[3] Since the severe side effects of dexoxadrol are attributed to its high NMDA receptor affinity, novel analogues with affinities between those of dexoxadrol (K_i = 39 nM) and memantine (K_i = 1.2 μM) should display an improved side-effect profile. The following modifications of the dexoxadrol structure have already been described in the literature: the residues at the acetalic center have been modified; the amino moiety has been altered from a cyclic amine (piperidine) to aliphatic primary, secondary, and tertiary amines; the distance between the dioxolane ring and the amino moiety has been changed; the dioxolane ring has been enlarged to the corresponding dioxane ring; furthermore, the piperidine ring has been replaced by a pyrrolidine ring and the dioxolane ring by a cyclopentane ring.[3] But in no case has the piperidine substructure itself been modified or substituted.

In this article, we wish to present a synthesis of dexoxadrol derivatives along a synthetic route that allows manifold substitution of the piperidine moiety. Pharmacological properties of these new dexoxadrol analogues are also included.

2. Chemistry

The key step of our synthetic strategy comprises the construction of 2-substituted piperidines **7** from aldehydes **4** with acetalic substructures $R_{acetalic}$. Condensation of these aldehydes **4** with benzylamine should lead to the corresponding imines **5**, which subsequently react in a

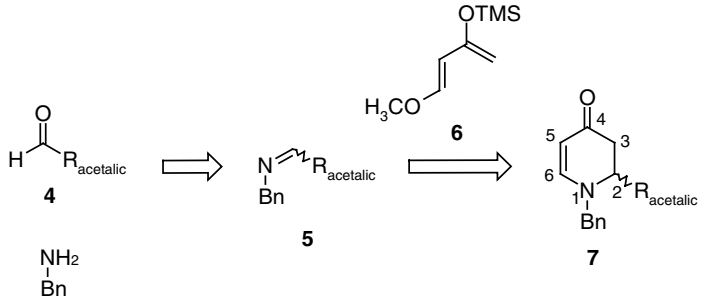
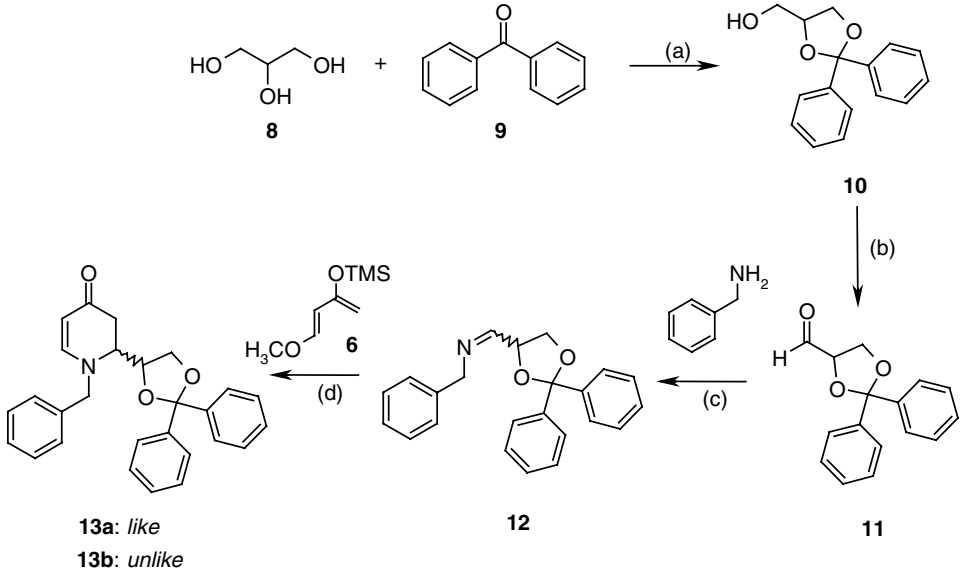


Figure 2. Plan for the synthesis of dexoxadrol analogues substituted at the piperidine ring.



Scheme 1. Synthesis of dihydropyridones **13a/b** (all compounds are racemic). Reagents and conditions: (a) $TosOH{\cdot}H_2O$, toluene, reflux, 6 h, yield 73%; (b) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, 30 min, then NEt_3, rt, yield 72%; (c) benzylamine, trimethyl orthoformate, rt, 16 h; (d) $Yb(OTf)_3$, **6**, THF, 0 °C (4 h) then 25 °C (16 h), yield 70% from **11**.

hetero Diels–Alder reaction[5] with Danishefsky's diene **6**[6] to afford dihydropyridones **7**. The dihydropyridones **7** allow the introduction of various substituents in positions 3, 4, 5, and 6 and, therefore, represent ideal precursors for the synthesis of substituted piperidine derivatives[7] (Fig. 2).

The synthesis was started with acetalization of benzophenone (**9**) with glycerol (**8**) to yield the (diphenyldioxolanyl)methanol **10**. Swern oxidation[8] of the primary alcohol **10** afforded the aldehyde **11**, which was condensed with benzylamine to give the imine **12**. $Yb(OTf)_3$-catalyzed hetero Diels–Alder reaction of the imine **12** with freshly[9] prepared[10] Danishefsky's diene **6** yielded the 1,2-disubstituted dihydropyridone **13** as a mixture of diastereomers. The diastereomeric ratio of **13a**:**13b** (59:41) was determined by integration of characteristic signals in the ^1H NMR spectrum (Scheme 1).

Selective reduction of the double bond of **13** with $LiEt_3BH$ in the presence of $BF_3{\cdot}OEt_2$[11] afforded the N-protected piperidin-4-ones **14a** (like configuration) and **14b** (unlike configuration), which were separated by flash chromatography. Finally, debenzylation with H_2 and Pd/C provided the desired 4-oxo-dioxadrols **15a** and **15b**[12] (Scheme 2).

It was not possible to determine unequivocally the relative configuration of **15a** and **15b** by interpretation of their NMR spectra. Therefore, **15b** was carefully recrystallized (Et_2O) to obtain colorless crystals suitable for an X-ray crystal structure analysis, which proved the unlike configuration (*SR*/*RS*) of the centers of chirality (Fig. 3).

3. NMDA receptor affinity

The affinity of the four compounds **14a**, **14b**, **15a** and **15b** to the phencyclidine binding site of the NMDA receptor was examined in competition experiments using the radioligand [^3H]-MK-801. The receptor material was prepared by homogenization and fractional centrifugation of the grey substance of pig brain cortex. The non-specific binding was determined in the presence of

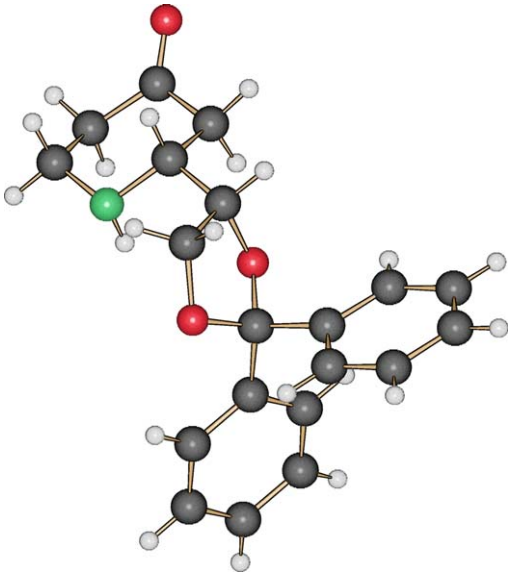
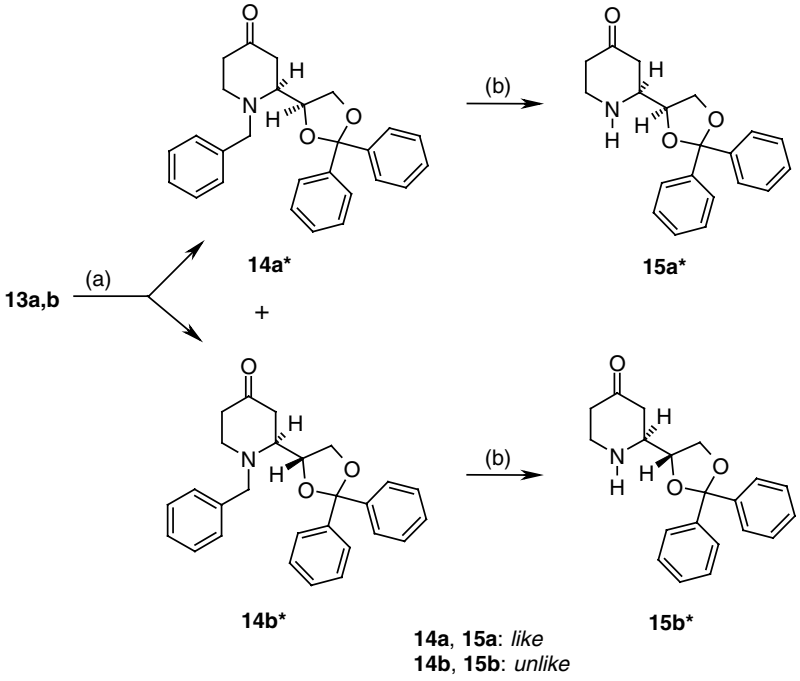


Figure 3. X-ray crystal structure of unlike configured oxo-dexoxadrol derivative **15b** (racemate).



Scheme 2. Synthesis of 4-oxo-dexoxadrol derivatives (only one enantiomer is shown, all compounds are racemic). Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, THF, −78 °C, 30 min, then $LiEt_3BH$, 1 h, −78 °C, yields of **14a**: 55%, **14b**: 37%. (b) H_2, balloon, Pd/C 10%, methanol, 2 h or 4 h, rt, yields of **15a**: 78%, **15b**: 86%.

Table 1. Affinities of **14** and **15** toward the phencyclidine binding site of the NMDA receptor

Compound	NMDA receptor affinity ([^{3}H]-MK-801)
14a	96%[a]
14b	95%[a]
15a	K_i = 470 ± 173 nM (n = 3)
15b	84%[a]
Dexoxadrol (**2**)	K_i = 39 ± 10 nM (n = 3)

[a] Specific binding of the radioligand at a concentration of 10 μM of the test compound.

a large excess of cold MK-801.[13–15] The K_i-values were calculated according to the equation of Cheng and Prussoff.[16] The NMDA receptor binding data are summarized in Table 1.

4. Discussion

Table 1 shows that the tertiary amines **14a** and **14b** do not interact significantly with the phencyclidine binding site within the NMDA receptor. Comparison of the various NMDA receptor affinities of the secondary amines indicates that only the racemate **15a** (like configuration) displays considerable NMDA receptor affinity, whereas its diastereomeric racemate **15b** (unlike configuration) does not bind significantly. These results support the literature data that tertiary amines generally reveal lower affinity than secondary and primary amines and, furthermore, the stereoisomers with (*S*,*S*)-(like) configuration display higher affinities than their enantiomers and unlike configured diastereomeres.[17]

The NMDA receptor affinity of **15a** (racemate) is about 12 times lower than the affinity of enantiomerically pure dexoxadrol. However, the K_i-value of 470 nM is in the desired affinity range (50–1000 nM). Therefore, further properties of **15a** were investigated.

According to Lipinski's 'rule of 5' the number of H-bond acceptors ($n < 10$) and H-bond donors ($n < 5$), the molecular weight (MW < 500), and the lipophilicity ($\log P < 5$) determine the pharmacokinetic of a drug, in particular its crossing of the blood–brain barrier.[18] Since the first three parameters are in agreement with the 'rule of 5,' the $\log P$ value of **15a** was determined with an HPLC method.[19] This method led to a $\log P$ value of 2.0 indicating sufficient water solubility and good penetration into the central nervous system. These results prompted the in vivo evaluation of oxo-dexoxadrol **15a** in animal models.

The analgesic potency was investigated in the mouse formalin assay, a model for neuropathic pain. However, a dose of 0.3 mg/kg of **15a** did not cause significant activity in this assay. The safety of **15a** was evaluated by observing mice behavior after intraperitoneal application of the test compound (Irwin screen).[20] At a dose of 1.0 mg/kg of **15a** the mice showed excitation, abnormal gait, and stereotypes. Increasing the dose to 30 mg/kg additionally led to convulsions, tremor, and the Skraup tail phenomenon. Due to these observations in the formalin assay and the Irwin screen the pharmacological evaluation of **15a** was terminated at this point.

5. Conclusion

Herein, we have demonstrated that the Lewis acid-catalyzed hetero Diels–Alder reaction of Danishefsky's diene **6** with imines provides piperidine derivatives bearing acetalic substituents in position 2 in good yields. In comparison with the lead compound dexoxadrol (**2**) the NMDA receptor affinity of racemic oxo-dexoxadrol **15a** (K_i = 470 nM) is considerably reduced indicating the H-bond acceptor in position 4 of the piperidine ring being disadvantageous for the NMDA receptor interaction. However, the carbonyl moiety in position 4 of **15a** allows several further variations of the piperidine substituents, including non-polar residues and substituents with H-bond donor properties.

6. Experimental

6.1. Chemistry, general

Thin-layer chromatography (TLC): silica gel 60 F_{254} plates (Merck). Flash chromatography (FC):[21] Silica gel 60, 40–63 μm (Merck). MS, MAT GCQ (Thermo-Finnigan); EI, electron impact; IR, IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Unity m400 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. Elemental analysis: CHNO-Rapid Analysator (Fons-Heraeus). THF was dried with sodium and was freshly distilled before use. $CHCl_3$ was distilled over CaH_2 and stored over molecular sieves 4 Å. Petroleum ether fraction bp 40–60 °C. $Yb(OTf)_3$ (Aldrich) was stored in a desiccator over P_4O_{10} in vacuo at room temperature. Danishefsky's diene **6** was stored under N_2 at −25 °C.[9]

6.2. *trans*-1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene, 6)

Procedure modified according to Refs. 9 and 10. Anhydrous LiBr (4.32 g, 49.8 mmol) was filled into a 100 mL Schlenk flask, which was immediately sealed by a rubber septum, flushed with N_2, and heated to approximately 400 °C with a heat gun. The flask was allowed to cool down to room temperature under gentle N_2 flow, then THF (25 mL) was added. It was stirred until LiBr had completely dissolved. Afterwards the mixture was cooled to −15 °C, chlorotrimethylsilane (4.72 mL, 37.3 mmol) and *trans*-4-methoxybut-3-en-2-one (2.50 mL, 25 mmol) were slowly added, and the mixture was stirred for 15 min. Then NEt_3 (5.18 mL, 37.3 mmol) was added, the solution was stirred at −15 °C for 1 h and another 24 h at 40 °C. Then the reaction mixture was transferred with 30 mL of cold (4 °C) pentane into a separating funnel loaded with ice (15 g), a cold saturated solution of NaH-

CO_3 (15 mL), cold brine (15 mL), and cold pentane (30 mL) (4 °C each). The organic layer was separated and the aqueous layer was extracted twice with cold pentane (30 mL). The combined organic layers were washed with cold brine (15 mL), cold water (5× 15 mL), dried ($MgSO_4$), filtered, and concentrated (400 mbar; 40 °C), and the resulting brownish oil was distilled in vacuo to yield 3.19 g (74%) of a clear colorless liquid, $bp_{10\,Torr}$ 66–67 °C (Ref. 10, $bp_{7\,Torr}$ 65–70 °C.).

6.3. (±)-(2,2-Diphenyl-1,3-dioxolan-4-yl)methanol (10)

Glycerol 98% (**8**, 4.14 g, 44 mmol), benzophenone (**9**, 7.29 g, 40 mmol) and *p*-toluenesulfonic acid monohydrate (0.38 g, 2.0 mmol) were refluxed in toluene (50 mL) at a water separator for 6 h. After cooling down Et_2O and a saturated solution of $NaHCO_3$ were added. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo. Flash chromatographic purification (*n*-hexane/EtOAc = 7:3) of the residue afforded 7.55 g (73%) of **10** as a colorless solid, mp 50.5–51.5 °C; $R_f = 0.22$ (*n*-hexane/EtOAc = 7:3); IR (neat): 3421 (br m, –O–H), 1449 (s, –C–H deformation), 1204 (s)/1026 (s)/991 (s, –C–O–C–); ^{1}H NMR ($CDCl_3$): δ 1.84 (t, $J = 6.4$ Hz, 1H, OH), 3.66 (dd, $J = 11.9/5.0$ Hz, 1H, 5-H), 3.83 (dd, $J = 11.8/3.5$ Hz, 1H, 5-H), 4.00 (dd, $J = 8.0/6.1$ Hz, 1H, CH_2OH), 4.05 (dd, $J = 8.0/7.0$ Hz, 1H, CH_2OH), 4.34 (dddd, $J = 7.1/5.8/4.9/3.6$ Hz, 1H, 4-H), 7.26–7.42 (m, 6H, –Ph), 7.47–7.58 (m, 4H, –Ph); ^{13}C NMR ($CDCl_3$): δ 63.5 (C-5), 66.5 (*C*H_2OH), 77.2 (C-4), 110.3 (C-2), 126.1 (2 Ph-C), 126.4 (2 Ph-C), 128.3 (Ph-C), 128.39 (2 Ph-C), 128.40 (2 Ph-C), 128.46 (Ph-C), 142.0/142.1 (2 quart Ph-C). Spectroscopic and analytical data of **10**, which has been prepared from the corresponding chloromethyl derivative, are given in Ref. 22. However, these data do not match with the structure.

6.4. (±)-2,2-Diphenyl-1,3-dioxolane-4-carbaldehyde (11)

Under N_2 CH_2Cl_2 (5 mL) and oxalyl chloride (103 μL, 1.2 mmol) were cooled down to −78 °C. Then a solution of dry DMSO (171 μL, 2.4 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise and the mixture was stirred for 10 min at −78 °C. Afterwards, a solution of **10** (256 mg, 1.0 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise and the solution was stirred for another 30 min at −78 °C before NEt_3 (707 μL, 5.0 mmol) was added. After warming to room temperature, *n*-hexane was added (10 mL), the mixture was filtered, and the precipitate was washed with Et_2O (10 mL). The organic layer was concentrated (600 mbar, 40 °C) and the filtration procedure was repeated once. Then the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether/EtOAc = 8:2) to afford 182 mg (72%) of **11** as a highly hygroscopic colorless oil, $R_f = 0.17$ (petroleum ether/EtOAc = 8:2); IR (neat): 1734 (s, C═O), 1206 (s)/1072 (s)/991 (s, –C–O–C–); ^{1}H NMR ($CDCl_3$): δ 4.08 (t, $J = 8.4$ Hz, 1H, 5-H), 4.14 (dd, $J = 8.7/4.8$ Hz, 1H, 5-H), 4.41 (ddd, $J = 8.0/4.8/1.9$ Hz, 1H, 4-H), 7.20–7.30 (m, 6H, –Ph), 7.44–7.47 (m, 4H, –Ph), 9.65 (d, $J = 1.9$ Hz, 1H, C*H*O); ^{13}C NMR ($CDCl_3$): δ 66.5 (C-5), 80.4 (C-4), 111.9 (C-2), 126.1 (2 Ph-C), 126.4 (2 Ph-C), 128.3 (Ph-C), 128.39 (2 Ph-C), 128.40 (2 Ph-C), 128.5 (Ph-C), 141.1/141.2 (2 quart Ph-C), 201.4 (*C*HO); MS (70 eV) *m/e* (rel int): 255 (MH^+, 6), 225 (M−CHO, 65), 177 (M−Ph, 36), 167 (PhCPh, 100), 105 (PhCO, 40); Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 74.97; H, 5.60.

6.5. (±)-1-Benzyl-2-(2,2-diphenyl-1,3-dioxolan-4-yl)-2,3-dihydropyridin-4(1*H*)-one (13a and 13b)

The aldehyde **11** (773 mg, 3.0 mmol) was dissolved in trimethyl orthoformate (7 mL), benzylamine (332 μL, 3.0 mmol) was added, and the solution was stirred overnight at room temperature. The mixture was evaporated to dryness, the obtained yellow oil (**12**) was dissolved in THF (20 mL), and the resulting solution was cooled down to 0 °C. Then a solution of $Yb(OTf)_3$ (337 mg, 0.61 mmol) in THF (4 mL) was added and it was stirred at 0 °C for 15 min. Afterwards, diene **6** (984 μL, 5.17 mmol) was added and it was stirred for another 4 h at 0 °C before the reaction mixture was allowed to warm to room temperature overnight. Then, water (5 mL) and after 15 min Et_2O (20 mL), water, a saturated solution of $NaHCO_3$, and brine were added, the organic layer was separated and the aqueous layer was extracted with Et_2O (3×). The organic layer was dried (K_2CO_3), filtered and concentrated in vacuo. Flash chromatographic purification (petroleum ether/EtOAc = 1:1) of the oily residue yielded 874 mg (70%) of **13** as a yellow oil, $R_f = 0.12$ (petroleum ether/EtOAc = 1:1); IR (neat): 1636 (m, C═O), 1577 (s, C═C), 1205 (s)/1162 (m, characteristic dihydropyridone fingerprint), 1073 (m, –C–O–C–); ^{1}H NMR ($CDCl_3$): δ 1.91 (d, $J = 16.8$ Hz, 0.41H, 3^x-H), 2.42 (dd, $J = 16.8/2.0$ Hz, 0.59H, 3^o-H), 2.64 (dd, $J = 16.8/8.2$ Hz, 0.59H, 3^o-H), 2.69 (dd, $J = 17.0/7.2$ Hz, 0.41H, 3^x-H), 3.39–3.43 (m, 0.41 H, 2^x-H), 3.63 (dd, $J = 8.6/5.9$ Hz, 0.41H, OCH_2^x), 3.72–3.75 (m, 0.59H, 2^o-H), 3.93 (dd, $J = 8.2/7.0$ Hz, 0.59H, OCH_2^o), 3.96 (dd, $J = 8.4/6.5$ Hz, 0.41H, OCH_2^x), 4.00 (dd, $J = 8.2/6.3$ Hz, 0.59H, OCH_2^o), 4.24 (td, $J = 6.5/4.9$ Hz, 0.59H, OCH^o), 4.27 (d, $J = 15.3$ Hz, 0.59H, PhCH_2^o), 4.42 (d, $J = 15.3$ Hz, 0.59H, PhCH_2^o), 4.43 (d, $J = 14.3$ Hz, 0.41H, PhCH_2^x), 4.65 (d, $J = 14.9$ Hz, 0.41H, PhCH_2^x), 4.75 (dt, $J = 9.9/6.3$ Hz, 0.41H, OCH^x), 4.89 (d, $J = 7.4$ Hz, 1H, 0.41 5^x-H + 0.59 5^o-H), 6.99–7.11 (m, 3H, 2× –Ph + 0.41 6^x-H + 0.59 6^o-H), 7.18–7.31 (m, 9H, –Ph), 7.39–7.44 (m, 4H, –Ph); ^{13}C NMR ($CDCl_3$): δ 37.0 (C-3^o), 37.6 (C-3^x), 56.6 (C-2^o), 58.8 (C-2^x), 59.5 (Ph*C*^{o}H$_2$), 60.2 (Ph*C*^{x}H$_2$), 67.0 (O*C*^{o}H$_2$), 67.2 (O*C*^{x}H$_2$), 74.4 (O*C*^{x}H), 77.4 (O*C*^{o}H), 97.4 (C-5^x), 98.6 (C-5^o), 109.8 (O*C*^{o}O), 110.9 (O*C*^{x}O), 125.9/126.1/126.2/126.4/127.6/127.8/128.4/128.5/128.6/129.2/129.3/136.7/137.1/142.0/142.1/142.2 (Ph-C), 153.2 (C-6^x), 153.8 (C-6^o), 189.1 (C-4^x), 189.9 (C-4^o); MS (70 eV) *m/e* (rel int): 411 (M, 2), 229 (M−Ph_2CO, 38), 186 (M-diphenyldioxolanyl, 39), 91 ($PhCH_2$, 100).

^{o} = index for major diastereomer **13a** (59%; ^{1}H NMR integral for 2^o-H); ^{x} = index for minor diastereomer **13b** (41%; ^{1}H NMR integral for 2^x-H).

6.6. (±)-(2*RS*)-1-Benzyl-2-[(4*RS*)-2,2-diphenyl-1,3-dioxolan-4-yl]piperidin- 4-one (14a) and (±)-(2*RS*)-1-benzyl-2-[(4*SR*)-2,2-diphenyl-1,3-dioxolan-4-yl]piperidin-4-one (14b)

Under N_2**13** (340 mg, 0.83 mmol) was dissolved in THF (8.3 mL) and the solution was cooled down to −78 °C. Then $BF_3 \cdot OEt_2$ (115 μL, 0.91 mmol) was added dropwise and it was stirred for 30 min at −78 °C. Afterwards, a solution of 1 M $LiEt_3BH$ in THF (0.91 mL, 0.91 mmol) was added very slowly and the solution was stirred for another 60 min at −78 °C. After addition of a saturated solution of $NaHCO_3$ (200 μL) and EtOAc (20 mL), the reaction mixture was warmed to room temperature. The solution was washed with a saturated solution of $NaHCO_3$ and brine, the organic layer was dried (K_2CO_3), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (petroleum ether/EtOAc = 8:2) to afford 125 mg (37%) of **14b** (R_f = 0.22) as a colorless oil and 187 mg (55%) of **14a** (R_f = 0.16) as a colorless oil.

Compound **14a:** IR (neat): 1710 (s, C═O), 1450 (m, –C–H deformation), 1204 (s)/1069 (s, –C–O–C–); ^{1}H NMR ($CDCl_3$): δ 2.31 (dtd, *J* = 15.1/4.5/1.4 Hz, 1H, 5-H), 2.50 (dddd, *J* = 15.2/9.3/5.9/0.7 Hz, 1H, 5-H), 2.64 (ddd, *J* = 14.9/5.8/0.9 Hz, 1H, 3-H), 2.70 (ddd, *J* = 14.9/4.3/1.5 Hz, 1H, 3-H), 2.95 (dddd, *J* = 13.5/5.9/4.8/1.0 Hz, 1 H, 6-H), 3.12–3.20 (m, 2H, 2-H + 6-H), 3.87 (s, 2H, PhCH_2), 3.88 (dd, *J* = 8.2/6.7 Hz, 1H, OCH_2), 4.08 (dd, *J* = 8.2/7.0 Hz, 1H, OCH_2), 4.29 ('q,' *J* = 6.8 Hz, 1H, OC*H*), 7.22–7.35 (m, 11H, –Ph), 7.38–7.41 (m, 2H, –Ph), 7.48–7.51 (m, 2H, –Ph); ^{13}C NMR ($CDCl_3$): δ 38.1 (C-5), 39.6 (C-3), 47.8 (C-6), 57.1 (Ph*C*H_2), 62.4 (C-2), 68.6 (O*C*H_2), 76.4 (O*C*H), 110.7 (O*C*O), 126.2 (2 Ph-C), 126.3 (2 Ph-C), 127.7 (Ph-C), 128.25 (2 Ph-C), 128.28 (Ph-C), 128.4 (Ph-C), 128.5 (2 Ph-C), 128.77 (2 Ph-C), 128.79 (2 Ph-C), 138.7 (quart Bn-C), 142.0/142.4 (2 quart benzophenone-C), 208.7 (C-4); MS (70 eV) *m/e* (rel int): 413 (M, 0.37), 336 (M−Ph, 1.5), 188 (M-diphenyldioxolanyl = *N*-benzylpiperidinone, 47), 91 (PhCH_2, 100); Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 77.94; H, 6.13; N, 3.11.

Compound **14b:** IR (neat): 1714 (s, C═O), 1450 (m, –C–H deformation), 1205 (s)/1070 (s, –C–O–C–); ^{1}H NMR ($CDCl_3$): δ 2.21 (ddd, *J* = 14.7/5.1/1.6 Hz, 1H, 3-H), 2.31 (dddd, *J* = 15.0/5.9/4.6/1.4 Hz, 1H, 5-H), 2.40–2.48 (m, 1H, 5-H), 2.66 (ddd, *J* = 14.7/5.8/1.2 Hz, 1H, 3-H), 2.82 (dt, *J* = 12.8/6.1 Hz, 1H, 6-H), 3.16 (ddd, *J* = 12.8/8.1/4.7 Hz, 1H, 6-H), 3.31 (dt, *J* = 7.5/5.4 Hz, 1H, 2-H), 3.91 (d, *J* = 14.2 Hz, 1H, PhCH_2), 3.93 (t, *J* = 7.6 Hz, 1H, OCH_2), 4.04 (dd, *J* = 7.8/6.7 Hz, 1H, OCH_2), 4.11 (d, *J* = 13.8 Hz, 1H, PhCH_2), 4.36 ('q,' *J* = 7.2 Hz, 1H, OC*H*), 7.25–7.39 (m, 11H, –Ph), 7.46–7.53 (m, 4H, –Ph); ^{13}C NMR ($CDCl_3$): δ 37.8 (C-5), 40.1 (C-3), 45.7 (C-6), 56.6 (Ph*C*H_2), 59.7 (C-2), 65.1 (O*C*H_2), 74.7 (O*C*H), 108.3 (O*C*O), 124.0/124.1/125.4/126.2/126.4/126.5/126.6 (15 Ph-C), 137.3 (quart Bn-C), 140.1/140.3 (2 quart benzophenone-C), 206.9 (C-4); MS (70 eV) *m/e* (rel int): 336 (M−Ph, 1.2), 188 (M-diphenyldioxolanyl = *N*-benzylpiperidinone, 55), 91 (PhCH_2, 100); Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.14; H, 6.52; N, 3.30.

6.7. (±)-(2*RS*)-2-[(4*RS*)-2,2-Diphenyl-1,3-dioxolan-4-yl]piperidin-4-one (15a) (4-oxo-α-dioxadrol,[12] 15a)

The *N*-benzylpiperidone **14a** (170 mg, 0.41 mmol) was dissolved in MeOH (6 mL), Pd/C 10% (70 mg) was added, and the suspension was vigorously stirred under H_2-atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through Celite, which was rinsed with MeOH, and the filtrate was evaporated to dryness. Flash chromatographic purification (EtOAc/MeOH/NH_{3cc} = 94:5:1) of the oily residue yielded 104 mg (78%) of **15a** as a colorless solid, mp = 116.6–117.6 °C; R_f = 0.44 (EtOAc/MeOH/NH_{3cc} = 94:5:1); IR (neat): 3329 (w)/3305 (w, –N–H), 1712 (s, C═O), 1449 (s, –C–H deformation), 1204 (s)/1065 (s, –C–O–C–); ^{1}H NMR ($CDCl_3$): δ 2.17 (ddd, *J* = 14.1/11.8/0.8 Hz, 1H, 3-H), 2.31–2.36 (m, 1H, 5-H), 2.40 (dddd, *J* = 14.4/11.6/6.5/0.9 Hz, 1H, 5-H), 2.47 (ddd, 1H, *J* = 14.1/3.1/1.9 Hz, 3-H), 2.86 (ddd, *J* = 12.4/11.6/4.1 Hz, 1H, 6-H), 3.10 (ddd, *J* = 11.8/4.1/3.1 Hz, 1H, 2-H), 3.38 (ddd, *J* = 12.5/6.5/2.5 Hz, 1H, 6-H), 3.98 (dd, *J* = 7.8/7.0 Hz, 1H, OCH_2), 4.13 (dd, *J* = 7.8/5.9 Hz, 1H, OCH_2), 4.19 (ddd, *J* = 7.1/5.8/4.2 Hz, 1H, OC*H*), 7.26–7.37 (m, 6H, –Ph), 7.47–7.54 (m, 4H, –Ph), the NH-signal was not visible; ^{13}C NMR ($CDCl_3$): δ 43.1 (C-5), 44.8 (C-3), 45.6 (C-6), 59.1 (C-2), 66.2 (O*C*H_2), 78.8 (O*C*H), 110.4 (O*C*O), 126.2 (2 Ph-C), 126.4 (2 Ph-C), 128.41 (Ph-C), 128.42 (2 Ph-C), 128.5 (3 Ph-C), 141.8/142.0 (2 quart benzophenone-C), 208.7 (C-4); MS (70 eV) *m/e* (rel int): 182 (Ph_2CO, 57), 105 (PhCO, 68), 77 (–Ph, 100); Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.01; H, 6.49; N, 4.36.

6.8. (±)-(2*RS*)-2-[(4*SR*)-2,2-Diphenyl-1,3-dioxolan-4-yl]piperidin-4-one (4-oxo-β-dioxadrol,[12] 15b)

The *N*-benzylpiperidone **14b** (106 mg, 0.26 mmol) was dissolved in MeOH (5 mL), Pd/C 10% (43 mg) was added, and the suspension was vigorously stirred under H_2-atmosphere (balloon) at room temperature for 2 h. The reaction mixture was filtered through Celite, which was rinsed with MeOH, and the filtrate was evaporated to dryness. Flash chromatographic purification (EtOAc/MeOH/NH_{3cc} = 94:5:1) of the oily residue yielded 71 mg (86%) of **15b** as a colorless solid. Recrystallization for X-ray crystal structure analysis was performed with Et_2O, colorless solid, mp = 96.7–97.4 °C; R_f = 0.50 (EtOAc/MeOH/NH_{3cc} = 94:5:1); IR (neat): 3337 (w, –N–H), 1712 (s, C═O), 1205 (m)/1068 (m, –C–O–C–); ^{1}H NMR ($CDCl_3$): δ 2.13 (br s, 1H, –NH), 2.25 (d, *J* = 7.8 Hz, 2H, 3-H), 2.35 (br d, *J* = 14.5 Hz, 1H, 5-H), 2.44 (ddd, *J* = 14.3/11.9/6.6 Hz, 1H, 5-H), 2.85 (td, *J* = 12.0/3.7 Hz, 1H, 6-H), 2.93 ('q,' *J* = 7.2 Hz, 1H, 2-H), 3.40 (ddd, *J* = 12.2/6.6/2.3 Hz, 1H, 6-H), 3.93 (dd, *J* = 8.2/6.3 Hz, 1H, OCH_2), 4.03 (dd, *J* = 7.8/7.0 Hz, 1H, OCH_2), 4.11 ('q,' *J* = 6.7 Hz, 1H, OC*H*), 7.26–7.36 (m, 6H, –Ph), 7.46–7.53 (m, 4H, –Ph); ^{13}C NMR ($CDCl_3$): δ 42.7 (C-5), 45.26 (C-3), 45.36 (C-6), 60.0 (C-2), 67.0 (O*C*H_2), 79.3 (O*C*H), 110.4 (O*C*O), 126.3 (2 Ph-C), 126.4 (2 Ph-C), 128.43 (2 Ph-C), 128.48

(Ph-C), 128.52 (2 Ph-C), 128.6 (Ph-C), 141.9/142.1 (2 quart benzophenone-C), 208.2 (C-4); MS (70 eV) *m/e* (rel int): 246 (M−Ph, 3.4), 167 (PhCPh, 28), 105 (PhCO, 28), 98 (M-diphenyldioxolane = piperidinone, 100); Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 73.93; H, 6.45; N, 4.24.

6.9. X-ray crystal structure analysis of 15b

Formula $C_{20}H_{21}NO_3$, $M = 323.38$, colorless crystal $0.25 \times 0.20 \times 0.15$ mm, $a = 6.032(1)$ Å, $b = 34.556(1)$ Å, $c = 8.136(1)$ Å, $\beta = 101.23(1)$ °, $V = 1636.4(3)$ Å^3, $\rho_{calcd} = 1.291$ g cm^{-3}, $\mu = 0.87$ cm^{-1}, empirical absorption correction ($0.979 \leqslant T \leqslant 0.987$), $Z = 4$, monoclinic, space group $P2_1/n$ (no. 14), $\lambda = 0.71073$ Å, $T = 198(2)$ K, ω and ϕ scans, 5990 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda_{max}] = 0.66$ Å^{-1}, 3698 independent ($R_{int} = 0.023$) and 2693 observed reflections [$I \geqslant 2\sigma(I)$], 220 refined parameters, $R = 0.046$, $wR^2 \times 0.125$, max residual electron density 0.27 (−0.20) e Å^{-3}, hydrogens calculated and refined as riding atoms. The data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT,[23] data reduction Denzo-SMN,[24] absorption correction Denzo,[25] structure solution SHELXS-97,[26] structure refinement SHELXL-97,[27] graphics SCHAKAL.[28]

CCDC-296453 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, E-mail: deposit@ccdc.cam.ac.uk].

7. Receptor binding studies

7.1. General information

Homogenizer: Elvehjem Potter (B. Braun Biotech International). Centrifuge: High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Finnigan). Filter: Printed Filtermat Type A (Perkin Elmer), 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 (Type A) solid scintillator (Perkin Elmer). The solid scintillator was melted on the filtermat at a temperature of 95 °C for 5 min. After solidification of the scintillator at room temperature, the scintillation was measured using a MicroBeta Trilux scintillation analyzer (Perkin-Elmer). The counting efficiency was 40%. All experiments were carried out in triplicate using standard 96-well-multiplates (Diagonal). The IC_{50}-values were determined in competition experiments with six concentrations of the test compounds and were calculated with the program GraphPad Prism® 3.0 (GraphPad Software) by non-linear regression analysis. The K_i-values were calculated according to Cheng and Prusoff.[16] The K_i-values are given as mean values ± SEM from three independent assays.

7.2. Preparation of the tissue

Modified according to Refs. 13–15: Fresh pig brain cortex was homogenized with a potter (500–800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200*g* for 10 min at 4 °C. The supernatant was separated, and centrifuged at 23,500*g* for 20 min at 4 °C. The pellet was resuspended in buffer (5 mM Tris–acetate with 1 mM EDTA, pH 7.5) and centrifuged again at 23,500*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[29] using bovine serum albumin as standard, and subsequently the preparation was frozen (−83 °C) in 1.5 mL portions containing about 0.8 mg protein/mL.

7.3. Performance of the assay

Modified according to Refs. 13–15: The test was performed with the radioligand [^{3}H]-(+)-MK-801 (9.25 MBq; Biotrend). 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 200 µL for 120 min at 25 °C. The incubation was terminated by rapid filtration through the presoaked filtermats using a cell harvester. After washing five times with 300 µl of cold water, the filtermats were dried at 95 °C. Subsequently, the solid scintillator was placed on the filtermat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temperature. The bound radioactivity trapped on the filters was counted in a scintillation analyzer. Non-specific binding was determined with 10 µM (+)-MK-801.

Acknowledgments

We thank Dr. Jörg Fabian for determination of the log *P*-value. Thanks are also due to Degussa A. G., Janssen-Cilag GmbH, and Bristol-Myers Squibb for donation of chemicals and reference compounds. The performance of the behavioral studies with **15a** by Schwarz Pharma, Monheim, is gratefully acknowledged.

References and notes

1. Lipton, S. A. *Nat. Rev. Drug Disc.* **2006**, *5*, 160–170.
2. Stark, H.; Reichert, U.; Graßmann, S. *Pharmazie in unserer Zeit* **2000**, *4*, 228.
3. (a) Hardie, W. R.; Hidalgo, J.; Halverstadt, I. F.; Allen, R. E. *J. Med. Chem.* **1966**, *9*, 127; (b) Hardie, W. R.; Aaron, J. E. GB Patent 1 199 110, 1968; (c) Ornstein, P. L.; Zimmermann, D. M.; Leander, J. D.; Mendelson, L.; Reel, J. K.; Evrard In *Sigma and Phencyclidine-like Compounds as Molecular Probes in Biology*; Kamenka, J.-M., Domino, E. F., Eds.; NPP Books: Ann Arbor, MI, 1988; pp 19–25; (d) Thurkauf, A.; Mattson, M. V.; Richardson, S.; Mirsadeghi, S.; Ornstein, P. L.; Harrison, E. A., Jr.; Rice, K. C.; Jacobson, A. E.; Monn, J. A. *J. Med. Chem.* **1992**, *35*, 1323; (e) Aepkers, M.; Wünsch,

B. *Arch. Pharm. Pharm. Med. Chem.* **2004**, *337*, 67; (f) Utech, T. PhD thesis, University of Freiburg, Germany, 2003.
4. Jacobson, A. E.; Harrison, E. A.; Mattson, M. V.; Rafferty, M. F.; Rice, K. C.; Woods, J. H.; Winger, G.; Solomon, R. E.; Lessor, R. A.; Silverton, J. V. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 110.
5. For reviews concerning hetero Diels–Alder reactions, see: (a) Jørgensen, K. A. *Angew. Chem.* **2000**, *112*, 3702; (b) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099.
6. Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.
7. (a) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445; (b) Heintzelmann, G. R.; Weinreb, S. M. *J. Org. Chem.* **1996**, *61*, 4594; (c) Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151; (d) Kranke, B.; Hebrault, D.; Schultz-Kukula, M.; Kunz, H. *Synlett* **2004**, 671; (e) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240.
8. Manusco, J.; Swern, D. *Synthesis* **1981**, 165–185.
9. Diene **6** decomposes rapidly under standard storing conditions (4 °C, N_2) but is stable for at least 21 days when stored under N_2 at −25 °C in the darkness (proved by ^{1}H NMR spectroscopy).
10. Hansson, L.; Carlson, R. *Acta Chem. Scand.* **1989**, *43*, 188.
11. Comins, D.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053–5056.
12. The racemate consisting of dexoxadrol (**2**) and its enantiomer levoxadrol has been termed α-dioxadrol, the diastereomeric racemate β-dioxadrol.
13. McKernan, R. M.; Castro, S.; Poat, J. A.; Wong, E. H. F. *J. Neurochem.* **1989**, *52*, 777–785.
14. Höfner, G.; Wanner, K. T. *J. Rec. Sign. Trans. Res.* **1996**, *16*, 297–313.
15. Aepkers, M.; Wünsch, B. *Arch. Pharm. Pharm. Med. Chem.* **2004**, *337*, 67–75.
16. Cheng, Y.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.
17. Thurkauf, A.; Zenk, P. C.; Balster, R. L.; May, E. L.; George, C.; Carroll, F. I.; Mascarella, S. W.; Rice, K. C.; Jacobson, A. E.; Mattson, M. V. *J. Med. Chem.* **1988**, *31*, 2257.
18. Lipinski, C. A. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3.
19. OECD (Organization for Economic Co-operation and Development) 1989. OECD Guideline for testing of Chemicals. 117. Partition coefficient (*n*-octanol/water), HPLC-Method. OECD. Paris, France. Download under: http://www.oecd.org/dataoecd/17/36/1948177.pdf.
20. (a) Irwin, S. *Psychopharmacologia* **1968**, *13*, 222–257; (b) Campbell, D. E. S.; Richter, W. *Acta Pharmacol. Toxicol.* **1967**, *25*, 345–365.
21. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
22. Miyazawa, T.; Kurita, S.; Sakamoto, H.; Otomatsu, T.; Katsutoshi, H.; Yamada, T. *Biotechnol. Lett.* **1999**, *21*, 447–450.
23. B.V. Nonius, Delft, The Netherlands, 1998.
24. Otwinowski, Z.; Minor, W. *Methods in Enzymology* **1997**, *276*, 307–326.
25. Otwinowski, Z.; Borek, D.; Majewski, W.; Minor, W. *Acta Crystallogr.* **2003**, *A59*, 228–234.
26. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.
27. Sheldrick, G. M. Universität Göttingen, 1997.
28. Keller, E. Universität Freiburg, 1997.
29. Bradford, M. M. *Anal. Biochem.* **1976**, *72*, 248–254.