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Synthesis and NMDA-Receptor Affinity of Ring and Side Chain Homologous Dexoxadrol Derivatives

The regioselectivity during transacetalization of benzophenone dimethyl acetal (**4**) with butane-1,2,4-triol (**5**) is controlled by the reaction conditions. Thermodynamic control leads predominantly to the 1,3-dioxolane **6** whereas kinetic control favors the six-membered acetal **7**. The amines **2a**–**e** and **3a**–**e** are synthesized from the alcohols **6** and **7** and are investigated in receptor binding studies with radioligands for their affinity to the phencyclidine binding site of the NMDA-receptor. In both series the primary amines **2a** and **3a** show the highest NMDA-receptor affinity (**2a**: K_i = 3.38 μM; **3a**: K_i = 1.45 μM). The NMDA receptor slightly prefers the 1,3-dioxane derivatives **3a** and **3b** compared to **2a** and **2b** (factor 2–3). Low interactions of the amines **3a** and **3b** with various receptor and reuptake systems indicate selectivity for the NMDA receptor. Surprisingly, the piperidine derivative **2e** binds with high affinity at σ_1-receptors and, therefore, represents a novel lead compound for high affinity σ_1-receptor ligands.

Keywords: Dexoxadrol homologues; NMDA-receptor antagonists; Structure/affinity relationships; Regioselective acetalization

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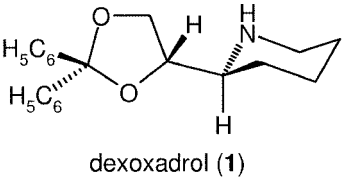
Introduction

Originally, dexoxadrol (**1**) was developed as an anaesthetic drug [1]. During the clinical evaluation it became obvious that non tolerable postanaesthetic side reactions, e.g. retrograde amnesia and psychotomimetic effects, are associated with the use of dexoxadrol. Therefore, the clinical development of dexoxadrol was terminated.

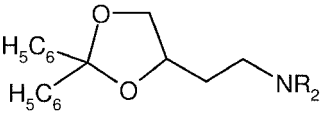
In the mid 1980s the "PCP-receptor" was postulated as the target system for phencyclidine (PCP) and related compounds. It was found that dexoxadrol interacted with the PCP-receptor with high affinity [2], which was later recognized as a binding site within the NMDA (N-methyl-D-aspartate) receptor-associated ion channel [3].

The physiological activation of the NMDA receptor is important for the development of neurons and thus for processes like learning and memory. However, an overstimulation of the NMDA receptor leads to an increased Ca^{2+}-ion influx into neurons which results in neuronal damage (excitotoxicity). Therefore, compounds blocking the excessive influx of Ca^{2+}-ions into neurons are of major interest as neuroprotective agents with different indications including stroke, epilepsy, Morbus Parkinson, and Morbus Alzheimer [4–6]. Thereby, a moderate affinity to the PCP-binding site of the NMDA receptor seems crucial; it results in inhibition of overactivation, but maintains the normal activity of the NMDA receptor.

Stimulated by the high affinity NMDA-receptor antagonist dexoxadrol (**1**), we planned the synthesis and pharmacological evaluation of two series of homologues. The first series comprises ligands with an increased distance between the oxygen heterocycle and the basic amino moiety (compare **2**). In the second series the five-membered 1,3-dioxolane ring is enlarged to an unsymmetrically substituted 1,3-dioxane ring (compare **3**). According to reported structure/affin-



dexoxadrol (**1**)



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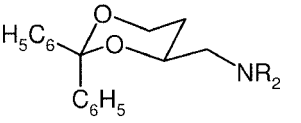

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Figure 1.

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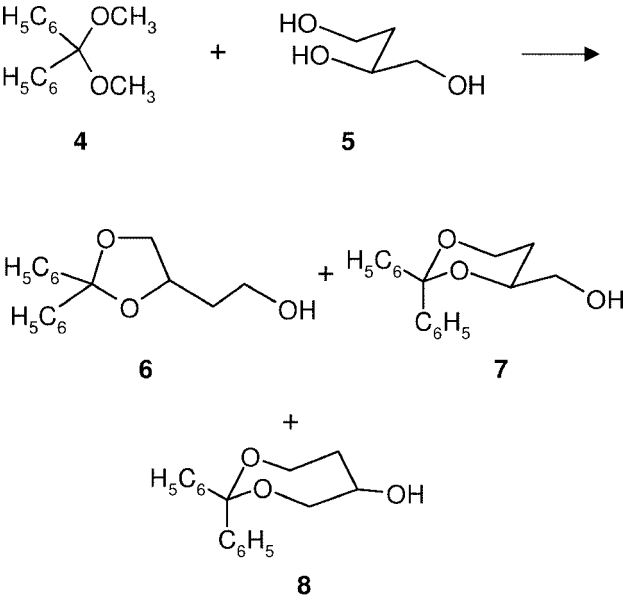
ity studies the complete piperidine ring is not essential for receptor binding [7].

Therefore, simple amino substituents replace the piperidine nucleus of dexoxadrol in the ligands within this series (see Figure 1).

Chemistry

At first the acetalization of benzophenone with butane-1,2,4-triol (**5**) was carefully investigated, since it represents the key step to obtain cyclic acetals with different ring sizes. However, the direct acetalization of benzophenone with butane-1,2,4-triol (**5**) failed to give cyclic acetals. Therefore, benzophenone was transformed into its dimethyl acetal **4** [8], which smoothly reacted with the triol 5. Heating of a mixture of **4**, **5**, *p*-toluenesulfonic acid and THF for 3 h led to the 1,3-dioxolane **6** and the 1,3-dioxane **7** in the ratio 89 : 11 (entry 1, Table 1; Scheme 1). The regioisomeric [9] acetals **6** and **7** were separated by flash chromatography and characterized spectroscopically. The ratio of **6** : **7** in the crude product was determined by integration of characteristic signals in the ^{1}H NMR spectrum (4.35 ppm (4-H of **6**), 4.03 ppm (6-H_{ax} of **7**)).



Scheme 1.

After transacetalization of a large amount of the dimethyl acetal **4** with the triol **5**, a third acetalic product could be isolated in 2.3% yield, which was identified as the corresponding seven-membered acetal **8**. Recording of the ^{1}H NMR spectrum of **8** in a $CDCl_3$ solution revealed fast isomerization of the 1,3-dioxepane **8** to the thermodynamically more stable five-membered dioxolane **6**.

Table 1. Regioselectivity during acetalization of benzophenone dimethyl acetal (**4**) with butane-1,2,4-triol (**5**).

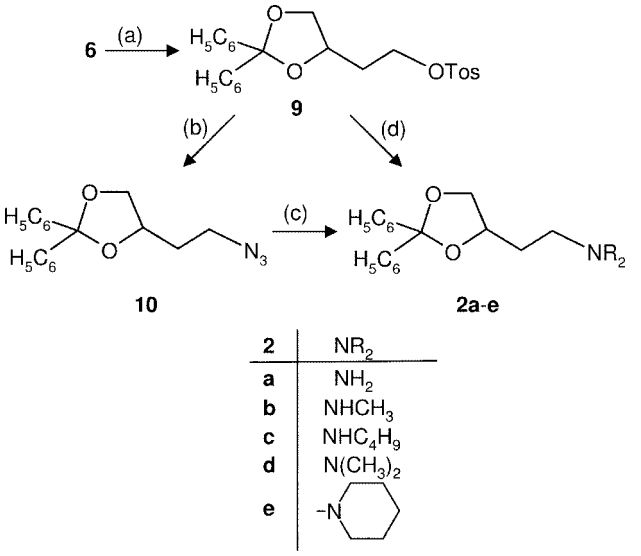
Entry	Temp	Reaction time	Ratio **6:7**
1	66 °C	3 h	89 : 11
2	66 °C	2 h	73 : 27
3	20 °C	10 d	41 : 59

Therefore, the ^{1}H NMR spectrum of **8** has to be recorded immediately after dissolving the sample in $CDCl_3$ or in another solvent (e.g. [D_6]-acetone). Since in the following equilibrium attempts the product ratio was spectroscopically determined by ^{1}H NMR (solvent $CDCl_3$), the signals of **8** were usually not found.

With the cyclic acetals **6** and **7** in hand the position of the equilibrium was determined. For this purpose *p*-toluenesulfonic acid was added to solutions of purified acetals **6** and **7** in THF, respectively, and both mixtures were heated to reflux. After 20 h the reactions were terminated and the mixtures were analyzed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of the products showed the 1,3-dioxolane **6** and the 1,3-dioxane **7** in ratios of 93 : 7 and 89 : 11, respectively. This result is in agreement with the general rule that thermodynamic control during the reaction of polyols with ketones favors formation of five-membered acetals [10, 11].

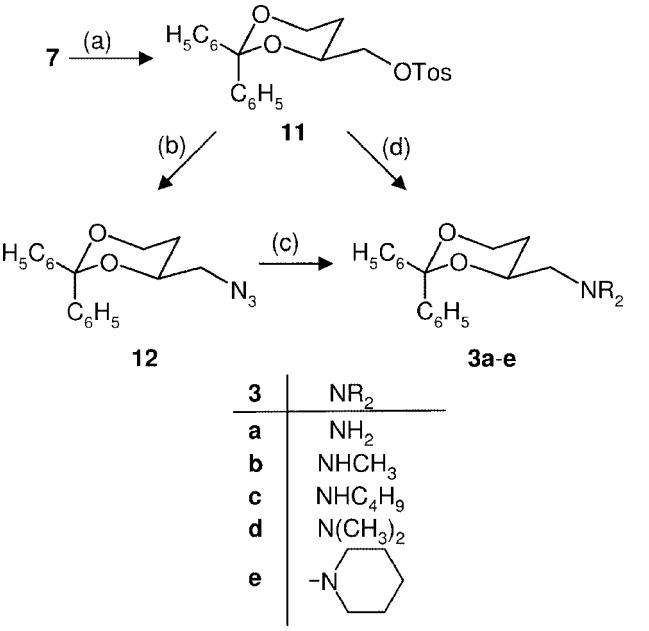
In order to increase the amount of the minor regioisomer **7** attempts with milder reaction conditions for the transacetalization of the benzophenone acetal **4** with the triol **5** were carried out. Indeed, after shortening of the reaction time (2 h, THF reflux) the ratio of **6** : **7** was shifted in favor of the 1,3-dioxane (**6** : **7** = 73 : 27; entry 2, Table 1). Further improvement was achieved by performing the transacetalization at room temperature leading predominantly to the six-membered 1,3-dioxane **7** with a ratio of **6** : **7** = 41 : 59 after 10 days (entry 3, Table 1). These results demonstrate that the ratio of regioisomeric acetals of polyols can be shifted in favor of the thermodynamically less stable regioisomer by kinetic control of the transacetalization.

Next, the obtained alcohols **6** and **7** were transformed into the amines **2** and **3**. For this purpose the alcohols **6** and **7** were activated with tosyl chloride to give the tosylates **9** and **11**, which underwent nucleophilic substitution. S_N2 reaction of the tosylates **9** and **11** with NaN_3 succeeded by refluxing dimethylformamide to yield the azides **10** and **12**, which were catalytically



2	NR_2
a	NH_2
b	$NHCH_3$
c	NHC_4H_9
d	$N(CH_3)_2$
e	-N

Scheme 2. (a) TosCl, NEt_3, CH_2Cl_2, 4 °C, 48 h, 96%. (b) NaN_3, DMF, 155 °C, 2.5 h, 87%. (c) H_2, Pd/C, THF, 1 bar, 20 °C, 1.5 h, 88%. (d) RR′NH, CH_3OH or EtOH, 20 °C, 4–6 d. **2b**: 93%; **2c**: 91%; **2d**: 90%; 2e: 88%.



3	NR_2
a	NH_2
b	$NHCH_3$
c	NHC_4H_9
d	$N(CH_3)_2$
e	-N

Scheme 3. (a) TosCl, NEt_3, CH_2Cl_2, 4 °C, 48 h, 74%. (b) NaN_3, DMF, 155 °C, 9 h, 91%. (c) H_2, Pd/C, THF, 1 bar, 20 °C, 4 h, 98%. (d) RRNH, CH_3OH or EtOH, 65 °C or 78 °C, 8–24 h **3b**: 88%; **3c**: 91%; **3d**: 92%; **3e**: 96%.

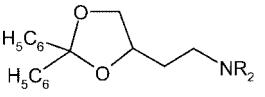
hydrogenated with H_2 and Pd/C to provide the primary amines **2a** and **3a** (Schemes 2 and 3).

The secondary amines **2b**, **c** and **3b**, **c** were prepared by substitution of the tosylates **9** and **11** with the primary amines methylamine and butan-1-amine, respectively. Reaction of the tosylates **9** and **11** with the secondary amines dimethylamine and piperidine led to the tertiary amines **2d**, **e** and **3d**, **e**, respectively. Whereas substitution of the (1,3-dioxolan-4-yl)ethyl tosylate **9** with amines took place at room temperature affording high yields of **2b–e** (88–93%), the analogous substitution of the (1,3-dioxan-4-yl)methyl tosylate 11 required heating of the reaction mixture to 65–78°C to complete the transformation (88–96% yield).

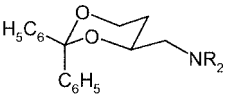
Receptor binding studies

The affinity of the amines **2a–e** and **3a–e** to the phencyclidine binding site of the NMDA receptor was

Table 2. Affinities of the amines **2** and **3** to the phencyclidine binding site of the NMDA receptor.



2a-e



3a-e

Compd.	NR_2	$K_i \pm$ SEM [μM]	Compd.	NR_2	$K_i \pm$ SEM [μM]
2a	NH_2	3.38 ± 0.29[a]	**3a**	NH_2	1.45 ± 0.09[a]
2b	NHMe	12.9 ± 0.24[a]	**3b**	NHMe	3.95 ± 0.21[a]
2c	NHBu	16.7	**3c**	NHBu	18.9
2d	NMe_2	30.1	**3d**	NMe_2	29.8
2e	$N(CH_2)_5$	19.9	**3e**	$N(CH_2)_5$	36.8
dexoxadrol		0.023 ± 0.0034[a]	(*S*)-ketamine		0.11 ± 0.011a

[a] For compounds with K_i-values lower than 15 μM three independent experiments (n = 3) were performed.

determined in competition experiments with a radioligand. In the assay pig brain cortex preparations were used. [^{3}H]-(+)-MK-801, which binds with high affinity and selectivity to the phencyclidine binding site of the NMDA receptor, was employed as radioligand. Nonspecific binding was determined in the presence of a large excess of non-tritiated (+)-MK-801 [12, 13].

The NMDA-receptor affinities of the amines **2** and **3** are summarized in Table 2. In both series the primary amines **2a** and **3a** display the highest NMDA-receptor affinity. The secondary amines with a methyl (**2b**, **3b**) or butyl (**2c**, **3c**) residue at the nitrogen atom show reduced NMDA-receptor affinity whereas interactions of the tertiary amines **2d**, **e** and **3d**, **e** with the NMDA receptor are quite low.

The NMDA-receptor affinity of the primary amine **3a** of the 1,3-dioxane series is higher by the factor 2.3 compared to the NMDA-receptor affinity of the corresponding primary amine **2a** of the 1,3-dioxolane series. A similar relationship is observed among the methylamines: The 1,3-dioxane derivative **3b** shows a lower K_i-value than the 1,3-dioxolane derivative **2b** (factor 3.3). Altogether, within both series of dexoxadrol homologues, novel NMDA-receptor antagonists are found with affinity in the range of 1−5 μM.

Since ligands with moderate NMDA-receptor affinity are of interest because of their potentially low side effects, the receptor binding profile of the most promising ligands **3a** and **3b** was determined by screening these ligands in several receptor and reuptake assays. The results in Table 3 point out that interactions of the methylamine **3b** with the investigated receptor and reuptake systems are very low. Obviously, the selectivity of the methylamine **3b** for the phencyclidine binding site of the NMDA receptor is high. With exception of the 5-HT_{1A}-receptor, the primary amine **3a** also displays very low affinity to the investigated receptor and reuptake systems indicating very high selectivity for the phencyclidine binding site of the NMDA receptor. However, an unexpected high affinity of the primary amine **3a** to the 5-HT_{1A}-receptor (IC_{50} = 29 nM) (entry 6, Table 3) was found, which even exceeds the NMDA-receptor affinity.

Tertiary amines with a phenyl residue in a definite distance often display high affinity to σ_1-receptors [14, 15]. Therefore, the tertiary amines **2d**, **e** and **3d**, **e** were investigated for their σ_1-receptor affinity. In the assay guinea pig brain homogenates were used as receptor source and the 1-selective ligand [^{3}H]-(+)-pentazocine was employed as radioligand [16, 17]. In the initial screening 1 μM solutions of the test compounds were incubated with the receptor preparation and the radioligand and the radioactivity trapped on the filters was determined. With exception of the piperidine derivative **2e** the binding of the radioligand was very high indicating low competition (see Table 4). Therefore, a complete competition curve was recorded only for the piperidine **2e** – the most promising σ_1-ligand. Thereby a K_i-value of 39.3 nM ± 3.3 nM (SEM, n = 3) was found. Thus, the piperidine **2e** represents a novel lead structure for the development of high affinity, selective σ_1-ligands.

Conclusion

Table 3. Affinities of the primary amine **3a** and the methylamine **3b** to various receptor and reuptake systems.

Entry	Receptor system (radioligand)	IC_{50} (μM)	
		3a	**3b**
1	NMDA, glutamate (CGP-39,653)	>10	>10
2	NMDA, glycine (MDL 105,519)	>10	>10
3	NMDA, polyamine (ifenprodil)	>10	>10
4	histamine H_1 (mepyramine)	>10	>10
5	dopamine D_1 (SCH 23,390)	>10	>10
6	serotonin 5-HT_{1A} (5-OH DPAT)	0.029	>1
7	serotonin 5-HT_{2A} (ketanserin)	>10	5.8
8	serotonin 5-HT_3 (GR 65,630)	>10	>10
9	noradrenaline α_1 (prazosine)	>10	>10
10	noradrenaline α_2 (idazoxane)	>10	>10
11	serotonin reuptake (serotonin)	>10	>10
12	noradrenaline reuptake (noradrenaline)	>10	2.2
13	dopamine reuptake (dopamine)	>10	8.6

Table 4. Affinities of the amines **2d**, **e** and **3d**, **e** for σ_1-receptors.

Compd.	% binding[a]
2d	70.0
2e	9.6
3d	77.0
3e	72.0

[a] In the table the binding of the radioligand [^{3}H]-(+)-pentazocine to σ_1-receptors in the presence of 1 μM of the test compounds is given.

We have shown that homologization of the oxygen heterocycle or the distance between the amine and the oxygen heterocycle of the lead structure dexoxadrol provides novel NMDA-receptor antagonists with μM-affinity levels. The NMDA-receptor affinities of the most promising ligands (**2a**, **3a**, **3b**) are considerably lower than the NMDA-receptor affinity of the lead compound dexoxadrol. However, the moderate affinity of these NMDA-receptor antagonists together with their high receptor selectivity should cause little side effects in vivo. Therefore, further variations of acetalic NMDA-receptor antagonists are in progress.

Acknowledgments

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Experimental

Chemistry, general

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. – Petroleum ether used refers to the fraction boiling at 40–60 °C. – Thin layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck, Darmstadt, Germany). – Flash chromatography (fc) [18]: Silica gel 60, 0.040–0.063 mm (Merck); parentheses include: Diameter of the column [cm], eluent, fraction size [mL], R_f. – Melting points: Melting point apparatus SMP 2 (Stuart Scientific), uncorrected. – Elemental analyses: Elemental Analyzer 240 (Perkin-Elmer) and Vario EL (Elementaranalysesysteme GmbH). – MS: MAT 312, MAT 8200, MAT 44, and TSQ 7000 (Finnigan); EI = electron impact, CI = chemical ionization. – High resolution MS (HR-MS): MAT 8200 (Finnigan). – IR: IR spectrophotometer 1605 FT-IR (Perkin-Elmer). – 1H NMR (300 MHz), ^{13}C NMR (75 MHz): Unity 300 FT NMR spectrometer (Varian), δ in ppm related to tetramethylsilane, coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and ^{1}H NMR signals were supported by 2D NMR techniques.

*Benzophenone dimethyl acetal (**4**)*

The synthesis reported in ref. [8] was slightly modified: A solution of benzophenone (18.2 g, 100 mmol), trimethyl orthoformiate (12.0 mL, 110 mmol) and *p*-toluenesulfonic acid monohydrate (0.95 g, 5 mmol) in methanol (150 mL) was stirred for 16 h at room temperature (r.t.). The product was filtered and recrystallized from methanol. Colorless solid (methanol), mp 105.6–107.0 °C (ref. [8] 107–108 °C), yield 17.8 g (78%). $C_{15}H_{16}O_2$ (228.29). ^{1}H NMR ($CDCl_3$): δ [ppm] = 3.14 (s, 6H, OCH_3), 7.19–7.33 (m, 6H, arom. H_{meta} and H_{para}), 7.49–7.53 (m, 4H, arom. H_{ortho}). – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2828 (OCH_3), 1093, 1062 (C-O).

*2-(2,2-Diphenyl-1,3-dioxolan-4-yl)ethan-1-ol (**6**), and (2,2-Diphenyl-1,3-dioxan-4-yl)methanol (**7**), and 2,2-Diphenyl-1,3-dioxepan-5-ol (**8**)*

A solution of benzophenone dimethyl acetal (**4**, 4.57 g, 20 mmol) and racemic butanetriol **5** (2.12. g, 20 mmol) in THF (50 mL) was dried with Na_2SO_4. Then a dried (Na_2SO_4) solution of *p*-toluenesulfonic acid monohydrate (0.033 mol/L, 30 mL, 1 mmol) in THF was added and the mixture was heated at reflux for 4 h. Then, Na_2SO_4 was separated, Et_2O (50 mL) was added and the mixture was washed with a saturated solution of $NaHCO_3$ (100 mL). The organic layer was dried ($MgSO_4$), filtered. and concentrated *in vacuo*. A ^{1}H NMR spectrum was recorded and the mixture of regioisomers was separated by fc (8 cm, petroleum ether : ethyl acetate = 7 : 3, fractions 35 mL).

6 (R_f = 0.13): Colorless oil, yield 1.86 g (34%). $C_{17}H_{18}O_3$ (270.3), calcd. C 75.5 H 6.71 found C 75.5 H 6.77. – MS (EI): m/z (%) = 270 (M, 0.4), 193 (M – Ph, 65), 182 (Ph_2CO, 74), 105 (PhCO, 100). – ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.85 (dtd, *J* = 14.2/6.0/4.8 Hz, 1H, CH_2CH_2OH), 1.95 (ddt, *J* = 14.2/7.8/5.8 Hz, 1H, CH_2CH_2OH), 2.03 (s, broad, 1H, O*H*), 3.77 (dd, *J* = 7.8/7.1 Hz, 1H, 5-H), 3.83 (t, *J* = 5.8 Hz, 2H, CH_2CH_2OH), 4.16 (dd, J = 7.8/6.6 Hz, 1H, 5-*H*), 4.35 (qd, *J* = 7.1/4.9 Hz, 1H, 4-*H*), 7.26–7.38 (m, 6H, arom. H_{meta} and H_{para}), 7.47–7.54 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 3410 (O-H), 2944 (C-H), 2883 (C-H), 1070 (s, C-O), 755, 700 (aryl).

7 (Rf = 0.20: Colorless oil, yield 1.0 g (19%). $C_{17}H_{18}O_3$ (270.3), calcd. C 75.5 H 6.71 found C 75.3 H 6.81. – MS (EI): *m/z* (%) = 270 (M, 0.9), 239 (M – CH_2OH, 6), 193 (M – Ph, 52), 182 (Ph_2CO, 66), 105 (PhCO, 100). – ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.34 (dtd, *J* = 12.9/2.4/1.7 Hz, 1H, 5-$H_{equat.}$), 1.99 (dtd, *J* = 12.9/12.0/5.9 Hz, 1H, 5-H_{axial}), 2.19 (s, broad, 1H, O*H*), 3.68 (dd, *J* = 11.7/6.1 Hz, 1H, CH_2OH), 3.74 (dd, *J* = 11.7/3.7 Hz, 1H, CH_2OH), 4.03 (td, *J* = 11.5/2.7 Hz, 1H, 6-H_{axial}), 4.06–4.16 (m, 2H, 4-H_{axial}, 6-$H_{equat.}$), 7.19–7.34 (m, 4H, arom. H_{meta}), 7.38–7.45 (m, 2H, arom. H_{para}), 7.47–7.57 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 3394 (O-H), 2951 (C-H), 2878 (C-H), 1101, 1024 (C-O), 750, 702 (aryl).

8 (R_f = 0.26): Colorless solid, mp 107.0–108.0 °C, yield 0.123 g (2.3%). $C_{17}H_{18}O_3$ (270.3), calcd. C 75.5 H 6.71 found C 75.5 H 6.78. – MS (EI): *m/z* (%) = 270 (M, 1.4), 240 (M – H_2O, 17), 193 (M – Ph, 27), 182 (Ph_2CO, 83), 105 (PhCO, 69). – ^{1}H NMR ($CDCl_3$ at once): δ [ppm] = 1.79 (dtd, *J* = 14.9/3.2/2.4 Hz, 1H, 6-*H*), 1.93 (dddd, *J* = 14.3/8.3/6.3/3.9

Hz, 1H, 6-*H*), 2.49 (s, broad, 1H, O*H*), 3.74–3.80 (m, 4H, 4-*H*, 7-*H*), 3.90 (qd, *J* = 3.9/2.0 Hz, 1H, 5-*H*), 7.19–7.35 (m, 6H, arom. H_{meta} and H_{para}), 7.58–7.64 (m, 4H, arom. H_{ortho}). – ^{1}H NMR ([D$_6$]-acetone): δ [ppm] = 1.67–1.77 (m, 1H, 6-*H*), 1.90–2.00 (m, 1H, 6-*H*), 2.96 (s, 1H, O*H*), 3.62 (ddd, *J* = 12.4/8.1/2.6 Hz, 1H, 7-*H*), 3.60–3.74 (m, 1H, 5-*H*), 3.81 (ddd, *J* = 12.4/7.0/2.9 Hz, 1H, 7-*H*), 3.84–3.90 (m, 2H, 4-*H*), 7.17–7.24 (m, 2H, arom. H_{para}), 7.26–7.33 (m, 4H, arom. H_{meta}), 7.58–7.64 (m, 4H, arom H_{ortho}). – ^{13}C NMR ([D$_6$]-acetone): δ [ppm] = 38.7 (1C, *C*-6), 59.5 (1C, *C*-7), 67.9 (1C, *C*-5), 69.0 (1C, *C*-4), 104.2 (1C, C-*2*), 127.0 (4C, arom. *C*H_{ortho}), 128.1 (2C, arom. *C*H_{para}), 128.7 (4C, arom. *C*H_{meta}), 145.0 (1C, arom. $C_{quart.}$), 145.1 (1C, arom. $C_{quart.}$). – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3444 (O-H), 2942 (C-H), 1083 (C-O).

*2-(2,2-Diphenyl-1,3-dioxolan-4-yl)ethyl tosylate (**9**)*

A solution of **6** (1.35 g, 5 mmol) and triethylamine (0.84 mL, 6 mmol) in CH_2Cl_2 (15 mL) was cooled in an ice bath. A solution of *p*-toluenesulfonyl chloride (1.91 g, 10 mmol) in CH_2Cl_2 (10 mL) was slowly added and the reaction mixture was stirred at 4 °C for 48 h. The mixture was concentrated *in vacuo* and the residue was purified by fc (6 cm, petroleum ether : ethyl acetate = 4 : 1, fractions 20 mL, R_f = 0.28). Colorless solid, mp 59–63 °C, yield 2.04 g (96%). $C_{24}H_{24}O_5S$ (424.51), calcd. C 67.9 H 5.70 found C 68.0 H 5.69. – MS (EI): *m/z* (%) = 424 (M, 1.6), 347 (M – Ph, 95), 155 (tos, 14), 105 (PhCO, 100). – ^{1}H NMR (CDCl$_3$): δ [ppm] = 1.96 ("q", *J* = 6.4 Hz, 2H, CH_2CH$_2$Otos), 2.45 (s, 3H, PhCH_3), 3.68 (dd, *J* = 7.9/6.4 Hz, 1H, 5-*H*), 4.07 (dd, *J* = 7.9/6.4 Hz, 1H, 5-*H*), 4.21 (t, *J* = 6.4 Hz, 2H, CH$_2$CH_2Otos), 4.24 ("quint", *J* = 6.4 Hz, 1H, 4-*H*), 7.26–7.36 (m, 8H, arom. H_{meta}, H_{para} and 3-*H*, 5-*H* (tos)), 7.39–7.46 (m, 4H, arom. H_{ortho}), 7.79 (d, *J* = 8.3 Hz, 2H, arom. 2-*H*, 6-*H* (tos)). – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2928 (C-H), 2860 (C-H), 1356, 1182 (SO_2), 1096 (C-O), 838 (aryl), 750, 704 (aryl).

*4-(2-Azidoethyl)-2,2-diphenyl-1,3-dioxolane (**10**)*

A solution of **9** (0.47 g, 1.1 mmol) and NaN_3 (0.72 g, 11 mmol) in DMF (15 mL) was heated to reflux for 2.5 h. The solvent was removed in vacuo (< 10 mbar, < 60 °C) and the residue was dissolved in Et_2O (10 mL). The suspension was washed with saturated solutions of $NaHCO_3$ (10 mL) and NaCl (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Further purification of **10** was unnecessary. Colorless oil, yield 0.28 g (87%). $C_{17}H_{17}N_3O_2$ (295.34), calcd. C 69.1 H 5.80 N 14.23 found C 69.1 H 5.82 N 14.55. – MS (EI): *m/z* (%) = 295 (M, 1.1), 218 (M–Ph, 62), 182 (Ph_2CO, 13), 105 (PhCO, 100). – ^{1}H NMR (CDCl$_3$): δ [ppm] = 1.85 (dtd, *J* = 14.0/7.6/4.6 Hz, 1H, CH_2CH$_2$N$_3$), 1.94 (ddt, *J* = 14.0/7.9/6.1 Hz, 1H, CH_2CH$_2$N$_3$), 3.50 (t, broad, *J* = 6.9 Hz, 2H, CH$_2$CH_2N$_3$), 3.75 (dd, *J* = 7.9/6.7 Hz, 1H, 5-*H*), 4.15 (dd, *J* = 7.9/6.7 Hz, 1H, 5-*H*), 4.29 (dtd, *J* = 7.9/6.7/4.6 Hz, 1H, 4-*H*), 7.27–7.38 (m, 6H, arom. H_{meta} and H_{para}), 7.47–7.55 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 2943 (C-H), 2882 (C-H), 2097 (N_3), 1089 (C-O), 756, 703 (aryl).

*2-(2,2-Diphenyl-1,3-dioxolan-4-yl)ethan-1-amine (**2a**)*

A mixture of **10** (0.15 g, 0.5 mmol), Pd/C (10%, 7.5 mg) and THF (10 mL) was stirred under hydrogen atmosphere (1 bar) for 1.5 h at room temperature. The mixture was filtered with Celite® AFA and the solvent was evaporated *in vacuo* to afford the pure primary amine **2a**. Colorless oil, yield 0.12 g (88%). $C_{17}H_{19}NO_2$ (269.34). – HR-MS: calcd. 269.1416 found 269.1417. – MS (EI): *m/z* (%) = 269 (M, 0.6), 192 (M–Ph, 24), 105 (PhCO, 85), 87 (O-CH$_2$-CH-(CH$_2$)$_2$-NH$_2$, 69). – MS (CI): *m/z* (%) = 270 (M + H, 50), 192 (M – Ph, 15), 88 (O-CH$_2$-CH-(CH$_2$)$_2$-NH$_2$ + H, 100). – ^{1}H NMR (CDCl$_3$): δ [ppm] = 1.19 (s, broad, 2H, NH_2), 1.72 (dtd, *J* = 13.7/7.2/4.9 Hz, 1H, CH_2CH$_2$NH$_2$), 1.86 (dtd, *J* = 13.7/7.2/6.4 Hz, 1H, CH_2CH$_2$NH$_2$), 2.85 (dt, *J* = 12.5/7.0 Hz, 1H, CH$_2$CH_2NH$_2$), 2.92 (ddd, *J* = 12.5/7.3/6.4 Hz, 1H, CH$_2$CH_2NH$_2$), 3.71 (t, *J* = 7.5 Hz, 1H, 5-*H*), 4.14 (dd, *J* = 7.6/6.7 Hz, 1H, 5-*H*), 4.26 (tdd, *J* = 7.3/6.7/4.9 Hz, 1H, 4-*H*), 7.26–7.37 (m, 6H, arom. H_{meta} and H_{para}), 7.49–7.55 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 3367 (N-H), 2941, 2879 (C-H), 1590 (N-H), 1087, 1067 (C-O), 754, 702 (aryl).

*2-(2,2-Diphenyl-1,3-dioxolan-4-yl)-N-methylethan-1-amine (**2b**)*

The tosylate **9** (0.43 g, 1.0 mmol) was dissolved in a solution of methylamine in ethanol (7.5 mL, 8.03 M, 60 mmol CH_3NH_2) and the mixture was stirred for 4 d at room temperature. The solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). The organic layer was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL) and water (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield pure methylamine **2b**. Pale yellow oil, yield 0.264 g (93.3%). $C_{18}H_{21}NO_2$ (283.37). – HR-MS (for M – CH_2NHCH_3): calcd. 239.1072 found 239.1071. – MS (EI): *m/z* (%) = 283 (M, 0.2), 239 (M – CH_2NHCH_3, 2.8), 206 (M – Ph, 4), 105 (PhCO, 42), 101 (O-CH$_2$-CH-(CH$_2$)$_2$-NH-CH$_3$, 81). – ^{1}H NMR (CDCl$_3$): δ [ppm] = 1.63 (s, 1H, N*H*), 1.78 (dddd, *J* = 13.7/7.6/6.7/5.2 Hz, 1H, CH_2CH$_2$NH), 1.92 (dtd, *J* = 13.7/7.3/6.4 Hz, 1H, CH_2CH$_2$NH), 2.43 (s, 3H, NHCH_3), 2.71 (dt, *J* = 11.9/7.0 Hz, 1H, CH$_2$CH_2NH), 2.79 (ddd, *J* = 11.9/7.6/6.4 Hz, 1H, CH$_2$CH_2NH), 3.71 (dd, *J* = 7.6/6.7 Hz, 1H, 5-*H*), 4.14 (dd, *J* = 7.6/7.0 Hz, 1H, 5-*H*), 4.25 (qd, *J* = 7.0/5.2 Hz, 1H, 4-*H*), 7.26–7.37 (m, 6H, arom. H_{meta} and H_{para}), 7.48–7.54 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 3322 (N-H), 2939, 2882 (C-H), 2793 (C-H), 1087, 1069 (C-O), 753, 701 (aryl).

*N-[2-(2,2-Diphenyl-1,3-dioxolan-4-yl)ethyl]butan-1-amine (**2c**)*

A solution of **9** (0.21 g, 0.50 mmol) and butan-1-amine (2.0 mL, 20 mmol) in methanol (5 mL) was stirred for 6 d at room temperature. The mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). The CH_2Cl_2 layer was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford pure butylamine **2c**. Pale yellow solid, mp 46–48 °C, yield 0.15 g (91%). $C_{21}H_{27}NO_2$ (325.45). – HR-MS (for M–$CH_2CH_2CH_3$): calcd. 282.1494 found 282.1494. – MS (EI): *m/z* (%) = 325 (M, 0.8), 282 (M – $CH_2CH_2CH_3$, 5.5), 248 (M – Ph, 14), 143 (O-CH$_2$-CH-(CH$_2$)$_2$-NH-C$_4$H$_9$, 88), 100 ((CH$_2$)$_2$-NH-C$_4$H$_9$, 95). – ^{1}H NMR (CDCl$_3$): δ [ppm] = 0.91 (t, *J* = 7.3 Hz, 3H, NHCH$_2$CH$_2$CH$_2$CH_3), 1.33 (sext, *J* = 7.3 Hz, 2H, NHCH$_2$CH$_2$CH_2CH$_3$), 1.45 (quint, *J* = 7.3 Hz, 2H, NHCH$_2$CH_2CH$_2$CH$_3$), 1.48 (s, broad, 1H, N*H*), 1.78 (dddd, *J* = 13.2/7.8/6.8/5.4 Hz, 1H, CH_2CH$_2$NH), 1.92 (dtd, *J* = 13.2/7.3/6.3 Hz, 1H, CH_2CH$_2$NH), 2.59 (t, *J* = 7.3 Hz, 2H, NHCH_2CH$_2$CH$_2$CH$_3$), 2.73 (ddd, *J* = 11.7/7.3/6.8 Hz, 1H, CH$_2$CH_2NH), 2.82 (ddd, *J* = 11.7/7.8/6.3 Hz, 1H, CH$_2$CH_2NH), 3.71 (dd, *J* = 7.8/7.3 Hz, 1H, 5-*H*), 4.13 (dd, *J* = 7.8/6.3 Hz, 1H, 5-*H*), 4.24 (tdd, *J* = 7.3/6.3/5.4 Hz, 1H, 4-*H*), 7.26–7.37 (m, 6H, arom. H_{meta} and H_{para}), 7.48–7.54 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 3345 (N-H), 2930, 2873 (C-H), 1085 (C-O), 756, 702 (aryl).

*2-(2,2-Diphenyl-1,3-dioxolan-4-yl)-N,N-dimethylethan-1-amine (**2d**)*

The tosylate **9** (0.43 g, 1.0 mmol) was dissolved in a solution of dimethylamine in ethanol (10.8 mL, 5.6 M, 60 mmol $(CH_3)_2NH_2$) and the mixture was stirred for 4 d at room temperature. The mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). The CH_2Cl_2 layer was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL) and water (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the pure dimethylamine **2d**. Pale yellow oil, yield 0.27 g (90%). $C_{19}H_{23}NO_2$ (297.40). – HR-MS: calcd. 297.1729 found 297.1721. – MS (CI): *m/z* (%) = 298 (M + H, 100), 116 (O-CH_2-CH-$(CH_2)_2$-N$(CH_3)_2$, 66). – 1H NMR ($CDCl_3$): δ [ppm] = 1.74 (ddt, *J* = 13.4/9.5/5.8 Hz, 1H, C$H_2$$CH_2$N), 1.92 (dddd, *J* = 13.4/9.2/7.0/5.5 Hz, 1H, C$H_2$$CH_2$N), 2.22 (s, 6H, N(C$H_3$)$_2$), 2.36 (ddd, *J* = 12.2/9.2/6.1 Hz, 1H, CH_2CH_2N), 2.48 (ddd, *J* = 12.2/9.5/5.5 Hz, 1H, CH_2CH_2N), 3.71 (dd, *J* = 7.3/7.0 Hz, 1H, 5-*H*), 4.14 (dd, *J* = 7.3/6.4 Hz, 1H, 5-*H*), 4.22 (quint, *J* = 6.5 Hz, 1H, 4-*H*), 7.26–7.36 (m, 6H, arom. H_{meta} and H_{para}), 7.48–7.54 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 2944, 2863 (C-H), 2817, 2765 (C-H), 1088, 1068 (C-O), 753, 701 (aryl).

*1-[2-(2,2-Diphenyl-1,3-dioxolan-4-yl)ethyl]piperidine (**2e**)*

A mixture of **9** (0.21 g, 0.50 mmol), piperidine (2.0 mL, 20 mmol) and methanol (5 mL) was stirred at room temperature for 3 d. The mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). The CH_2Cl_2 layer was washed with a saturated solution of $NaHCO_3$ (10 mL) and water (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the pure piperidine **2e**. Colorless oil, yield 0.15 g (88%). $C_{22}H_{27}NO_2$ (337.46), calcd. C 78.3 H 8.06 N 4.15 found C 78.1 H 8.12 N 4.11.- MS (EI): *m/z* (%) = 337 (M, 0.6), 260 (M – Ph, 14), 155 (O-CH_2-CH-$(CH_2)_2$-N(CH_2)5, 71), 98 (CH_2-N$(CH_2)_5$, 100). – 1H NMR ($CDCl_3$): δ [ppm] = 1.41–1.48 (m, 2H, 4-$H_{pip.}$), 1.54–1.62 (m, 4H, 3-$H_{pip.}$, 5-$H_{pip.}$), 1.80 (ddt, *J* = 13.2/9.5/5.9 Hz, 1H, C$H_2$$CH_2$N), 1.96 (dddd, *J* = 13.2/9.5/6.6/5.1 Hz, 1H, C$H_2$$CH_2$N), 2.33–2.43 (m, 4H, 2-$H_{pip.}$, 6-$H_{pip.}$), 2.38 (ddd, *J* = 12.5/9.5/6.2 Hz, 1H, CH_2CH_2N), 2.52 (ddd, *J* = 12.5/9.5/5.1 Hz, 1H, CH_2CH_2N), 3.72 (dd, *J* = 7.0/6.6 Hz, 1H, 5-$H_{diox.}$), 4.15 (dd, *J* = 7.0/6.6 Hz, 1H, 5-$H_{diox.}$), 4.20 (qd, *J* = 6.6/5.9 Hz, 1H, 4-$H_{diox.}$), 7.27–7.37 (m, 6H, arom. H_{meta} and H_{para}), 7.48–7.54 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 2934 (C-H), 2769 (C-H), 1085 (C-O), 760, 705 (aryl).

*(2,2-Diphenyl-1,3-dioxan-4-yl)methyl tosylate (**11**)*

A solution of **7** (1.35 g, 5 mmol) and triethylamine (0.84 mL, 6 mmol) in CH_2Cl_2 (15 mL) was cooled in an ice bath. A solution of *p*-toluenesulfonyl chloride (1.91 g, 10 mmol) in CH_2Cl_2 (10 mL) was slowly added and the reaction mixture was stirred at 4 °C for 48 h. The mixture was concentrated *in vacuo* and the residue was purified by fc (6 cm, petroleum ether : ethyl acetate = 4 : 1, fractions 30 mL, R_f = 0.35). Colorless solid, mp 70–74 °C, yield 1.56 g (74%). $C_{24}H_{24}O_5S$ (424.51), calcd. C 67.9 H 5.70 found C 68.0 H 5.76. – MS (EI): *m/z* (%) = 424 (M, 2.8), 347 (M – Ph, 83), 155 (Tos, 23), 105 (PhCO, 100). – 1H NMR ($CDCl_3$): δ [ppm] = 1.39 (dtd, *J* = 12.7/2.4/2.0 Hz, 1H, 5-$H_{equat.}$), 1.83 (dtd, *J* = 12.7/11.7/5.9 Hz, 1H, 5-H_{axial}), 2.44 (s, 3H, PhCH_3), 4.00 (td, *J* = 11.7/2.4 Hz, 1H, 6-H_{axial}), 4.07 (ddd, *J* = 11.5/5.9/2.0 Hz, 1H, 6-$H_{equat.}$), 4.08 (dd, *J* = 10.3/3.9 Hz, 1H, CH_2Otos), 4.19 (dd, *J* = 10.3/6.8 Hz, 1H, CH_2Otos), 4.24 (dddd, *J* = 11.7/6.8/3.9/2.4 Hz, 1H, 4-H_{axial}), 7.19–7.33 (m, 6H, arom. H_{meta} and H_{para}), 7.36–7.42 (m, 4H, arom. H_{ortho}), 7.48 (d, J = 8.8 Hz, 2H, arom. 3-*H*, 5-*H* (tos)), 7.84 (d, *J* = 8.8 Hz, 2H, arom. 2-*H*, 6-*H* (tos)). – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2970 (C-H), 2878 (C-H), 1361, 1174 (SO2), 1102 (C-O), 832 (aryl), 748, 709 (aryl).

*4-(Azidomethyl)-2,2-diphenyl-1,3-dioxane (**12**)*

A solution of **11** (0.21 g, 0.50 mmol) and NaN_3 (0.33 g, 5 mmol) in DMF (10 mL) was heated to reflux for 9 h. The solvent was evaporated *in vacuo* (< 10 mbar, < 60 °C) and the residue was dissolved in Et_2O (5 mL). The suspension was washed with a saturated solution of $NaHCO_3$ (5 mL) and water (5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Further purification of **12** was unnecessary. Colorless oil, yield 0.134 g (91%). $C_{17}H_{17}N_3O_2$ (295.34), calcd. C 69.1 H 5.80 N 14.23 found C 69.6 H 5.74 N 13.86. – MS (EI): *m/z* (%) = 295 (M, 13), 239 (M – CH_2N_3, 50), 218 (M – Ph, 100), 105 (PhCO, 82). – 1H NMR ($CDCl_3$): δ [ppm] = 1.38 (dtd, *J* = 12.8/2.4/1.8 Hz, 1H, 5-$H_{equat.}$), 1.94 dtd, *J* = 12.8/11.6/5.8 Hz, 1H, 5-H_{axial}), 3.21 (dd, *J* = 12.8/3.4 Hz, 1H, CH_2N_3), 3.50 (dd, *J* = 12.8/7.6 Hz, 1H, CH_2N_3), 4.06 (td, *J* = 11.6/2.4 Hz, 1H, 6-H_{axial}), 4.12 (ddd, *J* = 11.6/5.8/1.8 Hz, 1H, 6-$H_{equat.}$), 4.18 (dddd, *J* = 11.6/7.6/3.4/2.4 Hz, 1H, 4-H_{axial}), 7.16–7.32 (m, 4H, arom. H_{meta}), 7.38–7.44 (m, 2H, arom. H_{para}), 7.53–7.59 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 2967 (C-H), 2879 (C-H), 2095 (N_3), 1102 (C-O), 749, 704 (aryl).

*1-(2,2-Diphenyl-1,3-dioxan-4-yl)methanamine (**3a**)*

A mixture of **12** (97.5 mg, 0.33 mmol),), Pd/C (10%, 5 mg) and THF (10 mL) was stirred under a hydrogen atmosphere (1 bar) for 4 h at room temperature. The mixture was filtered with Celite® AFA and the solvent was evaporated *in vacuo* to afford the pure primary amine **3a**. Colorless oil, yield 86.7 mg (98%). $C_{17}H_{19}NO_2$ (269.34). – HR-MS: calcd. 269.1416 found 269.1417. – MS (EI): *m/z* (%) = 269 (M, 2), 239 (M – CH_2NH_2, 100), 192 (M – Ph, 18), 105 (PhCO, 83). – MS (CI): *m/z* (%) = 270 (M + H, 22), 239 (M – CH_2NH_2, 35), 88 (O$(CH_2)_2$CHCH_2NH_2 + H, 62). – 1H NMR ($CDCl_3$): δ [ppm] = 1.37 (dtd, *J* = 12.8/2.7/1.8 Hz, 1H, 5-$H_{equat.}$), 1.45 (s, broad, 2H, NH_2), 1.91 (dtd, *J* = 12.8/11.9/5.8 Hz, 1H, 5-H_{axial}), 2.83 (dd, *J* = 13.1/4.0 Hz, 1H, CH_2NH_2), 2.92 (dd, *J* = 13.1/7.0 Hz, 1H, CH_2NH_2), 3.95 (dddd, *J* = 11.9/7.0/4.0/2.7 Hz, 1H, 4-H_{axial}), 4.03 (td, *J* = 11.6/2.7 Hz, 1H, 6-H_{axial}), 4.10 (ddd, *J* = 11.6/5.8/1.8 Hz, 1H, 6-$H_{equat.}$), 7.18–7.32 (m, 4H, arom. H_{meta}), 7.38–7.43 (m, 2H, arom. H_{para}), 7.50–7.58 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 3374 (N-H), 2952, 2875 (C-H), 1593 (N-H), 1101, 1026 (C-O), 749, 707 (aryl).

*1-(2,2-Diphenyl-1,3-dioxan-4-yl)-N-methylmethanamine (**3b**)*

The tosylate **11** (0.21 g, 0.50 mmol) was dissolved in a solution of methylamine in ethanol (5 mL, 8.03 M, 40 mmol CH_3NH_2) and the mixture was heated to reflux for 8 h. The mixture was concentrated *in vacuo* and the procedure was repeated four times. After complete transformation the residue was dissolved in CH_2Cl_2 (10 ml) and washed with a saturated solution of $NaHCO_3$ (2 × 10 mL) and water (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield pure methylamine **3b**. Colorless oil, yield 0.125 g (88%). $C_{18}H_{21}NO_2$ (283.37). – HR-MS: calcd. 283.1572 found 283.1573. – MS (EI): *m/z* (%) = 283 (M, 2.7), 239 (M – CH_2NHCH_3, 48), 206 (M – Ph, 4), 105 (PhCO, 96), 101 (O-$(CH_2)_2$-CH-CH_2-NH-CH_3, 42). – 1H NMR ($CDCl_3$): δ [ppm] = 1.28 (dtd, *J* = 12.8/2.4/1.8 Hz, 1H, 5-$H_{equat.}$), 1.84 (dtd, *J* = 12.8/11.6/6.1 Hz, 1H, 5-H_{axial}), 2.04 (s, broad, 1H, N*H*), 2.42 (s, 3H, NHCH_3), 2.58 (dd, *J* = 12.2/3.7 Hz, 1H, CH_2NH), 2.77 (dd, *J* = 12.2/7.9 Hz, 1H, CH_2NH), 3.93 (td, *J* = 11.6/2.4 Hz,

1H, 6-H_{axial}), 3.99 (ddd, J = 11.6/6.1/1.8 Hz, 1H, 6-$H_{equat.}$), 4.06 (dddd, J = 11.6/7.9/3.7/2.4 Hz, 1H, 4-H_{axial}), 7.07–7.21 (m, 4H, arom. H_{meta}), 7.27–7.33 (m, 2H, arom. H_{para}), 7.38–7.47 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 3334 (N-H), 2948, 2877 (C-H), 2795 (C-H), 1102, 1028 (C-O), 749, 707 (aryl).

*N-[(2,2-Diphenyl-1,3-dioxan-4-yl)methyl]butan-1-amine (**3c**)*

A solution of **11** (0.21 g, 0.50 mmol) and butan-1-amine (4.0 mL, 40 mmol) in methanol (5 mL) was heated to reflux for 24 h. The solvent methanol and the excess of butan-1-amine were evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). The CH_2Cl_2 layer was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$), filtered and concentrated to yield pure butylamine **3c**. Colorless solid, mp 42–44 °C, yield 0.148 g (91%). $C_{21}H_{27}NO_2$ (325.45), calcd. C 77.5 H 8.30 N 4.30 found C 77.3 H 8.35 N 4.13. – MS (EI): *m/z* (%) = 325 (M, 3), 248 (M – Ph, 8), 239 (M – $CH_2NHC_4H_9$, 35), 143 (O-$(CH_2)_2$-CH-CH_2-NH-C_4H_9, 51), 105 (PhCO, 70). – ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.95 (t, J = 7.3 Hz, 3H, $NHCH_2CH_2CH_2CH_3$), 1.36–1.43 (m, 1H, 5-$H_{equat.}$), 1.39 (sext, J = 7.3 Hz, 2H, $NHCH_2CH_2CH_2CH_3$), 1.55 (quint, J = 7.3 Hz, 2H, $NHCH_2CH_2CH_2CH_3$), 1.92 (dtd, J = 12.5/11.6/5.8 Hz, 1H, 5-H_{axial}), 1.97 (s, broad, 1H, NH), 2.66 (dt, J = 11.3/7.3 Hz, 1H, $NHCH_2CH_2CH_2CH_3$), 2.72 (dt, J = 11.3/7.3 Hz, 1H, $NHCH_2CH_2CH_2CH_3$), 2.72 (dd, J = 12.2/3.7 Hz, 1H, CH_2NH), 2.90 (dd, J = 12.2/7.9 Hz, 1H, CH_2NH), 4.02 (td, J = 11.6/2.7 Hz, 1H, 6-H_{axial}), 4.08 (ddd, J = 11.6/5.8/1.8 Hz, 1H, 6-$H_{equat.}$), 4.14 (dddd, J = 11.6/7.9/3.7/2.4 Hz, 1H, 4-H_{axial}), 7.17–7.30 (m, 4H, arom. H_{meta}), 7.36–7.42 (m, 2H, arom. H_{para}), 7.47–7.56 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 3351 (N-H), 2956, 2928, 2872 (C-H), 1099, 1025 (C-O), 751, 706 (aryl).

*1-(2,2-Diphenyl-1,3-dioxan-4-yl)-N,N-dimethylmethanamine (**3d**)*

The tosylate **11** (0.21 g, 0.50 mmol) was dissolved in a solution of dimethylamine in ethanol (7.2 mL, 5.6 M, 40 mmol $(CH_3)_2NH_2$) and heated to reflux for 13 h. The volatile components were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). The CH_2Cl_2 layer was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford pure dimethylamine **3d**. Colorless oil, yield 0.137 g (92%). $C_{19}H_{23}NO_2$ (297.40). – HR-MS: calcd. 297.1729 found 297.1730. – MS (EI): *m/z* (%) = 297 (M, 8), 239 (M – $CH_2N(CH_3)_2$, 24), 220 (M – Ph, 13), 115 (O-$(CH_2)_2$-CH-CH_2-$N(CH_3)_2$, 74), 105 (PhCO, 76). – ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.46 (dtd, J = 12.7/2.4/2.0 Hz, 1H, 5-$H_{equat.}$), 1.88 (dtd, J = 12.7/11.2/6.3 Hz, 1H, 5-H_{axial}), 2.35 (s, 6H, $N(CH_3)_2$), 2.42 (dd, J = 13.2/4.9 Hz, 1H, CH_2N), 2.68 (dd, J = 13.2/6.8 Hz, 1H, CH_2N), 4.05 (td, J = 11.2/2.4 Hz, 1H, 6-H_{axial}), 4.08 (ddd, J = 11.2/6.3/2.0 Hz, 1H, 6-$H_{equat.}$), 4.05–4.15 (m, 1H, 4-H_{axial}), 7.16–7.32 (m, 4H, arom. H_{meta}), 7.38–7.44 (m, 2H, arom. H_{para}), 7.52–7.61 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 2944, 2874 (C-H), 2823, 2767 (C-H), 1099, 1026 (C-O), 754, 706 (aryl).

*1-[(2,2-Diphenyl-1,3-dioxan-4-yl)methyl]piperidine (**3e**)*

A solution of **11** (0.21 g, 0.50 mmol) and piperidine (4.0 mL, 40 mmol) in methanol (5 mL) was heated to reflux for 20 h. The volatile components were evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). The CH_2Cl_2 layer was washed with a saturated solution of $NaHCO_3$ (10 mL) and water (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford pure piperidine **3e**. Pale yellow oil, yield 0.163 g (96%). $C_{22}H_{27}NO_2$ (337.46), calcd. C 78.3 H 8.06 N 4.15 found C 78.1 H 8.17 N 4.38. – MS (EI): *m/z* (%) = 337 (M, 4), 260 (M – Ph, 11), 155 (O-$(CH_2)_2$-CH-CH_2-$N(CH_2)_5$, 63), 98 (CH_2-$N(CH_2)_5$, 100). – ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.42–1.50 (m, 2H, 4-$H_{pip.}$), 1.49 (dtd, J = 12.8/2.6/1.8 Hz, 1H, 5-$H_{equat.}$), 1.57–1.65 (m, 4H, 3-$H_{pip.}$, 5-$H_{pip.}$), 1.86 (dtd, J = 12.8/11.7/5.9 Hz, 1H, 5-H_{axial}), 2.44 (dd, J = 13.2/5.1 Hz, 1H, CH_2N), 2.49 (dt, J = 11.4/5.5 Hz, 2H, 2-$H_{pip.}$, 6-$H_{pip.}$), 2.57 (dt, J = 11.4/5.5 Hz, 2H, 2-$H_{pip.}$, 6-$H_{pip.}$), 2.70 (dd, J = 13.2/6.2 Hz, 1H, CH_2N), 4.04 (td, J = 11.4/2.6 Hz, 1H, 6-H_{axial}), 4.10 (ddd, J = 11.4/5.9/1.8 Hz, 1H, 6-$H_{equat.}$), 4.12 (dddd, J = 11.7/6.2/5.1/2.6 Hz, 1H, 4-H_{axial}), 7.16–7.31 (m, 4H, arom. H_{meta}), 7.37–7.43 (m, 2H, arom. H_{para}), 7.50–7.61 (m, 4H, arom. H_{ortho}). – IR (film): $\tilde{\nu}$ [cm^{-1}] = 2932 (C-H), 2779 (C-H), 1099 (C-O), 755, 707 (aryl).

Receptor binding studies

General

Teflon-glass-homogenizer: Potter®S (B. Braun Biotech International). – Rotor/stator homogenizer: Ultraturrax® T25 basic (Ika Labortechnik). – Centrifuge: High speed refrigerating centrifuge model J2-HS (Beckman). – Filter: Whatman glass fiber filters GF/B and GF/C presoaked in 1% (NMDA assay) or 0.5% (1-assay) polyethylene imine (in water) for 2 h at 4 °C before use. – Filtration was performed with a Brandel 24-well cell harvester. – Scintillation cocktail: Rotiszint eco plus (Roth). – Liquid scintillation analyzer: Tri-Carb 2100 TR (Canberra Packard), counting efficiency 66%. – All experiments were carried out in triplicate. – IC_{50}-values were determined from competition experiments with at least 6 concentrations of test compounds and were calculated with the curve-fitting program GraphPad Prism® 3.0 (GraphPad Software) by nonlinear regression analysis. – K_i-values were calculated according to Cheng and Prusoff [19]; K_D ((+)-MK-801) = 2.26 nM; K_D ((+)-pentazocine) = 2.90 nM; for compounds with high affinity (low K_i-values) mean values ± SEM from at least three independent experiments are given.

Investigation of the affinity for the phencyclidine binding site of the NMDA receptor [12, 13]

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

Preparation of the tissue: Fresh pig cortex was homogenized with a potter (500 rpm, 10 up-and-down strokes) in 10 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1000 g for 10 min at 4 °C. The supernatant was separated and centrifuged at 10000 g for 20 min at 4 °C. The pellet was resuspended in buffer (5 mM Tris acetate with 1 mM EDTA, pH 7.5) with an Ultraturrax (8000 rpm) and centrifuged at 20000 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 [20] using bovine serum albumin as standard, and subsequently the preparation was frozen (–83 °C) in 5 mL portions of about 1 mg protein/mL.

Performance of the assay: The test was performed with the radioligand [^{3}H]-(+)-MK-801 (832.5 GBq/mmol; (NEN TM Life Science Products, Zaventem, Belgium). The thawed membrane preparation (about 100 μg of the protein) was incubated with various concentrations of test compounds, 2 nM

[^{3}H]-(+)-MK-801, and buffer (5 mM Tris-acetate, 1 mM EDTA, pH 7.5) in a total volume of 500 μL for 90 min at 25 °C. The incubation was terminated by rapid filtration through presoaked Whatman GF/C filters (1% polyethylene imine in water for 3 h at 4 °C) using a cell harvester. After washing four times with 2 mL of cold buffer 3 mL of scintillation cocktail were added to the filters. After at least 8 h bound radioactivity trapped on the filters was counted in a liquid scintillation analyzer. Nonspecific binding was determined with 10 μM (+)-MK-801.

Investigation of the σ_1-receptor affinity [16, 17]

[^{3}H]-(+)-Pentazocine binding to guinea pig brain membrane preparations was performed according to standard radioligand binding assays [17], which were slightly modified as described below.

Membrane preparation: Thawed guinea pig brains (Dunkin Harley, Harlan-Sera-Lab, Loughborough, UK) were homogenized with an Ultraturrax (8000 rpm) in 10 volumes of cold 0.32 M sucrose. The homogenate was centrifuged at 1000 g for 10 min at 4 °C. The supernatant was separated and centrifuged at 22000 g for 20 min at 4 °C. The pellet was resuspended in 10 volumes of buffer (50 mM Tris HCl, pH 7.4) with an Ultraturrax (8000 rpm), incubated for 30 min at 25 °C and centrifuged at 22000 g (20 min, 4 °C). The pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford [20] using bovine serum albumin as standard, and subsequently the preparation was frozen (−83 °C) in 5 mL portions of about 2 mg protein/mL.

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

References

[1] W. R. Hardie, J. Hidalgo, I. F. Halverstadt, R. E. Allen, *J. Med. Chem.* **1966**, *9*, 127–136.

[2] L. G. Mendelsohn, G. A. Kerchner, V. Kalra, D. M. Zimmermann, J. D. Leander, *Biochem. Pharmacol.* **1984**, *33*, 3529–3535.

[3] D. Lodge in *Excitatory Amino Acid Receptors – Design of Agonists and Antagonists*, (Eds. P. Krogsgaard-Larsen, J. J. Hansen), Ellis Harwood Ltd., Chichester, **1992**, pp 201–215.

[4] E. H. F. Wong, J. A. Kemp, *Annu. Rev. Pharmacol. Toxicol.* **1991**, *31*, 401–425.

[5] K. Yamada, T. Nabeshima, *Drug News Persp.* **1991**, 524–529.

[6] H. Bräuner-Osborne, J. Egebjerg, E. O. Nielsen, U. Madsen, P. Krogsgaard-Larsen, *J. Med. Chem.* **2000**, *43*, 2609–2645.

[7] A. Thurkauf, M. V. Mattson, S. Richardson, S. Mirsadeghi, P. L. Ornstein, E. A. Harrison, Jr., K. C. Rice, A. E. Jacobson, J. A. Monn, *J. Med. Chem.* **1992**, *35*, 1323–1329.

[8] D. Seebach, A. K. Beck, R. Dahinden, M. Hoffmann, F. N. M. Kuehnle, *Croat. Chem. Acta* **1996**, *69*, 459–484.

[9] Herein, the products formed by reaction of OH-groups in different positions (1,2-; 1,3-; 1,4-) are termed regioisomers.

[10] A.I. Meyers, J. P. Lawson, D. G. Walker, R. J. Linderman, *J. Org. Chem.* **1986**, *51*, 5111–5123.

[11] R. Brückner, *Reaktionsmechanismen: Organische Reaktionen, Stereochemie, moderne Synthesemethoden*, Spektrum Akademischer Verlag, Heidelberg **1996**, p 257f.

[12] R. M. McKernan, S. Castro, J. A. Poat, E. H. F. Wong, *J. Neurochem.* **1989**, *52*, 777–785.

[13] G. Höfner, K. T. Wanner, *J. Rec. Sign. Transd. Res.* **1996**, *16*, 297–313.

[14] C. Kaiser, J. J. Pontecorvo, R. E. Mewshaw, *Neurotransmissions*, **1991**, 1–5.

[15] B. R. de Costa, L. Radesca, L. Di Paolo, W. D. Bowen, *J. Med. Chem.* **1992**, *35*, 38–47.

[16] C. A. Maier, B. Wünsch, *J. Med. Chem.* **2002**, *45*, 438–448.

[17] D. L. DeHaven-Hudkins, L. C. Fleissner, F. Y. Ford-Rice, *Eur. J. Pharmacol. Mol. Pharmacol. Sect.* **1992**, *227*, 371–378.

[18] W. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

[19] Y. Cheng, W. H. Prusoff, *Biochem. Pharmacol.* **1973,** *22*, 3099–3108.

[20] M. Bradford, *Anal. Biochem.* **1976**, *72*, 248–254.