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Original article

Synthesis of 4-(aminoalkyl) substituted 1,3-dioxanes as potent NMDA and σ receptor antagonists

Tina Utech, Jens Köhler, Bernhard Wünsch*

Institut für Pharmazeutische und Medizinische Chemie, Westfälischen Wilhelms-Universität Münster, Hittorfstraße 58-62, D-48149 Münster, Germany

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ABSTRACT

Elongation of the distance between the oxygen heterocycle and the basic amino moiety or ring expansion of the oxygen heterocycle of the NMDA receptor antagonists dexoxadrol and etoxadrol led to compounds with promising NMDA receptor affinity. Herein the combination of both structural features, i.e. elongation of the O-heterocycle – amine distance with a 1,3-dioxane ring is envisaged. The synthesis of aminoethyl-1,3-dioxanes **13**, **22**, **23** and **29** was performed by transacetalization of various acetals with pentane-1,3,5-triol, activation of the remaining free OH moiety with tosyl chloride and subsequent nucleophilic substitution. The corresponding 3-aminopropyl derivatives **33**–**35** were prepared by substitution of the tosylates with KCN and $LiAlH_4$ reduction. The highest NMDA receptor affinity was found for 1,3-dioxanes with a phenyl and an ethyl residue at the acetalic position (**23**) followed by diphenyl (**22**) and monophenyl derivatives (**13**). Generally the NMDA affinity of primary amines is higher than the NMDA affinity of secondary and tertiary amines. Altogether the primary amine **23a** ($K_i = 24$ nM) represents the most promising NMDA receptor antagonist of this series exceeding the NMDA affinity of the mono-homologues (2-aminoethyl)-1,3-dioxolanes (**3**,**4**) and (aminomethyl)-1,3-dioxanes (**5**,**6**). Whereas the primary amine **23a** turned out to be selective against σ_1 and σ_2 receptors the benzylamine **13d** was identified as potent ($K_i = 19$ nM) and selective σ_1 antagonist, which showed extraordinarily high antiallodynic activity in the capsaicin assay.

1. Introduction

The excitatory amino acid neurotransmitter (*S*)-glutamate mediates its effects through two types of receptors, which are termed ionotropic and metabotropic receptors. Herein we report on novel ligands interacting with the NMDA (*N*-methyl-D-aspartate) receptor, which represents the pharmacologically best characterized subtype of the ionotropic receptor class [1].

The NMDA receptor is a ligand gated ion channel, which controls the passage of cations across neuronal membranes. In addition to the control of Na^+-influx and K^+-outflow the NMDA receptor is responsible for the influx of Ca^{2+}-ions into neurons, which renders it unique among the ionotropic glutamate receptors. The manifold mechanisms controlling the Ca^{2+}-flow through the ion channel are the origin for synaptic plasticity and long term potentiation, which can be considered as cellular correlates for learning and memory [2–4].

However, overactivation of NMDA receptors leads to an increased influx of Ca^{2+}-ions into neurons resulting in an uncontrolled activation of several Ca^{2+}-dependent processes and at the end in damage of neuronal cells (excitotoxicity) [5]. Compounds blocking the excessive influx of Ca^{2+}-ions through the NMDA receptor associated ion channel into neurons are of major interest as neuroprotective agents, which may be used for the therapy of cerebral ischemia, stroke, epilepsy and trauma (brain injury). Furthermore, permanent increased activation of NMDA receptors is discussed to be involved in the development of chronic neurodegenerative disorders like Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis and alcohol dependence. Consequently, the NMDA receptor represents a promising target for the development of novel drugs for the therapy of acute and chronic neurological disorders [3,4,6,7].

There are several binding sites on the receptor protein for the modulation of the Ca^{2+}-influx and thus the NMDA receptor activity. The respective binding sites are termed according to their prototypical ligands, binding sites for (*S*)-glutamate, glycine, polyamines, Zn^{2+}, Mg^{2+}, H^+ and phencyclidine (1-(1-phenylcyclohexyl)piperidine, PCP) [3,8,9].

We are particularly interested in ligands interacting with the PCP binding site, which is located within the cation channel. Since ligands can only interact with this binding site after opening of the

* Corresponding author. Tel.: +49 251 8333311; fax: +49 251 8332144.
E-mail address: wuensch@uni-muenster.de (B. Wünsch).

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ion channel, compounds of this type are termed "open-channel blockers". Open-channel blockers are uncompetitive NMDA receptor antagonists and inhibit the influx of Ca^{2+}-ions into the neuron [3,8,9].

In the mid 1960s piperidine derivatives with an acetalic substituent in position 2 were synthesized by Hardie and coworkers [10]. These studies led to the enantiomerically pure compounds dexoxadrol (**1**) and etoxadrol (**2**, Fig. 1), which were clinically evaluated as analgesic and anesthetic drugs [11,12]. Unfortunately the clinical evaluation of both compounds had to be stopped, because psychotomimetic side effects, unpleasant dreams and aberrations were observed [13,14]. After detection and characterization of the NMDA receptor, it was shown that both compounds dexoxadrol and etoxadrol were blocking the ion channel by interaction with the PCP binding site [15,16]. The corresponding K_i-values are 112 nM [17] (23 nM [18]) for dexoxadrol and 107 nM [17] (20 nM [18]) for etoxadrol.

In literature some structure-affinity relationship studies dealing with these structurally and stereochemically interesting heterocyclic systems are reported [17–26]. It has been shown that the complete piperidine ring is not necessary for high NMDA receptor affinity, since 1,3-dioxolane derivatives bearing simple primary (aminomethyl) or secondary amines (methylaminomethyl) as piperidine substructures are also potent NMDA receptor antagonists. However, there are only few studies concerning the size of the oxygen heterocycle and the distance between the oxygen heterocycle and the basic amino group of the piperidine ring or its surrogate [17–21]. Recently we have reported on the synthesis and biological evaluation of side chain and ring homologues of dexoxadrol and etoxadrol. In the first type of homologues **3** and **4** the distance between the oxygen heterocycle and the basic amino group is enlarged to two methylene moieties (three bond lengths). The second type of homologues **5** and **6** contains a six-membered 1,3-dioxane ring instead of five-membered 1,3-dioxolane ring of **1** and **2**. Depending on the substitution pattern and the stereochemistry representatives of both types of homologues interact with NMDA receptors in a promising range [18] (see Fig. 1).

Therefore the idea came up to combine the side chain homologation and the ring expansion in one molecule. Herein we report on the synthesis and biological evaluation of double homologous 4-(2-aminoehtyl)-1,3-dioxanes with the general structure **7**.

2. Chemistry

For the synthesis of 2-aminoethyl substituted 1,3-dioxanes of type **7** pentane-1.3,5-triol (**8**) was required as central starting compound. According to literature the triol **8** was synthesized by reduction of dimethyl 3-oxoglutarate with $LiAlH_4$ [27]. However, the isolation of the triol **8** was very difficult due to its high polarity. The yield and the purity of the triol **8** were considerably improved by a modified work-up procedure, which led to the pure triol **8** in 43% isolated yield.

Pentanetriol **8** reacted with benzaldehyde dimethyl acetal (**9**) to afford stereoselectively the thermodynamically favored *cis*-configured 1,3-dioxane **10** (Scheme 1). The *cis*-configuration of **10** was proved by an NOE experiment showing the axial orientation of the protons in 2- and 4-position. After conversion of the primary alcohol **10** into the tosylate **11**, nucleophilic substitution with various amines led to the secondary and tertiary amines **13b–d**. The primary amine **13a** was obtained by hydrogenation (H_2, Pd/C) of the azide **12**, which was prepared by nucleophilic substitution of the tosylate **11** with NaN_3. The final amines **13a–d** were prepared and tested as racemic mixtures.

Transacetalization of benzophenone dimethyl acetal (**14**) and propiophenone dimethyl acetal (**15**) with pentanetriol **8** provided the 1,3-dioxanes **16** and **17**, respectively (Scheme 2).

In case of the non-symmetric acetal **15** only the diastereomer *trans*-**17** with an axially oriented phenyl residue and an equatorially oriented ethyl moiety was obtained. The stereodescriptor *trans* refers to the relative orientation of the phenyl and 2-hydroxyethyl

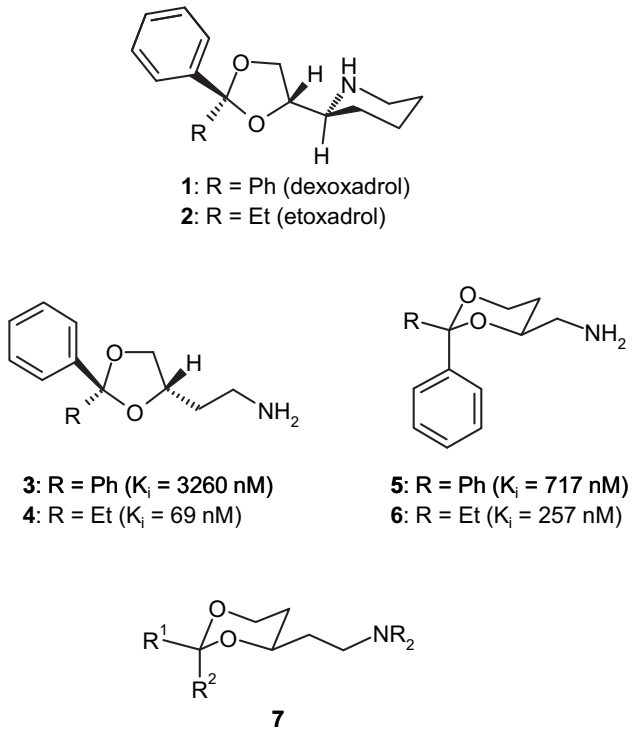
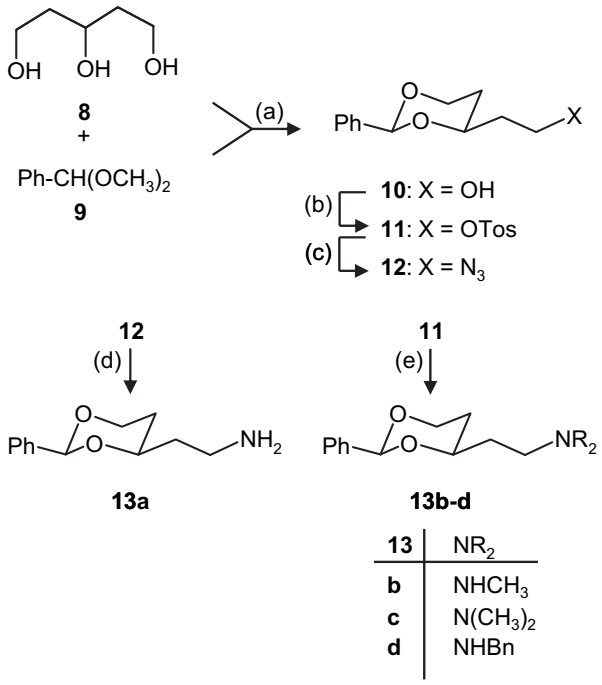
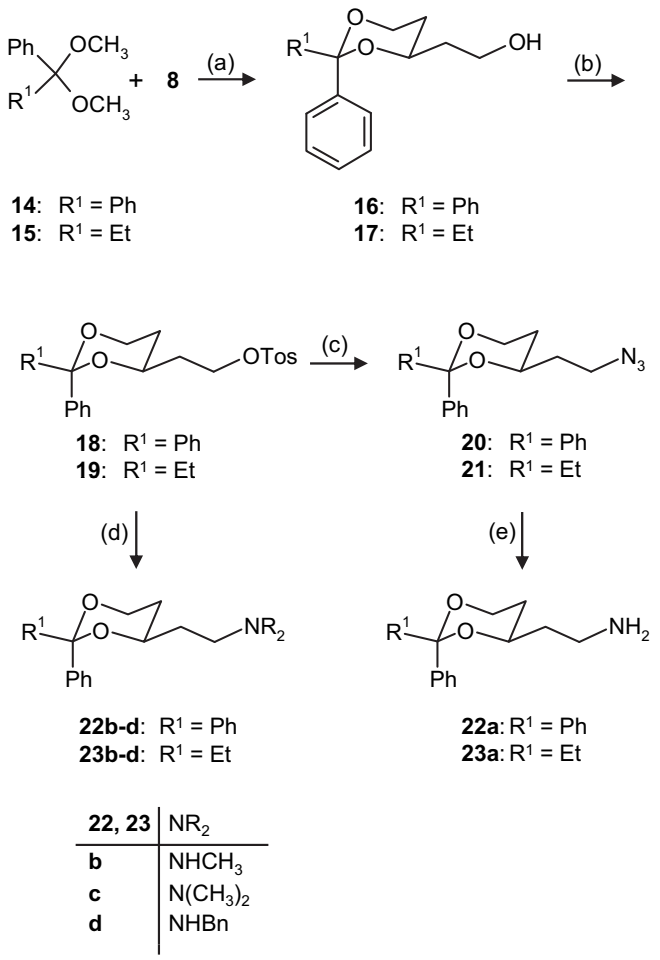


Fig. 1. Development of mono and double homologues of the potent NMDA receptor antagonists dexoxadrol and etoxadrol.



Scheme 1. Reagents and reaction conditions: (a) *p*-TosOH, THF, 12 h, reflux, 57%. (b) *p*-TosCl, pyridine, CH_2Cl_2, 15 h, 0–20 °C, 67%. (c) NaN_3, DMF, 2 h, reflux, 74%. (d) H_2, 1 bar, Pd/C, THF, 1 h, rt, 96%. (e) $MeNH_2$/EtOH or Me_2NH/EtOH or $BnNH_2$/toluene, 12 h, reflux, **13b** (56%), **13c** (51%), **13d** (67%).



Scheme 2. Reagents and reaction conditions: (a) *p*-TosOH, THF, 12 h, reflux, **16** (73%), **17** (70%). (b) *p*-TosCl, pyridine, CH_2Cl_2, 0–20 °C, **18** (79%), **19** (56%). (c) NaN_3, DMF, 2 h, reflux, **20** (69%), **21** (65%). (d) $MeNH_2$/EtOH or Me_2NH/EtOH or $BnNH_2$/toluene, 3–12 h, reflux, **22b** (41%), **22c** (80%), **22d** (65%), **23b** (44%), **23c** (44%), **23d** (71%). (e) H_2, 1 bar, Pd/C, EtOAc or MeOH, rt, **22a** (82%), **23a** (93%).

residues (Fig. 2). The relative configuration of *trans*-**17** was proved by NOE experiments. Irradiation with the resonance frequencies of the axial protons at 6-position (3.80 ppm) and at 4-position (3.96 ppm) led to an increased signal of the aromatic protons at 7.38–7.40 ppm, respectively. These effects are only possible when the phenyl moiety adopts the axial position.

The diastereomer *trans*-**17** appears to be energetically favored over *cis*-**17**, since it was formed under thermodynamically controlled conditions. The higher stability of *trans*-**17** is explained with steric interactions (Fig. 2). In case of *cis*-**17** strong interactions between the axially oriented ethyl moiety and the axially oriented protons at 4- and 6-position result. These interactions are reduced

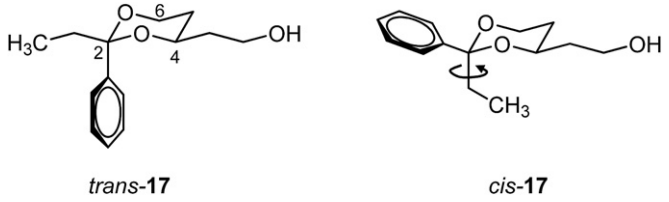


Fig. 2. Possible diastereomeric 1,3-dioxanes derived from propiophenone and pentanetriol **8**. The stereodescriptors *cis* and *trans* define the relative orientation of the 2-hydroxyethyl and phenyl moieties.

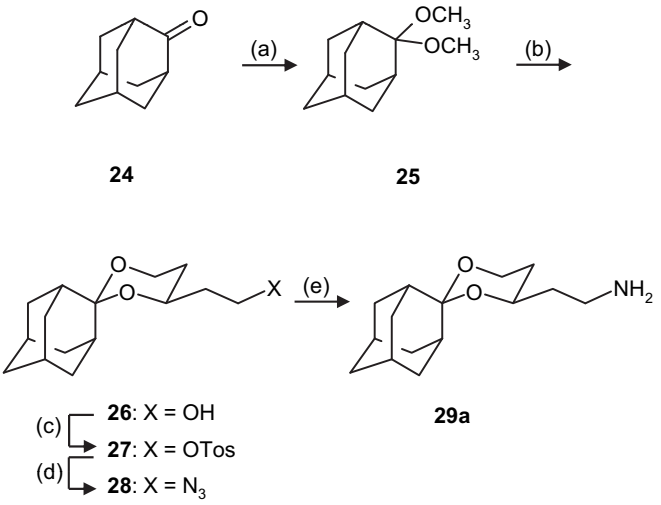
in case of *trans*-**17**, since the axially oriented phenyl group can adopt an orientation, which is perpendicular to the 1,3-dioxane plane. The free rotation of the axially oriented phenyl moiety of *trans*-**17** is considerably restricted, which results in minimized interactions between the *ortho*-protons and the axially oriented protons at 4- and 6-position [28–30].

The secondary and tertiary amines **22b–d** and **23b–d** were prepared by activation of the alcohols **16** and **17** with tosyl chloride and subsequent nucleophilic substitution. Nucleophilic substitution of the tosyloxy group of **18** and **19** with NaN_3 provided the corresponding azides **20** and **21**, which were reduced with H_2 in the presence of Pd/C to yield the primary amines **22a** and **23a**, respectively.

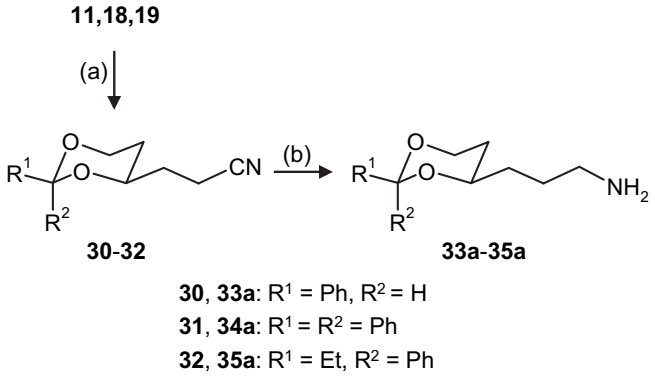
In order to replace the phenyl residues of **22a** or the phenyl and ethyl residues of **23a** by a bulky non-aromatic moiety, the adamantane derivative **29a** was envisaged (Scheme 3). The synthesis of **29a** [31] started with acetalization of adamantanone (**24**) with methanol and subsequent transacetalization of the resulting dimethyl acetal **25** with pentanetriol **8** to afford the 1,3-dioxane **26** in 52% yield. Tosylation and subsequent substitution with NaN_3 converted the alcohol **26** into the azide **28**, which was reduced with H_2 and Pd/C to give the primary amine **29a**.

Since some of the primary amines, in particular the primary amine **23a**, showed high NMDA receptor affinity (see Table 1) the homologous primary amines **33a–35a** should be included into this study. The homologization was achieved by substitution of the tosylates **11**, **18** and **19** with KCN and subsequent reduction of the respective nitriles **30–32** with $LiAlH_4$ (Scheme 4).

During the selectivity tests unexpected high σ_1 receptor affinities of the benzaldehyde derivatives **13a–13d** and **33a** were found. Therefore the corresponding homologous secondary and tertiary amines **33b–33d** were also prepared and evaluated pharmacologically. The synthesis of the propylamines **33b–33d** started with alcohol **36**, which was accessible by regioselective transacetalization of benzaldehyde dimethyl acetal (**9**) with racemic butane-1,2,4-triol [32,33]. After Swern oxidation [34] of the alcohol **36**, aldehyde **37** was converted via a Wittig reaction into the α,β-unsaturated ester **38**. Hydrogenation and subsequent $LiBH_4$ reduction of the saturated ester **39** gave the propanol **40**, which was transformed into the secondary and tertiary amines **33b–33d** via nucleophilic substitution of the tosylate **41** (Scheme 5).



Scheme 3. Reagents and reaction conditions: (a) MeOH, $HC(OMe)_3$, *p*-TosOH, 12 h, reflux, 82%. (b) **8**, *p*-TosOH, THF, 12 h, reflux, 52%. (c) *p*-TosCl, NEt_3, CH_2Cl_2, 15 h, 0–20 °C, 92%. (d) NaN_3, DMF, 2 h, reflux, 53%. (e) H_2, 1 bar, Pd/C, MeOH, 1 h, rt, 97%.



Scheme 4. Reagents and reaction conditions: (a) KCN, DMSO or DMF, 5–6 h, reflux, **30** (68%), **31** (81%), **32** (53%). (b) $LiAlH_4$, THF, 2 h, 0 °C, **33a** (45%), **34a** (89%), **35a** (57%).

3. Pharmacology

3.1. Receptor binding studies

The affinities of the 2-aminoethyl and 3-aminopropyl 1,3-dioxanes to the phencyclidine binding site of the NMDA receptor were determined in competition experiments with the radioligand [^{3}H]-(+)-MK-801, which interacts with the ion channel binding site with high affinity and selectivity. In the assay membrane preparations from pig brain cortex were used as receptor material. Non-specific binding was determined by saturation of the specific binding sites with a large excess of non-tritiated (+)-MK-801 [35–37].

There are several compounds interacting both with the phencyclidine binding site of the NMDA receptor and with σ receptors [26,38,39]. Therefore in the past the enigmatic σ receptor has been regarded to be identical with the phencyclidine binding site of the NMDA receptor [40]. This hypothesis was disproved by further investigations demonstrating the σ receptor to be an unique receptor [41,42]. The cross reactivity of ligands with both receptor types prompted us to investigate the σ receptor affinities of the amines in addition to their NMDA receptor affinities.

In the σ_1 assay homogenates of guinea pig brains were used as receptor material. The σ_1 selective ligand [^{3}H]-(+)-pentazocine was employed as radioligand, and the non-specific binding was determined by saturation of the specific binding sites with a large excess of haloperidol [43,44]. The σ_2 assay was performed with rat liver membrane preparations and the non-selective radioligand [^{3}H]-ditolylguanidine. In order to gain σ_2 selectivity an excess of the σ_1 selective ligand (+)-pentazocine was added to occupy the σ_1 receptors. A concentration of 10 μM of non-tritiated ditolylguanidine was used for the determination of non-specific binding.

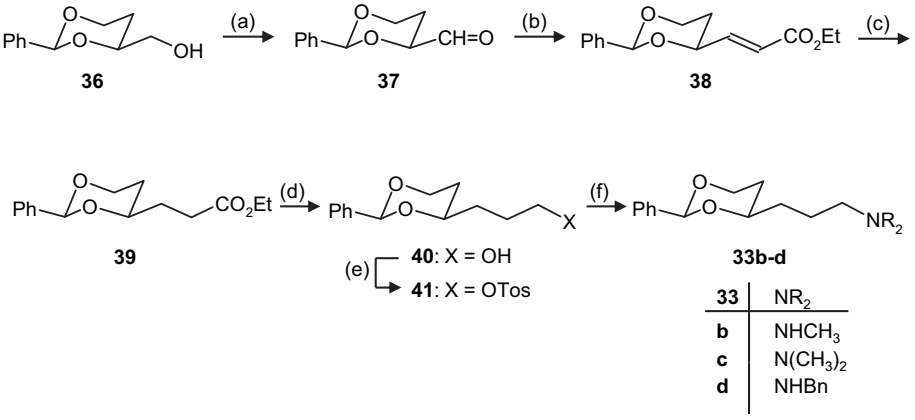
3.2. Results and discussion

Table 1 clearly shows that 1,3-dioxanes with only one phenyl substituent at the acetalic 2-position (**13a**–**d**) do not interact significantly with the phencyclidine binding site of the NMDA receptor. Introduction of two phenyl residues (**22a**,**b**) as in dexoxadrol leads to slightly increased NMDA receptor affinity. The most promising compounds of this series are the etoxadrol derived propiophenone derivatives **23** bearing a phenyl and an ethyl residue at 2-position. Replacement of the phenyl and ethyl moieties of **23a** with a lipophilic, sterically demanding but non-aromatic substituent (**29a**) was not tolerated by the NMDA receptor. The same trend Ph,Et > Ph,Ph > Ph,H was observed for 4-(aminoethyl)-1,3-dioxolanes **3** and **4** and 4-(aminomethyl)-1,3-dioxanes **5** and **6** [18].

The primary amine **23a** represents the most potent NMDA receptor antagonist ($K_i = 24$ nM) of these double homologous etoxadrol derivatives. The secondary amine **23b** with a small methyl residue at the N-atom and the tertiary amine **23c** with two methyl moieties show 6-fold and 30-fold reduced NMDA receptor affinities, respectively. Introduction of a large lipophilic benzyl residue at the N-atom (**23d**) leads to almost complete loss of NMDA receptor affinity. The mono-homologous 4-(aminoethyl)-1,3-dioxolanes **3**,**4** and 4-(aminomethyl)-1,3-dioxanes **5**,**6** show the same tendency of $NH_2 > NHCH_3 > N(CH_3)_2$ [18,21].

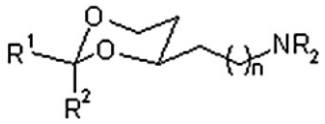
Generally it was found that double-homologous aminoethyl substituted 1,3-dioxanes, e.g. **23a** ($K_i = 24$ nM), which are derived from etoxadrol, show higher NMDA receptor affinities than their mono-homologous 4-(aminoethyl)-1,3-dioxolanes (e.g. (*S*,*S*)-**4**, $K_i = 69$ nM) and 4-(aminomethyl)-1,3-dioxanes (e.g. (*S*,*S*)-**6**, $K_i = 257$ nM). However, a further homologization of the aminoethyl derivatives to aminopropyl derivatives **33a**–**35a** led to considerably reduced NMDA receptor affinities.

Due to the cross reactivity of NMDA and σ ligands the σ_1 and σ_2 affinities of all amines were determined (see Table 1). In the benzaldehyde (**13**), benzophenone (**22**) and propiophenone (**23**) series the benzylamines **13d**, **22d** and **23d** represent the most potent σ_1 ligands, respectively. The σ_1 affinity of the benzylamines can be correlated with the size of the substituent in 2-position: Replacement of one of the phenyl residues in 2-position of **22d** with an ethyl residue (**23d**) led to a 10-fold increase of σ_1 affinity and the 1,3-dioxane **13d** with a proton at 2-position shows the highest σ_1 affinity of this series ($K_i = 19$ nM). Elongation of the side chain of



Scheme 5. (a) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, −78 °C. (b) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 3 h, rt, 62% (from **36**). (c) H_2, 1.5 bar, Pd/C, EtOAc, 4 h, 88%. (d) $LiBlH_4$, THF, 4 h, 0 °C, 55%. (e) *p*-TosCl, NEt_3, CH_2Cl_2, 1 h, 0 °C, 56%. (f) $MeNH_2$/EtOH or Me_2NH/EtOH or $BnNH_2$/toluene, 12 h, reflux, **33b** (58%), **33c** (36%), **33d** (76%).

Table 1
NMDA, σ_1 and σ_2 receptor affinities of 4-aminoalkyl-1,3-dioxanes.



Compd.	R^1	R^2	*n*	NR_2	$K_i \pm$ SEM [nM] ($n = 3$)		
					NMDA	σ_1	σ_2
13a	Ph	H	1	NH_2	>10 μM	165 ± 20	>10 μM
13b	Ph	H	1	$NHCH_3$	>10 μM	449 ± 29	>10 μM
13c	Ph	H	1	$N(CH_3)_2$	>10 μM	1650 ± 60	1830 ± 93
13d	Ph	H	1	NHBn	>10 μM	19 ± 1.0	92 ± 40
22a	Ph	Ph	1	NH_2	2350 ± 180	>10 μM	>10 μM
22b	Ph	Ph	1	$NHCH_3$	6870 ± 230	>10 μM	>10 μM
22c	Ph	Ph	1	$N(CH_3)_2$	>10 μM	660 ± 82	>10 μM
22d	Ph	Ph	1	NHBn	>10 μM	320 ± 12	2750 ± 230
23a	Et	Ph	1	NH_2	24 ± 2.0	955 ± 145	>10 μM
23b	Et	Ph	1	$NHCH_3$	154 ± 6.0	856 ± 109	>10 μM
23c	Et	Ph	1	$N(CH_3)_2$	713 ± 83	511 ± 28	>10 μM
23d	Et	Ph	1	NHBn	>10 μM	27 ± 2.0	903 ± 190
29a	Adamantane		1	NH_2	>10 μM	1250 ± 30	>10 μM
33a	Ph	H	2	NH_2	>10 μM	167 ± 13	581 ± 90
33b	Ph	H	2	$NHCH_3$	>10 μM	327 ± 51	6320 ± 1460
33c	Ph	H	2	$N(CH_3)_2$	>10 μM	1220 ± 340	>10 μM
33d	Ph	H	2	NHBn	>10 μM	164 ± 15	3890 ± 2000
34a	Ph	Ph	2	NH_2	>10 μM	175 ± 45	>10 μM
35a	Et	Ph	2	NH_2	7670 ± 830	6450 ± 73	542 ± 170
Dexoxadrol					19 ± 2.5		
Etoxadrol					22 ± 3.9		
Phencyclidine					28 ± 4.6		
(+)-Pentazcoine						3.5 ± 0.2	
Ditolylguanidine							64 ± 11

the benzylamine **13d** by one methylene moiety led to the propylamine **33d** with 10-fold decreased σ_1 affinity.

With exception of the benzylamine **13d** ($K_i = 92$ nM) the σ_2 affinities of the amines are generally rather low.

Since the NMDA receptor prefers primary amines and the σ_1 receptor benzylamines, both ligand types are selective over the other receptor types. E.g. the most potent NMDA receptor antagonist **23a** shows a 40-fold selectivity against the σ_1 receptor and >400-fold selectivity against the σ_2 subtype. On the other hand the most promising σ_1 ligands **13d** and **23d** do not interact significantly with NMDA receptors. However, the selectivity against the σ_2 subtype differs considerably. Whereas the potent σ_1 ligand **23d** shows a 33-fold selectivity over the σ_2 receptor, only 5-fold selectivity over the σ_2 subtype was observed for **13d**. Despite the moderate selectivity against the σ_2 subtype **13d** reveals an excellent selectivity over more than 60 other targets [45].

3.3. Analgesic activity

The high σ_1 affinity of the benzylamines **13d** and **23d** stimulated an in vivo study with these ligands. Sensitization by subplantar capsaicin injection was used to assess the effect of the σ_1 ligands **13d** and **23d** on mechanical allodynia. Subplantar capsaicin (8-methyl-N-vanillylnon-6-enamide) injection initially evokes a nocifensive behavior that is characterized by lifting and guarding the injected paw and typically lasts up to 5 min following injection. Afterwards hypersensitivity to both thermal and mechanical stimuli is evidenced [46,47].

Mice were treated with the σ_1 ligands **13d** and **23d** 30 min before capsaicin injection into the mid-plantar surface of the right hind paw. Withdrawal latencies to mechanical stimuli by a von Frey filament (1 g) were determined 15 min after capsaicin injection. Whereas the propiophenone derivative **23d** did not show any analgesic activity up to a dose of 32 mg/kg body weight, the benzaldehyde derivative **13d** was extremely potent. Doses of 1.0 and 0.50 mg/kg led to 100% analgesia and a dose of 0.25 mg/kg showed still more than 70% analgesia. Even at the very low dose of 0.125 mg/kg around 10% analgesic activity was observed. The high antiallodynic potency indicates **13d** to be a σ_1 receptor antagonist [45].

4. Conclusion

A series of aminoethyl and aminopropyl substituted 1,3-dioxanes, which are considered as ring and side chain homologues of the NMDA antagonists dexoxadrol and etoxadrol, has been synthesized and pharmacologically evaluated. The most potent NMDA antagonists result, when the acetalic position is substituted with a phenyl and an ethyl residue. Primary amines are more potent than secondary amines and these are more potent than tertiary amines. The most promising NMDA antagonist **23a** ($K_i = 24$ nM) exceeds the NMDA affinity of the mono-homologues **4** (aminoethyl-1,3-dioxolane) and **6** (aminomethyl-1,3-dioxane). **23a** reveals an excellent selectivity over σ_1 and σ_2 receptors.

Surprisingly this study did not only lead to the characterization of the novel NMDA antagonist **23a** but also to the identification of the σ_1 antagonist **13d**. The benzylamine **13d** represents a very potent ($K_i = 19$ nM) and selective σ_1 ligand, which shows extraordinarily high antiallodynic activity in the capsaicin assay.

5. Experimental

5.1. Chemistry

5.1.1. General

Petroleum ether used refers to the fraction boiling at 40–60 °C. Thin layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck).

Flash chromatography (fc): Silica gel 60, 0.040–0.063 mm (Merck); parentheses include: diameter of the column [cm], height of SiO_2 column, eluent, fraction size [mL], R_f-value. Melting points: Melting point apparatus SMP 2 (Stuart Scientific), uncorrected. Elemental analyses: Elemental Analyzer Vario EL (Elementaranalysesysteme GmbH). MS: MAT 312, MAT 8200, MAT 44, and TSQ 7000 (Finnigan); EI = electron impact, CI = chemical ionization. High resolution MS (HRMS): MAT 8200 (Finnigan). IR: IR spectrophotometer 1600 FT-IR and 2000 FT-ATR-IR (Perkin–Elmer). ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz): Unity 300 FT NMR spectrometer (Varian), δ in ppm related to tetramethylsilane, coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and of ^{1}H NMR signals were supported by 2D NMR techniques.

5.1.2. Pentane-1,3,5-triol (**8**) (synthesis modified according to Ref. [27])

Under ice-cooling a solution of dimethyl 3-oxoglutarate (11.5 g, 66 mmol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (5.4 g, 140 mmol) in THF (100 mL) and the reaction mixture was stirred under reflux for 48 h. Excess of $LiAlH_4$ was destroyed with water (100 mL) at rt, H_2SO_4 (25%) was added until the precipitate was dissolved completely (pH 1) and the mixture was heated to reflux for further 17 h. THF was evaporated in vacuo, water (300 mL) was added and the mixture was alkalized (pH 10) with NH_3 (25%). The resulting precipitate of $Al(OH)_3$ was removed by suction through a filter paper with a sufficient amount of sand on top of it and washed with water. The filtrate was concentrated in vacuo, the dry residue was suspended in ethanol (100 mL) and the mixture was heated to reflux for 17 h. Insoluble Li_2SO_4 was filtered off at 50 °C and washed with ethanol (100 mL). The organic layer was removed in vacuo and the residue was distilled in a Kugelrohr apparatus under high vacuum. Colorless oil, bp 160–210 °C, 0.14 mbar. The crude material was purified by fc (8 cm, 15 cm, EtOAc:MeOH = 4:1, 30 mL, R_f = 0.21) and a second Kugelrohr distillation. Colorless oil, bp 190–210 °C, 0.12 mbar, yield 3.39 g (43%). $C_5H_{12}O_3$ (120.1). MS (EI): m/z (%) = 121 [MH, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3294 (O–H), 2938 (C–H), 1041 (C–O). ^{1}H NMR (CD_3OD): δ (ppm) = 1.60–1.74 (m, 4H, CH_2–CH–CH_2), 3.70 (t, J = 6.6 Hz, 4H, CH_2–OH), 3.88 (tt, J = 8.1/4.5 Hz, 1H, CH_2–CH–CH_2).

5.1.3. cis-2-(2-Phenyl-1,3-dioxan-4-yl)ethan-1-ol (**10**)

A solution of pentane-1,3,5-triol (**8**, 700 mg, 5.8 mmol), benzaldehyde dimethyl acetal (**9**, 1.2 mL, 8.0 mmol) and *p*-toluenesulfonic acid (20 mg, 0.1 mmol) in THF (20 mL) was heated to reflux for 12 h. The solvent was removed in vacuo, the residue was dissolved in Et_2O (15 mL) and the mixture was extracted with a saturated solution of $NaHCO_3$ (5 mL). The Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue was purified by fc (4 cm, petroleum ether:EtOAc = 60:40, 20 mL, R_f = 0.25). Colorless oil, yield 681 mg (57%). $C_{12}H_{16}O_3$ (208.3). HRMS: calcd. for $C_{12}H_{16}O_3$ 208.1093; found 208.1099. Anal. calcd. C 69.21, H 7.74; found C 68.86, H 8.06. MS (EI): m/z (%) = 208 [M, 59], 177 [M–CH_2OH, 8], 105 [PhCO, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3427 (OH), 2942, 2877 (C–H), 1167, 1090 (C–O), 757, 735 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.52 (dq, J = 13.4/2.4 Hz, 1H, 5-H_{eq}), 1.77–1.99 (m, 4H, CH_2–CH_2–OH and 5-H_{ax}), 3.81 (ddd, J = 11.5/6.1/4.8 Hz, 1H, CH_2–CH_2–OH), 3.86 (ddd, J = 11.5/6.4/4.8 Hz, 1H, CH_2–CH_2–OH), 3,97 (td, J = 11.3/2.4 Hz, 1H, 6-H_{ax}), 4.12 (ddt, J = 11.2/5.8/2.4 Hz, 1H, 4-H_{ax}), 4.27 (ddd, J = 11.3/5.2/1.8 Hz, 1H, 6-H_{eq}), 5.53 (s, 1H, 2-H_{ax}), 7.32–7.39 (m, 3H, H_{arom}), 7.45–7.48 (m, 2H, H_{arom}).

5.1.4. cis-[2-(2-Phenyl-1,3-dioxan-4-yl)ethyl] p-toluenesulfonate (**11**)

A cold solution of *p*-toluenesulfonyl chloride (3.6 g, 19 mmol) in CH_2Cl_2 (10 mL) was added slowly to a cold solution of alcohol **10** (2.0 g, 9.6 mmol) and pyridine (9.5 mL, 9.6 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 15 h at rt. The solvent was removed in vacuo and the residue was purified by fc (5 cm, 15 cm, petroleum ether:EtOAc = 7:3, 20 mL, R_f = 0.40). Colorless solid, mp 78 °C, yield 2.3 g (67%). $C_{19}H_{22}SO_5$ (362.5). Anal. calcd. C 62.96, H 6.12, S 8.85; found C 62.86, H 6.11, S 8.57. MS (EI): m/z (%) = 362 [M, 100], 155 [tos, 46], 105 [PhCO, 86]. IR (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2966, 2870 (C–H), 1357, 1175 (SO_2), 1096, 1021 (C–O), 780, 743 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.48 (dtd, J = 13.4/2.7/1.5 Hz, 1H, 5-H_{eq}), 1.77 (qd, J = 13.4/5.1 Hz, 1H, 5-H_{ax}), 1.91 (dt, J = 10.1/4.3 Hz, 2H, CH_2–CH_2–Otos), 2.37 (s, 3H, Ph–CH_3), 3.91–3.99 (m, 2H, 4-H_{ax} and 6-H_{eq}), 3.92 (td, J = 12.5/2.7 Hz, 1H, 6-H_{ax}), 4.16 (dt, J = 10.1/4.8 Hz, 1H, CH_2–CH_2–Otos), 4.21–4.29 (m, 1H, CH_2–CH_2–Otos), 5.37 (s, 1H, 2-H_{ax}), 7.26–7.38 (m, 7H, H_{arom}, 3-H_{PhCH3} and 5-H_{PhCH3}), 7.78 (d, J = 8.2 Hz, 2H, 2-H_{PhCH3} and 6-H_{PhCH3}).

5.1.5. cis-4-(2-Azidoethyl)-2-phenyl-1,3-dioxane (**12**)

A mixture of tosylate **11** (150 mg, 0.41 mmol) and NaN_3 (130 mg, 2.0 mmol) in DMF (10 mL) was heated to reflux for 2 h. After cooling down excess of DMF was evaporated in vacuo. The residue was purified by fc (2 cm, 15 cm, petroleum ether:EtOAc = 19:1, 2 mL, R_f = 0.32). Colorless oil, yield 71 mg (74%). $C_{12}H_{15}N_3O_2$ (233.3). HRMS (EI): calcd. for $C_{12}H_{14}N_3O_2$ 232.1086; found 232.1086. MS (EI): m/z (%) = 232 [M–H, 32], 105 [PhCO, 100]. MS (CI): m/z (%) = 234 [MH, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 2951, 2875 (C–H), 2093 (N_3), 1099, 1018 (C–O), 782, 749 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.53 (dtd, J = 13.1/2.4/1.5 Hz, 1H, 5-H_{eq}), 1.76 – 1.98 (m, 3H, CH_2–CH_2–N_3 and 5-H_{ax}), 3.44 (ddd, J = 12.5/6.7/2.1 Hz, 1H, CH_2–CH_2–N_3), 3.53 (ddd, J = 12.5/6.1/2.7 Hz, 1H, CH_2–CH_2–N_3), 3.89 (td, J = 11.6/2.7 Hz, 1H, 6-H_{ax}), 3.95–4.04 (m, 1H, 4-H_{ax}), 4.28 (ddd, J = 11.6/5.1/1.5 Hz, 1H, 6-H_{eq}), 5.52 (s, 1H, 2-H_{ax}), 7.32–7.40 (m, 3H, H_{arom}), 7.47–7.50 (m, 2H, H_{arom}).

5.1.6. cis-2-(2-Phenyl-1,3-dioxan-4-yl)-ethan-1-amine (**13a**)

A mixture of azide **12** (30 mg, 0.12 mmol) and Pd/C (6 mg, 5%) in THF (5 mL) was stirred under H_2 (balloon) for 1 h at rt. The mixture was filtered over Celite®. Since the filtrate contained traces of the catalyst Pd/C the solvent was removed in vacuo, the residue was dissolved in methanol (2 mL) and the filtration over Celite® was repeated. The filtrate was concentrated in vacuo. Pale yellow oil, yield 24 mg (96%). $C_{12}H_{17}NO_2$ (207.3). HRMS (EI): calcd. for $C_{12}H_{17}NO_2$ 207.1254; found 207.1259. Anal. calcd. C 69.54, H 8.26, N 6.76; found C 69.10, H 8.57, N 6.30. MS (EI): m/z (%) = 207 [M, 1], 163[M^+–$CH_2CH_2NH_2$, 9], 101[M–PhCO, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3367 (NH_2), 2920, 2852 (C–H), 1662 (NH_2), 1101, 1023 (C–O), 748, 727 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.50 (dtd, J = 13.7/2.4/1.5 Hz, 1H, 5-H_{eq}), 1.67 (dddd, J = 13.7/11.9/11.2/4.3 Hz, 1H, 5-H_{ax}), 1.75–1.92 (m, 4H, CH_2–CH_2–NH_2), 2.87 (t, J = 6.9 Hz, 2H, CH_2–CH_2–NH_2), 3.93–4.01 (m, 1H, 4-H_{ax}), 3.96 (td, J = 11.6/2.7 Hz, 1H, 6-H_{ax}), 4.26 (ddd, J = 11.6/4.8/1.2 Hz, 1H, 6-H_{eq}), 5.51 (s, 1H, 2-H_{ax}), 7.28–7.38 (m, 3H, H_{arom}), 7.45–7.49 (m, 2H, H_{arom}).

5.1.7. cis-N-Methyl-2-(2-phenyl-1,3-dioxan-4-yl)ethan-1-amine (**13b**)

Tosylate **11** (100 mg, 0.27 mmol) was added to an ethanolic solution of methylamine (8 M, 5 mL, 40 mmol). The mixture was heated to reflux for 12 h. After cooling down the excess of methylamine and ethanol was evaporated in vacuo. The yellow residue was dissolved in CH_2Cl_2 (10 mL) and the solution was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by fc (2 cm, 15 cm, CH_2Cl_2:MeOH = 8:1, 5 mL, R_f = 0.29). Pale yellow oil, yield 33 mg (56%). $C_{13}H_{19}NO_2$ (221.3). HRMS (EI): calcd. for $C_{13}H_{19}NO_2$ 221.1415; found 221.1415. MS (EI): m/z (%) = 221 [M, 3], 177 [M–CH_2–$NHCH_3$, 3], 115 [O–$(CH_2)_2$–CH–$(CH_2)_2$–$NHCH_3$, 58], 105 [PhCO, 33], 44 [–CH_2–$NHCH_3$, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3390 (N–H); 2953, 2852 (C–H); 2732 (NH$\underline{CH_3}$), 1098, 1020

(C–O), 749 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.52 (dtd, J = 13.1/2.7/1.8 Hz, 1H, 5-H_{eq}), 1.74–1.87 (m, 1H, 5-H_{ax}), 1.87–2.02 (m, 3H, CH_2–CH_2–NHCH_3), 2.48 (s, 3H, NHCH_3), 2.80–2.89 (m, 2H, CH_2–CH_2–NHCH_3), 3.89–4.03 (m, 1H, 4-H_{ax}), 3.96 (td, J = 11.9/2.4 Hz, 1H, 6-H_{ax}), 4.24 (ddd, J = 11.9/4.8/1.2 Hz, 1H, 6-H_{eq}), 5.51 (s, 1H, 2-H_{ax}), 7.32–7.38 (m, 3H, H_{arom}), 7.45–7.49 (m, 2H, H_{arom}).

5.1.8. *cis-N,N-Dimethyl-2-(2-phenyl-1,3-dioxan-4-yl)ethan-1-amine (**13c**)*

Tosylate **11** (100 mg, 0.27 mmol) was added to an ethanolic solution of dimethylamine (5.6 M, 5 mL, 28 mmol) and the mixture was heated to reflux for 12 h. After cooling down the excess of dimethylamine and ethanol was evaporated in vacuo. The yellow residue was dissolved in CH_2Cl_2 (10 mL) and the mixture was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by fc (2 cm, 15 cm, CH_2Cl_2:MeOH = 8:1, 5 mL, R_f = 0.19). Pale yellow oil, yield 32 mg (51%). $C_{14}H_{21}NO_2$ (235.30). HRMS (EI): calcd. for $C_{14}H_{21}NO_2$ 235.1570; found 235.1572. MS (EI): m/z (%) = 235 [M, 4.5], 129 [M–PhCHO, 40], 105 [PhCO, 13], 58 [$-CH_2-N(CH_3)_2$, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 2950, 2858 (C–H), 2766 (N($\underline{CH_3}$)$_2$), 1101, 1025 (C–O), 749 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.53 (dtd, J = 13.1/2.4/1.2 Hz, 1H, 5-H_{eq}), 1.69–1.94 (m, 1H, 5-H_{ax}), 1.82–1.94 (m, 2H, CH_2–CH_2–N(CH_3)$_2$), 2.29 (s, 6H, N(CH_3)$_2$), 2.51 (t, J = 7.4 Hz, 2H, CH_2–CH_2–N(CH_3)$_2$), 3.89–3.98 (m, 1H, 4-H_{ax}), 3.96 (td, J = 11.3/2.4 Hz, 1H, 6-H_{ax}), 4.25 (ddd, J = 11.3/5.2/1.2 Hz, 1H, 6-H_{eq}), 5.51 (s, 1H, 2-H_{ax}), 7.31–7.38 (m, 3H, H_{arom}), 7.45–7.49 (m, 2H, H_{arom}).

5.1.9. *cis-N-Benzyl-2-(2-phenyl-1,3-dioxan-4-yl)ethan-1-amine (**13d**)*

A solution of tosylate **11** (400 mg, 1.10 mmol) and freshly distilled benzylamine (0.15 mL, 2 mmol) in toluene (5 mL) was heated to reflux for 12 h. After cooling down the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and the solution was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic layer was dried ($MgSO_4$), evaporated in vacuo and the residue was purified by fc (2 cm, 15 cm, CH_2Cl_2:MeOH = 80:10, 2 mL, R_f = 0.31). Pale yellow oil, yield 220 mg (67%). $C_{19}H_{23}NO_2$ (297.4). HRMS (EI): calcd. for $C_{19}H_{23}NO_2$ 297.1729; found 297.1728. MS (EI): m/z (%) = 297 [M, 2], 191 [O–$(CH_2)_2$–CH–$(CH_2)_2$–NHBn, 60], 120 [CH_2–NHBn, 36], 91 [tropylium, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 2769 (C–H), 1112, 1000 (C–O), 751, 663 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.52 (dtd, J = 13.1/2.4/1.2 Hz, 1H, 5-H_{eq}), 1.77 (dddd, J = 13.1/11.9/11.2/4.6 Hz, 1H, 5-H_{ax}), 1.82–1.96 (m, 3H, CH_2–CH_2–NHBn), 2.83 (t, J = 6.7 Hz, 2H, CH_2–CH_2–NHBn), 3.81 (s, 2H, NHCH_2Bn), 3.94–4.03 (m, 1H, 4-H_{ax}), 3.97 (td, J = 11.6/2.7 Hz, 1H, 6-H_{ax}), 4.27 (ddd, J = 11.6/4.8/1.2 Hz, 1H, 6-H_{eq}), 5.52 (s, 1H, 2-H_{ax}), 7.22–7.39 (m, 8H, H_{arom}), 7.47–7.50 (m, 2H, H_{arom}).

For the preparation of the hydrochloride **13d**·HCl the amine **13d** (100 mg, 0.34 mmol) was dissolved in Et_2O_{abs} (2 mL) and a solution of HCl in Et_2O was added slowly until no further precipitate was formed. The solid was separated and recrystalized with iPr_2O. Colorless solid, mp 177 °C (iPr_2O), yield 44 mg (39%). Anal. calcd. C 68.35, H 7.25, N 4.19; found C 68.09, H 7.39, N 3.88.

5.1.10. *2-(2,2-Diphenyl-1,3-dioxan-4-yl)ethan-1-ol (**16**)*

Benzophenone dimethyl acetal (**14**, 913 mg, 4.0 mmol) was added to a solution of pentane-1,3,5-triol (**8**, 340 mg, 2.8 mmol) and *p*-toluenesulfonic acid (86.1 mg, 0.5 mmol) in THF (10 mL). The mixture was heated to reflux for 12 h. The solvent was removed in vacuo, the residue was dissolved in Et_2O and the solution was extracted with a saturated solution of $NaHCO_3$ (5 mL). The Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue was purified by fc (4 cm, petroleum ether:EtOAc = 60:40, 10 mL, R_f = 0.36). Colorless solid, mp 61 °C, yield 332 mg (73%). $C_{18}H_{20}O_3$ (284.4). Anal. calcd. C 76.03, H 7.10; found C 75.89, H 7.00. MS (EI): m/z (%) = 284 [M, 2], 239 [M–CH_2CH_2OH, 2], 207 [M–Ph, 100], 105 [$PhCO^+$,64]. IR (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3294 (OH), 2954, 2934, 2874 (C–H), 1096, 1025 (C–O), 768, 746 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.39 (dq, J = 12.8/2.3 Hz, 1H, 5-H_{eq}), 1.76–1.85 (m, 1H 5-H_{ax}), 1.88–2.01 (m, 2H, CH_2–CH_2–OH), 2.14 (dd, J = 6.1/4.7 Hz, 1H, CH_2–CH_2–OH), 3.90–3.96 (m, 2H, CH_2–CH_2–OH), 4.04 (dt, J = 11.6/2.5 Hz, 1H, 6-H_{ax}), 4.08 (td, J = 11.6/2.1 Hz, 1H, 6-H_{eq}), 4.12–4.20 (m, 1H, 4-H_{ax}), 7.17–7.30 (m, 4H, H_{arom}), 7.36–7.48 (m, 4H, H_{arom}), 7.53–7.54 (m, 2H, H_{arom}).

5.1.11. *trans-2-(2-Ethyl-2-phenyl-1,3-dioxan-4-yl)ethan-1-ol (**17**)*

Propiophenone dimethyl acetal **15** (324.5 mg, 1.8 mmol) and *p*-toluenesulfonic acid (20 mg, 0.1 mmol) were added to a solution of pentane-1,3,5-triol (**8**, 115 mg, 0.9 mmol) in THF (10 mL). The mixture was heated to reflux for 12 h. The mixture was concentrated in vacuo, the residue was dissolved in Et_2O and the solution was extracted with a saturated solution of $NaHCO_3$ (5 mL). The Et_2O layer was dried over $MgSO_4$, evaporated in vacuo and the residue was purified by fc (4 cm, 15 cm, petroleum ether:EtOAc = 6:4, 10 mL, R_f = 0.36). Colorless oil, yield 150 mg (70%). $C_{14}H_{20}O_3$ (236.4). Anal. calcd. C 71.16, H 8.53; found C 70.99, H 8.25. MS (CI): m/z (%) = 237 [MH, 100], 135 [$PhCOC_2H_5 + H^+$, 54]. EA: IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3420 (OH), 2942, 2877 (C–H), 1166, 1099 (C–O), 757, 736 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.81 (t, J = 7.4 Hz, 3H, CH_2–CH_3), 1.27 (dq, J = 12.8/2.4 Hz, 1H, 5-H_{eq}), 1.66–1.90 (m, 3H, CH_2–CH_2–OH and 5-H_{ax}), 1.75 (q, J = 7.4 Hz, 2H, CH_2–CH_3), 2.55 (s broad, 1H, CH_2–CH_2–OH), 3.80 (td, J = 12.2/2.4 Hz, 1H, 6-H_{ax}), 3.85–3.90 (m, 1H, 6-H_{eq}), 3.89 (t, J = 5.4 Hz, 2H, CH_2–CH_2–OH), 3.92–4.00 (m, 1H, 4-H_{ax}), 7.28–7.33 (m, 1H, H_{arom}), 7.36–7.43 (m, 4H, H_{arom}).

5.1.12. *[2-(2,2-Diphenyl-1,3-dioxan-4-yl)ethyl] p-toluenesulfonate (**18**)*

A cold solution of *p*-toluenesulfonyl chloride (260 mg, 1.4 mmol) in CH_2Cl_2 (10 mL) was added slowly to a cold solution of alcohol **16** (200 mg, 0.70 mmol) and pyridine (0.6 mL, 0.8 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 4 h at rt. CH_2Cl_2 was evaporated in vacuo and the residue was purified by fc (2 cm, 15 cm, petroleum ether:EtOAc = 7:3, 5 mL, R_f = 0.46). Colorless solid, mp 108 °C, yield 245 mg (79%). $C_{25}H_{26}O_5S$ (438.5). Anal. calcd. C 68.47, H 5.97, S 7.31; found C 68.24, H 5.88, S 6.94. MS (EI): m/z (%) = 438 [M, 3], 361 [M–Ph, 100], 155 [tos, 9], 105 [PhCO, 70]. IR (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2956, 2892 (C–H), 1094, 1019 (C–O), 780, 747 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.34 (dq, J = 12.8/2.4 Hz, 1H, 5-H_{eq}), 1.82 (dtd, J = 12.8/11.6/5.7 Hz, 1H, 5-H_{ax}), 1.90–1.97 (m, 2H, CH_2–CH_2–Otos), 2.45 (s, 3H, –Ph–CH_3), 3.97 (td, J = 11.6/2.4 Hz, 1H, 6-H_{ax}), 4.02–4.12 (m, 2H, 4-H_{ax} and 6-H_{eq}), 4.24 (dt, J = 9.1/5.2 Hz, 1H, CH_2–CH_2–Otos), 4.50 (ddd, J = 9.7/5.2/4.6 Hz, 1H, CH_2–CH_2–Otos), 7.16–7.31 (m, 4H, H_{arom}), 7.33–7.51 (m, 8H, H_{arom}, 3-H_{PhCH3} and 5-H_{PhCH3}), 7.48 (d, J = 8.2 Hz, 2H, 2-H_{PhCH3} and 6-H_{PhCH3}).

5.1.13. *trans-[2-(2-Ethyl-2-phenyl-1,3-dioxan-4-yl)ethyl] p-toluenesulfonate (**19**)*

A cold solution of *p*-toluenesulfonyl chloride (1.3 g, 7.0 mmol) in CH_2Cl_2 (5 mL) was added slowly to a cold solution of alcohol **17** (1.0 g, 4.2 mmol) and pyridine (5.7 mL, 8 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for 2 h at 0 °C and for 12 h at rt. CH_2Cl_2 was evaporated in vacuo and the residue was purified by fc (3 cm, 15 cm, petroleum ether:EtOAc = 7:3, 10 mL, R_f = 0.39). Colorless solid, mp 80 °C, yield 900 mg (56%). $C_{21}H_{26}O_5S$ (390.5). Anal. calcd. C 64.59, H 6.71, S 8.21; found C 64.58, H 6.62, S 7.95. MS (EI): m/z (%) = 390 [M, 0.5], 361 [M–C_2H_5, 100], 155 [tos, 16], 105 [PhCO, 54]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 2968, 2886 (C–H); 1356, 1188 (SO_2): 1090, 1016 (C–O); 765, 726 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.75 (t, J = 7.6 Hz, 3H,

CH_2–CH_3), 1.22 (dq, J = 12.8/2.4 Hz, 1H, 5-H_{eq}), 1.66 (q, J = 7.6 Hz, 2H, CH_2–CH_3), 1.59–1.73 (m, 1H, 5-H_{ax}), 1.79–1.86 (m, 2H, CH_2–CH_2–Otos), 2.45 (s, 3H, Ph–CH_3), 3.78 (td, J = 12.5/2.4 Hz, 1H, 6-H_{ax}), 3.81 (ddd, J = 12.5/5.4/1.8 Hz, 1H, 6-H_{eq}), 3.76–3.87 (m, 1H, 4-H_{ax}), 4.19 (dt, J = 9.7/5.1 Hz, 1H, CH_2–CH_2–Otos), 4.38 (ddd, J = 9.7/7.6/6.3 Hz, 1H, CH_2–CH_2–Otos), 7.26–7.41 (m, 7H, H_{arom}, 3-H_{PhCH3} and 5-H_{PhCH3}), 7.81 (d, J = 8.2 Hz, 2H, 2-H_{PhCH3} and 6-H_{PhCH3}). ^{1}H NMR (C_6D_6): δ (ppm) = 0.52 (dq, J = 12.2/2.1 Hz, 1H, 5-H_{eq}), 0.90 (t, J = 7.3 Hz, 3H, CH_2–CH_3), 1.31 (qd, J = 12.5/5.2 Hz, 1H, 5-H_{ax}), 1.38–1.47 (m, 2H, CH_2–CH_2–Otos), 1.81 (s, 3H, Ph–CH_3), 1.86 (q, J = 7.3 Hz, 2H, CH_2–CH_3), 3.43 (td, J = 11.5/2.7 Hz, 1H, 6-H_{ax}), 3.50–3.63 (m, 2H, 4-H_{ax} and 6-H_{eq}), 3.98 (dt, J = 10.1/5.2 Hz, 1H, CH_2–CH_2–Otos), 4.34 (ddd, J = 10.1/7.6/5.5 Hz, 1H, CH_2–CH_2–Otos), 6.69 (d, J = 7.9 Hz, 2H, 3-H_{PhCH3} and 5-H_{PhCH3}), 7,13–7.18 (m, 1H, H_{arom}), 7.31 (t, J = 7.6 Hz, 2H, H_{arom}), 7.44 (d, J = 7.1 Hz, 2H, H_{arom}), 7.78 (d, J = 8.2 Hz, 2H, 2-H_{PhCH3} and 6-H_{PhCH3}).

5.1.14. 4-(2-Azidoethyl)-2,2-diphenyl-1,3-dioxane (**20**)

A mixture of tosylate **18** (80 mg, 0.18 mmol) and NaN_3 (113 mg, 1.8 mmol) in DMF (5 mL) was heated to reflux for 2 h. After cooling down DMF was evaporated in vacuo and the residue was purified by fc (2 cm, 15 cm, petroleum ether:EtOAc = 7:3, 5 mL, R_f = 0.60). Colorless oil, yield 38 mg (69%). $C_{18}H_{19}N_3O_2$ (309.4). Anal. calcd. C 69.88, H 6.19, N 13.60; found C 69.40, H 6.14, N 13.94. MS (EI): m/z (%) = 309 [M, 12], 232 [M–Ph, 100], 182 [$(Ph)_2CO$, 31]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 2951, 2875 (C–H), 2091 (N_3), 1097, 1023 (C–O), 762, 746 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.42 (dq, J = 12.8/2.4 Hz, 1H, 5-H_{eq}), 1.78 (dddd, J = 12.8/11.9/10.1/3.4 Hz, 1H, 5-H_{ax}), 1.83–2.02 (m, 2H, CH_2–CH_2–N_3), 3.63 (t, J = 7.2 Hz, 2H, –CH_2–CH_2–N_3), 4.03 (td, J = 11.3/2.4 Hz, 1H, 6-H_{ax}), 4.05–4.13 (m, 2H, 4-H_{ax} and 6-H_{eq}), 7.17–7.32 (m, 4H, H_{arom}), 7.38–7.62 (m, 4H, H_{arom}), 7.80–7.83 (m, 2H, H_{arom}).

5.1.15. trans-4-(2-Azidoethyl)-2-ethyl-2-phenyl-1,3-dioxane (**21**)

A mixture of tosylate **19** (43 mg, 0.26 mmol) and NaN_3 (113 mg, 1.8 mmol) in DMF (5 mL) was heated to reflux for 2 h. After cooling down DMF was evaporated in vacuo. The residue was purified by fc (2 cm, 15 cm, petroleum ether:EtOAc = 9:1, 5 mL, R_f = 0.41). Colorless oil, yield 45 mg (65%). $C_{14}H_{19}N_3O_2$ (261.3). HRMS (CI): calcd. for $C_{12}H_{14}N_3O_2$ 232.1084; found 232.1086. Anal. calcd. C 64.35, H 7.33, N 16.08; found C 64.23, H 7.56, N 15.82. MS (CI): m/z (%) = 262 [MH^+, 100], 232 [M–C_2H_5, 40], 184 [M–Ph, 6], 105 [PhCO, 1]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 2973, 2876 (C–H), 2093 (N_3), 1090, 1025 (C–O), 756, 745 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.78 (t, J = 7.4 Hz, 3H, CH_2–CH_3), 1.26 (dq, J = 12.8/2.4 Hz, 1H, 5-H_{eq}), 1.67–1.86 (m, 3H, 5-H_{ax} and CH_2–CH_2–N_3), 1.72 (q, J = 7.4 Hz, 2H, CH_2–CH_3), 3.50–3.53 (m, 2H, CH_2–CH_2–N_3), 3.77 (td, J = 11.6/2.7 Hz, 1H, 6-H_{ax}), 3.75–3.82 (m, 1H, 4-H_{ax}), 3.85 (ddd, J = 11.6/5.5/1.8 Hz, 1H, 6-H_{eq}), 7.24–7.41 (m, 5H, H_{arom}).

5.1.16. 2-(2,2-Diphenyl-1,3-dioxan-4-yl)ethan-1-amine (**22a**)

A mixture of azide **20** (85 mg, 0.2 mmol) and Pd/C (51 mg, 5%) in EtOAc (3 mL) was stirred under a H_2 atmosphere (balloon) for 12 h at rt. The mixture was filtered over Celite® and the filtrate was concentrated in vacuo. Pale yellow oil, yield 52 mg (82%). $C_{18}H_{21}NO_2$ (283.4). HRMS: calcd. for $C_{18}H_{21}NO_2$ 283.1578; found 283.1572. MS (EI): m/z (%) = 283 [M, 5], 239 [M–$CH_2CH_2NH_2$, 4], 206 [M^+–Ph, 36], 105 [PhCO, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3420 (N–H); 2928, 2855 (C–H); 1728 (N–H); 1096, 1024 (C–O); 749, 712 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.39 (dq, J = 12.8/2.1 Hz, 1H, 5-H_{eq}), 1.66 (dddd, J = 12.7/11.2/10.3/3.6 Hz, 1H, 5-H_{ax}), 1.73 (s broad, 2H, –NH_2), 1.82–1.98 (m, 2H, CH_2–CH_2–NH_2), 2.98 (dt, J = 12.5/7.3 Hz, 1H, CH_2–CH_2–NH_2), 3.05 (ddd, J = 12.5/7.9/6.1 Hz, 1H, CH_2–CH_2–NH_2), 3.95–4.09 (m, 2H, 4-H_{ax} and 6-H_{eq}), 4.02 (td, J = 11.3/2.1 Hz, 1H, 6-H_{ax}), 7.18–7.30 (m, 4H, H_{arom}), 7.36–7.41 (m, 2H, H_{arom}), 7.49–7.54 (m, 4H, H_{arom}).

5.1.17. 2-(2,2-Diphenyl-1,3-dioxan-4-yl)-N-methylethan-1-amine (**22b**)

Tosylate **18** (100 mg, 0.23 mmol) was dissolved in an ethanolic solution of methylamine (8 M, 5 mL, 40 mmol) and the mixture was heated to reflux for 12 h. After cooling down it was concentrated in vacuo. The pale yellow residue was dissolved in CH_2Cl_2 (10 mL), the mixture was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by fc (2 cm, 15 cm, CH_2Cl_2:MeOH = 8:1, 2 mL, R_f = 0.16). Pale yellow oil, yield 28 mg (41%). $C_{19}H_{23}NO_2$ (297.4). HRMS: calcd. for $C_{19}H_{23}NO_2$ 297.1729; found 297.1728. MS (EI): m/z (%) = 297 [M, 1], 220 [M–Ph, 5], 115 [$O(CH_2)_2CH(CH_2)_2NHCH_3$, 100], 105 [PhCO, 56]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3328 (N–H); 2953, 2875 (C–H), 2732 ($NHCH_3$), 1098, 1020 (C–O), 768, 749 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.40 (dq, J = 12.8/2.4 Hz, 1H, 5-H_{eq}), 1.92 (dddd, J = 12.8/11.9/11.2/5.7 Hz, 1H, 5-H_{ax}), 2.01–2.12 (m, 2H, CH_2–CH_2–$NHCH_3$), 2.63 (s, 3H, $NHCH_3$), 3.04 (ddd, J = 11.9/6.4/5.5 Hz, 1H, CH_2–CH_2–$NHCH_3$), 3.20 (ddd, J = 11.9/6.1/5.5 Hz, 1H, CH_2–CH_2–$NHCH_3$), 3.99 (td, J = 11.5/2.4 Hz, 1H, 6-H_{ax}), 4.02–4.09 (m, 2H, 4-H_{ax} and 6-H_{eq}), 7.19–7.31 (m, 4H, H_{arom}), 7.37–7.48 (m, 6H, H_{arom}). A signal for the N*H*-proton is not seen in the spectrum. As described for the preparation of **13d**·HCl the hydrochloride **22b**. HCl was prepared from **22b** (20 mg, 0.07 mmol). Colorless solid, mp 164 °C, yield 10 mg (42%).

5.1.18. 2-(2,2-Diphenyl-1,3-dioxan-4-yl)-N,N-dimethylethan-1-amine (**22c**)

Tosylate **18** (100 mg, 0.23 mmol) was dissolved in an ethanolic solution of dimethylamine (5.6 M, 7 mL, 39.2 mmol) and the mixture was heated to reflux for 4 h. After cooling down dimethylamine and ethanol were evaporated in vacuo. The yellow residue was dissolved in CH_2Cl_2 (10 mL) and the mixture was extracted with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was purified by fc (3 cm, 15 cm, CH_2Cl_2:MeOH = 8:1, 2 mL, R_f = 0.21). Pale yellow oil, yield 57 mg (80%). $C_{20}H_{25}NO_2$ (311.4). HRMS: calcd. for $C_{20}H_{25}NO_2$ 311.1893; found 311.1893. MS (EI): m/z (%) = 311 [M, 1], 234 [M–Ph, 2], 176 [M–Ph–CH_2– $N(CH_3)_2$, 2],105 [PhCO, 31], 58 [–CH_2–$N(CH_3)_2$, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 2947, 2869 (C–H), 2815, 2763 ($N(CH_3)_2$), 1097, 1025 (C–O), 760, 745 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.41 (dq, J = 12.8/2.4 Hz, 1H, 5-H_{eq}), 1.75 (dtd, J = 12.8/11.9/2.4 Hz, 1H, 5-H_{ax}), 1.82–1.98 (m, 2H, CH_2–CH_2–$N(CH_3)_2$), 2.34 (s, 6H, $N(CH_3)_2$), 2.58 (ddd, J = 11.9/9.1/6.1 Hz, 1H, CH_2–CH_2–$N(CH_3)_2$), 2.68 (ddd, J = 11.9/9.4/5.5 Hz, 1H, CH_2–CH_2–$N(CH_3)_2$), 3.99 (td, J = 11.3/2.4 Hz, 1H, 6-H_{ax}), 4.03–4.16 (m, 2H, 4-H_{ax} and 6-H_{eq}), 7.15–7.30 (m, 4H, H_{arom}), 7.35–7.41 (m, 2H, H_{arom}), 7.49–7.54 (m, 4H, H_{arom}). As described for the preparation of **13d**·HCl the hydrochloride **22c**. HCl was prepared from **22c** (57 mg, 0.20 mmol). Colorless solid, mp 94 °C, yield 46 mg (65%).

5.1.19. N-Benzyl-2-(2,2-diphenyl-1,3-dioxan-4-yl)ethan-1-amine (**22d**)

A mixture of tosylate **18** (200 mg, 0.45 mmol) and freshly distilled benzylamine (0.10 mL, 0.9 mmol) in toluene (5 mL) was heated to reflux for 5 h. After cooling down excess of benzylamine and toluene was evaporated in vacuo. The yellow residue was dissolved in CH_2Cl_2 (10 mL) and the mixture was extracted with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by fc (2 cm, 15 cm, EtOAc, 5 mL, R_f = 0.22). Pale yellow oil, yield 110 mg (65%). $C_{25}H_{27}NO_2$ (373.5). Anal. calcd. C 80.39, H 7.29, N 3.75; found C 79.90, H 7.08, N 3.56. MS (EI): m/z (%) = 373 [M, 5], 296 [M–Ph, 9], 191 [O–$(CH_2)_2$–CH–$(CH_2)_2$–NH–Bn, 90] 105 [PhCO, 75], 91 [tropylium, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3325

(N–H), 2952, 2876 (C–H); 2816 (CH–NHBn); 1101, 1026 (C–O); 766, 744 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.37 (dq, J = 13.1/2.1 Hz, 1H, 5-H_{eq}), 1.74 (dtd, J = 13.1/11.3/4.1 Hz, 1H, 5-H_{ax}), 1.86–1.93 (m, 2H, CH_2–CH_2–NHBn), 2.93 (td, J = 6.7/1.5 Hz, 2H, CH_2–CH_2–NHBn), 3.84 (d, J = 14.0 Hz, 1H, NH–CH_2–Ph), 3.85 (d, J = 14.3 Hz, 1H, NH–CH_2–Ph), 4.00 (td, J = 11.3/2.4 Hz, 1H, 6-H_{ax}), 4.02–4.09 (m, 2H, 4-H_{ax} and 6-H_{eq}), 7.14–7.28 (m, 6H, H_{arom}), 7.31–7.38 (m, 6H, H_{arom}), 7.46–7.50 (m, 3H, H_{arom}). A signal for the N*H*-proton is not seen in the spectrum. As described for the preparation of **13d**·HCl, the hydrochloride **22d**·HCl was prepared from **22d** (100 mg, 0.27 mmol). Colorless solid, mp 157 °C, yield 54 mg (49%).

5.1.20. *trans-2-(2-Ethyl-2-phenyl-1,3-dioxan-4-yl)ethan-1-amine (**23a**)*

A mixture of azide **21** (40 mg, 0.15 mmol), Pd/C (5%, 16 mg) and methanol (3 mL) was stirred under a H_2 atmosphere (balloon) for 1 h at rt. The mixture was filtered over Celite® and the filtrate was concentrated in vacuo. Pale yellow oil, yield 32.6 mg (93%). $C_{14}H_{21}NO_2$ (235.3). HRMS (EI): calcd. for $C_{14}H_{21}NO_2$ 235.1572; found 235.1572. MS (EI): m/z (%) = 235 [M, 6.11]; 206 [M–C_2H_5, 52], 105 [PhCO, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3355 (NH_2), 2940, 2871 (C–H), 1663 (NH_2), 1092, 1025 (C–O), 756, 727 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.79 (t, J = 7.5 Hz, 3H, CH$_2$–CH_3), 1.25 (dq, J = 12.8/2.1 Hz, 1H, 5-H_{eq}), 1.56 (dtd, J = 12.5/11.2/3.9 Hz, 1H, 5-H_{ax}), 1.64–1.81 (m, 4H, CH_2–CH$_2$–NH_2), 1.73 (q, J = 7.5 Hz, 2H, CH_2–CH$_3$), 2.87 (dt, J = 12.5/7.0 Hz, 1H, CH$_2$–CH_2–NH$_2$), 2.94 (ddd, J = 12.5/7.3/6.4 Hz, 1H, CH$_2$–CH_2–NH$_2$), 3.75–3.91 (m, 2H, 4-H_{ax} and 6-H_{eq}), 3.76 (td, J = 11.2/2.4 Hz, 1H, 6-H_{ax}), 7.25–7.32 (m, 1H, H_{arom}), 7.33–7.41 (m, 4H, H_{arom}).

5.1.21. *trans-2-(2-Ethyl-2-phenyl-1,3-dioxan-4-yl)-N-methylethan-1-amine (**23b**)*

Tosylate **19** (100 mg, 0.26 mmol) was dissolved in an ethanolic solution of methylamine (8.0 M, 5 mL, 40 mmol) and the mixture was heated to reflux for 3 h. After cooling down the mixture was concentrated in vacuo. The yellow residue was dissolved in CH_2Cl_2 (10 mL) and the mixture was extracted with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by fc (2 cm, 15 cm, CH_2Cl_2:MeOH = 8:1, 3 mL, R_f = 0.1). Pale yellow oil, yield 30 mg (44%). $C_{15}H_{23}NO_2$ (249.4). HRMS (CI): calcd. for $C_{15}H_{24}NO_2$ 250.1806; found 250.1807. MS (EI): m/z (%) = 249 [M^+, 1], 220 [M^+–C_2H_5, 63], 172 [M^+–Ph, 51], 105 [PhCO, 20], 77 [Ph, 10]. MS (CI): m/z (%) = 250 [MH^+, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3325 (N–H), 2953, 2875 (C–H), 2732 (NHCH$_3$), 1098, 1020 (C–O), 768, 749 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.79 (t, J = 7.3 Hz, 3H, CH$_2$–CH_3), 1.25 (dq, J = 12.8/1.9 Hz, 1H, 5-H_{eq}), 1.50 (s broad, 1H, N*H*CH$_3$), 1.61 (dddd, J = 12.5/11.9/11.5/5.2 Hz, 1H, 5-H_{ax}), 1.67–1,86 (m, 2H, CH_2–CH$_2$–NHCH$_3$), 1.72 (q, J = 7.3 Hz, 2H, CH_2–CH$_3$), 2.46 (s, 3H, CH$_2$–CH$_2$–NHCH_3), 2.72 (dt, J = 11.5/7.1 Hz, 1H, CH$_2$–CH_2–NHCH$_3$), 2.78 (ddd, J = 11.5/7.6/6.1 Hz, 1H, CH$_2$–CH_2–NHCH$_3$), 3.73 (td, J = 11.5/2.1 Hz, 1H, 6-H_{ax}), 3.83 (ddd, J = 11.5/5.5/1.5 Hz, 1H, 6-H_{eq}), 3.69–3.78 (m, 1H, 4-H_{ax}), 7.25–7.40 (m, 5H, H_{arom}). Direct fc purification of the product without extracting the mixture with a saturated solution of $NaHCO_3$ led to a salt of amine **23b** and *p*-toluenesulfonic acid. Colorless solid, (R_f = 0.14), mp 134 °C, yield 78 mg (74%). Anal. calcd. C 62.09, H 7.41, N 3.32, S 7.60; found C 61.84, H 7.40, N 3.22, S 7.32. As described for the preparation of **13d**·HCl, the hydrochloride **23b**·HCl was prepared from **23b** (15 mg, 0.06 mmol). Colorless solid, mp 148 °C, yield 7.0 mg (41%).

5.1.22. *trans-[2-(2-Ethyl-2-phenyl-1,3-dioxan-4-yl)]-N,N-dimethylethan-1-amine (**23c**)*

Tosylate **19** (102 mg, 0.26 mmol) was dissolved in an ethanolic solution of dimethylamine (5.6 M, 5 mL, 28 mmol) and the mixture was stirred for 12 h at rt. The mixture was concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (10 mL) and the solution was extracted with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by fc (2 cm, 15 cm, CH_2Cl_2:MeOH = 8:1, 3 mL, R_f = 0.15). Pale yellow oil, yield 30 mg (44%). $C_{16}H_{25}NO_2$ (263.4). HRMS (EI): calcd. for $C_{16}H_{25}NO_2$ 263.1886; found 263.1885. MS (EI): m/z (%) = 263 [M, 0.6], 234 [M–C_2H_5, 1], 186 [M–Ph, 4], 129 [O–(CH$_2$)$_2$–CH–(CH$_2$)$_2$–N(CH$_3$)$_2$, 33], 58 [–CH$_2$–N(CH$_3$)$_2$, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 2968, (C–H), 2715 (N(CH$_3$)$_2$), 1026, 1011 (C–O), 756, 726 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.76 (t, J = 7.6 Hz, 3H, CH$_2$–CH_3), 1.26 (dq, J = 12.8/1.9 Hz, 1H, 5-H_{eq}), 1.58–1.83 (m, 3H, CH_2–CH$_2$–N(CH_3)$_2$ and 5-H_{ax}), 1.70 (q, J = 7.6 Hz, 2H, CH_2–CH$_3$), 2.30 (s, 6H, N(CH_3)$_2$), 2.46 (ddd, J = 11.9/9.4/6.1 Hz, 1H, CH$_2$–CH_2–N(CH$_3$)$_2$), 2.57 (ddd, J = 11.9/9.7/5.5 Hz, 1H, CH$_2$–CH_2–N(CH$_3$)$_2$), 3.71 (td, J = 11.3/2.4 Hz, 1H, 6-H_{ax}), 3.81 (ddd, J = 11.3/5.5/1.8 Hz, 1H, 6-H_{eq}), 3.69–3.75 (m, 1H, 4-H_{ax}), 7.22–7.38 (m, 5H, H_{arom}). As described for the preparation of **13d**·HCl the hydrochloride **23c**· HCl was prepared from **23c** (20 mg, 0.06 mmol). Colorless solid, mp 165 °C, yield 7.0 mg (41%).

5.1.23. *trans-N-Benzyl-2-(2-ethyl-2-phenyl-1,3-dioxan-4-yl)ethan-1-amine (**23d**)*

A solution of tosylate **19** (300 mg, 0.78 mmol) and freshly distilled benzylamine (0.10 mL, 1.4 mmol) in toluene (10 mL) was heated to reflux for 5 h. After cooling down the mixture was concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (10 mL) and the solution was extracted with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was purified by fc (2 cm, 15 cm, EtOAc, 10 mL, R_f = 0.28). Pale yellow oil, yield 180 mg (71%). $C_{21}H_{27}NO_2$ (325.5). HRMS (EI): calcd. for $C_{21}H_{27}NO_2$ 325.2042; found 325.2041. MS (EI): m/z (%) = 325 [M, 0.8]; 191 [O–(CH$_2$)$_2$–CH–(CH$_2$)$_2$–NHBn, 100], 120 [CH$_2$–NHBn, 81], 106 [NHBn, 54], 91 [tropylium, 95]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3456 (NH), 2926 (C–H), 1489 (NH); 1092 (C–O); 756, 699 (ArC–H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.79 (t, J = 7.6 Hz, 3H, CH$_2$–CH_3), 1.25 (dq, J = 12.8/2.4 Hz, 1H, 5-H_{eq}), 1.61–1.88 (m, 3H, CH_2–CH$_2$–NHBn and 5-H_{ax}), 1.73 (q, J = 7.6 Hz, 2H, CH_2–CH$_3$), 1.95 (s broad, 1H, CH$_2$–CH$_2$–N*H*Bn), 2.86 (td, J = 6.7/2.9 Hz, 2H, CH$_2$–CH_2–NHBn), 3.73–3.90 (m, 2H, 4-H_{ax} and 6-H_{eq}), 3.77 (td, J = 12.2/2.4 Hz, 1H, 6-H_{ax}), 3.86 (d, J = 15.8 Hz, 1H, –NH–CH_2–Ph), 3.87 (d, J = 15.8 Hz, 1H, NH–CH_2–Ph) 7.26–7.39 (m, 10H, H_{arom}). As described for the preparation of **13d**·HCl the hydrochloride **23d**·HCl was prepared from **23d** (50 mg, 0.15 mmol). Colorless solid, mp 155 °C, yield 26 mg (48%).

5.1.24. *Adamantan-2-one dimethyl acetal (**25**) [31]*

A mixture of adamantan-2-one (**24**, 2.0 g, 13.3 mmol), methanol (10 mL), trimethyl ortho formate (1.6 mL, 12 mmol) and *p*-toluenesulfonic acid (100 mg, 0.5 mmol) was heated to reflux for 12 h. The solvent was removed in vacuo, the residue was dissolved in Et_2O (5 mL) and the mixture was extracted with a saturated solution of $NaHCO_3$ (5×). The Et_2O layer was dried ($MgSO_4$) and concentrated in vacuo. Colorless solid, mp 184 °C, yield 2.1 g (82%). $C_{12}H_{20}O_2$ (196.3). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.58–1.65 (m, 6H, H_{Adam}), 1.79–1.90 (m, 6H, H_{Adam}), 1.97–2.10 (m, 2H, 1-H_{Adam} and 3-H_{Adam}), 3.15 (s, 6H, (OCH$_3$)$_2$). For further analytical data see Ref. [31].

5.1.25. *2-(Spiro[adamantan-2,2′-[1,3]dioxan]-4′-yl)ethanol (**26**)*

A mixture of triol **8** (330 mg, 2.7 mmol), acetal **25** (580 mg, 3 mmol), THF (10 mL) and *p*-toluenesulfonic acid (10 mg, 0.16 mmol) was heated to reflux for 12 h. The solvent was removed in vacuo, the residue was dissolved in Et_2O and the mixture was extracted with a saturated solution of $NaHCO_3$ (5×). The Et_2O layer was dried ($MgSO_4$), concentrated in vacuo and the residue was purified by fc (2 cm, petroleum ether:EtOAc = 6:4, 5 mL, R_f = 0.43).

Colorless solid, mp 54 °C, yield 396 mg (52%). $C_{15}H_{24}O_3$ (252.35). Anal. calcd. C 71.40, H 9.59; found C 71.32, H 9.43. MS (EI): *m/z* (%) = 252 [M, 34], 207 [M−CH_2CH_2OH, 73], 150 [$C_{10}H_{14}O$, 100]. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3443 (OH); 2932 (C−H); 1099 (C−O). ^1H NMR ($CDCl_3$): δ (ppm) = 1.40 (dtd, *J* = 13.1/2.7/1.5 Hz, 1H, 5-H_{eq}), 1.54–1.84 (m, 14H, 5-H_{ax}, CH_2−CH_2−OH and 11H_{Adam}), 1.90–2.08 (m, 2H, H_{Adam}), 2.55 (dd, *J* = 5.8/4.8 Hz, 1H, CH_2−CH_2−O*H*), 2.81 (s broad, 1H, 3-H_{Adam}), 3.75 (ddd, *J* = 12.2/5.5/1.5 Hz, 1H, 6-H_{eq}), 3.76–3.83 (m, 2H, CH_2−CH_2−OH), 3.98 (td, *J* = 12.2/2.7 Hz, 1H, 6-H_{ax}), 4.14 (ddt, *J* = 11.9/4.8/2.7 Hz, 1H, 4-H_{ax}).

5.1.26. [2-(Spiro[adamantan-2,2′-[1,3]dioxan]-4′-yl)ethyl] p-toluenesulfonate (**27**)

A cold solution of *p*-toluenesulfonyl chloride (514 mg, 2.7 mmol) in CH_2Cl_2 (5 mL) was added slowly to a cold solution of alcohol **26** (350 mg, 1.4 mmol) and NEt_3 (1.4 mL, 1.4 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for 2 h at 0 °C and for 12 h at rt. Then the mixture was concentrated in vacuo and the residue was purified by fc (2 cm, 15 cm, petroleum ether:EtOAc = 7:3, 10 mL, R_f = 0.35). Colorless solid, mp 93 °C, yield 521 mg (92%). $C_{22}H_{30}O_5S$ (406.5). Anal. calcd. C 64.99, H 7.44, S 7.88; found C 64.78, H 7.39, S 8.03. MS (EI): *m/z* (%) = 406 [M, 5], 207 [M−CH_2CH_2Otos, 25], 199 [−CH_2CH_2Otos, 86]. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2908 (C−H), 1360, 1188 (SO_2), 1097, 1063 (C−O), 778, 721 (ArC−H). ^1H NMR ($CDCl_3$): δ (ppm) = 1.38 (dtd, *J* = 12.8/2.7/1.5 Hz, 1H, 5-H_{eq}), 1.47–1.90 (m, 15H, 5-H_{ax}, CH_2−CH_2−Otos and 12H_{Adam}), 2.02–2.05 (m, 1H, 1-H_{Adam}), 2.44 (s, 3H, $PhCH_3$), 2.71 (s broad, 1H, 3-H_{Adam}), 3.76 (ddd, *J* = 11.9/5.8/1.5 Hz, 1H, 6-H_{eq}), 3.93 (td, *J* = 11.9/2.7 Hz, 1H, 6-H_{ax}), 3.95–4.03 (m, 1H, 4-H_{ax}), 4.11–4.19 (m, 1H, CH_2−CH_2−Otos), 4.20 (ddd, *J* = 10.3/9.4/4.8 Hz, 1H, CH_2−CH_2−Otos), 7.34 (d, *J* = 7.9 Hz, 2H, 3-H_{PhCH3} and 5-H_{PhCH3}), 7.78 (d, *J* = 8.2 Hz, 2H, 2-H_{PhCH3} and 6-H_{PhCH3}). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.6 (1C, O−SO_2−PhCH_3), 27.1, 27.46, 31.26, 32.94, 33.03, 33.50, 33.55, 5.98, 36.31, 36.57, 39.2 (11C, CH_2−CH_2−O, C-5$_{Diox}$ and 9C_{Adam}), 58.2 (1C, C-6$_{Diox}$), 62.9 (1C, C-4$_{Diox}$), 66.8 (1C, CH_2−CH_2−O), 100.4 (1C, C-2$_{Diox}$), 124.5 (2C, C-3$_{arom}$ and C-5$_{arom}$), 126.2 (2C, C-2$_{arom}$ and C-6$_{arom}$), 133.1 (1C, C-4$_{arom}$), 144.7 (1C, C-1$_{arom}$). The assignment of the signals was supported by HETCOR spectra.

5.1.27. 4′-(2-Azidoethyl)spiro[adamantan-2,2′-[1,3]dioxane] (**28**)

Tosylate **27** (250 mg, 1.62 mmol) was dissolved in DMF (10 mL) and after addition of NaN_3 (313 mg, 5 mmol) the mixture was heated to reflux for 2 h. After cooling down it was concentrated in vacuo. The residue was purified by fc (2 cm, 15 cm, petroleum ether:EtOAc = 8:2, 5 mL, R_f = 0.74). Colorless oil, yield 150 mg (53%). $C_{15}H_{23}N_3O_2$ (277.4). HRMS (EI): calcd. for $C_{15}H_{23}N_3O_2$ 277.1787; found 277.1790. MS (CI): *m/z* (%) = 278 [MH, 19], 151 [$C_{10}H_{15}O^+$, 17]. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2909 (C−H), 2090 (N_3), 1099 (C−O). ^1H NMR ($CDCl_3$): δ (ppm) = 1.42 (dtd, *J* = 12.8/2.9/1.5 Hz, 1H, 5-H_{eq}), 1.53–1.83 (m, 15H, 5-H_{ax}, CH_2−CH_2−N_3, 12H_{Adam}), 1.97–2.05 (m, 1H, 1′-H_{Adam}), 2,76 (s broad, 1H, 3′-H_{Adam}), 3.36–3.50 (m, 2H, CH_2−CH_2−N_3), 3.78 (ddd, *J* = 11.7/5.5/1.5 Hz, 1H, 6-H_{eq}), 3.93–4.03 (m, 1H, 4-H_{ax}), 3.96 (td, *J* = 11.7/2.9 Hz, 1H, 6-H_{ax}).

5.1.28. 2-(Spiro[adamantan-2,2′-[1,3]dioxan]-4′-yl)ethan-1-amine (**29a**)

A mixture of azide **28** (80 mg, 0.25 mmol), Pd/C (5%, 23 mg) and methanol (3 mL) was stirred under a H_2 atmosphere (balloon) for 1 h at rt. The mixture was filtered over Celite® and the filtrate was concentrated in vacuo. Pale yellow oil, yield 70 mg (97%). $C_{15}H_{25}NO_2$ (251.36). HRMS (EI): calcd. for $C_{15}H_{25}NO_2$ 251.1884; found 251.1885. MS (EI): *m/z* (%) = 251 [M, 0.5], 101 [−O$(CH_2)_2$CH$(CH_2)_2NH_2$, 100]. IR (film): $\tilde{\nu}$ (cm^{-1}) = 3362 (NH_2), 2907 (C−H), 1062 (C−O). ^1H NMR ($CDCl_3$): δ (ppm) = 1.39 (dtd, *J* = 13.1/2.7/1.5 Hz, 1H, 5-H_{eq}), 1.52–1.85 (m, 17H, 5-H_{ax}, CH_2−CH_2−NH_2, 12H_{Adam}), 2.02–2.05 (m, 1H, 1-H_{Adam}), 2.73–2.94 (m, 3H, 3-H_{Adam} and CH_2−CH_2−NH_2), 3.78 (ddd, *J* = 11.9/5.5/1.5 Hz, 1H, 6-H_{eq}), 3.91–4.03 (m, 1H, 4-H_{ax}), 3.96 (td, *J* = 11.9/2.7 Hz, 1H, 6-H_{ax}).

5.1.29. cis-3-(2-Phenyl-1,3-dioxan-4-yl)propanenitrile (**30**)

A mixture of tosylate **11** (100 mg, 0.27 mmol) and KCN (156 mg, 2.7 mmol) in DMSO (15 mL) was heated to reflux for 5 h and then stirred for 12 h at rt. DMSO was evaporated in vacuo. The oily residue was dissolved in petroleum ether:EtOAc (9:1, 10 mL) and the mixture was washed with a saturated solution of $NaHCO_3$ (2 × 20 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo. Colorless oil, yield 40 mg (68%). $C_{13}H_{15}NO_2$ (217.3). HRMS (EI): calcd. for $C_{13}H_{15}NO_2$ 217.1098; found 217.1102. Anal. calcd. C 71.87, H 6.96, N 6.45; found C 71.44, H 7.43, N 6.17. MS (EI): *m/z* (%) = 217[M, 45], 177[M^+−CH_2CN, 22], 105 [PhCO, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 2924 (C−H), 2245 (CN), 1062 (C−O), 749, 727 (ArC−H). ^1H NMR ($CDCl_3$): δ (ppm) = 1.56 (dtd, *J* = 13.1/2.4/1.5 Hz, 1H, 5-H_{eq}), 1.84 (dddd, *J* = 13.1/11.9/11.3/5.1 Hz, 1H, 5-H_{ax}), 1.89–1.96 (m, 2H, CH_2−CH_2−CN), 2.52 (ddd, *J* = 10.6/9.1/6.4 Hz, 1H, CH_2−CH_2−CN), 2.57 (ddd, *J* = 10.6/9.4/7.6 Hz, 1H, CH_2−CH_2−CN), 3.96–4.04 (m, 1H, 4-H_{ax}), 3.98 (td, *J* = 11.9/2.4 Hz, 1H, 6-H_{ax}), 4.29 (ddd, *J* = 11.9/5.1/1.5 Hz, 1H, 6-H_{eq}), 5.53 (s, 1H, 2-H_{ax}), 7.33–7.40 (m, 3H, H_{arom}), 7.45–7.49 (m, 2H, H_{arom}).

5.1.30. 3-(2,2-Diphenyl-1,3-dioxan-4-yl)propanenitrile (**31**)

A mixture of tosylate **18** (650 mg, 1.78 mmol) and KCN (1.1 g, 17 mmol) in DMSO (15 mL) was heated to reflux for 5 h. Then excess of DMSO was evaporated in vacuo. The yellow residue was dissolved in petroleum ether:EtOAc (9:1, 10 mL) and the mixture was extracted with a saturated solution of $NaHCO_3$ (2 × 20 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo. Colorless solid, mp 135 °C, yield 421 mg (81%). $C_{19}H_{19}NO_2$ (293.4). HRMS (EI): calcd. for $C_{19}H_{19}NO_2$ 293.1412; found 293.1415. Anal. calcd. C 77.79, H 6.53, N 4.77; found C 77.74, H 6.50, N 4.66. MS (EI): *m/z* (%) = 293 [M, 5], 216 [M−Ph, 100] 182 [$(Ph)_2CO$, 6]. IR (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2925 (C−H), 2246 (CN), 1097 (C−O), 799, 745 (ArC−H). ^1H NMR ($CDCl_3$): δ (ppm) = 1.46 (dq, *J* = 13.0/2.1 Hz, 1H, 5-H_{eq}), 1.86–2.09 (m, 3H, 5-H_{ax} and CH_2−CH_2−CN), 2.67 (ddd, *J* = 11.8/6.9/5.6 Hz, 1H, CH_2−CH_2−CN), 2.76 (ddd, *J* = 11.8/7.3/5.5 Hz, 1H, CH_2−CH_2−CN), 4.05–4.13 (m, 1H, 4-H_{ax}), 4.06 (td, *J* = 11.5/2.5 Hz, 1H, 6-H_{ax}), 4.12 (dt, *J* = 11.5/1.8 Hz, 1H, 6-H_{eq}), 7.20–7.46 (m, 4H, H_{arom}), 7.41–7.46 (m, 2H, H_{arom}), 7.50–7.55 (m, 4H, H_{arom}).

5.1.31. trans-3-(2-Ethyl-2-phenyl-1,3-dioxan-4-yl)propanenitrile (**32**)

A mixture of tosylate **19** (100 mg, 0.25 mmol) and KCN (150 mg, 2.5 mmol) in DMF (5 mL) was heated to reflux for 6 h. Then DMF was evaporated in vacuo. The oily residue was purified by fc (2 cm, 15 cm, petroleum ether:EtOAc = 7:3, 2 mL, R_f = 0.55). Colorless oil, yield 33 mg (53%). $C_{15}H_{19}NO_2$ (245.3). HRMS (EI): calcd. for $C_{13}H_{14}NO_2$ 216.1026; found: 216.1024. Anal. calcd. C 73.44, H 7.81, N 5.71; found C 73.18, H 8.30, N 5.53. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 2970 (C−H), 2246 (CN), 1091 (C−O), 819, 757 (ArC−H). MS (EI): *m/z* (%) = 216 [M−C_2H_5, 100], 168 [M−Ph, 23], 105 [PhCO, 88]. MS (CI): *m/z* (%) = 246 [MH, 100]. ^1H NMR ($CDCl_3$): δ (ppm) = 0.80 (t, *J* = 7.3 Hz, 3H, CH_2−CH_3), 1.29 (dq, *J* = 12.8/2.4 Hz, 1H, 5-H_{eq}), 1.65–1.93 (m, 3H, CH_2−CH_2−CN and 5-H_{ax}), 1.74 (q, *J* = 7.3 Hz, 2H, CH_2−CH_3), 2.51–2.69 (m, 2H, CH_2−CH_2−CN), 3.77–3.91 (m, 2H, 4-H_{ax} and 6-H_{eq}), 3.79 (td, *J* = 11.9/2.7 Hz, 1H, 6-H_{ax}), 7.25–7.42 (m, 5H, H_{arom}).

5.1.32. cis-3-(2-Phenyl-1,3-dioxan-4-yl)propan-1-amine (**33a**)

Under N_2 at 0 °C a solution of $LiAlH_4$ in THF (1 M, 0.1 mL, 0.1 mmol) was added to a solution of **30** (42 mg, 0.19 mmol) in Et_2O (5 mL). The mixture was stirred for 2 h at 0 °C. Then one equivalent of water was added. The mixture was dried over $MgSO_4$, filtered

and evaporated in vacuo. Pale yellow oil, yield 18 mg (45%). $C_{13}H_{19}NO_2$ (221.3). HRMS (EI): calcd. for $C_{13}H_{18}NO_2$ 220.1335; found 220.1337. MS (EI): *m/z* (%) = 220 [M−H, 7], 115 [M−PhCHO, 65], 105 [Ph−CO, 54]. MS (CI): *m/z* (%) = 222 [MH^+, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3368 (NH_2), 2924 (C−H), 1022 (C−O), 804, 748 (ArC−H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.34 (s broad, 2H, CH_2−CH_2−CH_2−NH_2), 1.51 (dtd, *J* = 13.4/2.4/1.5 Hz, 1H, 5-H_{eq}), 1.56–1.76 (m, 4H, CH_2−CH_2−CH_2−NH_2), 1.80 (dddd, *J* = 13.4/11.9/11.2/5.1 Hz, 1H, 5-H_{ax}), 2.72 (t, *J* = 6.4 Hz, 2H, CH_2−CH_2−CH_2−NH_2), 3.77–3.87 (m, 1H, 4-H_{ax}), 3.94 (td, *J* = 11.6/2.4 Hz, 1H, 6-H_{ax}), 4.25 (ddd, *J* = 11.6/5.2/1.5 Hz, 1H, 6-H_{eq}), 5.49 (s, 1H, 2-H_{ax}), 7.27–7.37 (m, 3H, H_{arom}), 7.47 (dd, *J* = 7.9/1.5 Hz, 2H, H_{arom}).

5.1.33. 3-(2,2-Diphenyl-1,3-dioxan-4-yl)propan-1-amine (**34a**)

Under N_2 at 0 °C a solution of $LiAlH_4$ in THF (1 M, 0.3 mL, 0.3 mmol) was added to a solution of **31** (19 mg, 0.06 mmol) in Et_2O (3 mL). The mixture was stirred for 2 h at 0 °C. Then one equivalent of water was added. The mixture was dried over $MgSO_4$, filtered and concentrated in vacuo. Colorless oil, yield 16 mg (89%). $C_{19}H_{23}NO_2$ (297.4). HRMS (EI): calcd. for $C_{19}H_{20}O_2$ 280.1462; found 280.1463. MS (EI): *m/z* (%) = 280 [M−NH_3, 3], 105 [Ph−CO, 100]. MS (CI): *m/z* (%) = 298 [MH^+, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3368 (NH_2), 2925 (C−H), 1097 (C−O), 799, 745 (ArC−H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.39 (dq, *J* = 12.8/2.1 Hz, 1H, 5-H_{eq}), 1.53–1.93 (m, 7H, 5-H_{ax}, NH_2, CH_2−CH_2−CH_2−NH_2), 2.77 (t, *J* = 6.8 Hz, 2H, CH_2−CH_2−CH_2−NH_2), 3.89 (ddt, *J* = 11.5/7.0/2.4 Hz, 1H, 4-H_{ax}), 4.00 (td, *J* = 11.5/2.4 Hz, 1H, 6-H_{ax}), 4.08 (ddd, *J* = 11.5/4.8/1.8 Hz, 1H, 6-H_{eq}), 7.14–7.29 (m, 4H, H_{arom}), 7.31–7.41 (m, 2H, H_{arom}), 7.49–7.54 (m, 4H, H_{arom}).

5.1.34. trans-3-(2-Ethyl-2-phenyl-1,3-dioxan-4-yl)propan-1-amine (**35a**)

Under N_2 at 0 °C a solution of $LiAlH_4$ in THF (1 M, 0.1 mL, 0.1 mmol) was added to a solution of **32** (36 mg, 0.14 mmol) in Et_2O (5 mL). The mixture was stirred for 2 h at 0 °C. Then one equivalent of water was added. The mixture was dried over $MgSO_4$, filtered and evaporated in vacuo. Pale yellow oil, yield 20 mg (57%). $C_{15}H_{23}NO_2$ (249.4). HRMS (EI): calcd. for $C_{13}H_{18}NO_2$ 220.1337; found 220.1337. MS (EI): *m/z* (%) = 220 [M−C_2H_5, 71], 115 [$NH_2(CH_2)_3CH(CH_2)_2O$, 55], 105 [Ph−CO, 80], 77 [Ph, 28]. MS (CI): *m/z* (%) = 250 [MH^+, 100]. IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3367 (NH_2), 2928 (C−H), 1092 (C−O), 804, 757 (ArC−H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.79 (t, *J* = 7.3 Hz, 3H, CH_2−CH_3), 1.27 (dq, *J* = 12.8/2.4 Hz, 1H, 5-H_{eq}), 1.42–1.77 (m, 5H, 5-H_{ax}, CH_2−CH_2−CH_2−NH_2), 1.71 (s broad, 2H, CH_2−CH_2−CH_2−NH_2), 1.72 (q, *J* = 7.3 Hz, 2H, CH_2−CH_3), 2.75 (t, *J* = 6.8 Hz, 2H, CH_2−CH_2−CH_2−NH_2), 3.60–3.69 (m, 1H, 4-H_{ax}), 3.76 (td, *J* = 11.3/2.4 Hz, 1H, 6-H_{ax}), 3.87 (ddd, *J* = 11.3/5.2/1.8 Hz, 1H, 6-H_{eq}), 7.27–7.31 (m, 1H, H_{arom}), 7.34–7.38 (m, 4H, H_{arom}).

5.1.35. Ethyl (E)-3-(cis-2-phenyl-1,3-dioxan-4-yl)prop-2-enoate (**38**)

Under N_2 CH_2Cl_2 (20 mL) was cooled down to −78 °C. Oxalyl chloride (0.1 mL, 1.1 mmol) was added. The mixture was stirred for 2 min before DMSO (0.15 mL, 2.2 mmol) was added. 10 min later a solution of the alcohol **36** (195 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added and the mixture was stirred for 15 min at −78 °C. NEt_3 (0.7 mL, 5 mmol) was added and the mixture was stirred for 15 min at rt (formation of aldehyde **37**). Then a solution of ethoxycarbonylmethylenetriphenylphosphorane (552 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) was added and the mixture was stirred for 3 h at rt. The mixture was concentrated in vacuo and the residue was purified by fc (4 cm, 15 cm, petroleum ether:EtOAc = 7:3, 20 mL, R_f = 0.43). Only the (*E*)-Isomer was isolated. Colorless oil, yield 162 mg (62%). $C_{15}H_{18}O_4$ (262.2). MS (EI): *m/z* (%) = 262 [M^+, 6]. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2976 (C−H), 1738 (C=O), 1661 (C=C), 10,965 (C−O), 756 (ArC−H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.29 (t, *J* = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.86 (dtd, *J* = 13.4/2.4/1.2 Hz, 1H, 5-H_{eq}), 1.93 (dddd, *J* = 13.4/12.2/11.5/4.8 Hz, 1H, 5-H_{ax}), 4.02 (td, *J* = 11.5/2.7 Hz, 1H, 6-H_{ax}), 4.2 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 4.32 (ddd, *J* = 11.5/4.8/1.2 Hz, 1H, 6-H_{eq}), 4.52–4.56 (m, 1H, 4-H_{ax}), 5.59 (s, 1H, 2-H_{ax}), 6.13 (dd, *J* = 15.8/1.8 Hz, 1H, CH=C*H*−CO), 6.96 (dd, *J* = 15.8/3.9 Hz, 1H, C*H*=CH−CO), 7.34–7.41 (m, 3H, H_{arom}), 7.49–7.53 (m, 2H, H_{arom}).

5.1.36. Ethyl 3-(cis-2-phenyl-1,3-dioxan-4-yl)propanoate (**39**)

The α,β-unsaturated ester **38** (1.56 g, 6.0 mmol) was dissolved in EtOAc (5 mL) and Pd/C (5%, 0.3 mg) was added. The mixture was shaken for 4 h under an H_2 atmosphere (1.5 bar). The mixture was filtered over Celite® and the filtrate was concentrated in vacuo. The residue was purified by fc (3 cm, 15 cm, petroleum ether:-EtOAc = 7:3, 10 mL, R_f = 0.42). Colorless oil, yield 1.4 g (88%). $C_{15}H_{20}O_4$ (264.3). Anal. calcd. C 68.16, H 7.63; found C 68.04, H 7.51. MS (EI): *m/z* (%) = 264 [M^+, 25], 105 [PhCO, 100]. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2959 (C−H), 1731 (C=O), 1092 (C−O), 752 (ArC−H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.24 (t, *J* = 7.3 Hz, 3H, $COOCH_2CH_3$), 1.27 (dtd, *J* = 13.1/2.4/1.5 Hz, 1H, 5-H_{eq}), 1.84 (dddd, *J* = 13.1/12.2/11.3/4.8 Hz, 1H, 5-H_{ax}) 1.93 (q, *J* = 7.3 Hz, 2H, CH_2−CH_2−COOEt), 2.49–2.53 (m, 2H, CH_2−CH_2−COOEt), 3.84–3.94 (m, 1H, 4-H_{ax}), 3.96 (td, *J* = 11.3/2.4 Hz, 1H, 6-H_{ax}), 4.12 (q, *J* = 7.3 Hz, 2H, $COOCH_2CH_3$), 4.27 (ddd, *J* = 11.3/4.8/1.5 Hz, 1H, 6-H_{eq}), 5.21 (s, 1H, 2-H_{ax}), 7.33–7.39 (m, 3H, H_{arom}), 7.47–7.56 (m, 2H, H_{arom}).

5.1.37. cis-3-(2-Phenyl-1,3-dioxan-4-yl)propan-1-ol (**40**)

Under N_2 at 0 °C a solution of $LiBH_4$ in THF (2 M, 3.2 mL, 6.4 mmol) was added to a solution of ester **39** (1.8 g, 6.4 mmol) in Et_2O (15 mL). After stirring for 4 h at 0 °C one equivalent of water was added. The mixture was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by fc (4 cm, 15 cm, petroleum ether:EtOAc = 6:4, 10 mL, R_f = 0.20). Colorless oil, yield 784 mg (55%). $C_{13}H_{18}O_3$ (222.3). Anal. calcd. C 70.30, H 8.20; found C 70.04, H 7.93. MS (EI): *m/zm/z* (%) = 222 [M^+, 12], 163 [M^+−$(CH_2)_3OH$, 19], 105 [Ph−CO, 100]. IR (film): $\tilde{\nu}$ (cm^{-1}) = 3425 (OH), 2946 (C−H), 1104 (C−O), 753, 699 (ArC−H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.46 (dtd, *J* = 13.4/2.4/1.2 Hz, 1H, 5-H_{eq}), 1.62–1.71 (m, 5H, CH_2−CH_2−CH_2−O*H*), 1.80 (dddd, *J* = 13.1/12.2/11.3/4.8 Hz, 1H, 5-H_{ax}), 3.58–3.63 (m, 2H, CH_2−CH_2−CH_2−OH), 3.78–3.85 (m, 1H, 4-H_{ax}), 3.90 (td, *J* = 11.3/2.4 Hz, 1H, 6-H_{ax}), 4.21 (ddd, *J* = 11.3/4.8/1.2 Hz, 1H, 6-H_{eq}), 5.46 (s, 1H, 2-H_{ax}), 7.23–7.33 (m, 3H, H_{arom}), 7.39–7.44 (m, 2H, H_{arom}).

5.1.38. cis-[3-(2-Phenyl-1,3-dioxan-4-yl)propyl] p-toluenesulfonate (**41**)

A cold solution of *p*-toluenesulfonyl chloride (400 mg, 2.1 mmol) in CH_2Cl_2 (5 mL) was added slowly to a cold solution of alcohol **40** (235 mg, 1.0 mmol) and NEt_3 (1.6 mL, 1.4 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for 1 h at 0 °C and then it was stored for 12 h at 3–5 °C. The mixture was concentrated in vacuo and the residue was purified by fc (2 cm, 15 cm, petroleum ether:EtOAc = 7:3, 2 mL, R_f = 0.32). Colorless oil, yield 198 mg (50%). $C_{20}H_{24}O_5S$ (376.5). Anal. calcd. C 63.81, H 6.43, S 8.52; found C 63.40, H 6.48, S 8.40. MS (EI): *m/z* (%) = 376 [M^+, 58], 105 [PhCO, 64]. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2952 (C−H), 1470, 1206 (SO_2): 1007 (C−O), 817 (ArC−H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.46 (dtd, *J* = 13.1/2.4/1.2 Hz, 1H, 5-H_{eq}), 1.59–1.67 (m, 2H, CH_2−CH_2−CH_2−Otos), 1.74–1.97 (m, 2H, CH_2−CH_2−CH_2−Otos), 1,75 (dddd, *J* = 13.1/12.5/11.3/4.8 Hz, 1H, 5-H_{ax}), 2.44 (s, 3H, PhCH_3), 3.78 (ddt, *J* = 12.2/6.1/2.4 Hz, 1H, 4-H_{ax}), 3.93 (td, *J* = 11.3/2.7 Hz, 1H, 6-H_{ax}), 4.04 (dt, *J* = 9.7/6.4 Hz, 1H, CH_2−CH_2−CH_2−Otos), 4.12 (ddd, *J* = 9.7/6.4/5.1 Hz, 1H, CH_2−CH_2−CH_2−Otos), 4.25 (ddd, *J* = 11.3/4.8/1.2 Hz, 1H, 6-H_{eq}), 5.45 (s, 1H, 2-H_{ax}), 7.30–7.38 (m, 5H, H_{arom}, 3-H_{PhCH3} and 5-H_{PhCH3}), 7.42–7.46 (m, 2H, H_{arom}), 7.78 (d, *J* = 8.2 Hz, 2H, 2-H_{PhCH3} and 6-H_{PhCH3}).

*5.1.39. cis-N-Methyl-3-(2-phenyl-1,3-dioxan-4-yl)propan-1-amine (**33b**)*

Tosylate **41** (280 mg, 0.27 mmol) was dissolved in an ethanolic solution of methylamine (8 M, 5 mL, 40 mmol) and the mixture was heated to reflux for 12 h. After cooling down the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and the solution was extracted with a saturated solution of $NaHCO_3$ (2×10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. Pale yellow oil, yield 37 mg (58%). $C_{14}H_{21}NO_2$ (235.4). HRMS (CI): calcd. for $C_{14}H_{21}NO_2$ 236.1375; found 236.1373. MS (EI): m/z (%) = 129 [M^+−PhCHO, 9], 105 [PhCO, 33]. MS (CI): m/z (%) = 236 [MH^+, 100]. IR (film): $\tilde{\nu}$ (cm^{-1}) = 3435(N−H), 2954 (C−H), 2742 (NH$\underline{CH_3}$), 1045 (C−O), 735 (ArC−H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.41 (dtd, J = 13.1/2.4/1.2 Hz, 1H, 5-H_{eq}), 1.58−1.67 (m, 3H, CH_2−CH_2−CH_2−N$H$$CH_3$), 1.74 (dddd, J = 13.1/12.5/11.2/4.8 Hz, 1H, 5-H_{ax}), 1.82−1.98 (m, 2H, CH_2−CH_2−CH_2−NHCH$_3$), 2.34 (s, 3H, NHCH_3), 2.92 (q, J = 7.3 Hz, 2H, CH_2−CH_2−CH_2−NHCH$_3$), 3.77−3.85 (m, 1H, 4-H_{ax}), 3.88 (td, J = 11.9/2.4 Hz, 1H, 6-H_{ax}), 4.19 (ddd, J = 11.9/4.8/1.2 Hz, 1H, 6-H_{eq}), 5.46 (s, 1H, 2-H_{ax}), 7.30−7.36 (m, 3H, H_{arom}), 7.43−7.47 (m, 2H, H_{arom}).

*5.1.40. cis-N,N-Dimethyl-3-(2-phenyl-1,3-dioxan-4-yl) propan-1-amine (**33c**)*

Tosylate **41** (100 mg, 0.26 mmol) was dissolved in an ethanolic solution of dimethylamine (5.6 M, 5 mL, 28 mmol) and the mixture was heated to reflux for 12 h. After cooling down the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and the mixture was extracted with a saturated solution of $NaHCO_3$ (2×10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. Pale yellow oil, yield 23 mg (36%). $C_{15}H_{23}NO_2$ (249.4). HRMS (EI): calcd. for $C_{15}H_{22}NO_2$ 248.1646; found 248.1650. MS (EI): m/z (%) = 248 [M^+−H, 100], 105 [PhCO, 38]. MS (CI): m/z (%) = 250 [MH^+, 100]. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2935 (C−H), 2764 (N($\underline{CH_3}$)$_2$), 1045 (C−O), 749 (ArC−H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.52 (dtd, J = 13.1/2.4/1.5 Hz, 1H, 5-H_{eq}), 1.57−1.74 (m, 4H, CH_2−CH_2−CH_2−N(CH$_3$)$_2$), 1.82 (dddd, J = 13.1/12.5/11.3/4.8 Hz, 1H, 5-H_{ax}), 2.23 (s, 6H, N(CH_3)$_2$), 2.30 (t, J = 7.1 Hz, 2H, CH_2−CH_2−CH_2−N(CH$_3$)$_2$), 3.84 (ddt, J = 12.2/7.1/2.4 Hz, 1H, 4-H_{ax}), 3.96 (td, J = 11.3/2.4 Hz, 1H, 6-H_{ax}), 4.27 (ddd, J = 11.3/4.8/1.5 Hz, 1H, 6-H_{eq}), 5.51 (s, 1H, 2-H_{ax}), 7.31−7.38 (m, 3H, H_{arom}), 7.49 (dd, J = 7.6/1.8 Hz, 2H, H_{arom}).

*5.1.41. cis-N-Benzyl-3-(2-phenyl-1,3-dioxan-4-yl)propan-1-amine (**33d**)*

A solution of tosylate **41** (100 mg, 0.26 mmol) and freshly distilled benzylamine (0.30 mL, 0.40 mmol) in toluene (5 mL) was heated to reflux for 12 h. After cooling down the mixture was concentrated in vacuo and the residue was purified by fc (2 cm, 15 cm, ethyl acetate: 2 mL, R_f = 0.12). Pale yellow oil, yield 62 mg (76%). $C_{20}H_{25}NO_2$ (311.4). HRMS (EI): calcd. $C_{20}H_{25}NO_2$ 311.1884; found 311.1885. MS (EI): m/z (%) = 311 [M^+, 3], 206 [M^+−NHBn, 34], 120 [CH_2−NHBn, 77], 91 [tropylium, 100]. IR (film): $\tilde{\nu}$ (cm^{-1}) = 3393 (NH), 2924 (C−H), 1026 (C−O), 744, 698 (ArC−H). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.51 (dtd, J = 13.1/2.4/1.2 Hz, 1H, 5-H_{eq}), 1.56−1.74 (m, 5H, CH_2−CH_2−CH_2−NHBn), 1.80 (dddd, J = 13.1/12.5/11.6/4.8 Hz, 1H, 5-H_{ax}), 2.68 (t, J = 6.4 Hz, 2H, CH_2−CH_2−CH_2−NHBn), 3.77−3.88 (m, 1H, 4-H_{ax}), 3.79 (s, 2H, NHCH_2Ph), 3.95 (td, J = 11.6/2.4 Hz, 1H, 6-H_{ax}), 4.26 (ddd, J = 11.6/4.8/1.2 Hz, 1H, 6-H_{eq}), 5.50 (s, 1H, 2-H_{ax}), 7.21−7.39 (m, 8H, H_{arom}), 7.49 (dd, J = 7.5/2.1 Hz, 2H, H_{arom}).

5.2. Receptor binding studies

5.2.1. General

Homogenizer: Potter®S (B. Braun Biotech International). Ultraturrax: Euroturrax® T20 (Ika Labortechnik). Centrifuge: High speed cooling centrifuge model J2-HS (Beckman). Filter: Whatman glass fiber filters GF/B and GF/C, presoaked in 1% (NMDA assay) or 0.5% (σ_1 assay) polyethylenimine (in water) for 2 h at 4 °C before use. Filtration was performed with a Brandel 24-well cell harvester. Scintillation cocktail: Rotiscint Eco Plus (Roth). Liquid scintillation analyzer: TriCarb 2100 TR (Canberra Packard), counting efficiency 65%. All experiments were carried out in triplicates. IC_{50}-values were determined in competition experiments with at least 6 concentrations of test compounds and were calculated with the program GraphPad Prism® 3.0 (GraphPad Software) by nonlinear regression analysis. K_i-values were calculated according to Cheng and Prusoff [48]. The K_i-values are given as mean value ± SEM from three independent experiments.

5.2.2. Investigation of the affinity towards the phencyclidine binding site of the NMDA receptor

[^{3}H]-(+)-MK-801 binding to pig brain cortex membrane preparations was performed according to standard radioligand binding assays [18,21], which were slightly modified as described below.

5.2.2.1. Preparation of the tissue. Fresh pig brain cortex was homogenized with a potter (500 rpm, 10 up-and-down strokes) in 10 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1000g for 10 min at 4 °C. The supernatant was separated and centrifuged at 10,000g for 20 min at 4 °C. The pellet was resuspended in buffer (5 mM Tris−acetate with 1 mM EDTA, pH 7.5) with an Ultraturrax (8000 rpm) and centrifuged at 20,000g (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 [49] using bovine serum albumin as standard, and subsequently the preparation was frozen (−83 °C) in 5 mL portions of about 1 mg protein/mL.

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

5.2.3. Investigation of the σ_1 receptor affinity

[^{3}H]-(+)-Pentazocine binding to guinea pig brain membrane preparations was performed according to standard radioligand binding assays [43,44], which were slightly modified as described below.

5.2.3.1. Membrane preparation. Thawed guinea pig brains (Dunkin Hartley, Harlan-Sera-Lab) were homogenized with an ultraturrax (8000 rpm) in 10 volumes of cold 0.32 M sucrose. The homogenate was centrifuged at 1000g for 10 min at 4 °C. The supernatant was separated and centrifuged at 22,000g for 20 min at 4 °C. The pellet was resuspended in 10 volumes of buffer (50 mM Tris−HCl, pH 7.4) with an ultraturrax (8000 rpm), incubated for 30 min at 25 °C and centrifuged at 22,000g (20 min, 4 °C). The pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford [49] using bovine serum albumin as standard, and subsequently the preparation was frozen (−83 °C) in 5 mL portions of about 2 mg protein/mL.

5.2.3.2. Performance of the σ_1 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. Non-specific binding was determined with 10 μM haloperidol.

5.2.4. Investigation of the σ_2 receptor affinity

The assay was performed as described in Refs. [43,44].

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