Phenol—Benzoxazolone bioisosteres: Synthesis and biological evaluation of tricyclic GluN2B-selective N-methyl-D-aspartate receptor antagonists

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Abstract
Tricyclic tetrahydrooxazolo[4,5-h]-[3]benzazepin-9-ols 22 were designed as phenol bioisosteres of tetrahydro-3-benzazepine-1,7-diols. Key features of the synthesis are the introduction of the trifluoromethylsulfonyl and allyl protective groups at the heterocyclic N-atoms. Two methods were developed to convert the triflyl-protected ketone 16 into tricyclic alcohols 21 bearing various N-substituents. According to the first method, trifluoromethanesulfinate was removed by K2CO3. Following the selective reduction of the imino moiety of 17 with NaBH(OAc)3 afforded the aminoketone 18, which was reductively alkylated and reduced. According to the second method, both the imine and the ketone of the iminoketone 17 were reduced with NaBH4 to yield the aminoacohol 20, which was alkylated or reductively alkylated to form tertiary amines 21f–21r. In the last step, the allyl protective group of 21 was removed with RhCl3 and HCl to obtain oxazolones 22. In receptor binding studies using [3H]ifenprodil as radioligand ketone, 22m showed the highest GluN2B affinity (Ki = 88 nM). However, a reduced affinity toward GluN2B subunit-containing N-methyl-D-aspartate (NMDA) receptors was observed for oxazolones 22 compared to bioisosteric 3-benzazepine-1,7-diols. High selectivity of 22m for the ifenprodil binding site of GluN2B-NMDA receptors over the 1-(1-phenylcyclohexyl)piperidine binding site and σ2 receptors was observed, but only negligible selectivity over σ1 receptors. In two-electrode voltage clamp experiments, the 4-phenylbutyl derivative 22d (Ki = 422 nM) demonstrated 80% inhibition of ion flux at a concentration of 1 µM. The differences in GluN2B affinity and inhibitory activity are explained by docking studies. In conclusion, 22d is regarded as a novel scaffold of highly potent GluN1/GluN2B antagonists.

KEYWORDS
allyl protective group, GluN2B subunit, intramolecular Friedel-Crafts acylation, NMDA receptor, radioligand receptor binding studies, two-electrode voltage clamp experiments
1 | INTRODUCTION

In the mammalian brain, (S)-glutamate represents the most important excitatory neurotransmitter. It interacts with metabotropic (G protein-coupled) and ionotropic (ion channel-coupled) receptors. Three ionotropic glutamate receptor classes are differentiated, which are termed N-methyl-D-aspartate (NMDA), 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionate (AMPA), and kainate receptors. All three ionotropic glutamate receptors play a key role in excitatory neurotransmission in the central nervous system.\(^1-3\)

The heterotetrameric NMDA receptor contributes considerably to processes leading to long-term potentiation (LTP), a special form of synaptic plasticity, which correlates with learning and memory.\(^4,5\) On the other hand, acute and chronic overactivation of the NMDA receptor is involved in the condition of excitotoxicity, a self-amplifying process of neuronal damaging by increased release of the excitatory neurotransmitter (S)-glutamate. Therefore, drugs inhibiting the ion flux of Ca\(^{2+}\) through the NMDA receptor are of great interest for the treatment of acute neuronal disease states (e.g., stroke, brain injury, epileptic seizure, and migraine) and chronic neurodegenerative processes (e.g., Parkinson’s disease, Alzheimer’s disease, and multiple sclerosis).\(^3,6-8\)

Seven protein variants are known, which are able to form the heterotetrameric NMDA receptor: one GluN1 subunit existing in eight splice variants GluN1a-h, four GluN2 subunits termed GluN2A-D and two GluN3 subunits termed GluN3A and GluN3B. Usually, a functional NMDA receptor consists of two mandatory GluN1 and two additional subunits, that can be different combinations of the GluN2 and GluN3 subunits. GluN3 subunits are found predominantly in the prenatal phase of an individual and are therefore not considered in this project.\(^9\) The activation of the NMDA receptor requires slight depolarization to release the Mg\(^{2+}\)-block as well as simultaneous binding of two coagonists: (S)-glutamate interacts with its binding site on the GluN2 subunit, and glycine interacts with its binding site on the GluN1 subunit.

Although the GluN1 subunit is expressed ubiquitously throughout the central nervous system, different expression levels of the GluN2 subunits, which are encoded by four different genes, are found in different brain regions. Thus, the features of the GluN2 subunit determine the properties and gating characteristics of different NMDA receptor subtypes.\(^10-13\)

Herein, we focus on NMDA receptors containing the GluN2B subunit (GluN2B-NMDA receptors). The GluN2B subunit is predominantly expressed in the cortex, hippocampus, and striatum of the human brain.\(^12\) Compared to NMDA receptors with the GluN2A subunit, GluN2B-NMDA receptors exert slower channel opening kinetics and thus slower Ca\(^{2+}\) influx.\(^14\) Negative allosteric modulators selectively targeting GluN2B-NMDA receptors represent promising drug candidates for the treatment of various CNS disorders including neurodegenerative diseases. Compared to nonselective open-channel NMDA receptor antagonists (e.g., phencyclidine, [S]-ketamine), selective GluN2B-NMDA receptor antagonists show a better side effect profile.\(^15,16\)

β-Aminoalcohol ifenprodil (1) represents the prototypical negative allosteric modulator of GluN2B-NMDA receptors (Figure 1). It interacts with an allosteric binding site at the interface between the amino-terminal domains of the GluN1 and GluN2B subunit, which is termed the ifenprodil binding site.\(^16-18\) In Japan, racemic

![Figure 1](image-url)
Unlike-configured ifenprodil is approved as a cerebral vasodilator. Ongoing clinical trials investigate the potential of ifenprodil for the treatment of drug addiction, idiopathic pulmonary fibrosis, and Covid-19 infections. Additionally, the promising activity of ifenprodil was detected in animal models of Alzheimer’s disease and neuropathic pain.

Two main problems are associated with ifenprodil. (1) Ifenprodil shows a poor selectivity for the ifenprodil binding site of GluN2B-NMDA receptors over related σ1, σ2, α1, 5-HT1A, and 5-HT2 receptors. The selectivity profile depends on the relative and absolute configuration of ifenprodil. (2) The bioavailability of ifenprodil is rather low due to fast biotransformation. In particular, the removal of the PMB moiety was tried with (NH4)2[Ce(NO3)6], with acid (TFA, HCl), and with α-chloroethyl chloroformate. As the PMB protective group could not be removed, the desired oxazolobenzazepine 9, its regiosomer 10, and the tetrahydroisoquinoline 11. Due to the missing substituent at the oxazolone N-atom, acid 8 can also attack the 4-position leading to the regiosomer 10. The formation of the ring-contracted tetrahydroisoquinoline 11 was unexpected as the analogous PMB-protected acid did not lose CO to form an analogous tetrahydroisoquinoline. Due to separation and purification problems, the yield of 9 did not exceed 31% even after optimization of the cyclization reaction. Elimination of trifluoromethanesulfinate (CF3SO2-) with K2CO3 in refluxing acetonitrile followed by reduction of cyclic imine with NaBH(OAc)3 and reductive alkylation with benzaldehyde and NaBH(OAc)3 provided the benzylamine 13 in 17% yield. In summary, oxazolo-annulated 3-benzazepine 13 without N-3-substituent was available, but in very low yield, which is due to side reactions during the intramolecular Friedel–Crafts acylation and isolation and purification problems.

Thus, the introduction of a protective group at N-3 appeared to be beneficial for the preparation of a large series of oxazolo-annulated 3-benzazepines of type A. At first, the introduction of a triisopropylsilyl protective group into ester 7 was performed. However, the resulting silyl-protected ester could not be saponified without removal of the silyl protective group (see Supporting Information: Scheme S1). Introduction of a methoxymethyl (MEM) protective group into 7 and subsequent saponification of the ester were successful. However, the intramolecular Friedel–Crafts acylation required acidic conditions, which led to cleavage of the MEM protective group (see Supporting Information: Scheme S2).

Thus, a protective group, which was stable under basic (saponification of the ester) and acidic conditions (intramolecular Friedel–Crafts acylation) had to be selected. We chose the allyl protective group, which should fulfill these requirements, but could be cleaved off at the end of the synthesis by an Rh-catalyzed isomerization and hydrolysis.

The allyl protective group was introduced by reacting the ester 7 with allyl bromide. The resulting allyl-protected ester 14 was hydrolyzed with LiOH.H2O to afford the acid 15. The overall yield of the acid 15 could be increased to 92% by increasing the reaction temperature to 50°C during allylation of 7 and conducting the hydrolysis of the ester 14 in a consecutive manner without isolation of the intermediate ester 14. After careful optimization of the subsequent intramolecular Friedel–Crafts acylation of acid 15, a yield of 76% of the tricyclic ketone 16 was obtained. The key features to achieving high yields were a rather long reaction time at low temperature, limited amounts of P4O10 (ca. 4 equivalents), and aqueous workup of P4O10 as the acid 15 and the ketone 16 showed strong adsorption at P4O10 (Scheme 2).

In the next step, the triflyl protective group had to be removed. For this purpose, the tricyclic ketone 16 was treated with K2CO3 in acetone to eliminate trifluoromethanesulfinate (CF3SO2-) and

2 RESULTS AND DISCUSSION

2.1 Synthesis

Very recently, we have reported the synthesis of oxazolo-annulated 3-benzazepines of type A bearing a p-methoxybenzyl (PMB) moiety at the N-atom of the oxazoline ring (N-3). Unfortunately, it was not possible to remove this N-protective group without destroying the molecule. In particular, the removal of the PMB moiety was tried with H2 and different catalysts, with (NH4)2[Ce(NO3)6], with acid (TFA, HCl), and with α-chloroethyl chloroformate.

As the PMB-protective group could not be removed, the synthesis of unsubstituted oxazolo-annulated 3-benzazepines of type A was performed without a protective group at the N-atom (Scheme 1). Thus, Mitsunobo reaction of the alcohol with N-triflylglycine methyl ester (6) led to ester 7, which was hydrolyzed to yield acid 8. P4O10.CH3SO3H mediated intramolecular Friedel–Crafts acylation of acid 8 provided three products: The desired oxazolobenzazepine 9, its regiosomer 10, and the tetrahydroisoquinoline 11. Due to the missing substituent at the oxazolone N-atom, acid 8 can also attack the 4-position leading to the regiosomer 10. The formation of the ring-contracted tetrahydroisoquinoline 11 was unexpected as the analogous PMB-protected acid did not lose CO to form an analogous tetrahydroisoquinoline. Due to separation and purification problems, the yield of 9 did not exceed 31% even after optimization of the cyclization reaction. Elimination of trifluoromethanesulfinate (CF3SO2-) with K2CO3 in refluxing acetonitrile followed by reduction of cyclic imine with NaBH(OAc)3 and reductive alkylation with benzaldehyde and NaBH(OAc)3 provided the benzylamine 13 in 17% yield. In summary, oxazolo-annulated 3-benzazepine 13 without N-3-substituent was available, but in very low yield, which is due to side reactions during the intramolecular Friedel–Crafts acylation and isolation and purification problems.
form the iminoketone 17. Without isolation, the iminoketone 17 was reduced with NaBH(OAc)₃ to give the aminoketone 18, which was reductively alkylated with benzaldehyde and NaBH(OAc)₃. For the reaction of iminoketone 17 with NaBH(OAc)₃ acetone had to be carefully removed, since it could reductively alkylate the secondary amine 18 as well leading to N-isopropyl side products. After optimization of this sequence, the benzylated aminoketone 19a was isolated in 37% yield. Subsequent reduction of the ketone 19a with NaBH₄ led to the alcohol 21a in 82% yield. Conducting the complete sequence from ketone 16 up to the tricyclic alcohol 21a in a consecutive manner without isolation of intermediates provided a yield of 33%. Following this consecutive procedure, the oxazolobenzazepineols 21a–21d were obtained in 33%–76% yield (Scheme 2).

Acetone, which was used for the removal of the trifly protective group, had to be removed carefully to avoid the competing introduction of an isopropyl moiety. Alternatively, acetone could be replaced by acetonitrile during the elimination of CF₃SO₂⁻. Thus, following the same procedure as described above, but using CH₃CN provided the PMB derivative 21e in 48% yield over three steps.

It turned out that the intermediate ketones 19 were relatively unstable, which is most likely the reason for fluctuating yields. Moreover, the diversity of potential substituents at the benzazepine N-atom (N-7) by using alkyl halides in addition to aldehydes and ketones should be increased. For this purpose, the elimination of CF₃SO₂⁻ of ketone 16 was conducted in CH₃CN at 60–70°C to yield the intermediate iminoketone 17. Subsequently, the iminoketone 17 was reduced with NaBH₄ (instead of NaBH(OAc)₃), which led to reduction of both the imino and keto moiety. According to this strategy, the unstable ketones 18 and 19 did not occur as intermediates which resulted in a lower number of side products (lower number of spots on the tlc) facilitating the purification of the final products. After removal of methanol, the aminoalcohol 20 was alkylated with diverse alkyl halides to form the tertiary amines 21f–21k. In addition to alkylation with alkyl halides, reductive alkylation of aminoalcohol 20 with various aldehydes afforded alkylated oxazolobenzazepines 21n–21r.

To remove the allyl protective group, the allyl derivatives 21 were treated with RhCl₃, which led to isomerization of the double bond yielding enamines. Subsequent hydrolysis of the produced enamines with HCl provided the oxazolobenzazepines 22 without substituent at N-3. In case of 21j and 21k, the 1,3-dioxane moiety (ketal) was also hydrolyzed to afford the desired ketones 22l and 22m (Scheme 3).
SCHEME 2  Synthesis of benzoxazolone derivatives 22 with various substituents at the 3-benzazepine N-atom (N-7). Reagents and reaction conditions: (a) H2C═CH–CH2Br (allyl bromide), K2CO3, CH3CN, rt, 60 h, 78%. (b) LiOH·H2O, THF/H2O 7:3, 0°C, 1 h, 97%. (c) P4O10 (4 equiv.), CH2Cl2, rt, 16 h then 35°C, 24 h, P2O10 workup, 76%. (d) K2CO3, acetone, (rt, 16 h, then 40–60°C, 5–18 h; for the synthesis of 21e CH3CN was used as solvent. (e) K2CO3, CH3CN, 60–70°C, 2.5–8 h. (f) CH3CN, aldehyde, NaBH(OAc)3, rt, 1–16 h, 41%–79% (21n–21r). (g) CH3OH, NaBH4, rt, 1–16 h, 33%–76% (21a–21e). (h) NaBH4, CH3OH, rt, 1–16 h. (i) R–X, CH3CN, K2CO3, 50–80°C, 4–60 h, 57%–74% (21f–21k). (j) Aldehyde, NaBH(OAc)3, CH3CN or CH2Cl2, rt, 16 h, 41%–79% (21n–21r). (l) 1: RhCl3·3H2O (0.1 equiv.), protic solvent, 75–90°C, 1.5–4 h; 2: HCl (2–4 M), 70–100°C, 2–16 h. Residues R are defined in Table 1.

SCHEME 3  Synthesis of ketones 22l and 22m. Reagents and reaction conditions: (a) 1. RhCl3·3H2O (0.1 equiv.), EtOH, HO, HOAc, 90°C, 3 h; 2. HCl, 70–90°C, 3–16 h, 51% (22l), 33% (22m).
Altogether, a set of oxazolobenzazepines 22 with 14 different substituents at N-7 was prepared. Preferred substituents contained a phenyl moiety connected via a spacer of 4–6 bond lengths with the basic 3-benzazepine N-atom (N-7). These types of substituents are similar to the structural environment of the basic N-atom of the lead compounds 1–4 in Figure 1.

2.2 | Pharmacological activity

2.2.1 | Affinity toward the ifenprodil binding site of the GluN2B-NMDA receptor

A receptor binding assay was used to determine the affinity of the synthesized oxazolobenzazepines 21 and 22 toward GluN2B-NMDA receptors. In this assay, mouse fibroblast cells Ltk− expressing the GluN1a and GluN2B subunit, which form the heterotetrameric NMDA receptor, served as receptor material. The test compounds compete with the radioligand [3H]ifenprodil for the limited number of ifenprodil binding sites in the preparation. The radioactivity remaining at the receptor is a measure of the affinity of the test compound. [45]

In series 21 with N-allyl moiety, the GluN2B affinity appears to be rather low. In the series of homologous phenylalkyl substituted derivatives 21a–21f the highest GluN2B affinity was observed for the phenylbutyl derivative 21d (Ki = 515 nM). Introduction of an S-atom (21h), an SO2 moiety (21i), and a 1,3-dioxane ring (21j, 21k) in the side chain or reduction of the conformational flexibility by biphenyl residues (21n–21p) resulted in reduced GluN2B affinity. Only an O-atom (21g, Kf = 400 nM) within the side chain was tolerated by the ifenprodil binding site. Unexpectedly, the piperiddinylbenzyl substituted oxazolobenzazepine 21q showed the highest GluN2B affinity (Ki = 194 nM) of the N-allyl derivatives 21 (Table 1).

In general, it was expected that removal of the N-allyl protective group led to high GluN2B affinity as the unprotected oxazolone ring of compounds 22 can serve as a H-bond donor comparable to the OH moiety of phenols 1–3. The successful bioisosteric replacement of a phenol by a benzoazolone moiety has already been demonstrated with besnonprodil 4.

However, the GluN2B affinity of the homologous phenylalkyl substituted derivatives 22a–22f was only slightly increased compared to the allyl analogs 21a–21f. The highest GluN2B affinity was observed for the phenylbutyl derivative 22d (Ki = 422 nM). Replacement of a CH2 moiety in the side chain of 22d by an O-atom (22g) or a SO2 moiety (22i) was not tolerated by the ifenprodil binding site. However, a carbonyl moiety instead of a CH2 moiety reducing the electron density of the terminal phenyl ring resulted in comparable (22i, Ki = 565 nM) or considerably increased GluN2B affinity (22m, Ki = 88 nM). Introduction of conformationally restricted biphenyl side chains at the benzazepine N-atom led to moderate GluN2B affinity (22n, Ki = 559 nM) and (22o, Ki = 373 nM). In contrast to 21q, the piperiddinylbenzyl derivative 22q with unsubstituted benzoxazolone moiety unexpectedly showed only negligible GluN2B affinity (Table 1).

2.2.2 | Two-electrode voltage clamp experiments

Affinity screening revealed clear structure affinity relationships and allowed the identification of the compounds with the highest GluN2B affinity. However, previous studies have indicated that the high affinity of the ifenprodil-derived compound does not automatically translate into high ion channel inhibition. [41,46,47] Therefore, the inhibitory activity of the most promising derivatives 21q (Ki = 194 nM), 22d (Ki = 422 nM), and 22m (Ki = 88 nM) was tested in two-electrode voltage-clamp (TEVC) experiments using GluN1a/GluN2B expressing oocytes. Addition of 10 µM glycine and 10 µM (S)-glutamate induced a characteristic NMDA-specific ion current that was inhibited by the application of 10 µM of 21q, 22d, and 22m. [31,46]

To evaluate the activity of the test compounds, the inhibitory activity of ifenprodil (1) was also recorded at concentrations of 1 and 10 µM. Compounds achieving more than 80% inhibitory activity at 10 µM were tested at a concentration of 1 µM as well. The results are summarized in Table 2.

All tested compounds were able to inhibit the agonist-induced current moderately (21q) or strongly (1, 22d, 22m) at 10 µM concentration (Table 2). The highest inhibitory activity was obtained by 10 µM of ifenprodil (1), which was not significantly different (p > 0.05) from the inhibitory activity of 10 µM 22d. On the other hand, the activity of 21q and 22m at 10 µM was significantly reduced compared to ifenprodil (1) and 22d (statistical analysis see Table S1). Since the inhibitory activity of ifenprodil (1) and 22d at 10 µM were close to full inhibition of NMDA receptors, the activity of 1 µM for both test compounds was evaluated. Similar to the observed inhibitory effect at 10 µM, the activity of 1 µM of 22d was not significantly different compared to the respective activity at 1 µM ifenprodil (1). Both compounds were able to inhibit the agonist-induced current by 77% (1) and 80% (22d) suggesting IC50 values in the nanomolar range. Even at a concentration of 1 µM, the inhibitory activities of 1 and 22d were significantly higher than the inhibitory activity of 21q at 10 µM underlining the high potency of ifenprodil (1) and 22d.

2.2.3 | Interactions with the ifenprodil binding site

The evaluation of the interactions between the ligands and their receptor binding site local in silico docking was performed using the crystal structure of a functional heterotetrameric NMDA receptor (PDB 4PE5). [18] The virtual docking box was placed around the ifenprodil-binding site formed at the interface of the amino-terminal domains of the GluN1 and GluN2B subunits. The subdomains R1 and R2 of the GluN2B subunit form this binding site (Figure 2). To generate reliable docking results the docking procedure was optimized and tested by redocking of (1R,2S)-1. The lowest RMSD value obtained by redocking of (1R,2S)-1 compared to the crystal structure was 1.4 Å (Figure 2C).

In previous studies, it was shown that ligands with (R)-configuration at the benzylic position represent the eutomers. [36,46] Therefore,
### Table 1

Interaction of oxazolobenzazepines 21 and 22 with the ifenprodil and phencyclidine binding sites of the N-methyl-D-aspartate receptor and with both σ receptor subtypes.

| Compound | R                  | $K_i \pm \text{SEM (nM)} (n = 3)^a$ | GluN2B | PCP | $\sigma_1$ | $\sigma_2$ |
|----------|--------------------|------------------------------------|--------|-----|------------|------------|
| 21a      | $\text{CH}_2\text{Ph}$ | 18%                               | 32%    | 257 | 3%         |
| 21b      | $(\text{CH}_2)_2\text{Ph}$ | Nd                                | Nd     | Nd  | Nd         | Nd         |
| 21c      | $(\text{CH}_2)_3\text{Ph}$ | 1100                              | 18%    | 539 | 43%        |
| 21d      | $(\text{CH}_2)_4\text{Ph}$ | 515                               | 48%    | 200 | 1250       |
| 21e      | $(\text{CH}_2)_4\text{Ph}-4\text{OCH}_3$ | 1270                             | 13%    | 544 | 35%        |
| 21f      | $(\text{CH}_2)_5\text{Ph}$ | 2190                              | 26%    | 144 | 557        |
| 21g      | $(\text{CH}_2)_5\text{OPh}$ | 400                               | 1%     | 47% | 39%        |
| 21h      | $(\text{CH}_2)_5\text{SPh}$ | 1520                              | 16%    | 404 | 745        |
| 21i      | $(\text{CH}_2)_5\text{SO}_2\text{Ph}$ | 1390                             | 13%    | 0%  | 416        |
| 21j      | $(\text{CH}_2)_5\text{F}$ | 1%                                | 27%    | 25% | 376        |
| 21k      | $(\text{CH}_2)_5\text{Bu}$ | 2%                                | 0%     | 360 | 13%        |
| 21l      | $(\text{CH}_2)_5\text{CH}_2$ | 14%                              | 30%    | 345 | 0%         |
| 21m      | $(\text{CH}_2)_5\text{F}$ | 545                               | 22%    | 3980| 41%        |
| 21n      | $(\text{CH}_2)_5\text{N}$ | 194 ± 21                          | 51%    | 238 | 591        |
| 21o      | $(\text{CH}_2)_5\text{SO}_2\text{Ph}$ | 837                               | 48%    | 24% | 26%        |
| 21p      | $(\text{CH}_2)_5\text{S}$ | 26%                               | 20%    | 95 ± 14| 24%     |
| 21q      | $(\text{CH}_2)_5\text{S}$ | 7%                                | 37%    | 24% | 990        |
| 21r      | $(\text{CH}_2)_5\text{S}_2$ | 770                              | 39%    | 4%  | 134        |
| 21s      | $(\text{CH}_2)_5\text{S}_2$ | 422                              | 34%    | 32% | 576        |
| 21t      | $(\text{CH}_2)_5\text{S}_2$ | 463                              | 12%    | 89 ± 36| 191     |
| 21u      | $(\text{CH}_2)_5\text{S}_2$ | 1000                             | 33%    | 46% | 46%        |
| 21v      | $(\text{CH}_2)_5\text{S}_2$ | 49%                              | 17%    | 13% | 603        |

(Continues)
configured compounds 21q, 22d, and 22m were used for the docking experiments. The docking poses with the lowest virtual dissociation constant for each compound are displayed in Figure 3. The virtual dissociation constant determined for 22d (4.05 nM) was higher than the virtual dissociation constants of 21q (0.051 nM) and 22m (0.069 nM), which are very similar. This order of virtual dissociation constants correlates with the order of in vitro determined $K_i$ values. The virtual dissociation constant of the reference compound ifenprodil (1R,2S)-1 was 2.740 nM.

The docking poses displayed in Figure 3 demonstrate clear differences between the more active compounds 1, 22d, and 22m compared to the less active compound 21q. Previous experimental data showed that simultaneous interactions with amino acids from R1 (GluN2B Q110, I111, F114) and R2 (GluN2B F174, P177, E236) as well

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**TABLE 1** (Continued)

| Compound | R | $K_i \pm SEM$ (nM) ($n=3$)* |
|----------|---|--------------------------|
| 22l      |  | 565 | 41% | 23% | 635 |
| 22m      |  | 88 ± 18 | 1% | 16 ± 3.4 | 6% |
| 22n      |  | 559 | 12% | 377 | 18% |
| 22o      |  | 373 | 35% | 845 | 21% |
| 22p      |  | 29% | 11% | 507 | 51% |
| 22q      |  | 38% | 47% | 136 | 284 |
| 22r      |  | 23% | 25% | 2330 | 1930 |

(1R,2R)-Iifenprodil[31] 5.8 ± 1.3 Nd 125 ± 24 98 ± 34
3 (WMS-1410)[34] 84 ± 18 Nd 123 33 ± 18
Eliprodil 13 ± 2.5 Nd Nd Nd
(+)-Pentazocine Nd Nd 5.4 ± 0.5 Nd
Haloperidol Nd Nd 6.3 ± 1.6 78 ± 2.3
Di-o-tolylguanidine Nd Nd 89 ± 29 57 ± 18

Abbreviation: Nd, not determined.

*Values in % reflect the removal of the radioligand at a test compound concentration of 1 µM.

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**TABLE 2** Inhibitory activity of 1, 21q, 22d, and 22m in TEVC measurements using GluN1a/GluN2B expressing oocytes.

| Compound | Conc. (µM) | Inhibition (%) | n |
|----------|------------|----------------|---|
| 1        | 1          | 77 ± 2         | 6 |
| 1        | 10         | 89 ± 3         | 5 |
| 21q      | 10         | 21 ± 3         | 5 |
| 22d      | 1          | 80 ± 1         | 6 |
| 22d      | 10         | 88 ± 2         | 5 |
| 22m      | 10         | 76 ± 1         | 6 |

Note: Inhibitory activity was evaluated in presence of 10 µM glycine/10 µM (S)-glutamate at 1 or 10 µM concentrations of the respective inhibitor. The number of independent oocytes (n) is given for each compound and concentration.

(R)-configured compounds 21q, 22d, and 22m were used for the docking experiments. The docking poses with the lowest virtual dissociation constant for each compound are displayed in Figure 3. The virtual dissociation constant determined for 22d (4.05 nM) was higher than the virtual dissociation constants of 21q (0.051 nM) and 22m (0.069 nM), which are very similar. This order of virtual dissociation constants correlates with the order of in vitro determined $K_i$ values. The virtual dissociation constant of the reference compound ifenprodil (1R,2S)-1 was 2.740 nM.

The docking poses displayed in Figure 3 demonstrate clear differences between the more active compounds 1, 22d, and 22m compared to the less active compound 21q. Previous experimental data showed that simultaneous interactions with amino acids from R1 (GluN2B Q110, I111, F114) and R2 (GluN2B F174, P177, E236) as well
as interactions with a loop formed by GluN1 amino acids S132-L135, are required for high activity of ifenprodil-derived compounds. These simultaneous interactions prevent the necessary repositioning of R1 and R2 subdomains as well as the upward movement of the benzyl side chain of F176 for the transition of the receptor from the nonconductive to the conductive state. Both protein movements have to be inhibited to lock the receptor in a nonconductive state. Contrary to these findings, 21q occupies an overlapping but slightly different binding site preventing direct interactions with the amino acids of the R2 subdomain, which are required to inhibit the repositioning of F176. Consequently, the proposed molecular mechanism of inhibition can only be partially fulfilled by 21q. On the other hand, compounds (1R,2S)-1, 22d, and 22m adopt poses allowing simultaneous interactions with the previously mentioned amino acids. All three compounds show π,π-interactions with F176 as well as an H-bond interaction with Q110. Moreover, bioisosteric replacement of the phenol by a benzoxazolone scaffold in compounds 22d and 22m did not disturb H-bonding with E236, which has also previously been identified as an important interaction partner in the R2 subdomain.

Although a significant difference in activity of 1 and 22d was not observed, the activity of 22m was reduced considerably. This observation could be explained by the docking studies. While
22d and (1R, 2S)-1 can interfere strongly with F114, the tert-butyl moiety of 22m reduces the direct π,π-interactions with this amino acid. We showed in a previous mutagenesis study the necessity of strong π,π-interactions with F114 for high activity.46

2.2.4 | Receptor selectivity

In addition to the interaction of the oxazolobenzazepines 21 and 22 with the ifenprodil binding site of the NMDA receptor, their interactions with the phencyclidine (1-(1-phenylcyclohexyl)piperidine, PCP) binding site were investigated using the radioligand [3H]-(+)-MK-801 and pig brain cortex membrane preparations.48,49 The PCP binding site is located within the ion channel pore of the NMDA receptor. Ligands interacting with the PCP binding site do not differentiate between different NMDA receptor subtypes.3,14 Therefore, our ligands should not interact with this potential binding site. Indeed, at a concentration of 1 µM of the test compounds 21 and 22 did not compete significantly with the radioligand indicating very low affinity toward the PCP binding site within the ion channel pore of the NMDA receptor.

Furthermore, the affinity of 21 and 22 toward both σ receptor subtypes was tested in radioligand receptor binding studies. In brief, [3H]-(+)-pentazocine (σ1) and [3H]di-α-tolyguanidine (σ2) were used as radioligands. Guinea pig brain preparations (σ1) and rat liver preparations (σ2) were employed as receptor material.50–52 Some of the allyl derivatives 21 showed moderate σ1 affinity (e.g., 21f, K1 = 144 nM), but none of them exhibited a higher σ1 affinity than 100 nM. The σ2 affinity of the allyl derivatives 21 was even lower (K2(σ2) > 370 nM). In the series of oxazolobenzazepines 22 without allyl protective group, three compounds 22a, 22f, and 22m achieved Kσ2-values in the low two-digit nanomolar range. All three compounds interacted selectively or preferably with the σ2 receptor. The 3-phenylpropyl and 5-phenylpentyl substituted oxazolobenzazepines 22c and 22f were the most potent σ2 ligands, but their Kσ2-values are still higher than 100 nM (K2(σ2) = 134 and 191 nM, respectively).

Altogether, the piperidinylbenzyl substituted derivative 21q reveals high selectivity for GluN2B-NMDA receptors over the PCP binding site, but no selectivity over both σ receptor subtypes. Although the affinity toward GluN2B-NMDA receptors is only moderate (K1 = 422 nM), the phenylbutyl derivative 22d is selective over the PCP binding site and σ1 receptors, but not over the σ2 subtype. 22m with a butanoylphenyl substructure showed the highest GluN2B-NMDA receptor affinity (K2(σ2) = 88 nM) of this series of compounds with high selectivity over the PCP binding site and σ2 receptors. Unfortunately, 22m interacted with even higher affinity with σ1 receptors (K2(σ1) = 16 nM).

3 | CONCLUSION

Due to fast metabolic degradation, in particular conjugation with glucuronic acid,32,35 the phenol of the potent GluN2B antagonist 3 was replaced bioisostERICally by the metabolically more stable benzoazolone moiety that is also found in the potent GluN2B antagonist besnonprodil (4).

Performing the reaction sequence without a protective group at the benzoazolone moiety using acid 8 for the intramolecular Friedel Crafts acylation, led to the desired tricyclic ketone 9 and finally to the benzylated ketone 13 without a substituent at the oxazolone ring. However, due to side reactions (nonregioselective Friedel Crafts acylation, ring contraction) and purification problems originating from the zwitterionic nature of the intermediates and products (acidity of benzoazolone, basicity of amine), the yields were rather low. Therefore, a protective group had to be introduced into the benzoazolone system.

Attempts to conduct the reaction sequence with the MEM or trisopropylsilyl protective group did not result in the tricyclic oxazolobenzazepines due to the low stability of the protective groups. After introduction of the PMB protective group, the desired oxazolobenzazepines could be prepared, but the protective group could not be cleaved off without destroying the compounds.38 However, the allyl protective group showed the optimal properties surviving all transformations. At the end of the synthesis, it could be removed upon isomerization with Rh3+ and subsequent hydrolysis of the formed enamines.

To obtain compounds with diverse N-substituents, the triflyl-protective group of ketone 16 was removed by β-elimination of trifluoromethanesulfinate. Two main methods were developed to convert the resulting iminoketone 17 into the alcohols 21. According to the first method, NaBH(OAc)3 reduced selectively the imino moiety of iminoketone 17 providing aminoketone 18, which was reductively alkylated and finally reduced to give alcohols 21a–21e. Alternatively, the iminoketone 17 was completely reduced with NaBH4 to form aminoaic alcohol 20, which was alkylated with alkyl halides or with aldehydes and NaBH(OAc)3.

In receptor binding studies, 21q (K1 = 194 nM), 22d (K1 = 422 nM), and 22m (K1 = 88 nM) showed the highest affinity toward the ifenprodil binding site. Since previous studies have shown that high affinity does not always translate into high activity,41,46,47 TEVC analysis for these compounds was performed. The activity was compared to the same concentration of ifenprodil (1). All compounds show moderate (21q) to high inhibitory activity (1, 22d, 22m) at a concentration of 10 µM. Moreover, the inhibitory activity of the bioisosteric benzoazolone analog 22d was not significantly different from the activity of ifenprodil (1) at the same concentration level. Even at 1 µM, 22d achieved inhibition of 80% pointing to a nanomolar IC50 value. The corresponding 3-benzazepine bioisostere 3 with a phenolic OH moiety shows also a nanomolar IC50 value. Further activity differences between 21q, 22d, and 22m could be explained by insufficient positioning at the binding site and subsequent alteration of interactions with different amino acids.
In summary, 22d was identified as a promising new candidate for further experimental evaluation.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General remarks

Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. Thin layer chromatography (TLC): Silica gel 60 F 254 plates (Merck). Flash chromatography (FC): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column (d), fraction size (v), eluent, Rf value. Melting point: Melting point apparatus SMP3 (Stuart Scientific), uncorrected. MS: MAT GCQ (Thermo-Finnigan); EI, MAT LCQ (Thermo Finnigan); ESI. 1H NMR (400 MHz), 13C NMR (100 MHz): Mercury Plus AS 400 NMR spectrometer (Varian); δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution; assignments of 13C and 1H NMR signals were supported by 2D NMR techniques. IR: IR spectroscopy.

4.1.2 | HPLC methods to determine the purity

HPLC method 1: HPLC: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 μm); LiChroCART® 250–254 mm cartridge; flow rate: 1.0 ml/min; injection volume: 5.0 μl; detection at λ = 210 nm; solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid; gradient elution: (A %): 0–4 min: 90%, 4–29 min: 90 → 0%, 29–31 min: 0%, 31–31.5 min: 0 → 90%, 31.5–40 min: 90%. Data acquisition: HSM software; manual integration.

HPLC method 2: HPLC: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 μm); LiChroCART® 250–4 mm cartridge; Guard Column: LiChrospher® 60 RP-select B (5 μm), LiChroCART® 4–4 mm cartridge; flow rate: 1.0 ml/min; injection volume: 5.0 μl; detection at λ = 210 nm; solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: methanol with 0.05% (v/v) trifluoroacetic acid; gradient elution: (A %): 0–1 min: 80%, 1–22 min: 80 → 0%, 22–30 min: 0%, 30–31.5 min: 0 → 80%, 31.5–40 min: 80%. Data acquisition: HSM software; manual integration.

4.1.3 | Synthetic procedures

4.1.3.1 | Methyl 2-[(2-oxo-2,3-dihydrobenzoxazol-5-yl)ethyl]-N-(trifluoromethyl-sulfonyl) aminoacetate (7)

Nonprotected benzoxazolone 5 (1.58 g, 8.82 mmol), TINHCH2CO2CH3 (6, 1.95 g, 8.82 mmol), and PPh3 (2.31 g, 8.82 mmol) were dissolved in THF (48 ml) under N2 atmosphere and the mixture was cooled down to 0°C. DIAD (1.79 g, 8.82 mmol) was added dropwise and the reaction mixture was stirred for 30 min at 0°C. Then the cooling bath was removed and the reaction was completed by stirring overnight at RT.

The solvent was removed under reduced pressure giving a pale yellow oil as a crude product, which was purified by flash column chromatography (Ø 5 cm, 20 cm, ethyl acetate/n-hexane 3:5, fraction size 30 ml, Rf = 0.23). Colorless solid 140–141°C, yield 2.9 g (93%). Purity: HPLC method 1; tR = 19.0 min, purity 98.3%. C22H19F4O5S δ (ppm) = 87% (28M+Na, 100), 405 (M+Na, 5).

4.1.3.2 | 2-[(2-Oxo-2,3-dihydrobenzoxazol-5-yl)ethyl]-N-(trifluoromethyl-sulfonyl)-4-carboxylic acid (8)

Methyl ester 7 (383.8 mg, 1.0 mmol) was dissolved in a mixture of THF/H2O (7:3) (22 ml) and cooled down to 0°C. LiOH.H2O (277.0 mg, 6.6 mmol) was added to this vigorously stirred solution and stirring was continued for 2 h at rt. Then H2O (20 ml) was added and pH was adjusted to pH 1–2 with conc. HCl. The reaction mixture was extracted with ethyl acetate (4×), the organic layers were dried (Na2SO4) and the solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 3 cm, 18 cm, ethyl acetate/n-hexane 1:1 + 0.5% HCO2H, fraction size 30 ml, Rf = 0.18). Colorless solid, m.p. 200–201°C, yield 325.0 mg (88%). Purity: HPLC method 1; tR = 17.2 min, purity 99.3%. C22H19F4O5S δ (ppm) = 368.3. MS (EI); m/z = 368 (M, 25), 161 (M–HO2CH2–N–SO2CF3–H, 100), 148 (M–HO2CH2)(CH2)=N–SO2CF3, 61). 1H NMR (CD3OD): δ (ppm) = 2.99 (t, J = 7.8 Hz, 2H, Ph–CH2CH2N), 3.69 (t broad, J = 7.6 Hz, 2H, Ph–CH2CH2N), 4.15 (s broad, 2H, N–CH2–CO2CH3), 6.94 (d, J = 1.6 Hz, 1H, 4-Hphenyl), 6.95 (dd, J = 7.2/1.7 Hz, 1H, 6-Hphenyl), 7.16 (dd, J = 7.2/1.7 Hz, 1H, 7-Hphenyl). A signal for the NH-proton is not seen in the 1H NMR spectrum.

Unless otherwise noted, the purity of all test compounds is >95% according to one of these HPLC methods.
4.1.3.3  |  7-(Trifluoromethylsulfonyl)-5,6,7,8-tetrahydrooxazolo-[4,5-h]-[3]benzazepine-2,9(3H)-dione (9)

Under N₂ atmosphere and at 0°C, carboxylic acid 8 (110.5 mg, 0.30 mmol) was dissolved in dichloroethane (1 ml) and a saturated solution of P₂O₅ in methanesulfonic acid (3 ml) was added dropwise. The mixture was stirred at rt for 65 h. Then H₂O (20 ml) was added and the suspension was neutralized by K₂CO₃. The aqueous layer was extracted with ethyl acetate (3x), the combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 20 cm, ethyl acetate/n-hexane 2:1, fraction size 10 ml, Rₖ = 0.2). Colorless solid, m.p. 258–259°C, yield 33.0 mg (31%). C₁₂H₉F₃N₂O₅S (Mᵣ = 350.3). MS (ESI): m/z (%) = 699 (2M – H, 100), 349 (M – H, 35). \(^1\)H NMR (CDCl₃): δ [ppm] = 3.21 (t, J = 7.7 Hz, 2H, CH₂CH₂N), 3.71 (s broad, 2H, PH₂CH₂CH₂N), 3.79 (s, J = 6.9 Hz, 2H, NCH₂CH₂CH₃). 5.26–5.34 (m, 2H, NCH₂CH₂CH₃). 5.85–5.95 (m, 1H, NCH₂CH₂CH₂). 6.80 (d, J = 8.1 Hz, 1H, 5H) phenyl). 7.15 (d, J = 8.2 Hz, 1H, 7H phenyl). IR (neat): ν [cm⁻¹] = 2956 (w, νCH₃ aliph.), 1761 (s, νCO ester + νCO oxazolone), 1623 (w)/1495 (m, νC=O arom.), 1355 (m)/1184 (s, νsulfonamide), 1137 (s, νC=O).

4.1.3.4  |  7-Benzyl-5,6,7,8-tetrahydrooxazolo[4,5-h]-[3]benzazepine-2,9(3H)-dione (13)

Under N₂ atmosphere, triflval derivative 9 (60.0 mg, 0.17 mmol) was dissolved in acetonitrile (2 ml) and K₂CO₃ (71.0 mg, 0.51 mmol) was added. The mixture was stirred at 60°C for 40 h. Then again acetonitrile (2 ml) and K₂CO₃ (47.0 mg, 0.34 mmol) were added and the mixture was heated to reflux for 3 h. Then K₂CO₃ was filtered off and NaBH(OAc)₃ (72.3 mg, 0.43 mmol) was added. The mixture was stirred for 30 min at rt before benzaldehyde (106 mg, 1 mmol) immediately followed by NaBH(OAc)₃ (72.0 mg, 0.34 mmol) were added. Stirring was continued for 1 h at rt. Then, the suspension was filtered and the solvent was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 20 cm, ethyl acetate/n-hexane 2:3, fraction size 10 ml, Rₖ = 0.17). Pale yellow solid, yield 8.7 mg (17%). C₁₄H₁₂F₃N₂O₅S (Mᵣ = 308.3). MS (ESI): m/z (%) = 615 (2M – H, 24), 307 (M – H, 77). \(^1\)H NMR (CDCl₃): δ [ppm] = 2.89 (t, J = 6.5 Hz, 2H, 6-H), 3.04 (t, J = 6.9 Hz, 2H, 5-H), 3.48 (s, 2H, 8-H), 3.72 (s, 2H, N-CH₂-C₆H₅), 6.98 (s, 1H, 4-H), 7.12–7.27 (m, 5H, N-CH₂-C₆H₅), 7.44 (s, 1H, 10-H). A signal for the NH-proton is not seen in the \(^1\)H NMR-spectrum. IR (neat): ν [cm⁻¹] = 2924 (m)/2853 (w, νCH₃ aliph.), 1767 (s, νCO oxazolone), 1668 (s)/1606 (s)/1490 (s, νC=O arom.), 1384 (s)/1187 (s, νsulfonamide), 1143 (s, νC=O).

4.1.3.5  |  Methyl 2-[N-[2-(3-Allyl-2-oxo-2,3-dihydrobenzoxazol-5-yl)ethyl]-N-(trifluoromethyl-sulfonyl)amino]acetic acid (14)

K₂CO₃ (415 mg, 3 mmol) and allyl bromide (157 mg, 1.3 mmol) were added to a solution of 7 (382.3 mg, 1 mmol) in acetonitrile (12 ml) and the mixture was stirred at rt for 60 h. Then the solution was filtered and solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 3 cm, 20 cm, ethyl acetate/n-hexane 1:2, fraction size 20 ml, Rₖ = 0.33). Pale yellow oil, yield 330 mg (78%). Purity: HPLC method 1; tᵣₖ = 21.4 min, purity 99.3%. C₁₄H₁₇F₂N₂O₅S (Mᵣ = 422.4). MS (ESI): m/z (%) = 867 (2M+Na, 100), 445 (M+Na, 6), 423 (M + H, 1). \(^1\)H NMR (CDCl₃): δ [ppm] = 2.97 (t, J = 7.7 Hz, 2H, PH₂CH₂CH₂N), 3.71 (s broad, 2H, PH₂CH₂CH₂N), 3.79 (s, J = 6.9 Hz, -OCH₃), 4.03 (s broad, 2H, N-CH₂-CO₂CH₃), 4.44 (dd, J = 5.5/1.6 Hz, 2H, NCH₂CH₂CH₃), 5.26–5.34 (m, 2H, NCH₂CH₂CH₃), 5.85–5.95 (m, 1H, NCH₂CH₂CH₂), 6.80 (d, J = 1.5 Hz, 1H, 4H phenyl), 6.93 (dd, J = 8.2/1.7 Hz, 1H, 6H phenyl), 7.15 (d, J = 8.2 Hz, 1H, 7H phenyl). IR (neat): ν [cm⁻¹] = 3300–3100 (br, νC=O-νH), 2943 (w, νC=H aliph.), 1764 (s, νC=O oxazolone), 1733 (s, νC=O carboxylic acid), 1624 (w)/1495 (m, νC=O arom.), 1384 (s)/1185 (s, νsulfonamide), 1137 (s, νC=O).
4.1.3.7 | 3-Allyl-7-(trifluoromethylsulfonyl)-5,6,7,8-tetrahydrooxazolo[4,5-h]-[3]benzazepine-2,9(3H)-dione (16)
Carboxylic acid 15 (3.73 g, 9.14 mmol) was dissolved in the N₂ atmosphere in dry CH₂Cl₂ (450 ml) and P₂O₅ (5.2 g, 36.6 mmol) was added under vigorous stirring. Stirring was continued overnight at rt and the transformation was completed by stirring at 35°C for an additional 24 h. P₂O₅ was filtered off and the solvent of the filtrate was removed completely giving colorless crystals as crude product, which was recrystallized with ethyl acetate. The residual solid matter of P₂O₅ H₂O (50 ml) was added and the suspension was stored overnight at rt. The aqueous suspension of P₂O₅ was filtered off and the solvent of the filtrate was removed to a small volume. This procedure was repeated once more followed by addition of acetonitrile (40 ml) and benzaldehyde (106 mg, 1 mmol). Directly afterward NaBH(OAc)₃ (424 mg, 2.0 mmol) was added and stirring was continued for 1 h. Then a saturated NaHCO₃ solution (50 ml) was added and the mixture was extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a brown oil as crude product, which was recrystallized in ethyl acetate under addition of petroleum ether. Colorless crystals, total yield 2.71 g (76%), M.p.: 219°C (decomposition). Purity: HPLC method 1; tᵣ = 19.9 min, purity 96.5%. C₁₅H₁₅F₃N₂O₃S (Mᵢ = 390.3). MS (EI): m/z (%) = 1194 (M+Na, 2), 803 (M+Na, 100), 413 (M+Na, 2), 210 (M, 1). ¹H NMR (CDCl₃; δ [ppm] = 3.15 (t, J = 6.6 Hz, 2H, Ph-CH₂-CH₂-N), 8.34 (broad, 2H, 2H, Ph-CH₂-CH₂-N), 4.33 (broad, 2H, N-CH₂-CO-Ph), 4.50 (d, 2H, NCH₂CH₂Ph), 5.29-5.39 (m, 2H, NCH₂CH₂C₆H₅), 5.86-5.89 (m, 1H, NCH₂CH₂C₆H₅), 6.83 (s, 1H, 4-Hphenyl), 7.65 (s, 1H, 10-Hphenyl), IR (neat); ν (cm⁻¹) = 2924 (m)/2853 (w), 1681 (s, vC=O oxazolone), 1628 (s, vC=O ketone), 1546 (M), 1120 (s, vC·OH). ¹³C NMR (CDCl₃): δ [ppm] = 2.95 (t, J = 6.5 Hz, 2H, 6-H), 3.56 (s, 2H, 10-HPh), 3.74 (s, 2H, N-CH₂-Ph), 4.47 (d, J = 5.6 Hz, 2H, NCH₂CH₂CH₂), 5.31-5.36 (m, 2H, NCH₂CH₂C₆H₅), 5.86-6.01 (m, 1H, NCH₂CH₂C₆H₅), 6.77 (s, 1H, 4-H), 7.05-7.37 (m, 5H, N-CH₂-C₆H₅), 7.58 (s, 1H, 10-H).

4.1.3.8 | 3-Allyl-7-benzyl-5,6,7,8-tetrahydrooxazolo[4,5-h]-[3]benzazepine-2,9(3H)-dione (19a)
N-Triflylketone 16 (390 mg, 1.0 mmol) was dissolved in dry acetone (40 ml) under N₂ atmosphere and K₂CO₃ (276.4 mg, 2 mmol) was added. The suspension was stirred at 40°C for 16 h. Then H₂O (50 ml) was added and the solution was extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (Na₂SO₄) and the mixture was concentrated at approximately 5 ml. Then acetonitrile (10 ml) was added and the solvent was again removed to a small volume. This procedure was repeated once more followed by addition of acetonitrile (40 ml) and benzaldehyde (106 mg, 1 mmol). Directly afterward NaBH(OAc)₃ (424 mg, 2.0 mmol) was added and stirring was continued for 1 h. Then a saturated NaHCO₃ solution (50 ml) was added and the mixture was extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a brown oil as crude product, which was recrystallized in ethyl acetate under addition of petroleum ether. Colorless crystals, total yield 2.63 mg (82%).

4.1.3.9 | 3-Allyl-7-benzyl-9-hydroxy-3,5,6,7,8,9-hexahydrooxazolo[4,5-h]-[3]benzazepine-2-one (21a)
(a) Purified benzylketone 19a (34.8 mg, 0.1 mmol) was dissolved in dry methanol (3 ml) under an N₂ atmosphere and NaBH₄ (11.4 mg, 0.3 mmol) was added. The solution was stirred overnight at rt. Then H₂O (10 ml) was added and the mixture was extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a yellowish oil as crude product, which was purified by flash column chromatography (Ø 1.5 cm, 21 cm, ethyl acetate/n-hexane 1:1, fraction size 10 ml, Rₛ = 0.18). Colorless crystals, yield 26.3 mg (82%).
(b) The crude benzylketone 19a was used without purification in this reaction. Dry methanol (20 ml) and NaBH₄ (227 mg, 6 mmol) were added under an N₂ atmosphere and the solution was stirred for 1 h at rt. Then H₂O (50 ml) was added and the mixture was extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a yellow oil as crude product, which was purified by flash column chromatography (details see under procedure [a]).

Colorless crystals, yield 115.6 mg (33%). M.p.: 125°C. Purity: HPLC method 2; tᵣ = 12.7 min, purity 97.1%. C₂₁H₂₂N₂O₄S (Mᵢ = 350.4). MS (EI): m/z (%) = 350 (M, 4), 259 (M-Benzyl, 9), 134 (benzyl-NCH₂(CH₂)₃), 100, 91 (benzyl, 29). ¹H NMR (CDCl₃); δ [ppm] = 2.41 (t, J = 11.7 Hz, 1H, 1-H), 2.74 (dd, J = 12.1 Hz, 1H, 8-H), 2.71 (dd, J = 15.2/6.4 Hz, 1H, 5-H), 2.99 (dd, J = 12.2/6.5 Hz, 1H, 6-H), 3.18 (dd, J = 11.7/7.2 Hz, 1H, 8-H), 3.25-3.35 (m, 1H, 5-H), 3.72 (s, 2H, N-CH₂-Ph), 4.40 (d, J = 5.5 Hz, 2H, NCH₂CH₂CH₂), 4.64 (d, J = 7.0 Hz, 1H, 9-H), 5.24-5.31 (m, 2H, NCH₂CH₂CH₂), 5.82-5.93 (m, 1H, NCH₂CH₂CH₂), 6.67 (s, 1H, 4-H), 7.09 (s, 1H, 10-H), 7.27-7.39 (m, 5H, N-CH₂-C₆H₅). A signal for the OH-proton is not seen in the ¹H NMR-spectrum. IR (neat); ν (cm⁻¹) = 3473 (m, νO-H), 2915 (m)/2812 (m, νC-H aliph.), 1762 (s, νC·O oxazolone), 1619 (w)/1492 (w), 1361 (s, νC=C arom.), 735 (s)/698 (s, νC-H subst. arom.).
were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a yellow oil as crude product, which was purified by flash column chromatography (Ø 3 cm, 17 cm, ethyl acetate/n-hexane 2:1, fraction size 20 ml, Rᵣ = 0.20). Colorless crystals, yield 182.3 mg (40%). M.p.: 123°C. Purity: HPLC method 1; tᵣ = 16.3 min, purity 98.8%. C₂₃H₂₃N₂O₃ (M = 364.4). MS (EI): m/z (%) = 751 (2M + Na, 10), 365 (M+H, 100). ¹H NMR (CDCl₃): δ [ppm] = 2.53 (t, J = 11.6 Hz, 1H, 6-H), 2.66 (dd, J = 12.1 Hz, 1H, 8-H), 2.73 (dd, J = 15.3/6.1 Hz, 1H, 5-H), 2.78–2.92 (m, 4H, N–CH₂–CH₂–Ph), 3.06 (dd, J = 12.2/6.5 Hz, 1H, 6-H), 3.20 (dd, J = 12.1/6.8 Hz, 1H, 8-H), 3.24–3.34 (m, 1H, 7-H), 4.41 (d, J = 5.5 Hz, 2H, NCH₂CH₂), 4.62 (d, J = 6.9 Hz, 1H, 9-H), 5.24–5.32 (m, 2H, NCH₂CH₂–), 5.83–5.94 (m, 1H, NCH₂CH₂–), 6.68 (s, 1H, 4-H), 7.08 (s, 1H, 10-H), 7.18–7.34 (m, 5H, N–CH₂–CH₂–C₆H₃). A signal for the OH-proton is not seen in the ¹H NMR spectrum. IR (neat): ν [cm⁻¹] = 3420 (m, νO–H), 2927 (m)/2858 (w, νC–H aliph.), 1768 (s, νC=O oxazolone), 1619 (w). 1H NMR (CDCl₃): δ [ppm] = 3.17 (m, 1H, 8–H), 5.31 (m, 2H, N–CH₂–), 5.83 (s, 1H, 4–H), 6.67 (s, 1H, 10–H), 7.16–7.32 (m, 5H, –CH₂–C₆H₃). A signal for the OH-proton is not found in the ¹H NMR spectrum. IR (neat): ν [cm⁻¹] = 3414 (m, νO–H), 2937(m)/2813 (w, νC=H aliph.), 1767 (s, νC=O oxazolone), 1619 (w)/1602 (w)/1492 (s, νC=O arom.), 750 (s)/699 (s, νC=C arom.). 4.1.3.12 | 3-Allyl-9-hydroxy-7(4-phenylbutyl)-3,5,6,7,8,9-hexahydrooxazolo[4,5-h]-[3]benzazepine-2-one (21d)

N-Triflylketone 16 (390 mg, 1.0 mmol) was dissolved in dry acetonitrile (40 ml) under an N₂ atmosphere and K₂CO₃ (276.5 mg, 2.0 mmol) was added. The suspension was stirred at 40°C for 16 h. Then H₂O (30 ml) was added and the solution was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was concentrated to approximately 5 ml. Acetonitrile (10 ml) was added and the solvent was again removed to a small volume. This procedure was repeated once more followed by the addition of acetonitrile (20 ml) and 4-phenylbutanal (193 mg, 1.3 mmol). Directly afterwards NaBH₄(OAc)₃ (423 mg, 2.0 mmol) was added and stirring was continued for 1 h. Then a saturated NaHCO₃ solution (50 ml) was added and the mixture was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed to a small volume under reduced pressure. Dry methanol (10 ml) and brine (20 ml) were added and the mixture was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed to a small volume under reduced pressure giving a yellow oil as crude product, which was purified by flash column chromatography (Ø 3 cm, 21 cm, ethyl acetate/n-hexane 2:1, fraction size 20 ml, Rᵣ = 0.10). Yellow oil, yield 182 mg (46%). Purity: HPLC method 1; tᵣ = 17.6 min, purity 97.8%. C₂₂H₂₄N₂O₃ (% = 392.5). MS (ESI): m/z (%) = 1199 (3M+Na, 2), 807 (2M+Na, 5), 393 (M+H, 100), 375 (M–OH, 13). ¹H NMR (CDCl₃): δ [ppm] = 1.51–1.73 (m, 4H, N–CH₂–C₆H₃–C₂H₅–Ph), 2.40 (t, J = 11.4 Hz, 1H, 10–H), 2.53 (d, J = 12.1 Hz, 1H, 8–H), 2.56–2.67 (m, 4H, N–CH₂–C₂H₅–C₂H₅–Ph), 2.70 (dd, J = 15.2/6.2 Hz, 1H, 5–H), 2.95 (dd, J = 12.4/6.4 Hz, 1H, 6–H), 3.09–3.17 (m, 1H, 8–H), 3.24–3.34 (m, 1H, 5–H), 4.41 (dt, J = 5.5/1.5 Hz, 2H, N–CH₂–CH₂–), 4.61 (d, J = 7.0Hz, 1H, 9–H), 5.24–5.32 (m, 2H, N–CH₂–CH₂–), 5.83–5.94 (m, 1H, N–CH₂–CH₂–), 6.67 (s, 1H, 4–H), 7.09 (s, 1H, 10–H), 7.15–7.32 (m, 5H, –CH₂–C₆H₃). A signal for the OH-proton could not be found in the ¹H NMR spectrum. IR (neat): ν [cm⁻¹] = 3420 (m, νO–H), 2933 (m)/2858 (w, νC=H aliph.), 1767 (s, νC=O oxazolone), 1619 (w)/1604 (w)/1492 (s, νC=O arom.), 749 (s)/699 (s, νC=C arom.). 4.1.3.13 | 3-Allyl-9-hydroxy-7(4-methoxybenzyl)-3,5,6,7,8,9-hexahydrooxazolo[4,5-h]-[3]benzazepine-2-one (21e)

Under N₂ atmosphere, N-triflylketone 16 (39.5 mg, 0.10 mmol) was dissolved in dry acetonitrile (4.5 ml) and K₂CO₃ (41.1 mg, 0.30 mmol) was added. The suspension was stirred at 40°C for 5 h. Then H₂O (10 ml) was added and the solution was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the mixture was concentrated to approximately 2 ml. 4-Methoxybenzaldehyde
(60.0 mg, 0.44 mmol) and NaBH(OAc)₃ (47.0 mg, 0.22 mmol) were added and the mixture was stirred at rt under N₂ atmosphere for 1.5 h. Then H₂O (5 ml) and saturated NaHCO₃ solution (5 ml) were added and the solution was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was concentrated to a small volume. Dry MeOH (5 ml) and NaBH₄ (19 mg, 0.50 mmol) were added and the solution was stirred at rt under N₂ atmosphere for 1 h. Then NaHCO₃ solution (5 ml, 10%) and brine (5 ml) were added and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 16 cm, ethyl acetate/n-hexane 2:1 + 0.5%, N,N-dimethylmethane, fraction size 10 ml, Rf = 0.15). Colorless crystals, yield 56.2 mg (68.2%). M.p.: 87°C. Purity: HPLC method 2; tᵢ = 13.1 min, purity 99.6%. C₂₂H₂₃NO₃ (Mᵢ = 406.5). MS (EI): m/z (%) = 406 (M, 12), 388 (M–H₂O, 6), 273 (M–Ph(CH₂)₂CO₂), 190 (Ph(CH₂)₅(N(CH₃)₂CH₃), 55). 91 (Benzyl, 6). ¹H NMR (CDCl₃): δ [ppm] = 2.12 (t, J = 7.9 Hz, 2H, 2-Hpentyl), 1.61–1.70 (m, 2H, 4-Hpentyl), 2.42 (t, J = 11.8 Hz, 1H, 6-H), 2.54 (d, J = 11.8 Hz, 1H, 8-H), 2.56 (t, J = 7.4 Hz, 2H, 1-Hpentyl). 2.62 (t, J = 7.7 Hz, 2H, 5-Hpentyl). 2.71 (dd, J = 15.3/6.2 Hz, 1H, 5-H). 2.96 (dd, J = 12.3/6.3 Hz, 1H, 6-H), 3.13 (dd, J = 11.7/7.4 Hz, 1H, 8-H), 3.29 (m, 1H, 5-H), 4.41 (td, J = 5.5/1.4 Hz, 2H, N–CH₂–CH=CH₂), 4.62 (d, J = 6.9 Hz, 1H, 9-H), 5.24–5.32 (m, 2H, N–CH₂–CH=CH₂), 5.83–5.94 (m, 1H, N–CH=CH₂), 6.68 (s, 1H, 4-H), 7.09 (s, 1H, 10-H), 7.15–7.21 (m, 2H, 2-H/4-H/6-H), 7.26–7.31 (m, 2H, 3-H/5-H/phenyl). A signal for the OH-proton is not found in the ¹H NMR-spectrum. IR (neat): ν [cm⁻¹] = 3457 (w, vO=O), 2931 (m)/(2855 (w, vC=H aliph.), 1767 (s, vC=O oxazolone), 1619 (w)/(1492 (s, vC=O arom.), 749 (s)/(698 (s, νmonosubst. arom.)).

4.1.3.15 | 3-Allyl-9-hydroxy-7-(3-phenoxypropyl)-3,5,6,7,8,9-hexahydrooxazolo[4,5-h]:[3]benzazepin-2-one (21g)

Under N₂ atmosphere, N-triflylketone 16 (44.1 mg, 0.11 mmol) was dissolved in dry acetonitrile (6 ml) and K₂CO₃ (51 mg, 0.37 mmol) was added. The suspension was stirred at 60°C for 8 h. Then H₂O (5 ml) was added and the solution was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the mixture was concentrated to a small volume. Methanol (2 ml) and NaBH₄ (13.0 mg, 0.34 mmol) were added and the mixture was stirred under N₂ atmosphere at rt over night. Then H₂O (15 ml) was added and the solution was stirred under N₂ atmosphere, N-triflylketone 16 (44.1 mg, 0.11 mmol) was dissolved in dry acetonitrile (6 ml) and K₂CO₃ (51 mg, 0.37 mmol) was added. The suspension was stirred at 60°C for 8 h. Then H₂O (5 ml) was added and the solution was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure. Acetonitrile (3 ml), 1-bromo-3-phenoxy-propane (72.9 mg, 0.34 mmol) and K₂CO₃ (47 mg, 0.34 mmol) were added and the mixture was stirred at 50°C for 22 h. Then H₂O (5 ml) and brine (5 ml) were added and the solution was extracted with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 17 cm, ethyl acetate/n-hexane 2:1 + 0.5% N,N-dimethylmethane, fraction size 10 ml, Rf = 0.15). Colorless solid, yield 33.0 mg (74%). M.p.: 99°C. Purity: HPLC method 2; tᵢ = 13.4 min, purity 98.3%. C₂₂H₂₃NO₃ (Mᵢ = 394.5). MS (EI): m/z (%) = 811 (2M+Na, 17), 375 (M+H, 100), 377 (M–OH, 9). ¹H NMR (CDCl₃): δ [ppm] = 1.96–2.07 (m, 2H, 2-Hphenoxypyropyl). 2.49 (t, J = 11.6 Hz, 1H, 6-H), 2.61 (d, J = 12.1 Hz, 1H, 8-H), 2.74 (dd, J = 15.3/6.2 Hz, 1H, 5-H), 2.80 (t, J = 7.2 Hz, 2H, 1-Hphenoxypyropyl), 3.00 (dd, J = 12.3/6.5 Hz, 1H, 6-H), 3.18 (ddd, J = 12.0/
7.0/1.2 Hz, 1H, 8-H), 3.25–3.35 (m, 1H, 5-H), 4.01–0.49 (m, 2H, 3-Hphenoxopyrpylorpy), 4.41 (td, J = 5.5/1.5 Hz, 2H, N–CH2–CH(═CH2), 4.65 (d, J = 6.9 Hz, 1H, 9-H), 5.24–5.33 (m, 2H, N–CH2–CH(═CH2), 5.82–5.95 (m, 1H, N–CH2–CH(═CH2), 6.69 (s, 1H, 4-H), 6.88–6.98 (m, 3H, 2H/3-H/6-Hphenox). A signal for the OH-proton is not found in the 1H NMR-spectrum. IR (neat): ν [cm⁻¹] = 3445 (w, νC–H aliph.), 1766 (s, νC=O oxazolone), 1619 (w)/1583 (w)/1492 (s, νC=O arom.), 738 (s)/690 (s, νmonosubst. arom.).

4.1.3.16 | 3-Allyl-9-hydroxy-7-[3-(phenylsulfonyl)propyl]-5,6,7,8,9-hexahydrooxazolo[4,5-h]-[3]benzazepin-2-one (21h)

Under the N2 atmosphere, N-triflylketone 16 (158 mg, 0.40 mmol) was dissolved in dry acetonitrile (21 ml) and K2CO3 (168 mg, 1.22 mmol) was added. The suspension was stirred at 70°C for 3 h. Then H2O (15 ml) was added and the solution was extracted with CH2Cl2 (3x). The combined organic layers were dried (Na2SO4) and the solution was concentrated to approximately 2 ml. Methanol (6 ml) and NaBH4 (30.6 mg, 0.81 mmol) were added and the mixture was stirred at rt under N2 atmosphere for 1 h. Then H2O (15 ml) was added and the solution was extracted with CH2Cl2 (3x). The combined organic layers were dried (Na2SO4) and the solvent was removed completely under reduced pressure. To the crude intermediate 1-chloro-3-phenylsulfonylpropene (176.7 mg, 0.81 mmol), TBAI (55.7 mg, 0.15 mmol), K2CO3 (165.9 mg, 1.20 mmol) and acetonitrile (5 ml) were added and the suspension was stirred at 80°C overnight. Then H2O (15 ml) was added and the solution was extracted with CH2Cl2 (3x). The combined organic layers were dried (Na2SO4) and the solvent was removed under reduced pressure given a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 15 cm, ethyl acetate/n-hexane 3:1:0.5%, N,N-dimethylethanamine, fraction size 10 ml, Rf = 0.15). Pale yellow oil, yield 113 mg (63%). Purity: HPLC method 1; tR = 15.0 min, purity 97.5%. 1H NMR (CDCl3): δ [ppm] = 1.90–2.04 (m, 2H, N–CH2–CH2–CH2–SO2), 2.44 (t, J = 11.5 Hz, 1H, 6-H), 2.59 (d, J = 12.2 Hz, 1H, 8-H), 2.64–2.68 (m, 2H, N–CH2–CH2–CH2–SO2), 2.73 (dd, J = 15.6/6.8 Hz, 1H, 5-H), 2.82–2.90 (m, 1H, 6-H), 2.96–3.04 (m, 1H, 8-H), 3.13–3.25 (m, 3H, N–CH2–CH2–CH2–SO2–CH2), 4.41 (d, J = 5.5 Hz, 2H, N–CH2–CH2–CH2–SO2), 4.64 (d, J = 7.0 Hz, 1H, 9-H), 5.24–5.32 (m, 2H, N–CH2–CH2–CH2–SO2–CH2), 5.82–5.93 (m, 1H, N–CH2–CH2–CH2–SO2–CH2), 6.67 (s, 1H, 4-H), 7.11 (s, 1H, 10-H), 7.56–7.63 (m, 2H, 3-H/5-Hphenyl), 7.66–7.71 (m, 1H, 4-Hphenyl), 7.90–7.95 (m, 2H, 2-H/6-Hphenyl). A signal for the OH-proton is not found in the 1H NMR-spectrum. IR (neat): ν [cm⁻¹] = 3300–3600 (w, νC=OH), 2934 (w)/2817 (w, νC–H aliph.), 1765 (s, νC=O oxazolone), 1620 (w)/1585 (w)/1493 (s, νC=O arom.), 1304 (m)/1145 (m, νC=O arom.)

4.1.3.17 | 3-Allyl-9-hydroxy-7-[3-(phenylsulfonyl)propyl]-5,6,7,8,9-hexahydrooxazolo[4,5-h]-[3]benzazepin-2-one (21i)

Under N2 atmosphere, N-triflylketone 16 (157 mg, 0.40 mmol) was dissolved in dry acetonitrile (21 ml) and K2CO3 (167.4 mg, 1.21 mmol) was added. The suspension was stirred at 70°C for 4 h. Then H2O (15 ml) was added and the solution was extracted with CH2Cl2 (3x). The combined organic layers were dried (Na2SO4) and the solution was concentrated to approximately 2 ml. Methanol (6 ml) and NaBH4 (50.4 mg, 0.80 mmol) were added and the mixture was stirred at 70°C for 3 h. Then H2O (15 ml) was added and the solution was extracted with CH2Cl2 (3x). The combined organic layers were dried (Na2SO4) and the solvent was removed completely under reduced pressure. To the crude intermediate 1-chloro-3-phenylsulfonylpropene (176.7 mg, 0.81 mmol), TBAI (55.7 mg, 0.15 mmol), K2CO3 (165.9 mg, 1.20 mmol) and acetonitrile (5 ml) were added and the suspension was stirred at 80°C overnight. Then H2O (15 ml) was added and the solution was extracted with CH2Cl2 (3x). The combined organic layers were dried (Na2SO4) and the solvent was removed under reduced pressure given a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 15 cm, ethyl acetate/n-hexane 3:1:0.5%, N,N-dimethylethanamine, fraction size 10 ml, Rf = 0.15). Pale yellow oil, yield 113 mg (63%). Purity: HPLC method 1; tR = 15.0 min, purity 97.5%. 1H NMR (CDCl3): δ [ppm] = 1.90–2.04 (m, 2H, N–CH2–CH2–CH2–SO2), 2.44 (t, J = 11.5 Hz, 1H, 6-H), 2.59 (d, J = 12.2 Hz, 1H, 8-H), 2.64–2.68 (m, 2H, N–CH2–CH2–CH2–SO2), 2.73 (dd, J = 15.6/6.8 Hz, 1H, 5-H), 2.82–2.90 (m, 1H, 6-H), 2.96–3.04 (m, 1H, 8-H), 3.13–3.25 (m, 3H, N–CH2–CH2–CH2–SO2–CH2), 4.41 (d, J = 5.5 Hz, 2H, N–CH2–CH2–CH2–SO2), 4.64 (d, J = 7.0 Hz, 1H, 9-H), 5.24–5.32 (m, 2H, N–CH2–CH2–CH2–SO2–CH2), 5.82–5.93 (m, 1H, N–CH2–CH2–CH2–SO2–CH2), 6.67 (s, 1H, 4-H), 7.11 (s, 1H, 10-H), 7.56–7.63 (m, 2H, 3-H/5-Hphenyl), 7.66–7.71 (m, 1H, 4-Hphenyl), 7.90–7.95 (m, 2H, 2-H/6-Hphenyl). A signal for the OH-proton is not found in the 1H NMR-spectrum. IR (neat): ν [cm⁻¹] = 3300–3600 (w, νC=OH), 2934 (w)/2817 (w, νC–H aliph.), 1765 (s, νC=O oxazolone), 1620 (w)/1585 (w)/1493 (s, νC=O arom.), 1304 (m)/1145 (m, νC=O arom.)
under N₂ atmosphere for 1 h. Then H₂O (15 ml) was added and the solution was extracted with CH₂Cl₂ (5x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed completely under reduced pressure. To the crude intermediate 1-chloro-3-[2-(4-fluorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]propane (234.7 mg, 0.82 mmol), TBAI (73.9 mg, 0.20 mmol), K₂CO₃ (165.9 mg, 1.20 mmol) and acetonitrile (5 ml) were added and the suspension was stirred at 80°C for 24 h. Then H₂O (15 ml) was added and the solution was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solution was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 3 cm, 13 cm, ethyl acetate/n-hexane 3:2 + 0.5%, N,N-dimethylethanolamine, fraction size 10 ml, Rₜ = 0.20).

Pale yellow oil, yield 154 mg (70%). Purity: HPLC method 1; tᵣ = 22.2 min, purity 95.6%. C₃₃H₄₄N₂O₅ (M = 548.7). MS (EI): m/z (%) = 548 (M, 5), 530 (M-H₂O, 38), 332 (4-tert-butylyphenyl-C(C₆H₅)O₂-CH₂-CH₂-CH₂-N(CH₃)₂(CH₃)), 273.2 (M-4-tert-butylyphenyl-C(C₆H₅)O₂-CH₂-CH₂), 65.1H NMR (CDCl₃); δ [ppm] = 0.58 (s, 3H, C(CH₃)₂), 1.25 (s, 3H, C(CH₃)₂), 1.34 (s, 9H, C(CH₃)₃), 1.60-1.76 (m, 4H, N-CH₂-CH₂-CH₂-C), 2.35 (t, J = 11.7 Hz, 1H, 6-H), 2.46-2.53 (m, 3H, N-CH₂-CH₂-CH₂-C, 8-H), 2.66 (dd, J = 15.2/6.2 Hz, 1H, 5-H), 2.89-2.96 (m, 1H, 6-H), 3.09 (dd, J = 12.0/6.7 Hz, 1H, 8-H), 3.26 (m, 1H, 5-H), 3.36 (d, J = 11.0 Hz, 2H, O-CH₂), 3.47 (d, J = 10.9 Hz, 2H, O-CH₂), 4.40 (d, J = 5.5 Hz, 2H, N-CH₂-CH₂), 4.58 (d, J = 6.8 Hz, 1H, 9-H), 5.24-5.31 (m, 2H, N-CH₂-CH₂), 5.82-5.93 (m, 1H, N-CH₂-CH₂), 6.66 (s, 1H, 4-H), 7.07 (s, 1H, 10-H), 7.29 (d, J = 8.4 Hz, 2H, 3-H/5-H-t-butylphenyl). A signal for the OH-proton is not found in the ¹H NMR-spectrum. IR (neat): ν [cm⁻¹] = 3453 (w, νC=O), 2952 (m)/2868 (w, νC-H aliph.). 1773 (s, νC=O oxazolone), 1619 (w)/1493 (s, νC=C aron.); 1081 (s, νC-O-C).

4.1.3.20 | 3-Allyl-9-hydroxy-7-(4-phenylbenzyl)-3,5,6,7,8,9-hexahydrooxazolo[4,5-h]-[3]benzaepin-2-one (21n)

N-Triflylketone 16 (78.0 mg, 0.20 mmol) was dissolved in dry acetonitrile (10 ml) under N₂ atmosphere and K₂CO₃ (82.9 mg, 0.6 mmol) was added. The suspension was stirred at 40°C for 16 h. Then H₂O (10 ml) was added and the solution was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the mixture was concentrated at approximately 2 ml. Methanol (3 ml) and NaBH₄ (15.1 mg, 0.40 mmol) were added and the mixture was stirred for 1 h at rt. Then H₂O (5 ml) and brine (5 ml) were added and the solution was extracted with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure. Acetonitrile (3 ml), 4-biphenylnaldehyde (43.7 mg, 0.24 mmol) and NaBH(OAc)₃ (84.8 mg, 0.4 mmol) were added to the residue and the mixture was stirred for 16 h at rt. Then K₂CO₃ solution (5 ml, 10%) and brine (5 ml) were added and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 3 cm, 13 cm, ethyl acetate/n-hexane 1:1 + 0.5%, N,N-dimethylethanolamine, fraction size 10 ml, Rₜ = 0.17). Pale yellow oil, yield 154 mg (70%). Purity: HPLC method 1; tᵣ = 22.2 min, purity 95.6%. C₃₃H₄₄N₂O₅ (M = 548.7). MS (EI): m/z (%) = 548 (M, 5), 530 (M-H₂O, 38), 332 (4-tert-butylyphenyl-C(C₆H₅)O₂-CH₂-CH₂-CH₂-N(CH₃)₂(CH₃)), 273.2 (M-4-tert-butylyphenyl-C(C₆H₅)O₂-CH₂-CH₂), 65.1H NMR (CDCl₃); δ [ppm] = 0.58 (s, 3H, C(CH₃)₂), 1.25 (s, 3H, C(CH₃)₂), 1.34 (s, 9H, C(CH₃)₃), 1.60-1.76 (m, 4H, N-CH₂-CH₂-CH₂-C), 2.35 (t, J = 11.7 Hz, 1H, 6-H), 2.46-2.53 (m, 3H, N-CH₂-CH₂-CH₂-C, 8-H), 2.66 (dd, J = 15.2/6.2 Hz, 1H, 5-H), 2.89-2.96 (m, 1H, 6-H), 3.09 (dd, J = 12.0/6.7 Hz, 1H, 8-H), 3.26 (m, 1H, 5-H), 3.36 (d, J = 11.0 Hz, 2H, O-CH₂), 3.47 (d, J = 10.9 Hz, 2H, O-CH₂), 4.40 (d, J = 5.5 Hz, 2H, N-CH₂-CH₂), 4.58 (d, J = 6.8 Hz, 1H, 9-H), 5.24-5.31 (m, 2H, N-CH₂-CH₂), 5.82-5.93 (m, 1H, N-CH₂-CH₂), 6.66 (s, 1H, 4-H), 7.07 (s, 1H, 10-H), 7.29 (d, J = 8.4 Hz, 2H, 3-H/5-H-t-butylphenyl). A signal for the OH-proton is not found in the ¹H NMR-spectrum. IR (neat): ν [cm⁻¹] = 3453 (w, νC=O), 2952 (m)/2868 (w, νC-H aliph.). 1773 (s, νC=O oxazolone), 1619 (w)/1493 (s, νC=C aron.); 1081 (s, νC-O-C).
4.1.3.21 | 3-Allyl-9-hydroxy-7-[4-(methylphenyl)benzyl]-3,5,6,7,8,9-hexahydroxazolo[4,5-h] [3]benzazepin-2-one (21a)

Under N₂ atmosphere, N-triflylketone 16 (124 mg, 0.32 mmol) was dissolved in dry acetonitrile (16 ml) and K₂CO₃ (133 mg, 0.96 mmol) was added. The suspension was stirred at 60°C for 5.5 h. Then H₂O (15 ml) was added and the solution was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solution was concentrated to approximately 2 ml. Methanol (8 ml) and NaBH₄ (24.3 mg, 0.64 mmol) were added and the mixture was stirred at rt under N₂ atmosphere for 1 h. Then H₂O (5 ml) and brine (5 ml) were added and the solution was extracted with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure. Acetonitrile (5 ml), 4-(4-methylphenyl)benzaldehyde (91.3 mg, 0.47 mmol) and NaBH(OAc)₃ (136.2 mg, 0.64 mmol) were added to the residue and the mixture was stirred overnight at rt. K₂CO₃ solution (10 ml, 10%) was added and the solution was extracted with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 3 cm, 16 cm, ethyl acetate/n-hexane 3:2 + 0.5% N,N-dimethylethamamine, fraction size 10 ml, Rₜ = 0.25). Colorless crystals, yield 57 mg (41%). M.p.: 177°C. Purity: HPLC method 2; tₙ = 17.3 min, purity 96.1%. C₂₈H₂₂FN₂O₃ (Mₚ = 440.5) MS (EI); m/z (%) = 440 (M, 2), 422 (M–H₂O, 6), 259 (M–4-(methylphenyl)benzyl, 14), 224 (CH₃(Ph)₂–CH₂–N(CH₃)₂(CH₂)_8, 80), 181 (CH₃(Ph)₂–CH₂, 100). ¹H NMR (CDCl₃); δ [ppm] = 2.40 (s, 3H, –CH₃), 2.43 (t, J = 12.0 Hz, 1H, 6-H), 2.58 (d, J = 12.0 Hz, 1H, 8-H), 2.73 (dd, J = 15.3/6.4 Hz, 1H, 5-H), 3.04 (dd, J = 11.9/6.2 Hz, 1H, 6-H), 3.23 (dd, J = 11.6/7.2 Hz, 1H, 8-H), 3.33 (m, 1H, 5-H), 3.76 (s, 2H, N–CH₂–Ph), 4.41 (td, J = 5.5/1.4 Hz, 2H, N–CH₂–CH=CH=CH₂), 4.66 (d, J = 6.9 Hz, 1H, 9-H), 5.24–5.32 (m, 2H, N–CH₂–CH=CH=CH₂), 5.38–5.94 (m, 1H, N–CH₂–CH=CH=CH₂), 6.68 (s, 1H, 4-H), 7.10 (s, 1H, 10-H), 7.25 (d, J = 8.3 Hz, 2H, 3-H/5-H₄, methylphényl), 7.40 (d, J = 8.1 Hz, 2H, 2-H/6-H₄phenyl), 7.50 (d, J = 8.1 Hz, 2H, 2(H/6-H₄phenyl), 7.62 (d, J = 8.2 Hz, 2H, 3-H/5-H₄benzyl). A signal for the OH-proton is not found in the ¹H NMR-spectrum. IR (neat); ʋ [cm⁻¹] = 3087 (w, νC=O), 2919 (m)/(2844 (w, νC–H aliph.), 1772 (s, νC=O oxazolone), 1617 (w)/1489 (s, νC=C arom.), 803 (s, νs subst. arom.).

4.1.3.22 | 3-Allyl-9-hydroxy-7-[2-fluoro-4-phenylbenzyl]-3,5,6,7,8,9-hexahydroxazolo[4,5-h] [3]benzazepin-2-one (21p)

Under N₂ atmosphere, N-triflylketone 16 (122 mg, 0.31 mmol) was dissolved in dry acetonitrile (17 ml) and K₂CO₃ (129 mg, 0.94 mmol) was added. The suspension was stirred at 63°C for 5.5 h. Then H₂O (10 ml) was added and the solution was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solution was concentrated to approximately 2 ml. Methanol (5 ml) and NaBH₄ (23.5 mg, 0.62 mmol) were added and the mixture was stirred at rt under N₂ atmosphere for 1.5 h. Then H₂O (15 ml) was added and the solution was extracted with CH₂Cl₂ (8x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed completely under reduced pressure. To the crude intermediate CH₂Cl₂ (5 ml), 2-fluoro-4-phenylbenzaldehyde (74.5 mg, 0.37 mmol) and NaBH(OAc)₃ (131.4 mg, 0.62 mmol) were added and the mixture was stirred at rt overnight. Then K₂CO₃ solution (15 ml, 10%) was added and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 18 cm, ethyl acetate/n-hexane 2.3 + 0.5% N,N-dimethylethamamine, fraction size 10 ml, Rₜ = 0.12). Colorless crystals, yield 122 mg (67%). M.p.: 73–74°C. Purity: HPLC method 2; tₙ = 16.1 min, purity 98.8%. C₂₇H₂₄F₁₂N₂O₃ (Mₚ = 444.5). MS (EI); m/z (%) = 444 (M, 1), 426 (M–H₂O, 4), 228 (phenyl-2-fluorophenyl-CH₂–N(CH₃)₂(CH₂), 100), 185 (phenyl-2-fluorophenyl-CH₂), 95. ¹H NMR (CDCl₃); δ [ppm] = 2.47 (t, J = 11.6 Hz, 1H, 6-H), 2.62 (d, J = 12.1 Hz, 1H, 8-H), 2.76 (dd, J = 15.4/6.3 Hz, 1H, 5-H), 3.00 (dd, J = 12.4/6.4 Hz, 1H, 6-H), 3.19 (dd, J = 11.7/7.4 Hz, 1H, 8-H), 3.32 (dd, J = 14.6/11.7 Hz, 1H, 5-H), 3.75 (s, 2H, N–CH₂–Ph), 4.42 (dt, J = 5.5/1.5 Hz, 2H, N–CH₂–CH=CH₂), 4.69 (d, J = 7.0 Hz, 1H, 9-H), 5.25–5.32 (m, 2H, N–CH₂–CH=CH₂), 5.83–5.94 (m, 1H, N–CH₂–CH=CH₂), 6.69 (s, 1H, 4-H), 7.12 (s, 1H, 10-H), 7.18 (m, 2H, 3-H/5-H₄fluorophenyl), 7.35–7.48 (m, 4H, 3-H/4-H/H₄phenyl, 6-H₂fluorophenyl), 7.53–7.58 (m, 2H, 2-H/ 6-phenyl). A signal for the OH-proton is not found in the ¹H NMR-spectrum. IR (neat); ʋ [cm⁻¹] = 3450 (w, νH₂O), 2939 (w)/2814 (w, νC–H aliph.), 1767 (s, νC=O oxazolone), 1621 (w)/1581 (w)/1492 (m, νC=C arom.), 751 (m)/698 (s, νs subst. arom.).
C_{26}H_{31}N_{2}O_{3} (M = 433.6), MS (El): m/z (%) = 433 (M, 14), 174 (CH2−Ar−piperidine, 100). 1H NMR (CDCl3): δ [ppm] = 1.54−1.62 (m, 2H, 4-H \_\_piperidine), 1.67−1.75 (m, 4H, 3-H, 5-H \_\_piperidine), 2.35 (t, J = 11.6 Hz, 1H, 6-H), 2.50 (d, J = 12.0 Hz, 1H, 8-H), 2.68 (dd, J = 15.2/6.2 Hz, 1H, 5-H), 3.00 (m, 1H, 1-H), 3.16 (t, J = 5.5 Hz, 4H, 2-H/6-H \_\_piperidine), 3.20 (dd, J = 12.5/7.0 Hz, 1H, 8-H), 3.29 (m, 1H, 5-H), 3.63 (s, 2H, N−CH2−Ar), 4.40 (dt, J = 5.4/1.4 Hz, 2H, N−CH2−CH=CH2), 4.61 (d, J = 6.8 Hz, 1H, 9-H), 5.23−5.31 (m, 2H, N−CH2−CH=CH2), 5.82−5.93 (m, 1H, N−CH2−CH=CH2), 6.66 (s, 1H, 4-H), 6.90 (d, J = 8.6 Hz, 2H, 3H−5/H \_benzyl), 7.07 (s, 1H, 10-H), 7.19 (d, J = 8.6 Hz, 2H, 2-H/6-H \_benzyl). A signal for the OH-proton is not found in the 1H NMR-spectrum. IR (neat): ν [cm−1] = 3300−3000 (w, νC=O), 2928 (w)/2821 (w, νC−H \_aliph.), 1763 (s, νC=O \_oxazoline), 1610 (m)/1491 (s, νC=C \_arom.).

4.1.3.24 | 3-Allyl-7-(9,10-dihydro-9,10-ethanoanthracene-11-yl)methyl-9-hydroxy-3,5,6,7,8,9-hexahydrooxazolo[4,5-h]-[3]benzazepin-2-one (21a)
Under N2 atmosphere, N-triflylketone 16 (166 mg, 0.43 mmol) was dissolved in dry acetonitrile (21 ml) and K2CO3 (173 mg, 1.25 mmol) was added. The suspension was stirred at 63°C for 5.5 h. Then H2O (15 ml) was added and the solution was extracted with CH2Cl2 (3x). The combined organic layers were dried (Na2SO4) and the solution was concentrated to approximately 2 ml. Methanol (6 ml) and NaBH4 (30.3 mg, 0.80 mmol) were added and the mixture was stirred at rt under N2 atmosphere for 1.5 h. Then H2O (15 ml) was added and the solution was extracted with CH2Cl2 (5x). The combined organic layers were washed (Na2SO4) and the solvent was removed completely under reduced pressure. To the crude intermediate CH2Cl2 (5 ml), 9,10-dihydro-9,10-ethanoanthracene-11-carbaldehyde (141 mg, 0.60 mmol) and NaBH4(OAc)2 (170 mg, 0.80 mmol) were added and the mixture was stirred at rt overnight. Then K2CO3 solution (20 ml, 5%) was added and the aqueous layer was extracted with CH2Cl2 (3x). The combined organic layers were dried (Na2SO4) and the solvent was removed under reduced pressure to give a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 18 cm, ethyl acetate/n-hexane 2.5:0.5 %). N,N-dimethylethanamine, fraction size 10 ml, Rf = 0.20). Colorless crystals, yield 160 mg (79%). M.p.: 197°C. Purity: HPLC method 1: τR = 19.5 min, purity 99.2%. C26H30N2O3 (M = 434.6). MS (EI): m/z (%) = 434 (M, 14), 406 (M−H2O, 1), 273 (M−(9,10-dihydro-9,10-ethanoanthracene), 100), 262 (9,10-dihydro-9,10-ethano-11-antihyd-CH2=N(CH2)2, 22). 1H NMR (CDCl3): δ [ppm] = 1.15−1.23 (m, 1H, 11-H \_ethanoanthracene), 1.95−2.40 (m, 5H, 5-H/8-H/6-H, 12-H \_ethanoanthracene), 2.47 (dd, J = 12.2/2.76 Hz, 1H, N−CH2−CH), 2.66−2.76 (m, 1H, N−CH2−CH), 2.84−3.12 (m, 2H, 8-H/6-H), 3.26−3.40 (m, 1H, 5-H), 4.25−4.36 (m, 2H, 9-H/10-H \_ethanoanthracene), 4.41 (d, J = 5.5 Hz, 2H, N−CH2−CH=CH2), 4.57−4.64 (m, 1H, 9-H), 5.24−5.32 (m, 2H, N−CH2−CH=CH2), 5.82−5.94 (m, 1H, N−CH2−CH=CH2), 6.68 (s, 1H, 4-H), 7.08 (s, 1H, 10-H), 7.09−7.16 (m, 1H, 2-H/3-H/6-H/7-H \_ethanoanthracene), 7.23−7.32 (m, 1H/4-H/5-H/8-H \_ethanoanthracene). A signal for the OH-proton is not found in the 1H NMR spectrum. IR (neat): ν [cm−1] = 3453 (w, νC=O), 2939 (w), 1770 (s, νC=O \_oxazoline), 1619 (w)/1493 (s, νC=C \_arom.), 753 (s, ν1,2-diastubl \_arom.).
5-H), 4.91 (d, J = 7.1 Hz 1H, 9-H), 6.86 (s, 1H, 4-H), 7.14–7.30 (m, 5H, N-CH₂-CH₂-C₆H₅), 7.33 (s, 1H, 10-H). Signals for the OH- and NH-protons could not be detected in the ¹H NMR spectrum. IR (neat): ¯ν [cm⁻¹] = 3410 (νs, νO-H), 2923 (m)2851 (w)/2816 (w, νC=O aliph.), 1739 (s, νC=O oxazolone), 1621 (w)/1488 (s, νC=N arom.), 756 (m)/693 (s, νmonosubst. arom.).

4.1.3.27 | 9-Hydroxy-7-(4-phenylpropyl)-3,5,6,7,8,9-hexahydrooxazolo[4,5-h]-[3]benzazepin-2-one (22c)

Allyl derivative 21c (161 mg, 0.43 mmol) was dissolved in EtOH (4.5 ml) under N₂ atmosphere and conc. HCl (54.2 µl, 0.65 mmol) was added. A solution of RhCl₃, 3H₂O (11.3 mg, 0.043 mmol) in EtOH (2 ml) was added dropwise. The solution was stirred at 90°C for 2h before the solvent was removed under reduced pressure. 4 M HCl (15 ml) was added to the crude intermediate and stirring was continued for 4 h at 100°C. Then 10 M NaOH and at the end saturated NaHCO₃ solution were added until pH 7 followed by extraction with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 15 cm, ethyl acetate/n-hexane 4:1 + 1% N-ethylmethylamine, fraction size 10 ml, Rₘ = 0.07). Pale yellow crystals, yield 47.3 mg (33%). M.p.: 190°C (decomposition). Purity: HPLC method 1; tᵣ = 14.3 min, purity 95.5%. C₂₂H₂₂N₂O₃ (Mₑ = 338.4). MS (EI; m/z (%)) = 338 (M, 10), 320 (M-H₂O, 20), 233 (M-CH₂-CH₂-CH₂, 100), 215 (M-H₂O-CH₂-CH₂-CH₂, 18), 91 (benzyl, 22). ¹H NMR (CD₂OD): δ [ppm] = 1.80–1.91 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-CH₂, 2.28–2.32 (m, 1H, 6-H, 6.25–2.44 (m, 1H, 8-H, 2.48–2.58 (m, 2H, N-CH₂-C₆H₅-CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-Ar, 2.64 (t, J = 7.5 Hz, 2H, N-CH₂-C₆H₅-CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-Ar, 2.87–2.97 (m, 3H, 5-H/6-H/8-H), 3.00 (d, J = 12.1 Hz, 1H, 5-H), 4.88 (d, J = 7.1 Hz 1H, 9-H), 6.84 (s, 1H, 4-H), 7.12–7.29 (m, 5H, N-CH₂-C₆H₅), 7.31 (s, 1H, 10-H). Signals for the OH- and NH-protons are not seen in the ¹H NMR spectrum. IR (neat): ν [cm⁻¹] = 3435 (vO, νO-H), 2924 (m)/2854 (w, νC=H aliph.), 1741 (s, νC=O oxazolone), 1620 (m)/1489 (s, νC=N arom.), 759 (s)/695 (s, νmonosubst. arom.).

4.1.3.28 | 9-Hydroxy-7-(4-phenylbutyl)-3,5,6,7,8,9-hexahydrooxazolo[4,5-h]-[3]benzazepin-2-one (22d)

Allyl derivative 21d (130 mg, 0.33 mmol) was dissolved in EtOH (3 ml) under N₂ atmosphere and conc. HCl (41.4 µl, 0.55 mmol) was added. A solution of RhCl₃, 3H₂O (9 mg, 0.033 mmol) in EtOH (2 ml) was added dropwise. The solution was stirred at 90°C for 4h before the solvent was removed under reduced pressure. 4 M HCl (10 ml) was added to the crude intermediate and stirring was continued for 4 h at 100°C. Then 10 M NaOH and at the end saturated NaHCO₃ solution were added until pH 7 followed by extraction with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 1 cm, 10 cm, ethyl acetate/n-hexane 5:1 + 0.5% N,N-dimethylamylamine, fraction size 5 ml, Rₘ = 0.10). Colorless crystals, yield 30.09 mg (62%). M.p.: 147°C. Purity: HPLC method 2; tᵣ = 13.3 min, purity 96.0%. C₂₂H₂₂N₂O₃ (Mₑ = 366.5). MS (EI; m/z (%)) = 366 (M, 4), 348 (M-H₂O, 9), 233 (M-Ph-CH₂), 190 (Ph-CH₂=CH-CH=CH₂, 20), 91 (benzyl, 10). ¹H NMR (CDCl₃): δ [ppm] = 1.32–1.41 (m, 2H, 3-H/pentyl), 1.48–1.60 (m, 2H, 2-H/pentyl), 1.61–1.70 (m, 2H, 4-H/pentyl), 2.41 (t, J = 11.6 Hz, 1H, 6-H), 2.54 (d, J = 12.0 Hz, 1H, 8-H), 2.57 (t, J = 7.4 Hz, 2H, 1-H/pentyl), 2.62 (t, J = 7.7 Hz, 2H, 5-H/pentyl), 2.70 (dd, J = 15.3/6.2 Hz, 1H, 5-H), 2.96 (dd, J = 12.0/6.1 Hz, 1H, 6-H), 3.13 (dd, J = 11.8/7.1 Hz, 1H, 8-H), 3.28 (t, J = 13.0 Hz, 1H, 5-H), 4.62 (d, J = 7.0 Hz, 1H, 9-H), 6.78 (s, 1H, 4-H), 7.08 (s, 1H, 10-H), 7.15–7.21 (m, 3H, 2-H/4-H/6-H/pentyl), 7.27–7.32 (m, 2H, 3-H/5-H/pentyl). Signals for the OH- and NH-protons are not seen in the ¹H NMR spectrum. IR (neat): ν [cm⁻¹] = 3431 (νs, νO-H), 2928 (w)/2856 (w, νC=H aliph.), 1740 (s, νC=O oxazolone), 1618 (w)/1489 (s, νC=N arom.), 760 (m)/694 (s, νmonosubst. arom.).

4.1.3.30 | 9-Hydroxy-7-(3-phenoxypyropyl)-3,5,6,7,8,9-hexahydrooxazolo[4,5-h]-[3]benzazepin-2-one (22g)

Allyl derivative 21g (50.0 mg, 0.13 mmol) was dissolved in EtOH (2 ml) and conc. HCl (11 µl, 0.13 mmol) was added. A solution of RhCl₃, 3H₂O (3.4 mg, 0.013 mmol) in EtOH (1 ml) was added dropwise. The solution was stirred at 80°C for 3.5 h before the solvent was removed under reduced pressure. After addition of 3 M
HCl (4 ml) to the crude intermediate, stirring was continued for 6 h at 90°C. Then H₂O (10 ml) was added and the mixture was stirred overnight at rt. The solution was neutralized by addition of 10 M NaOH and at the end saturated NaHCO₃ solution followed by extraction with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 1 cm, 11 cm, ethyl acetate/n-hexane

\[ \text{Purity: HPLC method 1; } t = 5.0 \text{ min} \]

\[ \text{yield } 32.5 \text{ mg (33%). M.p.: } 144°C. \text{ Purity: HPLC method 1; } \]

\[ \mathbf{H} \text{ NMR (CDCl₃): } \delta [\text{ppm}] = 1.75 \text{ (s, 3H, } \text{CH}_2\text{)} , 4.65 \text{ (s, 2H, } \text{CH}_2\text{)} , 7.30 \text{ (s, 1H, } \text{H}) ] \]

\[ \text{Signals for the OH- and NH-protons are not seen in the } \mathbf{H} \text{ NMR-spectrum. IR (neat): } \nu [\text{cm}^{-1}] = 3300 \text{ (vC=O)} , 1766 \text{ (s, vC=O)} , 1624 \text{ (s, vC=O)} , 1516 \text{ (m, vC=O)} \]

\[ \text{yield } 32.5 \text{ mg (33%). M.p.: } 144°C. \text{ Purity: HPLC method 1; } \]

\[ \mathbf{H} \text{ NMR (CDCl₃): } \delta [\text{ppm}] = 1.75 \text{ (s, 3H, } \text{CH}_2\text{)} , 4.65 \text{ (s, 2H, } \text{CH}_2\text{)} , 7.30 \text{ (s, 1H, } \text{H}) ] \]

\[ \text{Signals for the OH- and NH-protons are not seen in the } \mathbf{H} \text{ NMR-spectrum. IR (neat): } \nu [\text{cm}^{-1}] = 3300 \text{ (vC=O)} , 1766 \text{ (s, vC=O)} , 1624 \text{ (s, vC=O)} , 1516 \text{ (m, vC=O)} \]
4.1.3.34 | 9-Hydroxy-7-(4-phenylbenzyl)-3,5,6,7,8,9-hexahydroxazolo[4,5-h]-3-benzazepin-2-one (22n)

Under N₂ atmosphere, allyl derivative 21n (51.1 mg, 0.12 mmol) was dissolved in ETOH (2 ml) and conc. HCl (15 µL, 0.18 mmol) was added. A solution of RhCl₂, 3H₂O (3.2 mg, 0.012 mmol) in ETOH (1 ml) was added dropwise. The solution was stirred at 75°C for 2 h before the solvent was removed under reduced pressure. After addition of 4 M HCl (6 ml) to the crude intermediate, stirring was continued for 3 h at 90°C. Then 10 M NaOH and at the end saturated NaHCO₃ solution was added until pH 7 followed by extraction with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 1 cm, 9 cm, ethyl acetate/n-hexane 5:1 + 0.5% N,N-dimethylethanolamine, fraction size 5 ml, Rᵢ = 0.13).

Colorless crystals, yield 7.0 mg (15%). M.p.: 210–211°C. Purity: HPLC method 2; tᵣ = 15.5 min, purity 99.5%. C₂₅H₂₁NO₂ (M = 400.5). MS (ESI): m/z (%) = 401 (M+H, 100), 383 (M–OH, 3). ¹H NMR (CDCl₃): δ [ppm] = 2.40 (t, J = 12.0 Hz, 1H, 2H), 2.45 (t, J = 12.0 Hz, 1H, 6-H), 2.61 (d, J = 11.7 Hz, 1H, 8-H), 2.73 (dd, J = 15.2/6.1 Hz, 1H, 5–H), 3.02 (m, 1H, 6–H), 3.22 (dd, J = 11.3/7.3 Hz, 1H, 8–H), 3.31 (m, 1H, 5–H), 3.77 (s, 2H, N–CH₂–Ph), 4.67 (d, J = 6.9 Hz, 1H, 9-H), 6.78 (s, 1H, 4-H), 7.08 (s, 1H, 10–H), 7.25 (d, J = 6.7 Hz, 2H, 3–H/5–H methylphenyl), 7.39 (d, J = 8.0 Hz, 2H, 2–H/6–H benzyl), 7.49 (d, J = 8.0 Hz, 2H, 2–H/6–H 4-methylphenyl), 7.56 (d, J = 8.1 Hz, 2H, 3–H/5–H benzyl). Signals for the OH- and NH-protons are not seen in the ¹H NMR-spectrum. IR (neat): ν [cm⁻¹] = 3500–3000 (w, νCO), 2923 (s)/2852 (m, νCH₃), 1670 (s, νCO₂ axazolane), 1621 (s)/1490 (s, νC–C arom.), 804 (s, νC=O ester).
A solution of RhCl₃. 3H₂O (2.2 mg, 0.008 mmol) in isopropanol (0.5 ml) was added and stirring was continued at 90°C for 2.5 h. Then conc. HCl (0.7 ml) was added and the solution was heated at 90°C under stirring for 3 h. Then saturated K₂CO₃ solution was added until slightly basic reaction and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 1 cm, 14 cm, ethyl acetate/n-hexane 3:1 + 0.5% N,N-dimethylethanamine, fraction size 10 ml, Rₑ = 0.1). Colorless crystals, yield 17.5 mg (54%). M.p.: 197°C (decomposition). Purity: HPLC method 1; 97.6%. C₂₈H₂₆N₂O₃ (% = 438 (M, 12), r = 4 µmin, 254 of 26 R = 14.8 min). MS (EI): m/z (%) = 543.4 (M⁺, 14), 262 (9,10-Dihydro-9,10-ethanooanthracene), 233 (M⁺-9,10-Dihydro-9,10-ethanooanthracene), 204 (M⁺-9,10-Dihydro-9,10-ethanooanthracene), 174 (CH₂-C arom.), 147 (CH₂-C arom.), 125 (CH₂-C arom.), 106 (CH₂-C arom.), 88 (CH₂-C arom.), 70 (CH₂-C arom.).

4.2 Receptor binding studies

4.2.1 Materials

Guinea pig brains, rat brains, and rat livers were commercially available (Harlan-Winkelmann). Pig brains were a donation from the local slaughterhouse. The recombinant Ltk(−) cells stably expressing the GluN2B receptor were obtained from Prof. Dr. Dieter Steinhilber. Homogenizers: Elvejem Potter (B. Braun Biotech International) and Soniprep™ 150 (MSE). Centrifuges: Cooling centrifuge Eppendorf 5424 R (Eppendorf) and High-speed cooling centrifuge model Sorvall® RC-5C plus (Thermo Fisher Scientific). Multiplates: standard 96 well multiplates (Diagonal). Shaker: self-made device with adjustable temperature and turbulence speed (scientific workshop of the institute). Harvester: MicroBeta® FilterMate 96 Harvester. Filter: Printed Filtermat Typ A and B. Scintillator: Meltilex® (Type A or B) solid-state scintillator. Scintillation analyzer: MicroBeta® Trilux (all Perkin Elmer LAS).

4.2.2 Cell culture and preparation of membrane homogenates for the GluN2B assay

Mouse Ltk(−) cells stably transfected with the dexamethasone-inducible eukaryotic expression vectors pMSG GluN1a, pMSG GluN2B (1:5 ratio) were grown in modified Earl’s medium (MEM) containing 10% of standardized FCS (Biochrom AG). The expression of the NMDA receptor at the cell surface was induced after the cell density of the adherent growing cells had reached approximately 90% of confluency. For the induction, the original growth medium was replaced by a growth medium containing 4 µM dexamethasone and 4 µM ketamine (final concentration). After 24 h, the cells were rinsed with phosphate-buffered saline solution (PBS; Biochrom AG), harvested by mechanical detachment, and pelleted (10 min, 5000×g).

For the binding assay, the cell pellet was resuspended in PBS solution and the number of cells was determined using a Scepter® cell counter (MERCK Millipore). Subsequently, the cells were lysed by sonication (4°C, 6 x 10 s cycles with breaks of 10 s). The resulting cell fragments were centrifuged with a high-performance cool centrifuge (23,500×g, 4°C). The supernatant was discarded and the pellet was resuspended in a defined volume of PBS yielding cell fragments of approximately 500,000 cells/ml. The suspension of membrane homogenates was sonicated again (4°C, 2 x 10 s cycles with a break of 10 s) and stored at −80°C.

A solution of RHCl3. 3H2O (2.2 mg, 0.008 mmol) in isopropanol (0.5 ml) was added and stirring was continued at 90°C for 2.5 h. Then conc. HCl (0.7 ml) was added and the solution was heated at 90°C under stirring for 3 h. Then saturated K2CO3 solution was added until slightly basic reaction and the aqueous layer was extracted with CH2Cl2 (3x). The combined organic layers were dried (Na2SO4) and the solvent was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 1 cm, 12 cm, ethyl acetate/n-hexane 3:1 + 0.5% N,N-dimethylethanamine, fraction size 10 ml, Rₑ = 0.1). Colorless crystals, yield 17.5 mg (54%). M.p.: 197°C (decomposition). Purity: Elemental analysis: Calcd. C 70.21 H 6.92 N 10.68, found C 69.81 H 6.94 N 10.70. Compound was not stable during our standard HPLC purity analysis. C23H27N3O3 (% = 393.5). MS (EI): m/z (%) = 393 (M, 34), 375 (M–H2O, 8), 334 (M–H2O–C3H8, 20), 174 (CH2=Ar–piperidine, 100). 1H NMR (CDCl3): δ [ppm] = 1.54–1.62 (m, 2H, 4–Hpiperidine), 1.68–1.76 (m, 4H, 3=H, 5=Hpiperidine), 2.35 (t, J = 11.7 Hz, 1H, 6–H), 2.45 (d, J = 12.0 Hz, 1H, 6–H), 2.66 (dd, J = 13.5/6.2 Hz, 1H, 5–H), 2.96–3.03 (m, 1H, 6–H), 3.16 (t, J = 5.4 Hz, 4H, 2=H–5=Hpiperidine), 3.17–3.23 (m, 2H, 5=H–8=H), 3.36 (s, 2H, N–CH2=Ar), 4.61 (d, J = 6.8 Hz, 1H, 9–H), 6.72 (s, 1H, 4–H), 6.91 (d, J = 8.6 Hz, 2H, 3=H–5=Hbenzoyl), 7.06 (s, 1H, 10–H), 7.19 (d, J = 8.6 Hz, 2H, 2=H–6=Hbenzoyl). Signals for the OH- and NH-protons are not seen in the 1H NMR-spectrum. IR (neat): ν [cm⁻¹] = 3500–3000 (w, V=O, 1186), 1625 (w) 1490 (s, ν(C=O oxazolone), 754 (s, ν(1,2-disubst. arom.).
4.2.3 | Preparation of membrane homogenates from pig brain cortex\(^{[48,49]}\)

Fresh pig brain cortex was homogenized with the potter (500–800 rpm, 10 up and down strokes) in six volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200 g for 20 min at 4°C. The pellet was resuspended in 5–6 volumes of TRIS/EDTA buffer (5 mM TRIS/1 mM EDTA, pH 7.5) at room temperature. The nonspecific binding was determined with 10 µM unlabeled ifenprodil. The \(K_d\) value of ifenprodil is 7.6 nM.

4.2.4 | General protocol for the binding assay

The test compound solutions were prepared by dissolving approximately 10 µmol (usually 2–4 mg) of the test compound in DMSO so that a 10 mM stock solution was obtained. To obtain the required test solutions for the assay, the DMSO stock solution was diluted with the respective assay buffer. The filtermats were presoaked in 0.5% aqueous polyethylenimine solution for 2 h at room temperature before use. All binding experiments were carried out in duplicates in 96-well multiplates. The concentrations given are the final concentrations in the assay. Generally, the assays were performed by addition of 50 µl of the respective assay buffer, 50 µl test compound solution in various concentrations (10\(^{-5}\), 10\(^{-6}\), 10\(^{-7}\), 10\(^{-8}\), 10\(^{-9}\), and 10\(^{-10}\) mol/L), 50 µl of corresponding radioligand solution and 50 µl of the respective receptor preparation into each well of the multiplate (total volume 200 µl). The receptor preparation was always added last. During the incubation, the multipeples were shaken at a speed of 500–600 rpm at the specified temperature. Unless otherwise noted, the assays were terminated after 120 min by rapid filtration using the harvester. During the filtration, each well was washed five times with 300 µl of water. Subsequently, the filtermats were dried at 95°C. The solid scintillator was melted on the dried filtermats at a temperature of 95°C for 5 min. After solidifying the scintillator at room temperature, the trapped radioactivity in the filtermats was measured with the scintillation analyzer. Each position on the filtermat corresponding to one well of the multiplate was measured for 5 min with the \([\text{H}]\)-counting protocol. The overall counting efficiency was 20%. The IC\(_{50}\) values were calculated with the program GraphPad Prism\(^*\) 3.0 (GraphPad Software) by nonlinear regression analysis. Subsequently, the IC\(_{50}\) values were transformed into \(K_I\) values using the equation of Cheng and Prusoff.\(^{[53]}\) The \(K_I\) values are given as mean value ± SEM from three independent experiments.

4.2.5 | Performance of the GluN2B binding assay\(^{[45]}\)

The competitive binding assay was performed with the radioligand \([\text{H}]\)-ifenprodil (60 Ci/mmol; BIONTREND). The thawed cell membrane preparation from the transfected L(tk-) cells (about 20 µg protein) was incubated with various concentrations of test compounds, 5 nM \([\text{H}]\)-ifenprodil, and TRIS/EDTA-buffer (5 mM TRIS/1 mM EDTA, pH 7.5) at 37°C. The nonspecific binding was determined with 10 µM unlabeled ifenprodil. The \(K_d\) value of ifenprodil is 7.6 nM.

4.2.6 | Performance of the PCP binding assay\(^{[48,49]}\)

The assay was performed with the radioligand \([\text{H}]\)-(+)-MK-801 (22.0 Ci/mmol; Perkin Elmer). The thawed membrane preparation of pig brain cortex (about 100 µg of the protein) was incubated with various concentrations of test compounds, 2 nM \([\text{H}]\)-(+)-MK-801, and TRIS/EDTA buffer (5 mM TRIS/1 mM EDTA, pH 7.5) at room temperature. The nonspecific binding was determined with 10 µM unlabeled (+)-MK-801. The \(K_d\) value of (+)-MK-801 is 2.26 nM.

4.2.7 | Performance of \(\sigma_1\) and \(\sigma_2\) receptor assays\(^{[50–52]}\)

The interaction with \(\sigma_1\) and \(\sigma_2\) receptors was performed as described in Meyer et al.\(^{[50]}\), Miyata et al.\(^{[51]}\), and Hasebein et al.\(^{[52]}\)

4.3 | TEVC measurement

The compound activity was evaluated by TEVC measurements as previously described.\(^{[36,46]}\) Xenopus laevis oocytes were purchased from Ecocyte Bioscience (Dortmund) and injected with 0.8 ng cRNA of GluN1-1a and 0.8 ng cRNA of GluN2B subunit. Injected oocytes were incubated for 5 days at 18°C in Barth’s solution (88 NaCl mM, 1 mM KCl, 0.4 mM CaCl\(_2\), 0.33 mM Ca(NO\(_3\))\(_2\), 0.6 mM MgSO\(_4\), 5 mM TRIS-HCl, 2.4 mM NaHCO\(_3\), supplemented with 80 mg/L theophylline, 63 mg/L benzylpenicillin, 40 mg/L streptomycin, and 100 mg/L gentamycin). After incubation, TEVC measurements were performed with Ba\(^{2+}\) Ringer solution (10 mM HEPES, 90 mM NaCl, 1 mM KCl, 1.5 mM BaCl\(_2\), adjusted to pH 7.4 using 1 M NaOH). For channel activation, Ba\(^{2+}\) ringer was supplemented with 10 µM glutamate and 10 µM (S)-glutamate. The compound activity was evaluated in presence of both agonists in concentrations of 1 or 10 µM of the different compounds. All measurements were performed at a constant holding potential of -70 mV using recording pipettes backfilled with 3 M KCl (resistance 0.5–1.5 MΩ). The number of independent oocytes is given for each tested compound and concentration. The activity was calculated by the following equation:

\[
\text{Inhibition (\%)} = 1 - \frac{l_b - l_a}{l_b - l_c}
\]

where \(l_a\) displays the current in absence of both agonists, \(l_b\) represents the resulting current in presence of 10 µM glycine and 10 µM (S)-glutamate and \(l_c\) represents the resulting current in presence of 10 µM glycine and 10 µM (S)-glutamate.
presence of both agonists and the test compound. Statistical significance of mean differences was analyzed by one-way analysis of variance. p-values are indicated by ns for \( p > 0.05 \), * for \( p < 0.05 \), ** for \( p < 0.01 \), and *** for \( p < 0.001 \).

### 4.4 Docking studies

Docking was performed using YASARA 21, implemented AutoDock program, and AMBER15IPQ force field as previously described.\[46\] Ligands were constructed in YASARA using SMILES codes with semiempirical quantum mechanics force field (MOPAC). Generated ligands were constructed in YASARA using SMILES codes with program, and AMBER15IPQ force field as previously described.\[46\] Docking was performed using YASARA 21, implemented AutoDock 4.4

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