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Role of the phenolic OH moiety of GluN2B-selective NMDA antagonists with 3-benzazepine scaffold

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ABSTRACT

In order to analyze the role of the phenolic OH moiety of ifenprodil (**1**) and 3-benzazepin-1,7-diol **2** for the affinity and selectivity at GluN2B subunit containing NMDA receptors, the 3-benzazepin-1-ols **3** were designed, synthesized and pharmacologically evaluated and furthermore, the molecular interactions of the phenylbutyl derivative **3c** with the GluN2B receptor were investigated. In order to avoid decarbonylation during the intramolecular Friedel–Crafts acylation of **11**, the *N*-atom has to be protected with a trifluoromethylsulfonyl group. The second key step of the synthesis was the removal of the *N*-triflyl group, which was realized by K_2CO_3 induced elimination of trifluoromethanelsulfinate ($F_3CSO_2^-$). In receptor binding studies with the radioligand [^{3}H]ifenprodil the 3-benzazepin-1-ol **3c** revealed a GluN2B affinity of 73 nM indicating that the phenolic OH moiety of **1** and **2** is not essential but favorable for high GluN2B affinity. In docking studies 3-benzazepin-1-ol **3c** shows the same binding pose as ifenprodil-keto **1A** in the X-ray crystal structure. H-bond interactions and lipophilic interactions of **3c** and **1A** are very similar.

The NMDA (*N*-methyl-D-aspartate) receptor belongs to the family of ionotropic glutamate receptors which is activated by the neurotransmitter (*S*)-glutamate and plays an important role in central nervous system functions. The NMDA receptor is involved in neuronal plasticity and is responsible for long term changes in synapse function that are considered to influence higher cognitive functions.[1] Thus, the NMDA receptor represents an important target for several neurological disorders.[2]

The heterotetrameric NMDA receptor is composed of four subunits.[3] Cloning of the different NMDA receptor subunits revealed the existence of three types of subunits, which are termed GluN1, GluN2 and GluN3 subunits. The GluN1 subunit prevails in eight splice variants (GluN1a-h), whereas the GluN2 and GluN3 subunits are encoded by four (GluN2A-D) and two different genes (GluN3A-B), respectively. Each subunit consists of an amino terminal domain (ATD), a ligand binding domain (LBD), a transmembrane domain (TMD) and an intracellularly located carboxy terminal domain (CTD).[4] The NMDA receptor has a variety of binding sites which permit the modulation of the opening state of the ligand-gated ion channel. Among them, the agonist binding sites for (*S*)-glutamate and glycine are located in the GluN2 and GluN1 (or GluN3) subunit, respectively. The binding sites for phencyclidine (1-(1-phenylcyclohexyl)piperidine, PCP) and Mg^{2+}-ions are located within the ion channel. The ATD possesses the binding sites for Zn^{2+}-ions, H^+, polyamines and ifenprodil (**1**).[3,4]

Overstimulation of the NMDA receptor is caused by an excess of (*S*)-glutamate, which induces an increased influx of Ca^{2+}-ions leading to excitotoxicity. Some selectivity in blocking NMDA receptors can be achieved, as the subunit composition of the NMDA receptor varies depending on the regions of the central nervous system. The GluN1 subunit is ubiquitously present in the brain, whereas the distribution of the different GluN2 subunits differs considerably in various regions of the central nervous system. In particular, GluN2B subunits are located mainly in the hippocampus, cortex and striatum.[4] Thus, the development of subunit selective antagonists represents a fascinating approach to inhibit NMDA receptor overactivation. Ligands addressing selectively the ifenprodil binding site of GluN2B containing NMDA receptors behave as negative allosteric modulators, which do not affect the activity of NMDA receptors without GluN2B subunits. Thus GluN2B selective NMDA antagonists are of interest to reduce the side effects produced by non-selective channel blockers.[5]

In 1971 ifenprodil (**1**) was developed as an α_1 adrenoceptor antagonist.[6] (Fig. 1) Unfortunately, **1** turned out to have low selectivity, since it interacted with several other receptors and ion channels like 5-HT_{1A}, $5HT_2$, σ and NMDA receptors as well.[7] The high GluN2B affinity accorded ifenprodil (**1**) the lead compound status

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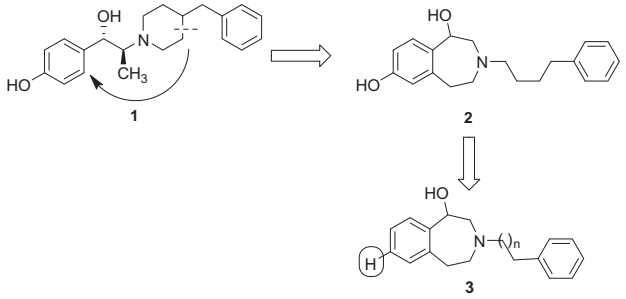
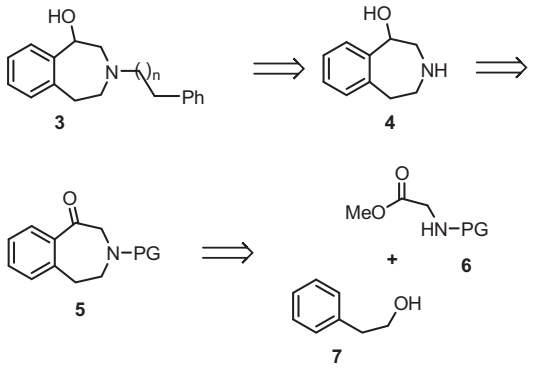


Figure 1. Development of 3-benzazepin-1-ols **3** as GluN2B selective NMDA antagonists.

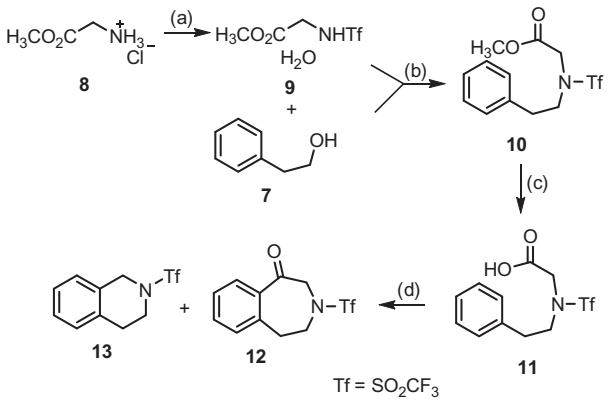
for the development of GluN2B selective NMDA antagonists. With the aim of increasing the selectivity of **1** without losing GluN2B affinity, the 3-benzazepine **2** with reduced conformational freedom was successfully developed as novel type of GluN2B antagonist.[8,9] In order to analyze the contribution of the particular structural elements of the 3-benzazepine **2** for receptor binding, the synthesis and pharmacological evaluation of 3-benzazepin-1-ols **3** lacking the phenolic 7-OH moiety was envisaged (Fig. 1).

In Scheme 1 the retrosynthesis of 3-benzazepines **3** is shown. According to the plan, the phenylalkyl side chain should be introduced as last step by alkylation or reductive alkylation of the secondary amine **4**. The amino alcohol **4** will be obtained by deprotection and reduction of ketone **5**, which will be synthesized by an intramolecular Friedel–Crafts acylation of a carboxylic acid. The starting material for the intramolecular Friedel–Crafts acylation will be prepared by condensation of 2-phenylethanol (**7**) with the protected glycine derivative **6**. The glycine derivative **6** has to be supplied with an appropriate protecting group (PG), which allows condensation with 2-phenylethanol (**7**) and intramolecular Friedel–Crafts acylation and, moreover, can be removed after establishing the 3-benzazepine ring. Since it was shown that tosyl and acyl protecting groups are not suitable for the synthesis of the desired 3-benzazepines by intramolecular Friedel–Crafts acylation in such a non-activated aromatic ring, the trifluoromethylsulfonyl (triflyl) protecting group was selected.[10]

In order to obtain tetrahydro-3-benzazepin-1-one, glycine ester HCl (**8**·HCl), which was prepared by esterification of glycine with methanol in the presence of $SOCl_2$, was reacted with triflic anhydride to afford the sulfonamide **9** in 70% yield.[11] Mitsunobu reaction[12] of sulfonamide **9** with 2-phenylethanol (**7**) in the presence of PPh_3 and diisopropyl azodicarboxylate (DIAD) provided the tertiary sulfonamide **10** in 90% yield. Hydrolysis of the ester **10** was carried out with LiOH in a THF/H_2O mixture providing the carboxylic acid **11** in 95% yield (Scheme 2).



Scheme 1. Retrosynthesis of tetrahydro-3-benzazepin-1-ols **3**.



Scheme 2. Preparation of ketone **12**; Reagents and reaction conditions: (a) Tf_2O, NEt_3, CH_2Cl_2, −70 °C to rt, 70%. (b) PPh_3, DIAD, THF, 0 °C to rt, 90%. (c) LiOH, THF/H_2O 7:3, rt, 95%. (d) P_4O_{10} (8 equiv), CH_2Cl_2, 40 °C, 3 h, 67% (**12**).

At first the intramolecular Friedel–Crafts acylation of the carboxylic acid **11** was tried with different Lewis acids, such as $SnCl_4$ and $FeCl_3$.[9] Unfortunately, these Lewis acids did not lead to the desired ketone **12** (Table 1, entries 1 and 2).

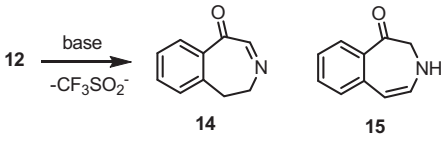
Then, the cyclization of **11** was performed with P_4O_{10} in CH_2Cl_2 as reported in the literature.[10] At 0 °C the ketone **12** was obtained in 70% yield, while the isoquinoline **13** was produced in 10% yield (Table 1, entry 3). But a very fast and clean conversion was observed upon reacting of the acid **11** with P_4O_{10} in refluxing CH_2Cl_2 leading to the ketone **12** in 67% yield and the isoquinoline **13** in 20% yield after 3 h (Table 1, entry 4). The isoquinoline side product **13**, which was formed by decarbonylation of acid **11**, was not mentioned in the report.[10] The cyclization in boiling CH_2Cl_2 was considered the standard procedure as the desired ketone **12** was obtained in comparable yields within a short period of time.

Removal of the triflyl protecting group of **12** was the next crucial reaction step to obtain the 3-benzazepin-1-ols **3**. The triflyl group is known to be one of the strongest electron withdrawing groups in organic chemistry. It was used for monoalkylation purposes and, moreover, in few examples it served as protecting group of amines.[13] In this project, it was used to increase the NH-acidity of sulfonamide **9** for the Mitsunobu reaction and as an electron sink for the prevention of the undesired decarbonylation reaction, which is induced by the electron donating properties of the *N*-atom. Once its role has been fulfilled, it should be removed. In literature the reductive cleavage of the S-N bond of triflamide by $LiAlH_4$ was reported.[14] Organic neutral super-electron donor mediated S–N bond cleavage was also described in recent years.[15] Base-induced elimination of triflinate anion $CF_3SO_2^-$ represents a further method to deprotect an amino moiety.[16,17] But unfortunately most of these methods lack direct practical implications and in some cases led to undesired side product formation.[17] Thus, the establishment of an efficient and mild deprotection method of the *N*-triflyl group to afford the corresponding amine is of high importance generally and in particular for this project.

Table 1
Optimization of the intramolecular Friedel–Crafts acylation of **11**

Entry	Reagent	Conditions	Yield of **12**	Yield of **13**
1	$SnCl_4$, $(F_3CCO)_2O$	CH_2Cl_2, −30 °C, 24 h	–	–
2	$FeCl_3$, $(F_3CCO)_2O$	CH_2Cl_2, −30 °C, 24 h	–	–
3[a]	P_4O_{10}	CH_2Cl_2, 0 °C, 36 h	70%	10%
4	P_4O_{10}	CH_2Cl_2, 40 °C, 3 h	67%	20%

[a] These reaction conditions are reported in literature giving 65% of the ketone **12**.[10]



Scheme 3. Base-promoted removal of triflyl protecting group of **12**.

Table 2
Optimization of the base-promoted removal of the triflyl protecting group

Entry	Base	Condition	Result
1	LDA	THF, −78 °C	Decomposition of **12**
2	NaHMDS	THF, −78 °C	Decomposition of **12**
3	KO^{t}Bu	THF, −20 °C	Decomposition of **12**
4	K_3PO_4	CH_3CN, 80 °C, 3 h	Full conversion to **15**
5	Cs_2CO_3	CH_3CN, 80 °C, 30 min	Full conversion to **15**
6	K_2CO_3	CH_3CN, 80 °C, 3 h	Full conversion to **14**

Due to the carbonyl moiety in 1-position of the 3-benzazepine ring of **12**, which increases the acidity in α-position, a base-promoted removal of the triflyl group was envisaged (Scheme 3). According to the literature, strong bases such as *n*-BuLi and ^{t}BuLi can be used for $CF_3SO_2^-$ elimination and subsequently nucleophilic addition to the imine intermediate occurs.[17] Thus we started with non-nucleophilic strong bases LDA and NaHMDS to generate only the imine intermediate **14** and to avoid the nucleophilic addition. However, both bases led to fast and complete decomposition of the ketone **12**. The same result was obtained with KO^{t}Bu (Table 2, entries 1–3). Reaction of the ketone **12** with the relatively mild bases K_3PO_4 and Cs_2CO_3 (Table 2, entries 4 and 5) removed the triflyl group in a clean conversion. However, careful analysis of the ^{1}H NMR spectrum (CD_3CN) of the crude product resulted in compound **15**. The doublet at 5.44 ppm and the multiplet at 6.66 ppm indicate unequivocally the presence of a double bond, which confirms the structure of **15** instead of **14** (Fig. 3). Therefore, the very weak base K_2CO_3 was used (Table 2, entry 6). Again, a clean and complete conversion of ketone **12** took place, but in contrast to the reactions with K_3PO_4 and Cs_2CO_3, the imine **14** was produced exclusively. The ^{1}H NMR spectrum of the non-purified product displays two multiplets at 3.19 and 4.01 ppm belonging to the 4-CH_2 and 5-CH_2 moieties of **14** and a triplet at 7.86 ppm for 2-H confirming the structure of product **14** (Fig. 2).

It is assumed that the desired imine **14** is formed by elimination of trifluoromethyltriflinate ($F_3CSO_2^-$) upon treatment of ketone **12** with K_3PO_4, Cs_2CO_3 and K_2CO_3. However, in the presence of the bases K_3PO_4 and Cs_2CO_3 the imine **14** was further rearranged to provide the thermodynamically more stable enamine **15**.

After optimization of the $F_3CSO_2^-$ elimination, the ketone **12** was treated with K_2CO_3 in refluxing acetonitrile. The formed α-imino ketone **14** was subsequently reduced with $NaBH_4$ to provide the β-amino alcohol **4** as a central building block (Scheme 4). In order to vary the distance between the central basic nitrogen atom of the 3-benzazepine scaffold and the phenyl residue at the end of the side chain, various phenylalkyl residues were attached at the aminoalcohol **4**. Reductive alkylation of the secondary amine **4** with benzaldehyde and phenylpropionaldehyde in the presence of $NaBH(OAc)_3$ provided the benzyl and phenylpropyl derivatives **3a** and **3b** in 66% and 57% yield, respectively. Direct alkylation of secondary amine **4** with 1-chloro-4-phenylbutane, tetrabutylammonium iodide (Bu_4NI) and K_2CO_3 furnished the phenylbutyl substituted 3-benzazepin-1-ol **3c** in 51% yield. The yields of the final alkylated 3-benzazepines **3** were calculated over three steps starting from the triflyl protected 3-benzazepine **12**.

The affinity toward GluN2B containing NMDA receptors of the synthesized 3-benzazepin-1-ols **3** was determined in a competitive radioligand binding assay developed in our group.[18] Tritium labeled ifenprodil ([^{3}H]**1**) was used as radioligand in this assay. Membrane homogenates prepared by ultrasonic irradiation of L (tk-)cells stably expressing recombinant human GluN1a/GluN2B subunits of the NMDA receptor served as receptor material.[19,20] The high density of NMDA receptors renders this system selective. Addition of dexamethasone to the growth medium induced the expression of NMDA receptors. During this period the NMDA antagonist ketamine interacting with the phencyclidine (PCP) binding site was added to the growth medium to inhibit cell death by uncontrolled influx of Ca^{2+} ions via the produced NMDA receptors.

In Table 3 the affinity of the 3-benzazepines **2** and **3** toward various receptors is summarized. The 4-phenylbutyl substituted 3-benzazepinol **3c** with the same *N*-phenyl distance as the lead compound ifenprodil reveals a K_i-value of 73 nM, which is 5-fold higher than the K_i value of the lead compound **2** bearing an additional phenolic OH moiety in 7-position. Thus it can be concluded that removal of the phenolic OH moiety of **2** retains GluN2B affinity although at a lower level. According to the pharmacophore model,[3] the phenolic OH group is regarded as pharmacophoric element and therefore its presence is recommended for ligands with high

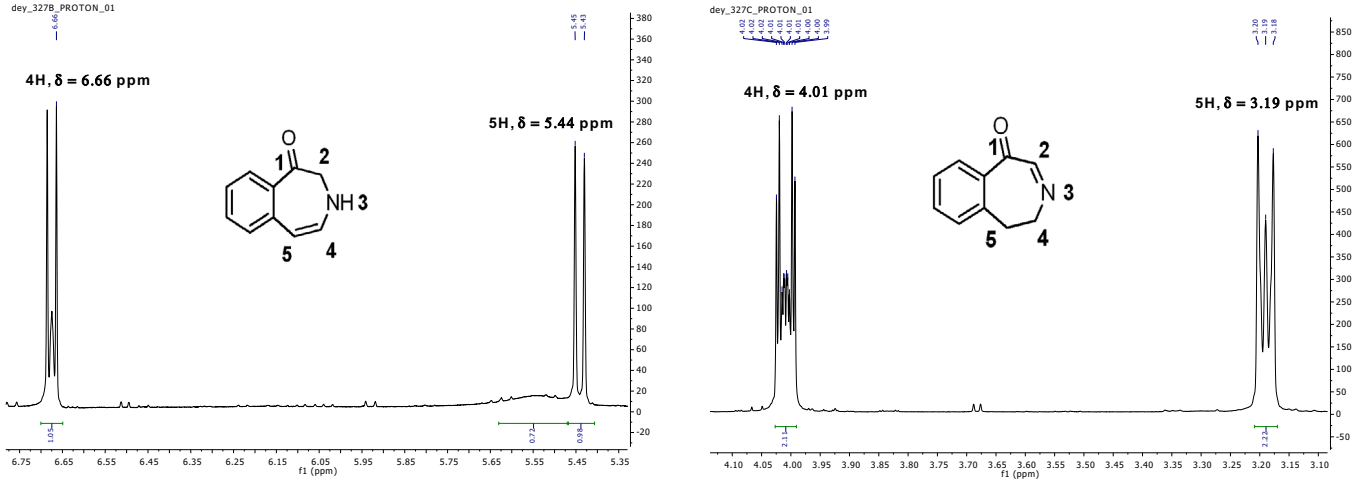
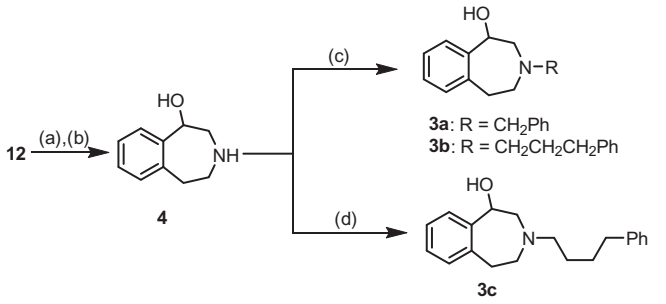


Figure 2. Parts of the ^{1}H NMR spectra of the crude products **15** (left) and **14** (right).



Scheme 4. Transformation of ketone **12** into alkylated 3-benzazepines **3**. Reagents and conditions: (a) K_2CO_3, CH_3CN, 80 °C, 72 h. (b) $NaBH_4$, 0 °C to rt, CH_3OH; (c) R′CHO, $NaBH(OAc)_3$, CH_2Cl_2, rt, 16 h; (d) $Ph(CH_2)_4Cl$, Bu_4NI, K_2CO_3, 80 °C, CH_3CN, 60 h.

GluN2B affinity. In the crystal structure of the GluN1b/GluN2B dimer together with ifenprodil the phenolic OH group of ifenprodil forms an H-bond interaction with a water molecule present in the binding site.

The homologs **3a** and **3b** with a shorter benzyl and phenylpropyl side chain show considerably lower GluN2B affinity than the 4-phenylbutyl substituted derivative **3c**. In particular the difference in GluN2B affinity of the phenylpropyl (**3b**) and phenylbutyl (**3c**) derivatives indicates a sharp relationship between the structure and GluN2B affinity.

In order to analyze the profile of the 3-benzazepinols **3**, their σ_1 and σ_2 affinity[21–23] as well as their affinity toward the PCP binding site of the NMDA receptor were determined.[24,25] The most promising GluN2B ligand **3c** did not show significant interactions with the PCP binding site of the NMDA receptor, which indicates high selectivity for the ifenprodil binding site over the PCP binding site of the NMDA receptor. Additionally the 3-benzazepinol **3c** revealed high selectivity over the σ_1 receptor with a GluN2B/σ_1 selectivity factor of 9. However, **3c** interacted with σ_2 receptors with the same affinity (K_i = 76 nM) as with the ifenprodil binding site of GluN2B containing NMDA receptors. Compared with the lead compound **2**, removal of the phenolic OH moiety in **3c** retains high selectivity against the PCP binding site and σ_1 receptors, but reduces the selectivity over the σ_2 subtype considerably.

Whereas the phenylpropyl derivative **3b** revealed moderate to low affinity (K_i >400 nM) to all four receptor systems investigated, the benzyl derivative **3a** showed unexpectedly high σ_1 receptor affinity of 31 nM. Obviously, the length of the side chain determines the receptor selectivity with the shorter phenylmethyl derivative **3a** preferring σ_1 receptors and the longer phenylbutyl derivative **3c** GluN2B receptors.

In order to analyze the binding mode and the effect of the removal of the phenolic –OH group on GluN2B binding, the 3-benzazepin-1-ol **3c** as well as ifenprodil were docked into the binding pocket formed at the interface of GluN1 and GluN2B subunits of the NMDA receptor.[26] The free binding enthalpy of ifenprodil and **3c** were calculated as −9.28 kcal/mol and −8.90 kcal/mol, respectively. These energy values correlate nicely with the experimentally determined binding affinities of ifenprodil (K_i = 10 nM) and **3c** (K_i = 73 nM).

In the X-ray crystal structure of the N-terminal domains of the NMDA receptor,[26] ifenprodil **1** is presented in the keto form **1A**. In the following discussion of the docking experiments, the docked compound is referred as ifenprodil-keto **1A**. The docking studies revealed that the 3-benzazepin-1-ol **3c** adopts a similar binding mode (Fig. 3A) as the crystallized ligand ifenprodil-keto **1A**. The phenyl ring attached to the tetramethylene linker of **3c** is embedded in the hydrophobic region of the receptor as the benzyl moiety of **1A**. It forms hydrophobic interactions with Tyr109 (GluN1) and Ile111 (GluN2B). The benzene ring of the benzazepine **3c** adopts a similar orientation as the phenol of **1A** and shows the same hydrophobic interaction with Phe176 of the GluN2B subunit. The protonated benzazepine *N*-atom of **3c** forms an H-bond with the carbonyl moiety of Gln110 (GluN2B), analogously to the H-bond produced by the protonated piperidine *N*-atom of **1A** in the crystal

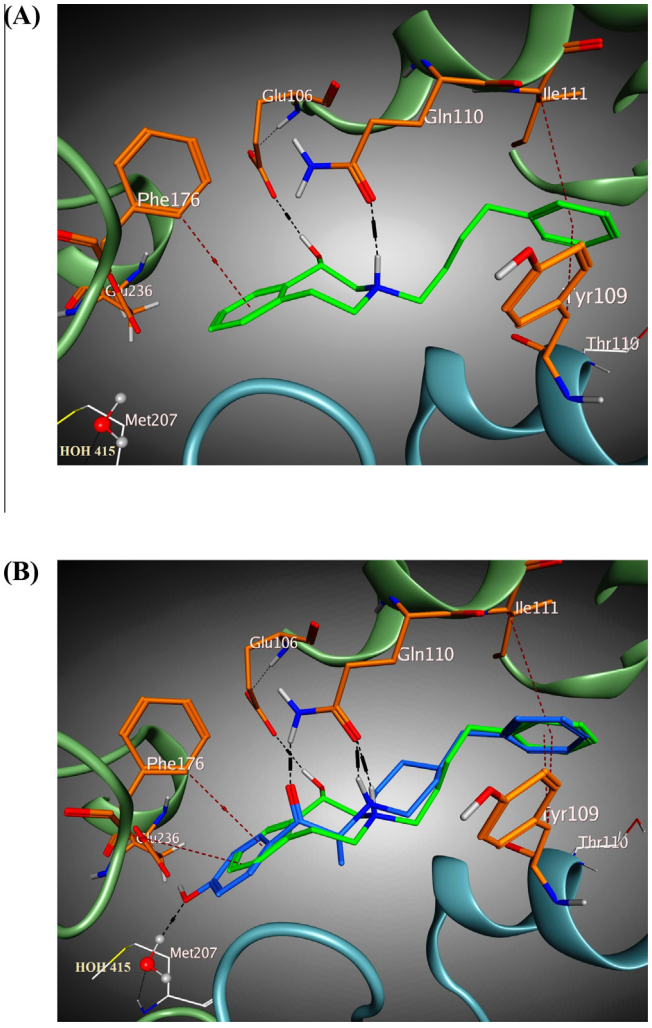


Figure 3. Binding mode of 3-benzazepin-1-ol **3c** in the binding pocket of GluN2B subunit containing NMDA receptors. (**A**) Position of **3c** (lime) in the binding pocket and its crucial interactions with GluN1 and GluN2B subunits. (**B**) Superposition of **3c** (lime) and ifenprodil-keto **1A** (sky blue) in the binding pocket. H-bonds are shown in black and the hydrophobic interactions are shown in dark red. GluN1 residues are colored in cyan and GluN2B in green.

Table 3
Receptor affinities of 3-benzazepines **2** and **3**

Compd	K_i ± SEM [nM] (n = 3)			
	GluN2B	σ_1	σ_2	PCP
2	14 ± 1.5	194[a]	>10 μM	35%[b]
3a	887[a]	31 ± 3	1300[a]	3%
3b	404[a]	2200[a]	598[a]	9%
3c	73 ± 2.0	676[a]	76 ± 26	11%[b]
Ifenprodil	10 ± 0.7	125 ± 24	98 ± 34	—
Haloperidol	—	6.3 ± 1.6	78 ± 2.3	—
Di-o-tolylguanidine	—	89 ± 29	58 ± 18	—
Dexoxadrol	—	—	—	32 ± 7.4

[a] Due to low affinity the affinity was recorded only once (n = 1).
[b] Inhibition of the radioligand binding at a test compound concentration of 10 μM.

structure. Additionally, the hydroxy moiety of **3c** forms an H-bond with the carboxy group of Glu106 (GluN2B), whilst the keto group of **1A** forms an H-bond interaction with the NH_2 group of the amide of Gln110 (GluN2B). This might be due to the fact that the OH moiety in the seven-membered 3-benzazepine ring of **3c** is shifted toward the GluN2B subunit thus allowing the formation of an H-bond interaction with the carboxylate of Glu106 (GluN2B) (Fig. 3B).

In conclusion, the importance of the phenolic OH moiety for the affinity and selectivity toward GluN2B subunit containing NMDA receptors was analyzed by a deconstruction approach. The phenolic OH moiety of 3-benzazepine-1,7-diol **2** was removed to obtain the 3-benzazepin-1-ol **3c** without substituents in the aromatic portion. In order to prepare the 3-benzazepin-1-ol **3c**, the introduction of the *N*-triflyl protecting group was essential. Thus a mild method for the removal of the *N*-triflyl protecting group with K_2CO_3 was developed. It was shown that the 3-benzazepin-1-ol **3c** without phenolic OH moiety still interacts with GluN2B containing NMDA receptors but with 5-fold reduced affinity compared with phenol **2**. Although high selectivity against the PCP binding site and σ_1 receptors was retained, σ_2 receptors were addressed with similar affinity as the GluN2B receptors indicating loss of selectivity by removal of the OH moiety. Pharmacophore based docking studies were performed with MOE[27] to analyze the interactions of the 3-benzazepin-1-ol **3c** with the receptor binding pocket. These docking studies revealed the same binding pose and similar H-bond and hydrophobic interactions for both, docked 3-benzazepin-1-ol **3c** and crystallized ifenprodil-keto **1A**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.12.067.

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