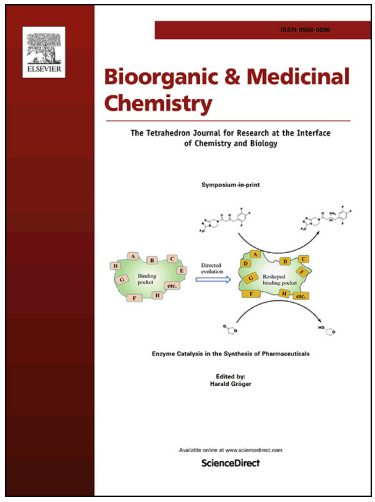
# Accepted Manuscript

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# Modification of the 4-phenylbutyl side chain of potent 3-benzazepine-based GluN2B receptor antagonists

Marina Wagner,[a] Dirk Schepmann,[a] Simon M. Ametamey,[b] Bernhard Wünsch*[a,c]

[a] Institut für Pharmazeutische und Medizinische Chemie der Universität Münster, Corrensstraße 48, D-48149 Münster, Germany Tel.: +49-251-8333311; Fax: +49-251-8332144; Email: wuensch@uni-muenster.de

[b] Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, ETH Zurich, Zurich, Switzerland

[c] Cells-in-Motion Cluster of Excellence (EXC 1003 – CiM), Westfälische Wilhelms-Universität Münster, Germany

## Abstract

Excitotoxicity driven by overactivation of NMDA receptors represents a major mechanism of acute and chronic neurological and neurodegenerative disorders. Negative allosteric modulators interacting with the ifenprodil binding site of the NMDA receptor are able to interrupt this ongoing neurodamaging process. Starting from the potent 3-benzazepine-1,7-diol **4a** novel NMDA receptor antagonists were designed by modification of the N-(4-phenylbutyl) side chain. With respect to developing novel fluorinated PET tracers, regioisomeric fluoroethoxy derivatives **11**, **12, 14**, and **15** were synthesized. Analogs **19** and **20** with various heteroaryl moieties at the end of the N-side chain were prepared by Sonogashira reaction and nucleophilic substitution. The fluoroethyl triazole **37** was obtained by 1,3-dipolar cycloaddition. In several new ligands, the flexibility of the (hetero)arylbutyl side chain was restricted by incorporation

of a triple bond. The affinity towards the ifenprodil binding site was tested in an established competition assay using [$^3$H]ifenprodil as radioligand. Introduction of a fluoroethoxy moiety at the terminal phenyl ring, replacement of the terminal phenyl ring by a heteroaryl ring and incorporation of a triple bond into the butyl spacer led to considerable reduction of GluN2B affinity. The phenol **15** ($K_i$ = 193 nM) bearing a *p*-fluoroethoxy moiety at the terminal phenyl ring represents the most promising GluN2B ligand of this series of compounds. With exception of **15** showing moderate $\sigma_2$ affinity ($K_i$ = 79 nM), the interaction of synthesized 3-benzazepines towards the PCP binding site of the NMDA receptor, $\sigma_1$ and $\sigma_2$ receptors was rather low ($K_i$ > 100 nM).

**Keywords:** glutamate receptors; NMDA receptor; GluN2B antagonists; ifenprodil binding site; 3-benzazepines; arylbutynyl analogs; structure-affinity relationships; selectivity

## 1. Introduction

The NMDA receptor belongs to the class of ionotropic glutamate receptors, which are activated by the excitatory amino acid neurotransmitter (*S*)-glutamate. Its name is derived from the synthetic prototypical agonist *N*-methyl-D-aspartate (NMDA). The NMDA receptor is particularly involved in coincidence detection,[1] i.e. two agonists, (S)-glutamate and glycine, are required for opening of the ligand gated ion channel. Moreover, the voltage-dependent $Mg^{2+}$ block has to be removed by depolarization of the surrounding membrane, before the agonists are able to open the ion channel. In contrast to the other two ionotropic glutamate receptors (AMPA, kainate receptors), the NMDA receptor shows a high permeability for $Ca^{2+}$ ions, which activate various intracellular pathways.[2] The simultaneous detection of at least two different signals

together with the high $Ca^{2+}$ permeability resulting in stabilization of synaptic connections can be used to explain memory formation.[3]

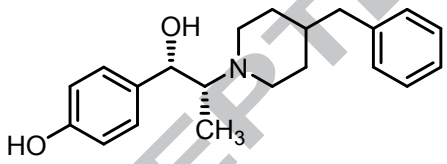
On the other hand, overactivation of the NMDA receptor leading to massive influx of $Ca^{2+}$ ions results in necrosis and apoptosis of neurons.[2,4] These excitotoxic effects are involved in acute (e.g. cerebral ischemia, stroke, trauma) and chronic neurological and neurodegenerative disorders (e.g. depression, Huntington's, Parkinson's, Alzheimer's disease) rendering the NMDA receptor a promising target for the development of novel drugs.[3,5-9]

The heterotetrameric NMDA receptor is formed by four subunits. Seven different subunits are known so far: One GluN1 subunit with eight splice variants (GluN1a-h), four GluN2 subunits (GluN2A-D) and two GluN3 subunits (GluN3A-B). Each subunit consists of four domains: the carboxy terminal domain (CTD) located intracellularly, the membrane spanning transmembrane domain (TMD) controlling the ion flux, the ligand binding domain (LBD) with the glycine and glutamate binding sites on the GluN1 and GluN2 subunit, respectively, and the amino terminal domain (ATD). Both the LBD and the ATD are located extracellularly and can interact with extracellular signal molecules.[7,10,11]

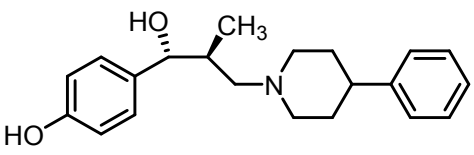
GluN2B subunit containing NMDA receptors are of particular interest, since the GluN2B subunit is expressed only in some regions of the central nervous system, including cortex, hippocampus and striatum. The concentration in other regions, e.g. cerebellum is rather low. Moreover, interaction with an additional binding site located at the GluN1/GluN2B subunit interface can modulate the opening state of the ion channel pore. Positive and negative allosteric modulators addressing the ifenprodil

binding site affect only NMDA receptors containing the GluN2B subunit, which is restricted to only some regions of the brain, leading to increased selectivity.[10-12]

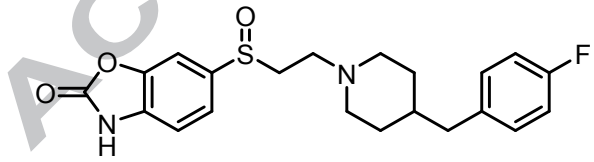
Very recently, insights into the structure of the NMDA receptor have been gained. In 2011, a dimer of the ATDs of a GluN1 and a GluN2B subunit have been crystallized together with some ligands, including ifenprodil (**1**) and Ro 25-6981 (**2**).[13] (Figure 1) Three years later the structure of the complete NMDA receptor containing two GluN1 and two GluN2B subunits together with glutamate, glycine and some antagonists was reported.[14,15] All structures show the binding site for ifenprodil and analogs at the interface between GluN1 and GluN2B subunits. Cryo electron microscopy studies showed the NMDA receptor in the active (channel open) and inactive (channel closed) form.[16,17] According to the structural analysis, an H-bond between the amide moiety of glutamine 110 and the protonated amino moiety of ligands represents the key interaction.



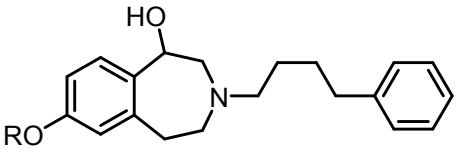

ifenprodil (**1**)#




Ro 25-6981 (**2**)




besonprodil (**3**)




**4a**: R = H
**4b**: R = $CH_3$

Figure 1. Lead compounds ifenprodil (**1**), Ro 25-6981 (**2**), besonprodil (**3**) and 3-benzazepines **4** with high GluN2B affinity.

# only one enantiomer of racemic *erythro*-ifenprodil is shown.

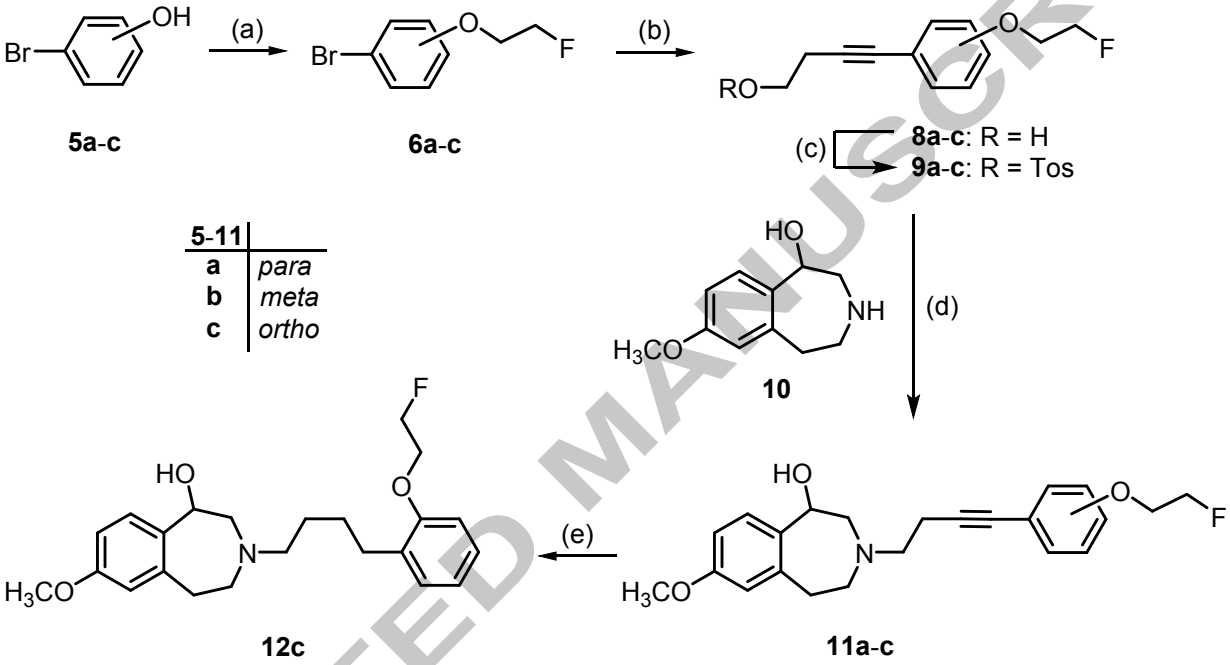
In order to address selectively NMDA receptors with GluN2B subunit expressed in only some regions of the central nervous system, we are interested in positive and negative allosteric modulators interacting with the ifenprodil binding site. The prototypical ligand, giving name to this binding site is ifenprodil (**1**)[18,19] showing high GluN2B affinity but moderate selectivity and low bioavailability.[20] (Figure 1) Ro 25-6981 (**2**), and besonprodil (**3**) represent negative allosteric modulators of GluN2B subunit containing NMDA receptors. (Figure 1)

Recently, the 3-benzazepines **4a** and **4b** interacting with the ifenprodil binding site were developed by rearrangement of ifenprodil (**1**).[21,22] The promising GluN2B affinity, selectivity and metabolic stability of **4a**[23] and **4b** prompted us to further develop the 3-benzazepine GluN2B compound class. Herein, we report on the variation of the 4-phenylbutyl side chain at the 3-benzazepine N-atom. In particular, the flexible tetramethylene spacer should be rigidified by introduction of a triple bond, the phenyl ring should be replaced by heteroaryl moieties and the possibility of introducing an F-atom in the 4-phenylbutyl substituent should be exploited. Finding an optimal position for an F-atom would allow the development of a fluorinated PET tracer for imaging of GluN2B subunit containing NMDA receptors.

## 2. Synthesis

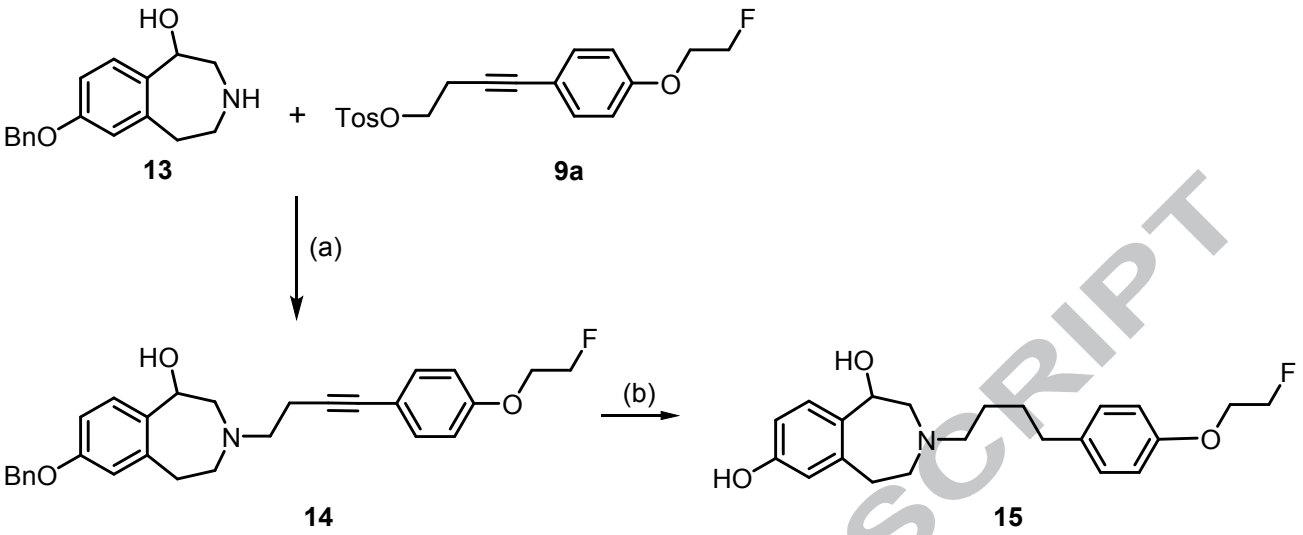
The synthesis of 4-phenylbutynyl derivatives **11** with a fluoroethoxy substituent in different positions started with fluoroethylation of para-, meta- and ortho-bromophenols **5a**-**c** with (2-fluoroethyl) tosylate to provide the fluoroethyl ethers **6a**-**c**.[24-26] Sonogashira coupling[27,28] of the phenyl bromides **6a**-**c** with but-3-yn-1-ol (**7**) resulted in the phenylbutynols **8a**-**c**. Although phenylbutynols **8a**-**c** are commercially available, a clear procedure for their synthesis could not be found in the literature. After tosylation

of the primary alcohols **8a**-**c**, nucleophilic substitution with the 3-benzazepine **10**[22] provided the phenylbutynyl substituted 3-benzazepines **11a**-**c** in 68 – 95 % yields. Finally, the *ortho*-substituted fluoroethoxy derivative **11c** was hydrogenated to yield the [*o*-(fluoroethoxy)phenyl]butyl derivative **12c**.

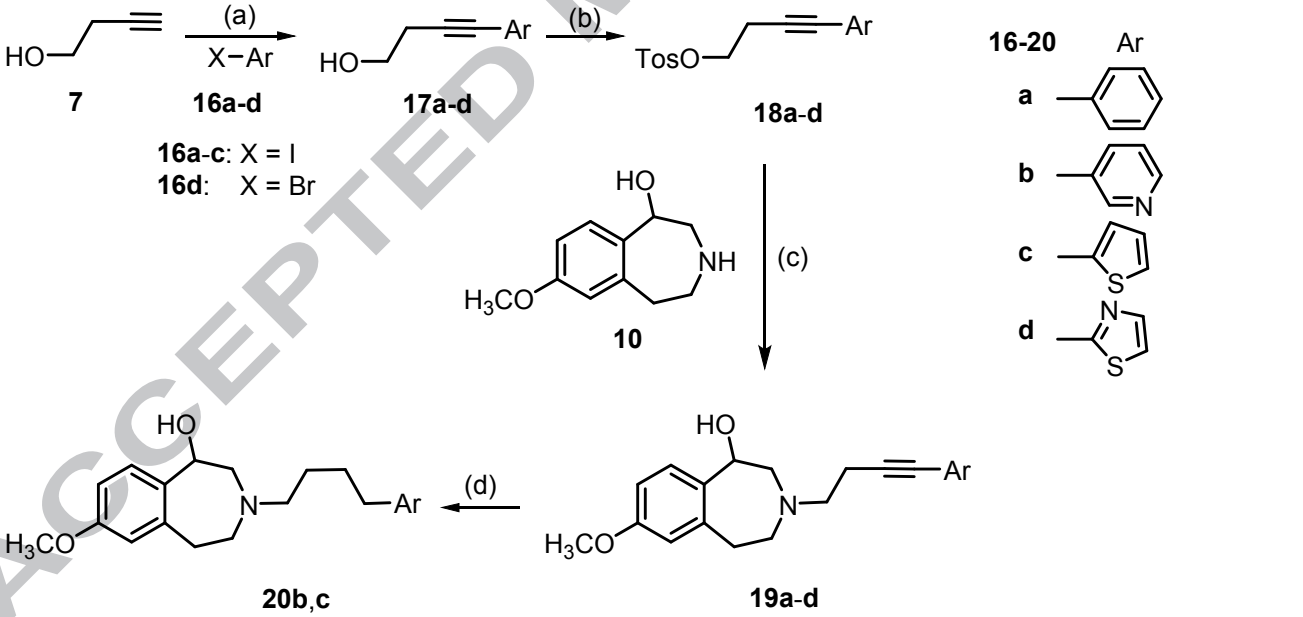



Scheme 1: Synthesis of fluoroethoxy derivatives **11** and **12**. Reagents and reaction conditions: (a) (2-fluoroethyl) tosylate, $CH_3CN$, $K_2CO_3$, reflux, 16 h, 98 - 100 %. (b) but-3-yn-1-ol (**7**), $Pd(PPh_3)_4$, CuI, $NEt_3$, reflux, 16 h, 42 – 83 %. (c) TosCl, $NEt_3$, DMAP, $CH_2Cl_2$, rt, 16 h, 53 – 86 %. (d) $CH_3CN$, $K_2CO_3$, reflux, 36 – 72 h, 68 – 95 %. (e) only **11c**: $H_2$, Pd/C, $CH_3OH$, rt, 16 h, 97 %.

In order to obtain a phenol instead of methyl ethers **11** and **12**, the 3-benzazepine **13** bearing a benzyloxy moiety in 7-position[21] was used for the nucleophilic substitution of tosylate **9a**. Treatment of **14** with $H_2$ and Pd/C led to hydrogenation of the triple bond and hydrogenolytic removal of the benzyl group yielding the phenol **15** with a phenylbutyl side chain.




Scheme 2: Synthesis of fluoroethoxy substituted phenol **15**. Reagents and reaction conditions: (a) $CH_3CN$, $K_2CO_3$, reflux, 72 h, 100 %. (b) $H_2$, Pd/C, $CH_3OH$, rt, 30 min, 69 %.

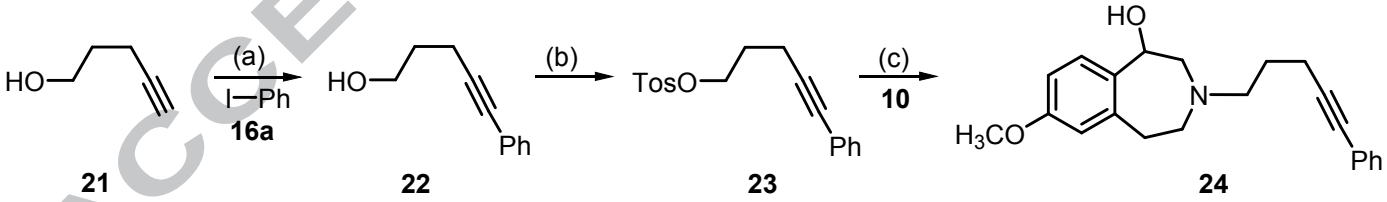



Scheme 3: Synthesis of various arylbutynyl and arylbutyl derivatives **19** and **20**. Reagents and reaction conditions: (a) $Pd(PPh_3)_4$, CuI, $NEt_3$, reflux, 16 h, 62 – 100 %. (b) TosCl, $NEt_3$, DMAP, $CH_2Cl_2$, rt, 16 h, 42 – 85 %. (c) $CH_3CN$, $K_2CO_3$, reflux, 72 h, 72 – 78 %. (d) only **19b**, **19c**: $H_2$, Pd/C, $CH_3OH$, rt, 16 h, 90 % (**20b**), 86 % (**20c**).

Next, various heteroaryl substituents should be introduced instead of the terminal phenyl ring. For this purpose, the Sonogashira reaction of butynol **7** was performed

with various (het)aryl iodides **16a**-**c** or bromide **16d**. The resulting primary alcohols **17a**-**d**[28-30] were converted into the tosylates **18a**-**d**,[31,32] which were subsequently reacted with 3-benzazepine **10** to afford the (hetero)arylbutynyl substituted 3-benzazepines **19a**-**d**. The pyridyl and thienyl derivatives **19b** and **19c** were reacted with $H_2$ and Pd/C to provide the pyridylbutyl and thienylbutyl substituted 3-benzazepines **20b** and **20c** in 90 % and 86 % yield, respectively.

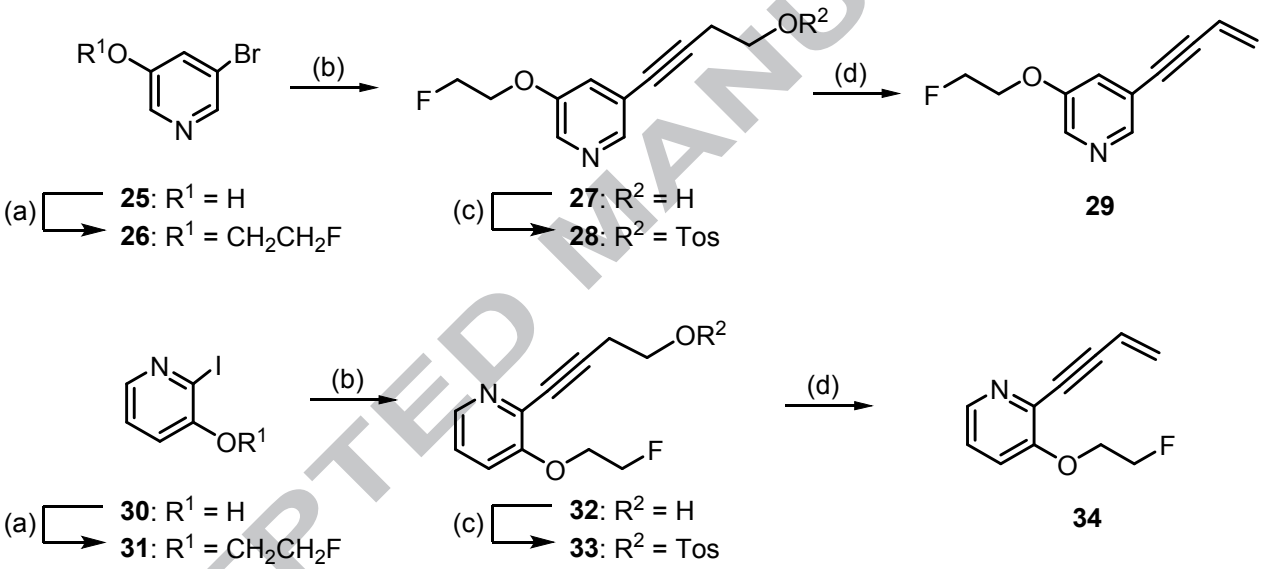
Since the triple bond is more rigid and considerably shorter than the single bond, the complete butynyl spacer of **11**, **14**, and **19** is shorter than the more flexible saturated butyl spacer of **12**, **15**, and **20**. Therefore, the butynyl spacer of **19a** was exemplarily extended by one methylene moiety resulting in the homologous phenylpentynyl derivative **24**. Sonogashira reaction of iodobenzene (**16a**) was performed with pentynol **21** instead of butynol **7** to afford the phenylpentynol **22**[29] in 92 % yield. Activation of primary alcohol **22** with tosyl chloride provided the tosylate **23**,[33] which was transformed with 3-benzazepine **10** into phenylpentynyl derivative **24**.




Scheme 4: Synthesis of homologous phenylpentynyl derivative **24**. Reagents and reaction conditions: (a) $Pd(PPh_3)_4$, CuI, $NEt_3$, reflux, 16 h, 92 %. (b) TosCl, $NEt_3$, DMAP, $CH_2Cl_2$, rt, 16 h, 39 %. (c) **10**, $CH_3CN$, $K_2CO_3$, reflux, 72 h, 100 %.

With the aim to exploit the terminal pyridyl moiety to introducing an F-atom for potential PET tracers, fluoroethoxypyridines **26**[34] and **31** were prepared by alkylation of pyridin-

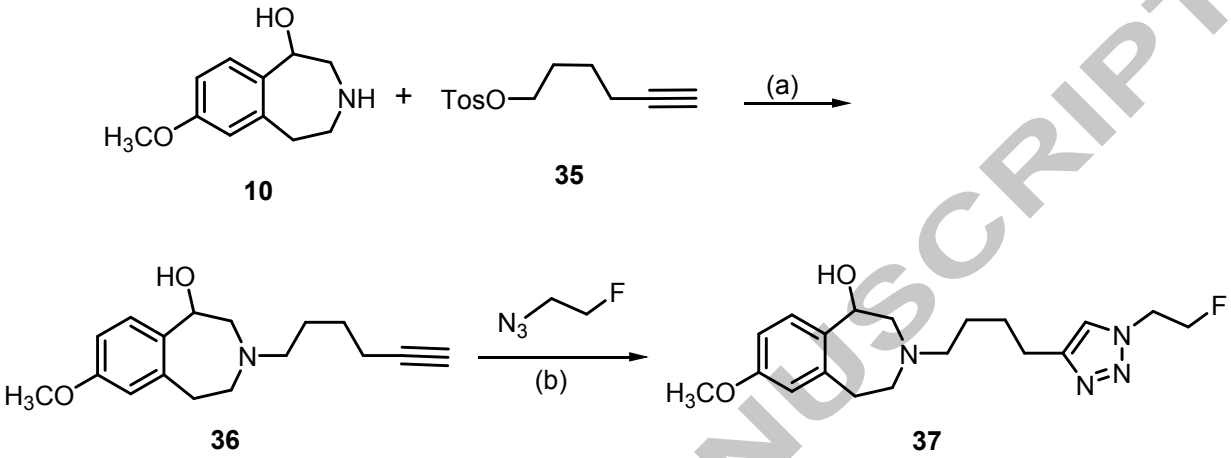
3-ols **25** and **30** with (2-fluoroethyl) tosylate. Sonogashira coupling of halopyridines **26** and **31** with butynol **7** led to the pyridylbutynols **27** and **32**, which were reacted with tosyl chloride to give the tosylates **28** and **33**. Reaction of tosylates **28** and **33** with the secondary amine **10** did not provide the desired substitution products, but unexpectedly, elimination products **29** and **34** in more than 50 % yield. The formation of the but-3-en-1-ynyl derivatives **29** and **34** might be explained by increased acidity of the methylene protons adjacent to the triple bond due to the strong electron withdrawing 3-pyridyl moiety.




Scheme 5: Synthesis of pyridyl derivatives **29** and **34** with a but-3-en-1-ynyl substituent. Reagents and reaction conditions: (a) 2-fluoroethyl tosylate, $CH_3CN$, $K_2CO_3$, reflux, 16 h, 73 % (**26**), 89 % (**31**). (b) but-3-yn-1-ol (**7**), $Pd(PPh_3)_4$, CuI, $NEt_3$, reflux, 16 h, 85 % (**27**), 71 % (**32**). (c) TosCl, $NEt_3$, DMAP, $CH_2Cl_2$, rt, 16 h, 73 % (**28**), 62 % (**33**). (d) **10**, $CH_3CN$, $K_2CO_3$, reflux, 72 h, 50 % (**29**), 58 % (**34**).

Finally, it was planned to introduce an F-atom by a 1,3-dipolar cycloaddition (Click reaction). For this purpose, 3-benzazepine **10** was alkylated with (hex-5-yn-1-yl) tosylate (**35**)[35] to form the tertiary amine **36** in 92 % yield. 1,3-Dipolar cycloaddition of

alkyne **36** with 1-azido-2-fluoroethane in the presence of Cu(I) generated *in situ* by ascorbate reduction of $CuSO_4$ regioselectively led to the fluoroethyltriazole **37**. Due to purification problems, the yield of triazole **37** did not exceed 11 %.



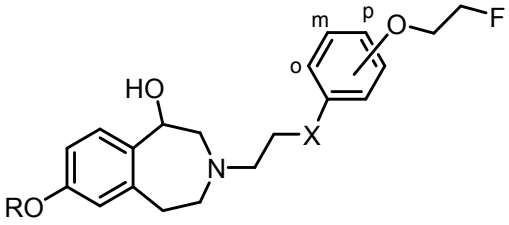

Scheme 6: Synthesis of fluoroethyltriazole **37** by 1,3-dipolar cycloaddition. Reagents and reaction conditions: (a) $CH_3CN$, $K_2CO_3$, reflux, 48 h, 92 %. (b) Na ascorbate, $CuSO_4$, DMF, rt, 16 h, 11 %.

## 3. Receptor affinity

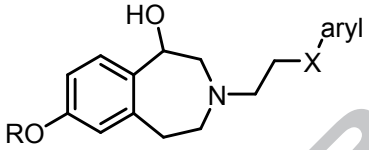
*GluN2B affinity*

The affinity towards GluN2B subunit containing NMDA receptors was determined in radioligand binding studies. Mouse fibroblast L(tk-) cells stably transfected with dexamethasone-inducible expression vectors containing the genetic information for the human GluN1a and human GluN2B subunits were used as receptor material. Tritium labeled [$^3$H]ifenprodil was employed as radioligand competing with the test compounds for binding at the ifenprodil binding site.[36,37] The GluN2B affinity of the test compounds is summarized in Table 1

Table 1. Receptor affinity of 3-benzazepines with modified 4-phenylbutyl side chain.




**11**, **12**, **14**, **15**




**19**, **20**, **24**, **37**

| compd. | R | X | position of $O(CH_2)_2F$ | aryl | $K_i$ ± SEM [nM] (n = 3)[a] GluN2B | PCP | $\sigma_1$ | $\sigma_2$ |
|---|---|---|---|---|---|---|---|---|
| **4a**[21] | H | $-CH_2CH_2-$ | - | - | 84 ± 18 | 0 % | 123 | 32 ± 13 |
| **4b**[22] | $CH_3$ | $-CH_2CH_2-$ | - | - | 706 ± 100 | 25 % | 211 | 96 ± 24 |
| **11a** | $CH_3$ | -C≡C- | *para* | - | 3 % | 0 % | 701 | 12 % |
| **11b** | $CH_3$ | -C≡C- | *meta* | - | 3 % | 0 % | 9 % | 23 % |
| **11c** | $CH_3$ | -C≡C- | *ortho* | - | 4 % | 4 % | 31 % | 22 % |
| **12c** | $CH_3$ | $-CH_2CH_2-$ | *ortho* | - | 19 % | 0 % | 715 | 593 |
| **14** | Bn | -C≡C- | *para* | - | 0 % | 0 % | 0 % | 12 % |
| **15** | H | $-CH_2CH_2-$ | *para* | - | 193 | 0 % | 705 | 79 ± 12 |
| **19a** | $CH_3$ | -C≡C- | - |  | 18 % | 15 % | 565 | 15 % |
| **19b** | $CH_3$ | -C≡C- | -- |  | 1 % | 0 % | 5 % | 9 % |
| **19c** | $CH_3$ | -C≡C- | - |  | 13 % | 0 % | 21 % | 20 % |
| **19d** | $CH_3$ | -C≡C- | - |  | 0 % | 0 % | 0 % | 0 % |
| **20b** | $CH_3$ | $-CH_2CH_2-$ | - |  | 0 % | 0 % | 274 | 397 |
| **20c** | $CH_3$ | $-CH_2CH_2-$ | - |  | 20 % | 0 % | 340 | 562 |
| **24** | $CH_3$ | $-CH_2C\equiv C-$ | - |  | 460 | 9 % | 164 | 878 |
| **37** | $CH_3$ | $-CH_2CH_2-$ | 1-$CH_2CH_2F$ |  | 0 % | 0 % | 28 % | 0 % |
| Ifenprodil | | | | | 10 ± 0.7 | - | 125 ± 24 | 98 ± 34 |
| Eliprodil | | | | | 13 ± 2.0 | - | - | - |

| | | | | |
|---|---|---|---|---|
| Dexoxadrol | - | 32 ± 7.4 | - | - |
| Haloperidol | - | - | 6.3 ± 1.6 | 78 ± 2.3 |
| Di-*o*-tolylguanidine | - | - | 89 ± 29 | 57 ± 18 |

[a] The $K_i$ values of potent compounds were recorded three times (n = 3). For low-affinity or very low-affinity compounds the competition curves were recorded only once (single value) or the inhibition (in %) of the radioligand binding at a test compound concentration of 1 µM is given.

Table 1 clearly shows that the introduction of a triple bond into the arylbutyl side chain generally leads to very low GluN2B affinity. This might be due to the reduced conformational flexibility of the linear triple bond or, alternatively, to the reduced distance between the basic amine and the terminal aryl moiety. The moderate GluN2B affinity ($K_i$ = 460 nM) of the 3-benzazepine **24** with an enlarged phenylpentynyl side chain points to the second argument of the shortened distance. The GluN2B affinity of the 5-phenylpentynyl derivative **24** is comparable with the GluN2B affinity of the 4-phenylbutyl derivative **4b**.

Independent on a butyl or butynyl spacer heteroaryl rings (compounds **19** and **20**) were not tolerated by the ifenprodil binding site of the NMDA receptor. This is also valid for the fluoroethyltriazolyl derivative **37**. Since the corresponding thienyl and pyridyl derivatives **20b** and **20c** are also inactive, the negligible GluN2B affinity of **37** was attributed to the triazole heterocycle rather than the fluoroethyl side chain.

Since we had the development of a fluorinated PET tracer in mind, analogs with a 2-fluoroethoxy moiety in various positions of the terminal phenyl ring were prepared. For ligands **11a**-**c** with a triple bond within the butyl spacer only negligible GluN2B affinity was found. The highest GluN2B affinity was detected for the *p*-fluoroethoxy derivative

**15** ($K_i$ = 193 nM) with a butyl spacer and a phenolic OH moiety. However, this affinity is more than two-fold lower than the GluN2B affinity of the corresponding unsubstituted phenol **4a** and, therefore, not appropriate for the development of a PET tracer to image GluN2B subunit containing NMDA receptors.

*Affinity towards related receptors*

In order to analyze the effect of modified arylbutyl side chain on the interaction with other receptors, the affinity towards the phencyclidine (PCP) binding site,[38,39] $\sigma_1$ and $\sigma_2$ receptors was determined.[40-42]

The PCP binding site is located within the channel pore of NMDA receptors. Since ligands cannot differentiate between the PCP binding site of different GluN2 receptor subtypes, interaction with the PCP binding site should be excluded. At a concentration of 1 µM, the herein synthesized 3-benzazepines could not compete with the radioligand [$^3$H](+)-MK-801[38,39] for binding at the PCP binding site. It was concluded that the substituted 3-benzazepines do not interact with the PCP binding site (Table 1).

The prototypical GluN2B antagonist ifenprodil shows a moderate to high affinity towards $\sigma_1$ and $\sigma_2$ receptors. Therefore, the $\sigma_1$ and $\sigma_2$ affinity of the 3-benzazepines was also recorded in radioligand receptor binding studies.[40-42] In general, the $\sigma_1$ affinity of all test compounds is rather low. The highest $\sigma_1$ affinity was found for the pyridylbutyl derivative **20b** ($K_i$ = 274 nM) and phenylpentynyl derivative **24** ($K_i$ = 164 nM). However, the $K_i$ values of these compounds are still higher than 100 nM and, therefore, of low interest (Table 1). A considerable $\sigma_2$ affinity was only found for the *p*-fluoroethoxy derivative **15** exhibiting a $K_i$ value of 79 nM. This compound represents the most active

GluN2B ligand as well, but, unfortunately, shows higher $\sigma_2$ affinity than GluN2B affinity (Table 1).

## 3. Conclusion

The phenylbutyl substituent of the potent GluN2B antagonist **4a** was modified with the aim to uncover a fluorinated ligand with high GluN2B affinity, which could be developed as a fluorinated PET tracer for imaging of NMDA receptors containing the GluN2B subunit. Introduction of a 2-fluoroethoxy moiety in ortho-, meta- or para-position of the terminal phenyl moiety (compounds **11**-**15**) led to a considerably reduced affinity towards the ifenprodil binding site. A heteroaryl moiety (compounds **19**, **20**, **37**) instead of the terminal phenyl ring was not tolerated by the GluN2B receptor. Also shortening and rigidifying the butyl spacer by the introduction of a triple bond (compounds **11**, **14**, **19**) resulted in very low GluN2B affinity. However, a moderate GluN2B affinity ($K_i$ = 460 nM) was detected for the 3-benzazepine **24** with a longer phenylpentynyl substituent at the N-atom.

## 4. Experimental Part

### 4.1. Chemistry, general methods

Flash chromatography (fc): Silica gel 60, 40–63 µm (VWR); parentheses include: diameter of the column (d), length of the stationary phase (l), fraction size (V) and eluent. MS: MicroTOFQII mass spectrometer (Bruker Daltonics, Bremen, Germany); deviations of the found exact masses from the calculated exact masses were 5 mDa or less; the data were analyzed with DataAnalysis® (Bruker Daltonics). NMR: NMR spectra were recorded in deuterated solvents on Agilent DD2 400 MHz and 600 MHz spectrometers (Agilent, Santa Clara CA, USA); chemical shifts ($\delta$) are reported in parts per million (ppm) against the reference compound tetramethylsilane ($\delta$ = 0 ppm).

Assignment of $^{1}H$ and $^{13}C$ NMR signals was supported by 2-D NMR techniques were necessary.

### 4.2. HPLC method for the determination of the purity

The purity of all compounds was determined by the HPLC system described in the Supporting Information.

### 4.3. Synthetic procedures

**3-{4-[4-(2-Fluoroethoxy)phenyl]but-3-yn-1-yl}-7-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (11a)**

3-Benzazepine **10** (46.8 mg, 0.24 mmol, 1 eq) was dissolved in $CH_3CN$ (20 mL). After addition of **9a** (104 mg, 0.29 mmol, 1.2 eq) in $CH_3CN$ (2 mL) and $K_2CO_3$ (265 mg, 1.9 mmol, 8 eq), the suspension was heated to reflux for 72 h. $K_2CO_3$ was filtered off and the solvent was removed in vacuo. The residue was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). Yellow solid, mp 79 °C, yield 62.9 mg (0.16 mmol, 68 %). $C_{23}H_{26}FNO_3$ (383.5). $R_f$ = 0.26 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). HPLC: 99.5 %, $t_R$ = 18.77 min. $^{1}H$-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.56 – 2.75 (m, 5H, $NCH_2CH_2CCPh$, 2-H, 4-H and 5-H), 2.94 (t, *J* = 7.1 Hz, 2H, $NCH_2CH_2CCPh$), 3.08 – 3.16 (m, 1H, 4-H), 3.24 – 3.30 (m, 1H, 2-H), 3.30 – 3.38 (m, 1H, 5-H), 3.78 (s, 3H, $OCH_3$), 4.19 (dt, *J* = 27.7/4.1 Hz, 2H, $OCH_2CH_2F$), 4.64 (d, *J* = 6.7 Hz, 1H, 1-H), 4.74 (dt, *J* = 47.6/4.5 Hz, 2H, $OCH_2CH_2F$), 6.61 – 6.71 (m, 2H, 6-H and 8-H), 6.81 – 6.85 (m, 2H, 3-$H_{arom.}$ and 5-$H_{arom.}$), 7.12 (d, *J* = 8.1 Hz, 1H, 9-H), 7.32 – 7.37 (m, 2H, 2-$H_{arom.}$ and 6-$H_{arom.}$). A signal for the OH proton is not seen in the spectrum. $^{13}C$-NMR (151 MHz, $CDCl_3$): δ [ppm] = 18.2 (1C, $NCH_2CH_2CCPh$), 37.0 (1C, C-5), 55.4 (1C, $OCH_3$), 55.9 (1C, C-4), 58.6 (1C, $NCH_2CH_2CCPh$), 60.6 (1C, C-2), 67.2

(d, *J* = 20.4 Hz, 1C, O*C*$H_2$CH$_2$F), 72.5 (1C, C-1), 81.7 (1C, NCH$_2$CH$_2$C*C*Ph), 81.9 (d, *J* = 171.0 Hz, 1C, OCH$_2$*C*H$_2$F), 86.5 (1C, NCH$_2$CH$_2$*C*CPh), 110.4 (1C C-8), 114.7 (2C, C-3$_{arom.}$ and C-5$_{arom.}$), 116.5 (1C, C-1$_{arom.}$), 116.8 (1C, C-6), 130.0 (1C, C-9), 133.1 (2C, C-2$_{arom.}$ and C-6$_{arom.}$), 135.4 (1C, C-9a), 141.1 (1C, C-5a), 158.1 (1C, C-4$_{arom.}$), 159.1 (1C, C-7). IR: $\tilde{\nu}$ [cm$^{-1}$] = 2913 (C-H$_{aliph.}$), 2824 (O-CH$_3$), 1605, 1582, 1508 (C=C$_{arom.}$), 1443 (CH$_2$ deform.), 1281, 1250 (C-O), 1111 (C-OH), 1042 (C-O). Exact Mass (APCI): m/z = 384.1982 (calcd. 384.1969 for $C_{23}H_{27}FNO_3$ [MH]$^+$).

**3-{4-[3-(2-Fluoroethoxy)phenyl]but-3-yn-1-yl}-7-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (11b)**

3-Benzazepine **10** (43.7 mg, 0.24 mmol, 1 eq) was dissolved in $CH_3CN$ (20 mL). After addition of **9b** (98.2 mg, 0.27 mmol, 1.2 eq) in $CH_3CN$ (2 mL) and $K_2CO_3$ (254 mg, 1.84 mmol, 8 eq), the suspension was heated to reflux for 36 h. $K_2CO_3$ was filtered off and the solvent was removed in vacuo. The residue was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). Yellow oil, yield 76.8 mg (0.20 mmol, 83 %). $C_{23}H_{26}FNO_3$ (383.5), $R_f$ = 0.20 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). HPLC: 99.2 %, $t_R$ = 18.56 min. $^1$H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.60 – 2.81 (m, 5H, NCH$_2$C*H*$_2$CCPh, 2-H, 4-H and 5-H), 2.98 (t, *J* = 7.1 Hz, 2H, NC*H*$_2$CH$_2$CCPh), 3.13 (dd, *J* = 12.4/6.1 Hz, 1H, 4-H), 3.24 – 3.40 (m, 2H, 2-H and 5-H), 3.78 (s, 3H, OC*H*$_3$), 4.19 (dt, *J* = 27.7/4.1 Hz, 2H, OC*H*$_2$CH$_2$F), 4.63 – 4.83 (m, 3H, OCH$_2$C*H*$_2$F and 1-H), 6.62 – 6.70 (m, 2H, 6-H and 8-H), 6.87 (dd, *J* = 8.4/2.6 Hz, 1H, 4-H$_{arom.}$), 6.94 – 6.98 (m, 1H, 2-H$_{arom.}$), 7.02 (d, *J* = 7.6 Hz, 1H, 6-H$_{arom.}$), 7.13 (d, *J* = 8.0 Hz, 1H, 9-H), 7.19 (t, *J* = 8.0 Hz, 1H, 5-H$_{arom.}$). A signal for the OH proton is not seen in the spectrum. $^{13}$C NMR (101 MHz, $CDCl_3$): δ [ppm] = 18.1 (1C, NCH$_2$*C*H$_2$CCPh), 36.7 (1C, C-5), 55.4 (1C, O*C*H$_3$), 55.9 (1C, C-4), 58.4 (1C,

NCH$_2$CH$_2$CCPh), 60.6 (1C, C-2), 67.3 (1C, OCH$_2$CH$_2$F), 72.3 (1C, C-1), 81.94 (1C, NCH$_2$CH$_2$CCPh), 81.96 (d, *J* = 170.8 Hz, 1C, OCH$_2$CH$_2$F), 87.8 (1C, NCH$_2$CH$_2$CCPh), 110.5 (1C, C-8), 115.3 (1C, C-4$_{arom.}$), 116.8 (1C, C-6), 117.3 (1C, C-2$_{arom.}$), 124.7 (1C, C-1$_{arom.}$), 124.8 (1C, C-6$_{arom.}$), 129.6 (1C, C-5$_{arom.}$), 129.9 (1C, C-9), 135.3 (1C, C-9a), 140.9 (1C, C-5a), 158.3 (1C, C-3$_{arom.}$), 159.1 (1C, C-7). IR: $\tilde{\nu}$ [cm$^{-1}$] = 3399 (O-H), 2947, 2913 (C-H$_{aliph.}$), 2831 (OCH$_3$-H), 1605, 1578, 1489 (C=C$_{arom.}$), 1427 (CH$_2$ deform.), 1292, 1261 (C-O), 1188 (C-OH), 1045 (C-O). Exact Mass (APCI): m/z = 384.1978 (calcd. 384.1969 for $C_{23}H_{27}FNO_3$ [MH]$^+$).

**3-{4-[2-(2-Fluoroethoxy)phenyl]but-3-yn-1-yl}-7-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (11c)**

3-Benzazepine **10** (61.1 mg, 0.32 mmol, 1 eq) was dissolved in $CH_3CN$ (20 mL). After addition of **9c** (137 mg, 0.38 mmol, 1.2 eq) in $CH_3CN$ (2 mL) and $K_2CO_3$ (354 mg, 2.56 mmol, 8 eq), the suspension was heated to reflux for 72 h. $K_2CO_3$ was filtered off and the solvent was removed in vacuo. The residue was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). Yellow oil, yield 117 mg (0.30 mmol, 95 %). $C_{23}H_{26}FNO_3$ (383.5). $R_f$ = 0.30 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). HPLC: 98.5 %, $t_R$ = 18.45 min. $^1$H-NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.61 – 2.82 (m, 5H, NCH$_2$C*H*$_2$CCPh, 2-H, 4-H and 5-H), 3.01 (t, *J* = 7.2 Hz, 2H, NC*H*$_2$CH$_2$CCPh), 3.12 – 3.20 (m, 1H, 4-H), 3.27 – 3.39 (m, 2H, 2-H and 5-H), 3.78 (s, 3H, OC*H*$_3$), 4.27 (dt, *J* = 27.3/4.2 Hz, 2H, OC*H*$_2$CH$_2$F), 4.63 – 4.70 (m, 1H, 1-H), 4.76 (dt, *J* = 47.4/4.2 Hz, 2H, OCH$_2$C*H*$_2$F), 6.62 – 6.70 (m, 2H, 6-H and 8-H), 6.86 (d, *J* = 8.3 Hz, 1H, 3-H$_{arom.}$), 6.92 (t, *J* = 7.5 Hz, 1H, 5-H$_{arom.}$), 7.13 (d, *J* = 8.1 Hz, 1H, 9-H), 7.21 – 7.25 (m, 1H, 4-H$_{arom.}$), 7.38 (dd, *J* = 7.6/1.7 Hz, 1H, 6-H$_{arom.}$). A signal for the OH proton is not seen in the spectrum. $^{13}$C-NMR (151 MHz, $CDCl_3$): δ [ppm] = 18.3 (1C, NCH$_2$*C*H$_2$CCPh), 36.7 (1C,

C-5), 55.4 (1C, O*C*$H_3$), 55.8 (1C, C-4), 58.6 (1C, N*C*$H_2$C$H_2$C*C*Ph), 60.5 (1C, C-2), 68.3 (d, *J* = 21.0 Hz, 1C, O*C*$H_2$C$H_2$F), 72.4 (1C, C-1), 78.0 (1C, NC$H_2$C$H_2$C*C*Ph), 82.1 (d, *J* = 171.0 Hz, 1C, OC$H_2$*C*$H_2$F), 92.2 (1C, NC$H_2$C$H_2$*C*CPh), 110.5 (1C, C-8), 112.9 (1C, C-$3_{arom.}$), 113.8 (1C, C-$1_{arom.}$), 116.7 (1C, C-6), 121.5 (1C, C-$5_{arom.}$), 129.2 (1C, C-$4_{arom.}$), 129.9 (1C, C-9), 133.8 (1C, C-$6_{arom.}$), 135.3 (1C, C-9a), 141.1 (1C, C-5a), 159.06, 159.11 (2C, C-$2_{arom.}$ and C-7). IR: $\tilde{\nu}$ [cm$^{-1}$] = 3395 (O-H), 2947, 2913 (C-$H_{aliph.}$), 2832 (O$CH_3$-H), 1609, 1578, 1493 (C=$C_{arom.}$), 1443 ($CH_2$ deform.), 1258 (C-O), 1115 (C-OH), 1045 (C-O). Exact Mass (APCI): m/z = 384.1965 (calcd. 384.1969 for $C_{23}H_{27}FNO_3$ $[MH]^+$).

**3-{4-[2-(2-Fluoroethoxy)phenyl]butyl}-7-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (12c)**

**11c** (65.2 mg, 0.17 mmol, 1 eq) was dissolved in abs. $CH_3OH$ (5 mL) and the solution was added to a suspension of Pd/C (13.0 mg, 10 %) in $CH_3OH$ (10 mL). After the mixture had been stirred for 16 h under $H_2$ atmosphere (1 bar) at room temperature, the catalyst was removed by filtration over Celite® and the solvent was evaporated in vacuo. Yellow oil, yield 64.1 mg (0.17 mmol, 97 %). $C_{23}H_{30}FNO_3$ (387.5). $R_f$ = 0.24 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). HPLC: 97.1 %, $t_R$ = 18.91 min. $^1$H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.55 – 1.70 (m, 4H, NC$H_2$C*H*$_2$C*H*$_2$C$H_2$Ph), 2.45 (t, *J* = 11.9 Hz, 1H, 4-H), 2.55 (d, *J* = 12.1 Hz, 1H, 2-H), 2.60 – 2.71 (m, 5H, NC*H*$_2$C$H_2$C$H_2$C*H*$_2$Ph and 5-H), 2.97 – 3.06 (m, 1H, 4-H), 3.13 – 3.21 (m, 1H, 2-H), 3.27 (ddd, *J* = 14.8/11.8/2.5 Hz, 1H, 5-H), 3.77 (s, 3H, OC*H*$_3$), 4.22 (dt, *J* = 28.1/4.1 Hz, 2H, OC*H*$_2$C$H_2$F), 4.61 (d, *J* = 6.7 Hz, 1H, 1-H), 4.76 (dt, *J* = 47.5/4.1 Hz, 2H, OC$H_2$C*H*$_2$F), 6.61 – 6.70 (m, 2H, 6-H and 8-H), 6.82 (d, *J* = 8.0 Hz, 1H, 3-$H_{arom.}$), 6.92 (t, *J* = 7.4 Hz, 1H, 5-$H_{arom.}$), 7.11 (d, *J* = 8.1 Hz, 1H, 9-H), 7.13 – 7.19 (m, 2H, 4-$H_{arom.}$ and 6-$H_{arom.}$). A signal for the OH proton is not seen in the

spectrum. $^{13}$C NMR (101 MHz, $CDCl_3$): δ [ppm] = 26.8 (1C, $NCH_2\mathit{C}H_2CH_2CH_2Ph$), 27.7 (1C, $NCH_2CH_2\mathit{C}H_2CH_2Ph$), 30.2 (1C, $NCH_2CH_2CH_2\mathit{C}H_2Ph$), 36.7 (1C, C-5), 55.3 (1C, $O\mathit{C}H_3$), 56.1 (1C, C-4), 59.7 (1C, $N\mathit{C}H_2CH_2CH_2CH_2Ph$), 60.9 (1C, C-2), 67.5 (d, *J* = 20.5 Hz, 1C, $O\mathit{C}H_2CH_2F$), 72.3 (1C, C-1), 82.2 (d, *J* = 170.8 Hz, 1C, $OCH_2\mathit{C}H_2F$), 110.4 (1C, C-8), 111.6 (1C, C-$3_{arom.}$), 116.7 (1C, C-6), 121.2 (1C, C-$5_{arom.}$), 127.1 (1C, C-$4_{arom.}$), 129.8 (1C, C-9), 130.3 (1C, C-$6_{arom.}$), 131.4 (1C, C-$1_{arom.}$), 135.6 (1C, C-9a), 141.2 (1C, C-5a), 156.4 (1C, C-$2_{arom.}$), 159.0 (1C, C-7). IR: $\tilde{\nu}$ [$cm^{-1}$] = 3379 (O-H), 2928, 2859 (C-$H_{aliph.}$), 2832 ($OCH_3$-H), 1605, 1582, 1493 (C=$C_{arom.}$), 1451 ($CH_2$ deform.), 1242 (C-O), 1115 (C-OH), 1045 (C-O). Exact Mass (APCI): m/z = 388.2316 (calcd. 388.2282 for $C_{23}H_{31}FO_3$ $[MH]^+$).

**7-(Benzyloxy)-3-{4-[4-(2-fluoroethoxy)phenyl]but-3-yn-1-yl}-2,3,4,5-tetrahydro-1*H*-*3*-benzazepin-1-ol (14)**

§-Benzazepine **13** (269 mg, 1.00 mmol, 1 eq) was dissolved in $CH_3CN$ (40 mL). After addition of **9a** (435 mg, 1.20 mmol, 1.2 eq) in $CH_3CN$ (2 mL) and $K_2CO_3$ (1.1 g, 8.0 mmol, 8 eq), the suspension was heated to reflux for 72 h. $K_2CO_3$ was filtered off and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 2:1 + 1 % *N*,*N*-dimethylethylamine → cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). Yellow oil, yield 460 mg (1.00 mmol, 100 %). $C_{29}H_{30}FNO_3$ (459.6). $R_f$ = 0.34 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). HPLC: 95.8 %, $t_R$ = 20.62 min. $^1$H NMR (400 MHz, $CDCl_3$) : δ [ppm] = 2.52 – 2.75 (m, 5H, $NCH_2C\mathit{H}_2CCPh$, 2-H, 4-H and 5-H), 2.93 (t, *J* = 7.0 Hz, 2H, $NC\mathit{H}_2CH_2CCPh$), 3.06 – 3.16 (m, 1H, 4-H), 3.21 – 3.38 (m, 2H, 2-H and 5-H), 4.19 (dt, *J* = 27.7/4.0 Hz, 2H, $OC\mathit{H}_2CH_2F$), 4.63 (d, *J* = 6.6 Hz, 1H, 1-H), 4.74 (dt, *J* = 47.3/4.1 Hz, 2H, $OCH_2C\mathit{H}_2F$), 5.04 (s, 2H, O-$C\mathit{H}_2$-Ph), 6.71 – 6.76 (m, 2H, 6-H and 8-H), 6.81 – 6.86 (m, 2H, 3-$H_{arom.}$

and 5-$H_{arom.}$), 7.09 – 7.13 (m, 1H, 9-H), 7.29 – 7.44 (m, 7H, 2-$H_{arom.}$, 6-$H_{arom.}$ and benzyl). A signal for the OH proton is not seen in the spectrum. $^{13}$C NMR (101 MHz, $CDCl_3$): δ [ppm] = 18.3 (1C, $NCH_2\mathit{C}H_2CCPh$), 37.1 (1C, C-5), 55.9 (1C, C-4), 58.6 (1C, $N\mathit{C}H_2CH_2CCPh$), 60.6 (1C, C-2), 67.2 (d, *J* = 20.5 Hz, 1C, $O\mathit{C}H_2CH_2F$), 70.1 (1C, O-$\mathit{C}H_2$-Ph), 72.6 (1C, C-1), 81.7 (1C, $NCH_2CH_2C\mathit{C}Ph$), 81.9 (d, *J* = 170.9 Hz, 1C, $OCH_2\mathit{C}H_2F$), 86.6 (1C, $NCH_2CH_2\mathit{C}CPh$), 111.4 (1C C-8), 114.7 (2C, C-$3_{arom.}$ and C-$5_{arom.}$), 116.5 (1C, C-$1_{arom.}$), 117.7 (1C, C-6), 127.6, 128.0, 128.7 (5C, C-$2_{benzyl}$, C-$3_{benzyl}$, C-$4_{benzyl}$, C-$5_{benzyl}$ and C-$6_{benzyl}$), 130.0 (1C, C-9), 133.1 (2C, C-$2_{arom.}$ and C-$6_{arom.}$), 135.8 (1C, C-9a), 137.2 (1C, C-$1_{benzyl}$), 141.2 (1C, C-5a), 158.1 (1C, C-$4_{arom.}$), 158.3 (1C, C-7). IR: $\tilde{\nu}$ [$cm^{-1}$] = 3402 (O-H), 2913, 2824 (C-$H_{aliph.}$), 1605, 1578, 1504 (C=$C_{arom.}$), 1454 ($CH_2$ deform.), 1246 (C-O), 1165 (C-OH), 1053, 1026 (C-O). Exact Mass (APCI): m/z = 460.2296 (calcd. 460.2282 for $C_{29}H_{31}FNO_3$ $[MH]^+$).

**3-{4-[4-(2-Fluoroethoxy)phenyl]butyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine-1,7-diol (15)**

Alkyne **14** (103 mg, 0.22 mmol, 1 eq) was dissolved in abs. $CH_3OH$ (5 mL) and the solution was added to a suspension of Pd/C (20.6 mg, 10 %) in $CH_3OH$ (20 mL). After the mixture had been stirred for 16 h under $H_2$ atmosphere (1 bar) at room temperature, the catalyst was removed by filtration over Celite® and the solvent was removed in vacuo. Brown solid, mp 52 °C, yield 56.5 mg (0.15 mmol, 69 %). $C_{22}H_{28}FNO_3$ (373.5). $R_f$ = 0.56 ($CH_2Cl_2$:$CH_3OH$ = 9:1 + 2 % $NH_3$). HPLC: 95.9 %, $t_R$ = 16.32 min. $^1$H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.43 – 1.68 (m, 4H, $NCH_2C\mathit{H}_2C\mathit{H}_2CH_2Ph$), 2.35 (t, *J* = 12.0 Hz, 1H, 4-H), 2.47 (d, *J* = 11.9 Hz, 1H, 2-H), 2.50 – 2.62 (m, 5H, $NC\mathit{H}_2CH_2CH_2C\mathit{H}_2Ph$ and 5-H), 2.87 – 3.00 (m, 1H, 4-H), 3.06 – 3.22 (m, 2H, 2-H and 5-H), 4.18 (dt, *J* = 27.9/4.1 Hz, 2H, $OC\mathit{H}_2CH_2F$), 4.52 (d, *J* = 7.0 Hz, 1H, 1-H), 4.73 (dt, *J* = 47.4/4.1 Hz, 2H, $OCH_2C\mathit{H}_2F$), 6.51 (s, 2H, 6-H and 8-H), 6.82 – 6.88 (m, 2H, 3-

$H_{arom.}$ and 5-$H_{arom.}$), 6.96 (d, *J* = 7.9 Hz, 1H, 9-H), 7.06 – 7.13 (m, 2H, 2-$H_{arom.}$ and 6-$H_{arom.}$). Signals for the OH protons are not seen in the spectrum. $^{13}$C NMR (101 MHz, $CDCl_3$): δ [ppm] = 26.7 (1C, $NCH_2\mathit{C}H_2CH_2CH_2Ph$), 29.5 (1C, $NCH_2CH_2\mathit{C}H_2CH_2Ph$), 35.0 (1C, $NCH_2CH_2CH_2\mathit{C}H_2Ph$), 36.9 (1C, C-5), 56.2 (1C, C-4), 59.8 (1C, $N\mathit{C}H_2CH_2CH_2CH_2Ph$), 60.9 (1C, C-2), 67.4 (d, *J* = 20.5 Hz, 1C, $O\mathit{C}H_2CH_2F$), 72.6 (1C, C-1), 82.2 (d, *J* = 170.4 Hz ,1C, $OCH_2\mathit{C}H_2F$), 112.7 (1C C-8), 114.7 (2C, C-$3_{arom.}$ and C-$5_{arom.}$), 117.9 (1C, C-6), 129.5 (2C, C-$2_{arom.}$ and C-$6_{arom.}$), 130.1 (1C, C-9), 134.8 (1C, C-9a), 135.2 (1C, C-$1_{arom.}$), 141.5 (1C, C-5a), 156.1 (1C, C-7), 156.7 (1C, C-$4_{arom.}$). IR: $\tilde{\nu}$ [$cm^{-1}$] = 3275 (O-H), 2928, 2859, 2824 (C-$H_{aliph.}$), 1609, 1585, 1508 (C=$C_{arom.}$), 1450 ($CH_2$ deform.), 1242 (C-O), 1161 (C-OH), 1049 (C-O). Exact Mass (ESI): m/z = 374.2137 (calcd. 374.2126 for $C_{22}H_{29}FNO_3$ $[MH]^+$).

**7-Methoxy-3-(4-phenylbut-3-yn-1-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (19a)**

3-Benzazepine **10** (243 mg, 1.26 mmol, 1 eq) was dissolved in $CH_3CN$ (40 mL). After addition of tosylate **18a** (378 mg, 1.26 mmol, 1 eq) and $K_2CO_3$ (1.39 g, 10.1 mmol, 8 eq), the suspension was heated to reflux for 72 h. $K_2CO_3$ was filtered off and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). Yellow oil, yield 318 mg (0.99 mmol, 78 %). $C_{21}H_{23}NO_2$ (321.4). $R_f$ = 0.49 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). HPLC: 99.2 %, $t_R$ = 17.75 min. $^1$H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.54 – 2.73 (m, 5H, $NCH_2C\mathit{H}_2CCPh$, 2-H, 4-H and 5-H), 2.90 – 2.97 (m, 2H, $NC\mathit{H}_2CH_2CCPh$), 3.11 (ddt, *J* = 12.4/6.1/2.2 Hz, 1H, 4-H), 3.22 – 3.39 (m, 2H, 2-H and 5-H), 3.77 (s, 3H, $OC\mathit{H}_3$), 4.61 (d, *J* = 6.6 Hz, 1H, 1-H), 6.62 – 6.69 (m, 2H, 6-H and 8-H), 7.08 – 7.13 (m, 1H, 9-H), 7.24 – 7.43 (m, 5H, phenyl). A signal for the OH proton is not seen in the spectrum.

$^{13}$C NMR (101 MHz, $CDCl_3$): δ [ppm] = 18.3 (1C, $NCH_2\mathit{C}H_2CCPh$), 37.2 (1C, C-5), 55.4 (1C, $OCH_3$), 56.0 (1C, C-4), 58.6 (1C, $NCH_2CH_2CCPh$), 60.6 (1C, C-2), 72.7 (1C, C-1), 82.1 (1C, $NCH_2CH_2C\mathit{C}Ph$), 88.0 (1C, $NCH_2CH_2\mathit{C}CPh$), 110.4 (1C, C-8), 116.8 (1C, C-6), 123.7 (1C, C-$1_{phenyl}$), 127.9 (1C, C-$4_{phenyl}$), 128.4 (2C, C-$3_{phenyl}$ and C-$5_{phenyl}$), 130.1 (1C, C-9), 131.7 (2C, C-$2_{phenyl}$ and C-$6_{phenyl}$), 135.5 (1C, C-9a), 141.2 (1C, C-5a), 159.1 (1C, C-7). IR: $\tilde{\nu}$ [$cm^{-1}$] = 3399 (O-H), 2936, 2909 ($CH_{aliph.}$), 2832 ($OCH_3$-H), 1609, 1582, 1493 ($C{=}C_{arom.}$), 1462, 1439 ($CH_2$ deform.), 1250 (C-O), 1157 (C-OH), 1042 (C-O). Exact Mass (APCI): m/z = 322.1815 (calcd. 322.1802 for $C_{21}H_{24}NO_2$ $[MH]^+$).

**7-Methoxy-3-[4-(pyridin-3-yl)but-3-yn-1-yl]-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (19b)**

3-Benzazepine **10** (100 mg, 0.52 mmol, 1 eq) was dissolved in $CH_3CN$ (20 mL). After addition of tosylate **18b** (156 mg, 0.52 mmol, 1 eq) and $K_2CO_3$ (575 mg, 4.16 mmol, 8 eq), the suspension was heated to reflux for 72 h. $K_2CO_3$ was filtered off and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine → ethyl acetate + 1 % *N*,*N*-dimethylethylamine). Orange oil, yield 98.7 mg (0.31 mmol, 59 %). $C_{20}H_{22}N_2O_2$ (322.4). $R_f$ = 0.42 (ethyl acetate + 1 % *N*,*N*-dimethylethylamine). HPLC: 97.7 %, $t_R$ = 10.83 min. $^1$H NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.62 (t, *J* = 12.0 Hz, 1H, 4-H), 2.65 – 2.75 (m, 4H, $NCH_2C\mathit{H}_2CCPy$, 2-H and 5-H), 2.96 (t, *J* = 7.1 Hz, 2H, $NC\mathit{H}_2CH_2CCPy$), 3.08 – 3.14 (m, 1H, 4-H), 3.23 – 3.29 (m, 1H, 2-H), 3.29 – 3.36 (m, 1H, 5-H), 3.77 (s, 3H, $OC\mathit{H}_3$), 4.64 (d, *J* = 6.6 Hz, 1H, 1-H), 6.62 – 6.69 (m, 2H, 6-H and 8-H), 7.12 (d, *J* = 8.1 Hz, 1H, 9-H), 7.21 (dd, *J* = 7.9/4.9 Hz, 1H, 5-$H_{pyridine}$), 7.68 (dt, *J* = 8.0/1.9 Hz, 1H, 4-$H_{pyridine}$), 8.48 (dd, *J* = 4.8/1.7 Hz, 1H, 6-$H_{pyridine}$), 8.62 (d, *J* = 2.3 Hz, 1H, 2-$H_{pyridine}$). A signal for the OH proton is not seen in

the spectrum. $^{13}$C NMR (151 MHz, $CDCl_3$): δ [ppm] = 18.3 (1C, $NCH_2\mathit{C}H_2CCPy$), 37.0 (1C, C-5), 55.4 (1C, $OCH_3$), 55.9 (1C, C-4), 58.3 (1C, $NCH_2CH_2CCPy$), 60.6 (1C, C-2), 72.5 (1C, C-1), 78.9 (1C, $NCH_2CH_2C\mathit{C}Py$), 91.6 (1C, $NCH_2CH_2\mathit{C}CPy$), 110.5 (1C, C-8), 116.8 (1C, C-6), 120.8 (1C, C-$3_{pyridine}$), 123.1 (1C, C-$5_{pyridine}$), 130.0 (1C, C-9), 135.3 (1C, C-9a), 138.7 (1C, C-$4_{pyridine}$), 141.0 (1C, C-5a), 148.3 (1C, C-$6_{pyridine}$), 152.4 (1C, C-$2_{pyridine}$), 159.1 (1C, C-7). IR: $\tilde{\nu}$ [cm$^{-1}$] = 3352 (O-H), 2928, ($CH_{aliph.}$), 2832 (O-$CH_3$), 2222 (C ≡ C), 1609, 1582, 1501 (C=$C_{arom.}$), 1462, 1408 ($CH_2$ deform.), 1254 (C-O), 1157 (C-OH), 1042 (C-O). Exact Mass (APCI): m/z = 323.1747 (calcd. 323.1754 for $C_{20}H_{23}N_2O_2$ $[MH]^+$).

**7-Methoxy-3-[4-(thiophen-2-yl)but-3-yn-1-yl]-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (19c)**

3-Benzazepine **10** (100 mg, 0.52 mmol, 1 eq) was dissolved under $N_2$ atmosphere in $CH_3CN$ (20 mL). After addition of tosylate **18c** (159 mg, 0.52 mmol, 1 eq) and $K_2CO_3$ (575 mg, 4.16 mmol, 8 eq), the suspension was heated to reflux for 72 h. $K_2CO_3$ was filtered off and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 2:1 + 1 % *N*,*N*-dimethylethylamine). Yellow oil, yield 85.6 mg (0.26 mmol, 50 %). $C_{19}H_{21}NO_2S$ (327.4). $R_f$ = 0.43 (cyclohexane:ethyl acetate = 2:1 + 1 % *N*,*N*-dimethylethylamine). HPLC: 96.1 %, $t_R$ = 17.55 min. $^1$H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.59 (t, *J* = 12.0 Hz, 1H, 4-H), 2.63 – 2.74 (m, 4H, $NCH_2C\mathit{H}_2CCAr$, 2-H and 5-H), 2.94 (t, *J* = 7.1 Hz, 2H, $NC\mathit{H}_2CH_2CCAr$), 3.06 – 3.14 (m, 1H, 4-H), 3.21 – 3.28 (m, 1H, 2-H), 3.28 – 3.37 (m, 1H, 5-H), 3.78 (s, 3H, $ZC\mathit{H}_3$), 4.62 (d, *J* = 6.5 Hz, 1H, 1-H), 6.62 – 6.70 (m, 2H, 6-H and 8-H), 6.90 – 6.96 (m, 1H, 4-$H_{arom.}$), 7.09 – 7.15 (m, 2H, 9-H and 3-$H_{arom.}$), 7.17 (d, *J* = 5.2 Hz, 1H, 5-$H_{arom.}$). A signal for the OH proton is not seen in the spectrum. $^{13}$C NMR (101 MHz, $CDCl_3$): δ [ppm] = 18.5 (1C,

$NCH_2CH_2CCAr$), 37.1 (1C, C-5), 55.4 (1C, $OCH_3$), 55.9 (1C, C-4), 58.4 (1C, $NCH_2CH_2CCAr$), 60.6 (1C, C-2), 72.6 (1C, C-1), 75.3 (1C, $NCH_2CH_2CCAr$), 92.0 (1C, $NCH_2CH_2CCAr$), 110.4 (1C, C-8), 116.8 (1C, C-6), 123.8 (1C, C-$2_{arom.}$), 126.4 (1C, C-$5_{arom.}$), 127.0 (1C, C-$4_{arom.}$), 130.0 (1C, C-9), 131.5 (1C, C-$3_{arom.}$), 135.5 (1C, C-9a), 141.2 (1C, C-5a), 159.1 (1C, C-7). IR: $\tilde{\nu}$ [$cm^{-1}$] = 3399 (O-H), 3102, 3075 (=C-H), 2997, 2909 ($CH_{aliph.}$), 2832 (O-$CH_3$), 1609, 1582, 1501 (C=$C_{arom.}$), 1462, 1427 ($CH_2$ deform.), 1250 (C-O), 1157 (C-OH), 1042 (C-O). Exact Mass (APCI): m/z = 328.1366 (calcd. 328.1366 for $C_{19}H_{22}NO_2S$ $[MH]^+$).

**7-Methoxy-3-[4-(thiazol-2-yl)but-3-yn-1-yl]-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (19d)**

3-Benzazepine **10** (50 mg, 0.26 mmol, 1 eq) was dissolved in $CH_3CN$ (15 mL). After addition of tosylate **18d** (95.9 mg, 0.31 mmol, 1.2 eq) and $K_2CO_3$ (286 mg, 2.07 mmol, 8 eq), the suspension was heated to reflux for 72 h. $K_2CO_3$ was filtered off and the solvent was evaporated under reduced pressure. The residue was purified twice by flash column chromatography (1. d = 2 cm, h = 15 cm, V = 10 mL, ethyl acetate + 1 % *N*,*N*-dimethylethylamine, 2. d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). Orange oil, yield 20.9 mg (0.06 mmol, 23 %). $C_{18}H_{20}N_2O_2S$ (328.4). $R_f$ = 0.25 (ethyl acetate + 1 % *N*,*N*-dimethylethylamine). HPLC: 98.7 %, $t_R$ = 14.15 min. $^1$H NMR (600 MHz, $CDCl_3$):δ [ppm] = 2.63 – 2.86 (m, 5H, $NCH_2CH_2CCAr$, 2-H, 4-H and 5-H), 3.00 – 3.08 (m, 2H, $NCH_2CH_2CCAr$), 3.09 – 3.16 (m, 1H, 4-H), 3.24 – 3.29 (m, 1H, 2-H), 3.30 – 3.37 (m, 1H, 5-H), 3.78 (s, 3H, $OCH_3$), 4.66 – 4.75 (m, 1H, 1-H), 6.62 – 6.70 (m, 2H, 6-H and 8-H), 7.14 (d, *J* = 8.2 Hz, 1H, 9-H), 7.29 (d, *J* = 3.3 Hz, 1H, 5-$H_{arom.}$), 7.77 (d, *J* = 3.3 Hz, 1H, 4-$H_{arom.}$). $^{13}$C NMR (151 MHz, $CDCl_3$): δ [ppm] = 18.1 (1C, $NCH_2CH_2CCAr$), 36.5 (1C, C-5), 55.4 (1C, $OCH_3$), 55.8 (1C, C-4), 57.8 (1C, $NCH_2CH_2CCAr$), 60.5 (1C, C-2), 72.2 (1C, C-1), 75.6 (1C,

$NCH_2CH_2CCAr$), 93.5 (1C, $NCH_2CH_2CCAr$), 110.6 (1C, C-8), 116.7 (1C, C-6), 120.3 (1C, C-$5_{arom.}$), 129.8 (1C, C-9), 135.1 (1C, C-9a), 140.7 (1C, C-5a), 143.3 (1C, C-$4_{arom.}$), 149.0 (1C, C-$2_{arom.}$), 159.2 (1C, C-7). IR: $\tilde{\nu}$ [$cm^{-1}$] = 3383, 3109, 3078 (=C-H), 2997, 2936 (C-$H_{aliph.}$), 2832 ($OCH_3$-H), 2230 (C ≡ C), 1609, 1582, 1497, 1481 (C=$C_{arom.}$), 1462, 1435 ($CH_2$ deform.), 1254 (C-O), 1130 (C-OH), 1042 (C-O). Exact Mass (ESI): m/z = 329.1331 (calcd. 329.1318 for $C_{18}H_{21}N_2O_2S$ $[MH]^+$).

**7-Methoxy-3-[4-(pyridin-3-yl)butyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (20b)**

**19b** (69.2 mg, 0.21 mmol, 1 eq) was dissolved in abs. $CH_3OH$ (5 mL) and the solution was added to a suspension of Pd/C (13.8 mg, 10 %) in $CH_3OH$ (15 mL). After the mixture had been stirred for 16 h under $H_2$ atmosphere (1 bar) at room temperature, the catalyst was removed by filtration over Celite®. Evaporation of the solvent in vacuo and purification by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, ethyl acetate + 1 % *N*,*N*-dimethylethylamine) yielded **20b**. Yellow oil, yield 62.0 mg (0.19 mmol, 90 %). $C_{20}H_{26}N_2O_2$ (326.4). $R_f$ = 0.23 (ethyl acetate + 1 % *N*,*N*-dimethylethylamine). HPLC: 95.7 %, $t_R$ = 8.17 min. $^1$H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.53 – 1.70 (m, 4H, $NCH_2CH_2CH_2CH_2Py$), 2.45 (t, *J* = 11.9 Hz, 1H, 4-H), 2.55 (d, *J* = 12.1 Hz, 1H, 2-H), 2.59 – 2.71 (m, 5H, $NCH_2CH_2CH_2CH_2Py$ and 5-H), 2.95 – 3.01 (m, 1H, 4-H), 3.11 – 3.17 (m, 1H, 2-H), 3.22 – 3.29 (m, 1H, 5-H), 3.77 (s, 3H, $OCH_3$), 4.61 (d, *J* = 6.8 Hz, 1H, 1-H), 6.62 – 6.68 (m, 2H, 6-H and 8-H), 7.11 (d, *J* = 8.1 Hz, 1H, 9-H), 7.21 (dd, *J* = 7.8/4.8 Hz, 1H, 5-$H_{pyridine}$), 7.49 (dt, *J* = 7.9/1.9 Hz, 1H, 4-$H_{pyridine}$), 8.42 – 8.46 (m, 2H, 2-$H_{pyridine}$ and 6-$H_{pyridine}$). A signal for the OH proton is not seen in the spectrum. $^{13}$C NMR (151 MHz, $CDCl_3$) δ [ppm] = 26.6 (1C, $NCH_2CH_2CH_2CH_2Py$), 28.9 (1C, $NCH_2CH_2CH_2CH_2Py$), 33.0 (1C, $NCH_2CH_2CH_2CH_2Py$), 36.8 (1C, C-5), 55.3 (1C, $OCH_3$), 56.2 (1C, C-4), 59.5 (1C, $NCH_2CH_2CH_2CH_2Py$), 60.9 (1C, C-2), 72.3 (1C, C-1), 110.4 (1C, C-8), 116.7 (1C, C-

6), 123.5 (1C, C-$5_{pyridine}$), 129.7 (1C, C-9), 135.5 (1C, C-9a), 135.9 (1C, C-$4_{pyridine}$), 137.5 (1C, C-$3_{pyridine}$), 141.1 (1C, C-5a), 147.5 (1C, C-$6_{pyridine}$), 150.0 (1C, C-$2_{pyridine}$), 159.1 (1C, C-7). IR: $\tilde{\nu}$ [$cm^{-1}$] = 3283 (O-H), 3052, 3028 (=C-H), 2994, 2936, 2859 ($CH_{aliph.}$), 2836 ($OCH_3$-H), 1609, 1578, 1497 (C=$C_{arom.}$), 1462, 1423 ($CH_2$ deform.), 1250 (C-O), 1107 (C-OH), 1042 (C-O). Exact Mass (ESI): m/z = 327.2065 (calcd. 327.2067 for $C_{20}H_{27}N_2O_2$ $[MH]^+$).

**7-Methoxy-3-[4-(thiophen-2-yl)butyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (20c)**

**19c** (54.1 mg, 0.17 mmol, 1 eq) was dissolved in abs. $CH_3OH$ (5 mL) and the solution was added to a suspension of Pd/C (10.8 mg, 10 %) in $CH_3OH$ (15 mL). After the mixture had been stirred for 16 h under $H_2$ atmosphere (1 bar) at room temperature, the catalyst was removed by filtration over Celite®. The solvent was removed under reduced pressure. Brown solid, mp 79 °C, yield 48.5 mg (0.15 mmol, 86 %). $C_{19}H_{25}NO_2S$ (331.5). $R_f$ = 0.29 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). HPLC: 95.2 %, $t_R$ = 17.30 min. $^1$H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.54 – 1.77 (m, 4H, $NCH_2CH_2CH_2CH_2Ar$), 2.40 (t, *J* = 12.2 Hz, 1H, 4-H), 2.51 (d, *J* = 12.0 Hz, 1H, 2-H), 2.57 – 2.70 (m, 3H, $NCH_2CH_2CH_2CH_2Ar$ and 5-H), 2.87 (t, *J* = 7.4 Hz, 2H, $NCH_2CH_2CH_2CH_2Ar$), 2.96 – 3.04 (m, 1H, 4-H), 3.16 (ddd, *J* = 12.2/6.8/2.0 Hz, 1H, 2-H), 3.26 (ddd, *J* = 15.0/12.0/2.5 Hz, 1H, 5-H), 3.78 (s, 3H, $OCH_3$), 4.57 (d, *J* = 6.7 Hz, 1H, 1-H), 6.62 – 6.68 (m, 2H, 6-H and 8-H), 6.79 (dd, *J* = 3.3/1.3 Hz, 1H, 3-$H_{arom.}$), 6.92 (dd, *J* = 5.1/3.4 Hz, 1H, 4-$H_{arom.}$), 7.08 – 7.14 (m, 2H, 5-$H_{arom.}$ and 9-H). A signal for the OH proton is not seen in the spectrum. $^{13}$C NMR (101 MHz, $CDCl_3$): δ [ppm] = 26.7 (1C, $NCH_2CH_2CH_2CH_2Ar$), 29.6 (1C, $NCH_2CH_2CH_2CH_2Ar$), 29.9 (1C, $NCH_2CH_2CH_2CH_2Ar$), 37.2 (1C, C-5), 55.3 (1C, $OCH_3$), 56.3 (1C, C-4), 59.6 (1C, $NCH_2CH_2CH_2CH_2Ar$), 61.0 (1C, C-2), 72.6 (1C, C-1),

110.3 (1C, C-8), 116.8 (1C, C-6), 123.1 (1C, C-$5_{arom.}$), 124.3 (1C, C-$3_{arom.}$), 126.9 (1C, C-$4_{arom.}$), 129.9 (1C, C-9), 135.7 (1C, C-9a), 141.4 (1C, C-5a), 145.3 (1C, C-$2_{arom.}$), 159.0 (1C, C-7). IR: $\tilde{\nu}$ [$cm^{-1}$] = 3102, 3071, 3001 (=C-H), 2940 ($CH_{aliph.}$), 2820 ($OCH_3$-H), 1609, 1585, 1497 (C=$C_{arom.}$), 1466, 1431 ($CH_2$ deform.), 1254 (C-O), 1099 (C-OH), 1038 (C-O). Exact Mass (ESI): m/z = 332.1692 (calcd. 332.1679 for $C_{19}H_{26}NO_2S$, $[MH]^+$).

**7-Methoxy-3-(5-phenylpent-4-yn-1-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (24)**

3-Benzazepine **10** (40 mg, 0.21 mmol, 1 eq) was dissolved in $CH_3CN$ (20 mL). After addition of tosylate **23** (79.2 mg, 0.25 mmol, 1.2 eq) and $K_2CO_3$ (232 mg, 1.68 mmol, 8 eq) the suspension was heated to reflux for 72 h. $K_2CO_3$ was filtered off and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). Yellow oil, yield 71.5 mg (0.21 mmol, 100 %), $C_{22}H_{25}NO_2$ (335.4). $R_f$ = 0.27 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). HPLC: 95.7 %, $t_R$ = 18.47 min. $^1$H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.90 – 1.97 (m, 2H, $NCH_2CH_2CH_2CCPh$), 2.51 (t, *J* = 6.9 Hz, 2H, $NCH_2CH_2CH_2CCPh$), 2.60 – 2.71 (m, 1H, 4-H), 2.76 – 2.85 (m, 2H, 2-H and 5-H), 2.90 (t, *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CCPh$), 3.10 – 3.16 (m, 1H, 4-H), 3.25 – 3.31 (m, 1H, 2-H), 3.31 – 3.39 (m, 1H, 5-H), 3.78 (s, 3H, $OCH_3$), 4.78 (d, *J* = 7.2 Hz, 1H, 1-H), 6.62 – 6.71 (m, 2H, 6-H and 8-H), 7.17 (d, *J* = 8.3 Hz, 1H, 9-H), 7.27 – 7.42 (m, 5H, phenyl). A signal for the OH proton is not seen in the spectrum. $^{13}$C NMR (151 MHz, $CDCl_3$): δ [ppm] = 17.4 (1C, $NCH_2CH_2CH_2CCPh$), 25.5 (1C, $NCH_2CH_2CH_2CCPh$), 35.7 (1C, C-5), 55.4 (1C, $OCH_3$), 56.0 (1C, C-4), 58.8 (1C, $NCH_2CH_2CH_2CCPh$), 60.8 (1C, C-2), 71.6 (1C, C-1), 81.6 (1C, $NCH_2CH_2CH_2CCPh$), 88.9 (1C, $NCH_2CH_2CH_2CCPh$), 110.7 (1C, C-8), 116.6

(1C, C-6), 123.7 (1C, C-$1_{phenyl}$), 127.9 (1C, C-$4_{phenyl}$), 128.4 (2C, C-$3_{phenyl}$ and C-$5_{phenyl}$), 129.6 (1C, C-9), 131.7 (2C, C-$2_{phenyl}$ and C-$6_{phenyl}$), 134.9 (1C, C-9a), 140.5 (1C, C-5a), 159.2 (1C, C-7). IR: $\tilde{\nu}$ [$cm^{-1}$] = 3395 (O-H), 2940, 2909 ($CH_{aliph.}$), 2832 ($OCH_3$-H), 1609, 1582, 1489 ($C{=}C_{arom.}$), 1462, 1439 ($CH_2$ deform.), 1250 (C-O), 1157 (C-OH), 1042 (C-O). Exact Mass (APCI): m/z = 336.1968 (calcd. 336.1958 for $C_{22}H_{26}NO_2$ $[MH]^+$).

**3-(Hex-5-yn-1-yl)-7-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (36)**

Benzazepine **10** (100 mg, 0.52 mmol, 1 eq) was dissolved under $N_2$ in $CH_3CN$ (20 mL). $K_2CO_3$ (575 mg, 4.16 mmol, 8 eq) and **35**[35] (157 mg, 0.62 mmol, 1.2 eq) dissolved in $CH_3CN$ (1 mL) were added and the mixture was heated to reflux for 48 h. $K_2CO_3$ was filtered off and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). Colorless solid, mp 55 °C, yield 131 mg (0.48 mmol, 92 %). $C_{17}H_{23}NO_2$ (273.4). $R_f$ = 0.21 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethylamine). HPLC: 99.9 %, $t_R$ = 14.07 min. $^1$H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.58 (quint, *J* = 7.3 Hz, 2H, $NCH_2CH_2C\mathit{H}_2CH_2CCH$), 1.61 – 1.73 (m, *J* = 17.2/13.1/7.1 Hz, 2H, $NCH_2C\mathit{H}_2CH_2CH_2CCH$), 1.96 (t, *J* = 2.7 Hz, 1H, $NCH_2CH_2CH_2CH_2CC\mathit{H}$), 2.24 (td, *J* = 6.9/2.7 Hz, 2H, $NCH_2CH_2CH_2C\mathit{H}_2CCH$), 2.48 (t, *J* = 12.0 Hz, 1H, 4-H), 2.59 (d, *J* = 12.1 Hz, 1H, 2-H), 2.64 (t, *J* = 7.4 Hz, 2H, $NC\mathit{H}_2CH_2CH_2CH_2CCH$), 2.71 (dd, *J* = 15.3/6.4 Hz, 1H, 5-H), 3.01 – 3.07 (m, 1H, 4-H), 3.16 – 3.22 (m, 1H, 2-H), 3.25 – 3.32 (m, 1H, 5-H), 3.77 (s, 3H, $OC\mathit{H}_3$), 4.64 (d, *J* = 6.8 Hz, 1H, 1-H), 6.62 – 6.68 (m, 2H, 6-H and 8-H), 7.12 (d, *J* = 8.1 Hz, 1H, 9-H). A signal for the OH proton is not seen in the spectrum. $^{13}$C NMR (151 MHz, $CDCl_3$): δ [ppm] = 18.4 (1C, $NCH_2CH_2CH_2\mathit{C}H_2CCH$), 26.0 (1C, $NCH_2\mathit{C}H_2CH_2CH_2CCH$), 26.2 (1C, $NCH_2CH_2\mathit{C}H_2CH_2CCH$), 36.7 (1C, C-5), 55.4 (1C, $O\mathit{C}H_3$), 56.1 (1C, C-4), 59.3 (1C,

NCH$_2$CH$_2$CH$_2$CH$_2$CCH), 60.9 (1C, C-2), 68.8 (1C, NCH$_2$CH$_2$CH$_2$CH$_2$C*C*H), 72.3 (1C, C-1), 84.2 (1C, NCH$_2$CH$_2$CH$_2$CH$_2$*C*CH), 110.4 (1C, C-8), 116.7 (1C, C-6), 129.8 (1C, C-9), 135.5 (1C, C-9a), 141.1 (1C, C-5a), 159.1 (1C, C-7). IR: $\tilde{\nu}$ [cm$^{-1}$] = 3298 (O-H), 3140 (=C-H), 2940 (CH$_{aliph.}$), 1659, 1609, 1582, 1501 (C=C$_{arom.}$), 1458, 1435 (CH$_2$ deform.), 1254 (C-O), 1157 (C-OH), 1038 (C-O). Exact Mass (APCI): m/z = 274.1804 (calcd. 274.1802 for $C_{17}H_{24}NO_2$ [MH]$^+$).

**3-{4-[1-(2-Fluoroethyl)-1*H*-1,2,3-triazol-4-yl]butyl}-7-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (37)**

(2-Fluoroethyl) tosylate (32.9 mg, 0.15 mmol, 1 eq) was dissolved in DMF (5 mL). After addition of $NaN_3$ (14.6 mg, 0.23 mmol, 1.5 eq), the mixture was stirred for 24 h at room temperature. The alkyne **36** (29.1 mg, 0.15 mmol, 1 eq) dissolved in DMF (2 mL), sodium ascorbate (5.9 mg, 0.03 mmol, 0.2 eq) and $CuSO_4$ (2.4 mg, 0.02 mmol, 0.1 eq) were added and the mixture was stirred for 16 h at room temperature. After addition of $H_2O$ (30 mL) and EtOAc (30 mL) the layers were separated and the organic layer was washed with $H_2O$ (2 x 25 mL). The combined aqueous layers were extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over $Na_2SO_4$. After removal of the solvent in vacuo, the crude product was purified by flash column chromatography (d = 1 cm, h = 15 cm, V = 5 mL, ethyl acetate + 1 % *N*,*N*-dimethylethylamine). Green oil, yield 5.8 mg (0.02 mmol, 11 %). $C_{19}H_{27}FN_4O_2$ (362.4). $R_f$ = 0.63 ($CH_2Cl_2$:$CH_3OH$ = 9:1 + 2 % $NH_3$). HPLC: 86.9 %, $t_R$ = 13.03 min. $^1$H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.63 – 1.81 (m, 4H, NCH$_2$C*H$_2$*C*H$_2$*CH$_2$Ar), 2.65 (d, *J* = 12.0 Hz, 1H, 4-H), 2.71 – 2.84 (m, 6H, NC*H$_2$*CH$_2$CH$_2$C*H$_2$*Ar, 2-H and 5-H), 3.04 – 3.12 (m, 1H, 4-H), 3.24 (dd, *J* = 12.3/7.0 Hz, 1H, 2-H), 3.28 – 3.37 (m, 1H, 5-H), 3.78 (s, 3H, OC*H$_3$*), 4.64 (dt, *J* = 27.0/4.4 Hz, 2H, OC*H$_2$*CH$_2$F), 4.77 (d, *J* = 6.9 Hz, 1H, 1-H), 4.71 – 4.87 (m, 2H, OCH$_2$C*H$_2$*F), 6.61 – 6.73 (m, 2H, 6-H and 8-H), 7.17 (d, *J* = 8.2 Hz, 1H,

9-H), 7.46 (s, 1H, 5-$H_{triazole}$). A signal for the OH proton is not seen in the spectrum. $^{13}$C NMR (101 MHz, $CDCl_3$): δ [ppm] = 25.3 (1C, $NCH_2CH_2CH_2\mathit{C}H_2Ar$), 25.7, 27.0 (2C, $NCH_2\mathit{C}H_2\mathit{C}H_2CH_2Ar$), 35.4 (1C, C-5), 50.6 (d, *J* = 20.7 Hz, 1C, $O\mathit{C}H_2CH_2F$), 55.4 (1C, $O\mathit{C}H_3$), 55.9 (1C, C-4), 59.3 (1C, $N\mathit{C}H_2CH_2CH_2CH_2Ar$), 60.4 (1C, C-2), 71.4 (1C, C-1), 81.8 (d, *J* = 172.3 Hz, 1C, $OCH_2\mathit{C}H_2F$), 110.8 (1C, C-8), 116.5 (1C, C-6), 122.0 (1C, C-$5_{triazole}$), 129.6 (1C, C-9), 134.8 (1C, C-9a), 140.4 (1C, C-5a), 148.1 (1C, C-$4_{triazole}$), 159.2 (1C, C-7). IR: $\tilde{\nu}$ [$cm^{-1}$] = 3298 (=C-H), 2947 ($CH_{aliph.}$), 1655, 1609, 1582, 1501 ($C{=}C_{arom.}$), 1458, 1435 ($CH_2$ deform.), 1258 (C-O), 1157 (C-OH), 1038 (C-O). Exact Mass (ESI): m/z = 363.2204 (calcd. 363.2191 for $C_{19}H_{28}FN_4O_2$ $[MH]^+$).

### 4.4. Receptor binding studies

Experimental details concerning the affinity towards the ifenprodil binding site of GluN2B subunit containing NMDA receptors are reported in ref[36] and ref[37]. The assay to determine the affinity to the PCP binding site of the NMDA receptor is detailed in ref[38] and ref[39]. Details for the $\sigma_1$ and $\sigma_2$ assays are described in ref[40-42].

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**Supporting Information**

The Supporting Information contains general chemical methods, HPLC method to determine purity, several synthetic procedures (including some synthesis of early intermediates), experimental details of the receptor binding studies and $^{1}H$ and $^{13}C$ NMR spectra of all synthesized compounds.

**Conflict of interest**

The authors declare no conflict of interest.

**References**

[1] M. Sheng, B.L. Sabatini, T.C. Südhof, Synapses and Alzheimer's disease, Cold Spring Harbor Perspect. Biol. 4 (5) (2012).

[2] S. Li, M. Jin, T. Koeglsperger, N.E. Shepardson, G.M. Shankar, D.J. Selkoe, Soluble A*β* oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors, J. Neurosci. 31 (18) (2011) 6627–6638.

[3] Q. Zhou, M. Sheng, NMDA receptors in nervous system diseases, Neuropharmacol. 74 (2013) 69–75.

[4] N.-W. Hu, I. Klyubin, R. Anwyl, R. Anwy, M.J. Rowan, GluN2B subunit-containing NMDA receptor antagonists prevent A*β*-mediated synaptic plasticity disruption in vivo, Proc. Natl. Acad. Sci. U. S. A. 106 (48) (2009) 20504–20509.

[5] S. Davies, D.B. Ramsden, Huntington´s disease, J. Clin. Pathol.: Mol. Pathol. 54 (2001**)** 409–413.

[6] S.E. Lakhan, M. Caro, N. Hadzimichalis, NMDA receptor activity in neuropsychiatric disorders, *Front.* Psychiatry 4 (2013) 52.

[7] P. Paoletti, C. Bellone, Q. Zhou, NMDA receptor subunit diversity: Impact on receptor properties, synaptic plasticity and disease, Nat. Rev. Neurosci. 14 (2013) 383–400.

[8] M. Sheng, B.L. Sabatini, T.C. Südhof, Synapses and Alzheimer's disease, Cold Spring Harbor Perspect. Biol. 4 (2012) 5.

[9] R. Rönicke, M. Mikhaylova, S. Rönicke, J. Meinhardt, U.H. Schröder, M. Fändrich, G. Reiser, M.R. Kreutz, K.G. Reymann, Early neuronal dysfunction by amyloid β oligomers depends on activation of NR2B-containing NMDA receptors, Neurobiol. Aging 32 (2011) 2219–2228.

[10] P. Paoletti, Molecular Basis of NMDA Receptor Functional Diversity, Eur. J. Neurosci. 33 (2011) 1351–1365.

[11] P. Paoletti, J. Neyton, NMDA recetor subunits: function and pharmacology, Curr. Op. Pharmacol. 7 (2007) 39–47.

[12] D.J. Goebel, M.S. Poosch, NMDA receptor subunit gene expression in the rat brain: a quantitative analysis of endogenous mRNA levels of $NR1_{Com}$, NR2A, NR2B, NR2C, NR2D and NR3A, Mol. Brain Res. 69 (1999) 164–170.

[13] E. Karakas, N. Simorowski, H. Furukawa, Subunit arrangement and phenylethanolamine binding in GluN1/GluN2B NMDA receptors, Nature 475 (2011) 7355.

[14] E. Karakas, H. Furukawa, Crystal structure of a heterotetrameric NMDA receptor ion channel, Science 344 (2014) 992–997.

[15] C.-H. Lee W. Lü, J.C. Michel, A. Goehring, J. Du, X. Song, E. Gouaux, NMDA receptor structures reveal subunit arrangement and pore architecture, Nature 511 (2014) 191–197.

[16] N. Tajima, E. Karakas, T. Grant, N. Simorowski, R. Diaz-Avalos, N. Grigorieff, H. Furukawa, Activation of NMDA receptors and the mechanism of inhibition by ifenprodil, Nature 534 (2016) 63–68.

[17] S. Zhu, R.A. Stein, C. Yoshioka, C.H. Lee, A. Goehring, H.S. Mchaourab, E. Gouaux, Mechanism of NMDA Receptor Inhibition and Activation, Cell 165 (2016) 704–714.

[18] B.L. Chenard, I.A. Shalaby, B.K. Koe, R.T. Ronau, T.W. Butler, M.A. Prochniak, A.W. Schmidt, C.B. Fox, Separation of alpha.1-adrenergic and N-methyl-D-aspartate antagonist activity in a series of ifenprodil compounds, J. Med. Chem. 34 (1991) 3085–3090.

[19] C. Carter, J. Benavides, P. Legendre, J.D. Vincent, F. Noel, F. Thuret, K.G. Lloyd, S. Arbilla, B. Zivkovic, E.T. Mackenzie, Ifenprodil and SL 82.071 5 as Cerebral Anti-Ischemic Agents. II. Evidence for N-Methyl-D-Aspartate Receptor Antagonist Properties. J. Pharmacol. Exp. Ther. 247 (1988) 1222–1232.

[20] E. Falck, F. Begrow, E. Verspohl, B. Wünsch, Metabolism studies of ifenprodil, a potent GluN2B receptor antagonist, J. Pharm. Biomed. Anal. 88 (2014) 96–105.

[21] B. Tewes, B. Frehland, D. Schepmann, K. Schmidtke, T. Winckler, B. Wünsch, Conformationally constrained NR2B selective NMDA receptor antagonists derived from ifenprodil: Synthesis and biological evaluation of tetrahydro-3-benzazepine-1,7-diols, Bioorg. Med. Chem. 18 (2010) 8005–8015.

[22] B. Tewes, B. Frehland, D. Schepmann, K.-U. Schmidtke, T. Winckler, B. Wünsch, Design, Synthesis, and Biological Evaluation of 3-Benzazepin-1-ols as NR2B-Selective NMDA Receptor Antagonists, ChemMedChem 5 (2010) 687–695.

[23] E. Falck, F. Begrow, E.J. Verspohl, B. Wünsch, In vitro and in vivo biotransformation of WMS-1410, a potent GluN2B selective NMDA receptor antagonist, J. Pharm. Biomed. Anal. 94 (2014) 36–44.

[24] A. Banerjee, S. Maschauer, H. Hübner, P. Gmeiner, O. Prante, Click chemistry based synthesis of dopamine D4 selective receptor ligands for the selection of potential PET tracers, Bioorg. Med. Chem. Lett. 23 (2013) 6079–6082

[25] I. Berrebi-Betrand, X. Billot, T. Calmels, M. Capet, D. Danvy, S. Krief, O. Labeeuw, J.-M. Lecomte, N. Levoin, X. Ligneau, P. Robert, J.-C. Schwartz, Benzazeole Derivatives as Histamine H4 Receptor Ligands. International patent, WO 2012/041860 A1, 05.04.2012.

[26] G. Chiu, S. Li, P.J. Connolly, V. Pulito, J. Liu, S.A. Middleton, (Phenylpiperidinyl)cyclohexylsulfonamides: development of alpha1a/1d-selective adrenergic receptor antagonists for the treatment of benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS). Bioorg. Med. Chem. Lett. 17 (2007) 3930-3934.

[27] K. Sonogashira, Y. Tohda, N. Hagihara, A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines, Tetrahedron Lett. 16 (1975) 4467–4470.

[28] M. Feuerstein, H. Doucet, M. Santelli, Sonogashira reaction of heteroaryl halides with alkynes catalysed by a palladium-tetraphosphine complex, J. Mol. Catal. A. Chem. 256 (2006) 75–84.

[29] C. Molinaro, T.F. Jamison, Nickel-Catalyzed Reductive Coupling of Alkynes and Epoxides, J. Am. Chem. Soc. 125 (2003) 8076–8077.

[30] S.A. Glase, H.C. Akunne, T.G. Heffner, J.C. Jaen, R. G. MacKenzie, L.T. Meltzer, T.A. Pugsley, S.J. Smith, L.D. Wise, Aryl 1-But-3-ynyl-4-phenyl-1,2,3,6-tetrahydropyridines as Potential Antipsychotic Agents: Synthesis and Structure−Activity Relationships, J. Med. Chem. 39 (1996) 3179–3187.

[31] J. Peng, C. Chen, J. Chen, X. Su, C. Xi, H. Chen, Cu-Catalyzed Arylcarbocyclization of Alkynes with Diaryliodonium Salts through C–C Bond Formation on Inert C(sp3)–H Bond, Org. Lett. 16 (2014) 3776–3779.

[32] T. Nakamura, S. Saito, M. Yoshinaga, H. Ohta, M. Kawamura, T. Ishizaka, S. Satori, Heterocyclic Compound. International patent, WO 2009/038012 A1, 26.03.2009.

[33] Y. Shibata, Y. Otake, M. Hirano, K. Tanaka, Amide-Directed Alkenylation of $sp^2$ C−H Bonds Catalyzed by a Cationic Rh(I)/BIPHEP Complex Under Mild Conditions: Dramatic Rate Acceleration by a 1-Pyrrolidinecarbonyl Group, Org. Lett. 11 (2009) 689–692.

[34] H. Saji, H. Kimura, M. Ono, H. Matsumoto, Radioactive quinolinone derivative and pharmaceutical drug comprising the same, European patent, EP2 749 561 A1, 02.07.2014.

[35] E.C. Davison, M.E. Fox, A.B. Holmes, S.D. Roughley, C.J. Smith, G.M. Williams, J.E. Davies, P.R. Raithby, J.P. Adams, I.T. Forbes, N.J. Press, M.J. Thompson, Nitrone dipolar cycloaddition routes to piperidines and indolizidines. Part 9. Formal synthesis of (−)-pinidine and total synthesis of (−)-histrionicotoxin, (+)-histrionicotoxin and (−)-histrionicotoxin 235A, J. Chem. Soc., Perkin Trans. 1 (2002) 1494–1514

[36] D. Schepmann, B. Frehland, K. Lehmkuhl, B. Tewes, B. Wunsch, Development of a selective competitive receptor binding assay for the determination of the affinity to NR2B containing NMDA receptors, J. Pharm. Biomed. Anal. 53 (3) (2010) 603–608.

[37] F. Börgel, M. Szermerski, J.A. Schreiber, L. Temme, N. Strutz-Seebohm, K. Lehmkuhl, D. Schepmann, S.M. Ametamey, G. Seebohm, T.J. Schmidt, B. Wünsch, Synthesis and pharmacological evaluation of enantiomerically pure

GluN2B selective NMDA receptor antagonists, ChemMedChem 13 (2018) 1580–1587.

[38] A. Banerjee, D. Schepmann, J. Köhler, E.-U. Würthwein, B. Wünsch, Synthesis and SAR studies of chiral non-racemic dexoxadrol analogues as uncompetitive NMDA receptor antagonists, Bioorg. Med. Chem. 18 (22) (2010) 7855–7867.

[39] J. Köhler, K. Bergander, J. Fabian, D. Schepmann, B. Wünsch, Enantiomerically pure 1,3-dioxanes as highly selective NMDA and $\sigma_1$ receptor ligands, J. Med. Chem. 55 (20) (2012) 8953–8957.

[40] P. Hasebein, B. Frehland, K. Lehmkuhl, R. Fröhlich, D. Schepmann, B. Wünsch, Synthesis and pharmacological evaluation of *like*- and *unlike*-configured tetrahydro-2-benzazepines with the α-substituted benzyl moiety in the 5-position, Org. Biomol. Chem. 12 (29) (2014) 5407–5426.

[41] C. Meyer, B. Neue, D. Schepmann, S. Yanagisawa, J. Yamaguchi, E.-U. Würthwein, K. Itami, B. Wünsch, Improvement of $\sigma_1$ receptor affinity by late-stage C-H-bond arylation of spirocyclic lactones, Bioorg. Med. Chem. 21 (7) (2013) 1844–1856.

[42] K. Miyata, D. Schepmann, B. Wünsch, Synthesis and σ receptor affinity of regioisomeric spirocyclic furopyridines, Eur. J. Med. Chem. 83 (2014) 709–716.

**Graphical Abstract**