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FULL PAPER

Fluorinated GluN2B receptor antagonists with a 3-benzazepine scaffold designed for PET studies

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Abstract: In order to analyze the NMDA receptor distribution in the central nervous system, fluorinated ligands selectively addressing the ifenprodil binding site of GluN2B subunit containing NMDA receptors were developed. Various strategies to introduce a fluorine atom into the potent GluN2B ligand **2** (3-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1,7-diol) were pursued including the replacement of the benzylic OH moiety by a F-atom (**13**) and introduction of fluoroethoxy moieties at different positions (**14** (7-position), **17** (9-position) **18a-c** (1-position)). With respect to GluN2B affinity and selectivity over related receptors, the fluoroethoxy derivatives **14** and **18a** represent the most promising ligands. Radiosynthesis of fluoroethoxy derivative [^{18}F]**14** was performed by nucleophilic substitution of the phenol **2** with 2-[^{18}F]fluoroethyl tosylate. On rat brain slices the fluorinated PET tracer [^{18}F]**14** accumulated in regions with high density of NMDA receptors containing GluN2B subunits. The bound radioactivity could not be replaced by (*S*)-glutamate. However, the GluN2B ligands eliprodil, Ro 25-6981 and the non-labeled 3-benzazepine **14** were able to abolish the specific binding of [^{18}F]**14**.

Introduction

The excitatory amino acid neurotransmitter (*S*)-glutamate interacts with eight metabotropic receptors (i.e. G-protein coupled receptors) and three ionotropic receptors (i.e. ligand gated ion channels). Whereas all three ionotropic glutamate receptors (NMDA, AMPA, kainate receptors) control the passage of Na^+- and K^+-ions across the cell membrane, the opened NMDA (*N*-methyl-*D*-aspartate) receptor allows additionally the influx of Ca^{2+}-ions into the cell. The increase of intracellular Ca^{2+}-ion concentration is associated with neuronal development and neuronal growth, but also with excitotoxic effects. Therefore, the NMDA receptor represents an interesting target for the development of novel drugs for the treatment of various neurological and neurodegenerative disorders (e.g. depression, cerebral ischemia, stroke, Parkinson's, Alzheimer's and Huntington's disease.[1-6]

The NMDA receptor ion channel is structured by association of four proteins. These proteins belong to three types of subunits, GluN1, GluN2 and GluN3. Whereas eight splice variants of the GluN1 subunit (GluN1a-h) are known, four and two genes encode four GluN2A-D and two GluN3A-B subunits, respectively. In particular the expression of different GluN2 subunits differs considerably in various regions of the central nervous system. As an example, the GluN2B subunit is predominantly expressed in the hippocampus, striatum and cortex, but not in the cerebellum, where the GluN2C subunit is found in high density. Thus, subunit-selective NMDA receptor ligands will allow addressing only some regions of the central nervous system, whereas other regions without the particular subunit are not affected.[7-10]

Very recently, the structure of the heterotetrameric NMDA receptor containing two GluN1a splice variants and two GluN2B subunits together with various small molecules (glutamate, glycine, ifenprodil or Ro 25-6981) has been reported.[11,12] The structure shows the amino terminal domain (ATD) with the ifenprodil binding site at the interface between the GluN2B and GluN1a subunits, the ligand binding domain (LBD) with the glutamate (GulN2) and the glycine binding sites (GluN1) and the transmembrane domain (TMD) with the ion channel pore. Ligands interacting with the ifenprodil binding site within the ATD selectively modulate the opening state of only GluN2B subunit containing NMDA receptors as this binding site is only present at the interface between GluN2B and GluN1 subunits.

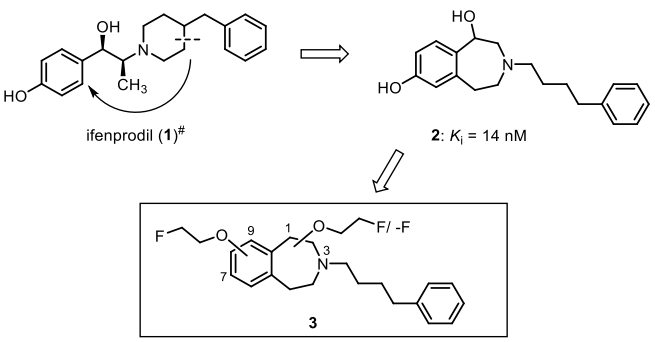


Figure 1. Design of GluN2B selective ligands **3** bearing a 2-fluoroethoxy moiety at various positions.

Ifenprodil (**1**) represents the prototypical ligand giving name to the ifenprodil binding site. (Figure 1) However, its selectivity is rather low, as it interacts with some types of Ca^{2+}-channels, α1, 5-HT_{1A}, 5-HT_2, σ_1 and σ_2 receptors as well, which results in side effects such as psychotomimetic effects, memory deficit and hypertension.[13-16] The selectivity could be considerably increased by rearrangement of the characteristic features of ifenprodil resulting in the 3-benzazepine **2**. (Figure 1) Ifenprodil and 3-benzazepine **2** display comparable GluN2B affinity, but **2** shows high selectivity against more than 100 relevant drug targets including adrenergic, serotonergic and σ receptors.[17]

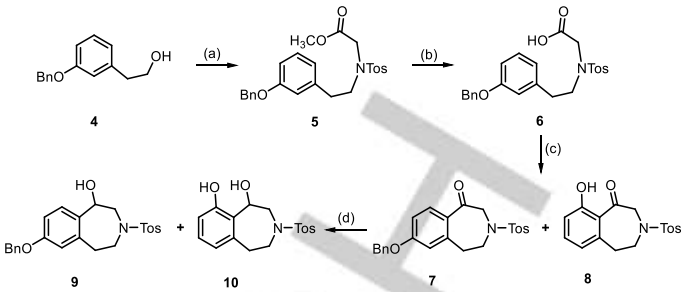
Since 1990 more than 60 compounds have been radiolabeled for in vivo imaging of the centrally located NMDA receptor. The majority of these radiotracers suffer from severe problems including (1) poor brain penetration, (2) extensive metabolism, (3) high non-specific and/or low specific binding, (4) homogenous brain distribution and/or (5) distribution inconsistent with known distribution of NMDA receptors.[18,19] Very recently, a 18-F-labeled memantine derivative was reported addressing the phencyclidine binding site within the channel pore with rather low affinity.[20] However, in case of open-channel blockers an additional problem exists since the PCP binding site within the channel pore is only accessible in the active state (open channel). Therefore, GluN2B subunit containing NMDA receptors were addressed by the 11-C-labeled dimethylaminopyridine [^{11}C]Ro-647312 showing high affinity towards the ifenprodil binding site.[21] A 11-C-labeled 3-benzazepine showing promising in vivo labeling of the ifenprodil binding site of GluN2B NMDA receptors was recently reported by us.[22] The 18-F-labeled piperidine derivative [^{18}F]MK-0657 revealed promising in vitro data, but low uptake into the brain.[23] In in vivo studies with 18-F-labeled benzoxazolone-based fluorophenyl derivative RGH-896 fast defluorination was observed resulting in high radioactivity in bones.[24]

Altogether, a fluorinated PET tracer selectively labeling NMDA receptors fulfilling all requirements of a PET tracer does not exist. Therefore, we decided to use 3-benzazepine 2 as starting point for the development of a fluorinated PET tracer for selective labeling of the ifenprodil binding site of GluN2B subunit containing NMDA receptors. As displayed in compound **3** fluoroethoxy groups will be introduced at various positions of the aromatic and aliphatic part of the 3-benzazepine moiety. Furthermore, an F-atom will be introduced in 1-position. (Figure 1)

Results and Discussion

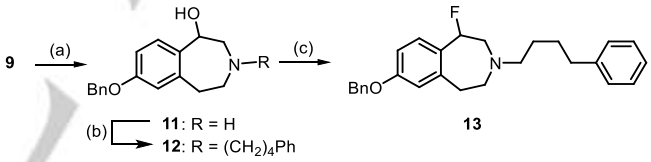
Synthesis

In order to obtain 3-benzazepin-1-one 7 and 3-bezazepin-1-ol 9a with a benzyl protected phenol efficiently, a similar synthetic approach was followed as described for the synthesis of the analogous methyl ethers. (Scheme 1).[25] At first tosylated glycine ester[26] was alkylated with benzyloxy substituted 2-phenylethanol 4 under Mitsunobu conditions.[27]



Scheme 1: Synthesis of central building blocks **9** and **10**. Reagents and reaction conditions: (a) $TosNHCH_2CO_2CH_3$, DIAD, Ph_3P, THF, 0 °C → RT, 24 h, 64 %. (b) NaOH, CH_3OH, reflux, 3 h, 90 %. (c) $SnCl_4$, trifluoroacetic anhydride, CH_2Cl_2, -15 °C, 18 h, 39 % mixture of **7** and **8**. (d) $NaBH_4$, CH_3OH, RT, 16 h, 48 % (**9**), 17 % (**10**).

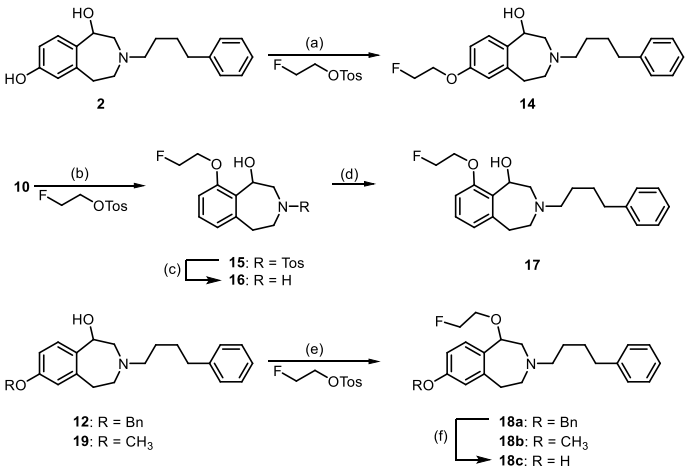
After saponification of the methyl ester **5**, various reaction conditions were tried to perform the intramolecular Friedel-Crafts acylation of carboxylic acid **6**. Treatment of acid **6** with trifluoroacetic anhydride for 30 min and subsequent addition of $SnCl_4$ afforded a mixture of 3-benzazepinones **7** and **8** in 39 % yield. During formation of the regioisomer with adjacent carbonyl and benzyloxy moieties, an unexpected cleavage of the benzyl ether was observed leading to the phenol **8**. After reduction of the mixture of ketones **7** and **8** with $NaBH_4$, the alcohols *9* and **10** were separated by flash chromatography. The benzyl ether **9**, which is the key intermediate of this study, had already been prepared by cleavage of the methoxy analog of benzyl ether **7** with $AlCl_3$ and subsequent benzylation of the resulting phenol.[17]



Scheme 2: Synthesis of fluorinated 3-benzazepine **13**. Reagents and reaction conditions: (a) Mg, CH_3OH, reflux, 6 h, 50 %. (b) 1-chloro-4-phenylbutane, Bu_4NI, CH_3CN, K_2CO_3, reflux, 72 h, 92 %. (c) Et_2NSF_3 (DAST), CH_2Cl_2, -78 °C, 1 h, then rt, 16 h, 53 %.

Removal of the tosyl protective group of **9** was performed with Mg in refluxing CH_3OH to yield the secondary amine **11**.[17] Upon reaction with 1-chloro-4-phenylbutane, the benzyloxy derivative **11** was converted into 4-phenylbutyl derivative **12**, which was obtained in 92 % yield, a yield that is slightly higher than the reported one.[17] The F-atom was introduced by reaction of **12** with diethylaminosulfur trifluoride (DAST)[28] to convert the benzylic OH moiety into a F-atom. The 1-fluoro derivative **13** was isolated in 53 % yield. Although **13** could be characterized spectroscopically, it showed fast degradation upon standing in solution. Due to the low stability of **13**, it could not be included into the biological studies. (Scheme 2)

In addition to the F-atom in benzylic position, a fluoroethyl moiety was considered as alternative F-containing substituent. This strategy will finally allow a facile radiofluorination, by using 18-fluorine labeled (2-fluoroethyl) tosylate as alkylating agent.



Scheme 3: Synthesis of fluoroethoxy derivatives. Reagents and reaction conditions: (a) CH_3CN, K_2CO_3, reflux, 16 h, 31 %. (b) CH_3CN, K_2CO_3, reflux, 72 h, 78 %. (c) Mg, CH_3OH, reflux, 16 h, 60 %. (d) 1-chloro-4-phenylbutane, TBAI, CH_3CN, K_2CO_3, reflux, 72 h, 46 %. (e) NaH, DMF, 24-36 h, 13 % (**18a**), 34 % (**18b**). (f) H_2, 1 bar, Pd/C, CH_3OH, RT, 30 min, 79 %.

At first, phenol **13c** was transformed into the fluoroethoxy derivative **14** by alkylation with (2-fluoroethyl) tosylate. The regioisomeric fluoroethoxy derivative **17** was prepared starting with the side product **10** formed during the intramolecular Friedel-Crafts acylation. Reaction of phenol **10** with (2-fluoroethyl) tosylate gave the fluoroethyl ether **15**. Removal of the tosyl group upon treatment with Mg in CH_3OH afforded the secondary amine **16**, which was alkylated with 1-chloro-4-phenylbutane to provide **17** in 46 % yield. (Scheme 3)

Next, it was investigated, whether the ifenprodil binding pocket tolerates a fluoroethyl moiety attached at the benzylic OH moiety of **12**. For this purpose, **12** and **19** were deprotonated with NaH and subsequently reacted with (2-fluoroethyl) tosylate to provide the fluoroethyl ethers **18a** and **18b**. The benzyl group of the benzyl ether **18a** was removed hydrogenolytically to give the phenol **18c**.

Pharmacological evaluation

GluN2B affinity

The GluN2B affinity of the fluoro derivative **13** and the fluoroethoxy derivatives **14**, **17** and **18** was recorded in competitive receptor binding studies. In brief, the receptor material was obtained from L(tk-) cells stably transfected with a vector encoding for the GluN1a and GluN2B subunits of the NMDA receptor. In the assay, [^{3}H]-labeled ifenprodil and the test compounds were competing for a limited number of receptors containing the ifenprodil binding site.[29]

Unfortunately, the benzyl fluoride **13** could not be included into the pharmacological study due to its low stability. In particular the donor substituent in 7-position induces a fast fluoride elimination.

Whereas a fluoroethoxy substituent in 9-position (**17**) led to negligible competition with the radioligand, the regioisomeric 7-fluoroethoxy derivative **14** revealed promising GluN2B affinity of 162 nM. The GluN2B affinity of 3-benzazepines with the fluoroethoxy moiety in 1-position was strongly dependent on the substituent in 7-position. **18c** with a phenolic OH moiety showed a K_i value of approx. 1 µM, the corresponding OCH_3 derivative **18b** revealed a K_i value of 470 nM, but the BnO derivative **18a** was the most potent GluN2B ligand of this series showing a K_i value of 71 nM. (Table 1)

The moderate GluN2B affinity of the fluoroethoxy derivative **14** was unexpected, since the corresponding methoxy derivative (R^1 = OH, R^2 = 7-OCH_3) showed very high GluN2B affinity (K_i = 5.4 nM) and high selectivity.[25] We assume that the ifenprodil binding pocket is rather limited around the alkoxy group: whereas the methoxy moiety fits nicely into the binding pocket, the slightly larger 2-fluoroethoxy moiety is too big to be well accepted by the binding pocket.

Alkylation of the hydroxy group in 1-position with a 2-fluoroethyl moiety also led to considerably reduced GluN2B affinity. This effect can be nicely observed by the Ki values recorded for the 1-OH compound **2** (K_i = 14 nM)[17] and the corresponding 1-FCH_2CH_2O compound **18c** (K_i = 1020 nM). It is postulated that the OH moiety in 1-position is required to establish H-bonds with some important amino acid residues in the binding pocket (e.g. Gln110, sSr132).

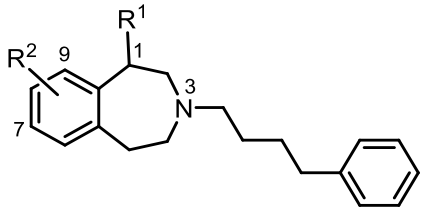
Selectivity against related binding sites and receptors

In order to characterize the fluoroethoxy derivatives **14**, **17** and **18** in more detail, the affinity towards the phencyclidine (PCP) binding site within the channel pore of the NMDA receptor[30,31] and the affinity towards both σ receptor subtypes[32-34] were determined in radioligand receptor binding studies. Up to a concentration of 1 µM the test compounds did not compete with the radioligand [^{3}H]MK-801 for the PCP binding site indicating very low PCP affinity and thus high selectivity for the ifenprodil binding site. (Table 1)

Due to similar pharmacophores[35-38] of σ receptor ligands and ligands binding at the ifenprodil binding site, the affinity towards σ_1 and σ_2 receptors was included into this study. Promising selectivity over both σ receptor subtypes was found for the most potent GluN2B ligands **14** and **18a**. Both compounds showed 7- and 10-fold selectivity for the ifenprodil binding site of NMDA receptors over σ_1 and σ_2 receptors, respectively.

The K_i values for interaction of **14** with σ_1 and σ_2 receptors are higher than 1 µM indicating very low affinity towards these receptors. The low σ_1 and σ_2 affinity of **14** is comparable with the low affinities of the lead compound **2**[17] and its corresponding methyl ether.[25] However, the GluN2B/σ_1 and GluN2B/σ_2 selectivity of 14 is considerably lower due to the reduced GluN2B affinity. Nevertheless the 7-10-fold selectivity stimulated the first radiosynthetic experiments.

Table 1. Receptor affinity of fluoro derivative **13** and fluoroethoxy derivatives **14**, **17** and **18** compared with reference compounds.



13, 14, 17, 18

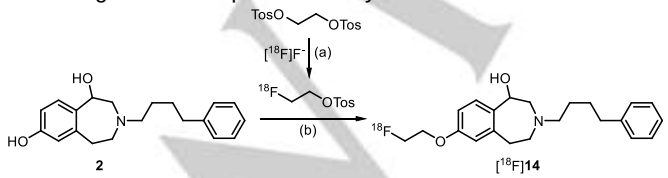
			K_i ± SEM [nM] (n = 3)[a]			
compd.	R^1	R^2	GluN2B	PCP	σ_1	σ_2
13	F	7-OBn	[b]	[b]	[b]	[b]
14	OH	7-(FCH_2CH_2O)	162 ± 22	9 %	1040	1700
17	OH	9-(FCH_2CH_2O)	21 %	0 %	5900	113
18a	FCH_2CH_2O	7-OBn	71 ± 29	0 %	469	773
18b	FCH_2CH_2O	7-OMe	470	0 %	214 ± 63	4 %
18c	FCH_2CH_2O	7-OH	1020	0 %	5700	1000
ifenprodil			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.

[b] Due to its high reactivity (low stability) the benzyl fluoride **13** could not be tested pharmacologically

Radiosynthesis of fluoroethoxy derivative [^{18}F]14

The remarkable selectivity over the PCP binding site, σ_1 and σ_2 receptors stimulated the radiosynthesis of **14**, although its K_i value for interaction with the ifenprodil binding site of GluN2B subunit containing NMDA receptors was only moderate.



Scheme 4: Radiosynthesis of 18-F-labeled fluoroethoxy derivative [^{18}F]**14**. Reagents and reaction conditions: (a) CH_3CN, Bu_4NOH, 90 °C, 4 min. (b) DMSO, NaOH, 12 min, 120 °C.

Fluoroethoxy derivative [^{18}F]**14** was obtained in a two-step radiosynthesis, starting from ^{18}F-labeling of ethylene ditosylate to give 2-[^{18}F]fluoroethyl tosylate. In the second reaction step, 2-[^{18}F]fluoroethyl tosylate was reacted with phenol **2**, to afford compound [^{18}F]**14** in non-decay corrected radiochemical yields of 4.4 – 16.7 % (1.3 – 4.1 GBq at the end of the synthesis). Radiochemical purity was greater than 98 % and specific molar radioactivity was between 85.6 and 179.9 GBq/µmol. (Scheme 4)

Autoradiography of fluoroethoxy derivative [^{18}F]**14**

Fluoroethoxy derivative [^{18}F]**14** was evaluated in autoradiography studies using rat brain slices. (Figure 2) High accumulation of radioactivity (fluoroethoxy derivative [^{18}F]**14**) was observed in the cortex, hippocampus, striatum and the hypothalamus, regions known to have high concentration of NMDA receptors with GluN2B subunit. As expected, treatment with (*S*)-glutamate did not lead to displacement of radioactivity on the slices indicating that (S)-glutamate had no effect on radioligand binding. The GluN2B antagonists eliprodil and Ro 25-6981 as well as the non-radioactive compound **14** abolished the binding of the radioligand suggesting in vitro specific binding of the radioligand [^{18}F]**14** to GluN2B subunit containing NMDA receptors.

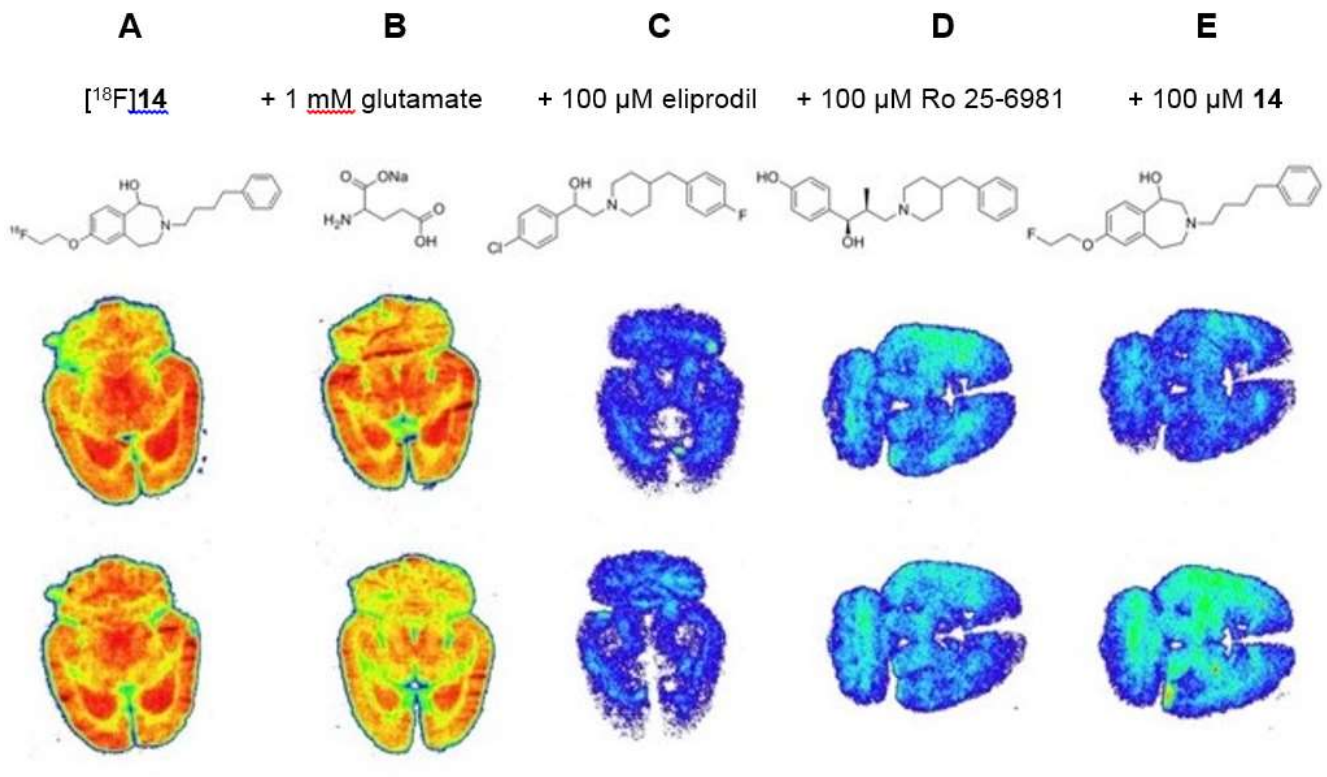


Figure 2: Rat brain slices incubated with Fluoroethoxy derivative [^{18}F]**14**. A: Incubation with PET tracer [^{18}F]**14** only; B – E: In addition to incubation with [^{18}F]**14**, glutamate (B), eliprodil (C), Ro 25-6981 (D) and **14** (E) were added.

Conclusions

The potent and subtype selective NMDA receptor antagonist **2** (K_i = 14 nM) represents the starting point for the development of fluorinated PET tracers deigned for imaging of NMDA receptors with GluN2B subunit in the central nervous system. Since introduction of the F-atom in benzylic position (**13**) resulted in a rather unstable compound, fluoroethoxy moieties were introduced in 1- (**18**), 7- (**14**) and 9-position (**17**). Promising GluN2B affinity and selectivity over σ receptors were found the 1-and 7-fluoroethoxy derivatives **18a** and **14**. Radiosynthesis of [^{18}F]**14** succeeded by alkylation of phenol **2** with 2-[^{18}F]fluoroethyl tosylate to give the PET tracer [^{18}F]**14** in good radiochemical yields and radiochemical purity. [^{18}F]**14** was able to label selectively NMDA receptors with GluN2B subunits of rat brain slices. The radioactivity could be blocked by co-incubation with the GluN2B ligands eliprodil, Ro 25-6981 and non-labeled **14**. According to these results, we conclude that the class of 3-benzazepines is well suited for the development of a fluorinated PET tracer for imaging of GluN2B subunit containing NMDA receptors. However, before *in vivo* evaluation we aim to increase the GluN2B affinity and selectivity over related receptors. According to our philosophy, pharmacological and physicochemical properties of ligands have to be optimized *in vitro* in order to reduce the number of animal experiments.

Experimental Section

Chemistry, General Methods

Oxygen and moisture sensitive reactions were carried out under nitrogen, dried with silica gel with moisture indicator (orange gel, VWR, Darmstadt, Germany) and in dry glassware (Schlenk flask or Schlenk tube). All solvents were of analytical or technical grade quality. Demineralized water was used. CH_2Cl_2 was distilled from CaH_2; THF was distilled from sodium/benzophenone; MeOH was distilled from magnesium methanolate. Thin layer chromatography (tlc): tlc silica gel 60 F_{254} on aluminum sheets (VWR). Flash chromatography (fc): Silica gel 60, 40–63 µm (VWR); parentheses include: diameter of the column (ø), length of the stationary phase (l), fraction size (v) and eluent. Automated flash chromatography: Isolera™ Spektra One (Biotage®); parentheses include: cartridge size, flow rate, eluent, fraction size was always 20 mL. Melting point: Melting point system MP50 (Mettler Toledo, Gießen, Germany), open capillary, uncorrected. MS: MicroTOFQII mass spectrometer (Bruker Daltonics, Bremen, Germany); deviations of the found exact masses from the calculated exact masses were 5 ppm 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 (*δ*) are reported in parts per million (ppm) against the reference substance tetramethylsilane and calculated using the solvent residual peak of the undeuterated solvent; coupling constants are given with 0.5 Hz resolution; assignment of ^{1}H and

^{13}C NMR signals was supported by 2-D NMR techniques were necessary.IR: FT/IR IR Affinity®-1 spectrometer (Shimadzu, Düsseldorf, Germany) using ATR technique.

HPLC method for the determination of the purity

Equipment 1: Pump: L-7100, degasser: L-7614, autosampler: L-7200, UV detector: L-7400, interface: D-7000, data transfer: D-line, data acquisition: HSM-Software (all from Merck Hitachi, Darmstadt, Germany); Equipment 2: Pump: LPG-3400SD, degasser: DG-1210, autosampler: ACC-3000T, UV-detector: VWD-3400RS, interface: DIONEX UltiMate 3000, data acquisition: Chromeleon 7 (equipment and software from Thermo Fisher Scientific, Lauenstadt, Germany); column: LiChrospher® 60 RP-select B (5 µm), LiChroCART® 250-4 mm cartridge; flow rate: 1.0 mL/min; injection volume: 5.0 µL; detection at λ = 210 nm; solvents: A: demineralized water with 0.05 % (V/V) trifluoroacetic acid, B: CH_3CN with 0.05 % (V/V) trifluoroacetic acid; gradient elution (% A): 0 - 4 min: 90 %; 4 - 29 min: gradient from 90 % to 0 %; 29 - 31 min: 0 %; 31 - 31.5min: gradient from 0 % to 90 %; 31.5 - 40 min: 90 %.

Synthetic procedures

Methyl *N*-[3-(benzyloxy)phenylethyl]-*N*-tosylglycinate (5)

2-[3-(Benzyloxy)phenyl]ethan-1-ol (**4**, 4.48 g, 19.6 mmol, 1.0 eq) was dissolved in abs. THF (250 mL) and the solution was cooled to 0 °C. PPh_3 (15.4 g, 58.8 mmol, 3.0 eq) was added. After addition of methyl (tosylamino)acetate (5.25 g, 21.6 mol, 1.1 eq), DIAD (11.6 mL, 58.8 mmol, 3.0 eq) was added dropwise and the mixture was stirred at 0 °C for 1 h. The mixture was warmed to room temperature and stirred for 24 h. After filtration, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (d = 10 cm, h 15 cm, V = 65 mL, cyclohexane:ethyl acetate = 4:1) to give **5**. Yellow oil, yield 5.67 g (64 %). $C_{25}H_{27}NO_5S$ (453.6). R_f = 0.80 (cyclohexane:ethyl acetate = 2:1). HPLC: 93.3 %, t_R = 23.99 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.41 (s, 3H, Ph-C*H*$_3$), 2.84 (t, *J* = 7.7 Hz, 2H, C*H*$_2$CH$_2$NTs), 3.46 (t, *J* = 7.8 Hz, 2H, CH$_2$C*H*$_2$NTs), 3.62 (s, 3H, OC*H*$_3$), 3.98 (s, 2H,C*H*$_2$COOCH$_3$), 5.03 (s, 2H, O-C*H*$_2$-Ph), 6.73 - 6.85 (m, 3H, 2-H$_{arom.}$, 4-H$_{arom.}$ and 6-H$_{arom.}$), 7.19 (t, *J* = 7.8 Hz, 1H, 5-H$_{arom.}$), 7.27 (d, *J* = 8.1 Hz, 2H, 3-H$_{tosyl}$ and 5-H$_{tosyl}$), 7.31 - 7.44 (m, 5H, benzyl), 7.70 (d, *J* = 7.9 Hz, 2H, 2-H$_{tosyl}$ and 6-H$_{tosyl}$). ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.7 (1C, Ph-*C*H$_3$), 35.3 (1C, *C*H$_2$CH$_2$NTs), 48.7 (1C, *C*H$_2$COOCH$_3$), 50.1 (1C, CH$_2$*C*H$_2$NTs), 52.3 (1C, O*C*H$_3$), 70.1 (1C, O-*C*H$_2$-Ph), 113.0 (1C, C-4$_{arom.}$), 115.6 (1C, C-2$_{arom.}$), 121.5 (1C, C-6$_{arom.}$), 127.5 (2C, C-2$_{tosyl}$ and C-6$_{tosyl}$), 127.6 (2C, C-2$_{benzyl}$ and C-6$_{benzyl}$), 128.1 (1C, C-4$_{benzyl}$), 128.7 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 129.7 (2C, C-3$_{tosyl}$ and C-5$_{tosyl}$), 129.8 (1C, C-5$_{arom.}$), 136.8 (1C, C-1$_{tosyl}$), 137.1 (1C, C-1$_{benzyl}$), 140.0 (1C, C-1$_{arom.}$), 143.6 (1C, C-4$_{tosyl}$), 159.1 (1C, C-3$_{arom.}$), 169.5 (1C, *C*OOCH$_3$). IR: $\tilde{\nu}$ [cm^{-1}] = 3032 (=C-H), 2951, 2870 (C-H$_{aliph.}$), 1751 (C=O), 1597, 1489 (C=C$_{arom.}$), 1450 (CH$_2$ deform.), 1153 (SO_2), 737 (=C-H deform.). Exact Mass (ESI): m/z = 476.1497 (calcd. 476.1502 for $C_{25}H_{27}NO_5SNa$ [M+Na]$^+$).

***N*-[3-(Benzyloxy)phenylethyl]-*N*-tosylglycine (6)**

5 (2.85 g, 6.29 mmol, 1.0 eq) was dissolved in CH_3OH (10 mL), 2 M NaOH (35 mL) was added and the mixture was heated to reflux for 3 h. At room temperature, HCl was added to adjust pH 2. After addition of brine (20 mL), the solution was extracted with CH_2Cl_2 (3 x 100 mL).The combined organic layers were washed with brine (3 x 100 mL) and dried over Na_2SO_4. The solution was concentrated in vacuo giving the crude product, which was purified by flash column chromatography (d = 4 cm, h = 15 cm, V = 20 mL, cyclohexane:ethyl acetate = 2:1 + 2 % AcOH) to yield **6**. Colorless solid, mp 132 °C, yield 2.58 g (90 %). $C_{24}H_{25}NO_5S$ (439.5). R_f = 0.13 (cyclohexane:ethyl acetate = 2:1 + 2 % AcOH). HPLC: 99.2 %, t_R = 22.71 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.40 (s, 3H Ph-C*H*$_3$), 2.83 (t, *J* = 7.7 Hz, 2H, C*H*$_2$CH$_2$NTs), 3.46 (t, *J* = 7.7 Hz, 2H, CH$_2$C*H*$_2$NTs), 3.97 (s, 2H, C*H*$_2$COOH), 5.03 (s, 2H, O-C*H*$_2$-Ph), 6.71 – 6.85 (m, 3H, 2-H$_{arom}$, 4-H$_{arom.}$ and 6-H$_{arom.}$), 7.18 (t, *J* = 7.8 Hz, 1H, 5-H$_{arom.}$), 7.25 – 7.44 (m, 7H, 3-H$_{tosyl}$ and 5-H$_{tosyl}$, benzyl), 7.69 (d, *J* = 7.9 Hz, 2H, 2-H$_{tosyl}$ and 6-H$_{tosyl}$). ^{13}C NMR (151 MHz; $CDCl_3$): δ [ppm] = 21.7 (1C, Ph-*C*H$_3$), 35.2 (1C, *C*H$_2$CH$_2$NTs), 48.7 (1C, *C*H$_2$COOH), 50.3 (1C, CH$_2$*C*H$_2$NTs), 70.1 (1C, O-*C*H$_2$-Ph), 113.1 (1C, C-4$_{arom.}$), 115.6 (1C, C-2$_{arom.}$), 121.4 (1C, C-6$_{arom.}$), 127.5 (2C, C-2$_{tosyl}$ and C-6$_{tosyl}$), 127.6 (2C, C-2$_{benzyl}$ and C-6$_{benzyl}$), 128.1 (1C, C-4$_{benzyl}$), 128.7 (2C, C-3$_{benzyl}$ and C-5$_{benzyl}$), 129.8 (2C, C-3$_{tosyl}$ and C-5$_{tosyl}$), 129.9 (1C, C-5$_{arom.}$), 136.5 (1C, C-1$_{tosyl}$), 137.0 (1C, C-1$_{benzyl}$), 139.7 (1C, C-1$_{arom.}$), 143.9 (1C, C-4$_{tosyl}$), 159.1 (1C, C-3$_{arom.}$), 173.8 (1C, *C*OOH). IR: $\tilde{\nu}$ [cm^{-1}] = 3032 (=C-H), 2932 2874 (CH$_{aliph.}$), 1717 (C=O), 1597 (C=C$_{arom.}$), 1346, 1157 (SO_2). Exact Mass (APCI): m/z = 440.1550 (calcd. 440.1526 for $C_{24}H_{26}NO_5S$ [MH]$^+$).

7-(Benzyloxy)-3-tosyl-2,3,4,5-tetrahydro-3-benzazepin-1-one (7) and 9-hydroxy-3-tosyl-2,3,4,5-tetrahydro-3-benzazepin-1-one (8)

The acid **6** (1.0 g, 2.28 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (80 mL) and the solution was cooled to -15 °C. Trifluoroacetic anhydride (1.20 mL, 8.55 mmol, 3.75 eq) was added and the solution was stirred for 30 min. Afterwards $SnCl_4$ (1.0 mL, 8.55 mmol, 3.75 eq) was slowly added and the solution was stirred for 18 h at -15 °C. Water (30 mL) was added before the solution was warmed to room temperature and neutralized with NaOH. After dilution with brine, the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash column chromatography (d = 4 cm, h = 15 cm, V = 20 mL, cyclohexane:ethyl acetate = 4:1), yielding a mixture of **7** and **8**. Colorless foam, yield 377 mg (39 %). $C_{24}H_{23}NO_4S$ (421.5). R_f = 0.35 (cyclohexane:ethyl acetate = 2:1). The NMR data were generated with another sample. Ratio **7**:**8** = 55:45. The signals for **7** are marked with letter **a**. Letter **b** indicates signals from **8**. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.33 (s, 3H, Ph-CH$_3$), 2.90 – 3.00 (m, 2H, 5-CH$_2$), 3.67 (t, *J* = 6.6 Hz, 2 · 0.55H, 4-CH$_2$, a), 3.73 (t, *J* = 6.6 Hz, 2 · 0.45H, 4-CH$_2$, b), 4.17 (s, 2 · 0.55H, 2-H, a), 4.33 (s, 2 · 0.45H, 2-CH$_2$, b), 5.10 (s, 2 · 0.55H, O-C*H*$_2$-Ph, a), 6.62 (d, *J* = 7.2 Hz, 0.45H, 6-H, b), 6.69 – 6.75 (m, 1H, 6-H and 8-H), 6.80 (dd, *J* = 8.7/2.4 Hz, 0.55H, 8-H, a), 7.02 – 7.12 (m, 2H, 3-H$_{tosyl}$ and 5-H$_{tosyl}$), 7.23 – 7.28 (m, 0.45H, 7-H, b), 7.33 – 7.48 (m, 2H, 2-H$_{tosyl}$, 6-H$_{tosyl}$; 0.55 H, 9-H, a; 5 · 0.55H, benzyl, a), 11.28 (s, 1H, O*H*, b). ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 21.57, 21.59 (1C, Ph-*C*H$_3$ and Ph-*C*H$_3$), 33.3 (0.55C, C-5, a), 34.1 (0.45C, C-5, b), 46.6 (0.55C, C-4, a), 46.9 (0.45C, C-4, b), 54.7 (0.55C, C-2, a), 55.0 (0.45C, C-2, b), 70.3 (0.55C, O-*C*H$_2$-Ph, a), 113.4 (0.55C, C-8, a), 115.8 (0.55C, C-6, a), 117.5 (0.45C, C-8, b), 118.9 (0.45C, C-9a, b), 120.9 (0.45C, C-6, b), 126.4 (2C, C-2$_{tosyl}$ and C-6$_{tosyl}$), 126.9, 128.5, 128.9 (5 · 0.55C, benzyl, a), 129.7 (2· 0.55C, C-3$_{tosyl}$ and C-5$_{tosyl}$, a), 129.8 (2· 0.45C, C-3$_{tosyl}$ and C-5$_{tosyl}$, b), 130.0 (0.55C, C-9a, a) 131.7 (0.55C, C-9, a), 136.09 (1C, C-1$_{tosyl}$), 136.10 (1C, C-1$_{benzyl}$), 140.0 (0.55C, C-5a, a), 140.3 (0.45C, C-5a,

b), 143.4 (0.55C, C-4_{tosyl}, a), 143.6 (0.45C, C-4_{tosl}, b), 162.7 (0.55C, C-7, a; 0.45C C-9, b) , 200.3 (0.55C, C-1, a), 205.1 (0.45C, C-1, b). IR: $\tilde{\nu}$ [cm^{-1}] = 3032 (=C-H), 2924, 2882 (C-$H_{aliph.}$), 1674 (C=O), 1597 (C=$C_{arom.}$), 1339, 1153 (SO_2). Exact Mass (ESI): m/z = 444.1245 (calcd. 444.1240 for $C_{24}H_{23}NO_4SNa$ $[M+Na]^+$, **7**), 354.0782 (calcd. 354.0770 for $C_{17}H_{17}NO_4SNa$ $[M+Na]^+$, **8**).

7-(Benzyloxy)-3-(*N*-tosyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (9) and 3-(*N*-tosyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine-1,9-diol (10)

$NaBH_4$ (153 mg, 3.94 mmol, 6 eq) was added to a suspension of **7**/**8** (277 mg, 1 eq) in abs. CH_3OH (20 mL) and the mixture was stirred 16 h at room temperature. Water (20 mL) and $CHCl_3$ (30 mL) were added and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 x 20 mL) and the combined organic layers were washed with H_2O (3 x 30 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 2:1) yielding the separated compounds **9** and **10** in a 3:1 ratio.

9 (R_f = 0.37 (cyclohexane:ethyl acetate = 2:1)): Colorless solid, mp 121 °C, yield 133 mg (48 %). $C_{24}H_{25}NO_4S$ (423.5). HPLC: 96.4 %, t_R = 22.85 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.40 (s, 3H, Ph-C*H*$_3$), 2.83 (dd, *J* = 15.3/7.5 Hz, 1H, 5-H), 3.08 (dd, *J* = 12.9/9.7 Hz, 1H, 4-H), 3.23 (d, *J* = 13.2 Hz, 1H, 2-H), 3.25 - 3.32 (m, 1H, 5-H), 3.62 (dd, *J* = 12.9/7.6 Hz, 1H, 4-H), 3.70 (dd, *J* = 13.2/7.1 Hz, 1H, 2-H), 4.83 (d, *J* = 6.8 Hz, 1H, 1-H), 5.02 (s, 2H, O-C*H*$_2$-Ph), 6.70 - 6.77 (m, 2H, 6-H, 8-H), 7.21 (d, *J* = 8.4 Hz, 1H, 9-H), 7.28 (d, *J* = 8.1 Hz, 2H, 3-H_{tosyl} and 5-H_{tosyl}), 7.30 - 7.40 (m, 5H, benzyl), 7.66 (d, *J* = 8.1 Hz, 2H, 2-H_{tosyl} and 6-H_{tosyl}). A signal for the OH proton is not seen in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.6 (1C, Ph-*C*H_3), 36.8 (1C, C-5), 48.6 (1C, C-4), 53.8 (1C, C-2), 70.1 (1C, O-*C*H_2-Ph), 72.9 (1C, C-1), 111.9 (1C, C-8), 117.6 (1C, C-6), 127.3 (2C, C-2_{tosyl} and C-6_{tosyl}), 127.5, 128.1, 128.7 (5C, benzyl), 129.4 (1C, C-9), 129.9 (2C, C-3_{tosyl} and C-5_{tosyl}), 134.0 (1C, C-9a), 135.5 (1C, C-1_{tosyl}), 136.9 (1C, C-1_{benzyl}), 140.1 (1C, C-5a), 143.7 (1C, C-4_{tosyl}), 158.5 (1C, C-7). IR: $\tilde{\nu}$ [cm^{-1}]: = 3341 (O-H), 3063, 3032 (=C-H), 2920, 2862 (C-$H_{aliph.}$), 1613, 1578, 1493 (C=$C_{arom.}$), 1331, 1153 (SO_2), 1096 (C-OH). Exact Mass (APCI): m/z = 422.1421 (calcd. 422.1432 for $C_{24}H_{24}NO_4S$ $[MH]^-$).

10 (R_f = 0.19 (cyclohexane:ethyl acetate = 1:1)): Colorless solid, mp 76 °C, yield 37.5 mg (17 %). $C_{17}H_{19}NO_4S$ (333.40). HPLC: 94.4 %, t_R = 18.68 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.41 (s, 3H, Ph-C*H*$_3$), 2.93 (dd, *J* = 7.3/4.0 Hz, 2H, 5-H_2), 3.12 (dt, *J* = 12.4/5.9 Hz, 1H, 4-H), 3.38 (dd, *J* = 13.9/6.9 Hz, 1H, 2-H), 3.60 (dt, *J* = 12.1/4.7 Hz, 1H, 4-H), 3.77 - 3.81 (m, 1H, 2-H), 5.36 (dd, *J* = 6.8/2.2 Hz, 1H, 1-H), 6.59 (d, *J* = 7.5 Hz, 1H, 6-H), 6.75 (dd, *J* = 8.1/1.2 Hz, 1H, 8-H), 7.04 (t, *J* = 7.8 Hz, 1H, 7-H), 7.30 (d, *J* = 8.0 Hz, 2H, 3-H_{tosyl} and 5-H_{tosyl}), 7.66 (d, *J* = 8.1 Hz, 2H, 2-H_{tosyl} and 6-H_{tosyl}), 8.49 (br s, 2H, $OH_{arom.}$ and benzylic OH). ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 21.7 (1C, *C*H_3), 35.2 (1C, C-5), 48.0 (1C, C-4), 53.0 (1C, C-2), 72.3 (C-1), 116.7 (1C, C-8), 122.0 (1C, C-6), 124.6 (1C, C-9a), 127.3 (2C, C-2_{tosyl} and C-6_{tosyl}), 129.1 (1C, C-7), 130.0 (2C, C-3_{tosyl} and C-5_{tosyl}), 134.9 (1C, C-1_{tosyl}), 137.9 (1C, C-5a), 144.0 (1C, C-4_{tosyl}), 156.3 (1C, C-9). IR: $\tilde{\nu}$ [cm^{-1}] = 3422 (O-H), 2978, 2920, 2855 (C-$H_{aliph.}$), 1589 (C=$C_{arom.}$), 1466 (CH_2 deform.), 1327, 1153 (SO_2), 1096 (C-OH). Exact Mass (ESI): m/z = 356.0928 (calcd. 356.0927 for $C_{17}H_{19}NO_4SNa$ $[M+Na]^+$).

7-(Benzyloxy)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (11) [17]

9 (84.2 mg, 0.20 mmol, 1 eq) and Mg (106 mg, 4.37 mmol, 22 eq) were suspended in abs. CH_3OH (20 mL) and the suspension was heated to reflux for 6 h. At 0 °C, conc. H_2SO_4 (0.5 mL) was added until no reaction of Mg was observed. 2 M NaOH was added to adjust pH 9 and the suspension was filtered. The filtrate was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, CH_2Cl_2: CH_3OH = 95:5 + 2 % NH_3) to afford **11**. Colorless solid, mp 138 °C, yield 26.9 mg (50 %). $C_{17}H_{19}NO_2$ (269.3). R_f = 0.14 (CH_2Cl_2:CH_3OH = 9:1 + 2 % NH_3). HPLC: 95.4 %, t_R = 15.23 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.65 (dd, *J* = 15.0/5.7 Hz, 1H, 5-H), 2.78 (t, *J* = 12.4 Hz, 1H, 4-H), 2.88 (d, *J* = 12.7 Hz, 2H, 2-H), 3.21 – 3.34 (m, 3H, 2-H, 4-H and 5-H), 4.60 (d, *J* = 6.1 Hz, 1H, 1-H), 5.04 (s, 2H, O-C*H*$_2$-Ph), 6.70 – 6.75 (m, 2H, 6-H and 8-H), 7.12 (d, *J* = 8.0 Hz, 1H, 9-H), 7.30 – 7.43 (m, 5H, benzyl). Signals for OH and NH protons are not seen in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 39.0 (1C, C-5), 49.5 (1C, C-4), 53.7 (1C, C-2), 70.1 (1C, O-*C*H_2-Ph), 74.1 (1C, C-1), 111.2 (1C, C-8), 118.0 (1C, C-6), 127.6, 128.1, 128.7 (5C, benzyl), 130.2 (1C, C-9), 135.9 (1C C-9a),137.2 (1C, C_{benzyl}-1), 141.9 (1C, C-5a), 158.3 (1C, C-7). IR: $\tilde{\nu}$ [cm^{-1}] = 3294 (N-H), 3032 (=C-H), 2905, 2851 (C-$H_{aliph.}$), 1612, 1578, 1493 (C=$C_{arom.}$), 1258 (C-OH). Exact Mass (APCI): m/z = 270.1531 (calcd. 270.1498 for $C_{17}H_{20}NO_2$ $[MH]^+$).

7-(Benzyloxy)-3-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (12)[17]

11 (150 mg, 0.56 mmol, 1 eq) was dissolved in CH_3CN (20 mL). After addition of 1-chloro-4-phenylbutane (0.14 mL, 0.85 mmol, 1.5 eq), K_2CO_3 (619 mg, 4.48 mmol, 8 eq) and TBAI (207 mg, 0.56 mmol, 1 eq), the suspension was heated to reflux for 72 h. After cooling to room temperature, K_2CO_3 was filtered off and the solvent was removed under reduced pressure. 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*-dimethylethanamine) to yield **12**. Colorless oil, yield 207 mg (92 %). $C_{27}H_{31}NO_2$ (401.6). R_f = 0.44 (cyclohexane:ethyl acetate = 2:1 + 1 % *N*,*N*-dimethylethanamine). HPLC: 97.6 %, t_R = 20.92 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.57 - 1.70 (m, 4H, NCH_2C*H*$_2$*C*H_2CH_2Ph), 2.45 - 2.54 (m, 1H, 4-H), 2.57 - 2.74 (m, 6H, NC*H*$_2CH_2CH_2C$*H*$_2$Ph, 2-H and 5-H), 3.02 (t, *J* = 8.9 Hz, 1H, 4-H), 3.18 (d, *J* = 10.5 Hz, 1H, 2-H), 3.24 - 3.32 (m, 1H, 5-H), 4.63 - 4.70 (m, 1H, 1-H), 5.03 (s, 2H, O-C*H*$_2$-Ph), 6.71 - 6.76 (m, 2H, 6-H and 8-H), 7.12 (d, *J* = 7.9 Hz, 1H, 9H), 7.16 - 7.43 (m, 10H, phenyl and benzyl). A signal for the OH proton is not seen in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 26.5 (1C, $NCH_2CH_2CH_2CH_2$Ph), 29.2 (1C, NCH_2CH_2C*H*$_2CH_2CH_2$Ph), 35.9 (1C, $NCH_2CH_2CH_2C$*H*$_2$Ph), 36.6 (1C, C-5), 56.1 (1C, C-4), 59.7 (1C, $NCH_2CH_2CH_2CH_2$Ph), 60.8 (1C, C-2), 70.1 (1C, O-*C*H_2-Ph), 72.2 (1C, C-1), 111.4 (1C, C-8), 117.6 (1C, C-6), 125.9, 127.6, 128.49, 128.52, 128.7 (10C, arom.), 129.7 (1C, C-9), 135.7 (1C, C-9a), 137.2 (1C, C-1_{benzyl}), 141.1 (1C, C-5a), 142.3 (1C, C-1_{phenyl}), 158.3 (1C, C-7). IR: $\tilde{\nu}$ [cm^{-1}] = 3348 (-OH), 3059, 3024 (=C-H), 2931, 2858, 2820 (C-$H_{aliph.}$), 1678, 1605, 1582, 1497 (C=$C_{arom.}$), 1242 (C-O). Exact Mass (APCI): m/z = 402.2405 (calcd. 402.2428 for $C_{27}H_{32}NO_2$ $[MH]^+$).

7-(Benzyloxy)-1-fluoro-3-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (13)

DAST (0.08 mL, 0.61 mmol, 4.2 eq) was dissolved under N_2 atmosphere in abs. CH_2Cl_2 (10 mL) at -78 °C. A solution of **12** (58.1 mg, 0.14 mmol, 1 eq) in CH_2Cl_2 (1 mL) was added. After the solution had been stirred for 1 h at -78 °C, the mixture was stirred for 16 h at rt. 2 M NaOH (3 mL) was added and the mixture was stirred for 30 min. H_2O (30 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash column chromatography chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 9:1 + 1 % *N*,*N*-dimethylethanamine) to afford **13**. Yellow oil, yield 29.9 mg (53 %). $C_{27}H_{30}FNO$ (403.5). ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.55 – 1.72 (m, 4H, $NCH_2CH_2CH_2CH_2Ph$), 2.43 – 3.17 (m, 10H, $NCH_2CH_2CH_2CH_2Ph$, 2-CH_2, 4-CH_2 and 5-CH_2), 5.06 (s, 2H, O-CH_2-Ph), 5.60 (d, *J* = 44.6 Hz, 1H, 1-H), 6.74 – 6.86 (m, 2H, 6-H and 8-H), 7.16 – 7.45 (m, 11H, 9-H, phenyl and benzyl). ^{19}F NMR (376 MHz, $CDCl_3$): δ [ppm] = -180.8.

7-(2-Fluoroethoxy)-2,3,4,5-tetrahydro-3-(4-phenylbutyl)-1*H*-3-benzazepine-1-ol (14)

To a solution of **2** (53.5 mg, 0.17 mmol, 1 eq.) in abs. CH_3CN (25 mL), K_2CO_3 (23.5 mg, 0.17 mmol, 1 eq) was added and the mixture was heated to reflux for 1 h. After addition of (2-fluoroethyl) tosylate (56.2 mg, 0.26 mmol, 1.5 eq) in CH_3CN (5 mL) the mixture was heated to reflux for 16 h. K_2CO_3 was filtered off and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (d = 1 cm, h = 15 cm, V = 5 mL cyclohexane:ethyl acetate = 3:1 + 1 % *N*,*N* dimethylethanamine → cycohexane:ethyl acetate = 1:2 + 1 % *N*,*N*-dimethylethanamine) to afford **14**. Colorless solid, mp 82 °C, yield 18.7 mg (0.05 mmol, 31 %). $C_{22}H_{28}FNO_2$ (357.5). R_f = 0.25 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethanamine). HPLC: 97.1 %, t_R = 17.68 min. ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.53 - 1.62 (m, 2H, $NCH_2CH_2CH_2CH_2Ph$), 1.63 - 1.71 (m, 2H, $NCH_2CH_2CH_2CH_2Ph$), 2.40 (t, *J* = 12.0 Hz, 1H, 4-H), 2.51 (d, *J* = 12.1 Hz, 1H, 2-H), 2.58 - 2.67 (m, 5H, $NCH_2CH_2CH_2CH_2Ph$ and 5-H), 3.00 (dd, *J* = 12.5/6.0 Hz, 1H, 4-H), 3.14 - 3.21 (m, 1H, 2-H), 3.22 - 3.32 (m, 1H, 5-H), 4.18 (dt, *J* = 27.9/4.1 Hz, 2H, OCH_2CH_2F), 4.58 (d, *J* = 6.7 Hz, 1H, 1-H), 4.73 (dt, *J* = 47.5/4.0 Hz, 2H, OCH_2CH_2F), 6.64 - 6.70 (m, 2H, 6-H, 8-H), 7.10 (d, *J* = 8.0 Hz, 1H, 9-H), 7.16 - 7.22 (m, 3H, 2-H_{phenyl}, 4-H_{phenyl} and 6-H_{phenyl}), 7.26 - 7.32 (m, 2H, 3-H_{phenyl} and 5-H_{phenyl}). A signal for the OH proton is not seen in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 26.8 (1C, $NCH_2CH_2CH_2CH_2Ph$), 29.3 (1C, $NCH_2CH_2CH_2CH_2Ph$), 35.9 (1C, C-5), 37.0 (1C, $NCH_2CH_2CH_2CH_2Ph$), 56.2 (1C, C-4), 59.8 (1C, $NCH_2CH_2CH_2CH_2Ph$), 60.9 (1C, C-2), 67.3 (d, *J* = 20.6 Hz, 1C, OCH_2CH_2F), 72.5 (1C, C-1), 82.0 (d, *J* = 170.7 Hz, 1C, OCH_2CH_2F), 111.0 (1C, C-8), 117.5 (1C, C-6), 125.9 (1C, C-4_{phenyl}), 128.48, 128.53 (4C, C-2_{phenyl}, C-3_{phenyl}, C-5_{phenyl} and C-6_{phenyl}), 129.9 (1C, C-9), 136.3 (1C, C-9a), 141.5 (1C, C-5a), 142.4 (1C, C-1_{phenyl}), 157.9 (1C, C-7). IR: $\tilde{\nu}$ [cm^{-1}] = 3071, 3024 (=C-H), 2932, 2859 (C-$H_{aliph.}$), 1609, 1498 (C=$C_{arom.}$), 1454 (CH_2 deform.), 1246, 1049 (C-O). Exact Mass (APCI): m/z = 358.2175 (calcd. 358.2177 for $C_{22}H_{29}FNO_2$ $[MH]^+$).

9-(2-Fluoroethoxy)-3-tosyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (15)

A mixture of **10** (143 mg, 0.43 mol, 1 eq), K_2CO_3 (475 mg, 3.44 mmol, 8 eq) and (2-fluoroethyl) tosylate (112 mg, 0.52 mmol, 1.2 eq) in CH_3CN (20 mL), was heated to reflux for 72 h. K_2CO_3 was filtered off and the solvent was removed under reduced pressure. After purification by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 2:1), **15** was obtained. Colorless foam, mp 92 °C, yield 127 mg (78 %). $C_{19}H_{22}FNO_4S$ (379.4). R_f = 0.42 (cyclohexane:ethyl acetate = 1:1). HPLC: 97.9 %, t_R = 20.46 min. ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.40 (s, 3H, Ph-CH_3), 2.76 – 2.83 (m, 1H, 5-H), 2.87 – 2.96 (m, 1H, 4-H), 3.09 (dd, *J* = 13.7/2.3 Hz, 1H, 2-H), 3.45 (ddd, *J* = 15.3/11.8/3.1 Hz, 1H, 5-H), 3.92 (ddd, *J* = 11.2/4.0/1.9 Hz, 1H, 4-H), 4.05 (dd, *J* = 13.8/7.1 Hz, 1H, 2-H), 4.20 (dt, *J* = 27.8/4.0 Hz, 2H, OCH_2CH_2F), 4.74 (dt, *J* = 47.4/4.3 Hz, 2H, OCH_2CH_2F), 5.65 (dd, *J* = 7.2/2.4 Hz, 1H, 1-H), 6.71 (d, *J* = 7.5 Hz, 1H, 6-H), 6.75 (d, *J* = 8.3 Hz, 1H, 8-H), 7.12 (t, *J* = 7.9 Hz, 1H, 7-H), 7.28 (d, *J* = 8.0 Hz, 2H, 3-H_{tosyl} and 5-H_{tosyl}), 7.67 (d, *J* = 8.0 Hz, 2H, 2-H_{tosyl} and 6-H_{tosyl}). A signal for the OH proton is not seen in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 21.6 (1C, CH_3), 35.4 (1C, C-5), 48.2 (1C, C-4), 51.1 (1C, C-2), 64.3 (1C, C-1), 68.4 (d, *J* = 20.3 Hz, 1C, OCH_2CH_2F), 82.0 (d, *J* = 170.8 Hz, 1C, OCH_2CH_2F), 111.5 (1C, C-8), 123.9 (1C, C-6), 127.3 (2C, C-2_{tosyl} and C-6_{tosyl}), 129.2 (1C, C-7), 129.5 (1C, C-9a), 129.8 (2C, C-3_{tosyl} and C-5_{tosyl}), 135.6 (1C, C-1_{tosyl}), 140.8 (1C, C-5a), 143.5 (1C, C-4_{tosyl}), 156.5 (1C, C-9). IR: $\tilde{\nu}$ [cm^{-1}] = 3503 (O-H), 2924, 2878 (C-$H_{aliph.}$), 1585 (C=$C_{arom.}$), 1450 (CH_2 deform.), 1331 (SO_2), 1258 (C-O), 1153 (SO_2). Exact Mass (ESI): m/z = 402.1138 (calcd. 402.1146 for $C_{19}H_{22}FNO_4SNa$ $[M+Na]^+$).

9-(2-Fluoroethoxy)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (16)

15 (105 mg, 0.28 mmol, 1 eq) and Mg (150 mg, 6.16 mmol, 22 eq) were suspended in abs. CH_3OH (25 mL) and the mixture was heated to reflux for 16 h. Conc. H_2SO_4 (1.0 mL) was added until a reaction of Mg was no longer observed. The pH was adjusted with 2 M NaOH to pH 9 and the suspension was filtered. Brine (30 mL) and CH_2Cl_2 (50 mL) were added to the filtrate and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, CH_2Cl_2:CH_3OH = 95:5 + 2 % NH_3 → CH_2Cl_2:CH_3OH = 9:1 + 2 % NH_3) to obtain **16**. Colorless solid, mp 132 °C, yield 37.2 mg (60 %). $C_{12}H_{16}FNO_2$ (225.3). R_f = 0.23 (CH_2Cl_2:CH_3OH = 9:1 + 2 % NH_3). HPLC: 92.1 %, t_R = 7.77 min. ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.68 – 2.86 (m, 3H, 2-H, 4-H and 5-H), 3.31 – 3.48 (m, 3H, 2-H, 4-H and 5-H), 4.10 – 4.30 (m, 2H, OCH_2CH_2F), 4.63 – 4.86 (m, 2H, OCH_2CH_2F), 5.59 (d, *J* = 6.2 Hz, 1H, 1-H), 6.72 – 6.78 (m, 2H, 6-H and 8-H), 7.10 (t, *J* = 7.9 Hz, 1H, 7-H). Signals for the OH and NH protons are not seen in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 38.2 (1C, C-5), 49.1 (1C, C-4), 52.5 (1C, C-2), 63.4 (1C, C-1), 68.6 (d, *J* = 20.5 Hz, 1C, OCH_2CH_2F), 82.0 (d, *J* = 170.8 Hz, 1C, OCH_2CH_2F), 111.6 (1C, C-8), 124.2 (1C, C-6), 128.6 (1C, C-7), 131.9 (1C, C-9a), 142.8 (1C, C-5a), 156.1 (1C, C-9). IR: $\tilde{\nu}$ [cm^{-1}] = 3298 (N-H), 3063, 3024 (=C-H), 2920 (O-H), 2801 (C-$H_{aliph.}$), 1585, 1447 (C=$C_{arom.}$), 1254, 1142 (C-O), 1053 (C-OH). Exact Mass (ESI): m/z = 226.1246 (calcd. 226.1238 for $C_{12}H_{17}FNO_2$ $[MH]^+$).

9-(2-Fluoroethoxy)-3-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ol (17)

1-Chloro-4-phenylbutane (0.03 mL, 0.21 mmol, 1.5 eq), TBAI (51.7 mg, 0.14 mol, 1 eq) and K_2CO_3 (155 mg, 1.12 mmol, 8 eq) were added to a solution of **16** (30.5 mg, 0.14 mmol, 1 eq) in CH_3CN (20 mL). After the suspension was heated to reflux for 72 h, K_2CO_3 was filtered off and the solvent was removed in vacuo. Purification by flash column chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 3:1 + 1 % *N*,*N*-Dimethylethanamine) led to **17**. Colorless solid, mp 68 °C, yield 22.4 mg (46 %). $C_{22}H_{28}FNO_2$ (357.5). R_f = 0.44 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethanamine). HPLC: 96.7 %, t_R = 18.80 min. ^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = 1.43 – 1.53 (m, 2H, $NCH_2CH_2CH_2CH_2Ph$), 1.55 – 1.64 (m, 2H, $NCH_2CH_2CH_2CH_2Ph$), 2.20 (t, *J* = 11.7 Hz, 1H, 4-H), 2.29 (dd, *J* = 12.6, 1.7 Hz, 1H, 2-H), 2.48 – 2.55 (m, 2H, $NCH_2CH_2CH_2CH_2Ph$), 2.57 – 2.64 (m, 3H, 5-H and $NCH_2CH_2CH_2CH_2Ph$), 2.95 – 3.01 (m, 1H, 4-H), 3.12 (dd, *J* = 12.6/6.6 Hz, 1H, 2-H), 3.28 – 3.37 (m, 1H, 5-H), 4.14 – 4.25 (m, 2H, OCH_2CH_2F), 4.57 (d, *J* = 6.4 Hz, 1H, O*H*), 4.67 – 4.82 (m, 2H, OCH_2CH_2F), 5.35 (td, *J* = 6.5/1.6 Hz, 1H, 1-H), 6.72 (d, *J* = 7.4 Hz, 1H, 6-H), 6.86 (d, *J* = 8.2 Hz, 1H, 8-H), 7.10 (t, *J* = 7.8 Hz, 1H, 7-H), 7.16 – 7.22 (m, 3H, 2-H_{phenyl}, 4-H_{phenyl}, 6-H_{phenyl}), 7.26 – 7.31 (m, 2H, 3-H_{phenyl} and 5-H_{phenyl}). ^{13}C NMR (101 MHz, DMSO-d6): δ [ppm] = 26.1 (1C, $NCH_2CH_2CH_2CH_2Ph$), 28.8 (1C, $NCH_2CH_2CH_2CH_2Ph$), 35.0 (1C, $NCH_2CH_2CH_2CH_2Ph$), 35.2 (1C, C-5), 55.0 (1C, C-4), 58.4 (1C, $NCH_2CH_2CH_2CH_2Ph$), 59.4 (1C, C-2), 62.4 (1C, C-1), 68.3 (d, *J* = 19.0 Hz, 1C, OCH_2CH_2F), 82.3 (d, *J* = 166.6 Hz, 1C, OCH_2CH_2F), 111.3 (1C, C-8), 122.8 (1C, C-6), 125.6 (1C, C-4_{phenyl}), 128.0 (1C, C-7), 128.19 (2C, C-3_{phenyl} and C-5_{phenyl}), 128.24 (2C, C-2_{phenyl}, and C-6_{phenyl}) , 131.7 (1C, C-9a), 142.2 (1C, C-1_{phenyl}), 142.6 (1C, C-5a), 155.4 (1C, C-9). IR: $\tilde{\nu}$ [cm^{-1}] = 3433 (O-H), 3086, 3024 (=C-H), 2928, 2855, 2808 (C-$H_{aliph.}$), 1585, 1467, 1447 (C=$C_{arom.}$), 1258 (C-O), 1096 (C-OH), 1045 (C-O). Exact Mass (ESI): m/z = 358.2207 (calcd. 358.2177 for $C_{22}H_{29}FNO_2$ [MH]$^+$).

7-(Benzyloxy)-1-(2-fluoroethoxy)-3-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (18a)

12 (233 mg, 0.58 mmol, 1 eq) was dissolved under N_2 atmosphere in DMF (20 mL) and NaH (34.8 mg, 0.87 mmol, 60 %) was added. After 45 min, (2-fluoroethyl) tosylate (139 mg, 0.64 mmol, 1.1 eq) in DMF (5 mL) was added and the solution stirred for 24 h at 70 °C. An additional amount of (2-fluoroethyl) tosylate (63.0 mg, 0.29 mmol, 0.5 eq) in DMF (5 mL) and NaH (34.8 mg, 0.87 mmol, 60 %) was added and the solution was stirred for 16 h at 70 °C. At room temperature, water (10 mL), CH_2Cl_2 (30 mL) and brine (20 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organic layers were washed with brine (3 x 10 mL). After drying over Na_2SO_4 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* dimethylethanamine) to yield **18a**. Colorless solid, mp 73 °C, yield 32.9 mg (13 %). $C_{29}H_{34}FNO_2$ (447.6). R_f = 0.55 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethanamine). HPLC: 96.9 %, t_R = 22.61 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.54 - 1.67 (m, 4H, $NCH_2CH_2CH_2CH_2Ph$), 2.49 - 2.94 (m, 9H, $NCH_2CH_2CH_2CH_2Ph$, 2-H, 4-H and 5-H), 3.01 (dd, *J* = 14.6/8.1 Hz, 1H, 5-H), 3.67 - 3.80 (m, 2H, OCH_2CH_2F), 4.48 - 4.65 (m, 3H, OCH_2CH_2F and 1-H), 5.05 (s, 2H, O-CH_2-Ph), 6.75 - 6.82 (m, 2H, 6-H an 8-H), 7.16 - 7.20 (m, 3H, 2-H_{phenyl}, 4-H_{phenyl} and 6-H_{phenyl}), 7.25 - 7.30 (m, 3H, 3-H_{phenyl}, 5-H_{phenyl} and 9-H), 7.31 - 7.45 (m, 5H, benzyl). ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 26.3, 29.5 (2C, $NCH_2CH_2CH_2CH_2Ph$ and $NCH_2CH_2CH_2CH_2Ph$), 35.8 (1C, C-5), 36.0 (1C, $NCH_2CH_2CH_2CH_2Ph$), 55.0 (1C, C-4), 59.3 (1C, $NCH_2CH_2CH_2CH_2Ph$), 59.8 (1C, C-2), 68.6 (d, *J* = 19.8 Hz, 1C, OCH_2CH_2F), 70.1 (1C, O-CH_2-Ph), 80.9 (1C, C-1), 83.3 (d, *J* = 169.2 Hz, 1C, OCH_2CH_2F), 111.4 (1C, C-8), 116.7 (1C, C-6), 125.8 (1C, C-4_{phenyl}), 127.5 (1C, C-9), 127.6 (2C, C-2_{benzyl} and C-6_{benzyl}), 128.1 (1C, C-4_{benzyl}), 128.4 (2C, C-3_{phenyl} and C-5_{phenyl}), 128.5 (2C, C-2_{phenyl} and C-6_{phenyl}), 128.7 (2C, C-3_{benzyl} and C-5_{benzyl}), 133.4 (1C, C-9a), 137.2 (1C, C-1_{benzyl}), 141.7 (1C, C-5a), 142.6 (1C, C-1_{phenyl}), 158.2 (1C, C-7). IR: $\tilde{\nu}$ [cm^{-1}] = 3024 (=C-H), 2928, 2866, 2800 (C-$H_{aliph.}$), 1612, 1582, 1493 (C=$C_{arom.}$), 1454 (CH_2 deform.), 1254 (C-O), 1115 (C-OH), 1034 (C-O). Exact Mass (APCI): m/z = 448.2646 (calcd. 448.2646 for $C_{29}H_{35}FNO_2$ [MH]$^+$).

1-(2-Fluoroethoxy)-7-methoxy-3-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (18b)

19 (113 mg, 0.35 mmol, 1 eq) was dissolved under N_2 atmosphere in DMF (5 mL) and NaH (42.0 mg, 1.05 mmol, 60 %) was added. After 30 min, (2-fluoroethyl) tosylate (**68**, 113 mg, 0.52 mmol, 1.5 eq) in DMF (2 mL) was added and the solution stirred for 24 h at room temperature. Water (10 mL), CH_2Cl_2 (30 mL) and brine (20 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organic layers were washed with brine (3 x 10 mL) and over Na_2SO_4. The solvent was removed under reduced pressure and 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*-dimethylethanamine) to obtain **18b**. Yellow oil, yield 43.8 mg (34 %). $C_{23}H_{30}FNO_2$ (371.5). R_f = 0.51 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethanamine). HPLC: 97.0 %, t_R = 20.24 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.53 - 1.68 (m, 4H, $NCH_2CH_2CH_2CH_2Ph$), 2.48 - 2.93 (m, 9H, $NCH_2CH_2CH_2CH_2Ph$, 2-H, 4-H and 5-H), 3.02 (dd, *J* = 14.8/8.2 Hz, 1H, 5-H), 3.67 - 3.79 (m, 2H, OCH_2CH_2F), 3.79 (s, 3H, OCH_3), 4.49 - 4.52 (m, 1H, 1-H), (dt, *J* = 47.7/4.3 Hz, 2H, OCH_2CH_2F), 6.66 - 6.75 (m, 2H, 6-H, 8-H), 7.15 - 7.20 (m, 3H, 2-H_{phenyl}, 4-H_{phenyl} and 6-H_{phenyl}), 7.25 - 7.30 (m, 3H, 3-H_{phenyl}, 5-H_{phenyl} and 9-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 26.2, 29.5 (2C, $NCH_2CH_2CH_2CH_2Ph$ and $NCH_2CH_2CH_2CH_2Ph$), 35.7 (1C, C-5), 36.0 (1C, $NCH_2CH_2CH_2CH_2Ph$), 55.0 (1C, C-4), 55.4 (1C, OCH_3), 59.3 (1C, $NCH_2CH_2CH_2CH_2Ph$), 59.8 (1C, C-2), 68.0 (d, *J* = 19.9 Hz, 1C, OCH_2CH_2F), 80.9 (1C, C-1), 83.3 (d, *J* = 169.2 Hz, 1C, OCH_2CH_2F), 110.5 (1C, C-8), 115.8 (1C, C-6), 125.8 (1C, C-4_{phenyl}), 127.6 (1C, C-9), 128.4 (2C, C-3_{phenyl} and C-5_{phenyl}), 128.5 (2C, C-2_{phenyl} and C-6_{phenyl}), 133.1 (1C, C-9a), 141.7 (1C, C-5a), 142.6 (1C, C-1_{phenyl}), 158.9 (1C, C-7). IR: $\tilde{\nu}$ [cm^{-1}] = 2936, 2859, 2808 (C-$H_{aliph.}$), 1607, 1582, 1497 (C=$C_{arom.}$), 1454 (CH_2 deform.), 1254, 1115, 1034 (C-O). Exact Mass (APCI): m/z = 372.2350 (calcd. 372.2333 for $C_{23}H_{31}FNO_2$ [MH]$^+$).

1-(2-Fluoroethoxy)-3-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-ol (18c)

18a (52.4 mg, 0.12 mmol, 1 eq) was dissolved in abs. CH_3OH (5 mL) and added to a suspension of Pd/C (10.5 mg, 10 %) in CH_3OH (15 mL). After the mixture had been stirred for 30 min under H_2 atmosphere (1 bar) at room temperature, the catalyst was removed by filtration over Celite®. The solvent was removed in vacuo and the residue was purified by flash column

chromatography (d = 2 cm, h = 15 cm, V = 10 mL, cyclohexane:ethyl acetate = 1:2 + 1 % *N*,*N*-dimethylethanamine) to afford **18c**. Yellow oil, yield 33.0 mg (79 %). $C_{22}H_{28}FNO_2$ (357.5). R_f = 0.23 (cyclohexane:ethyl acetate = 1:1 + 1 % *N*,*N*-dimethylethanamine). HPLC: 90.6 %, t_R = 18.48 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.55 – 1.65 (m, 4H, $NCH_2CH_2CH_2CH_2Ph$), 2.52 – 2.64 (m, 5H, $NCH_2CH_2CH_2CH_2Ph$ and 4-H), 2.70 – 2.84 (m, 3H, 2-H, 4-H and 5-H), 2.87 – 2.94 (m, 1H, 2-H), 2.96 – 3.02 (m, 1H, 5-H), 3.63 – 3.76 (m, 2H, OCH_2CH_2F), 4.49 – 4.62 (m, 3H, OCH_2CH_2F and 1-H), 6.59 – 6.68 (m, 2H, 6-H an 8-H), 7.14 – 7.29 (m, 6H, 9-H and phenyl). A signal for the OH proton is not seen in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 26.0, 29.5 (2C, $NCH_2CH_2CH_2CH_2Ph$), 35.2 (1C, C-5), 35.9 (1C, $NCH_2CH_2CH_2CH_2Ph$), 54.9 (1C, C-4), 59.3 (1C, $NCH_2CH_2CH_2CH_2Ph$), 59.6 (1C, C-2), 68.6 (d, *J* = 19.9 Hz, 1C, OCH_2CH_2F), 80.6 (1C, C-1), 83.3 (d, *J* = 169.1 Hz, 1C, OCH_2CH_2F), 112.7 (1C, C-8), 116.9 (1C, C-6), 125.9 (1C, C-4_{phenyl}), 127.9 (1C, C-9), 128.4 (2C, C-3_{phenyl} and C-5_{phenyl}), 128.5 (2C, C-2_{phenyl} and C-6_{phenyl}), 132.5 (1C, C-9a), 141.7 (1C, C-5a), 142.5 (1C, C-1_{phenyl}), 155.4 (1C, C-7). IR: $\tilde{\nu}$ [cm^{-1}] = 3024 (=C-H), 2940, 2913, 2828 (C-$H_{aliph.}$), 1616, 1582, 1497 (C=$C_{arom.}$), 1466, 1454 (CH_2 deform.), 1281 (C-OH), 1157, 1103, 1038 (C-O). Exact Mass (ESI): m/z = 358.2182 (calcd. 358.2177 for $C_{22}H_{29}FNO_2$ $[MH]^+$).

Receptor binding studies

Materials

Guinea pig brains and rat livers were commercially available (Harlan-Winkelmann, Borchen, Germany). Pig brains were a donation of the local slaughterhouse (Coesfeld, Germany). The recombinant L(tk-) cells stably expressing the GluN2B receptor were obtained from Prof. Dr. Dieter Steinhilber (Frankfurt, Germany). Homogenizers: Elvehjem Potter (B. Braun Biotech International, Melsungen, Germany) and Soniprep® 150, MSE, London, UK). Centrifuges: Cooling centrifuge model Rotina® 35R (Hettich, Tuttlingen, Germany) and High-speed cooling centrifuge model Sorvall® RC-5C plus (Thermo Fisher Scientific, Langenselbold, Germany). Multiplates: standard 96 well multiplates (Diagonal, Muenster, Germany). Shaker: self-made device with adjustable temperature and tumbling speed (scientific workshop of the institute). Harvester: MicroBeta® FilterMate 96 Harvester. Filter: Printed Filtermat Typ A and B. Scintillator: Meltilex® (Typ A or B) solid state scintillator. Scintillation analyzer: MicroBeta® Trilux (all Perkin Elmer LAS, Rodgau-Jügesheim, Germany).

Cell culture and preparation of membrane homogenates from GluN2B cells

Mouse L(tk-) 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, Berlin, Germany). 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 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, Berlin, Germany), harvested by mechanical detachment and pelleted (10 min, 5,000 x 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, Darmstadt, Germany). 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 x 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.

Preparation of membrane homogenates from pig brain cortex

Fresh pig brain cortex was homogenized with the potter (500-800 rpm, 10 up and down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1,200 x g for 10 min at 4 °C. The supernatant was separated and centrifuged at 31,000 x 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) and centrifuged again at 31,000 x g (20 min, 4 °C). The final pellet was resuspended in 5-6 volumes of buffer and frozen (-80 °C) in 1.5 mL portions containing about 0.8 mg protein/mL.

Preparation of membrane homogenates from guinea pig brain

5 guinea pig brains were homogenized with the potter (500-800 rpm, 10 up and down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1,200 x g for 10 min at 4 °C. The supernatant was separated and centrifuged at 23,500 x g for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 7.4) and centrifuged again at 23,500 x g (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5-6 volumes of buffer and frozen (-80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

Preparation of membrane homogenates from rat liver

Two rat livers were cut into small pieces and homogenized with the potter (500-800 rpm, 10 up and down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1,200 x g for 10 min at 4 °C. The supernatant was separated and centrifuged at 31,000 x g for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 8.0) and incubated at rt for 30 min. After the incubation, the suspension was centrifuged again at 31,000 x g for 20 min at 4 °C. The final pellet was resuspended in 5-6 volumes of buffer and stored at -80 °C in 1.5 mL portions containing about 2 mg protein/mL.

Protein determination

The protein concentration was determined by the method of Bradford.[39] modified by Stoscheck.[40] The Bradford solution was prepared by dissolving 5 mg of Coomassie Brilliant Blue G 250 in 2.5 mL of EtOH (95 %, v/v). 10 mL deionized H_2O and 5 mL phosphoric acid (85 %, m/v) were added to this solution, the mixture was stirred and filled to a total volume of 50 mL with deionized water. The calibration was carried out using bovine serum albumin as a standard in 9 concentrations (0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0 and 4.0 mg /mL). In a 96 well standard multiplate, 10 µL of the calibration solution or 10 µL of the

membrane receptor preparation were mixed with 190 µL of the Bradford solution, respectively. After 5 min, the UV absorption of the protein-dye complex at λ = 595 nm was measured with a plate reader (Tecan Genios®, Tecan, Crailsheim, Germany).

General procedures for the binding assays

The test compound solutions were prepared by dissolving approximately 10 µmol (usually 2-4 mg) of 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 rt before use. All binding experiments were carried out in duplicates in the 96 well multiplates. The concentrations given are the final concentration in the assay. Generally, the assays were performed by addition of 50 µL of the respective assay buffer, 50 µL of test compound solution in various concentrations (10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} and 10^{-10} mol/L), 50 µL of the 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 multiplates 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 of the scintillator at rt, 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 [^{3}H]-counting protocol. The overall counting efficiency was 20 %. The IC_{50} values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. Subsequently, the IC_{50} values were transformed into K_i values using the equation of Cheng and Prusoff.[41] The K_i values are given as mean value ± SEM from three independent experiments.

GluN2B binding site of the NMDA receptor

The competitive binding assay was performed with the radioligand [^{3}H]ifenprodil (60 Ci/mmol; BIOTREND, Cologne, Germany). 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 [^{3}H]-ifenprodil, and TRIS/EDTA-buffer (5 mM TRIS/1 mM EDTA, pH 7.5) at 37 °C. The non-specific binding was determined with 10 µM unlabeled ifenprodil. The K_d value of ifenprodil is 7.6 nM.[29]

PCP binding site of the NMDA receptor

The assay was performed with the radioligand [^{3}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 [^{3}H]-(+)-MK-801, and TRIS/EDTA buffer (5 mM TRIS/1 mM EDTA, pH 7.5) at rt. The non-specific binding was determined with 10 µM unlabeled (+)-MK-801. The K_d value of (+)-MK-801 is 2.26 nM.

σ_1 receptor

The assay was performed with the radioligand [^{3}H]-(+)-pentazocine (22.0 Ci/mmol; Perkin Elmer). The thawed membrane preparation of guinea pig brain cortex (about 100 µg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-pentazocine, and TRIS buffer (50 mM, pH 7.4) at 37 °C. The non-specific binding was determined with 10 µM unlabeled (+)-pentazocine. The K_d value of (+)-pentazocine is 2.9 nM.[42]

σ_2 receptor

The assays were performed with the radioligand [^{3}H]di-*o*-tolylguanidine (specific activity 50 Ci/mmol; ARC, St. Louis, MO, USA). The thawed rat liver membrane preparation (about 100 µg protein) was incubated with various concentrations of the test compound, 3 nM [^{3}H]di-*o*-tolylguanidine and buffer containing (+)-pentazocine (500 nM (+)-pentazocine in TRIS buffer (50 mM TRIS, pH 8.0)) at rt. The non-specific binding was determined with 10 µM non-labeled di-*o*-tolylguanidine. The K_d value of di-*o*-tolylguanidine is 17.9 nM.[43]

Radiosynthesis

Cyclotron produced ^{18}F-fluoride was trapped on a Waters Sep-Pak Accell Plus QMA Carbonate Plus Light cartridge and eluted with TBA-OH solution (1 mL, 46.7 mg/mL in MeOH). The eluate was collected in a sealed Wheaton reactor (size: 5 mL) and was azeotropically dried at 90 °C by addition of CH_3CN (3 × 1 mL) under reduced pressure and a stream of nitrogen, followed by full vacuum without nitrogen stream for 5 min at 90 °C. Ethylene di-tosylate (5 mg, 13.5 µmol) was dissolved in anhydrous CH_3CN (500 µL), added to the dried fluoride and reacted for 4 min at 90 °C. After complete reaction, CH_3CN (600 µL) was added to the reaction vial and the whole volume was transferred through a Waters Sep-Pak Silica Plus Light cartridge (preconditioned with 5 mL Et_2O). The reaction vial was rinsed with CH_3CN (500 µL) and transferred through the cartridge. The collected CH_3CN phase was diluted with H_2O (1.5 mL) and injected into a semi-preparative HPLC system, equipped with a Smartline Pump 1000, Smartline Manager 5000, Smartline UV detector 2500 (Knauer), 5 mL-loop and a GabiStar radio detector (Raytest). A semi-preparative reversed phase column was used (Waters Sunfire C18 10×150 mm, 5 µm) under isocratic conditions (50% 0.01 M H_3PO_4 in CH_3CN at 5 mL/min). The desired radio peak eluted between 5.78 and 6.15 min.

The collected radio peak was diluted with H_2O (25 mL) and loaded on a Water Sep-Pak C18 Plus Light cartridge (preconditioned with 5 mL EtOH, followed by 10 mL H_2O). The cartridge was washed with H_2O (2.5 mL) before it was dried with air (5 mL). 2-[^{18}F]fluoroethyl tosylate was eluted with anhydrous DMSO (1 mL) into a new Wheaton reactor (size: 5 mL), containing compound **2** (2 mg, 6.4 µmol) and 5 M NaOH (2.44 µL, 12.2 µmol). The mixture was reacted at 120 °C for 12 min and allowed to cool down for 5 min. The crude was diluted with H_2O (2 mL) and injected into the same HPLC system, using the following gradient: 0-20 min from 5 % B to 80 % B, 25 min: 80 % B; with A=0.01 M H_3PO_4 and B = CH_3CN at 4 mL/min. comment

Quality control of the radiolabeled compound was performed on an analytical Agilent 1100 series HPLC system with a 100 µL-loop, equipped with a GabiStar radiodetector (Raytest). An analytical HPLC column (Atlantis T3, C18, 3 µm, 150×4.6 mm, Waters) was used at a flow rate of 1 mL/min with a gradient method as follows:0-10 min from 40 % B to 60 % B, 10-11 min to 40 % B, 11-

15 min 40 % B; with 0.1% aqueous TFA (solvent A) and CH_3CN (solvent B).

Autoradiography

Slices (20 µm) of a Wistar rat brain (535 g, male rat) were pre-incubated for 10 min in HEPES buffer, containing 0.1% BSA at 0 °C. After pre-incubation time, radio tracer solutions of [^{18}F]**14** (10 nM) with and without blocking compounds were added to the brain slices (700 µL). For selectivity/ sensitivity, the following blockers were used: 1 mM (S)-glutamate, 100 µM eliprodil, 100 µM Ro 25-6981 and 100 µM [^{19}F]**14**. Incubation time was 45 min at room temperature. Slices were washed at 0 °C with HEPES buffer, 0.1 % BSA for 5 min, followed by 2 × 3 min HEPES buffer and 2 × 5 sec. H_2O. Brain slices were dried, placed in an imaging cassette, exposed to the film for 15 min and analyzed on a phosphor imager.

Animal experiments were in accordance with the Swiss legislation on animal welfare and approved by the Veterinary Office of the Canton Zurich, Switzerland (license ZH 02/2012).

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Keywords:

NMDA receptor • ifenprodil binding site • GluN2B subunit • 3-benzazepines • F-containing • radioligand receptor binding studies • GluN2B affinity • selectivity • radiosynthesis • autoradiography • displacement experiments

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Supporting Information Available

Supporting Information includes ^{1}H and ^{13}C NMR spectra of all synthesized compounds.

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Conflict of interest

There is no conflict of interest.

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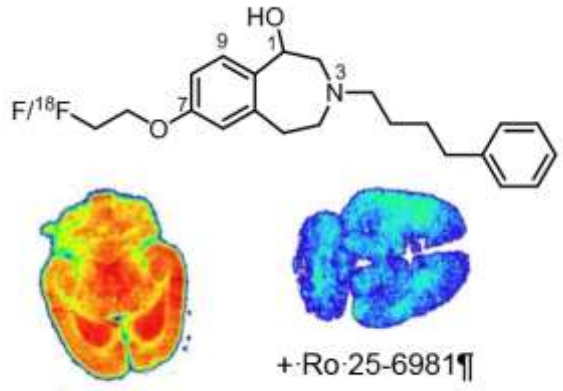
FULL PAPER

Graphical Abstract



Tetrahydro-3-bnzazepin-1,7-diols with high affinity and selectivity served as lead compounds for the development of fluorinated PET tracers for labeling of GluN2B subunit containing NMDA receptors. The 7-(2-fluoroethoxy) derivative showed moderate GluN2B affinity (K_i = 162 nM) but high selectivity over related receptors. The [^{18}F]labeled analog (radiochemical purity >98.9 %) was used for autoradiography of brain slices. Removal of the radioligand from its specific binding sites by different competitors (e.g. Ro 25-6981) confirmed the selective labeling of GluN2B receptors.