Noncompetitive NMDA Antagonists: A Novel Synthesis of 1-Phenyltetrahydro-3-benzazepines☆

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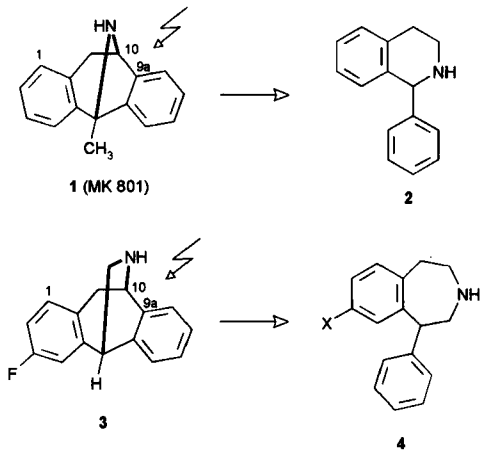
Summary

The key step in the synthesis of the pharmacologically interesting 1-phenyltetrahydro-3-benzazepine skeleton is the Michael addition of (2-lithiophenyl)acetaldehyde acetals, which are generated in situ upon treatment of the bromo acetals **5a,b** with *n*-butyllithium, to β-nitrostyrene (**6**). The reductive ring closure of the nitro acetals **7a,b** succeeded with zinc dust and hydrochloric acid to give the 3-benzazepines **11a,b** in good yields. The unsubstituted 3-benzazepine **11a** showed a considerable affinity for the phencyclidine binding site of the NMDA receptor (K_i = 6.41 μM), whereas donor substituents in the aryl moiety (**11b,c**) reduce the affinity for the NMDA receptor.



Scheme 1

Introduction

The ionotropic NMDA (*N-m*ethyl-*D-a*spartate) receptors are a widespread group of excitatory amino acid receptors within the central nervous system. They are involved in a number of physiological functions (e.g. learning, memory) and may even play a key role in synaptic plasticity and neuronal development. However, excessive release of glutamate resulting in overstimulation of NMDA receptors may be part of some acute and chronic neurodegenerative disorders, including epilepsy, stroke, morbus Parkinson, and morbus Alzheimer [1,2]. Therefore, compounds that block the enhanced influx of Ca^{2+} ions through the NMDA receptor associated ion channel are of considerable therapeutic interest.

The activity of the NMDA receptor associated ion channel may be controlled by several ligands which interact with different modulatory sites. The phencyclidine binding site, one of these modulatory sites, which is located within the cation channel, binds with high affinity the non-competitive tetracyclic NMDA antagonists **1** (MK 801) and **3** [3,4]. The 1-phenyl-1,2,3,4-tetrahydroisoquinoline **2**, which is derived from MK 801 (**1**) by cleavage of the C_{9a}/C_{10} bond showed considerable affinity for the phencyclidine binding site (IC_{50} of the racemate = 1.9 μM) as well [5]. However, the NMDA receptor affinity of the homologous 1-phenyl-3-benzazepines **4**, derived from **3** analogously by dissecting the C_{9a}/C_{10} bond, has not been investigated.

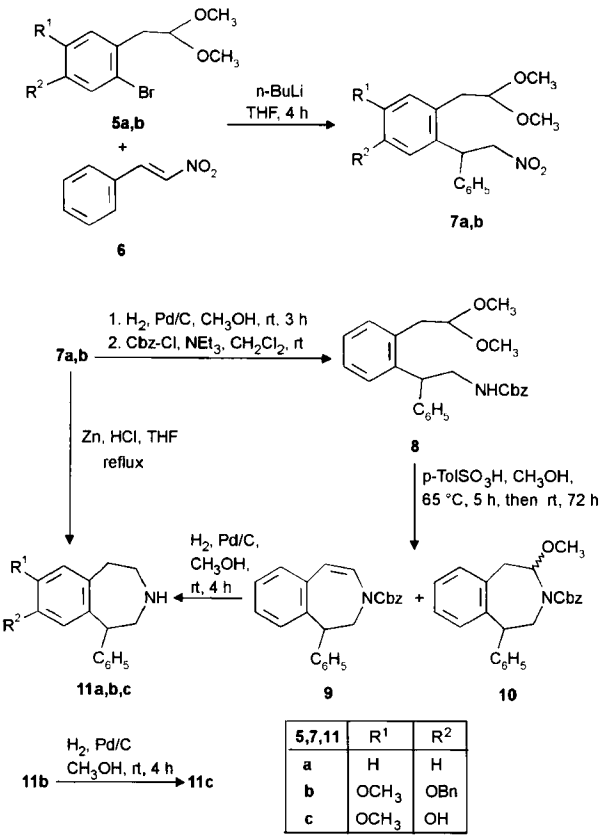
In this communication we report on a novel entry to 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepines and their affinities for the phencyclidine binding site of the NMDA receptor. In the literature several procedures for the synthesis of 2,3,4,5-tetrahydro-1*H*-3-benzazepines are already described [6]. The standard procedure is an acid-catalyzed intramolecular Friedel Crafts alkylation of 1-phenyl-2-(2-phenylethylamino)-ethan-1-ol derivatives which are obtained by the reaction of 2-phenylethan-1-amines with phenyloxiranes [6c,d]. This widely used cyclization reaction is facilitated by electron releasing substituents and retarded by electron withdrawing groups in the phenyl moiety.

Results and Discussion

Chemistry

Our approach for the synthesis of tetrahydro-3-benzazepines should be independent of the substitution pattern of the phenyl ring, because the key step should be a Michael addition of (2-lithiophenyl)acetaldehyde acetals to nitroalkenes.

The readily available (2-bromophenyl)acetaldehyde acetals **5a,b** were used as starting materials [7,8]. Thus, treatment of the bromo acetal **5a** with *n*-butyllithium at –78 °C afforded the corresponding aryllithium intermediate which was trapped with β-nitrostyrene (**6**) providing the nitro acetal **7a** in 42% yield.



5,7,11	R^1	R^2
a	H	H
b	OCH_3	OBn
c	OCH_3	OH

Scheme 2

Hydrogenation of the nitro acetal **7a** furnished a phenylethanamine which without purification was acylated with benzyl chloroformate to give the carbamate **8**. Heating of the carbamate **8** with *p*-toluenesulfonic acid in methanol provided the 1-phenyl-2,3-dihydro-1*H*-3-benzazepine **9** (28% yield) and the N/O-acetal **10** (14% yield of a 1:1 mixture of diastereomers). Treatment of the 3-benzazepine **9** with H_2 and Pd/C as catalyst led to hydrogenation of the double bond and hydrogenolytic cleavage of the benzyloxycarbonyl protective group to yield the known 1-phenyltetrahydro-1*H*-3-benzazepine **11a** [6c,d]. The reaction conditions for this three-step-conversion of the nitro acetal **7a** to the 3-benzazepine **11a** were not optimized, because heating of **7a** with an excess of zinc dust in aqueous hydrochloric acid directly gave the 3-benzazepine **11a** in 72% yield. Thus, the one-step-synthesis increased the yield of **11a** dramatically.

Starting with the dialkoxy substituted bromo acetal **5b**[8] the preparation of the methoxy benzyloxy substituted 3-benzazepine **11b** succeeded in the same manner as **11a**. In contrast to **5a** the bromine/lithium exchange at **5b** and the subsequent addition to β-nitrostyrene had to be performed at −100 °C (yield of **7b** 48%). The roundabout sequence with amine, carbamate and dihydro-3-benzazepine intermediates was not performed with **7b**, since the tetrahydro-3-benzazepine **11b** could be obtained in 86% yield after treatment of the nitro acetal **7b** with zinc dust and hydrochloric acid. Finally, the benzyl protective group of **11b** was cleaved by hydrogenolysis to give the 3-benzazepin-7-ol **11c**.

Pharmacology

The affinity of the 1-phenyltetrahydro-3-benzazepines **11a–c** for the phencyclidine binding site of the NMDA receptor was investigated by competition experiments with the radioligand ^{3}H-(+)-MK801 [1,9]. Thereby, K_i values of 6.41 μM, 17.9 μM, and 61.2 μM were found for the 3-benzazepines **11a**, **11b**, and **11c**, respectively. In comparison to the 1-phenyltetrahydroisoquinoline **2** (IC_{50} of the racemate = 1.9 μM)[5] the affinity of the homologous 1-phenyltetrahydro-3-benzazepine **11a** is somewhat lower (K_i = 6.41 μM). The introduction of two alkoxy substituents in the aryl moiety (**11b**, K_i = 17.9 μM) reduces the affinity for the phencyclidine binding site of the NMDA receptor and a further factor 3 lowering of the NMDA affinity is observed with the phenolic 3-benzazepine **11c** (K_i = 61.2 μM).

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Experimental

Chemistry

General: Unless noted otherwise, moisture and air sensitive reactions were conducted under dry nitrogen.– Anhydrous solvents were distilled and stored under nitrogen atmosphere (sodium benzophenone ketyl for THF, P_4O_{10} for CH_2Cl_2).– Column chromatography (cc): Silica gel 60, 0.063–0.200 mm (Merck).– Flash chromatography (fc):[10] Silica gel 60, 0.040–0.063 mm (Merck).– Melting points: Apparatus Dr. Tottoli (Büchi), uncorrected.– MS: Mass spectrometer 5989A (Hewlett Packard); CI = chemical ionization.– IR: Spectrophotometer 1600 FT-IR and 2000 FT-IR (Perkin-Elmer).– ^{1}H NMR spectra: GSX FT NMR spectrometer 400 MHz (Jeol), tetramethylsilane as internal standard. Analyses were correct to within ±0.4% of the calculated values.

(±)-2-[2-(2-Nitro-1-phenylethyl)phenyl]acetaldehyde Dimethyl Acetal (**7a**)

n-Butyllithium (1.6 M in *n*-hexane, 1.42 mL, 2.29 mmol) was added dropwise at −78 °C to a solution of **5a** (0.50 g, 2.04 mmol) in THF (20 mL). After 15 min at −78 °C a solution of β-nitrostyrene (**6**) (0.29 g, 1.95 mmol) in THF (10 mL) was added and the mixture was stirred for 4 h at −78 °C. The hydrolysis was performed with a saturated solution of NH_4Cl (15 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (15 mL), the combined organic layers were dried (Na_2SO_4), concentrated *in vacuo*, and the residue was purified by fc (diameter of the column 3 cm, petroleum ether/ethyl acetate, 85:15, R_f = 0.51). Orange oil, yield 0.27 g (42%).– IR (film): ν = 2833 (O*CH*$_3$), 1553 (NO_2), 1376 cm^{-1} (NO_2).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.90 [dd, *J* = 14.1/4.9 Hz, 1 H, Ar-C*H*$_2$-CH(OCH$_3$)$_2$], 3.04 [dd, *J* = 14.1/6.0 Hz, 1 H, Ar-C*H*$_2$-CH(OCH$_3$)$_2$], 3.28 [s, 3 H, Ar-CH$_2$-CH(OC*H*$_3$)$_2$], 3.31 [s, 3 H, Ar-CH$_2$-CH(OC*H*$_3$)$_2$], 4.38 ["t", *J* = 5.4 Hz, 1 H, Ar-CH$_2$-C*H*(OCH$_3$)$_2$], 4.93 (dd, *J* = 13.3/8.1 Hz, 1 H, Ar$_2$CH-C*H*$_2$-NO$_2$), 4.98 (dd, *J* = 13.3/8.1 Hz, 1 H, Ar$_2$CH-C*H*$_2$-NO$_2$), 5.36 (t, *J* = 8.1 Hz, 1 H, Ar$_2$C*H*-CH$_2$-NO$_2$), 7.21–7.33 (m, 9 H, aromat.).– MS (70 eV): *m/z* = 284 ($M^{\bullet+}$ − $CH_3O^{\bullet}$).– $C_{18}H_{21}NO_4$ (315.4).

(±)-2-[4-Benzyloxy-5-methoxy-2-(2-nitro-1-phenylethyl)phenyl]acetaldehyde Dimethyl Acetal (**7b**)

As described for **7a**, *n*-butyllithium (1.6 M in *n*-hexane, 5.50 mL, 8.80 mmol) was added dropwise at −100 °C to a solution of **5b** (3.04 g, 8.00 mmol) in THF (50 mL). After 15 min at −100 °C a solution of β-nitrostyrene (**6**) (1.16 g, 7.80 mmol) in THF (10 mL) was added, and the mixture was stirred for 4 h at −100 °C. Work-up: see **7a**. FC with petroleum ether/ethyl

acetate, 80:20, R_f = 0.45. Yellow oil, yield 1.74 g (48.1%).– IR (film): ν = 2834 (OCH_3), 1553 (NO_2), 1376 cm^{-1} (NO_2).– ^1H NMR ($CDCl_3$): δ (ppm) = 2.83 [dd, J = 14.5/5.4 Hz, 1 H, Ar-CH_2-CH(OCH_3)$_2$], 2.94 [dd, J = 14.5/5.4 Hz, 1 H, Ar-CH_2-CH(OCH_3)$_2$], 3.28 [s, 3 H, Ar-CH_2-CH(OCH_3)$_2$], 3.30 [s, 3 H, Ar-CH_2-CH(OCH_3)$_2$], 3.87 (s, 3 H, ArOCH_3), 4.32 [t, J = 5.4 Hz, 1 H, Ar-CH_2-CH(OCH_3)$_2$], 4.76 (d, J = 7.7 Hz, 2 H, Ar_2CH-CH_2-NO_2), 5.08–5.20 (m, 3 H, Ar_2CH-CH_2-NO_2 and Ar-OCH_2Ph), 6.66 (s, 1 H, 3-H aromat.), 6.77 (s, 1 H, 6-H aromat.), 7.02–7.40 (m, 10 H, Ar-CH-C_6H_5 and Ar-$OCH_2C_6H_5$).– MS (70 eV): m/z = 452 ($M^{\bullet+}$).– $C_{26}H_{29}NO_6$ (451.5).

(±)-Benzyl N-[2-[2-(2,2-Dimethoxyethyl)phenyl]-2-phenylethyl]carbamate **(8)**

Pd/C (10%, 250 mg) was added to a solution of **7a** (0.58 g, 1.84 mmol) in methanol (30 mL) and the reaction mixture was stirred for 3 h under hydrogen (3 bar, room temperature). After filtration with celite the organic layer was concentrated *in vacuo* to yield 0.43 g (82.0%) of a yellow, viscous oil. The residue was dissolved in CH_2Cl_2 (20 mL). At 0 °C 4-dimethylaminopyridine (10 mg), triethylamine (0.24 g, 2.42 mmol), and benzyl chloroformate (0.36 g, 2.09 mmol) were added and the reaction mixture was stirred for 24 h at room temperature. After addition of CH_2Cl_2 (10 mL) the organic layer was washed with a saturated solution of $NaHCO_3$ (10 mL), with 0.1 N HCl (10 mL) and with water (10 mL), dried (Na_2SO_4), evaporated *in vacuo*, and the residue was purified by fc (diameter of the column 3 cm, petroleum ether/ethyl acetate, 80:20, R_f = 0.26). Pale yellow oil, yield 0.30 g (45.0%).– IR (film): ν = 3340 (NH), 1720 (C=O), 1520 cm^{-1} (NH).– ^1H NMR ($CDCl_3$): δ (ppm) = 2.85 [dd, J = 14.1/4.7 Hz, 1 H, Ar-CH_2-CH(OCH_3)$_2$], 3.03 [dd, J = 14.1/6.8 Hz, 1 H, Ar-CH_2-CH(OCH_3)$_2$], 3.25 [s, 3 H, Ar-CH_2-CH(OCH_3)$_2$], 3.28 [s, 3 H, Ar-CH_2-CH(OCH_3)$_2$], 3.83 ("t", J = 8.1 Hz, 2 H, Ar_2CH-CH_2-NHCbz), 4.32 [dd, J = 6.8/4.7 Hz, 1 H, Ar-CH_2-CH(OCH_3)$_2$], 4.59 (t, J = 8.1 Hz, 1 H, Ar_2CH-CH_2-NHCbz), 4.94 (s br, 1 H, -N*H*-Cbz), 5.06 (s, 2 H, -CO_2CH_2-C_6H_5), 7.17–7.36 (m, 14 H, aromat.).– MS (CI): m/z = 388 ($M + H^+ - CH_3OH^{\bullet}$).– $C_{26}H_{29}NO_4$ (419.4).

(±)-Benzyl 1-Phenyl-2,3-dihydro-1H-3-benzazepine-3-carboxylate **(9)** *and (±)-cis-/trans-Benzyl 4-Methoxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-3-carboxylate* **(10)**

A solution of **8** (88.6 mg, 0.21 mmol) and *p*-toluenesulfonic acid (120 mg, 0.63 mmol) in methanol (10 mL) was refluxed for 5 h and stirred for 72 h at room temperature. After addition of a saturated solution of $NaHCO_3$ (10 mL) the mixture was extracted several times with CH_2Cl_2 (15 mL). The CH_2Cl_2 layer was dried (Na_2SO_4), concentated *in vacuo* and the residue was purified by fc (diameter of the column 1 cm, petroleum ether/ethyl acetate, 90:10). At first, compound **9** was eluted, then the fractions containing **10** were collected.

9 (R_f = 0.43): Yellow oil, yield 21.0 mg (27.9%).– IR (film): ν = 1714 (C=O), 1643 cm^{-1} (C=C).– ^1H NMR ($CDCl_3$): δ (ppm) = 3.40–3.59 (m, 2 H, 2-H), 4.50–5.02 (m, 3 H, 1-H and CO_2CH_2-Ph), 5.58–5.70 (m, 1 H, 5-H), 7.03–7.26 (m, 15 H, 4-H, 6-H, 7-H, 8-H, 9-H, Ar-CH-C_6H_5 and CO_2CH_2-C_6H_5).– MS (CI): m/z = 356 ($M + H^+$).– $C_{24}H_{21}NO_2$ (355.4).

10 (R_f = 0.30: Yellow oil, yield 11.6 mg (14.2%).– IR (film): ν = 1707 cm^{-1} (C=O).– ^1H NMR ($CDCl_3$): δ (ppm) = 2.96–3.36 (m, 5 H, 5-H (2 H) and -OCH_3), 3.38–3.40 (m, 1 H, 2-H), 4.04–4.21 (m, 1 × 0.63 H, 2-H), 4.51–4.78 (m, 1 × 0.37 H, 2-H), 5.00–5.15 (m, 2 H, CO_2CH_2-C_6H_5), 5.30 (dd, J = 9.5/5.7 Hz, 1 × 0.37 H, 4-H), 5.40 (dd, J = 10.2/4.7 Hz, 1 × 0.63 H, 4-H), 5.69–5.73 (m, 1 H, 1-H), 6.85–7.30 (m, 14 H, 6-H, 7-H, 8-H, 9-H, Ar-CH-C_6H_5 and CO_2CH_2-C_6H_5). According to the ^1H NMR spectrum the ratio of *cis*-**10** : *trans*-**10** = 63 : 37.– MS (70 eV): m/z = 356 ($M^{\bullet+} - CH_3O^{\bullet}$).– $C_{25}H_{25}NO_3$ (387.4).

(±)-1-Phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine **(11a)**[6c]

a) After addition of the catalyst Pd/C (10%, 40.0 mg) to a solution of **9** (118 mg, 0.33 mmol) in methanol (20 mL), the reaction mixture was stirred for 4 h under hydrogen (3 bar, room temperature). Then, it was filtered over celite, concentrated *in vacuo* and the residue was purified by cc (diameter of the column 1 cm, CH_2Cl_2/CH_3OH, 90:10, R_f = 0.31). Colourless oil, yield 27.2 mg (36.7%).

b) Zinc dust (1.40 g, 21.4 mmol) and 2 N HCl (8.6 mL) were added to a solution of **7a** (0.36 g, 1.14 mmol) in THF (25 mL). The mixture was refluxed for 3 h. After filtration 2 N NaOH was added (pH 10) and the mixture was extracted several times with Et_2O (20 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by cc (diameter of the column 1 cm, CH_2Cl_2/CH_3OH, 90:10, R_f = 0.31). Colourless oil, yield 183.6 mg (72%).

Note: Spectroscopic and analytical data are not given in ref.[6c].

IR (film): ν = 3321 cm^{-1} (br., NH).– ^1H NMR ($CDCl_3$): δ (ppm) = 2.90 ("t", J = 5.1 Hz, 2 H, 5-H), 3.00 ("t", J = 5.1 Hz, 2 H, 4-H), 3.36 (dd, J = 13.8/2.1 Hz, 1 H, 2-H), 3.59 (dd, J = 13.8/7.3 Hz, 1 H, 2-H), 4.29 (dd, J = 7.3/2.1 Hz, 1 H, 1-H), 6.88 (d, J = 7.3 Hz, 1 H, aromat.), 7.09–7.26 (m, 6 H, aromat.), 7.35 (td, J = 7.3/1.7 Hz, 2 H, aromat.).– MS (70 eV): m/z = 223 ($M^{\bullet+}$).– $C_{16}H_{17}N$ (223.3).

Preparation of **11a**·*HCl*

A 5 M solution of HCl in methanol (0.7 mL) was added dropwise to a solution of **11a** (71.3 mg, 0.32 mmol) in Et_2O. The solid was filtered and dried.

11a·HCl: Colourless solid (Et_2O), mp 196–198 °C (ref.[6c]: mp 182 °C), yield 72.9 mg (87.9%).

(±)-8-Benzyloxy-7-methoxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine **(11b)**

As described for **11a**, procedure b), zinc dust (0.30 g, 4.59 mmol) and 2 N HCl (2.0 mL) were added to a solution of **7b** (97.6 mg, 0.22 mmol) in THF (15 mL) and the mixture was heated to reflux for 4 h. Work-up: see **11a**. CC with CH_2Cl_2/CH_3OH, 90:10, R_f = 0.18. Pale yellow oil, yield 66.9 mg (86.0%).– IR (film): ν = 3330 cm^{-1} (NH).– ^1H NMR ($CDCl_3$): δ (ppm) = 2.72 (dd, J = 11.6/8.1 Hz, 1 H, 5-H), 2.83–2.90 (m, 2 H, 4-H), 3.00 (dd, J = 11.6/8.1 Hz, 1 H, 5-H), 3.14 (s broad, 1 H, N*H*), 3.28 (dd, J = 13.6/2.1 Hz, 1 H, 2-H), 3.36 (dd, J = 13.6/7.4 Hz, 1 H, 2-H), 3.80 (s, 3 H, Ar-OCH_3), 4.12 (dd, J = 7.4/2.1 Hz, 1 H, 1-H), 4.86 (s, 2 H, Ar-OCH_2Ph), 6.29 (s, 1 H, 9-H), 6.61 (s, 1 H, 6-H), 6.98 (d, J = 7.3 Hz, 1 H aromat.), 7.16–7.26 (m, 9 H, Ar-CH-C_6H_5 and Ar-$OCH_2C_6H_5$).– MS (70 eV): m/z = 359 ($M^{\bullet+}$), 268 ($M^{\bullet+} - CH_2C_6H_5^{\bullet}$).– $C_{24}H_{25}NO_2$ (359.5).

Preparation of **11b**·*HCl*

To a solution of **11b** (78.9 mg, 0.22 mmol) in Et_2O a 5 M solution of HCl in methanol (0.7 mL) was added dropwise. The solid was filtered and dried.

11b·HCl: Colourless solid (Et_2O), mp 130 °C (decomp.), yield 36.9 mg (36.9%).

(±)-8-Methoxy-5-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol **(11c)**

Pd/C (10%, 7.0 mg) was added to a solution of **11b** (33 mg, 0.92 mmol) in methanol (2 mL) and the reaction mixture was stirred for 4 h under hydrogen (1.2 bar, room temperature). After filtration with celite the solvent was evaporated *in vacuo*. Colourless solid (Et_2O), mp 112–115 °C, yield 20.4 mg (82.5%).– IR (KBr): ν = 3421 cm^{-1} (NH, OH).– ^1H NMR ($CDCl_3$): δ (ppm) = 2.74 (dd, J = 14.9/8.5 Hz, 1 H, 1-H), 2.89 (dd, J = 12.0/8.5 Hz, 1 H, 2-H), 2.96–3.02 (m, 1 H, 1-H or 2-H),), 3.08–3.13 (m, 1 H, 2-H or 1-H), 3.40 (d, J = 4.7 Hz, 2 H, 4-H), 3.81 (s, 3 H, Ar-OCH_3), 4.26 (t, J = 4.7 Hz, 1 H, 5-H), 6.31 (s, 1 H, 6-H), 6.59 (s, 1 H, 9-H), 7.06 (d, J = 7.3 Hz, 2 H aromat.), 7.13–7.29 (m, 3 H aromat.).– MS (70 eV): m/z = 269 ($M^{\bullet+}$).– $C_{17}H_{19}NO_2$ (269.3).

Pharmacology

Investigation of the Affinity for the Phencyclidine Binding Site of the NMDA Receptor[19]

The test was performed with the radioligand ^3H-(+)-MK 801 (825 Gbq/mol; Du Pont de Nemours) and receptor preparations from rat brain (cerebral cortex, Du Pont de Nemours, suspension in HEPES buffer, storage at –20 °C).– Scintillation cocktail: Rotiszint eco plus (Carl Roth GmbH). Filter: Whattman GF/B. Buffer: HEPES 20 mM (HEPES = 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid), pH = 7.4.

Performance: 200 µL of receptor preparation was incubated in 250 µL medium (total volume) containing 100 µM glutamic acid, 30 µM glycine, 20 µM HEPES (pH 7.4), about 2 nM ^{3}H-(+)-MK 801 and various concentrations of test compounds for 80 min at room temperature. The samples were rapidly filtered, under reduced pressure, through GF/B filters (Millipore sampling monifold XX 2702550) and washed with ice-cold buffer (10 mL). Bound radioactivity trapped on the filters was determinded by liquid scintillation spectrometry (Canberra Packard TriCarb 1600). Nonspecific binding was determined by using 1 µM (+)-MK 801. All experiments were carried out in triplicate.

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