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Synthesis and preliminary in vitro evaluation of a new memantine derivative 1-amino-3-[^{18}F]fluoromethyl-5-methyl-adamantane: A potential ligand for mapping the N-Methyl-D-Aspartate Receptor Complex

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SUMMARY

The new memantine derivative 1-amino-3-[^{18}F]fluoromethyl-5-methyl-adamantane (^{18}**F-MEM**) was prepared in a two-step reaction sequence for evaluation as a PET tracer. This involves the no-carrier-added nucleophilic radiofluorination of 1-[N-(tert-butyloxy)-carbamoyl]-3-(toluenesulfonyloxy)methyl-5-methyl-adamantane (3) with K^{18}F/Kryptofix 2.2.2 in DMSO and the subsequent deprotection of the resulting ^{18}**F-BOC-MEM** by addition of aqueous HCl. ^{18}**F-MEM** was obtained after purification by reversed phase HPLC in 22±7 % radiochemical yield (decay corrected to EOB) with a radiochemical purity > 99% and a total synthesis time of 100 min. ^{18}**F-MEM** is stable up to 6 h in aqueous solution at room temperature and revealed appropriate lipophilicity for good diffusion through the blood-brain-barrier. *In vitro* studies with the non-radioactive analog, 1-amino-3-fluoromethyl-5-methyl-adamantane (^{19}**F-MEM**) indicated that this compound binds selectively to the phencyclidine (PCP) binding site within the NMDA receptor complex.

KEY WORDS: ^{18}F, n.c.a. nucleophilic radiofluorination, NMDA receptor, PET, Memantine derivatives.

INTRODUCTION

The N-methyl-D-aspartate (NMDA) receptor is one of the ionotropic glutamatergic receptor type that mediates excitatory amino acid synaptic transmission (1, 2). The NMDA receptor has received increasing attention because of its involvment in both physiological and patho-physiological processes. Activation of the NMDA receptor is thought to play a role in long-term potential, synaptic plasticity, learning, memory and in the development of the brain. Overactivation of the receptor can lead to over-excitation of the target neurons to the point of cell death, probably caused by an excess accumulation of intracellular Ca^{2+} (3, 4, 5, 6, 7). It seems likely that the NMDA receptor contributes importantly to the etiology and progression of many neurological disease states such as those following traumatic head or spinal cord injury, stroke, perinatal ischaemia, in hypoglycemic conditions, or in epilepsy, Alzheimer's and Huntington's diseases (8, 9, 10). Thus, there has been great interest in the development of radioligands for imaging the NMDA receptor in living human brain by non-invasive

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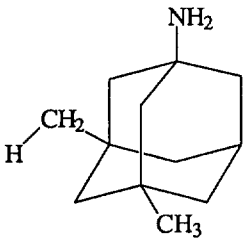
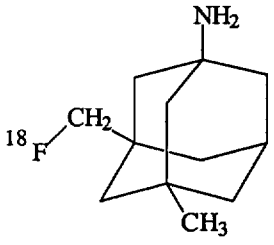
tomographic techniques. Because non-competitive NMDA antagonists have proved to be important tools for investigating the basic mechanisms of NMDA receptor function (11, 12), several radiolabelled compounds based on non-competitive antagonists have been synthesized for *in vivo* studies with PET or SPECT (e.g. 13, 14, 15, 16, 17). But the evaluation of their potential as tracer for PET or SPECT has not been encouraging.

The starting point for the present work was the finding that the clinically used drug memantine (1-amino-3,5-dimethyladamantane, Fig. 1) with beneficial effects in Parkinson's disease, in other neurogenic motor diseases, and in cerebrovascular and gerontopsychiatric diseases (18, 19), acts selectively at the NMDA gated ion channel (20, 21, 22, 23). In addition, its well known pharmacodynamics and pharmacokinetics (24, 25) (e.g. its ready ability to penetrate the blood brain barrier, its poor metabolism in man and the suggestion that none of the known metabolites is a potent NMDA antagonist) confer memantine distinct advantages within this class of compounds. Consequently, we pursued the approach of labelling memantine with positron emitting radionuclides to provide radioligands with potential for investigating the NMDA receptor complex by PET. In this manuscript we report on the preparation and the preliminary *in vitro* evaluation of the "cold" fluoro memantine derivative **^{19}F-MEM**, and the radiolabelling of the [^{18}F]fluorinated analog **^{18}F-MEM** by no carrier added nucleophilic radiofluorination.



MEMANTINE



^{18}F-MEM

Fig.1. Structures of memantine and the new [^{18}F]fluorinated memantine derivative **^{18}F-MEM**

EXPERIMENTAL

General

[^{18}F]Fluoride for nucleophilic labelling was produced by irradiation of 2.5 ml 98% enriched [^{18}O]H_2O by the ^{18}O(p,n)^{18}F reaction as described previously (26, 27). 1-Amino-3-hydroxymethyl-5-methyl-adamantane hydrochloride **1** was a kind gift from Merz +Co. GmbH Frankfurt am Main, Germany. Unless otherwise noted all other solvents and reagents were of analytical quality or HPLC grade and were purchased from Merck or Aldrich. Thin layer chromatography (TLC) was performed on silica gel plates (SIL G/UV$_{254}$, Merck) and

column chromatography on silica gel (Kieselgel 60, Merck) respectively. The proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Bruker AC-250 (Bruker) using TMS as an internal standard and are reported in ppm (δ) downfield. Mass spectra were recorded on a TRIO 2000 spectrometer (VG Organic, UK) using positive ion mode with electrospray as interface (ES^+). Melting points were determined on a Büchi 530 apparatus (Büchi, Switzerland) and are uncorrected.

Two systems were used for the isocratic HPLC separations:

System A (semi-preparative): Consisting of a Waters 510 pump, a Valco 6-port valve with 5 mL loop, a KNAUER UV detector (at 254 nm), a Geiger-Müller counter LND 714 with an Eberlein RM-14 instrument and a Knauer column Lichrosorb RP 18, 5 µm, 250x16 mm and 0.1% H_3PO_4: EtOH (85:15) at 5 mL/min.

System B (analytical): Consisting of a Rheodyne injector with 100 µl loop, a Merck-Hitachi L 6200 pump, a NaI scintillation detector (Scintillation Meter type 540, Mini Instruments Ltd, Burnham on Crouch/UK), a Merck-Hitachi L-4000 UV detector (at 215 nm), a Merck-Hitachi D-2500 Chroma integrator, a µ-Bondapak C_{18} column, 300x3.9 mm and 0.1% H_3PO_4: EtOH (85:15) at 2 mL/min.

1-[N-(tert-Butyloxy)carbamoyl]-3-hydroxymethyl-5-methyl-adamantane (2)

1.0 g (4.32 mmol) of 1-amino-3-hydroxymethyl-5-methyl-adamantane hydrochloride **1** was suspended in 20 mL CH_2Cl_2. 2 mL of NEt_3 were added, followed by 1.0 g (4.5 mmol) di-tert-butyl dicarbonate over 5 min. After stirring for 15 h at r.t. the mixture was washed with 0.5 M HCl (2 x 20 mL), H_2O (2 x 20 mL) and finally with saturated $NaHCO_3$ solution (1 x 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give **2** as colorless oil (1.2 g, 95%).

MS (m/e, relative abundance): 296 (M+1, 80), 281 (M - CH_3, 5), 240 (M - tert Bu, 8), 195 (M - BOC, 8)

^{1}H-NMR ($CDCl_3$): δ = 6.1 (s, 1H, amide), 4.55 (s, 1H, **OH**), 3.50 (s, 2H, O-**CH_2**), 2.50 (m, 1H, **CH**), 1.90 (m, 2H, **CH_2**), 1.65 (m, 4H, **CH_2**), 1.54 (s, 6H, **CH_2**), 1.40 (s, 9H, tert-but), 0.80 (s, 3H, **CH_3**).

1-[N-(tert-Butyloxy)carbamoyl]-3-(tosyl)methyl-5-methyl-adamantane (3)

885 mg (3 mmol) of the alcohol **2** were dissolved in 20 mL CH_2Cl_2, 1 mL of NEt_3 and tosyl chloride 590 mg (3.1 mmol) were added and the solution heated at reflux. The reaction was monitored by TLC and an additional 400 mg of tosylchloride was added after 3 h. After additional 17 h, the mixture was allowed to cool to r.t., washed with H_2O (20 mL) and saturated $NaHCO_3$ solution (20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum.

By means of column chromatography using CH_2Cl_2 / MeOH 95:5 as eluent, 984 mg (73%) of compound **3** were obtained as pale powder after crystalization from hexane/ether (6:4).

R_f (CH_2Cl_2 / MeOH 95:5) = 0.43

Melting point: 112-113°C

MS (m/e, relative abundance): 450 (M +1, 50), 449 (M, 20), 349 (M-tert Bu, 15), 434 (M - CH_3, 5), 309 (M-tosyl, 10)

^{1}H-NMR ($CDCl_3$): δ = 7.80 (d, 2H, arylH), 7.40 (d, 2H, arylH), 6.3 (s, 1H, amide), 3.66 (s, 2H, O-CH_2), 2.60 (s, 3H, Ph-CH_3), 2.20 (m, 1H, CH), 1.80 - 1.20 (m, 12H, CH_2), 1.45 (s, 9H, tert-but), 0.90 (s, 3H, CH_3).

1-Amino-3-fluoromethyl-5-methyl-adamantane (**^{19}F-MEM**)

1.1 mL (8.5 mmol) of (diethylamino)sulfur trifluoride (DAST) were added dropwise to a stirred, cooled (-50°C) suspension of 1-amino-3-hydroxymethyl-5-methyl-adamantane hydrochloride **1** (1.3 g, 5.6 mmol) in dry CH_2Cl_2 (20 mL) under argon. After 2h at -50°C followed by additional 4 h at room temperature, the reaction mixture was then quenched with a solution of K_2CO_3 (5.0 g, 36 mmol) in 25 mL H_2O at -78 °C and allowed to warm to r.t. The organic layer was separated, and the aqueous layer extracted with 20 mL CH_2Cl_2. The combined organic phases were washed with 25 mL H_2O, dried over Na_2SO_4 and evaporated. **^{19}F-MEM** precipitated as hydrochloride after addition of HCl-saturated ether solution to the residue and standing at 4°C. The solid obtained was recrystallized from CH_2Cl_2 to afford 0.90 g (80%) of a pure pale powder. Melting point: > 300 °C

MS (m/e, relative abundance): 198 (M+1, 100), 216 (M+H_2O, 10), 230 (M+MeOH, 18)

^{1}H-NMR ($CDCl_3$): δ = 3.35 (m, 2H, F-CH_2), 3.0 (m, 2H, CH_2), 2.15 (m, 1H, CH), 1.65-1.40 (m, 6H, CH_2), 1.30 (m, 4H, CH_2), 1.10 (s, 2H, NH_2), 0.80 (s, 3H, CH_3).

Radiochemical synthesis of 1-amino-3-[^{18}F]fluoromethyl-5-methyl-adamantane (**^{18}F-MEM**)

Aqueous [^{18}F]fluoride (150 - 500 µL, 2.59 GBq), obtained via ^{18}O(p,n)^{18}F reaction as described above, was placed into a 10 mL Reacti-vial® containing 3 mg K_2CO_3 and 15 mg Kryptofix 2.2.2 in 0.5 mL CH_3CN. The solvent was removed under a stream of nitrogen in a block heated to 100°C, followed by azeotropic evaporation with CH_3CN (3x, 0.6 mL). 3 mg of the precursor **3** were disolved in 0.5 mL dry DMSO and added to the residue with a syringe. The Reacti-vial® was heated at 125°C for 20 min. The reaction mixture was diluted with H_2O (6 mL) and passed through a Sep-Pak® C_{18} Cartridge (Millipore Corp.). The Cartridge was washed with H_2O (5 mL), the protected intermediate **^{18}F-BOC-MEM** was eluted from the Sep-Pak® with ether (8 mL) and collected in a new Reacti-vial®. After ether evaporation under a stream of nitrogen, **^{18}F-BOC-MEM** was subsequently deprotected by heating with 20% HCl (1 mL) for 5 min at 100°C. The final product **^{18}F-MEM** was neutralized with 3 N NaOH (2 mL) and purified by means of reversed-phase HPLC (system A, **^{18}F-MEM**: t_R = 17.5 min). The product fraction was collected, buffered with 0.3 mL of 0.6 M phosphate buffer and diluted with additional 0.35 mL H_2O (*aqua ad injectabilia*) / mL collected fraction to give, after sterile filtration, an isotonic and injectable radiopharmaceutical. The final concentration of ethanol was 9 % (v/v). Analytical HPLC (system B) revealed a virtually 100% radiochemical purity. The yield was 275 ± 100 MBq (n = 23) which corresponds to 22 ± 7 % decay corrected based on [^{18}F]F^-.

In vitro receptor screening

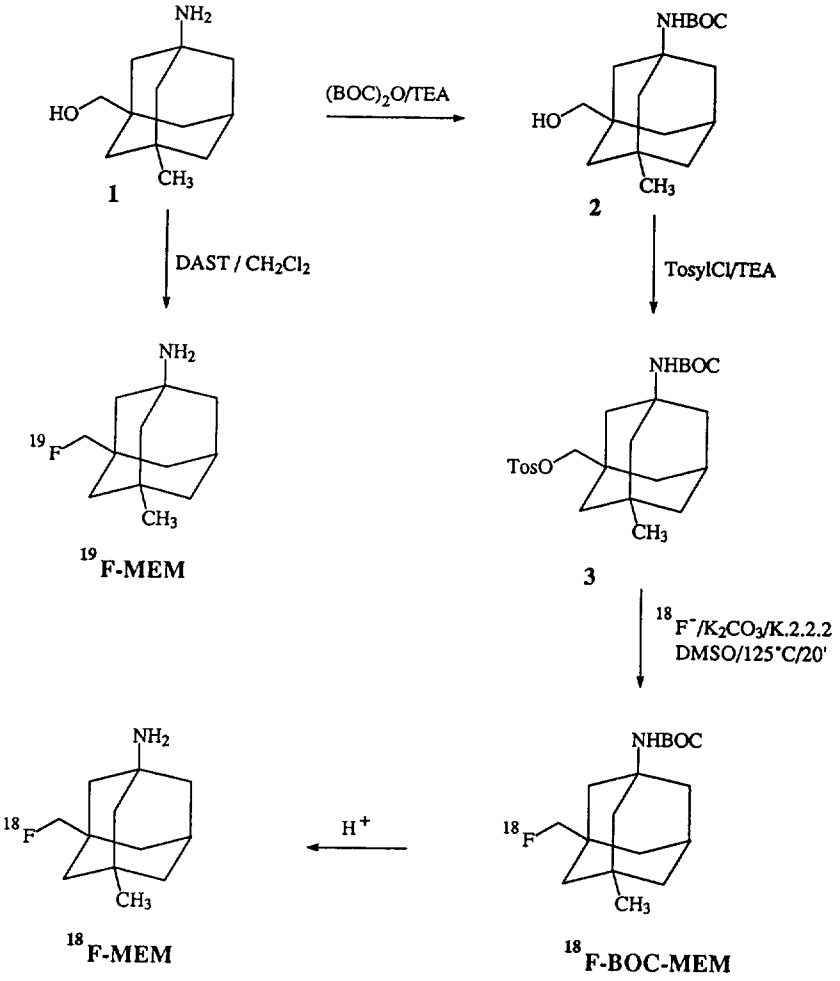
In vitro radioligand binding competitive experiments were carried out to determine the affinity of **^{19}F-MEM** for different CNS receptors as described (28). Inhibitory effects of

^{19}F-MEM (10 μM) on different putative receptors are documented in table 1. Values are expressed as the average of 2 to 3 separate observations with less than 15% variation.

RESULTS AND DISCUSSION

Chemistry

The synthesis of the standard **^{19}F-MEM**, and the preparation of the precursor **3** and its n.c.a. nucleophilic radiofluorination to give **^{18}F-MEM** are reported and outlined in scheme 1.



Scheme 1. Synthesis of **^{18}F-MEM** and **^{19}F-MEM**.

1-[N-(tert-Butyloxy)carbamoyl]-3-(toluenesulfonyloxy)methyl-5-methyl-adamantane **3** was prepared, starting from the reaction of 1-amino-3-hydroxymethyl-5-methyl-adamantane **1** with di-tert-butyl dicarbonate [$(BOC)_2O$]. The obtained alcohol **2** was activated towards nucleophilic displacement as the tosylate by reaction with tosyl chloride to afford compound **3**, which was isolated by column chromatography on silica gel. Spectral properties (NMR, MS) were consistent with the proposed structures.

Among the alkylsulfonates, the triflate leaving group has been reported to react rapidly with activated [^{18}F]fluoride (29). Unfortunatly, the 1-[N-(tert-butyloxy)carbamoyl]-3-(trifluoro-methylsulfonyloxy)methyl-5-methyl-adamantane, the triflate analog of compound **3**, does not appear to be a suitable precursor for the desired radiofluorination, due to its high instability, whereas prolonged storage of **3** up to 6 months at 4°C did not result in its decomposition. Therefore, the radiosynthesis via the tosylate pathway method (30, 31) was undertaken. The n.c.a nucleophilic radiofluorination of the tosylate **3** in DMSO using K^{18}F/Krytofix 2.2.2 as the fluorination agent (32) and the subsequent deprotection of the resulting **^{18}F-BOC-MEM** compound by addition of aqueous HCl led to **^{18}F-MEM**.

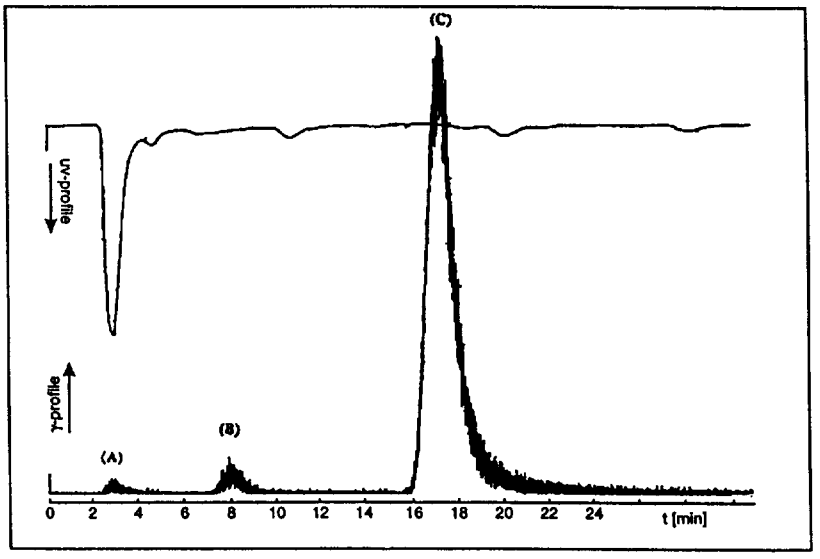


Fig.2. Semi-preparative reversed - phase HPLC of the crude reaction mixture (system A).
(A): [^{18}F]fluoride; (B): unknown by-product; (C): **^{18}F-MEM**

As shown in Fig. 2, the crude reaction mixture after the two-step reaction sequence, including the first purification by SEP-Pak®, contained only minor amount of [^{18}F$^-$]fluoride (t_R = 2.8 min). The retention time of **^{18}F-MEM** was 17.5 min, whereas the by-product with t_R = 7.8 min has not yet been identified. **^{18}F-MEM** was separated from unreacted materials and radioactive impurities by means of isocratic reversed-phase HPLC and was obtained in 22 ± 7 % radiochemical yield at a total synthesis time of 100 min. In order to determine the *in vitro* stability of the labelled product, additional analytical reversed-phase HPLC was performed 1, 2, 4 and 6 h after preparation. The radiochemical purity of **^{18}F-MEM** was

> 99 %. The non-radioactive standard **^{19}F-MEM** could not be obtained from the precursor **3** by the usual displacement reaction with fluoride anion, including KF, KF-Kryptofix 2.2.2 or n-Bu_4NF in acceptable yields. The reaction of (diethylamido)sulfur trifluoride (DAST) with alcohols to replace the hydroxyl group with fluorine appears to be a broadly general reaction with distinct advantages over other reagents. This reaction can be conducted under very mild conditions and in the presence of other functional groups (33, 34, 35). Thus, **^{19}F-MEM** was synthesized directly from the alcohol **1** via direct fluorination with DAST in cooled CH_2Cl_2 and was isolated as hydrochloride in nearly quantitative yield. Spectral properties of the isolated product (e.g. ^{1}H-NMR and MS) were consistent with the proposed compound **^{19}F-MEM**. The mass spectra (+ES) revealed a peak (198 = M + 1) with relative abundance of 100 % corresponding to the expected product. **^{19}F-MEM** was used for *in vitro* studies as well as standard to assess the identity of **^{18}F-MEM**. As shown in Fig.3, **^{18}F-MEM** coelutes with its non-radioactive analog **^{19}F-MEM** as assessed by HPLC (system B).

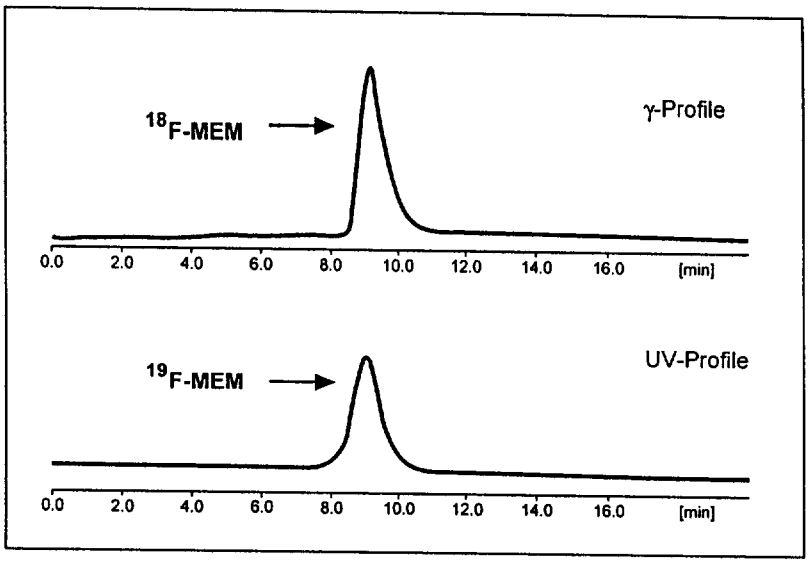


Fig.3. Analytical HPLC chromatogram of **^{18}F-MEM** and of added unlabelled **^{19}F-MEM** (system B).

In vitro stability and lipophilicity

^{18}F-MEM showed excellent *in vitro* stability at room temperature in aqueous solution. Up to 6 h after preparation neither HPLC nor TLC analysis of the compound gave any indication of disintegration products. To assess the lipophilicity of **^{18}F-MEM** the octanol-water partition coefficient (log P) was determined as follows: To ca 0.5 - 1.0 MBq of the **^{18}F-MEM** purified by HPLC, was added 1 g of the aqueous buffer solution (pH = 7.4). After the addition of 1 g n-octanol, the mixture was vortexed vigorously for 10 min. The layers were separated by centrifugation and 500 mg aliquots of the organic and aqueous phase were monitored for radioactivity. The procedure was repeated twice by addition of fresh buffer to the octanol and fresh octanol to the aqueous phases until constant partition coefficients were obtained. The

partition coefficient was calculated as log P = log ($cpm_{octanol}$ / cpm_{buffer}). The logP-value of 2.3 - 2.6 indicates that **^{18}F-MEM** is a lipophilic compound. This lipophilicy should be sufficient for a free diffusion through the blood-brain-barrier (36, 37, 38).

Binding assay

In vitro binding experiments were carried out to determine the affinity of **^{19}F-MEM** for different CNS receptors and to check whether the fluorination of memantine alters its ability to bind selectively to the PCP binding site within the NMDA receptor. As shown in table 1, **^{19}F-MEM** inhibited the binding of the NMDA-type receptor antagonist [^{3}H]TCP, the most potent thienyl analog of phencyclidine (PCP) known to specifically bind to the PCP binding site located within the NMDA receptor associated ion channel (39, 40, 41, 42). Furthermore, the selectivity of **^{19}F-MEM** for the NMDA receptor was supported by the lack of its interaction with the quisqualate- and kailate-type excitatory amino acid receptors, as assessed by [^{3}H]AMPA and [^{3}H]KA respectively. Finally, **^{19}F-MEM** failed to substantially alter the binding of radioligands to 20 other defined CNS receptors.

Table 1: Change in specific binding caused by **^{19}F-MEM**.

Putative receptor	**Radioligand**	% Inhibition
NMDA, PCP Site	[^{3}H]TCP	98
NMDA, Glycine Site	[^{3}H]Glycine	17
AMPA	[^{3}H]AMPA	10
Kainate	[^{3}H]Kainate	22
Adenosine A_1	[^{3}H]CPDPX	7
Adenosine A_2	[^{3}H]CGS-21680	1
Adrenergic α_1	[^{3}H]Prazosin	-14
Adrenergic $ß_2$	[^{3}H]CGP-12511	9
Ca^{2+} Channel	[^{3}H]Nitrendipine	3
Dopamine D_1	[^{3}H]SCH23390	14
Dopamine D_2	[^{3}H]Spiperone	33
GABA-A, Agonist Site	[^{3}H]Muscimol	4
GABA-A, Central	[^{3}H]Flunitrazepam	4
Cl- Channel	[^{3}H]TBOB	-9
GABA-B	[^{3}H]GABA	-13
Histamine H_1	[^{3}H]Pyrilamine	6
Muscarinic M_2	[^{3}H]NMS	-2
Nicotinic Ach	[^{3}H]Cytisine	3
Opiate δ	[^{3}H]DALDE	-5
Opiate μ	[^{3}H]DAGO	5
Na Channel	[^{3}H]Glyburide	14
Serotonin 5-HT_{1A}	[^{3}H]8-OH-DPAT	4
Serotonin 5-HT_2	[^{3}H]Ketanserin	1
Serotonin 5-HT_3	[^{3}H]GR65630	5

CONCLUSION

We have shown that the new [^{18}F]fluorinated memantine derivative, 1-amino-3-[^{18}F]fluoromethyl-5-methyl-adamantane (**^{18}F-MEM**) could be produced routinely in good radiochemical yield and high specific activity by n.c.a nucleophilic radiofluorination. The radiofluorinated compound is stable up to 6h in aqueous solution at room temperature and revealed appropriate lipophilicity for good diffusion through the blood-brain-barrier.
The non-radioactive analog **^{19}F-MEM** binds selectively to the PCP binding site of the NMDA receptor. These data suggest that fluorination of memantine does not alter its ability to act as selective NMDA antagonist. Thus, radiolabelled memantine analogs with appropriate positron emitting radionuclide may provide NMDA receptor affine agents for *in vivo* studies with PET. Furthermore, systematic *in vivo* investigations of **^{18}F-MEM** are currently under evaluation.

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