MAPPING CATION CHANNELS: SYNTHESIS OF [^{125}I] AND [^{18}F]ANALOGS OF MK-801.

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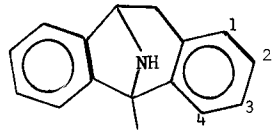
The potent anticonvulsant MK-801 binds noncompetitively to a subset of glutamate receptors referred to as N-methyl-D-aspartate (NMDA) receptors (1). NMDA is linked to a cation channel; MK-801 is thought to bind to this channel when it is in the open state. The aim of the synthetic work reported here is to develop SPECT and PET probes of this brain channel for the study of neurodegenerative diseases.

Iodination of (±)MK-801 produced 1-iodo-(±)MK-801 (1) as the major (80%) product as determined by GC/MS, ^{1}H-NMR (360 MHz), and ^{13}C-NMR (90 MHz). Competitive binding studies using rat cerebral cortex homogenates and ^{3}H-TCP show 1 to have



Compound	IC-50(nM)
(±)MK-801	30
(±)MK-801	100
N-methyl-(±)MK-801	200
1-iodo-(±)MK-801	1000

a 10-fold lower binding affinity than (±)MK-801 for the NMDA receptor channel. I-125-1, 60 Ci/mmol, was obtained by solid-state electrophilic exchange of 1 with NaI-125 $(NH_4)_2SO_4$. Rat brain (N=4) concentrates 1.53% of an i.v. injected dose of I-125-1 at 5 min. In vivo autoradiography in rats revealed selective tracer uptake in the NMDA receptor-rich hippocampus 30 min after i.v. injection. Synthesis of the ring isomer, I-125-3-iodo-(±)MK-801 (2) was accomplished by solid-state interhalogen exchange with 3-bromo-(±)MK-801. HPLC enrichment gave 2 with an effective specific activity of >400 Ci/mmol. Autoradiography with 2 provides clear delineation of rat hippocampus at 30 min.

A fluorine-18 labeled analog of MK-801, 13-[^{18}F]fluoromethylMK-801 (7), has been prepared in high specific activity by the routes shown in Figure 1. The amino alcohol 3 was prepared in 7 steps from trans-10,11-dibromo-dibenzosuberone and converted to the trityl ether 4. Reaction with triflic anhydride afforded the triflamide 5 with simultaneous hydrolysis of the trityl protecting group by traces of triflic acid. Reaction of the triflamide (1 mg, 2.7 µmol) with a mixture of no-carrier-added $(Bu)_4N^+{}^{18}F^-$ and $(Bu)_4N^+OH^-$ (2 µmol) in CH_3CN (100°C, 5-20 min) followed by acid hydrolysis (3N HCl, 100°C, 5-15 min) gave excellent yields of 7 (40-68% isolated radiochemical yields, uncorrected, 45-60 min synthesis time). This unusual [^{18}F]fluorination reaction presumably proceeds through the *in situ* formation of the cyclic sulfamate 6, a compound that was reported during the course of our work by Merck scientists (2). The cyclization, likely catalyzed here by $(Bu)_4N^+OH^-$, is analogous to Merck's observation that reaction of triflamide 5 with 2 equivalents of $(Bu)_4N^+F^-$ gives a high yield of unlabeled fluoromethylMK-801. We subsequently duplicated, albeit in low overall yields, the reported synthesis of the cyclic sulfamate 6, which was subsequently ring-opened to 7 in low yields (5-10%; unoptimized) by reaction with $(Bu)_4N^+{}^{18}F^-/(Bu)_4N^+OH^-$ in CH_3CN.

[^{18}F]FluoromethylMK-801 (7) is the sole radiolabeled organic product from this reaction as determined by TLC with 6 different systems (alumina, silica and C18 solid phases) and by HPLC. The product can be removed from unreacted [^{18}F]fluoride by simple liquid-liquid extraction. The desired product can be readily separated from chemical impurities, predominantly amino alcohol 3, by reverse-phase HPLC using 0.2 M ammonium formate:CH_3CN/60:40 as mobile phase. Multimillicurie amounts of this compound in very high specific activity (>2000 Ci/mol) are routinely available for evaluation as a ligand for PET studies of the NMDA-glutamate ion channel.

Reactions involving the MK-801 ring structure are unusual. Treatment of amino alcohol 3 with 2 equivalents of triflic anhydride yields the azetidine rather than the desired bis-triflate. The azetidine is also formed by treatment of the amino alcohol with DAST (diethylaminosulfur trifluoride). Finally, a cyclic urethane is formed by the reaction of amino alcohol 3 with t-BOC and base. The unexpected reactions of MK-801 do, however, provide a simple and unexpectedly easy method for fluorine-18 labeling of MK-801.

1. Wong, E.H.F., Knight, A.R., Woodruff, G.N., J. Neurochem. 50, 274 (1988).

2. Lyle, R.A., Magill, C.A., Pitzenberger, S.M., J. Am. Chem. Soc. 109, 7890 (1987).

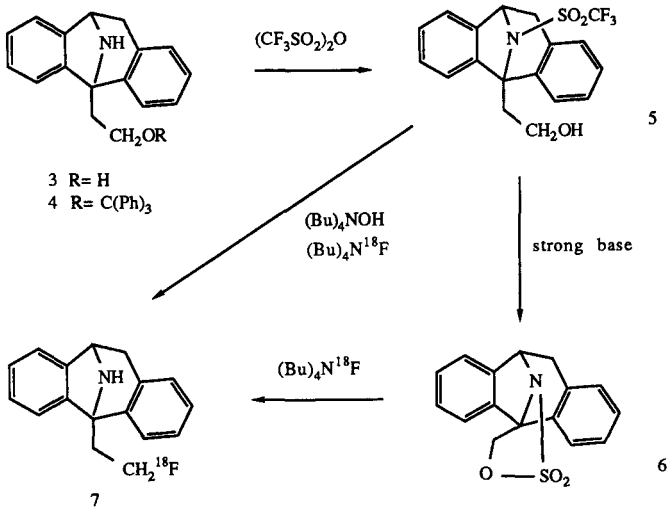


Figure 1. Synthesis of [^{18}F]FluoromethylMK801