SYNTHESIS OF [^{18}F]PHENCYCLIDINES FOR GLUTAMATE RECEPTOR MAPPING

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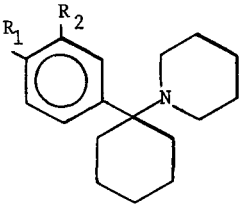
L-Glutamate is a major excitatory neurotransmitter in the mammalian brain. Excessive stimulation of excitatory amino acid receptors has been implicated in neurodegenerative disorders such as Alzheimers disease (1); hypofunction of the glutamate system may be involved in schizophrenic-like disorders (2). Three distinct pharmacological classes of glutamate receptors have been identified which reflect the actions of the relatively selective agonists kainate, quisqualate and N-methyl-D-aspartate (NMDA). Recent findings (3) suggest that drugs such as phencyclidine (PCP) and the PCP analog TCP bind either to an allosteric NMDA site or possibly to the open channel itself. These findings have created a renewed interest in developing a radiolabeled PCP-like compound for mapping NMDA-linked glutamate receptors in the mammalian brain by PET.

[^{18}F]Labeled analogs of PCP (1) are currently under investigation in our laboratories for imaging NMDA-type glutamate receptors in brain. This paper presents our preliminary efforts aimed at: 1) determining which position(s) fluorine can be incorporated in the PCP molecule without adversely affecting its PCP-like potency; 2) developing rapid synthetic methods for incorporating ^{18}F ($t_{½}$ = 110 min) into these compounds for use in in vivo mapping of the glutamate receptor complex by PET. We have shown that 3-amino-4-fluoroPCP (3) retains the high binding affinity and pharmacological potency of 3-aminoPCP (2): IC50-300 and 200 nM, respectively, in the ^{3}H-TCP competitive binding assay and ED50=4.48 and 4.55 µ/mol/kg, respectively, in the mouse platform test. The synthesis of 4-[^{18}F]fluoro-3-aminoPCP (6) was achieved by nucleophilic displacement of bromide in 4-bromo-3-nitroPCP (4) by nca [^{18}F]fluoride ion, followed by reduction of the nitro intermediate (5) with stannous chloride/HCl. In a typical synthesis 22 mCi of [^{18}F]fluoride affords 0.60 mCi (EOS) of 4-[^{18}F]fluoro-3-aminoPCP in a synthesis time of 115 min. Purification was achieved by reverse-phase HPLC. Biological evaluation of this new fluorine-18 ligand is in progress.



CMPD.#:	1 (PCP)	2	3	4	5	6
R_1 :	H	NH_2	NH_2	NO_2	NO_2	NH_2
R_2 :	H	H	F	Br	^{18}F	^{18}F

1. Young, A.B., Greenamyre, J.T., Maragos, W.F. and Penney Jr, J.B., In Hicks, T., Lodge, D., McLennan, H., ed., Excitatory Amino Acid Transmission. New York, Alan R. Liss, 1987, pp 224-240.

2. Olney, J.W., In Hicks, T., Lodge, D., McLennan, H., ed., Excitatory Amino Acid Transmission. New York, Alan R. Liss, 1987, pp 217-224.

3. Kemp, J.A., Foster, A.C. and Wong, E.H., TINS, 10, 294, (1987).

Table 1

Comparison of relative potencies* and affinities** of PCP analogs

Analog	M.W.	ED_{50} (μ/mol/kg)	95% C.L. (μ/mol/kg)	Relative Potency	IC_{50} nM	Relative Affinity
PCP	243	19.1	12.6-28.9	1	400	1
p-F-PCP	261	47.5	36.9-61.0	0.4	1200	0.33
m-NH_2-PCP	258	4.55	3.7- 5.7	4.2	200	2
p-F-m-NH_2-PCP	276	4.48	3.5- 5.8	4.3	300	1.33

*In the mouse platform test
**[^{3}H]TCP receptor binding sites