

SYNTHESIS OF RADIOLABELED INHIBITORS OF PRESYNAPTIC MONOAMINE UPTAKE SYSTEMS: [18F]GBR 13119 (DA), [11C]NISOXETINE (NE), AND [11C]FLUOXETINE (5-HT)

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The monoamine uptake systems are high affinity, high capacity transport complexes located on presynaptic neurons. These systems function to modulate monoamine neurotransmitter concentrations in the synapse. Separate systems for dopamine (DA), norepinephrine (NE) and serotonin (5-HT) have been distinguished pharmacologically using high affinity, selective inhibitors. The distribution of the uptake systems in brain reflect the appropriate monoaminergic neuron innervation, and thus appropriately radiolabeled inhibitors might serve as tools for the *in vivo* measurement of neuronal density using PET. Alterations in these monoamine uptake systems have been demonstrated in such important neurodegenerative diseases as Parkinson's and Alzheimer's Diseases (1,2). We describe here the synthesis of selective and high affinity positron-emitter labeled radioligands for each of the three monoamine uptake systems.

[18F]GBR 13119 for the Dopamine Uptake System. GBR 13119 (1-[(4-fluorophenyl)(phenyl)methoxy]ethyl-4-(3-phenylpropyl)piperazine) is one of a series of aryl dialk(en)ylpiperazines reported in 1980, which show very high affinity ($IC_{50}=1-3$ nM) and good selectivity for the dopamine uptake system (3). Extensive *in vivo* and *in vitro* studies have been done using [³H]GBR 12935, which is the nor-fluoro analog of GBR 13119. Both the affinity and selectivity determined *in vitro* are superior to mazindol or nomifensine: the latter has been recently reported in carbon-11 labeled form (4).

The synthesis of GBR 13119 in no carrier added fluorine-18 form is shown in Figure 1. This is a four step synthesis with fluorine-18 introduced in the first step via aromatic nucleophilic substitution using either 4-nitrobenzophenone or 4-(trimethylammonio)benzophenone trifluoromethanesulfonate. The intermediate 4-[¹⁸F]fluorobenzophenone does not have to be isolated, but can be reduced *in situ* with $LiAlH_4$. The resultant [¹⁸F]benzhydrol is then chlorinated ($SOCl_2$) and the benzylic chloride used in a condensation reaction with 1-(2-hydroxyethyl)-4-(3-phenylpropyl)piperazine to yield the desired [¹⁸F]GBR 13119 in good yields (10-20% EOS) and high radiochemical purity (>98%).

[11C]Nisoxetine for the Norepinephrine Uptake System. Nisoxetine (dl-N-methyl-3-(2-methoxyphenoxy)-3-phenylpropylamine) is a high affinity ($IC_{50}=1-3$ nM), selective inhibitor of the norepinephrine uptake system (5). The synthesis in carbon-11 form is shown in Figure 2. The nor-methyl amine

can be alkylated using either nca [^{11}C]methyl iodide or nca [^{11}C]formaldehyde. Reductive methylation with $^{11}\text{CH}_2\text{O}$ is done using aqueous phosphite as the reducing agent, giving a rapid and simple method for N-alkylation (6). Yields of the carbon-11 labeled products are satisfactory (25-50% EOB) in short reaction times (< 10 min) and high radiochemical purities. Use of low specific activity [^{11}C]formaldehyde results in formation of both the mono- and di-methylated amines.

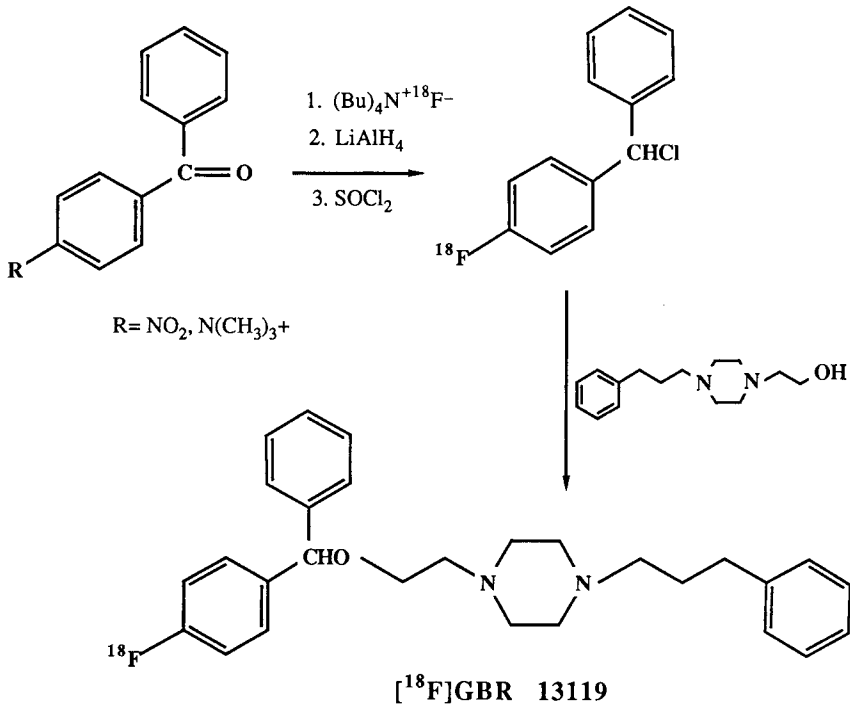
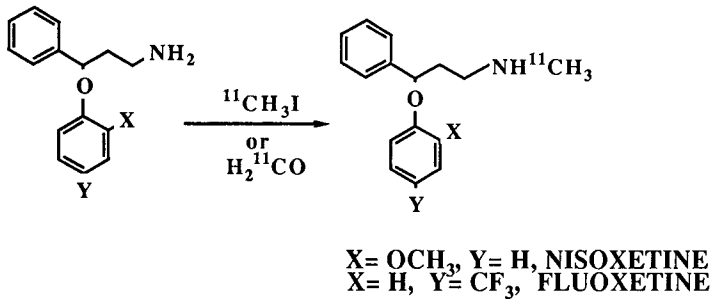
[^{11}C]Fluoxetine for the Serotonin Uptake System. Fluoxetine (dl-N-methyl-3-(4-trifluoromethylphenoxy)-3-phenylpropylamine) is a high affinity ($\text{IC}_{50}=25\text{ nM}$) and selective inhibitor of the serotonin uptake system (7). The synthesis in carbon-11 labeled form is completely analogous to that employed for nisoxetine (Figure 2) and can also be done using carbon-11 labeled methyl iodide or formaldehyde. Yields are again satisfactory (25-50% EOB).

All three of these compounds have been prepared in racemic form. Although GBR 13119 has one asymmetric center, the relative affinities of the stereoisomers has not been determined; it might be expected that there would be little receptor discrimination between the phenyl and p-fluorophenyl groups. For the phenylpropylamines nisoxetine and fluoxetine, the differences in affinities between racemates and resolved isomers are very small ((+)-nisoxetine= 3.4 nM, (+)-fluoxetine = 21 nM) and the differences may not be relevant to their use in vivo with PET.

In summary, syntheses of new radiotracers for PET studies of the three monoamine uptake systems have been accomplished. The application of these ligands to the in vivo study of pre-synaptic neurotransmitter processes is under study.

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Figure 1. Synthesis of [^{18}F]GBR 13119.Figure 2. Syntheses of [^{11}C]Nisoxetine and [^{11}C]Fluoxetine.