# Fluorine-18 Radiolabeled PET Tracers for Imaging Monoamine Transporters: Dopamine, Serotonin, and Norepinephrine

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**KEYWORDS**

• Fluorine-18 PET • Tropanes • Dopamine transporter
• Serotonin transporter • Norepinephrine transporter

The dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) are plasma membrane biogenic monoamine transporters that belong to the family of $Na^+/Cl^-$–dependent transporters.[1–8] In the central nervous system the DAT, SERT, and NET are located on presynaptic neurons and function to remove their respective neurotransmitter from the synapse thereby terminating the action of that neurotransmitter. These three transporters have each been implicated in numerous psychiatric disorders, such as depression, suicide, schizophrenia, Parkinson's disease (PD), and attention-deficit–hyperactivity disorder and are also the target of drugs of abuse, such as cocaine, amphetamines, and 3,4-methylenedioxymethamphetamine (Ecstasy). As such, these transporters have become therapeutic targets to treat psychiatric disorders and drug addiction.[9–11] The ability to image the DAT, SERT, and NET with PET or single-photon emission computed tomography (SPECT) may aid in the diagnosis and management of psychiatric disease by providing a means to measure the density of these transporters in specific brain regions.[12–17] Additionally, the availability of radiolabeled tracers for these transporters may aid in the development of new therapeutics by enabling the occupancy of the therapeutic to be measured.[18–24]

Numerous PET tracers for the DAT, SERT, and NET have been developed that are radiolabeled with carbon-11, but these are limited to use in the location where they are prepared and only allow for imaging times of up to about 2 hours because of the short half-life of $^{11}C$ ($t_{1/2}$ = 20.4 minutes).[25–27] The longer half-life of $^{18}F$ ($t_{1/2}$ = 109.8 minutes) allows for longer synthesis times and imaging sessions and for the transport of the $^{18}F$-labeled tracer to locations away from the cyclotron facility, which allows for PET imaging centers without onsite cyclotrons to use these tracers. In addition to the longer half-life of $^{18}F$, the positrons emitted from $^{18}F$-nuclides have a lower maximum energy (0.64 MeV)[26] than the positrons emitted from $^{11}C$-nuclides (0.97 MeV), which deposits less energy into tissue and also results in a shorter linear range that allows for higher spatial resolution.[28,29] Radiolabeling tracers with

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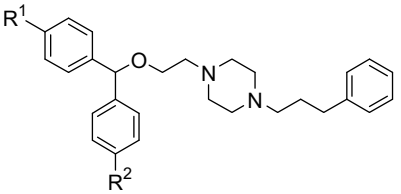
$^{11}$C is convenient because of the ubiquitous nature of carbon in organic compounds, whereas fluorine is far less common. Fluorine, however, has been shown to impart unique properties to organic molecules and is now being exploited extensively in medicinal chemistry.[30–36] Thus, numerous methods have been developed to introduce $^{18}$F or $^{19}$F into molecules.[37–41] This article focuses on fluorine-18 radiolabeled PET tracers for imaging the DAT, SERT, and NET. Several carbon-11 PET tracers are also included to allow for comparisons in instances where a tracer can be radiolabeled with either isotope or where fluorinated analogs of existing $^{11}$C-labeled tracers have been developed.

There are several performance criteria that should be met for a candidate brain PET tracer to become a useful tracer. High binding affinity to the target, especially if the target is of low density, enables highly specific and selective binding to the target. The goal is to obtain the highest possible target-to-nontarget uptake ratios which will result in PET images with high signal-to-noise ratios. If the tracer does not bind strong enough to the target, then the tracer is not retained in the tissue of interest and just passes through. If the tracer binds too strongly, then it does not dissociate from the target during the course of the PET study and accumulates in the tissue of interest and only blood flow is measured. A balance must be obtained that allows for the achievement of peak uptake in the target tissue in a short time frame ($^{18}$F allows for longer time frames compared with $^{11}$C) followed by a steady washout to allow for kinetic modeling of the behavior of the tracer.[42–47] Moderate lipophilicity in the range of log*P* = approximately 1 to 3 is necessary to allow for rapid entry into the brain and to limit nonspecific binding.[48–50] Low binding to plasma proteins is necessary to make as many tracer molecules as possible available for brain entry. Metabolism of the tracer is unavoidable but the resulting metabolites that are generated in the periphery, if they are radiolabeled, should be hydrophilic so that they cannot enter the brain. The generation of radiolabeled metabolites in the brain is also undesirable and any radiolabeled metabolites that are produced should have little or no affinity for the target of interest. As will become apparent below, meeting all of these criteria simultaneously is a difficult task.

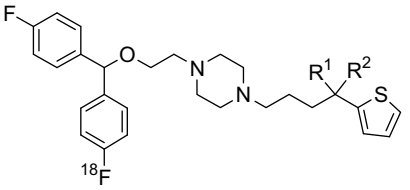
## DOPAMINE TRANSPORTER

The human DAT is a 620–amino acid transmembrane protein that is 98.9% homologous to the monkey DAT and 92% homologous to the rat DAT.[4,51–53] The DAT is found in high densities in the caudate, putamen, nucleus accumbens, and olfactory tubercle with lower densities in the substantia nigra, amygdala, and hypothalamus.[54–57] The DAT has been associated with numerous neuropsychiatric diseases including PD,[58–60] supranuclear palsy,[59] attention-deficit–hyperactivity disorder,[61] and Tourette's syndrome.[62] The ability to image the DAT with PET may aid in the diagnosis, monitoring, and treatment of these diseases.[13,15,17,63]

Early work toward developing an $^{18}$F-labeled DAT imaging agent focused on the GBR-compounds[64,65] [$^{18}$F]**1** and [$^{18}$F]**2** (**Fig. 1**).[66–71] PET imaging with [$^{18}$F]**2** in monkeys[72] showed rapid uptake into the striatum and cerebellum with maximum levels achieved within 2 to 3 minutes followed by a slow but steady washout. Washout was faster from the cerebellum than the striatum, which resulted in a striatum-to-cerebellum ratio of 1.76 at the end of the study. Radiotracer uptake was highest in the liver and kidneys because of metabolism of the tracer but low bone uptake indicated that the aryl-fluorine bond was stable to metabolic defluorination. The imaging results with [$^{18}$F]**2** were promising but the tracer still suffered from high lipophilicity and nonspecific binding. The synthesis and radiolabeling of the GBR-derivatives [$^{18}$F]**3** and [$^{18}$F]**4** has




[$^{18}$F]**1** $R^1$ = F, $R^2$ = $^{18}$F (GBR 12909)
[$^{18}$F]**2** $R^1$ = H, $R^2$ = $^{18}$F (GBR 13119)




[$^{18}$F]**3** $R^1$,$R^2$ = O (NNC 12-0817)
[$^{18}$F]**4** $R^1$ = H, $R^2$ = OH (NNC 12-0818)

**Fig. 1.** Structures of GBR-based DAT PET tracers.