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Post-target produced $[^{18}F]F_2$ in the production of PET radiopharmaceuticals

Abstract: Electrophilic radiofluorination was successfully carried out in the early years of PET radiochemistry due to its ease and fast reaction speed. However, at the present, the use of electrophilic methods is limited due to low specific activity (SA). Post-target produced $[^{18}F]F_2$ has significantly higher SA compared to other electrophilic approaches, and it has been used in the production of clinical PET radiopharmaceuticals at the Turku PET Centre for years. Here, we summarize the synthesis and use of these radiopharmaceuticals, namely [^{18}F]FDOPA, [^{18}F]CFT, [^{18}F]EF5 and [^{18}F]FBPA.

Keywords: Post-target produced $[^{18}F]F_2$, electrophilic fluorination, specific activity, radiopharmaceutical, PET.

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1 Introduction

Positron emission tomography (PET) is a unique molecular imaging modality that provides quantitative measures of biochemical parameters in living subjects. Using specific radiopharmaceuticals, PET can quantitatively measure important functional processes and biochemical parameters for the evaluation of organ and tissue function in living subjects, such as blood flow, oxygen consumption, and glucose metabolism. One advantage of PET is its use for the kinetic analysis of the accumulation of radioactivity in a single experimental subject over time.

The radiopharmaceuticals that are required for PET are labeled with a positron-emitting radionuclide, most often carbon-11 (^{11}C, $T_{1/2}$ = 20.4 min) or fluorine-18 (^{18}F, $T_{1/2}$ = 109.8 min). The ideal radiopharmaceutical has high affinity and selectivity for the targeted system, low non-specific binding, and suitable pharmacokinetics in relation to the half-life of the radionuclide. Additionally, the metabolism of the radiopharmaceutical must be insignificant or well characterized, since the PET method does not identify the chemical source of the radioactivity.

Carbon is the organic element, and ^{11}C is widely used in PET radiopharmaceuticals by substitution for a stable carbon, most often in a methyl moiety. However, the short half-life of ^{11}C can limit its use in PET. On the other hand, this short half-life offers the possibility to study one subject with several ^{11}C tracer injections in a single day. Despite the high theoretical specific activity (SA), the SA of ^{11}C-labeled radiopharmaceuticals is reduced by the large natural abundance of carbon and also by the SA decline with the half-life.

^{18}F is presently the most common positron-emitting radioisotope used in PET radiochemistry. Fluorine, as such, is the most electronegative element and is increasingly used in drugs [1], although it is highly uncommon in organic compounds in nature. Fluorine can be used to substitute a hydrogen atom or a hydroxyl group in a drug molecule; this substitution affects the physical, chemical and biological properties of the molecule. Fluorine substitution can improve the selectivity and the efficacy of a drug, or it can ease drug administration [2].

^{18}F can be incorporated into a molecule by either nucleophilic or electrophilic methods [3–6]. For applications other than radiolabelling, nucleophilic and electrophilic fluorinations are complementary processes that are used indiscriminately; the method of choice depends on the reactivity profile of the precursor to be fluorinated [7]. A similar degree of synthetic flexibility would significantly facilitate the production and evaluation of new ^{18}F radiotracers. This flexibility is not currently possible, however, since the range of reactions that are suitable for ^{18}F labeling remains limited in comparison with the number of transformations available to access non-labeled, fluorinated material [8, 9].

The majority of ^{18}F-labeled radiotracers are currently produced by nucleophilic fluorination, at least in part due to the easier availability of $[^{18}F]F^-$ compared to $[^{18}F]F_2$. $[^{18}F]F^-$ is produced *via* a no-carrier-added $^{18}O(p,n)^{18}F$ reaction, and the product is obtained as an aqueous solution with a high SA of up to 5,000 GBq/μmol [10–12].

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The SA of gaseous $[^{18}F]F_2$, produced using a F_2-carrier, is considerably lower. The SAs of $[^{18}F]F_2$, produced by the $^{20}Ne(d,\alpha)^{18}F$ or gaseous $^{18}O(p,n)^{18}F$ reactions, are 0.05–0.1 GBq/μmol [13] and 0.6–1.3 GBq/μmol [14, 15], respectively.

In order to improve the SA of an electrophilic ^{18}F-labeled precursor, post-target production of $[^{18}F]F_2$ was developed [16]. This labeling approach has been used for numerous non-clinical radiotracers [17–23]. In this paper, we focus on the synthesis of clinically available radiopharmaceuticals, using electrophilic fluorination with post-target produced $[^{18}F]F_2$.

The PET method is a tracer method based on radiopharmaceuticals [24] that are administrated to the study subjects in low amounts, in order to avoid toxicity or pharmacological effects; therefore, the SA of a radiopharmaceutical must be high. The SA is usually defined as the amount of radioactivity per molar mass. The theoretical maximum SA is inversely proportional to the half-life of a radionuclide, thus, the shorter the half-life, the higher the maximum SA. This theoretical maximum, however, is not achievable due to contamination with the stable isotope from the radionuclide production, and from the reagents and accessories used in the radiopharmaceutical production.

2 Electrophilic fluorination

Electrophilic fluorination was successfully carried out in the early years of PET radiochemistry, but its use is limited due to the low SA of the electrophilic labeling agents. This low SA stems from the necessary fluorine gas carrier that is used in the production [13–15, 25, 26]. $[^{18}F]F_2$ is very reactive, leading to low selectivity and, often, undesirable side reactions; sensitive functional groups of a precursor must be protected. In addition, half of the radioactivity is lost during the production of monofluorinated products. Thus, the development of high-yield $[^{18}F]F^-$ production methods and stereospecific nucleophilic radiofluorination have decreased the use of electrophilic labeling.

Electrophilic labeling is still the method used for the $[^{18}F]$-fluorination of electron-rich compounds, which are unavailable through nucleophilic labeling. In general, electrophilic labeling is faster and more easily automated than nucleophilic labeling; product is achieved by bubbling $[^{18}F]F_2$ with a noble gas through a reaction vessel containing an appropriate precursor, which is dissolved in a suitable solvent. Aromatic electrophilic substitution is the most commonly used electrophilic reaction. Aliphatic electrophilic addition to a double bond is also available, but seldom implemented [27, 28].

The selectivity of electrophilic labeling has been improved through demetallation reactions of organometallic precursors; suitable precursors include aryltrimethyltin, aryltrimethylgermanium, and arylmethylsilicon compounds. Mercurated precursors have also been used in demetallation reactions [29, 30]. However, the highest regiospecific fluorination yields were obtained using organotin moieties [31].

3 Post-target production of $[^{18}F]F_2$

Post-target production of $[^{18}F]F_2$ utilizes the high-yield, aqueous $^{18}O(p,n)^{18}F$ nuclear reaction. Azeotropically dried $[^{18}F]F^-$ is reacted with methyl iodide (CH_3I) in dry acetonitrile to generate methyl $[^{18}F]$fluoride ($[^{18}F]CH_3F$) with a radiochemical yield of 75% and high SA (2500 ± 300 GBq/μmol, [16]. Purified by gas chromatography, $[^{18}F]CH_3F$ is transferred to a discharge chamber made of quartz with a small, controllable amount (0.15–1 μmol) of carrier F_2 in neon. The mixture is atomized by an electrical discharge (35 kV, 400 μA, 10 s), after which a rearrangement and $^{18}F/^{19}F$ exchange produce $[^{18}F]F_2$. The reaction where a high-voltage electrical discharge atomizes the reactant in a mixture of highly purified $[^{18}F]CH_3F$ and F_2 in a neon matrix proceeds as follows: $n[^{18}F]CH_3F + mF_2 \rightarrow (m - 3n)[^{18}F]F_2 + 3n[^{18}F]HF + n[^{18}F]CF_4 (m \gg n)$, reaching a maximum conversion yield of 60% for $[^{18}F]F_2$.

The SA and the yield of $[^{18}F]F_2$ correlate with the amounts of $[^{18}F]CH_3F$ and carrier F_2 used, as well as with the efficiency of the $^{18}F/^{19}F$ exchange. The impurities in discharge chamber will decrease the yield and the SA; the purification of $[^{18}F]CH_3F$, as well as the purities of the carrier and transport gases, are crucial. 7.5 GBq of $[^{18}F]F_2$ with a SA of 55 GBq/μmol was achieved when using 0.15 μmol of carrier F_2 and an initial 37 GBq of $[^{18}F]F^-$ [16]. Larger amounts of carrier F_2 will increase the radiochemical yield (RCY) but decrease the SA.

In addition to the significant increase of $[^{18}F]F_2$ SA, another benefit of this approach is that the amounts of the reagents used in the synthesis of radiopharmaceuticals are considerably reduced in comparison to other electrophilic labeling approaches. Thus, the manipulations during the synthesis and the purification of the product are simplified. The whole process, from the production of $[^{18}F]F_2$ to the purification and formulation of a particular radiopharmaceutical, is performed with automated synthesis devices in a hot cell in a clean room environment.

4 [^{18}F]FDOPA

[^{18}F]FDOPA was first reported as a PET tracer for presynaptic dopaminergic functions in 1983 [32]. Striatal [^{18}F]FDOPA accumulation reflects the transport of [^{18}F]FDOPA into nigrostriatal nerve terminals, the activity of aromatic L-amino acid decarboxylase, storage of [^{18}F]fluorodopamine within vesicles, and the number of functioning nerve terminals [33, 34]. [^{18}F]FDOPA has been used for PET imaging to study Parkinson's Disease (PD) [35–38], as well as other neuropsychiatric disorders, such as mania, schizophrenia, autism, attention deficit hyperactivity disorders, and drug abuse [39]. Today, [^{18}F]FDOPA is increasingly implemented in the evaluation of neuroendocrine tumors [40], as well as insulinoma and beta-cell hyperplasia [41, 42]. More recently, the role of [^{18}F]FDOPA in the pancreas has been evaluated in preclinical studies [43, 44].

Fluorodestannylation [45] is a simple and regioselective means to produce [^{18}F]FDOPA. We have successfully used post-target produced $[^{18}F]F_2$ as a labeling agent in fluorodestannylation for the clinical production of [^{18}F]FDOPA for many years (Figure 1) [16, 46, 47]. In our method, $[^{18}F]F_2$ was bubbled through a solution of a stannylated, protected precursor in deuterated dichloromethane at room temperature, using an automated synthesis device built in-house. The solvent was evaporated using neon flow, after which HBr removed the protecting groups.

The final product was purified by semi-preparative HPLC using an eluent that is appropriate for human injections (saline/ascorbic acid/acetic acid). The average yield of the final product over 27 syntheses during the year 2013 was 1521 ± 274 MBq at the end of synthesis, with > 98% radiochemical purity and mean SA of 6.8 ± 1.8 GBq/μmol. The total synthesis time took 55 min.

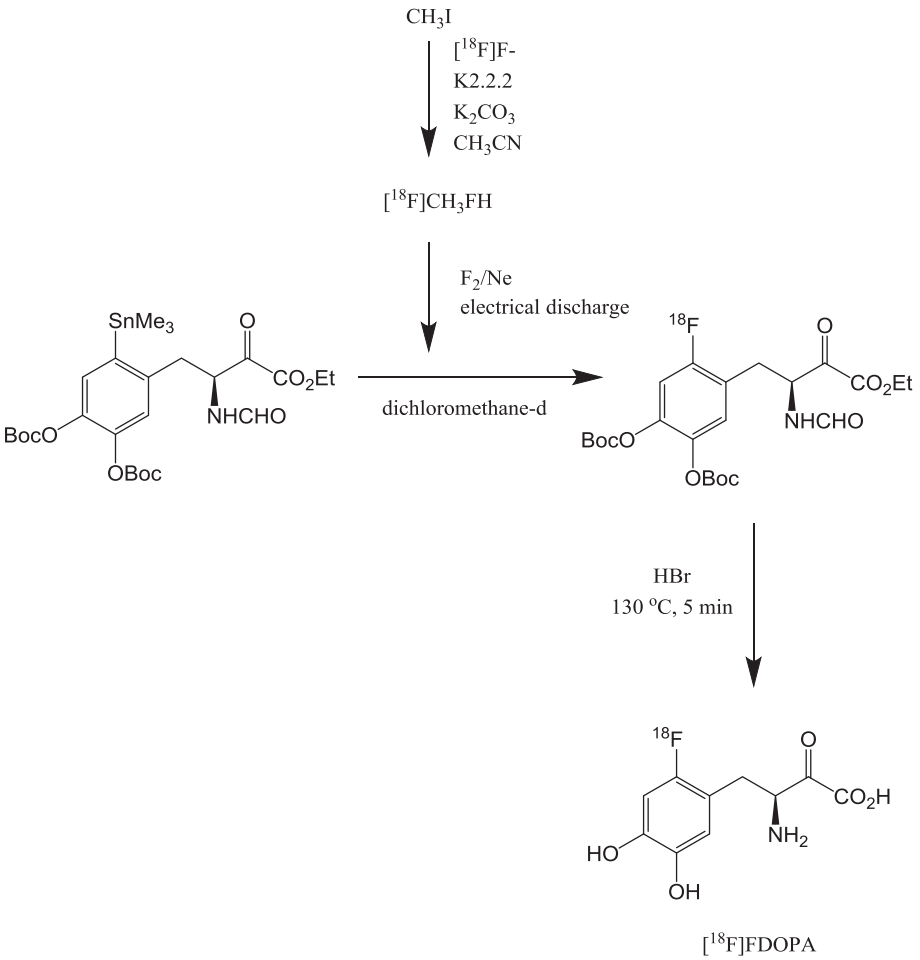


Fig. 1: Scheme of the synthesis of [^{18}F]FDOPA from post-target produced [^{18}F]F_2.

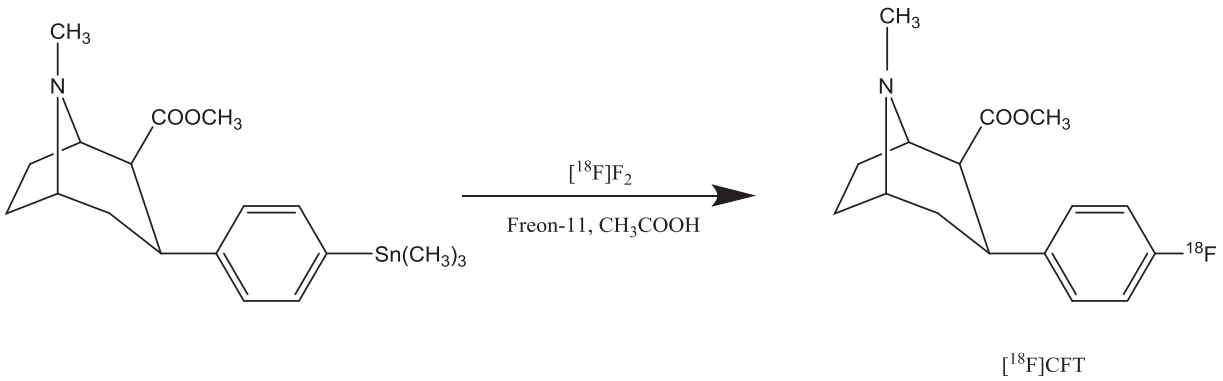


Fig. 2: Scheme of the synthesis of [^{18}F]CFT.

5 [^{18}F]CFT

[^{18}F]CFT (Figure 2) [48] is an analogue of cocaine with high affinity for monoamine transporters, especially dopamine transporters (DAT) and norepinephrine transporters (NET), in rat brain [49]. The suitability of [^{18}F]CFT as a radioligand for *in vivo* studies of DAT in humans has been evaluated [50], and [^{18}F]CFT has been used in human studies of PD [51–56], schizophrenia [57, 58], and detached personality [59]. The SA that was achieved by the electrophilic method was sufficient for human studies, and the injected amount of cold CFT was ~ 4 μg in all of the preceding studies, an amount that was well tolerated by human subjects [50].

The kinetics of [^{18}F]CFT was relatively slow, but the half-life of ^{18}F allowed equilibrium to be reached between specific and nonspecific binding at approximately four hours after administration in humans. In addition, a high target-to-non-target ratio and low metabolism make [^{18}F]CFT a suitable radiotracer for imaging DAT in humans, using PET [50]. The finding that [^{18}F]CFT shows specific uptake by the pancreas also warrants future studies in humans with potential utility in pancreatic imaging [49].

To the best of our knowledge, [^{18}F]CFT is currently the only neurotransporter or neuroreceptor tracer available that is synthesized *via* electrophilic fluorination. Post-target produced [^{18}F]F_2 offers a feasible method for generating PET radiopharmaceuticals, even with high SA, for neuroimaging through electrophilic fluorination. The SA of [^{18}F]CFT can potentially be increased through further optimization of this ^{19}F-^{18}F exchange reaction by decreasing the amount of carrier F_2. However, this change also results in a dramatic decrease in RCY.

The amount of carrier F_2 used in the production of [^{18}F]CFT (290–400 nmol) is a compromise, offering high enough SA and RCY values for several human PET studies from one production run. The average RCY in 24 syntheses of [^{18}F]CFT, calculated from the initial amount of [^{18}F]F^- (decay-corrected to end of bombardment), was 3.2 ± 1.0% (1202 ± 367 MBq). The SA, measured by analytical HPLC, was 14.5 ± 3.4 GBq/μmol (decay-corrected to end of synthesis).

6 [^{18}F]EF5

[^{18}F]EF5 is a promising PET radiopharmaceutical for tissue hypoxia [60] and is safe for use in patients [61]. [^{18}F]EF5 has been used to evaluate hypoxia in head and neck cancers in clinical studies [62]. [^{18}F]EF5 has also been used for the detection of hypoxia in atherosclerotic plaques in mice [63].

[^{18}F]EF5 is an example of a molecule that has been impossible to synthesize by nucleophilic fluorination; thus, it has been produced by electrophilic addition of post-target produced [^{18}F]F_2 to a double bond in the precursor (Figure 3) [28]. The fluorination was completed in a very acidic solution where the electron density of the nitroimidazole is reduced, and the double bond becomes more prone to electrophilic attack. The average yield of six production runs in 2013 was 715 ± 80 MBq at the end of synthesis. The average SA at the same time-point was 14.2 ± 2.8 GBq/μmol. The radiochemical purity exceeded 99% in all runs.

7 [^{18}F]FBPA

^{10}B-enriched 4-dihydroxyborylphenylalanine is one of the most used drugs in boron neutron capture therapy. Its fluorinated analogue, 4-dihydroxyboryl-2-[^{18}F]fluorophenylalanine ([^{18}F]FBPA) [64], has been used to evaluate the distribution and pharmacokinetics

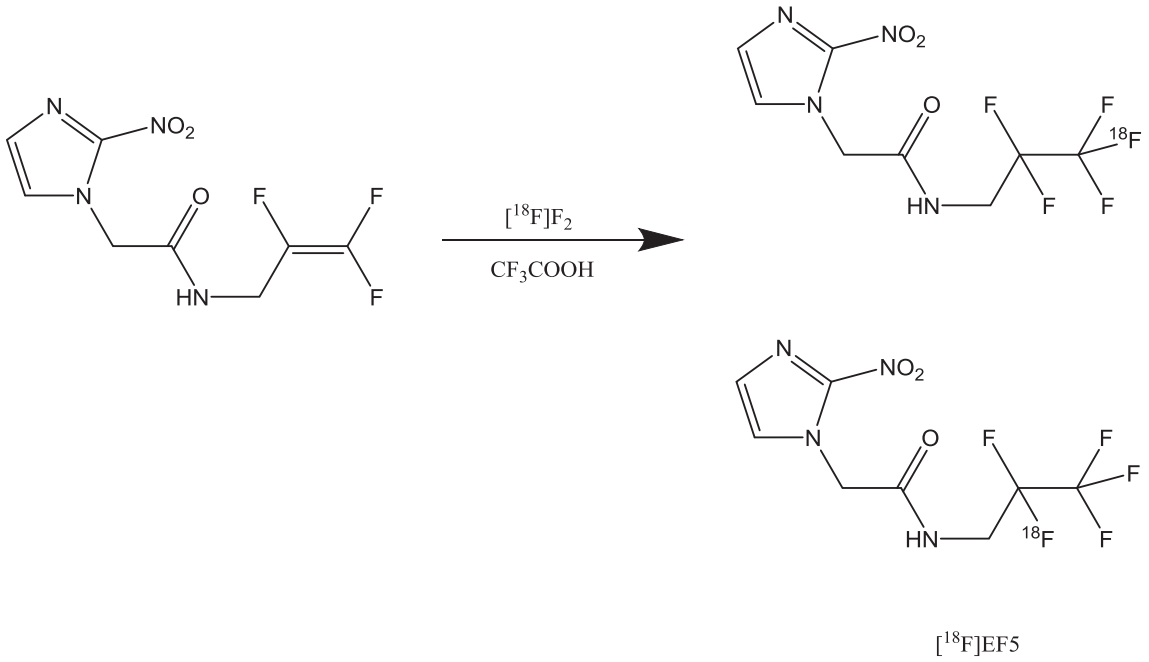


Fig. 3: Scheme of the synthesis of $[^{18}F]$EF5.

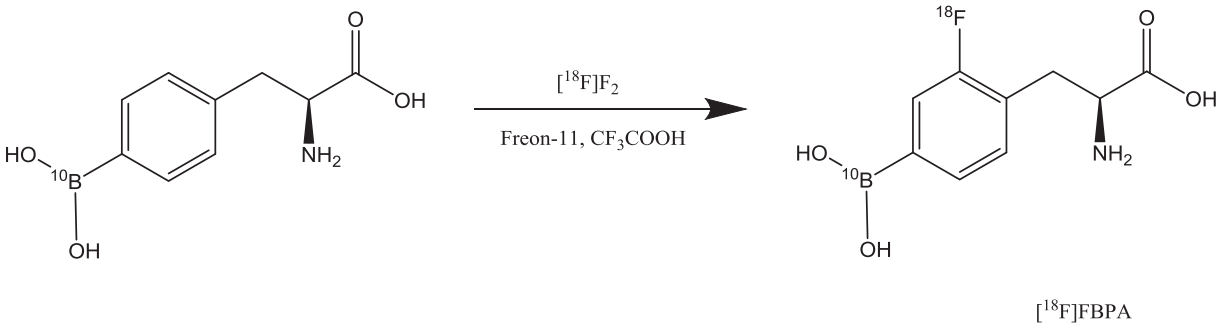


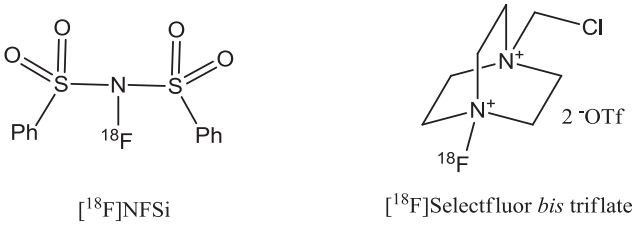
Fig. 4: Scheme of the synthesis of $[^{18}F]$FBPA.

of the molecule. For example, in patients with meningiomas or schwannomas, $[^{18}F]$FBPA is used to study the distribution and pharmacodynamics as an analogue of 4-dihydroxyborylphenylalanine, in order to determine the possibility of using BNCT for the treatment of these kinds of tumors [65].

$[^{18}F]$FBPA was synthesized by direct electrophilic fluorination of an aromatic ring (Figure 4) [66]. The structure of the precursor, 4-dihydroxyborylphenylalanine, enabled the formation of 2- or 3-fluorinated products. However, labeling the 3-position led to deboronation, leaving the 2-labeled product as the desired product. Due to the high reactivity of $[^{18}F]F_2$, several other radioactive byproducts were also formed, but the final product could be purified in 15 min, using semi-preparative HPLC.

8 Future aspects

The development of stable, reactive, and selective electrophilic ^{18}F-fluorination agents will help advance electrophilic ^{18}F-labeling technology in the future. Research to produce such labeling agents has already been done. A novel $[^{18}F]$NF reagent, $[^{18}F]$-*N*-fluorobenzenesulfonimide ($[^{18}F]$NFSi, Figure 5), has been prepared and used for the synthesis of ^{18}F-labeled allelic fluorides and α-fluorinated ketones from allylsilanes and silyl enol ethers, respectively [67]. More recently, the preparation of $[^{18}F]$selectfluor *bis*(triflate) ($[^{18}F]$selectfluor, Figure 5) and its ability to label different model compounds have been presented [68]. The suitability of $[^{18}F]$selectfluor as an electrophilic-labeling reagent has been proven in the production of $[^{18}F]$FDOPA [69].



[^{18}F]NFSi [^{18}F]Selectfluor *bis* triflate

Fig. 5: Molecular structures of [^{18}F]NFSi and [^{18}F]Selectfluor *bis* triflate.

[^{18}F]selectfluor has also been used in the radiofluorination of [^{18}F]tri- and [^{18}F]difluoromethyl arenes, which are not within reach with $[^{18}F]F_2$ [70]. Tri- and difluoro groups are important in drug design due to their abilities to improve cellular membrane permeability and inhibit drug metabolism. Therefore, a simple and reproducible method to radiolabel these groups could facilitate the use of PET technology in drug development.

The unlabeled analogues of [^{18}F]NFSi and [^{18}F]selectfluor are widely used in traditional chemistry. The availability of these stable and easy-to-handle radiofluorinated agents may also increase the use of electrophilic fluorination again in radiochemistry. At the moment, both agents are still produced using carrier-added $[^{18}F]F_2$. Thus, the development of a non-carrier-added production method would make both electrophilic and nucleophilic radiofluorination equally available methods for PET radiochemistry.

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