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COMMUNICATION

Silapiperidine-Silicon-Fluoride Acceptors (Pip-SiFA) for ^{18}F-Radiolabelling

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Silicon fluoride acceptors (SiFAs) are a promising radiopharmaceutical motif that promote mild and rapid ^{18}F-labeling via isotope exchange (SiFEx). Nevertheless, their use in biologically active small molecules is complicated by their poor pharmacokinetic properties that stem from their high lipophilicity and large steric profiles. In an effort to overcome these limitations, we report here the synthesis and properties of fluorosilapiperidines (Pip-SiFAs), which retain SiFEx efficiency on an endocyclic Si center that approaches more pharmocologically compatible motifs.

Positron emission tomography (PET) is a non-invasive imaging technique that is used to diagnose a range of human disorders, including various cancers[1], as well as diseases of the central nervous system and the cardiovascular system.[2,3] PET relies on the radioactive decay of positron-emitting isotopes, among which fluorine-18 (^{18}F) is preferred for its optimal half-life (109.8 min) and the low energy of its emitted β^+-particles (E(β^+)= 0.635 MeV) that provide high-resolution images. Nevertheless, strict time constraints imposed by the rate of radioactive decay require rapid radiosynthesis with minimal time lost to isotope incorporation or tracer purification in order to ensure radiochemical yields (RCY) of clinical relevance.

The most common methods for ^{18}F-labelling employ C–F bond formation via nucleophilic substitution at aliphatic (S_N2) or aromatic (S_NAr) carbon centers (Figure 1A).[4,5] These reactions typically necessitate elevated temperatures, a large excess of non-radioactive precursor, and often require protecting groups due to poor chemoselectivity. In addition, these protocols generally require purification of the tracer by high performance liquid chromatography (HPLC), leading to losses of RCY due to decay. Recent advances have introduced numerous alternative

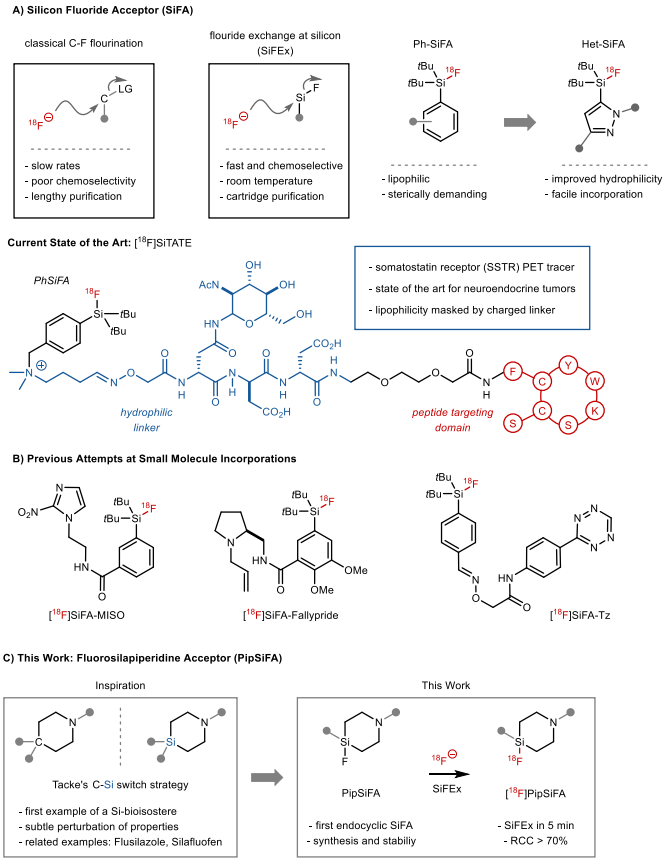

Figure 1: Current state of the art of SiFA-based radioligands. B) Previous attempts to incorporate SiFA motifs into small molecules. C) This work – Pip-SiFA development.

C–^{18}F fluorination strategies; however, many of these rely on transition metal-mediated processes[6] that introduce additional complexity to the synthesis and purification, and are often difficult to implement in clinical settings. Faster and more operationally simple ^{18}F-labelling strategies have thus been investigated over the past two decades, including the use of

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other elements, such as boron, sulfur, aluminum, and silicon (Si) as centers for ^{18}F-incorporation.[7-10] Among these, Si-fluoride acceptors (SiFAs) have achieved notable success, facilitating late-stage and high-yielding ^{18}F-labeling of polyfunctional peptides and peptidomimetics via isotopic exchange (SiFEx).[11] The advantages of SiFEx include mild and chemoselective conditions that obviate protecting groups and facilitate purifications. Driven by these desirable properties, and their ability to deliver clinically relevant molar activities (A_m), SiFA technology has delivered two radiopharmaceuticals in the past decade: [^{18}F]SiTATE (A_m: 60 GBq/μmol) and [^{18}F]rh-PSMA-7.3 (A_m: 291 GBq/μmol, approved by the FDA in 2023 as POSLUMA®), used for the diagnosis of neuroendocrine tumors and prostate cancer, respectively.[12] Nevertheless, significant pharmacokinetic limitations remain. To shield the kinetically labile Si–F bond from hydrolysis, traditional SiFAs incorporate two *tert*-butyl substituents on the Si-center, creating a large, lipophilic center that must be masked by polar functional groups. The development of SiTATE (Figure 1A), the somatostatin receptor subtype-2 (SSTR2)–targeting peptide PET tracer, is exemplary, as it required significant linker engineering that included a quaternized ammonium cation, an amino sugar, two aspartic acid residues and a polyethylene glycol (PEG) chain, to link the SiFA to the cyclic peptide. Although there have been efforts to incorporate classical SiFAs into more typical small molecules, such as [^{18}F]SiFA-MISO, [^{18}F]SiFA-Fallypride and the prosthetic tetrazine [^{18}F]SiFA-Tz (Figure 1B), poor pharmacokinetic properties have largely limited their advancement.[13-15]

Several studies have investigated the effects of substituents on SiFA properties, including our own work that explored remote substituent effects on the phenyl ring,[16] or the replacement of the phenyl ring with diverse heterocycles. The latter scaffold represents a new family of more polar heterocyclic SiFAs (HetSiFAs) that retained SiFEx efficiency and suitable stability for *in vivo* imaging (Figure 1A).[17] Nevertheless, these constructs retained both *tert*-butyl groups on the Si-center, mitigating the benefits of the more polar heterocycles. This prompted us to explore the reactivity of endocyclic Si-centers, and whether the constraints of a ring would affect the stability of the Si–F bond towards hydrolysis and efficiency in SiFEx. Endocyclic SiFAs present a conceptually new construct for further development, with the prospect of providing more biologically compatible SiFA motifs, suitable for PET tracers based on small molecules. Embedding the Si-center within a ring was hypothesized to enhance stability of the Si–F bond towards hydrolysis by disfavouring the trigonal bipyramidal silicon-ate intermediate that is believed to form upon nucleophilic attack of hydroxide (Figure 2A).[18] Whereas previous studies have shown that 4- and 5-membered silacycles are more susceptible to nucleophilic attack due to favourable strain release upon formation of the pentavalent silicon ate-complex (Figure 2B)[19], we aimed to explore whether an unstrained 6-membered ring would exert an opposite, stabilizing effect.[20] We were particularly interested in the biologically relevant silapiperidine, which was originally introduced as a Si-bioisostere of piperidine by Tacke and co-workers (Figure 1C).[21] Herein, we report the design and synthesis of piperidine-SiFAs (Pip-SiFAs) and report a promising candidate with moderate hydrolytic stability and high ^{18}F-labeling efficiency.

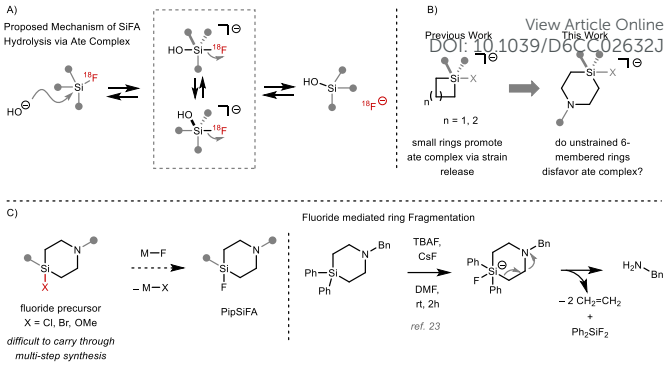
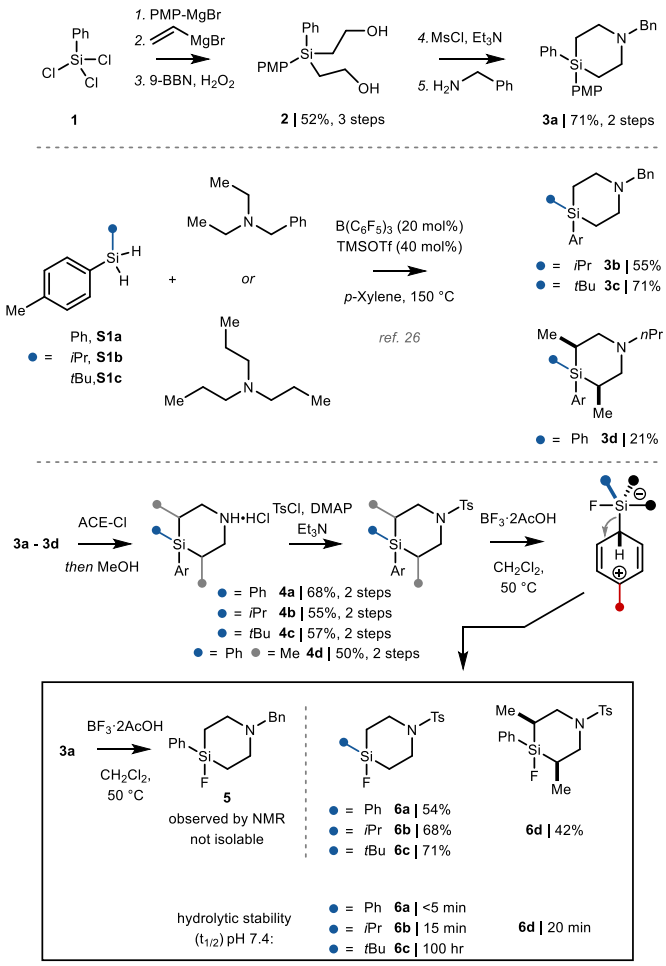


Figure 2: A) Mechanistic hypothesis for hydrolysis at the Si center. B) Previous work on strain-release silanes and the hypothesized stabilized counterpart. C) Potential challenges in Pip-SiFA synthesis.

From a synthetic perspective, the multi-step synthesis of PipSiFAs required a suitable leaving group on the Si center from which to install the Si-F bond. We reasoned that a late-stage introduction of this bond would be strategic to avoid the potential liabilities of carrying the Si-F bond through a synthetic sequence. Notably, traditional electrophilic Si–X precursors, where X = Cl or OMe, are prone to hydrolysis[22] and can thus be difficult to handle. Furthermore, we were aware of previous work by Cho and co-workers showing that a combination of *tetra*-butylammonium fluoride (TBAF) and cesium fluoride (CsF) can cleave the endocyclic C–Si bond to release the corresponding 1° amine,[23] revealing a potential risk of ring-opening following nucleophilic fluorination (Figure 2C). Recognizing these challenges, we opted to explore late-stage fluorination via de-arylation under acidic conditions, following precedent of Skrydstrup and co-workers.[24] To this end, we prepared a series of aryl-silanes **3a**-**3d**, possessing either a *para*-methoxyphenyl (PMP) or *para*-tolyl substituent on Si, by one of two synthetic sequences (Scheme 1). In the first, sequential addition of aryl and vinyl Grignard reagents to phenyl chlorosilane **1**, followed by hydroboration–oxidation afforded compound **2**. Next, di-mesylation followed by cyclization with benzylamine provided silapiperidine **3a** in five steps. For substrates **3b-3d**, we used a more convergent dehydrogenative coupling of 3° amines with dihydrosilanes[25] reported by Oestreich and co-workers[26] (Scheme 1). Briefly, treatment of compounds **S1a-S1c** with benzyl amine or tri-*n*-propylamine in the presence of catalytic $B(C_6F_5)_3$ (20 mol %) and TMSOTf (40 mol %) in *para*-xylenes at 150 °C afforded the cyclized compounds **3b-3d** in moderate to good yields. Chemoselective dealkylation of the 3° amine using ethyl chloroformate (ACE-Cl) afforded the corresponding free 2° amines that were directly *N*-tosylated to give compounds **4a-4d**.

Exposure of compounds **4a-4d** to $BF_3{\cdot}2AcOH$[24] effected the *ipso*-substitution of Si, affording the corresponding ^{19}F-Pip-SiFAs **6a-6d** in moderate to good yields. We note the anomalous behaviour of 3° benzyl amine **5**, which was only detected in crude mixtures, but underwent rapid hydrolysis to the

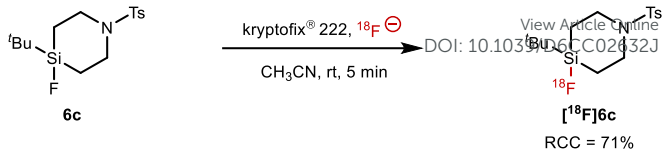


Scheme 1: Synthetic sequence for the preparation of Pip-SiFA constructs

corresponding silanol upon attempts at purification. By comparison, Pip-SiFAs **6a-6d**, bearing a non-basic *para*-toluene sulfonamide group, could be purified by recrystallization from a mixture of ether and hexanes or by normal phase chromatography.

Next, we measured the hydrolytic stabilities of Pip-SiFAs **6a-6d** in aqueous media. In a pH 7.4 buffer, compound **6a** underwent rapid hydrolysis to silanol **S2** (See SI for details), with a half-life below 5 minutes. In contrast, derivates **6b** and **6d**, containing more sterically shielded Si–F bonds, showed modest improvements in stability, with half-lives reaching 15–20 minutes (Scheme 1). The most stable candidate, **6c**, bearing a *tert*-butyl substituent on silicon, showed a remarkable increase in hydrolytic stability, with an observed half-life of 100 hours. Notably, Pip-SiFA **6c** retained a moderate half-life of 13 minutes at pH 10 (see SI for details). To place this value into context, our previous exocyclic pyrazole-HetSiFA, which has a half-life of ~2 hours at pH 10, is suitably stable for PET imaging in vivo.[17]

Finally, we evaluated the efficiency of ^{18}F-labelling for all of our novel Pip-SiFAs via SiFEx using the "Munich Method" (scheme 2, see SI for experimental details).[27] Compounds **6a, 6b,** and **6d**, with relatively poor hydrolytic stabilities, did not incorporate ^{18}F, likely due to rapid Si–^{18}F bond hydrolysis under the basic conditions of SiFEx. To our delight, however,



Scheme 2: ^{18}F-labelling of **6c** (SiFEx) using the "Munich Method" to give **[^{18}F]6c**.

compound **6c**, possessing a single *t*Bu group on Si, was successfully labelled with a radiochemical conversion (RCC) of 71% within 5 minutes at room temperature to give radiolabelled **[^{18}F]6c**. We note that RCCs decrease steadily at longer reaction times under otherwise identical radiolabelling conditions, indicating that the current Pip-SiFA scaffold remains susceptible to degradation or secondary reactivity during labelling (see SI for radiolabelling results). Nevertheless, these ^{18}F-labelling results provide an important proof of concept that an endocyclic SiFA can undergo ^{18}F-labelling by SiFEx, while offering a structural platform for lowering lipophilicity. Consistent with this design goal, calculated logP values indicate that Pip-SiFA **6c** is less lipophilic than phenyl-SiFA (cLogP: 3.87 versus 4.98). Moreover, related Pip-SiFA constructs also show substantially reduced cLogP values relative to our previously reported peptide-conjugated HetSiFAs[17] (Figure S1). Together, these results identify endocyclic SiFAs as promising, but not yet fully optimized, labelling motifs whose stability and pharmacokinetic properties can be improved through further structural refinement.

In conclusion, we have synthesized and characterized a small library of novel fluorinated silapiperidines (Pip-SiFAs). A key step of our synthetic strategy was the late-stage fluorination of Si bearing an electron-rich aromatic ring via *ipso* substitution with BF_3·2AcOH, affording Pip-SiFAs in moderate to good yields. Although compounds **6a**, **6b** and **6d** exhibited only moderate hydrolytic stability and could not be efficiently labelled with ^{18}F via SiFEx, Pip-SiFA **6c** showed significantly improved stability in aqueous media and underwent efficient isotopic exchange within minutes at room temperature. Moving forward, we aim to further enhance Si–F bond stability through topological engineering of endocyclic SiFAs, with the longer-term goal of advancing SiFA technology to druggable scaffolds with improved pharmacological properties.

Acknowledgements

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Conflicts of interest

Thomas A. Singleton is an employee and shareholder of FTx. Jean-Philip Lumb and Alexey Kostikov are paid consultants and shareholders of FTx.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). The supplementary information provided includes detailed synthetic procedures, characterization of new compounds, radiolabelling procedures with isotope incorporation data, and HPLC data pertaining to hydrolytic stability assays are available: DOI:xxxxxxx

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