The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)
01–30 NOVEMBER 2022 | ONLINE

Rapid Access to ^{18}F-Labeled PET Tracers via Sulfur [^{18}F]Fluoride Exchange Reaction

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

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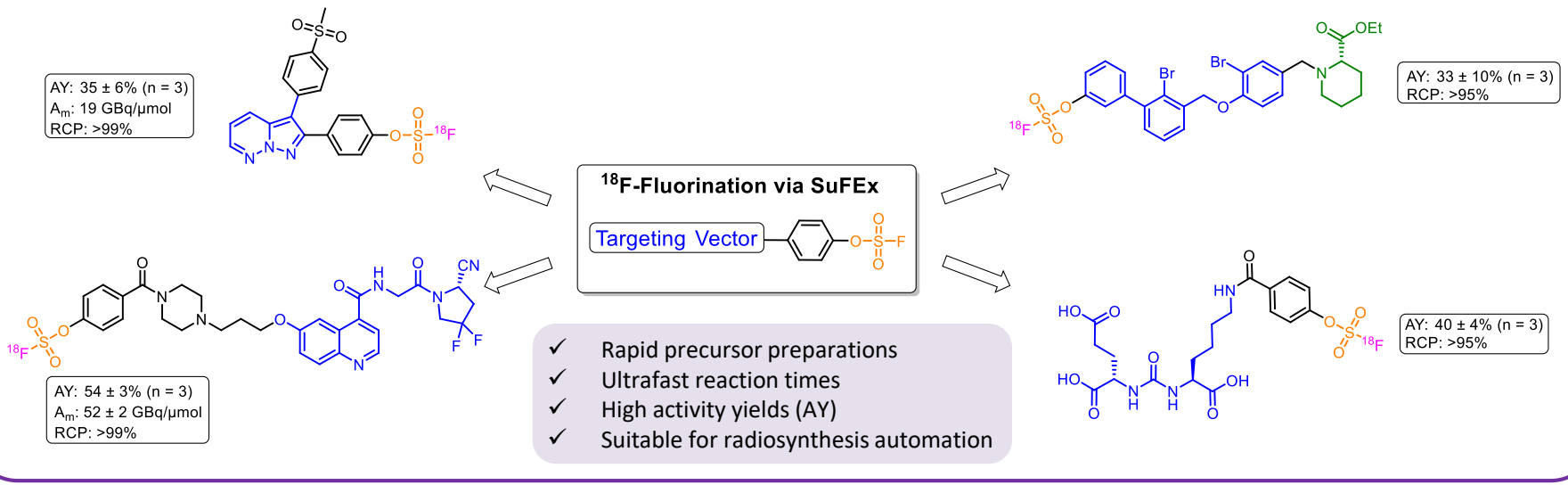
HZDR HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

Rapid Access to ^{18}F-Labeled PET Tracers via Sulfur [^{18}F]Fluoride Exchange Reaction

Graphical Abstract



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Abstract: Efficient ^{18}F-fluorination procedures for the production of radiopharmaceuticals are urgently needed to satisfy the increasing demand for clinical diagnostics using positron emission tomography (PET). However, the development of PET tracers is often a time-consuming and challenging process. This work examines the applicability of the recently described sulfur [^{18}F]fluoride exchange ([^{18}F]SuFEx) chemistry as a fast-screening approach towards a number of clinically-relevant PET tracer preparations.

The preparation of a number of ^{18}F-labeled compounds commenced with [^{18}F]fluoride loading onto a QMA-cartridge, which was eluted with a methanolic solution containing a base, followed by solvent removal under reduced pressure. Thereafter, the radiolabeling precursors in MeCN were added to the reaction vessels, and allowed to react via [^{18}F]SuFEx at room temperature for 5 min. The radiofluorination reactions were quenched by water dilution followed by C18 cartridge purification. The ^{18}F-labeled products were isolated by elution from the cartridge with EtOH and the identities of the products were confirmed by radio-UHPLC.

The optimized preparations of ^{18}F-labeled PSMA inhibitor, PD-L1 ligand, COXIB, and FAPI were accessed with high non-decay corrected isolated activity yields (AY) of 33-57% (n = 12) and >95% radiochemical purity (RCP) in 25 min. The automated radiosynthesis procedures afforded the radiolabeled products in an unoptimized 8-15% AY (n = 5), with >95% RCP in 40 min.

The ultra-fast [^{18}F]SuFEx reaction has permitted several structurally-diverse ^{18}F-labeled compounds for potential imaging to be rapidly accessed in excellent isolated AYs and high RCP. Presently, optimization of the automated radiosynthesis and biological assessment of the ^{18}F-labeled products is underway.

Keywords: Fluorine-18; positron emission tomography (PET); [^{18}F]SuFEx

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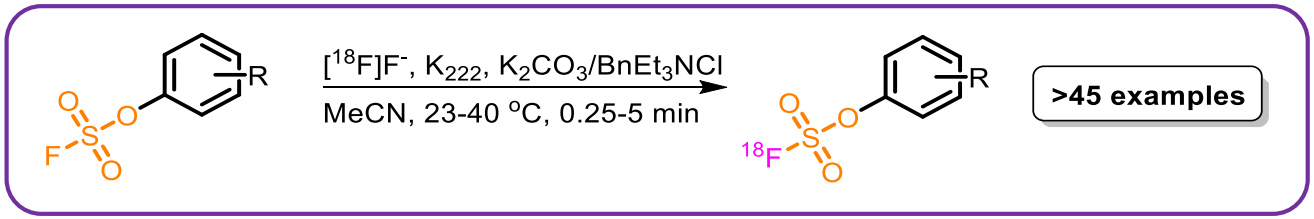
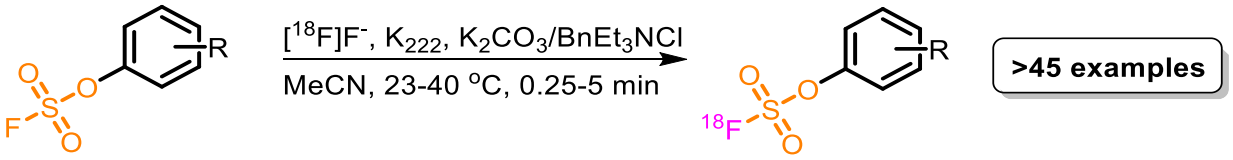
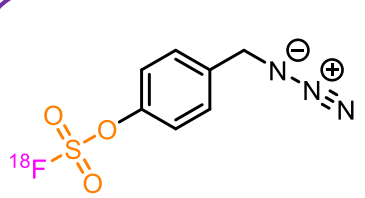
Introduction: [^{18}F]SuFEx reaction utility and scope



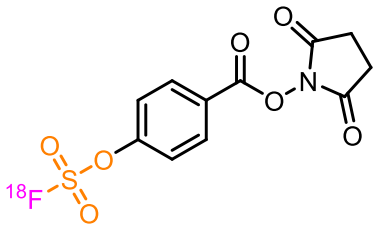
- Ultrafast Reaction Times
- High Radiochemical Yields
- High Radiochemical Purity
- SPE Purification
- Facile Automation
- Low Precursor Concentrations
- High Molar Activities
- In vivo Imaging*

Introduction: [^{18}F]SuFEx reaction utility and scope

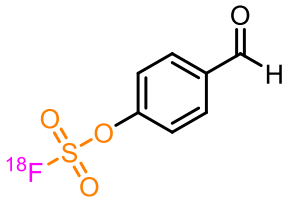




99% RCY_{HPLC}

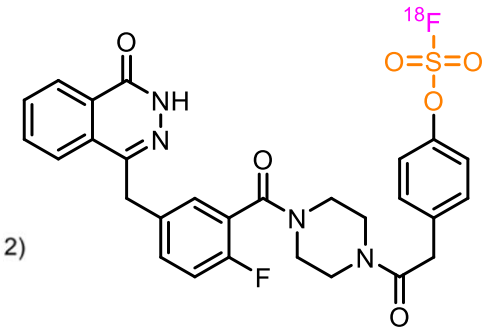


85% RCY_{HPLC}

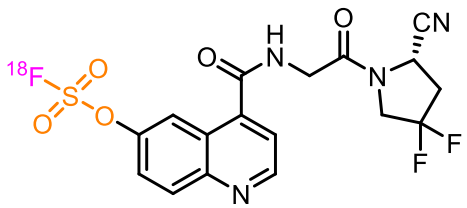


96% RCY_{HPLC}

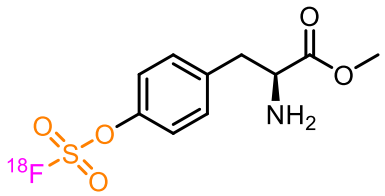
3.7-GBq scale	95–96% RCY_{HPLC} (n = 2)
37-GBq scale	88–93% RCY_{HPLC} (n = 2) 21–42% RCY_{isol} (n = 2) 103–111 GBq µmol^{-1} A_m (n = 2)
108 GBq scale	89% RCY_{HPLC} 280 GBq µmol^{-1} A_m



96% RCY



71 ± 7% RCC
47% AY

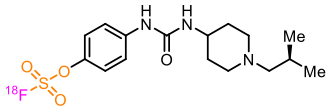


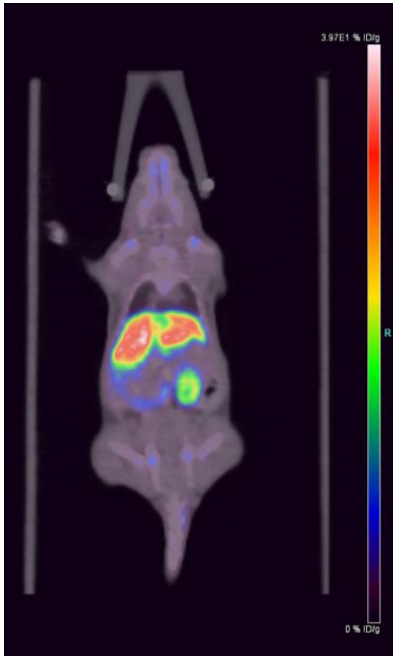
79 ± 1% RCC
22% AY

Q. Zheng et al. *J. Am. Chem. Soc.* **2021**, *143* (10): 3753-3763.

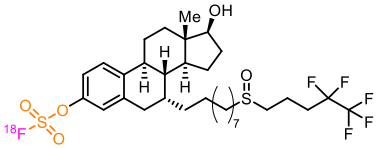
N. Walter et al. *Eur. J. Med. Chem.*, **2022**, 237, 114383.

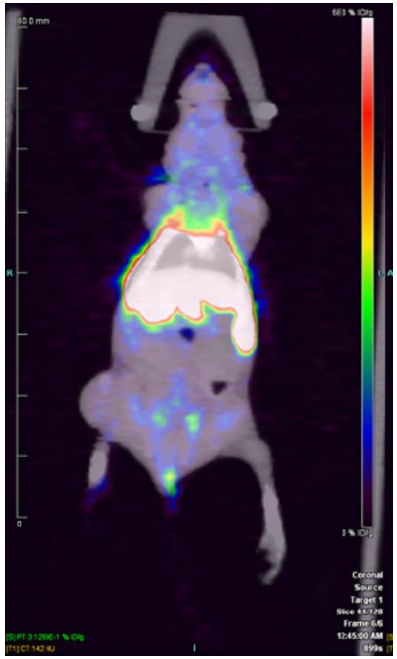
Introduction: [^{18}F]SuFEx reaction utility and scope



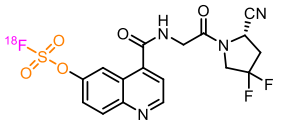


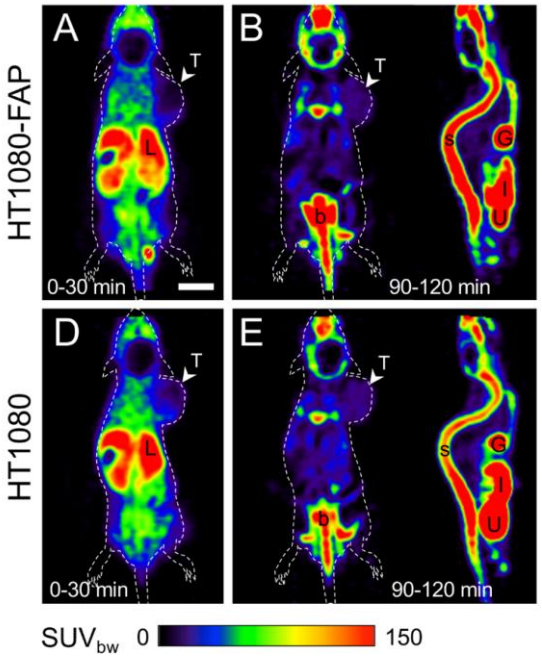
High liver uptake. No activity in bones/joints





High liver uptake. No activity in bones/joints





High liver uptake and high activity in bones/joints

Q. Zheng et al. *J. Am. Chem. Soc*. **2021**; *143* (10): 3753-3763. N. Walter et al. *Eur. J. Med. Chem*., **2022**, 237, 114383.

Results and discussion

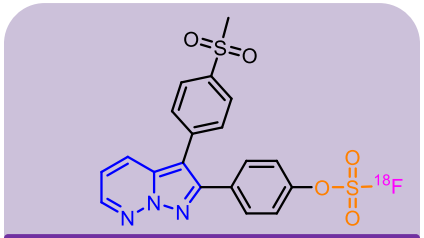
A

B

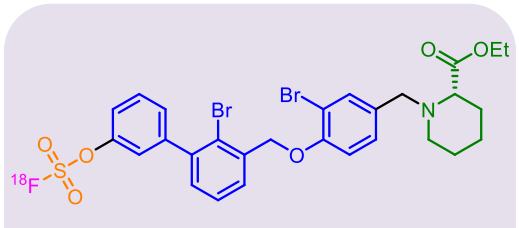
C

D

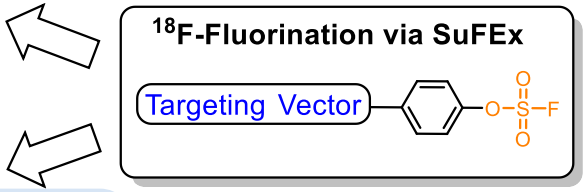
The application of the [^{18}F]SuFEx reaction towards four ^{18}F-labeled PET tracer preparation

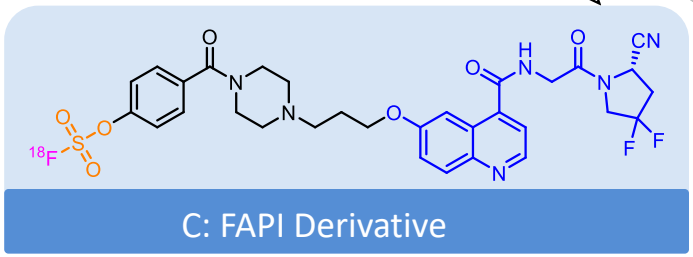


A: COX-2 Inhibitor

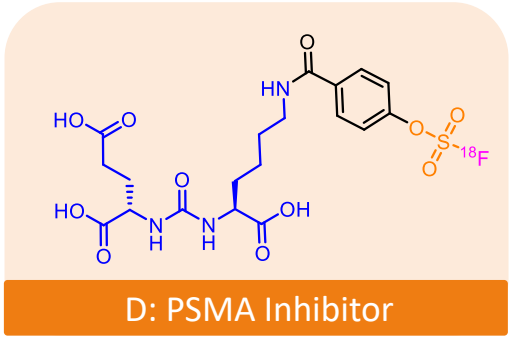


B: PD-L1 Inhibitor



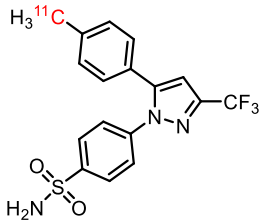


C: FAPI Derivative

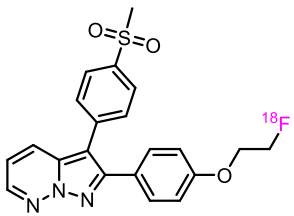


D: PSMA Inhibitor

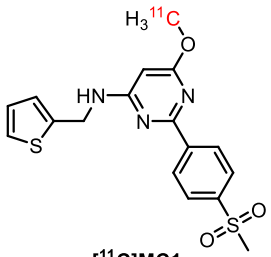
Results and discussion: Preparation of ^{18}F-labeled COXIB



[^{11}C]Celecoxib
Prabhakaran *et al.* (2005)

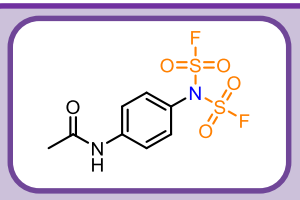


[^{18}F]Fluorethyl-COXIB
Kniess *et al.* (2017)



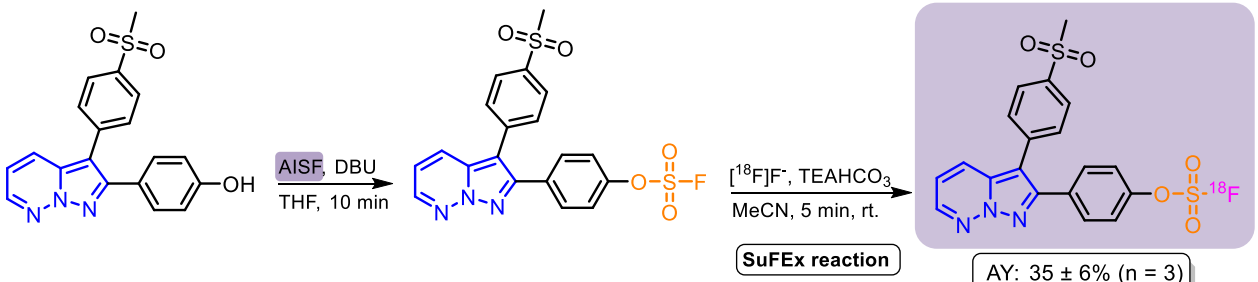
[^{11}C]MC1
Shresta *et al.* (2020)

Literature known COX-2 Inhibitors



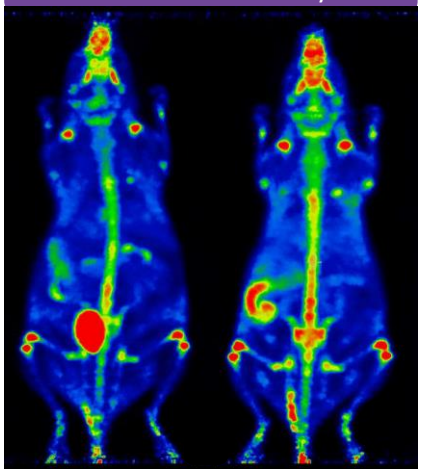
AISF: 4-[(acetylamino)phenyl]-imidodisulfuryl difluoride

- ✓ Commercially available
- ✓ Bench stable solid
- ✓ Fast and high yielding reactions



AY: 35 ± 6% (n = 3)
A_m: 49 GBq/μmol
RCP: >99%

PET images showing biodistribution in healthy mice



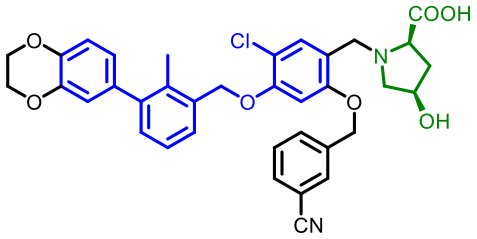
- Cyclooxygenase-2 (COX-2) Enzyme responsible for tumor-related inflammation
- COXIB: COX-2 inhibitor

S. Shrestha et al. *J. Neuroinflammation*, **2020**; *17*(1): 140. T. Kniess et al. *Appl. Radiat. Isot.* **2017**; *127*: 260-268. Prabhakaran et al. *J. Label. Comp. Radiopharm.* **2005**, *48*(12): 887-895.

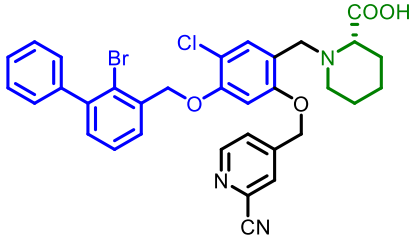
Results and discussion: Preparation of ^{18}F-labeled PD-L1 Inhibitor

B

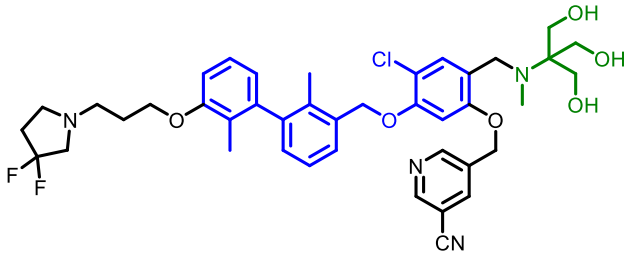
Literature known PD-L1 Inhibitors



IC_{50} = 1.4 nM
Chupak et al. WO2015160641A2 **2015**.

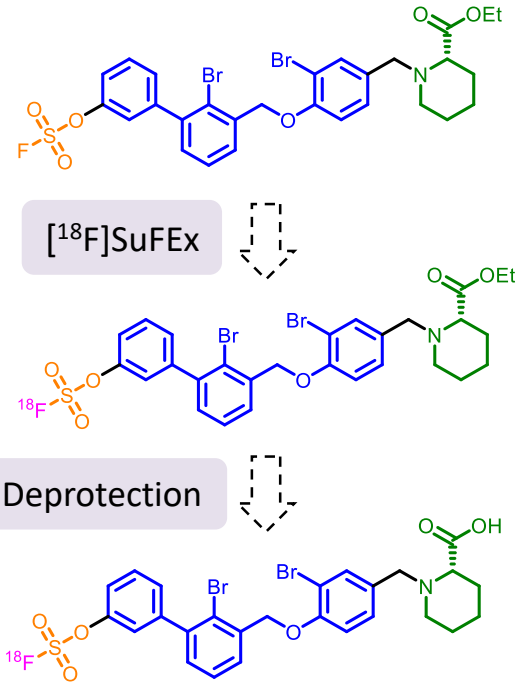


IC_{50} = 80 x 10^{-6} nM
Feng et al. WO2017202276 **2017**.



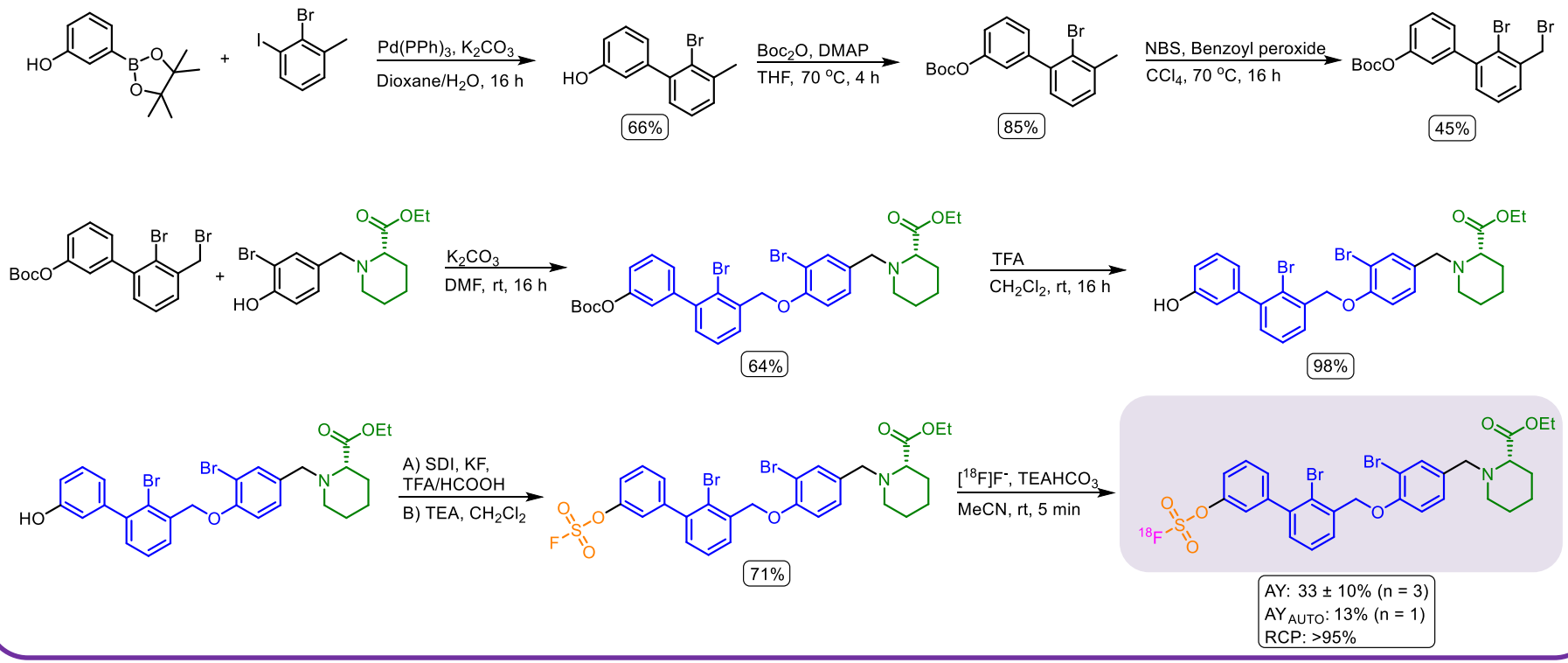
IC_{50} = 0.5 nM
Yeung et al. WO2017066227 A1 **2017**.

Planned Radiosynthesis Route



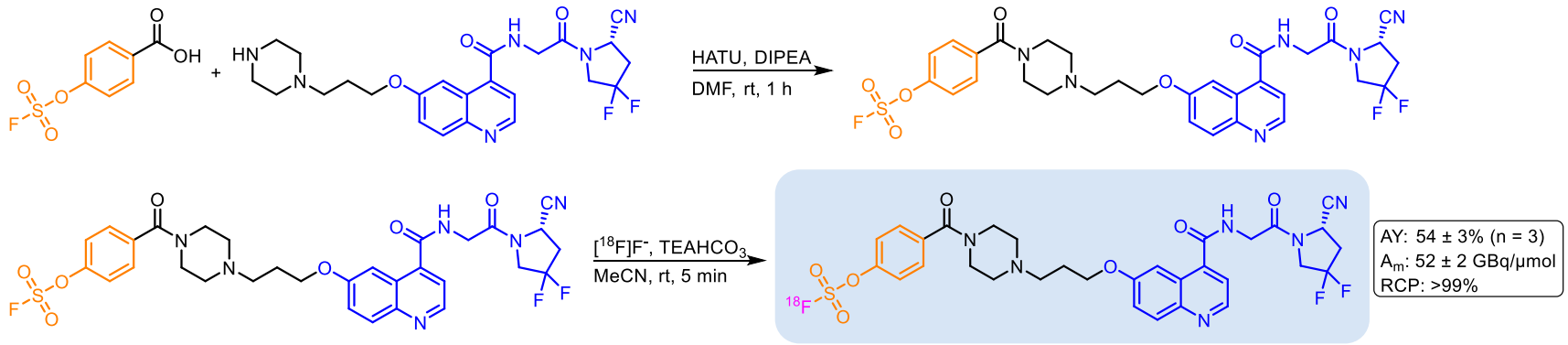
- **Overexpression** of **programmed cell death-ligand 1** (**PD-L1**) on various aggressive **cancers** suppresses the **adaptive immune system**, thereby allowing the cancer to evade immune detection and response.
- **Immune checkpoint inhibitor** therapies are able to break the blockade and **reactivate the immune system**.
- **Monitoring the PD-L1 expression** levels within tumors using radiotracers would provide clinicians with a tool for **therapy decisions**.

Results and discussion: Preparation of ^{18}F-labeled PD-L1 Inhibitor

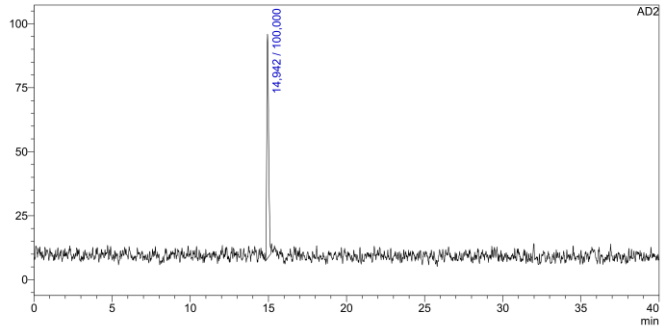


- **Deprotection** of radiofluorinated intermediate under basic conditions **not achieved**
- **Instability** of aryl-fluorosulfate under **basic conditions**
- **High lipophilicity** of compound an issue for biological evaluation

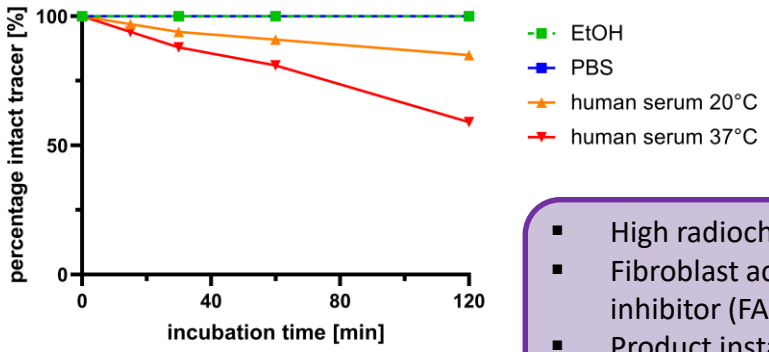
Results and discussion: Preparation of ^{18}F-labeled FAPI Derivative



Product Purity and Stability Studies



Radio-HPLC showing Radiochemical Purity



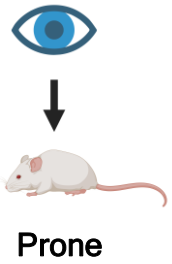
Tracer stability studies

- High radiochemical purity (RCP)
- Fibroblast activated protein inhibitor (FAPI)
- Product instability in human serum at 37 °C

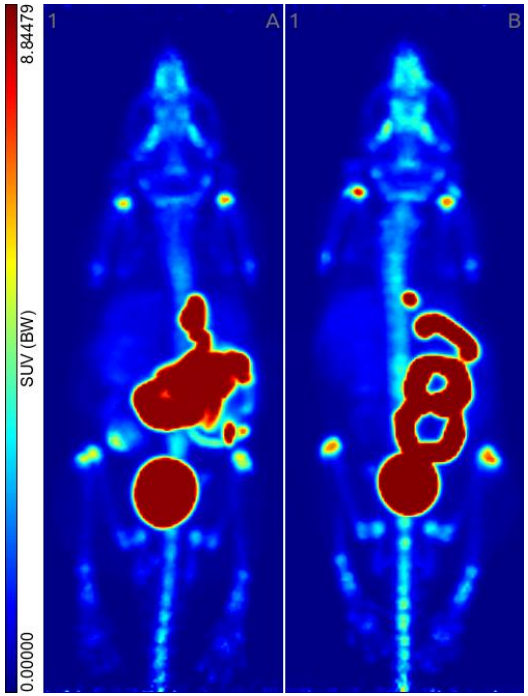
T. Lindner et al. *J. Nucl. Med.* **2018**, *59*(9)**,** 1415-1422. K. Jansen et al. *J. Med. Chem.* **2014**, *57*(7), 3053-3074.

Results and discussion: Preparation of ^{18}F-labeled FAPI Derivative

In vivo PET Experiments



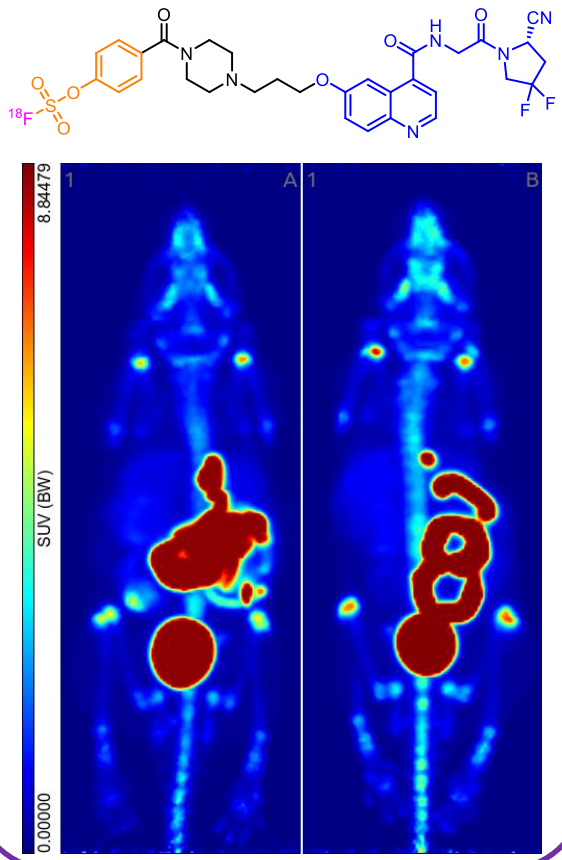
0-2 h p. i.

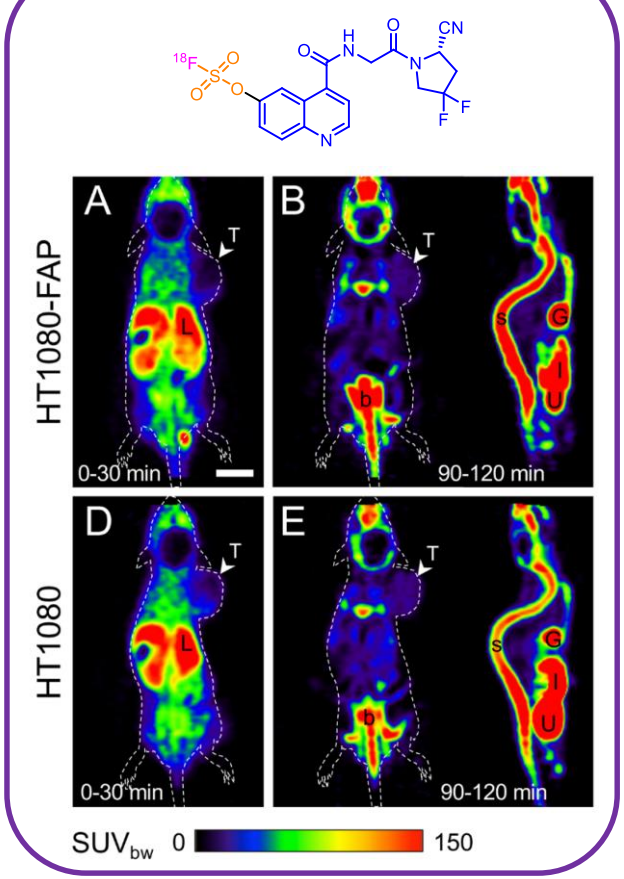


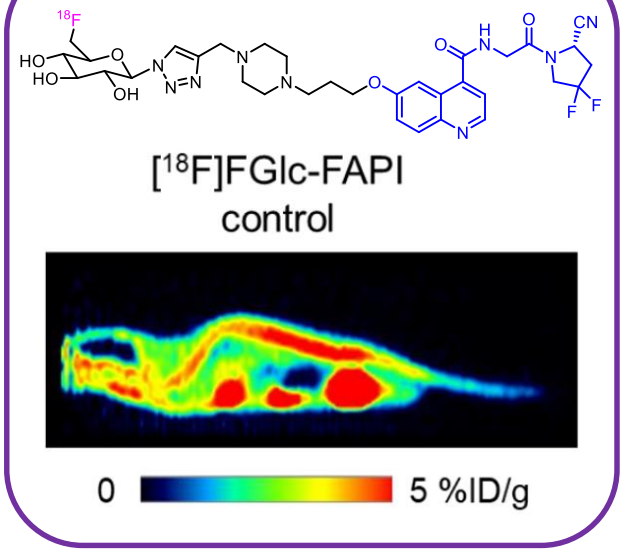
NMRI-Foxn1-nude mice, n=2

- High **uptake** in **bones** and **joints**
- ➢ Indication for **instability** of **fluorosulfate** *in vivo*
- Tracer accumulation in **intestine** and **gall bladder**
- Mainly **hepatobiliary tracer clearance**
- ➢ → Due to high lipophilicity

Results and discussion: Preparation of ^{18}F-labeled FAPI Derivative







- **High activity** in the **bones and joints** for three FAPI tracers
- Tracer **binding** or **defluorination**?

N. Walther et al., *Eur. J. Med. Chem*. **2022**, *237,* 114383. J. Toms et al., *J. Nuc. Med*. **2020**, 63

Results and discussion: ^{18}F-labeled PSMA Inhibitor preparation

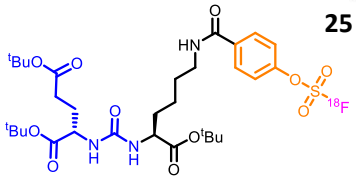
[^{18}F]Fluoride Purification

10 minutes

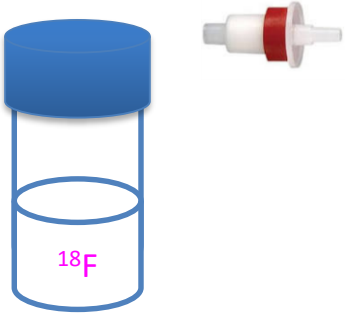
- ^{18}F-Suspension on cartridge
- ^{18}F-Elution with $BnEt_3NCl$ in MeOH
- Evaporation of MeOH

[^{18}F]SuFEx Reaction

25 minutes



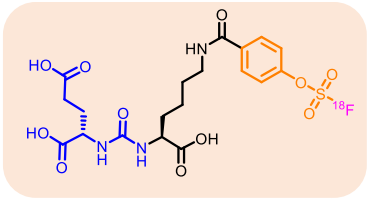
Protected PSMA Intermediate

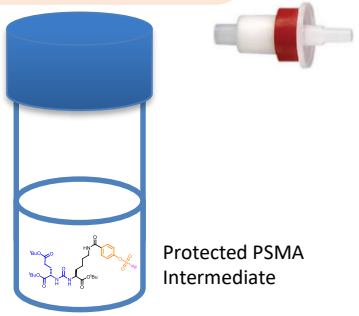


- Precursor addition in MeCN
- Radiolabeling: 5 mins at 23 °C
- C18 cartridge purification

Deprotection Reaction

25 minutes



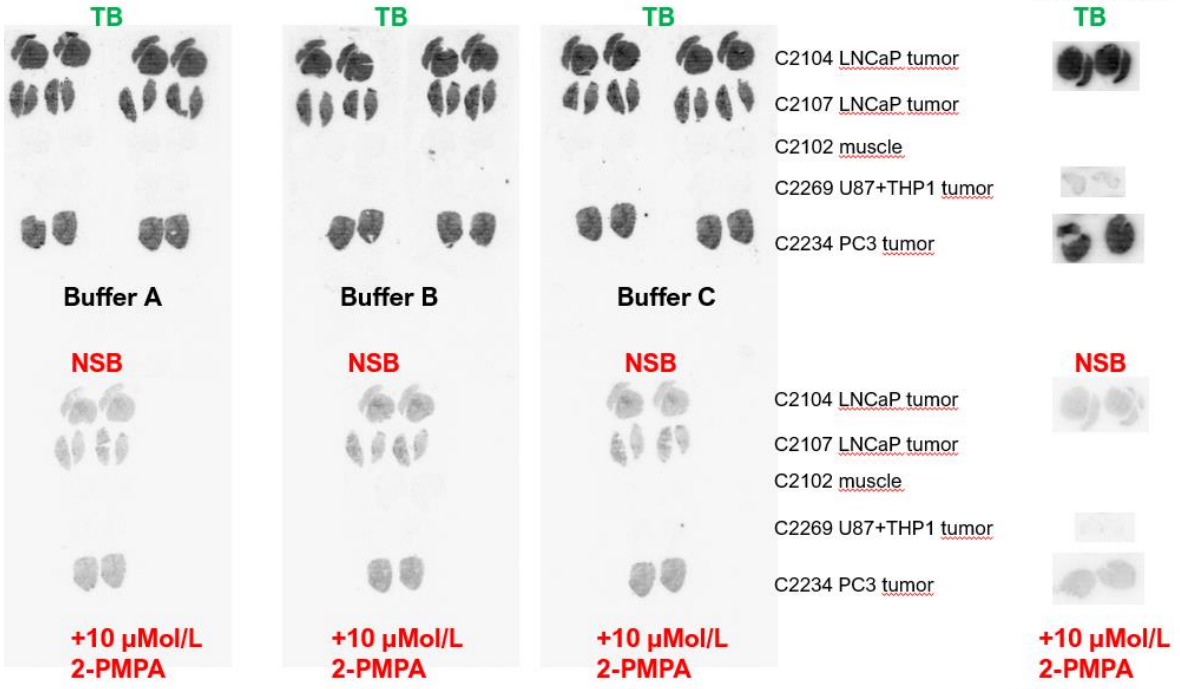


Protected PSMA Intermediate

- Conc. HCl addition
- Deprotection: 15 mins at 23 °C
- C18 cartridge purification

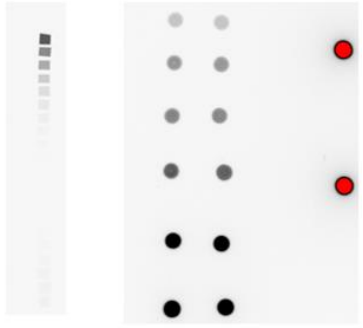
Results and discussion: ^{18}F-labeled PSMA Inhibitor

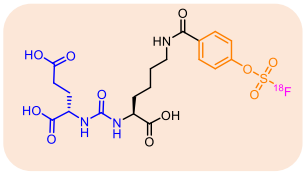
^{18}F-Labeled PSMA Binding Studies



TB= Total binding, NSB= Nonspecific binding

Previous binding studies

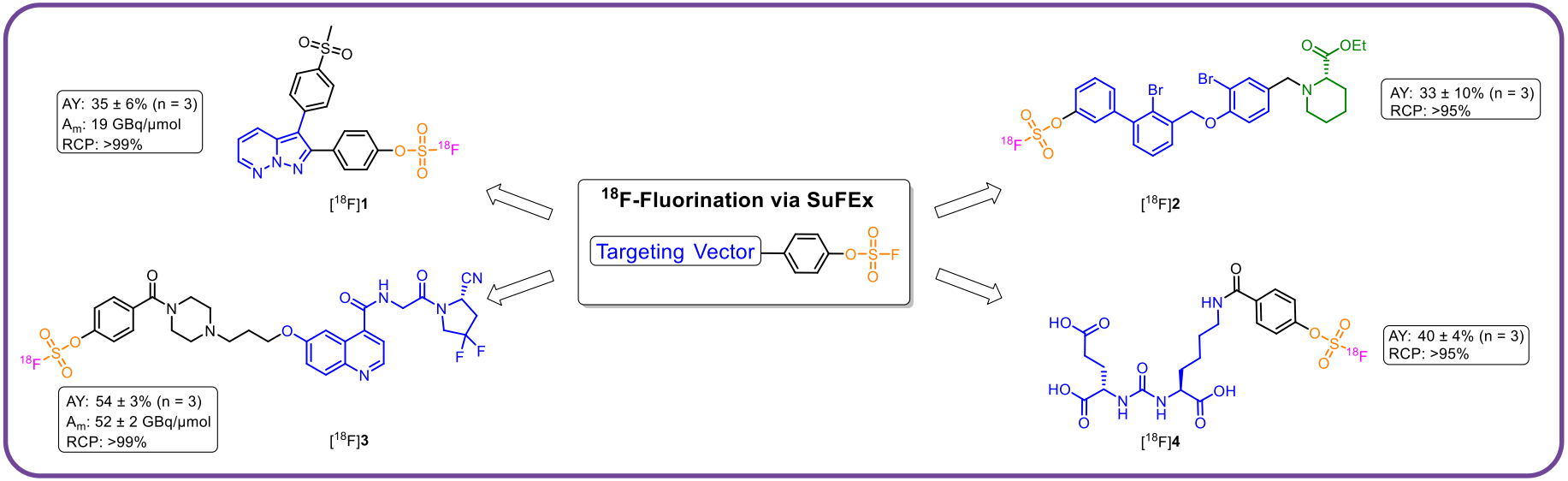




- Prostate specific membrane antigen (PSMA)
- PSMA used for prostate cancer imaging
- ^{18}F-labeled PSMA inhibitor showed high tumor cell binding

Conclusions

The [^{18}F]SuFEx reaction enables accelerated preparation of ^{18}F-labeled PET tracers



- Facile preparation of aryl fluorosulfate precursors
- High activity yields (AY) and radiochemical purity (RCP)
- Radiosynthesis automation for routine preparations
- In vivo investigations currently underway

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Acknowledgments

[^{18}F]SuFEx
YouTube Video ->

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