Abstract No.#: 1452

Radiosynthesis and biological evaluation of two ^{18}F-labeled PET radioligands for α-synuclein

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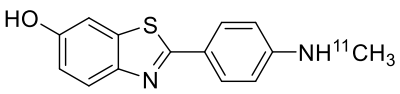
Parkinson disease and alpha-synuclein protein

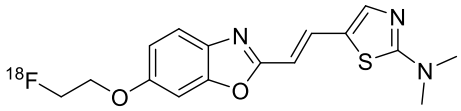
- Parkinson's Disease (PD) is the second most common neurodegenerative disease
- The motor symptoms of PD are caused by degeneration of dopaminergic neurons in the substantia nigra, which is accompanied by Lewy bodies (LBs) and Lewy neuritis (LNs)
- *α*-Synuclein is the main component of Lewy bodies and Lewy neuritis, and plays an important function in the CNS by regulating synaptic vesicle recycling and synthesis, vesicular storage and release of neurotransmitter
- Accumulation of *α*-synuclein aggregation may cause synaptic dysfunction and neuronal cell death
- *α*-synuclein is a pathological hallmark of Parkinson's disease (PD), Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA).
- A suitable PET radiotracer targeting α-synuclein could be useful in early diagnosis of PD, disease progression, and assessment of the efficacy of disease-modifying therapies

Neuropathology **2007**, *27*, 494–506.

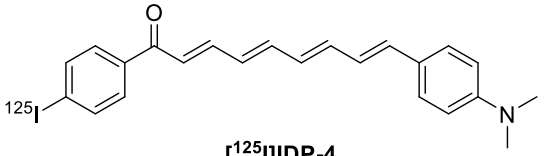
Radioligands for α-Synuclein



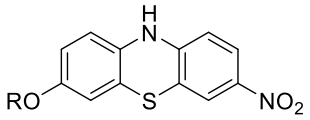
[^{11}C]PIB



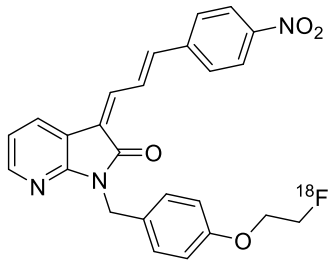
[^{18}F]BF227



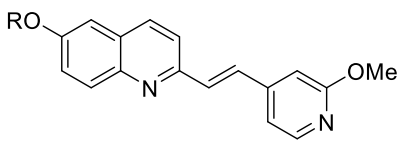
[^{125}I]IDP-4



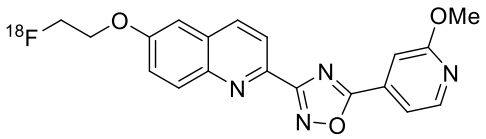
[^{11}C]SIL5 R = $^{11}CH_3$
[^{125}I]SIL23 R = (*E*)-$CH_2CHCH^{125}I$
[^{18}F]SIL26 R = $CH_2CH_2{}^{18}F$



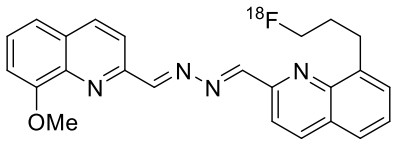
[^{18}F]WC-58a



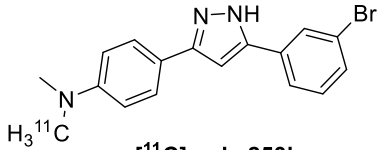
[^{11}C]13 R = $^{11}CH_3$
[^{18}F]14 R = $CH_2CH_2{}^{18}F$



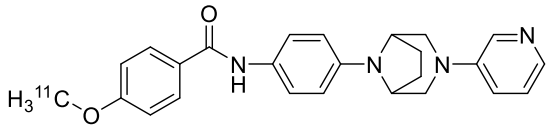
[^{18}F]28



[^{18}F]BQ2



[^{11}C] anle 253b

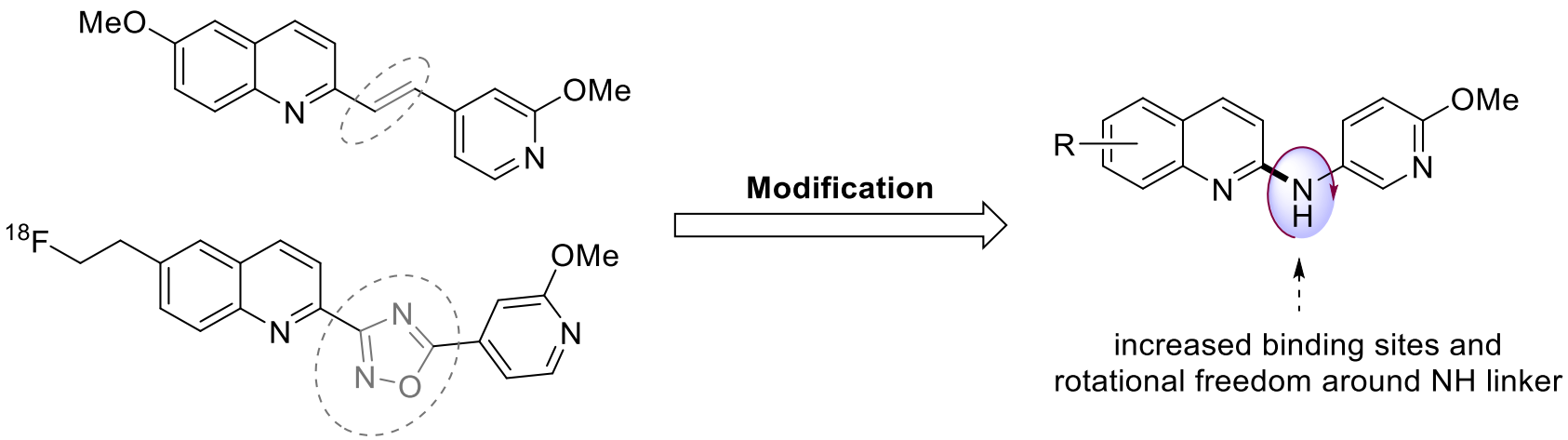


[^{11}C]KY-2-15

- Radiotracer [^{18}F]ACI-12589 was reported as PET radiotracer for imaging alpha-synuclein in the human brain by AC immune (https://clinicaltrials.gov/ct2/show/results/NCT05067192).
- Data suggested that [^{18}F]ACI-12589 tracer binding in the brain is consistent with expected patterns of *α*-synuclein pathology
- However, further evaluation of disease and target specificity, and potential PET signal retention in a-syn-positive PD/dementia are still needed.

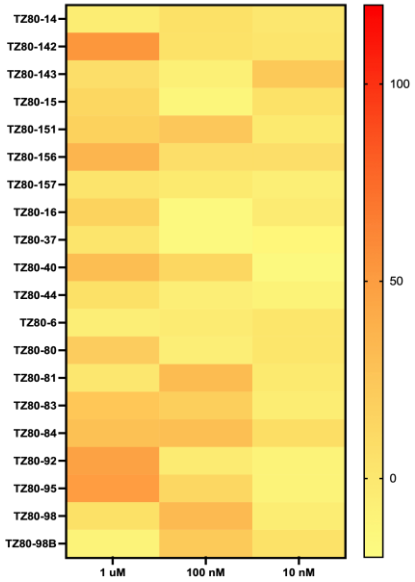
R. Wang, etc., *Analytical and Bioanalytical Chemistry*, **2023**, 415, 1589-1605.

Design and synthesis strategy

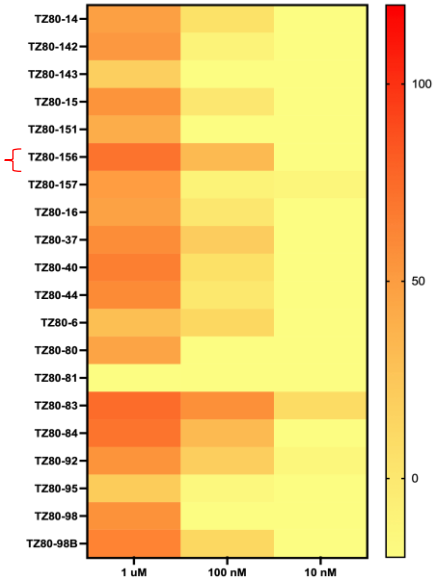


In vivo screening of each new compounds

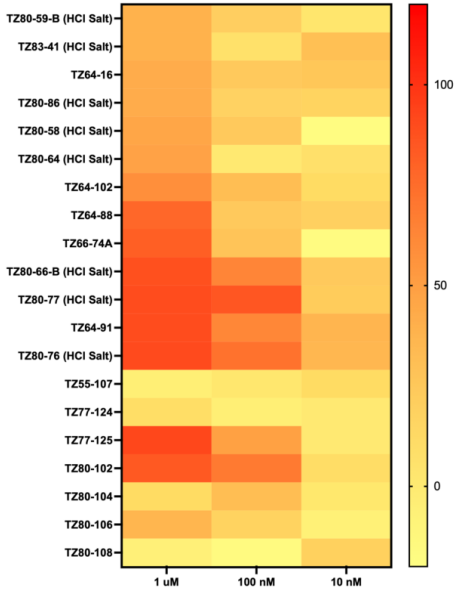
[^{3}H]BF2846 for alpha-synuclein fibrils



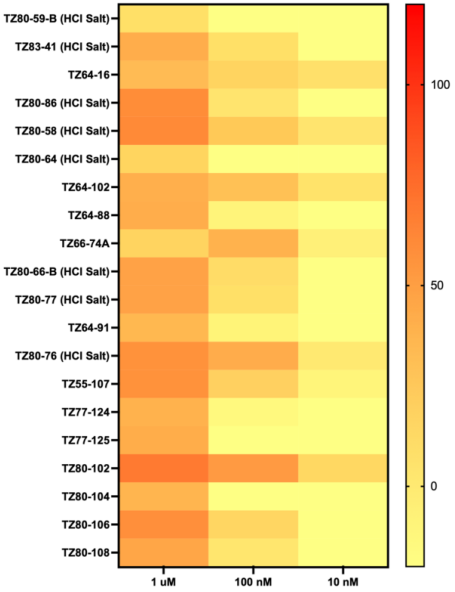
[^{3}H]PiB for AD tissues



BF2846 (site 9 asyn fibrils)

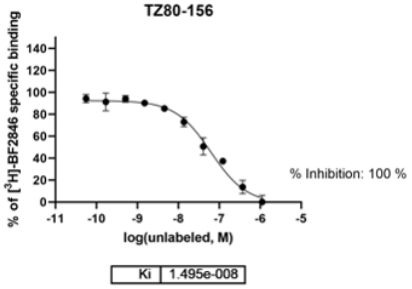


PiB (AD CAA- Hom.)

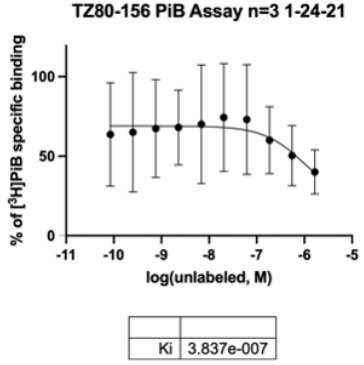


Name	Ki (nM), in a-syn fibrils v.s. [^{3}H]BF2846	max%inh_site9	Ki (nM) in AD vs [^{3}H]PiB	max % Inh PiB
TZ80-156	14.95± 19.07	100	>1000	NA
TZ83-41	12.5± 40.81	60	362 ± 372	40

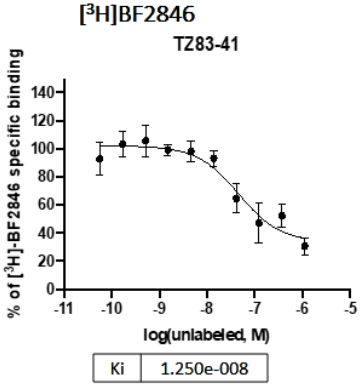
[^{3}H]BF2846



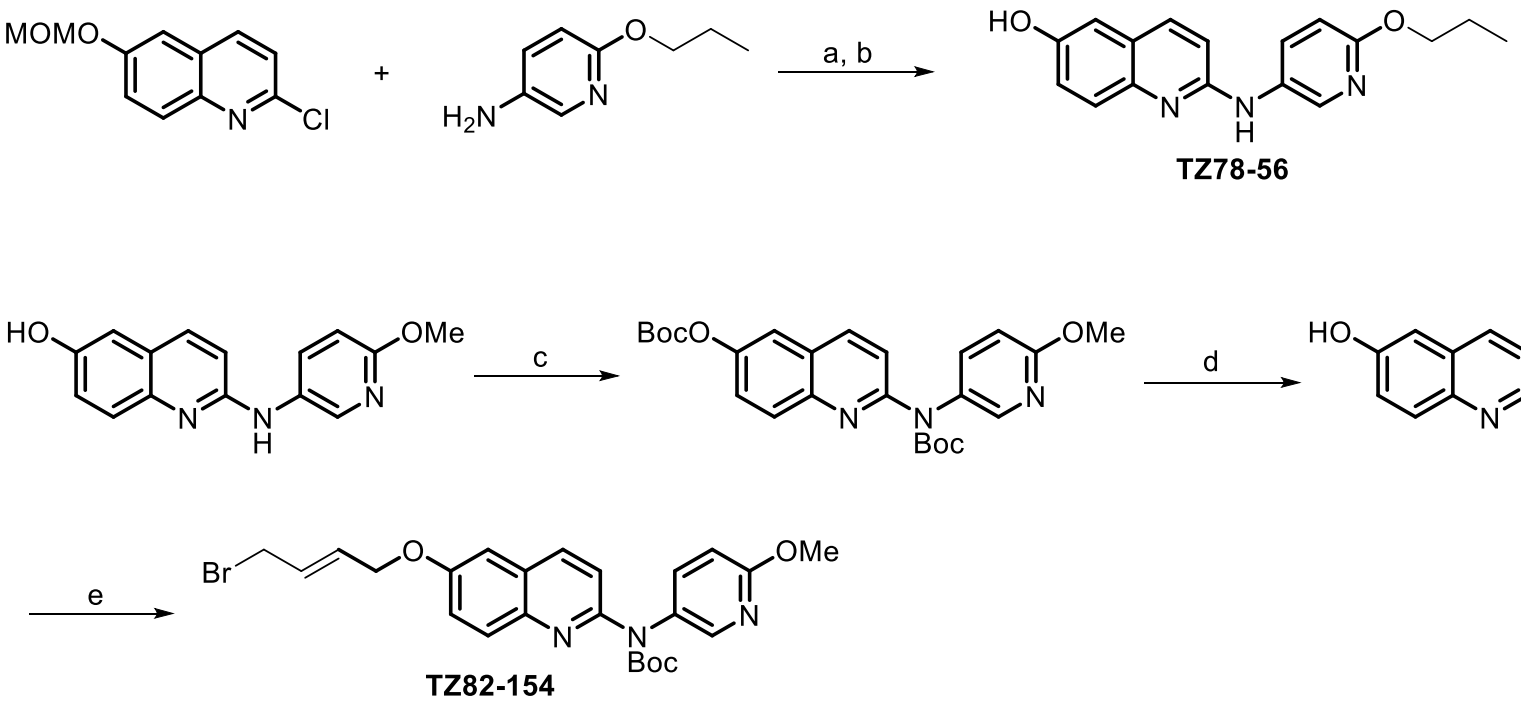
[^{3}H]PiB



[^{3}H]BF2846

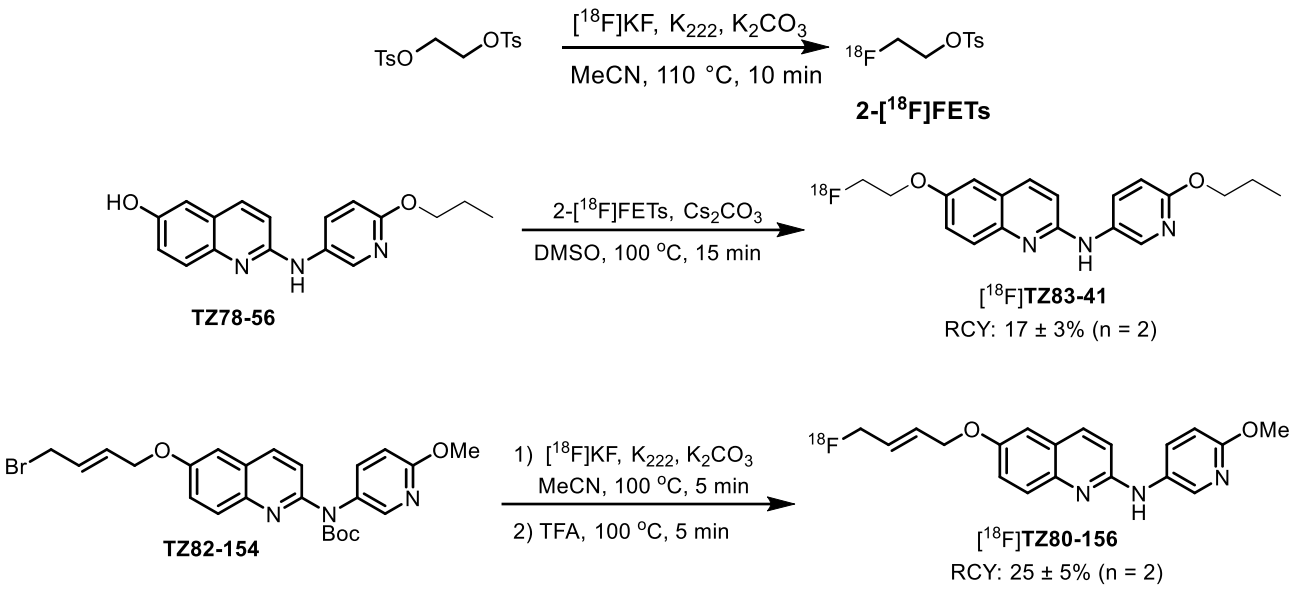


Syntheses of precursors



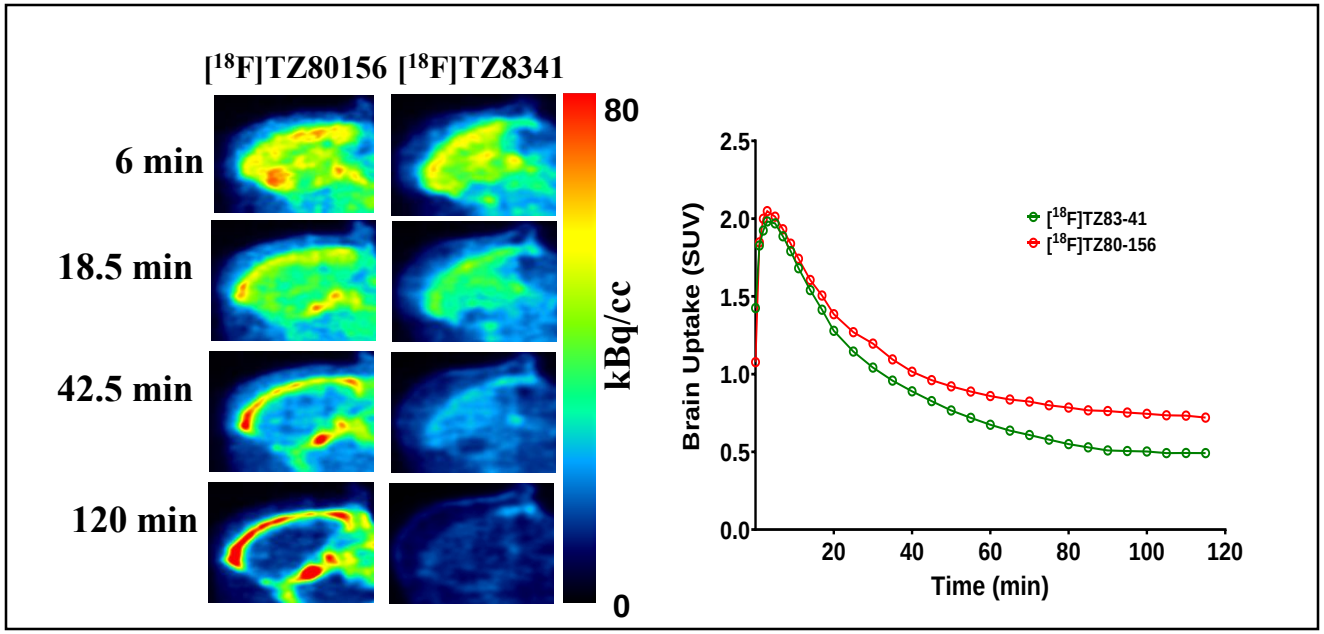
Reaction and conditions: (a) $Pd_2(dba)_3$, XantPhos, Cs_2CO_3, 1,4-dioxane, 110 ^oC; (b) 6 M HCl, MeOH, 70 ^oC; (c) Boc_2O, DMAP, RT; (d) Cs_2CO_3, MeOH, RT; (e) (*E*)-1,4-dibromobut-2-ene, Cs_2CO_3, acetone, RT.

Radiosynthesis of [^{18}F]TZ83-41 and [^{18}F]TZ80-156



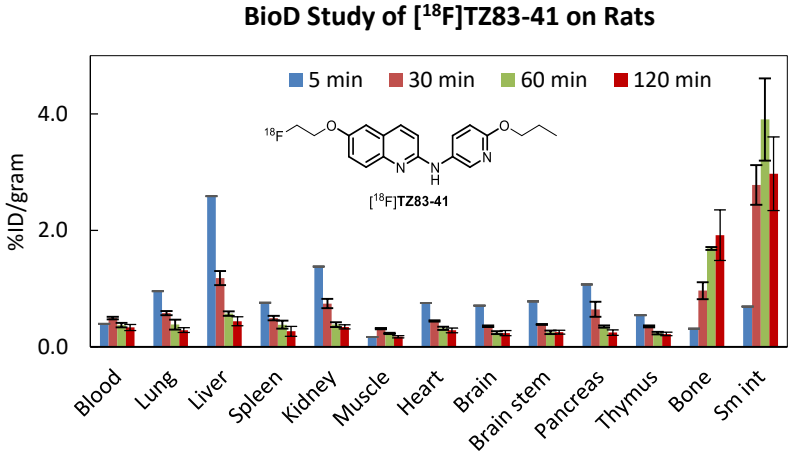
- Specific activity (SA): (> 37 GBq/μmol, at the end of synthesis (EOS).
- Radiochemical and chemical purity > 98%

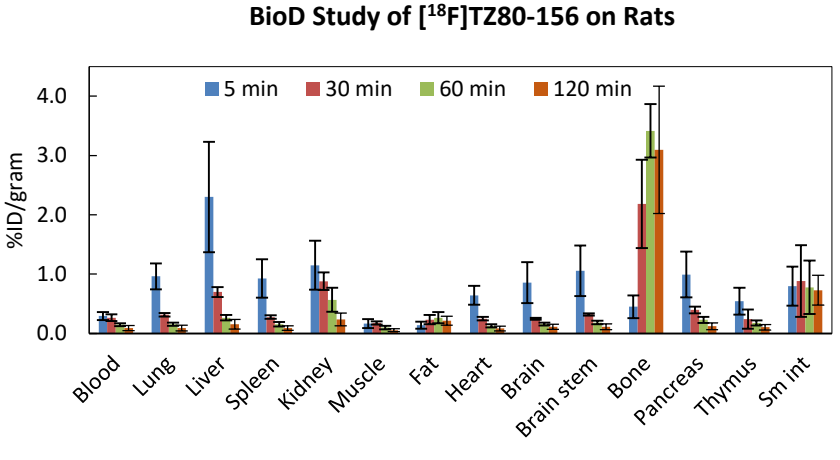
PET study in the brain nonhuman primate



- The brain standardized uptake values (SUVs) for [^{18}F]**TZ83-41** and [^{18}F]**TZ80-156** reached a maximum (~2.0) at 6-7 min post tracer injection, followed by a favorable washout rate from the NHP brain.
- It suggests that both radioligands could cross the blood brain barrier, [^{18}F]**TZ80-156** may have defluorination *in vivo*.

Tissue biodistribution in Sprague-Dawley rats





- [^{18}F]**TZ83-41** had a good brain uptake up to 0.71~0.24 %ID/gram from 5 to 120 min.
- For [^{18}F]**TZ80-156**, the brain uptake dramatically decreased to 0.25 at 30 min, and 0.16 at 60 min. Bone uptake increased from 0.45 at 5 min to 2.18 at 30 min and 3.09 at 120 min.

Radiometabolite analysis of NHP plasma samples

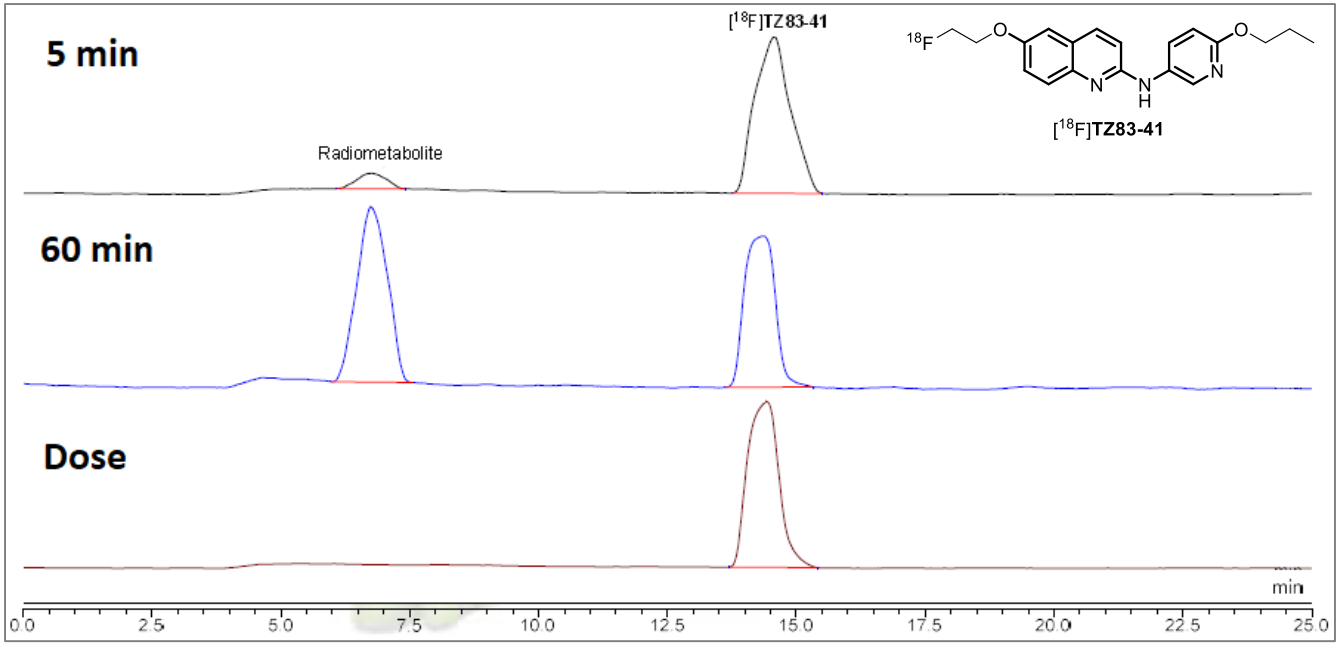


Table 1. HPLC metabolite analysis of NHP blood

	5 min	15 min	30 min	60 min	90 min	*In vitro* blood
Radiometabolite	7%	31%	41%	53%	62%	3%
[^{18}F]**TZ83-41**	93%	69%	59%	47%	38%	97%

- [^{18}F]**TZ83-41** is relatively stable in NHP plasma and only one hydrophilic radiometabolite (t_R = 6.8 min) is detected.

Summary and future plan

- *In vitro* binding showed two compounds are potent and selective for alpha-synuclein.
- Two new F-18 labeled radioligands, [^{18}F]TZ83-41 and [^{18}F]TZ80-156 were radiosynthesized successfully.
- Both radiotracers could cross the blood brain barrier (SUV up to 2.0) and possess a good brain washout kinetics in the NHP.
- Radiometabolite analysis and rat biodistribution showed that [^{18}F]TZ83-41 has no defluoroination *in vivo*.
- Further evaluation will focus on [^{18}F]TZ83-41 and determine if it be selected for translational clinic evaluation.

Acknowledgements

- Washington University Cyclotron Facility
- Small Animal Preclinical Imaging Facility
- Nonhuman Primate PET Facility
- U of Penn, Dr. Robert Mach's group
- U of Pittsburg, Dr. Chester Mathis's group

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THANK YOU FOR YOUR ATTENTION!

Washington University in St. Louis
School of Medicine

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Addition information

- ID: SS14
- **Room**: S504ab
- **Session Date:** June 25, 2023
- **Session Time:** 12:30 PM - 1:45 PM
  Session Type: Scientific Session
- **Session Title:** Developments in Cardiovascular and Neurological Imaging
- **Abstract # /Title:** P1452 - *Radiosynthesis and biological evaluation of two 18F-labeled PET radioligands for α-synuclein*
  Presentation Time: 1:05 PM - 1:15 PM (this includes 2 minutes for Q&A)
- Xuedan Wu
- Steven Liang
- Mausam Kalita
- Zhude Tu
- Divangana Lahad
- Allen Brooks
- Yadira Medina Guevara