Evaluation of Pyridyl Benzofuran Derivative for Targeted Alpha Therapy of Alzheimer's Disease

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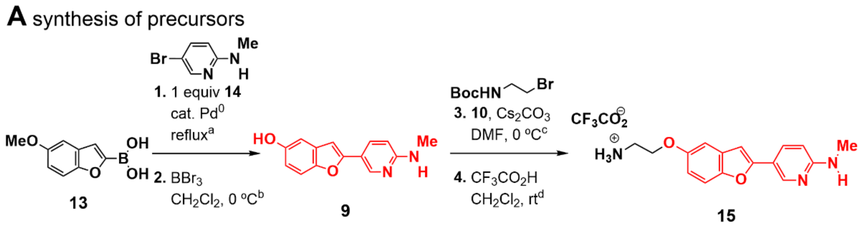
INTRODUCTION

- **Alzheimer's Disease (AD) impacts millions of people worldwide, and costs families billions of dollars annually[1]**
- **AD is characterized by several biomarkers, including Amyloid-beta (Aβ) plaques[2]**
- **Aβ plaques cause oxidative stress and neuronal death**
- **Low-dose Ionizing Radiation (LDIR) has been shown to generate an immune response toward Aβ plaques[3]**
- **Targeted Alpha Therapy (TAT) has shown great success in treating micro-metastasized tumors in cancer patients[4]**
- ***We hypothesize that TAT could be used to break apart Aβ plaques and activate an immune response toward the plaque fragments while minimizing off-target dose***

Synthesis of [Bi^{213}]-BiBPy (8)



METHODS

- **Synthesized BiBPy (8) and fluorescent-BPy (12) in six steps, inspired by previous syntheses[5]**
- **Measured specific activity and RCY by radioHPLC**
- **Lipophilicity measured to assess ability to cross blood brain barrier (BBB)**
- **Competition assays and fluorescent-BPy tissue staining used to measure specificity of plaque binding**
- **Tested breakdown of amyloid plaques *in vitro* by varying dose of [^{213}Bi]-BiBPy to APP/PS1 mouse brain homogenate and measured plaque concentration with ELISA and Western Blot**

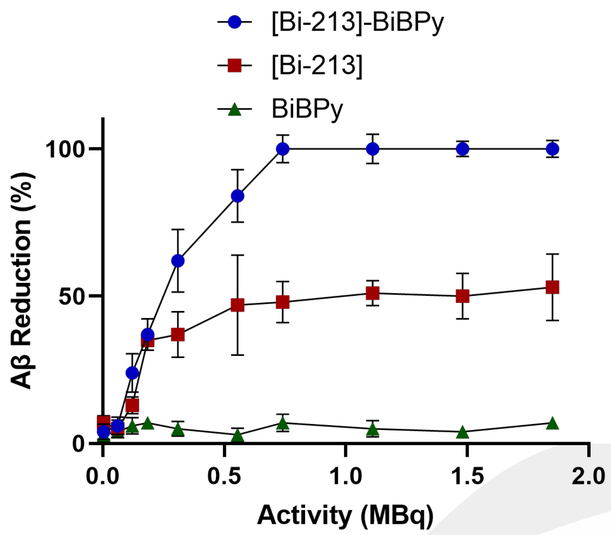
REFERENCES

1. Gaugler, J et al. 2020 DOI: 10.1002/alz.12068.
2. Jack, C. R., Jr. et al. 2018 DOI: 10.1016/j.jalz.2018.02.018.
3. Ceyzériat K, et al. 2020 DOI: 10.3233/JAD-190984.
4. Kratochwil, C, et al. 2016 DOI: 10.2967/jnumed.116.178673.
5. Cheng, Y, et al. 2012 DOI: 10.1021/jm201513c.

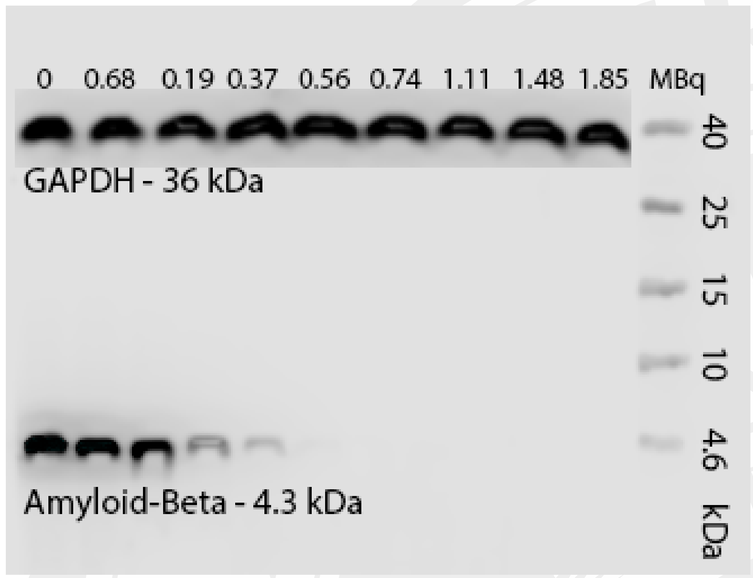
RESULTS

Analyzed Parameter	Experimental Value
Specific Activity (GBq/μg)	121 ± 2.2
Radiochemical Yield (%)	97 ± 1.5
K_D (nM)	11 ± 2
logP	0.14 ± 0.03
EC50 (kBq/pg Aβ)	3.72 ± 0.02

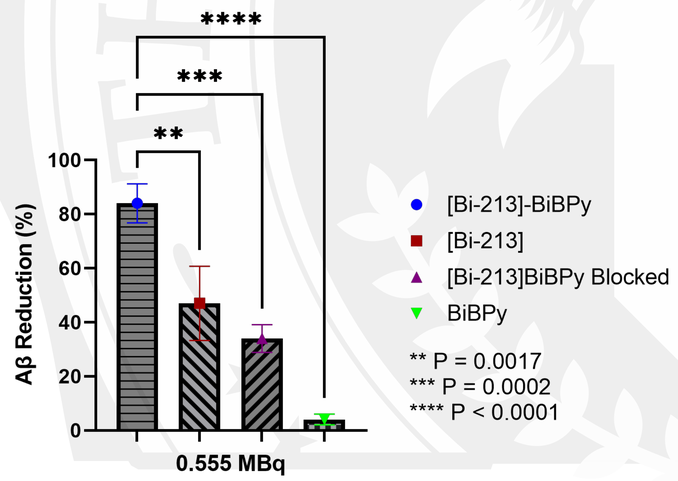
Dose Response of Aβ to [^{213}Bi]-BiBPy



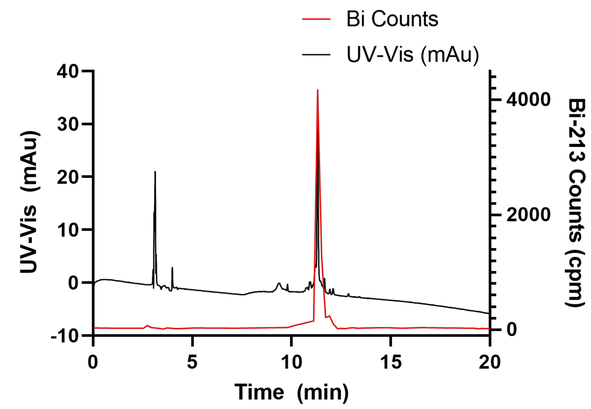
Western Blot of Aβ Dose Response



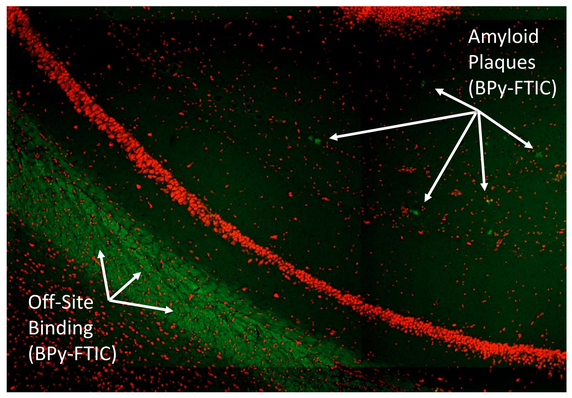
BiBPy Competition Assay



Radiolabeling



Fluorescent-BPy Staining



CONCLUSIONS

- **BiBPy was synthesized and radiolabeled with high purity and high specific activity**
- **Binding to amyloid-beta plaques confirmed by competition assay against Thioflavin-S, and by modification to Fluorescent-BPy and staining sections from APP/PS1 double transgenic mice**
- **May cross BBB based on the measured logP (target 0.1-3)**
- ***In vitro* dose response measurements of amyloid-beta plaques in brain homogenate to the presence of [^{213}Bi]-BiBPy display for the first time amyloid plaque response to TAT**

Future work to include:

- **Biodistribution and pharmacokinetics**
- **Effectiveness of targeting amyloid beta *in vivo***
- **Observation of immune response to TAT**

ACKNOWLEDGEMENTS

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