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Synthesis of Novel Fluorescent Molecular Probes for the Diagnosis of Alzheimer's Disease

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Introduction

- Alzheimer's disease (AD) is a detrimental, progressive neurodegenerative disease that is regarded as the most common and pervasive form of dementia, affecting an estimated 1 in 14 people over the age of 65 and 1 in every 6 people over the age of 80.[1,2]
- Traditional methods for the diagnosis of AD are expensive, provide poor resolution, and involve toxic radioactive materials.
- Misfolded proteins play a central role in the progression of AD and have been an area of intense research to investigate the neuropathology of the disease.

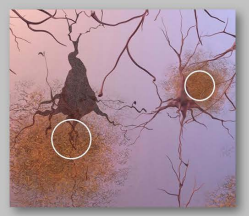


Figure 1. Protein plaques circled in white cause the onset of AD, building up between nerve cells and ultimately destroying them.[3]

Objectives

- To synthesize a series of novel fluorescent molecular probes that can bind to the protein-plaques that are caused by the onset of AD, providing a safer and earlier diagnosis.
- To characterize the final probes by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy and elemental analysis (EA).
- To determine the fluorescence properties of the final probes through UV-Vis spectroscopy and fluorometry.

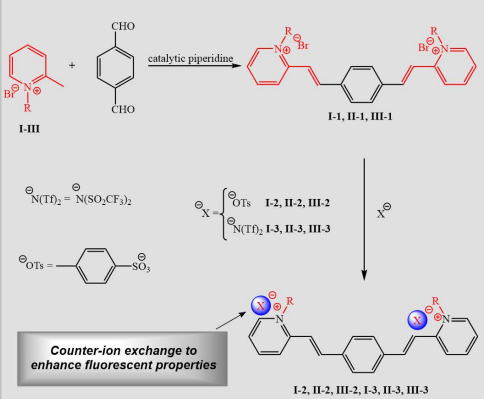
References

1. Siyue Ma, Guang Chen, Jie Xu, Yuxia Liu, Guoliang Li, Tao Chen, Yulin Li, Tony D. James, Current strategies for the development of fluorescence-based molecular probes for visualizing the enzymes and proteins associated with Alzheimer's disease, Coordination Chemistry Reviews, Volume 427, **2021**, 213553, ISSN 0010-8545, https://doi.org/10.1016/j.ccr.2020.213553.

2. National Health Service **2018**. Overview-Alzheimer's disease. Available from: https://www.nhs.uk/conditions/alzheimersdisease text=Who%20is%20affected%3F,over%20the%20age%20of%2080

3. Alzheimer's Association **2021**. What is Alzheimer's Disease? Available from: https://www.alz.org/alzheimers-dementia/what-is-alzheimers/brain_tour_part_2

Synthetic Methods



Scheme 1. General synthesis scheme of fluorescent molecular probes.

Results

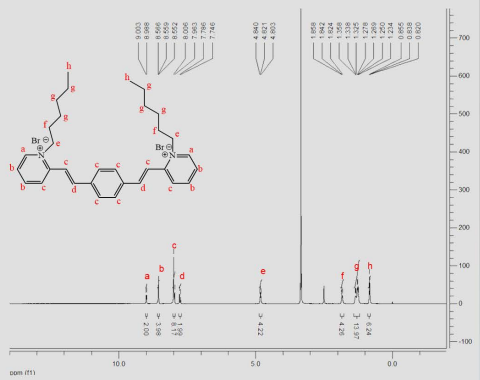


Figure 2. Representative ^{1}H NMR spectrum of *ortho*-C_6-styryl pyridinium bromide in DMSO-d_6.

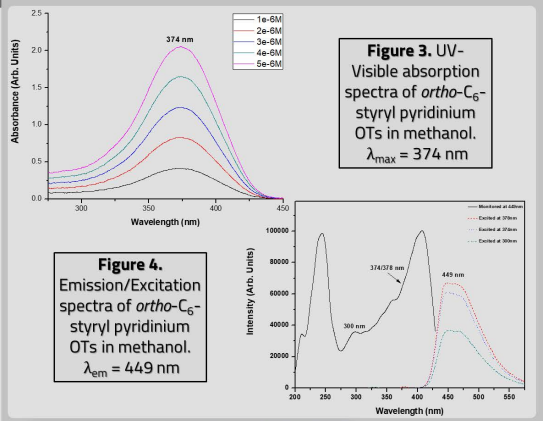


Figure 3. UV-Visible absorption spectra of *ortho*-C_6-styryl pyridinium OTs in methanol. λ_{max} = 374 nm

Figure 4. Emission/Excitation spectra of *ortho*-C_6-styryl pyridinium OTs in methanol. λ_{em} = 449 nm

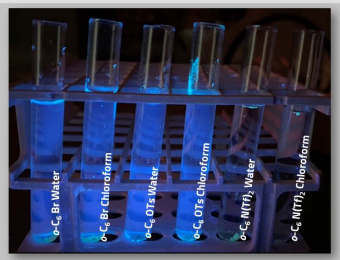


Figure 5. Solubility properties of the C_6 series in water/chloroform. Solubility in aqueous media renders this molecule suitable for *in vivo* imaging.

Figure 6. Dilute concentrations of *ortho*-C_6-styryl pyridinium tosylate in methanol (10^{-5} M) showing fluorescence under UV-light. This fluorophore can potentially bind to protein plaques and fluoresce under the microscope for improved AD diagnosis.

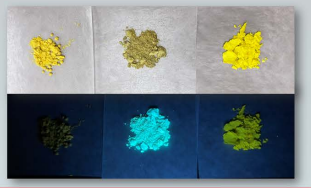


Figure 7. Solid-state fluorescence of the C_6 series triflimide, tosylate, and bromide salts (from left to right)

Conclusions

- A series of fluorescent molecular probes containing bromide, tosylate, and triflimide counterions with C_6, C_9, and C_{12} carbon chains were synthesized.
- The identities of the probes were confirmed using ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.
- The emission spectrum of *ortho*-C_6-styryl pyridinium tosylate shows a λ_{em} peak at 449 nm in methanol.
- The UV-Vis spectrum shows a λ_{max} peak at 374 nm in methanol.
- Bromide and tosylate salts exhibit fluorescence in the solid-state.
- Solubility testing shows that the salts containing bromide and tosylate counterions are soluble in water, making it suitable for *in vivo* imaging of aqueous systems.

Future Work

- The final probes can undergo ion exchange reactions to enhance fluorescent properties for improved *in vivo* imaging.
- Carbon-chain length modifications can be made to augment the lipophilicity of the probes, making it easier for it to cross the blood brain barrier.
- Structural modifications for *meta* and *para* positions possess different molecular properties (solubility, fluorescence, etc.)
- Biological testing to measure the affinity for plaques and fluorescence in the bound conformation.
- Measurement of fluorescence properties will be done in different solvents.

Acknowledgements

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