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Dibenzothiophene sulfonium salts as leaving groups for aromatic [18F]fluorination – exemplified by highly efficient direct labeling of the mGluR5 PET tracer [18F]FPEB

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Objectives Aromatic [18F]fluorination of small molecule PET tracers is attractive as it can result in increased metabolic stability and improved pharmacological profile. Despite recent progress in 18F chemistry, direct introduction of fluorine into aromatic groups remains challenging for complex drug-like molecules. To expand the arsenal of reactions available for 18F labeling we aimed to develop a practical synthetic method for formation of dibenzothiophene sulfonium salts and investigate their reactivity as leaving groups for reaction with [18F]fluoride.
Methods Structurally diverse dibenzothiophene sulfonium salts were synthesized by intramolecular cyclization of the respective thioethers (Fig. 1a). The effect of the substitution pattern on the ring closing reaction and labeling efficiency was investigated. An optimized dibenzothiophene sulfonium salt was used as leaving group for aromatic [18F]fluorination of the mGluR5 tracer [18F]FPEB (Fig. 1b).
Results The dibenzothiophene sulfonium salts were synthesized through an unprecedented intramolecular cyclization reaction of the corresponding diaryl thioethers mediated by *N*-chlorosuccinimide (NCS) and silver triflate. The resulting salts proved highly stable and could readily be purified by flash chromatography to afford the labeling precursors in 20-85% yield. [18F]Fluorination of these novel precursors proceeded smoothly (15 min, 50-110 ºC) in 20-80% analytical radiochemical yield (RCY). Using this method, the mGluR5 tracer [18F]FPEB was obtained in 60 ± 2% isolated RCY (decay corrected) under mild conditions (50 °C, 15 min, 2 mg precursor). In contrast, the established method for labeling of [18F]FPEB results in RCYs as low as 2-5% [1].
Conclusions A novel synthetic route to dibenzothiophene sulfonium salts *via* an intramolecular cyclization reaction has been developed that allows preparation of reactive precursors for direct aromatic [18F]fluorination. Applicability for PET has been demonstrated by highly efficient labeling of the mGluR5 tracer [18F]FPEB.
Acknowledgements
References [1] Sullivan, J. M.; Lim, K.; Labaree, D.; Lin, S.; McCarthy, T. J.; Seibyl, J. P.; Tamagnan, G.; Huang, Y.; Carson, R. E.; Ding, Y.-S.; Morris, E. D. *Journal of Cerebral Blood Flow & Metabolism* **2013**, *33*, 532-541

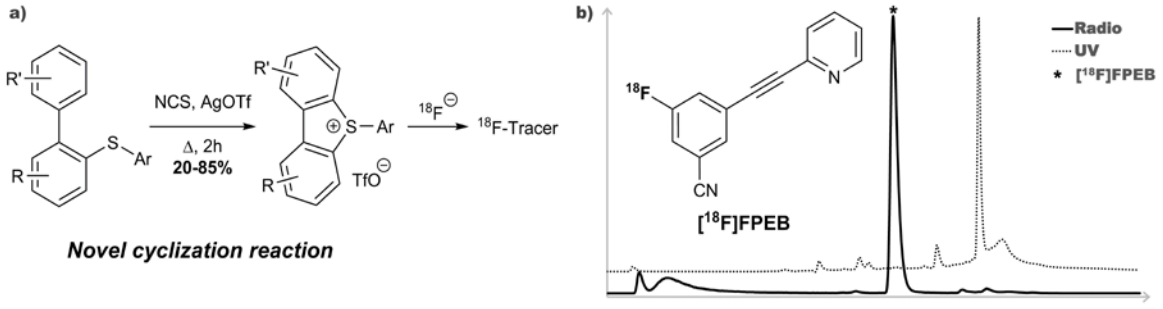

Figure 1: a) Synthesis of the dibenzothiophene sulfonium precursors by intramolecular cyclization. b) HPLC chromatogram of the crude labeling mixture of the mGluR5 tracer [^{18}F]FPEB.