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Functionalized Triarylsulfonium Salts for Aromatic [^{18}F]Fluorination of Drug-like Small Molecules

Kerstin Sander[1], Thibault Gendron[1], Elena Yiannaki[2], Klaudia Cybulska[2], Tammy L. Kalber[3], Mark Lythgoe[3], Erik Arstad[1, 2]

[1]Institute of Nuclear Medicine - Radiochemistry, University College London, London, United Kingdom, [2]Department of Chemistry, University College London, London, United Kingdom, [3]Centre for Advanced Biomedical Imaging, University College London, London, United Kingdom

Objectives Aromatic [^{18}F]fluorination of small molecule PET tracers is attractive, yet the drug-like chemical space that is accessible for labeling remains marginal [1]. In order to expand the repertoire of labeling reactions we aimed to develop a new strategy for incorporation of ^{18}F that combines broad substrate scope with high functional group tolerance, in particular to basic aliphatic moieties. We envisaged that the reaction of functionalized triarylsulfonium salts with [^{18}F]fluoride could provide a practical route to make drug-like PET tracers available for clinical applications.

Methods Functionalized triarylsulfonium salts were synthesized in one step from the respective thioethers. The effect of solvents, temperature and substitution pattern on ^{18}F-incorporation was investigated. Optimized labeling conditions were used to [^{18}F]fluorinate a novel brain PET tracer as well as a preclinical drug candidate.

Results Practical synthetic protocols were developed that allow sulfonium salts to be incorporated as leaving groups for [^{18}F]fluorination of drug-like molecules. Functionalized triarylsulfonium salts were obtained in 30–80% yield, proved to be highly stable and showed remarkable reactivity with [^{18}F]fluoride (Figure 1). Labeling of activated substrates proceeds at room temperature, and with heating the reaction occurs in the presence of unprotected alcohols and secondary amines. Furthermore, the use of electron rich spectator ligands allows regioselective [^{18}F]fluorination of non-activated aromatic moieties. Importantly, the method is fully compatible with Lewis bases, including aliphatic amines, imines and basic heterocycles, as well as other common functional groups, such as alcohols and carbonyls.

Conclusions A novel strategy for aromatic [^{18}F]fluorination using sulfonium salts as leaving groups has been developed. The method allows efficient labeling of electron neutral and electron deficient arenes in the presence of basic functional groups and heterocycles. This provides, for the first time, a broadly applicable and practical method for aromatic [^{18}F]fluorination of drug-like molecules and offers immediate benefits for applications to drug discovery and medical imaging with PET.

Acknowledgements

References [1] Brooks AF *et al*. (2014), Chem Sci, 5, 4545–4553.

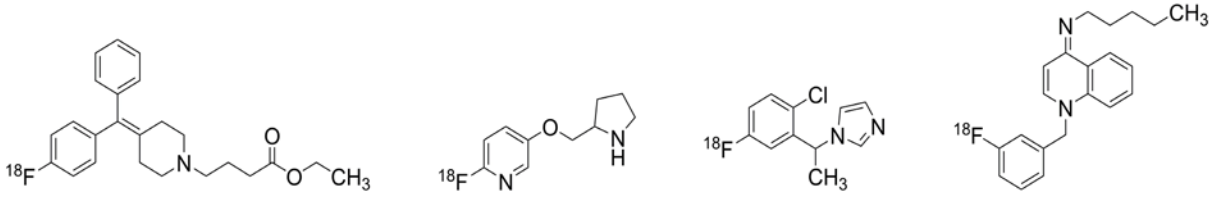

Figure 1. Drug-like molecules labelled with ^{18}F. Analytical radiochemical yields (RCY) with decay-corrected isolated RCY in brackets.