ABSTRACT

The introduction of fluorine or fluorinated functional groups has become a key strategy in agrochemical and pharmaceutical development. In peptide chemistry, fluorination has been shown to enhance metabolic stability, stabilize desired secondary structure and provide insight into biological interactions *via* ^{19}F NMR spectroscopy. Despite their promising properties, chalcogen-associated fluorinated groups remain underexplored in the peptide arena. Among these, the trifluoromethylthio (CF_3S) group has emerged as a privileged substituent due to its lipophilicity profile and strong electron-withdrawing properties.

In this study, we developed an efficient method for direct C(sp^2)–H trifluoromethylthiolation of aromatic amino acids (tryptophan, tyrosine, DOPA), as well as their biologically relevant monoamine analogs, such as serotonin, dopamine and tyramine. The developed method enabled the late-stage incorporation of the CF_3S moiety into tryptophan-containing peptides and facilitated the gram-scale synthesis of enantiopure Fmoc-protected building blocks (77–93 % yield). The latter were utilized in SPPS of model peptides and endomorphin-1 analogs. Furthermore, the local hydrophobic effect of the CF_3S group when incorporated into the peptide was investigated. A substantial increase in hydrophobic interactions was revealed, showing the potential of site-selective trifluoromethylthiolation for improving the drug-like properties of peptides. As part of this work, a library of fluorinated endomorphin-1 (EM1) analogs was synthesized, featuring various CF_3(S)-based modifications. A total of 10 ligands were evaluated *in vitro* for μ- and δ-opioid receptor binding affinity and functional activity, exhibiting comparable binding affinities (up to 1.38 nM K_i) to the parent EM1.

In the final part of the dissertation, the selective oxidation of CF_3S-amino acids to obtain corresponding trifluoromethyl sulfoxide and sulfone derivatives was investigated. The oxidized building blocks were successfully incorporated into peptides *via* SPPS, and their physico-chemical properties were analyzed. Additionally, we have developed a high-yielding synthetic route to protected perfluoro-*tert*-butyl serine analogs *via* Mitsunobu reaction.

The results presented in this doctoral dissertation advance the methodology for the incorporation of the CF_3S group and its higher oxidation congeners into amino acids and target peptides *via* SPPS or late-stage functionalization. The conducted physicochemical and biological activity studies enhance our understanding of the impact of sulfur-associated fluorinated motifs on peptide properties and pave the way for further application of emergent fluorinated functional groups in the design of peptide-based therapeutics or biomaterials.

Keywords:
amino acids, peptide chemistry, trifluoromethylthiolation, late-stage functionalization, endomorphin-1, SPPS, hydrophobicity, oxidation of sulfides, ^{19}F NMR spectroscopy.