# Trifluoromethylthiolation of Aromatic Amino Acids: Peptide late-stage functionalization, post-oxidation and local hydrophobicity modulation

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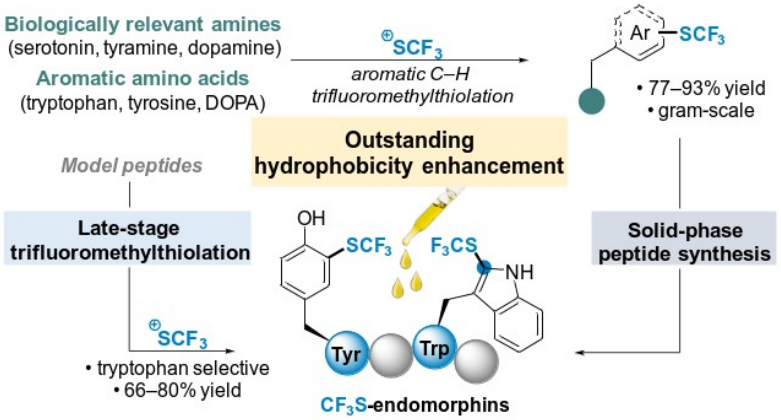
The incorporation of fluorine-containing motifs has become an integral part of medicinal chemistry in recent years.[1] Furthermore, the incorporation of fluorine atoms into peptides has been recognized as a means to improve metabolic stability, increase side-chain hydrophobicity and stabilize desired backbone conformations.[2] Due to the rapidly expanding role of peptide pharmaceuticals, the design of new tailor-made fluorinated amino acids (F-AAs) and their selective incorporation into peptides represents a privileged source of innovation.

Most known F-AAs are either monofluorinated or consist of the trifluoromethyl group.[3] However, other fluorinated groups, especially those bearing chalcogen atoms, are still largely unexplored in peptide chemistry. The trifluoromethylthio group ($CF_3S$–) is of particular interest because it has one of the highest lipophilicity parameters (Hansch–Leo parameter; $\pi$ = 1.44), a strong electron-withdrawing effect and a favorable pharmacological profile.[4] Therefore, the synthesis of trifluoromethylthiolated amino acids ($CF_3S$-AAs) and their incorporation into peptides seems to be a suitable strategy to increase their local hydrophobicity and membrane permeability and thus improve the drug profile of peptides.

We will present the method development for the preparation of new $CF_3S$-containing aromatic AA analogues such as tyrosine (Tyr) and tryptophan (Trp) and their related monoamine derivatives.[5] The methodology was then applied to the selective late-stage functionalization of Trp-containing model peptides and the ($CF_3S$)-AA building blocks were successfully used in the solid-phase peptide synthesis of neuropeptides. In addition, the oxidation of $CF_3S$-containing building blocks to their corresponding sulfoxides and sulfones will be presented.

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