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Abstract

Polyfluorinated Aromatic Porphyrin as A Photoactive Scaffold for Peptide Cyclisation †

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Abstract: Polyfluoroaromatic reagents readily react with thiols via SNAr and provide excellent templates on to which peptides can be assembled through side-chain macrocyclisation. We have previously investigated the reactivity of hexafluorobenzene (HFB) towards cysteine and related nucleophiles and we have subsequently extended these studies to fluorinated porphyrins, exploiting them as photoactive scaffolds for peptide cyclisation. We will describe how the di-substitution of tetrakis(pentafluorophenyl)porphyrin with the Skin Penetrating And Cell Entering (SPACE) peptide (ACTGSTQHQCG), presenting two cysteines in position i, i+8, successfully afforded the macrocyclised product under peptide-compatible conditions. By repeating this reaction with different peptide sequences and inter-thiol distances, we evaluate whether this chemistry is sequence-specific and we give important insights regarding the geometrical constraints of this macorcyclisation (e.g. minimal number of amino acids required to reach the para positions of adjacent meso phenyl groups). Moreover, crosslinking cysteines with tetrakis(pentafluorophenyl)porphyrin does not affect SPACE peptide uptake in skin cancer cells and the presence of the porphyrin core potentially imparts photodynamic properties to the conjugate. We anticipate that the remaining para positions are available for further conjugation and a similar methodology might also be applicable to bis(pentafluorophenyl)porphyrin. Since a growing number of APIs are protein or peptide-based, we believe that this work, together with future studies, could expand the application of peptides as therapeutic and diagnostic agents.