Synthesis and Reactivity of a Bis-Sultone Cross-Linker for Peptide Conjugation and [^{18}F]-Radiolabelling *via* Unusual "Double Click" Approach†

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A novel homobifunctional cross-linker based on a bis-sultone benzenic scaffold was synthesised. The potential utility of this bioconjugation reagent was demonstrated through the preparation of an original prosthetic group suitable for the [^{18}F]-labelling of peptides. The labelling strategy is based on the nucleophilic fluorination *via* the ring-opening of a first sultone moiety followed by the nucleophilic ring-opening of the second remanent sultone by a reactive amine of the biopolymer. Beyond the one-step radiolabelling of the peptide, the second main advantage of this strategy is the release of free sulfonic acid moieties making the separation of the targeted [^{18}F]-tagged sulfonated compound from its non-sulfonated precursor easier and thus faster. This first report of the successful use of bis-sultone moiety as a versatile bioconjugatable group was demonstrated through a comprehensive reactivity study involving various nucleophiles, especially those commonly found in biopolymers. An illustrative example, highlighting the potential of this unusual and promising "double click" conjugation approach, was devoted to the radiolabelling of a biological relevant peptide.