SOLID-PHASE SYNTHESIS OF PEPTIDES CONTAINING THIOL-MODIFIED PEPTIDE BONDS

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Combining the advantages of the thiol group in medicinal chemistry and the need for peptides and/or peptide-like structures with improved stability, bioavailability, better transport across cell membranes and selective binding, we have developed methods for the synthesis of peptides containing thiol-modified peptide bonds. In this work we describe two approaches. In the first approach, the amide bond [CO-NH] has been replaced by a thiol-modified [CH_2-S] isostere bond (thioether bond), using methods of solid-phase fragment condensation or solution fragment condensation. In the second approach, we describe the solid-phase synthesis of thiol-containing peptide-peptoid hybrids, where the amide bond [CO-NH] has been replaced by thiol containing peptoid bonds. In both replacements, suitably protected aminothiols derived from naturally occurring amino acids were used, allowing the synthesis of various thioether peptides and thiol-containing peptide-peptoid hybrids. The proposed methodologies were applied to the synthesis of small peptide-like structures containing the aforementioned thiol-modified peptide bonds, as well as to the synthesis of a thiol-containing peptide-peptoid hybrid of the N-terminal region of Hirudin [Hir (1-10)], and a Prothymosin a [ProTa (69-75)] dimer where the two ProTa monomers were linked by a thioether bond.

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