Novel Peptide Ligation Process Under Mild, Reagent-Free Conditions

Tech ID: 24535 / UC Case 2005-783-0

BRIEF DESCRIPTION

A novel peptide ligation process and compound for preparing native peptide bonds under mild, aqueous, reagent-free conditions, with water and carbon dioxide as the only byproducts.

BACKGROUND

Polypeptides are long, continuous chains of amino acid monomers linked by peptide bonds that make up proteins. Peptide ligation is the construction of large polypeptides formed by assembling two unprotected peptide segments. This concept is used to synthesize native backbone proteins or modified proteins. Chemical ligation has also enabled the systematic development of proteins that have been used as therapeutic agents. This new peptide ligation process allows scientists and researchers to construct new proteins, such as GLP-1 and other complex organic molecules.

DESCRIPTION

Researchers at the University of California have developed a novel peptide ligation process and compound for preparing native peptide bonds under mild, aqueous, reagent-free conditions, with water and carbon dioxide as the only byproducts. The reaction involves direct coupling of alpha-ketoacids and N-alkylhydroxylamines in a highly chemoselective amide bond formation process. Research has confirmed a high tolerance of this process to the presence of reactive functional groups including free amines, carboxylic acids, azides, and heterocycles. This demonstrates the potential of this reaction to serve as a peptide ligation process on both protected and unprotected substrates.

Despite the unparalleled ability of the native chemical ligation to form amide backbone bonds between two unprotected fragments, existing limitations include the challenge of forming a peptide bond with sulphur-containing functional groups or C-terminal thioesters. The incorporation of a sulphur or cysteine-containing auxiliary is commonly prohibited in the synthesis of therapeutic peptides, allowing KAHA ligation to serve as a favorable approach to the synthesis and production of therapeutics. Experiments have demonstrated couplings that produced the desired amide in 50%-99% isolated yield without epimerization. Unprotected amino acid residues do not interfere with the ligation process. The reactions are generally complete within 15 hours.

Related publications: **"Iterative, Aqueous Synthesis of 3-Oligopeptides without Coupling Reagents"** N. Carrillo, E. Davalos, J. Russak, and J. Bode

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OTHER INFORMATION

KEYWORDS

indchem, ligation, peptides, indpharma

CATEGORIZED AS

- **Biotechnology**
  - Other
- **Energy**
  - Bioenergy
- **Materials & Chemicals**
  - Other
- **Medical**
  - Therapeutics

RELATED CASES

2005-783-0

"Peptide synthesis reinvented" *www.cen-online.org*

Foreign patent rights are available in Canada and Japan.

ADVANTAGES

- High tolerance to the presence of reactive functional groups, including free amines, carboxylic acids, azides, and heterocycles
- Increases the potency and leads to the systematic development of proteins that can be used as therapeutic agents

APPLICATIONS

- synthesis of bioactive form of GLP-1 for diabetes treatment
- the construction of complex organic molecules, including synthetic proteins
- tandem ligation for complex biomolecule synthesis
- the coupling of unprotected molecules and template-directed peptide synthesis

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	7,737,293	06/15/2010	2005-783
United States Of America	Issued Patent	7,667,076	02/23/2010	2005-783

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