Modification of Peptides Using bis(thioether) ArylBridge (tAB^{TM}) Approach

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SUMMARY

Researchers in UCLA's Department of Medicine have developed a novel peptide bridging technology that is a more efficient and cost-effective alternative to stapling technology for the manufacturing of peptide therapeutics.

BACKGROUND

Stapled peptide technology utilizes chemical bonds to constrain peptides into α-helical conformations and results in an extension of potency due to increased resistance to proteases as well as greater cell permeability and bioactivity by the protein. Thus, stapled peptides have emerged as promising therapeutic candidates for treating a variety of human diseases. Numerous studies have been carried out to develop bioactive-stapled peptides. Among them, there are ring closing metathesis (RCM), azide-alkyne Huisgen cycloaddition (CuAAC), alkylation of cysteine, and lactam bridge formation. However, the RCM and CuAAC methods are very expensive and the latter two methods are generally low efficiency reactions. To address these problems, UCLA researchers have developed an alternative approach to producing stapled peptides that of very low cost and high efficiency.

INNOVATION

The novel approach developed from UCLA utilizes compounds for simultaneous S-alkylation of two strategically placed cysteine residues within the peptide, resulting in the formation of bis(thioether)-Aryl-Bridge (tAB^{TM}). The compounds necessary for this approach are both commercially available and inexpensive. The tAB^{TM} reaction can be performed both on resin and in solution. Two potential anticancer agents engineered by the tAB^{TM} approach possessed biological activity in vitro and in vivo.

APPLICATIONS

- Production of peptide-based therapeutics

ADVANTAGES

- Does not require use of expensive unusual amino acids and components; less expensive than stapling
- May be performed on a solid support and in solution using unprotected peptides
- May be performed in water-based solvents
- May be used to modify/stabilize alpha-helical and beta-hairpin peptides
- Additional versatility for modification and oligomerization of peptides

STATE OF DEVELOPMENT

Some of the tAB-developed peptides showed *in vitro* and *in vivo* bioactivity.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	9,556,229	01/31/2017	2012-754

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OTHER INFORMATION

KEYWORDS

Peptide stapling, protein therapeutics, a-helical, ß-hairpin, peptide manufacturing, S-alkylation, cysteine, peptide-based drug, thioether, protein stabilization, azide-alkyne huisgen cycloaddition, CuAAC, lactam bridge formation, cysteine, alkylation of cysteine, ring closing metathesis, RCM

CATEGORIZED AS

- **Biotechnology**
  - Other
- **Materials & Chemicals**
  - Biological
- **Medical**
  - Other
  - Therapeutics

RELATED CASES

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