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From Monomers to Dendrimers: Novel Synthetic Strategies for Highly Branched Peptide Nanostructures for Next-Generation Drug Delivery

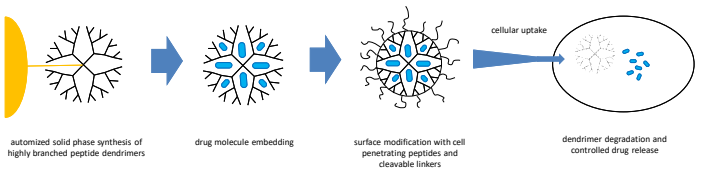
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MOTIVATION

DENDRITIC PEPTIDES ARE PROMISING DRUG DELIVERY SYSTEMS

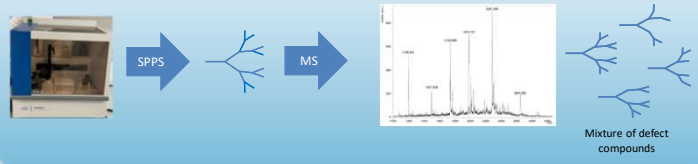
- readily available and inexpensive starting materials
- easy access through automated solid-phase peptide synthesis
- customizable structural design through selection of amino acids
- degradable into non-toxic metabolites through endogenous enzymes

PROJECT OUTLINE



CHALLENGE

Standard SPPS for peptide dendrimers bears high risk of structural defects



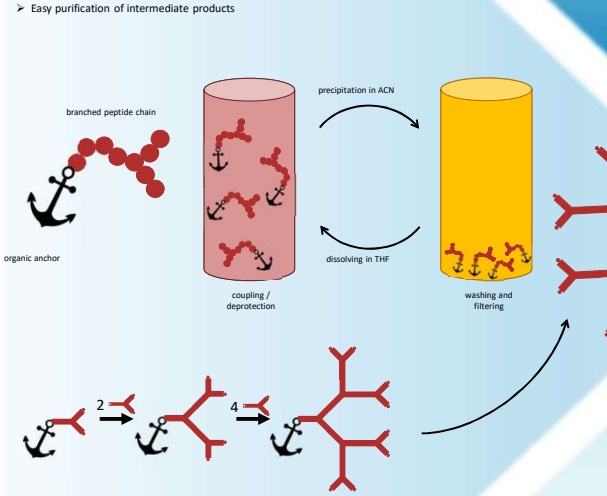
NEW APPROACH

Double-Stage Convergent Growth

- Batch Synthesis of branched Monomers in large scale
- Reduced coupling steps
- Easy purification of intermediate products

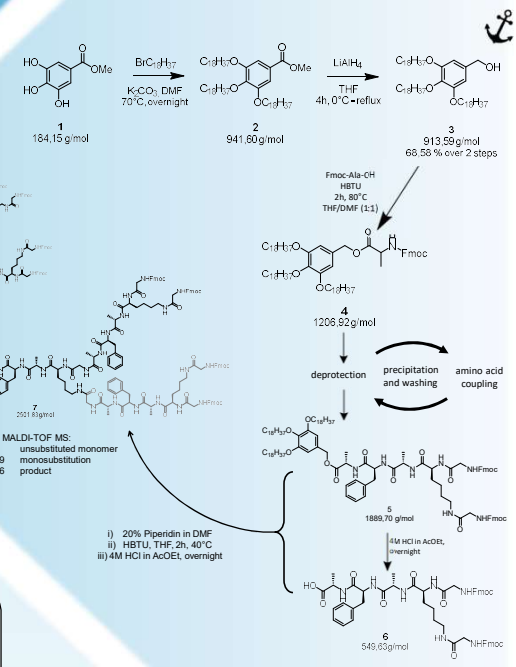
Key Findings

- 1st Generation dendrimers are built reliably
- Weakspots near branching centres
- Defect probability increased with higher degree of branching



SYNTHETIC WORK

Tag-assisted LPPS was applied for the synthesis of peptide dendrimers

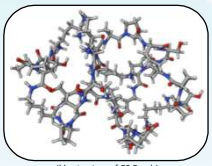


Benefits

- Less coupling steps minimize risk of structural defects
- High dilution prevents intermolecular agglomeration during coupling steps
- On-line reaction control is possible through mass spectrometry or TLC

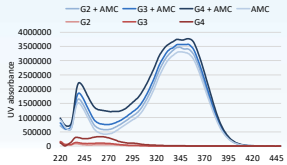
APPLICATION

Embedding of small organic molecules


possible structure of G2 Dendrimer

AMC: 7-Amino-4-methylcoumarin
G2: $((KSAP)_2KSAP)_2KSAP$
G3: $(((KSAP)_2KSAP)_2KSAP)_2KSAP$
G4: $((((KSAP)_2KSAP)_2KSAP)_2KSAP)_2KSAP$

Sample preparation:
1. 10 µmol AMC in DMF
2. 2 µmol dendrimer in EtOH
3. 1:8 dilution with water
4. Centrifugation
5. Analyze supernatant



Key Findings

- Presence of a dendrimer increases UV absorbance at 345 nm up to 13% with a 4th generation dendrimer
- UV absorbance increases with dendrimer generation

Key Findings

- Tag-assisted LPPS works for the synthesis of branched peptides.
- High temperatures promote reaction conversion.
- Still incomplete coupling ocurring.

SUMMARY

- ✓ Synthesis of branched peptide monomers through automated solid phase synthesis leads to deletions
- ✓ Double-stage Convergent Growth as an alternative method for peptide dendrimer synthesis
- ✓ Tag-assisted LPPS has been applied successfully for peptide dendrimer synthesis
- ✓ Peptide dendrimers were able to stabilize AMC in an aqueous solution

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