Solid-phase Synthesis of *N*-Substituted and Tetrazolo-Lipopeptides and Peptidosteroids by means of Aminocatalysis-Mediated Ugi Reactions

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Introduction

The application of peptides as drugs is limited due to their low oral absorption and metabolic stability, rapid excretion through the kidneys and liver, high immunogenicity and low hemolytic activity. Peptide as Cm-p5 (SRSELIVHQRLP), MIC (Candida albicans)= $3,4*10^{-7}$ mol/L, can hardly be therapeutically applied because of its easy proteolytic degradation. One strategy to reduce these drawbacks is the introduction of covalent modifications. For example, the N-substitution is one type of covalent modification that makes the peptides more resistant to proteases, and therefore more metabolically stable. The Ugi reaction can access this type of structural and funtional variety in a single reaction step.

Methods

The peptides were synthesized on solid phase using the Fmoc/tBu chemistry.

HPLC Conditions

- ✓ Buffer A: 0,1 TFA/H2O,
- ✓ Buffer B: 0,05 % TFA/CH_3CN
- ✓ Gradient: 5-60 % of Buffer B during 35 min.
- ✓ λ=226 nm. Flow:0,8 mL/min

Results

The new multicomponent methodology for the solid-phase synthesis of peptide *N*-substituted with lipid chains and steroid skeleton at different positions of the peptide backbone consists in the insertion of *n*-dodecylisocyanide and methyl 3-isocyanolithocolanoate in residues sensitive to endo and exo-peptidase proteolytic degradation, (i.e., arginine, histidine and the *N*- and *C*-termini) of the antifungal peptide Cm-p5 (Fig. 1). To implement the Ugi-4C and Ugi-4C-tetrazol reactions in solid phase, we developed a new multicomponent protocol comprising the aminocatalytic formation of the imine followed by reaction with acids and isocyanides.

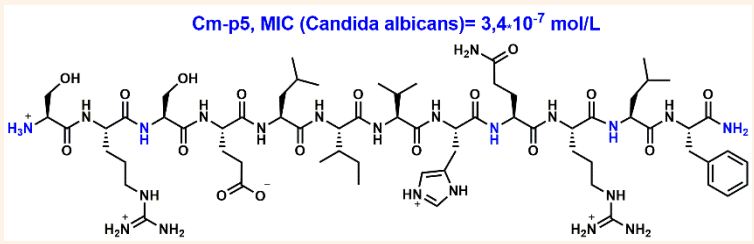
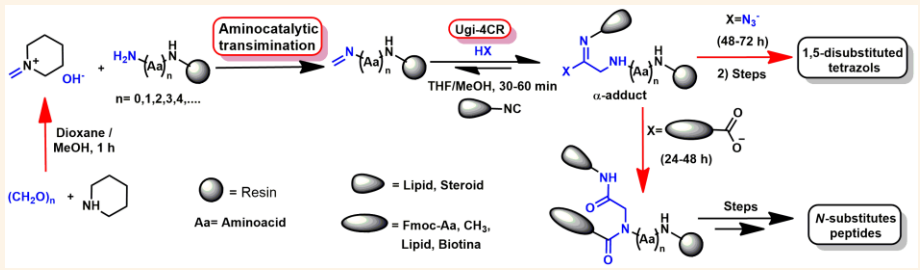


Fig. 1: Cm-p5 structure and activity



Scheme 1. Solid-phase synthesis of *N*-substituted peptides by means of aminocatalysis-mediated Ugi reaction.

The analitical and structural caracterization of the sinthetized compouds was performed by HPLC and ESI-MS (Fig. 1)

Acidic components may vary from acetic acid to Fmoc-amino acids, biotin, palmitic acid and hidrazoic acid, enabling the access to either *N*-substituted peptides or 1,5-disubstituted tetrazol, respectively obteniendose 12 new compound efficiently.

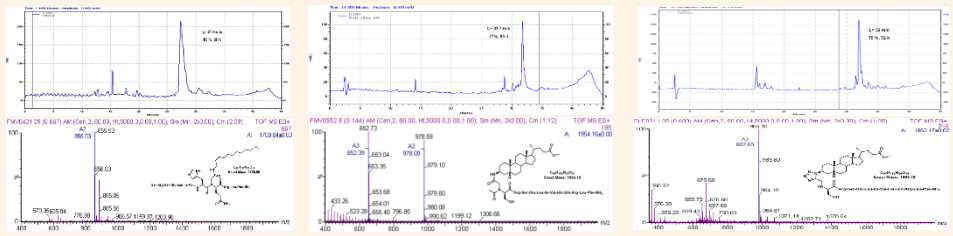
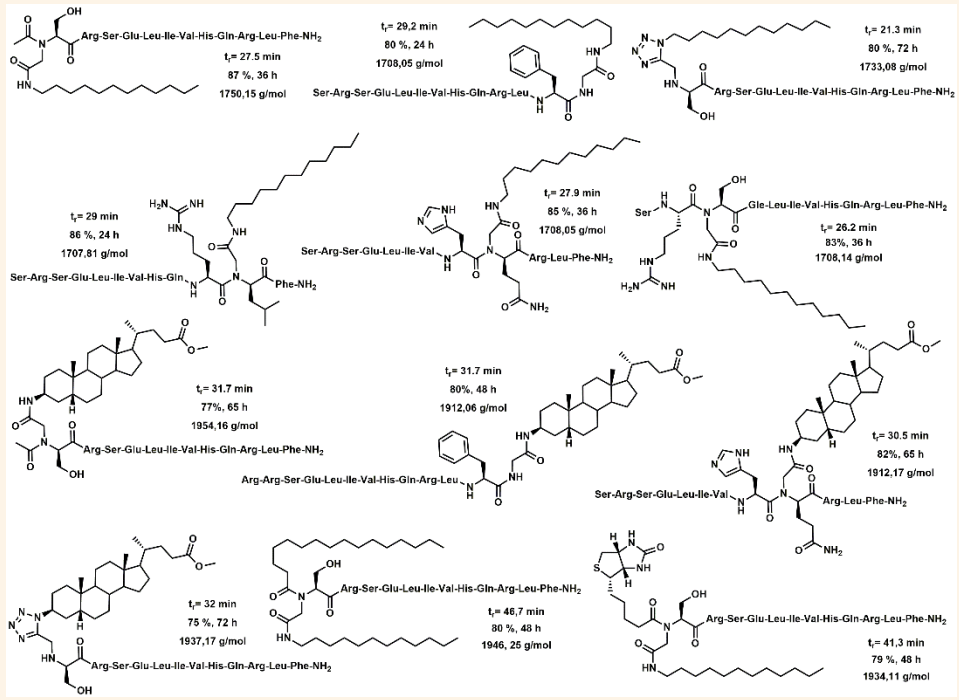


Fig. 1: HPLC and ESI-MS caracterization of some compounds



Scheme 2. *N*—Substituted and tetrazolo-lipopeptides and peptidosteroids structures synthethised by Ugi-4CR.

Conclusions

This methodology allows for the modification of peptides with steroids, lipids and biotin, while simultaneously enabling either the *N*-alkylation or heterocycle incorporation in one synthetic step. Such modifications confer the peptide greater hydrophobicity and metabolic stability, and can be used to modulate the biological applications of relevant peptide sequences.

References

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