CARBOGEN AMCIS
A Dishman Group Company

case study:

FIRST INDUSTRIAL (TOTAL) SYNTHESIS OF AMANITIN DERIVATIVES

by CARBOGEN AMCIS

in partnership with

Heidelberg PHARMA
Focused Cancer Therapies

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FIRST INDUSTRIAL (TOTAL) SYNTHESIS OF AMANITIN DERIVATIVES BY CARBOGEN AMCIS

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Senior Manager PR&D at CARBOGEN AMCIS

In this full case study, you'll find valuable insights into the synthesis approach and potential ADC applications. Specifically, the case study covers:

- A brief overview of the first total industrial synthesis of Amanitin derivatives entering Phase I & II clinical trials.
- Insights into the unique properties and structural challenges of the molecule.
- A detailed synthetic analysis of the approach and chemistry involved.
- Information on the successful collaboration and contributions from various sites within our organization.

It's perfect for biotech and pharma companies that would like to:

1 **Learn from an innovative synthesis:** Discover the first (total) industrial synthesis of Amanitin derivatives, offering insights into handling complex molecules and advancing them to clinical trials.

2 **Gain a competitive edge:** Understand the strategies that accelerated this novel compound to Phase I & II trials.

3 **Optimize production:** Get a detailed analysis of the synthetic approach and chemistry, which could enhance your own drug manufacturing processes.

4 **Leverage collaborative success:** See how effective collaboration across multiple sites can streamline drug development.

5 **Explore ADC applications:** Amanitin's potential in ADCs offers valuable knowledge for those working in this growing field.

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September 2024, University of Fribourg - SCS Fall Meeting – Emad El Sayed

At CARBOGEN AMCIS, we recently had the successful implementation of the first industrial (total) synthesis of Amanitin derivatives, a significant milestone in pharmaceutical manufacturing. This innovative project marks a leap forward as we advance into Phase I & II clinical trials.

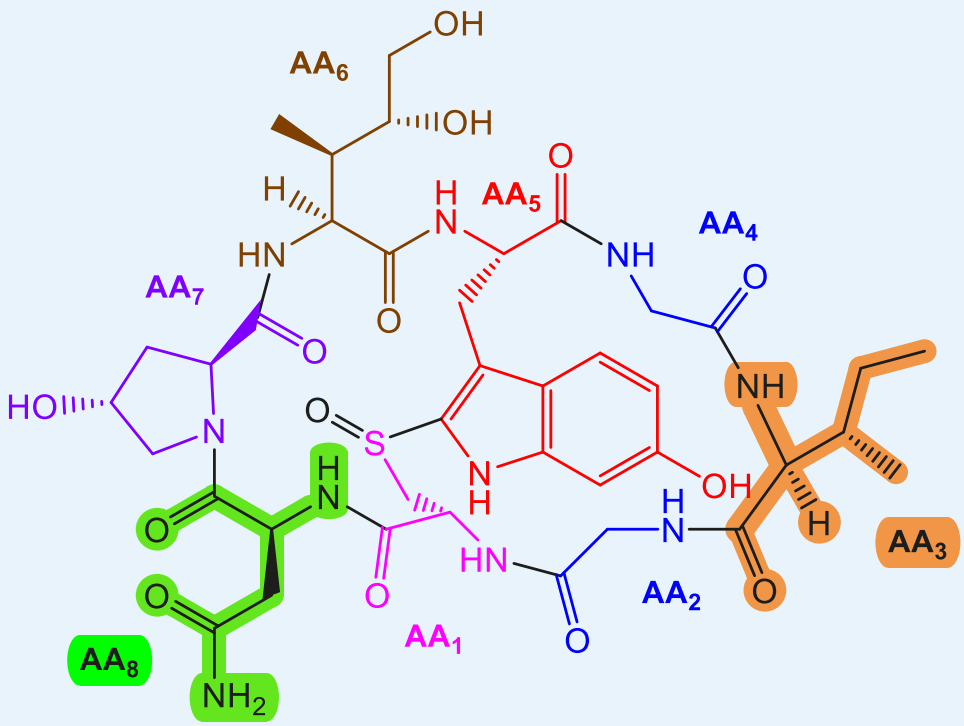
Key Highlights

- Amanitin is a highly potent toxin derived from the death cap mushroom (Amanita phalloides), with its unique structure and biological properties making it an ideal candidate for drug development.

Amanitin Structural Features

- Alpha-Amanitin: A bicyclic octapeptide with two oxidized amino acids (AA6 and AA7) that contribute to its toxicity. Amanitin acts as a highly selective allosteric inhibitor of RNA polymerase II (Pol II), making it particularly potent.

Alpha-Amanitin: A bicyclic octapeptide



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The unique properties and structural challenges of the molecule

- The cross-link 6-hydroxy-trptathionine-(R)-sulfoxide is a unique structure among natural products

Retrosynthetic analysis of the approach and chemistry

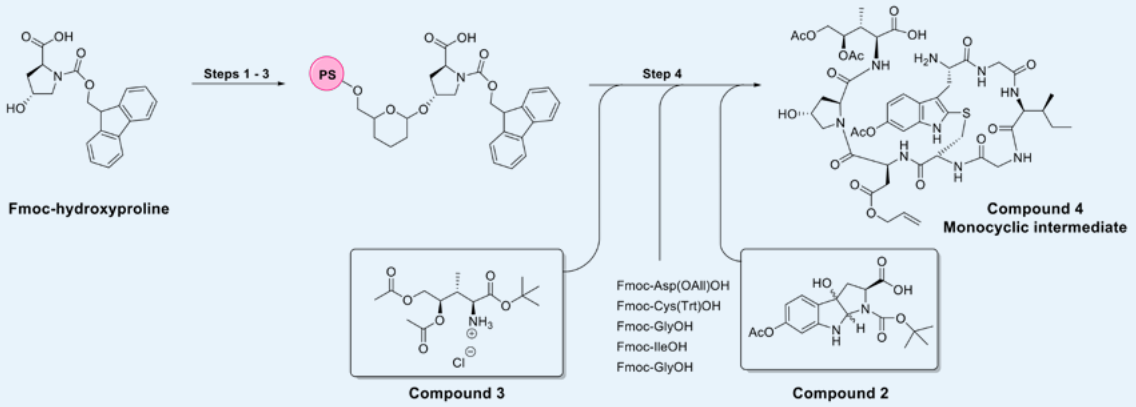
- Retrosynthetic analysis reveals the macrolactonization step (AA5-AA6) among the last steps of the synthesis.
- In addition, the Savige-Fontana cyclization is the key step for the formation of the cross-linked moiety.
- Besides the 5 protected amino acid derivatives used for the synthesis, it is clear that two advanced building blocks are also necessary to complete the structural integrity of the molecule.

Collaboration and Innovation

- This project was made possible through collaborative efforts across multiple CARBOGEN AMCIS sites and in partnership with Heidelberg Pharma.
- By combining expertise across chemistry, manufacturing, and research, we have pushed the boundaries of industrial synthesis for complex natural products.

Synthesis of Compound 4

Manufatured in Aarau site | Erik Lauterbach, Janos Kovacs



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Application in Antibody-Drug Conjugates (ADCs)

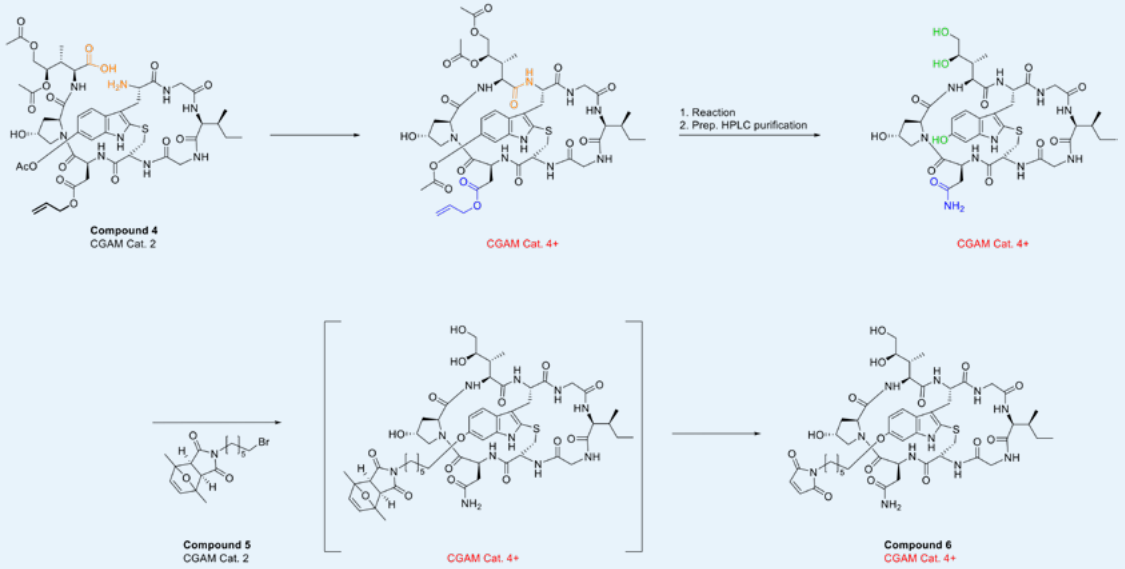
- Amanitin derivatives are being explored as payloads for Antibody-Drug Conjugates (ADCs), offering high toxicity and precise tumor targeting. This approach holds potential to increase the therapeutic index, minimizing side effects and improving the effectiveness of cancer treatments.

ADC Payload Example:

- ADC Payload: The compound synthesized (Compound 6) is manufactured at the Bubendorf site, designed for ADC conjugation using linkers developed at CARBOGEN AMCIS. This technology is key to achieving targeted tumor delivery with minimal systemic toxicity.

Synthesis of Compound 6

Manufactured in Bubendorf site | Simon Ruppenthal, Bick Vivant



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Looking Ahead

CARBOGEN AMCIS continues to innovate, focusing on the development of next-generation linker technologies for ADCs, paving the way for future advancements in precision oncology therapies.

Do you have any projects you think CARBOGEN AMCIS could help you with?

Contact us now: sales@carbogen-amcis.com