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An arylamine-diazotizing enzyme catalyses N-N bond formation in the biosynthesis of tasikamides

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PURPOSE OF THE ABSTRACT
An arylamine-diazotizing enzyme catalyses N-N bond formation in the biosynthesis of tasikamides

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Abstract

We discovered a family of novel cyclic peptides (tasikamides) that share a unique cyclic pentapeptide scaffold. Tasikamides A?C (1?3) contain a rare hydrazone group (C?N?N) that connects the cyclic peptide scaffold to an alkyl 5-hydroxylanthranilate (AHA) moiety. We found that the biosynthesis of 1?3 requires two biosynthetic gene clusters with one encoding a nonribosomal peptide synthetase (NRPS) pathway for assembling the cyclic peptide scaffold and another encoding the AHA-synthesizing pathway. The AHA gene cluster encodes three ancillary enzymes (Aha1, 2 and 11) that catalyse the diazotization of AHA to yield an aryl diazonium species (diazo-AHA), which undergoes Japp?Klingemann coupling with a cyclic peptide precursor to furnish the hydrazone group and yield 1?3. In vitro enzymatic assays suggest the N?N bond in the hydrazone group of 1?3 is forged via a HNO2-mediated mechanism, with Aha1 and Aha2 producing NO2?/HNO2 and Aha11 catalysing the diazotization of AHA to generate the reactive diazo-AHA. The findings raise the prospect of exploiting the arylamine-diazotizing enzymes for the in vivo synthesis of aryl compounds and modification of biological macromolecules.

References:
1. Biosynthesis of Tasikamides via Pathway Coupling and Diazonium-Mediated Hydrazone Formation, Ma, GL., Candra, H., Pang, LM, Xiong, J., Ding, Y., Tran, HT., Low, ZJ., Ye, H., Liu, M., Zheng, J., Fang, M., Cao, B., Liang, Z.-X. Journal of the American Chemical Society, 2022, 144, 4, 1622?1633.
2. Enaminone formation drives the coupling of biosynthetic pathways to generate cyclic lipopeptides, Candra, H., Ma, GL., En, SLQ, Liang, Z.-X., ChemBioChem 2022, 23 (22), e202200457.

FIGURES

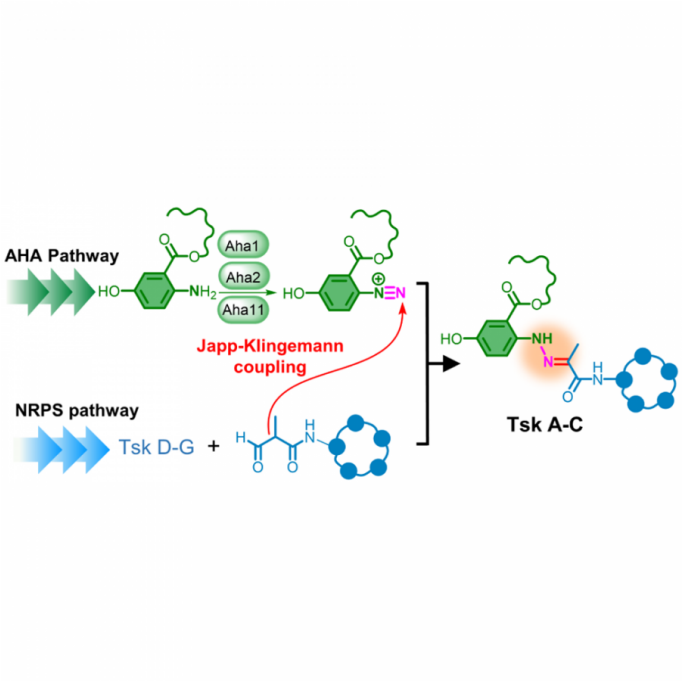

FIGURE 1

Diazonium-mediated hydrazone formation in biosynthesis

The AHA gene cluster encodes three enzymes (Aha1, 2 and 11) that catalyse the diazotization of AHA to yield an aryl diazonium species (diazo-AHA), which undergoes Japp–Klingemann coupling with a cyclic peptide precursor to furnish the hydrazone group and

FIGURE 2

KEYWORDS

Diazonium | cyclic peptide | biosynthesis | pathway coupling

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