

METHODS TO GENERATE NOVEL ACYL-TRNA SPECIES

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PATENT STATUS

Country	Type	Number	Dated	Case
Patent Cooperation Treaty	Reference for National Filings	WO/2023/164676	08/31/2023	2022-095

Patent Pending

BRIEF DESCRIPTION

The inventors have discovered PylRS enzymes that accept -thio acids, N-formyl-L-amino acids, and diverse -carboxyl acid monomers (malonic acids) that are formally precursors to polyketide natural products. These monomers are all accommodated and accepted by the translation apparatus in vitro. High-resolution structural analysis of the complex between one such PylRS enzyme and a meta-substituted 2-benzylmalonate derivative reveals an active site that discriminates pro-chiral carboxylates and accommodates the large size and distinct electrostatics of an -carboxyl acid substituent.

This discovery emphasizes the potential of PylRS for evolving new enzymes capable of encoding diverse non-L-amino acids in synergy with natural or evolved ribosomes. The absence of orthogonal aminoacyl-tRNA synthetase enzymes that accept non-L-amino acids is the primary bottleneck hindering the in vivo translation of sequence-defined hetero-oligomers.

SUGGESTED USES

These enzymes could be used to develop keto-peptide hybrid molecules that are privileged scaffolds for drug design.

ADVANTAGES

Towards the goal of charging tRNAs with non-L- α -amino acid monomers, PylRS enzymes have advantages of MjTyrRS in how they recognize the α -amine of their substrate.

RELATED MATERIALS

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

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OTHER INFORMATION

KEYWORDS

enzymes, in vivo

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