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TOPIC(s) : Biocatalytic cascade reactions / (Chemo)enzymatic strategies

Methyltransferase Cascade Reactions for the Benzylation of mRNA at the 5'-Cap

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PURPOSE OF THE ABSTRACT

Methyltransferases (MTases) provide excellent specificity in late-stage alkylation of biomolecules. Their dependence on S-adenosyl-L-methionine (SAM) mandates efficient access to SAM analogues for biocatalytic applications. We recently engineered a methionine adenosyltransferase (MAT) from *Methanocaldococcus jannaschii* to access SAM analogues with benzylic moieties. Here we explore their utility in MAT/MTase cascade reactions with NovO for regioselective benzylation of a coumarin substrate. Further, we apply the cascade for post-synthetic modification of mRNA at the 5' cap. In the case of the 4-chlorobenzyl group, protein production increased by 28 % in HeLa and 39-50 % in HEK cell lines compared to mRNA with a regular 5' cap, underlining the potential to improve mRNA based therapeutics.

FIGURES

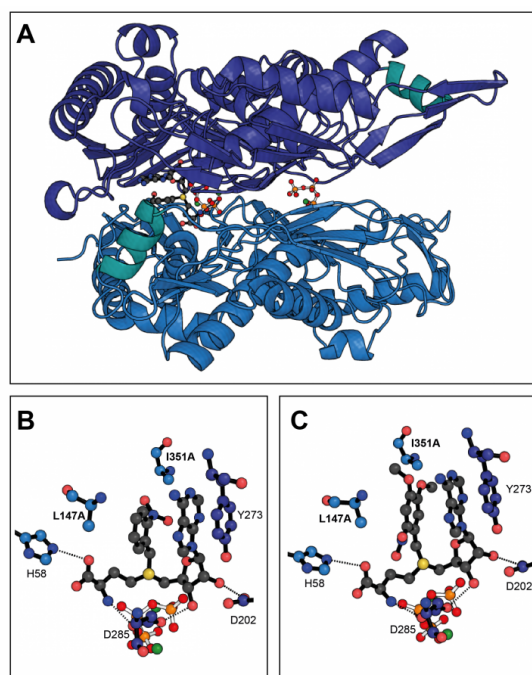


FIGURE 1

MjMAT L147A/I351A (PC-MjMAT)

Crystal structure of PC-MjMAT. A) The homodimeric structure (blue, dark blue) forms two active sites buried behind a "gating loop" (green) (PDB: 7P84). B) The active site with AdoONB. C) The active site with AdoDMNB (PDB: 7P8M).

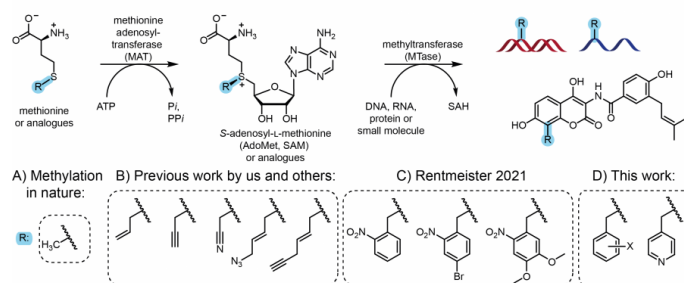


FIGURE 2

MAT/MTase cascade reaction

A) methylation in nature and application for site-specific B) alkylation, C) photocaging and D) (hetero-) benzylation.

KEYWORDS

Methyltransferase | S-adenosyl-L-methionine | SAM analogues | Methionine adenosyltransferase

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