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Recycling Non-natural Cofactors for Selective Alkylation by Methyltransferases

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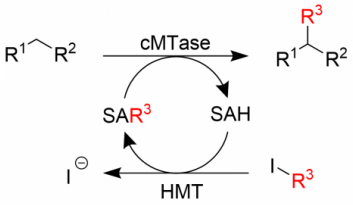
PURPOSE OF THE ABSTRACT
Carbon-carbon (C-C) bonds form the backbone of almost all organic molecules used in our society. The synthesis of those bonds, especially when introducing chiral centres, is often associated with non-selective and wasteful chemical processes. Enzymes are the key to alternative synthetic routes, as they catalyze reactions under mild conditions and with high selectivity. Carbon methyltransferases (cMTases) catalyze C-C bond formation via a methyl transfer, using the cofactor S-adenosyl methionine (SAM) as alkyl donor. Besides methyl groups, larger alkyl groups are also accepted by some cMTases [1]. The challenge for these alkylation reactions is their cofactor requirement. Non-natural SAM analogues (SAR) are needed to supply the cMTase with the desired alkyl group. The difficult chemical synthesis of SARs combined with their stoichiometric use, limits the application of cMTases.

Previous research indicated that halide methyltransferases (HMTs) can alkylate the cofactor S-adenosylhomocysteine (SAH) using small alkyl iodides as alkyl donor [2-4]. In this research, we explore the capacity of HMTs to alkylate the SAH cofactor with larger alkyl substituents to form SARs (Figure 1). We used a computational approach to design HMT mutants that could accept larger alkyl substituents. Experimental results on the screening of designed mutants will be discussed. The SAR recycling system can subsequently be combined with cMTases to selectively introduce alkyl substituents to targeted substrates.

FIGURES



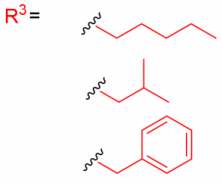


FIGURE 1

Figure 1.

Targeted selective C-C bond formation by cMTases via the transfer of large alkyl groups. This reaction is enabled by the formation of the SAR cofactor by an HMT using alkyl iodides as alkyl donor.

FIGURE 2

KEYWORDS

alkylation | methyltransferases | SAM cofactor

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