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# Selective methylations and alkylations using methyltransferases

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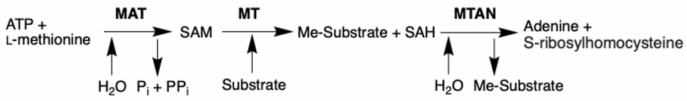
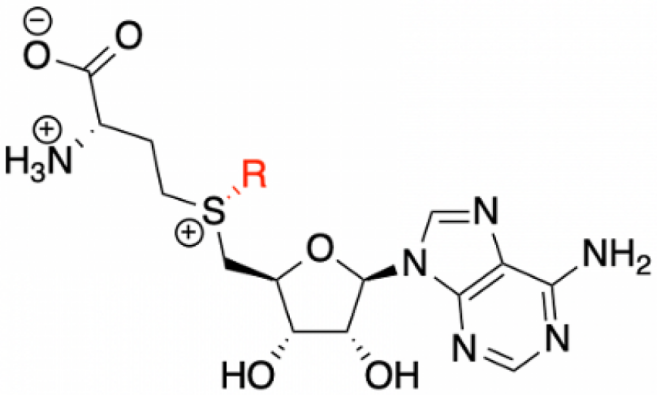
## PURPOSE OF THE ABSTRACT

Research into the utilisation of methyltransferase enzymes to perform selective methylations and alkylations in chemical synthesis is rapidly gaining momentum, in part due to the stringent substrate stereoselectivities and regioselectivities these biological catalysts offer [1]. In addition, these methyltransferases operate under mild conditions and avoid the use of toxic chemical reagents, such as methyl iodide and dimethyl sulfate [2,3,4], that would otherwise be used in equivalent traditional synthetic methods [5]. Therefore, there is a significant green chemistry component to this field of research.

A range of S-adenosylmethionine (SAM)-dependent methyltransferases are being explored to assess their ability to selectively methylate an array of valuable small molecule substrates of pharmaceutical relevance, given the impressive enhancements in bioactivity of drugs commonly observed post-methylation, known as the "magic methyl effect" [5]. Furthermore, an enlargement of the scope of non-methyl alkyl groups that these enzymes can transfer to substrates is being investigated, to probe the further expansion of chemical space in a selective manner. This is being carried out by the generation of SAM analogues that have their methyl group substituted for various alkyl moieties. Importantly, alkylations are performed in the context of a multi-enzyme in vitro SAM generation cascade that is necessary to ensure a continuous and immediate supply of SAM and its analogues [6], which are relatively unstable molecules and expensive to procure. This cascade also ensures the efficient removal of the methyltransferase inhibitor S-adenosylhomocysteine (SAH) generated by SAM mediated alkylations [7,8]. Furthermore, the properties of the methyltransferases and the accessory enzymes in the SAM generation cascades associated with them are being enhanced by directed evolution to improve activities, substrate selectivities and tolerance towards SAM analogues.

## FIGURES




### FIGURE 1

Multi-enzyme Cascades

The scheme for the MAT-MT-MTAN bioalkylation cascade. MAT = Methionine adenosyltransferase, MT = Methyltransferase, MTAN = Methylthioadenosine nucleosidase, SAH = S-adenosylhomocysteine.

### FIGURE 2

SAM Analogues

The SAM analogue molecular structure. Methyltransferases catalyse the transfer of the R-group (highlighted red) to various substrates, with R representing various alkyl groups.


## KEYWORDS

Methyltransferases | Bioalkylations | Green Chemistry | Directed Evolution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