BIOTRANS
LA ROCHELLE 2023

N°612 / PC
TOPIC(s) : Enzyme discovery and engineering / Biocatalytic cascade reactions

Substrate Profiling of Anion Methyltransferases for Promiscuous Synthesis of S-Adenosylmethionine Analogs from Haloalkanes

AUTHORS

Kai SCHÜLKE / UNIVERSITÄT BIELEFELD, UNIVERSITÄTSTR. 25, BIELEFELD
Stephan HAMMER / UNIVERSITÄT BIELEFELD, UNIVERSITÄTSTR. 25, BIELEFELD

PURPOSE OF THE ABSTRACT

Biocatalytic alkylation reactions can be performed with high chemo-, regio- and stereoselectivity using S-adenosyl-L-methionine (SAM)-dependent methyltransferases (MTs) and SAM analogs.[1–3] Currently, however, this methodology is limited in application due to the rather laborious protocols to access SAM analogs. It has recently been shown that halide methyltransferases (HMTs) enable synthesis and recycling of SAM and its analogs from S-adenosyl-L-homocysteine (SAH) and readily available haloalkanes as starting material.[4–6] We further expanded this work by using substrate profiling of the anion MT enzyme family to explore promiscuous SAM analog synthesis.[7] Our study shows that anion MTs are in general very promiscuous with respect to the alkyl chain as well as the halide leaving group. Substrate profiling further suggests that promiscuous anion MTs cluster in sequence space. Next to iodoalkanes, cheaper, less toxic, and more available bromoalkanes have been converted and several haloalkanes bearing short alkyl groups, alkyl rings, and functional groups such as alkene, alkyne and aromatic moieties are accepted as substrates. Further, we applied these SAM analogs as electrophiles in highly selective C-N and C-C bond formations with N-heteroarens and coumarins.[8,9]

FIGURES

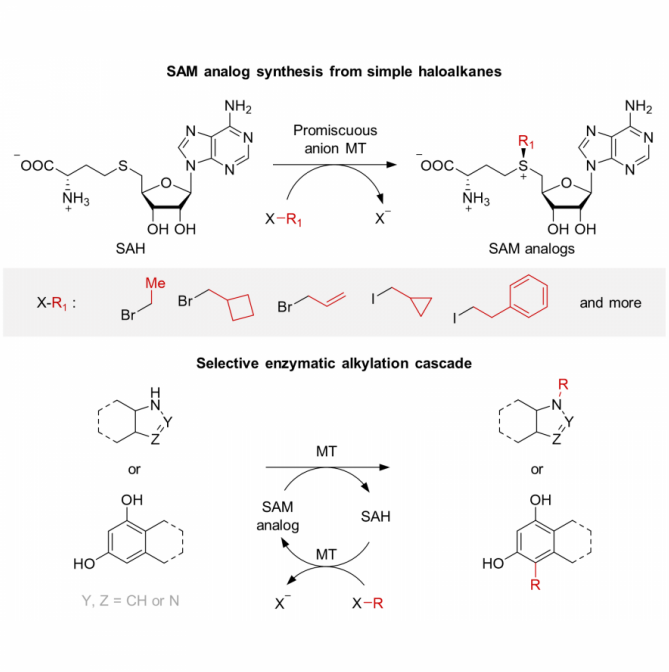

FIGURE 1

Enzymatic regeneration of SAM analogs via anion MT mediated alkylation of SAH with haloalkanes.
SAM analogs used as electrophiles in MTs catalyzed alkylation cascades.

FIGURE 2

KEYWORDS

Methyltransferases | Biocatalysis | Cascade | Cosubstrate Analogs

BIBLIOGRAPHY

1. I. J. W. McKean, P. A. Hoskisson, G. A. Burley, ChemBioChem 2020, 21, 2890-2897.
2. T. D. Huber, B. R. Johnson, J. Zhang, J. S. Thorson, Curr. Opin. Biotechnol. 2016, 42, 189-197.
3. F. Ospina, K. H. Schülke, S. C. Hammer, ChemPlusChem 2022, 87, e202100454.
4. C. Liao, F. P. Seebeck, Nat. Catal. 2019, 2, 696-701.
5. L. L. Bengel, B. Aberle, A. Egler□Kemmerer, S. Kienzle, B. Hauer, S. C. Hammer, Angew. Chem. Int. Ed. 2021, 60, 5554-5560.
6. Q. Tang, C. W. Grathwol, A. S. Aslan□Üzel, S. Wu, A. Link, I. V. Pavlidis, C. P. S. Badenhorst, U. T. Bornscheuer, Angew. Chem. Int. Ed. 2021, 60, 1524-1527.
7. K. H. Schülke, F. Ospina, K. Hörnschemeyer, S. Gergel, S. C. Hammer, ChemBioChem 2022, 23, e202100632.
8. F. Ospina, K. H. Schülke, J. Soler, A. Klein, B. Prosenc, M. Garcia-Borràs, S. C. Hammer, Angew. Chem. Int. Ed. 2022, 61, e202213056.
9. A. Hoffmann, K. H. Schulke, S. Hammer, A. Rentmeister, N. Cornelissen, Chem. Commun. 2023, DOI 10.1039/D3CC01036H.