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Application of the C3-Methyltransferase StspM1 as Catalyst for the Formation of the Pyrroloindole motive in Natural Product Synthesis

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PURPOSE OF THE ABSTRACT

The "Magic Methyl Effect" is a well-known phenomenon in medicinal chemistry, which describes that selective methylation of potential active drugs can boost their biological activity [1]. Using conventional chemical methods, methylation is still challenging regarding regio- and stereoselectivity [2]. In this context, the development of a suitable methylation method is an important task to produce active substances selectively and effectively. Having a look into nature, methyltransferases are used for methylation and to create interesting frameworks in a stereoselective manner [3].

In this work, the methyltransferase StspM1 is used for the diastereoselective methylation of diketopiperazines to form the pyrroloindole structural motive, which is widely present in different natural products like physostigmine, nocardioazine B and lansai B [4,5,6]. Besides the experimentally analyses of the substrate acceptance, the protein 3D structure was modelled and the binding mode of different DKP substrates and methylated products was predicted leading to interesting insides of the substrate binding and conversion within the binding pocket. For the synthetic utility of the methyltransferase, a cofactor recycling of SAM [7] was successfully implemented and the reaction conditions were optimized via a design of experiment approach. With this new established protocol, enzymatic methylation is feasible in a preparative scale with very good yields.

FIGURES

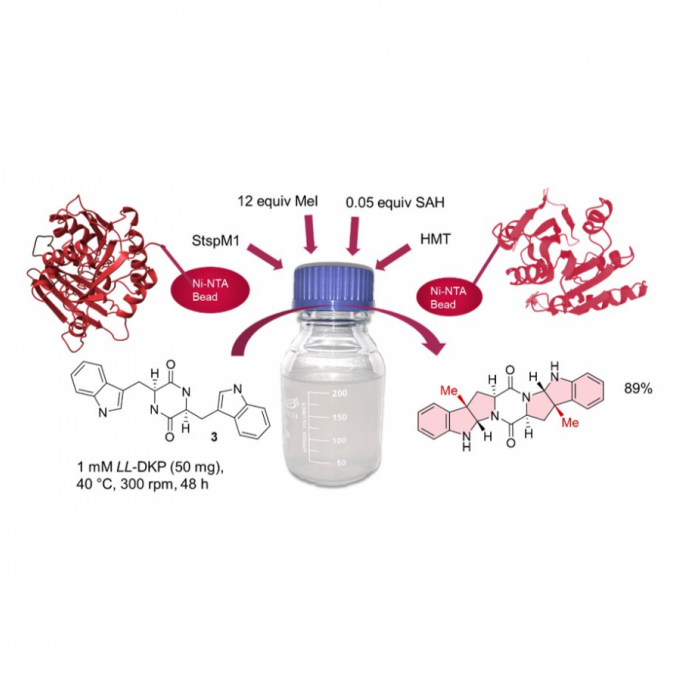

FIGURE 1

Biocatalytic methylation of LL-DKP

Application of StspM1 (immobilized) in preparative scale using a recycling system with the halide methyltransferase (HMT) and S-adenosyl homocysteine (SAH) to methylate the substrate diketopiperazine (LL-DKP).

FIGURE 2

KEYWORDS

Methylation | Indole | Preparative biocatalytic reaction

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