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Mirror, mirror on the wall: Application of an N-methyltransferase for preparative scale enzymatic kinetic resolution

AUTHORS

Benjamin CHAPPLE / INSTITUTE FOR BIOORGANIC CHEMISTRY, HEINRICH HEINE UNIVERSITY DÜSSELDORF, IN FORSCHUNGSZENTRUM JÜLICH, JÜLICH
Pascal SCHNEIDER / INSTITUTE FOR BIOORGANIC CHEMISTRY, HEINRICH HEINE UNIVERSITY DÜSSELDORF, IN FORSCHUNGSZENTRUM JÜLICH, JÜLICH
Mona HAASE / INSTITUTE FOR BIOORGANIC CHEMISTRY, HEINRICH HEINE UNIVERSITY DÜSSELDORF, IN FORSCHUNGSZENTRUM JÜLICH, JÜLICH
Jörg PIETRUSZKA / INSTITUTE FOR BIOORGANIC CHEMISTRY, HEINRICH HEINE UNIVERSITY DÜSSELDORF, IN FORSCHUNGSZENTRUM JÜLICH, JÜLICH

PURPOSE OF THE ABSTRACT

The attachment of a single methyl group can increase the potency of a pharmaceutical by up to three orders of magnitude – primarily due to conformational “gridlocking” – making the “magic methyl” effect intensely sought after. However, chemical methylation often lacks the selectivity needed to generate compounds of interest, underlining the need for new methylation methods. [1,2] Over the past years, methyltransferases have been making their way into the organic chemist's toolbox, offering high selectivity under benign reaction conditions. [3–7] Their practical use has been, e.g., exemplified in the enantiopure generation of various physostigmine analogues, [8,9] which bear the pyrroloindoline scaffold, a motif found in numerous naturally occurring alkaloids with similarly numerous biological activities. [10,11]

Being able to access both enantiomers of pyrroloindolines would be of additional use, as some enantiomeric drug pairs do not only differ in efficacy but may also have different targets and mechanisms of action. [12] In this work, we have characterised and applied an N-methyltransferase for the first time in a kinetic resolution of pyrroloindolines, in accord with the implementation of a supply system for the cofactor S-adenosyl methionine. Using two easily obtainable catalyst formulations, the enzymatic reaction can be performed on a preparative scale. The system can potentially be used for the selective chemoenzymatic access to the enantiomeric pair (+)-Posiphen and (-)-Phenserine, two synthetic pyrroloindolines of medical importance [13,14] and with separate biological targets and distinct mechanisms of action. [12]

FIGURES

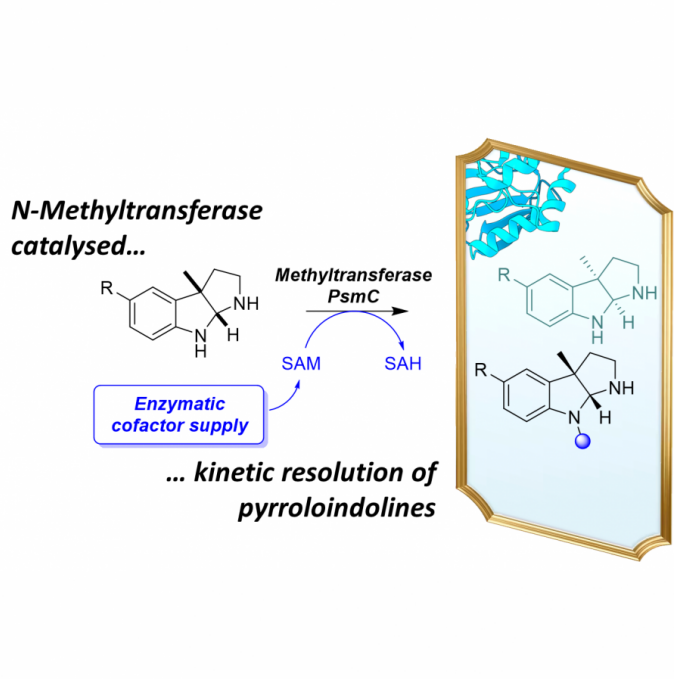

FIGURE 1

Enzymatic kinetic resolution by PsmC

The N-methyltransferase PsmC can be used for preparative scale enzymatic kinetic resolution of pyrroloindoles. SAM: S-adenosyl methionine; SAH: S-adenosyl homocysteine.

FIGURE 2

KEYWORDS

biocatalysis | methylation | kinetic resolution | pyrroloindolines

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