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Sulfurtransferases as molecular platforms to form C-SH bonds

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PURPOSE OF THE ABSTRACT

The formation of C-S bonds is of utmost importance in material sciences or medicinal chemistry, with for instance approximatively 20% of the approved FDA drugs containing sulfur atoms. While various chemical methods have been developed over the years, essentially based on the nucleophilicity of thiols, a great deal of effort is nowadays directed towards the development of milder and greener methods. Because a versatile methodology allowing for the direct synthesis of thiols from C-H bonds is still lacking, an alternative to the chemical approaches is the growing use of enzymes as biocatalysts. In this context, our project proposes to use sulfurtransferases (STs) as molecular platforms for the challenging formation of C-SH bond by sulfur atom transfer. Indeed, STs, which belong to the rhodanese-fold family, generate a persulfide intermediate on the catalytic cysteine residue in the presence of a suitable donor and the electrophilic distal sulfur atom can then be transferred to various nucleophilic acceptors. Thus, one key challenge relies on the substrate specificity of STs, i.e. on the capacity of nucleophilic compounds to reach their target. However, available structural data indicate that the active sites of some STs are quite solvent exposed therefore supporting the idea that persulfides could react with various nucleophile provided a minimal accessibility. Several STs of various origins were tested for their ability to accommodate unnatural substrates. An original kinetic method based on the fluorescence properties of an unnatural donor substrate was developed. This method was used to screen various STs / model acceptor substrates and the results show that both linear and cyclic acceptor substrates react, at least, with the persulfide intermediate of bacterial STs. Regarding the development of new ecofriendly reactional schemes for C-S bond formation using STs to deliver an activated sulfur atom to various nucleophilic molecules, the proof of concept has been established.with model substrates.

FIGURES

FIGURE 1

FIGURE 2

KEYWORDS

Sulfurtransferases | biocatalytic platforms | C-SH bonds | cysteine persulfide

BIBLIOGRAPHY