BROADENING THE SUBSTRATE SCOPE OF STRICTOSIDINE SYNTHASES BY SITE-DIRECTED MUTAGENESIS

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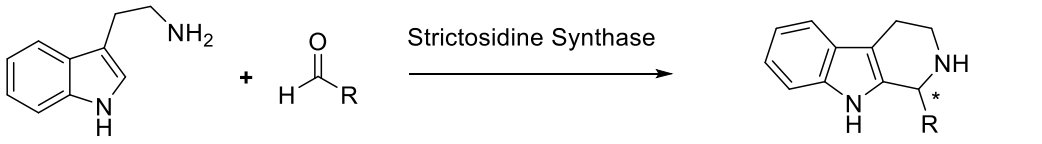
The condensation of ß-arylethylamines with carbonyl compounds (Pictet-Spengler reaction) is employed in the synthesis of tetrahydro-β-carboline and isoquinoline scaffolds which are common motifs in many naturally occurring alkaloids. These compounds exhibit a range of biological activities and are thus interesting targets for organic synthesis and medicinal chemistry.
Nature's equivalent to the Pictet-Spengler reaction is catalyzed by the so called Pictet-Spenglerases. Within this class of enzymes, strictosidine synthases (STRs, EC 4.3.3.2) have attracted attention [1-4]. These enzymes catalyse the formation of the 1,2,3,4-tetrahydro-β-carboline (*S*)-strictosidine, a key intermediate in the monoterpenoid indole alkaloid biosynthetic pathway in higher plants.
Previous studies suggested that the substrate tolerance of STRs is – especially regarding the aldehyde substrate - limited. Thus the conversion of only a few non-natural substrates has been reported so far [2, 5].



Tryptamine Non-natural aldehyde 1,2,3,4-Tetrahydro-ß-carboline

In order to further broaden the substrate scope and gain access to novel, potentially bioactive strictosidine derivatives, we investigated various non-natural aldehyde compounds for acceptance by various STRs. Additionally, variants of OpSTR (STR from *Ophiorhizza pumila*) bearing mutations in the active site were generated to further improve the selectivity of the enzyme towards aldehyde possessing a smaller side chains. The conversions achieved as well as the optical purities of the obtained products will be reported.

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