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VAO-mediated oxidation of C-N bond for thiazoline synthesis

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PURPOSE OF THE ABSTRACT
Heterocycles prevalently exist in the structures of drugs, natural products, and pharmacologically active synthetic molecules. Motivated by the significance of heterocycles in medicinal chemistry, chemists have made great effort to unveil the biosynthetic pathways of heterocycle-containing natural products, resulting in successful identification of enzymes catalyzing heterocycle formation in NRPs[1,2,3], polyketide-NRP hybrids[4,5], or RiPPs[6]. However, these enzymes typically catalyze intramolecular cyclization reactions on structurally complex substrates and are featured with limited substrate scope, thus dramatically reducing their synthetic application in medical chemistry.

Thiazoline and thiazole are two representative heterocycles found in natural products and drugs such as desferrithiocin, SP-420, SPB01403 and Uloric (as shown in Figure 1A). Chemical synthesis of thiazoline rings is majorly dependent on the condensation reaction of 2-aminoethane-1-thiol (or its derivatives) with a cyanide group, which is typically derived from an aldehyde group.[7] Here, we report our discovery of a new enzymatic transformation from aldehydes to thiazolines. This unique transformation is catalyzed by vanillyl alcohol oxidases (VAOs), which was previously characterized as a subfamily of FAD dependent oxidase to catalyze oxidation of alcohols or enantioselective hydroxylation of 4-alkylated phenols (Figure 1B).[8] The VAO-mediated synthesis of thiazolines from aldehydes is achieved via a cascade reaction, composed of a spontaneous cyclization and enzymatic benzylic oxidation. We found that VAOs exhibited substrate promiscuity towards a wide range of 4-hydroxybenzaldehyde derivatives (Figure 1C). Notably, methyl cysteine can also be recognized as the surrogate of 2-aminoethane-1-thiol, offering new opportunity to achieve the green and efficient synthesis of the clinical drug SP-420.

FIGURES

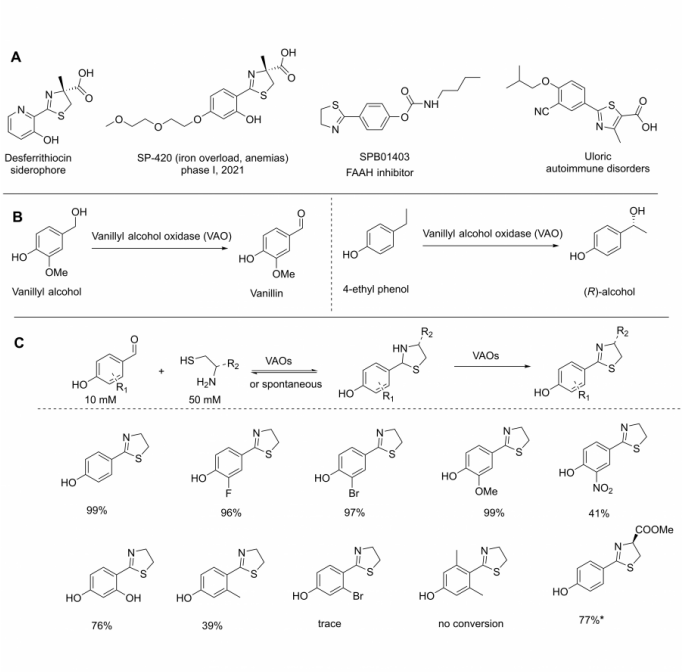

FIGURE 1

VAO-mediated oxidation of C-N bond for thiazoline synthesis

(A) Representative bioactive thiazoline and thiazole derivatives. (B) Original function of vanillyl alcohol oxidases

(C) chemo-enzymatic synthesis of thiazoline using VAO-mediated oxidation.

FIGURE 2

KEYWORDS

thiazoline | vanillyl alcohol oxidases | chemo-enzymatic synthesis | heterocycles

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