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Enzymatic synthesis of benzylisoquinoline alkaloids using a parallel cascade strategy and tyrosinase variants

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PURPOSE OF THE ABSTRACT

Benzylisoquinoline alkaloid derived pharmaceuticals are widely applied in modern medicines. Recent studies on the microbial production of benzylisoquinolines have highlighted key biological syntheses towards these natural products.1-3 Routes to non-natural benzylisoquinolines have been less explored, particularly halogenated compounds which are more challenging. In our previous work, up to seven enzymes were combined into one-pot cascades, yielding natural BIAs in good yields and enantiomeric excesses.4-5 Here, we show the use of a parallel cascade design incorporating a tyrosinase, tyrosine decarboxylase, transaminase, and norcoclaurine synthase, in order to generate halogenated benzylisoquinoline alkaloids in high enantiomeric excesses. Notably, mutagenesis studies were applied to generate tyrosinase variants, which enhanced the acceptance of halogenated tyrosines for use in the biocatalytic cascades developed.6

FIGURES

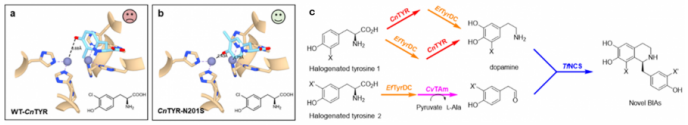

FIGURE 1

Figure 1. Scheme for parallel cascade design and molecular docking studies with WT-CnTYR and the variant.

a. Docking of 3-Cl-L-tyrosine with WT-CnTYR: the substrate can fit into the active sites of WT-CnTYR but not in a productive orientation. b. Docking of 3-Cl-L-tyrosine with CnTYR-N201S: the substrate fits well into the active sites of CnTYR-N201S. The fun

FIGURE 2

KEYWORDS

Biocatalysis | benzylisoquinoline alkaloid | Enzyme cascade

BIBLIOGRAPHY

[1] H. Minami, J. Kim, N. Ikezawa, T. Takemura, T. Katayama, H. Kumagai, F. Sato. Proc. Natl Acad. Sci. 2008, 105, 7393-7398.

[2] A. Nakagawa, H. Minami, JS. Kim, T. Koyanagi, T. Katayama, F. Sato, H. Kumagai. Nat. Commun. 2011, 2, 326.

[3] A. Nakagawa, E. Matsumura, T. Koyanagi, T. Katayama, N. Kawano, K. Yoshimatsu, K. Yamamoto, H. Kumagai, F. Sato, H. Minami. Nat. Commun. 2016, 7, 10390.

[4] Y. Wang, N. Tappertzhofen, D. M□ndez-S□nchez, M. Bawn, B. Lyu, JM. Ward, HC. Hailes. Angew. Chem. Int. Ed. 2019, 58, 10120-10125.

[5] F. Subrizi, Y. Wang, B. Thair, D. M□ndez-S□nchez, R. Roddan, M. C□rdenas-Fern□ndez, J. Siegrist, M. Richter, JN. Andexer, JM Ward, HC. Hailes. Angew. Chem. Int. Ed. 2021, 60,18673-18679.

[6] Y. Wang, F. Subrizi, EM. Carter, TD. Sheppard, JM. Ward, HC. Hailes. Nat. Commun. 2022, 13, 5436.