BIOTRANS
LA ROCHELLE 2023

N°825 / OC
TOPIC(s) : Enzyme discovery and engineering / Biocatalytic cascade reactions

Synthesis of Pharmaceutically Relevant Arylamines Enabled by a Novel Nitroreductase from Bacillus tequilensis

AUTHORS

Sara RUSSO / RIJKSUNIVERSITEIT OF GRONINGEN, NIJENBORGH 4, GRONINGEN
Alejandro PRATS LUJÁN / RIJKSUNIVERSITEIT OF GRONINGEN, ANTONIUS DEUSINGLAAN, 1, GRONINGEN
Henriette J ROZEBOOM / RIJKSUNIVERSITEIT OF GRONINGEN, NIJENBORGH 4, GRONINGEN
Hein J WIJMA / RIJKSUNIVERSITEIT OF GRONINGEN, NIJENBORGH 4, GRONINGEN
Marco W FRAAIJE / RIJKSUNIVERSITEIT OF GRONINGEN, NIJENBORGH 4, GRONINGEN
Corresponding author : Gerrit J POELARENDS / g.j.poelarends@rug.nl

PURPOSE OF THE ABSTRACT

Arylamines are essential building blocks for the production of high-value pharmaceuticals. Therefore, strategies for their efficient and cost-effective synthesis are of great interest[1]. The current industrial approach for producing arylamines is based on the catalytic hydrogenation of nitroaromatic precursors, which requires huge catalyst loadings and produces hazardous waste. Besides, these procedures typically lack chemo- and regioselectivity. Therefore, biocatalysis has gained ground as an interesting approach for arylamine synthesis. For example, flavin-dependent nitroreductases are attractive biocatalysts for this, as they perform the reduction of nitroaromatic compounds into aromatic amines with excellent specificity using mild reaction conditions[2–4].

Herein, we assess and characterize a novel nitroreductase from Bacillus tequilensis (BtNTR) that enables the synthesis of pharmaceutically relevant and structurally diverse arylamines. BtNTR was screened towards a panel of nitroarenes, including four intermediates used in the manufacture of blockbuster drugs (Figure 1). BtNTR showed a surprisingly high rate of amine formation (up to 98%) towards a variety of functionalized nitro heterocyclic molecules such as pyridines, benzenes, and pyrazoles. The enzyme has a wide pH optimum for activity and a melting temperature of 58°C, which make it a good candidate for industrial applications. In addition, we elucidated the enzyme crystal structure at 1.15 Å resolution. Guided by the structure, we conducted docking and molecular dynamics studies to better understand the catalytic mechanism. With this aim, we also performed pre-steady-state and steady-state kinetic analyses.

Overall, our results suggest that NRs have huge potential as biocatalysts for arylamine production. They constitute a green and selective tool for the synthesis of functionalized anilines that are not easily accessible using standard methods.

FIGURES

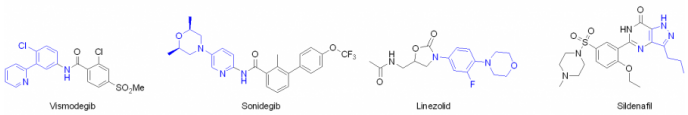

FIGURE 1

Example of pharmaceutically relevant arylamines

.

FIGURE 2

KEYWORDS

flavoprotein | nitroreductase | biocatalysis | arylamine

BIBLIOGRAPHY

[1]M. Hoogenraad, J. B. van der Linden, A. A. Smith, B. Hughes, A. M. Derrick, L. J. Harris, P. D. Higginson, A. J. Pettman, Org. Process Res. Dev. 2004, 8, 469-476.

[2]E. Akiva, J. N. Copp, N. Tokuriki, P. C. Babbitt, Proc. Natl. Acad. Sci. 2017, 114, E9549.

[3]A.-F. Miller, J. T. Park, K. L. Ferguson, W. Pitsawong, A. S. Bommarius, Mol. Basel Switz. 2018, 23, 211.

[4]W. Pitsawong, J. P. Hoben, A.-F. Miller, J. Biol. Chem. 2014, 289, 15203-15214.