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Editorial: Exploiting the power of biocatalysis: accessing optimized natural products analogues

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Editorial on the Research Topic
Exploiting the power of biocatalysis: accessing optimized natural products analogues

Biocatalysis is a powerful technique that has the potential to enable the production of valuable natural products, ranging from small molecules and peptides to polymer conjugates, with a remarkable regio- and stereoselectivity. Moreover, it stands out as a greener and more sustainable alternative to conventional chemical methods. However, biocatalysis requires further developments to achieve its full potential. This involves gaining comprehensive understanding of enzyme structure, kinetics, and selectivity, as well as testing the effect of mutation on enzyme activity and substrate selectivity.

The current Research Topic displays four articles whose authors utilized different tools to decipher enzyme function and characteristics as an essential step for the future application in biocatalysis. First, enzyme crystallization and mutations deciphered the catalytic process of an enzyme involved in the biosynthesis of the antitumor, podophyllotoxin. Second, Authors revealed the role an unobservant domain in determining selectivity and specificity of a modular protein involved in the synthesis of non-ribosomal peptides. Third, the spectrum of sustainable glycopeptides synthesis utilizing protease-catalyzed peptide synthesis was explored. Finally, classical biochemical tools were utilized to study the regioselectivity of a halogenase involved in biosynthesis of the antimicrobial, pyrrolnitrin.

Deoxypodophyllotoxin synthase (DPS) is a 2-oxoglutarate dependent non-heme iron (II) dioxygenase. The enzyme plays a crucial role in the biosynthesis of podophyllotoxin, converting the polycyclic aryllignan (-)-yatein into deoxypodophyllotoxin via the stereoselective ring-closing carbon-carbon bond formation (Lau and Sattely, 2015). Deoxypodophyllotoxin is a precursor in producing important chemotherapeutic agents. Given this fact, understanding the structure and function of DPS is essential. Podophyllotoxin is traditionally sourced from the slow-growing *Podophyllum hexandrum*, but synthetic biology platforms are being developed to meet demand. Generally, synthetic biology approaches require fully

characterized and optimized enzymes. Ingold et al. aimed to understand the mechanism and biocatalysis potential of DPS. Via X-ray crystallography, the authors provided a refined crystal structure of DPS with a higher resolution of 1.41 Å compared to previous crystals (Tang et al., 2022). The improved structure revealed critical insights into substrate binding and the catalytic mechanism. The authors highlighted the role of a D224-K187 salt bridge in maintaining substrate interactions and identified H165 as a potential base for proton abstraction during the aromatization step to form deoxypodophyllotoxin. Mutations at these key residues confirmed their importance in the catalytic process. This research provides a detailed structural and functional analysis of DPS. The findings enhance the understanding of how specific residues contribute to DPS's function, which is crucial for future engineering efforts.

Non-ribosomal peptides (NRP) represented an infinite source for new therapeutic drugs and many agro-ecological applications. Their engineering pose the potential for chemical diversification and development of many new unnatural products. However, the engineering of these modular proteins is intricate and implicate many obscure factors (Burkart and Ishikawa, 2023). These peptides are built by sequential incorporation of individual amino acids recruited by the individual enzyme modules. Each module consists of three domains, namely, adenylation domain (A), peptidyl carrier protein and a condensation domain (C). A plethora of literature have targeted A-domain as the key player determining which amino acids monomers would be selected (Lu et al., 2023; Xu et al., 2023). However, Ho et al. revealed that the C-domain do affect the selectivity and specificity of NRP synthases. Authors performed biochemical and structural characterization of the C-domain in the NRP synthase of the siderophore fuscachelin as a model. Their research revealed that C-domain is not so flexible for monomers having different configuration and/or branched side chain. In conclusion, the authors emphasize that the selectivity of the C-domain should be concomitantly considered along with A-domain selectivity in engineering new NRP synthases.

Glycopeptides constitute an increasingly important class of molecules for biomedical applications. Black et al. explored the use of protease-catalyzed peptide synthesis (PCPS) for the chemoenzymatic formation of glycopeptides. The latter approach offers an eco-friendly alternative to conventional synthetic methods not only for homopeptides, but also for peptide-polymer conjugates (Yazawa and Numata, 2014; Centore et al., 2020). The study synthesized glycan-terminated peptides *in situ* using PCPS, employing glycan-terminated Phe-OEt grafters and Leu-OEt monomers. Results demonstrated that the amine-linked glucose-Phe-OEt was slightly better than the amide-linked version as a grafter, likely due to the greater flexibility of the amine bond. Additionally, a feed ratio study revealed that the highest grafter efficiency (8.3% ± 2%) occurred at a grafter-to-monomer ratio of 1:7.5. A critical aspect of the research focused on the influence of glycan structure on the efficiency of the grafter. Particularly, the authors examined the length of polyethylene glycol (PEG) linker between the sugar moiety and the amino acid of the grafter. The researchers sought to determine the minimal spacer length required to reduce high-energy interactions within the active site, thereby enhancing grafter conversion rates. They discovered that a PEG spacer with three ethylene glycol units increased the grafter conversion rate from 8.3% ± 2% to 24.5% ± 1.8%. Computational modeling confirmed that the enhanced stability and binding interactions of longer PEG spacers contribute to their greater efficacy in glycopeptide synthesis. In summary, the study by Black et al. highlights the potential of PCPS in the sustainable synthesis of glycopeptides, with PEG spacers playing a crucial role in optimizing conversion rates. Further investigations into longer spacers and diverse glycans are anticipated to yield even more efficient chemoenzymatic synthetic methods.

Regioselectivity is one of the major advantages of biocatalysis over chemical synthesis. Gebauer et al. demonstrated the high regioselectivity of a halogenase, PrnC, involved in the biosynthesis of the antimicrobial pyrrolnitrin. Authors utilized Flavin reductase, as an electron supplier, and developed *in vitro* conditions using factorial design to get a full conversion of the substrate at 40°C. The enzyme and reaction kinetics were comparable to other known halogenases. It surpassed chemical halogenation reactions in terms of regioselectivity as demonstrated by the authors. Moreover, the enzyme had a satisfactory flexibility regarding substrate promiscuity which would make PrnC a valuable tool for future halogenation reactions. The authors were so devoted to synthesize a plethora of substrate and intermediates to get a full picture about the substrate promiscuity.

Author contributions

MN: Writing–original draft, Writing–review and editing. MK: Writing–original draft, Writing–review and editing. IE-A: Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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