Synthetic Anhydromuropeptides as Glycosyl Acceptors of Bacterial Transglycosylase

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The transglycosylases (TGases) in the bacterial peptidoglycan (PG) biosynthetic pathway remain underexploited antibiotic targets.[1] Current TGase inhibitors all contain a phospholipid moiety that complicates their preparation and pharmacokinetic properties, calling for the development of novel TGase inhibitors.[2] Here, we focused on anhydromuropeptides, a class of natural PG fragments that contain no phospholipids, and demonstrated that the synthetic anhydromuropeptide GlcNAc-*β*-1,6-anhydroMurNAc-pentapeptide was utilized by bacterial transpeptidase (TPase) for terminal D-amino acid exchange and cross-linking with long PG polymers. Importantly, *in vitro* TGase assay demonstrated that anhydromuropeptide and its analogue lacking the peptide were recognized and utilized by bacterial TGases as non-canonical anhydro glycosyl acceptors. Notably, incorporation of anhydromuropeptides into the growing PG strand by TGases terminates glycan chain elongation and impedes PG assembly, indicating the potential application of such anhydromuropeptides as novel classes of PG-terminating antibiotics.

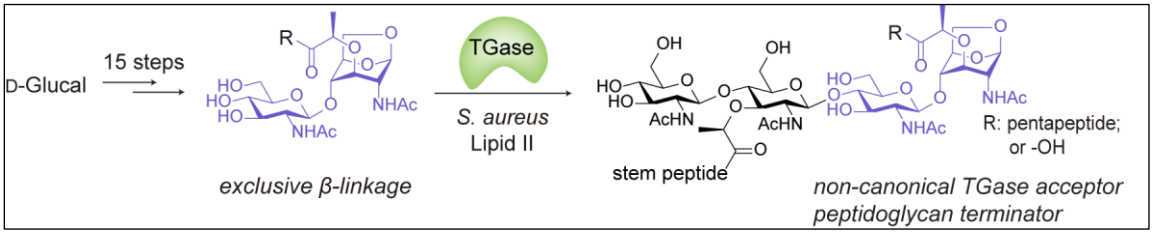

Figure Analogues of bacterial cell wall turnover products, GlcNAc-*β*-1,6-anhydroMurNAc-pentapeptide and GlcNAc-*β*-1,6-anhydroMurNAc were chemically synthesized. *In vitro* TGase reaction attested that both analogues are non-canonical anhydro glycosyl acceptors that terminate the growing PG.

References

[1] Chen, X.; Wong, C.-H.; Ma, C. *ACS Infect. Dis.* **2019**, *5*, 1493-1504.
[2] Ostash, B.; Walker, S. *Nat. Prod. Rep.* **2010**, *27*, 1594-1617.

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