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Natural product antibiotics: synthesis and next generation analogues

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Stellingen

Behorende bij het proefschrift

Natural Product Antibiotics: Synthesis and Next Generation Analogues

1. Genome mining offers substantial support for predicting the structures of natural products, however, its predictions often lack sufficient accuracy, necessitating careful interpretation. (*Chapters 2 and 3*).
2. If the structure of a natural product has never been confirmed via X-ray crystallography or total synthesis, then there is a high degree of probability that the molecule is misassigned. (*Chapters 2 and 3*).
3. While most of the amino acids within the evyactin structure are essential for its activity, the N-terminus offers site amenable to structural diversification via simple amide coupling. (*Chapter 4*)
4. As Sir James Black famously stated, "The most fruitful basis for the discovery of a new drug is to start with an old drug." Similarly, certain selective antibiotics, such as rifampicin, can be modified to broaden their effectiveness. (*Chapter 5*)
5. The choice of linker, though often underestimated during conjugate preparation, can have a profound impact on the activity of the final molecule. (*Chapter 5*)
6. Biologically active natural products would be difficult, and in most cases, unrealistic, to anticipate and rationally design. *Nature*, **2024**, 632, 39–49.
7. Semi- and total-synthesis approaches can enable the development of innovative antimicrobial agents by systematically modifying and expanding upon established drugs. *Chem. Rev.* **2017**, 117 (19), 12415-12474.
8. While most of the research has focused on conjugating β -lactam antibiotics to siderophores, numerous other antibiotic classes could benefit from this strategy. *Commun. Biol.* **2025**, 8, 1535.
9. Natural peptides can only be understood backwards, but they are often synthesized forwards. (*Inspired by Søren Kierkegaard*)
10. Industry experience needs to be well-appreciated in the academic community, as it can provide a unique approach to scientific research.
11. If the molecule of interest doesn't exhibit the desired or expected activity, identify assay conditions in which the same molecule will be more potent.
12. Failed projects often hold the opportunity to become successful in just one more attempt.

Vladyslav Lysenko
Leiden, 21st May 2026