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Authors

Holden, Jeffrey

Li, Huiying

Richo, Jerry

et al.

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Structural and biological characterization of NOS inhibitors with antimicrobial properties (585.5)

Jeffrey Holden, Huiying Li, Jerry Richo, Nathan Lim, Qing Jing, Soosung Kang, He Huang, Richard Silverman, Thomas Poulos

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Abstract

Nitric oxide produced by bacterial nitric oxide synthase (bNOS) protects Gram-positive pathogens *Bacillus anthracis* and *Staphylococcus aureus* against oxidative stress and a wide variety of antibiotics. Recently, we demonstrated that co-treatment with NOS inhibitors increases the killing efficacy of a common antimicrobial⁽¹⁾. Taking an interdisciplinary approach using microbial *in vitro* assays, spectroscopic binding analyses, enzyme kinetics and X-ray crystal structures we have identified a series of lead inhibitors for future structure-based drug design. Crystal structures of lead bNOS inhibitors have revealed an unprecedented mode of binding to the bacterial NOS that has not been previously observed in mammalian homologs. Continued exploitation of this novel-binding mode will be imperative for rationally designing a potent and selective bNOS inhibitor.

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References

- 1 Holden JK, *et al.* (2013) Structural and biological studies on bacterial nitric oxide synthase inhibitors. Proc Natl Acad Sci U S A.

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