THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

A Generative Deep Learning Approach to de novo Antibiotic Design

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There is an urgent need to develop structurally novel antibiotics to address the ongoing antimicrobial resistance crisis. Deep learning approaches can accurately identify antibacterial compounds from existing chemical libraries, but structural novelty remains limited by the number of enumerated compounds. Here, we sought to design structurally unprecedented antibiotics using generative artificial intelligence. We used pre-trained graph neural networks (GNNs) to comprehensively screen >106 million organic fragments in silico, predicting core scaffolds with selective antibacterial activity against Staphylococcus aureus or Neisseria gonorrhoeae. We then developed generative models based on genetic algorithms and variational autoencoders to expand these fragments into larger molecules with desired properties. We successfully synthesized six de novo-designed compounds, representative of two structural classes, and empirically validated five compounds to have selective antibacterial activity against S. aureus or N. gonorrhoeae. Two compounds – SA1 and NG1 – exhibited high potencies and selectivity indices. Compound SA1 was bactericidal against Gram-positive bacteria, including methicillin-resistant S. aureus (MRSA) and vancomycin-resistant enterococci, and dissipated the membrane pH gradient. Compound NG1 exhibited highly narrow-spectrum activity against N. gonorrhoeae, including ceftriaxone-resistant strains, and altered membrane fluidity. We further tested these compounds in mouse models of MRSA skin infection and N. gonorrhoeae vaginal infection and found that they both effectively reduced bacterial titers in vivo. We also synthesized structural analogs of SA1 and NG1 and found several analogs to be antibacterial, supporting the potential of these and other de novo-generated compounds for further development. Our approach enables the generative deep learning-guided de novo design of antibiotics, providing a platform for mapping uncharted regions of chemical space.

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