



The Design, Synthesis, and Antibacterial Evaluation of *N*-Formyl Hydroxylamine Derivatives as Novel Antibacterial Agents

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Abstract

The increased prevalence of multidrug-resistant bacteria from clinical isolates demands the need for new antibacterial agents with novel modes of action. Peptide Deformylase (PDF) is an essential enzyme for protein synthesis in both Gram-negative and Gram-positive bacteria.¹ PDF inhibitors represents a new type of antibacterial agent with a novel mode of action that could provide an alternative treatment for patients with community acquired pneumonia (CAP) and skin and skin structure infections (SSSIs) caused by pathogens resistant to current therapy.² This research examines a novel series of *N*-formyl hydroxylamine derivatives (**Figure 1**), designed and synthesized through a multistep protocol to perform as antibacterial agents.

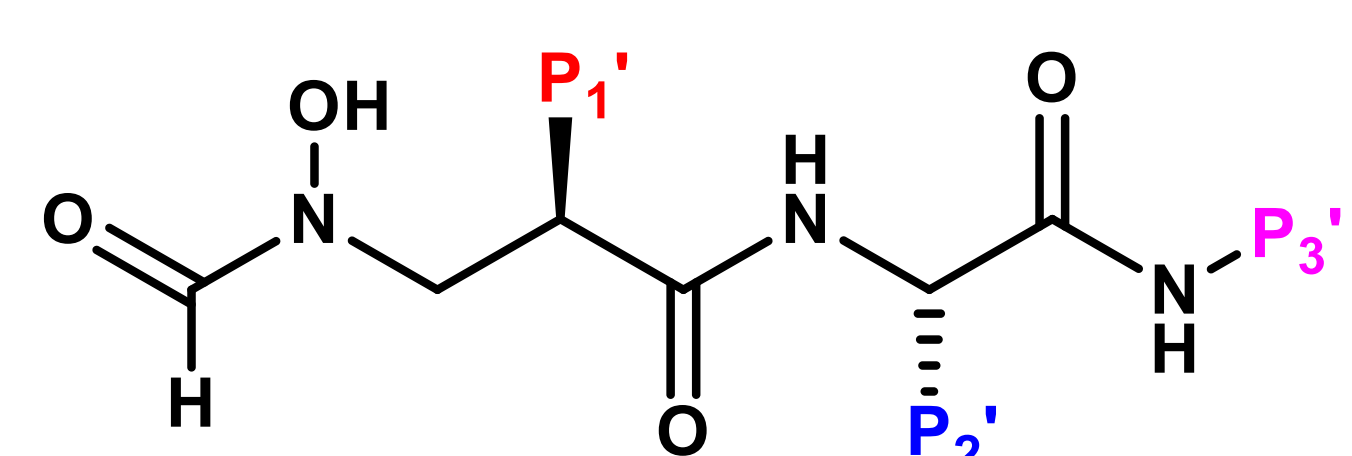


Figure 1: The general skeletal structure of a PDF inhibitor.

It is expected that the proposed modifications of the P_1' , P_2' , and P_3' moieties would provide increased potency and enhanced physicochemical properties. A medicinal chemistry approach from hit to lead optimization of this class of inhibitors will be presented.

Introduction

Bacterial peptide deformylase (PDF) is a metallo-enzyme that catalyses the removal of an *N*-formyl group from the terminal methionine residue in all newly synthesized bacterial polypeptides and is a highly conserved broad spectrum target.^{3,4} The discovery of the natural product Actinonin (**1**) as an early lead candidate triggered research in this field.⁵

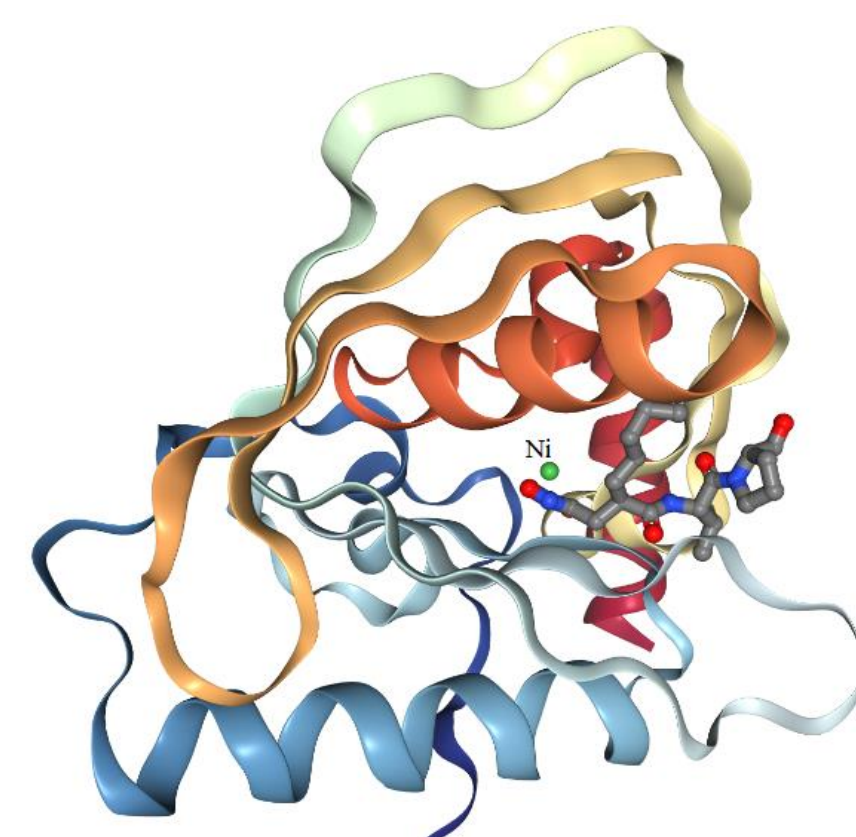
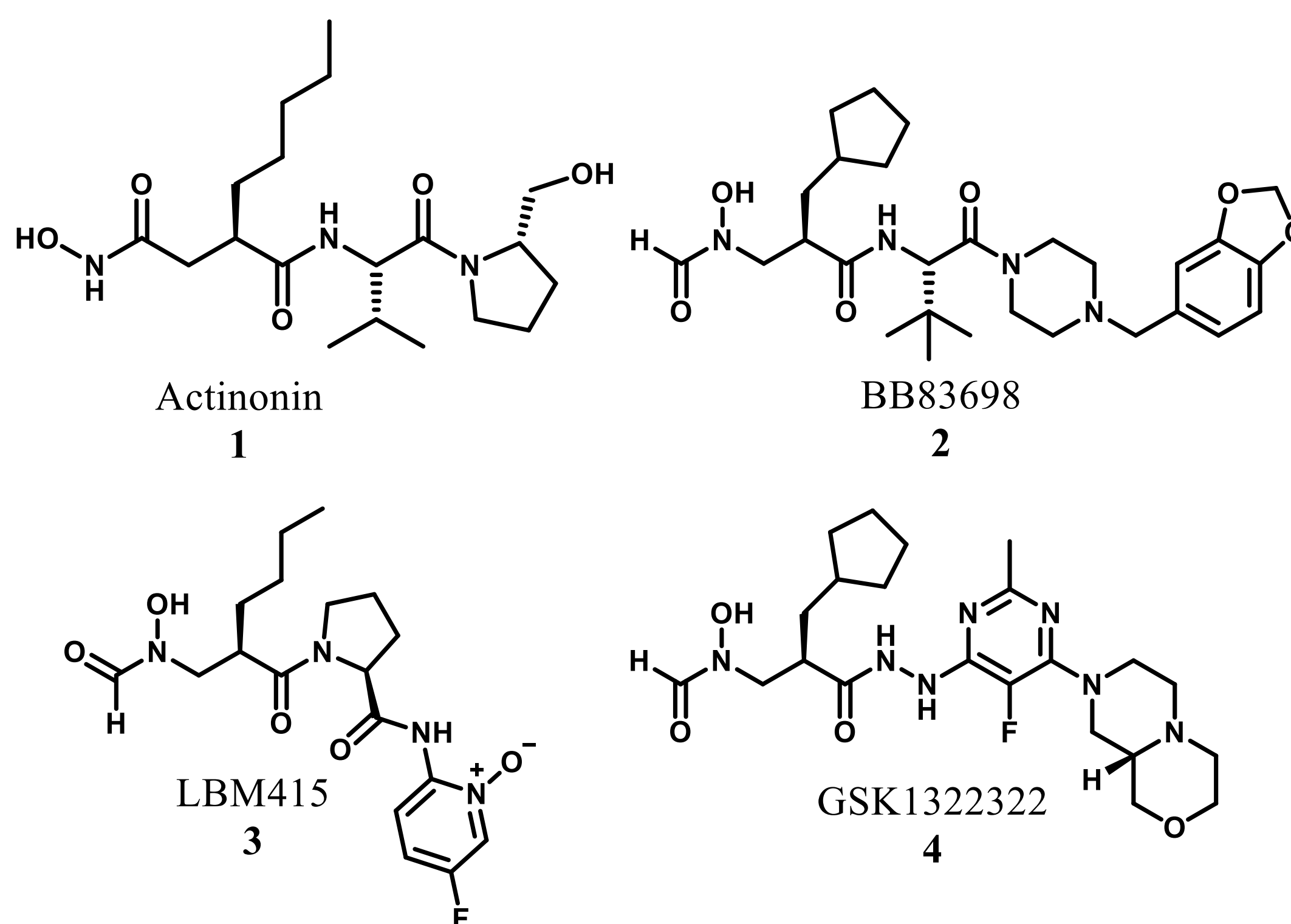


Figure 2: The crystal structure of actinonin (PDB: 1G2A) bound to *E. coli* PDF.

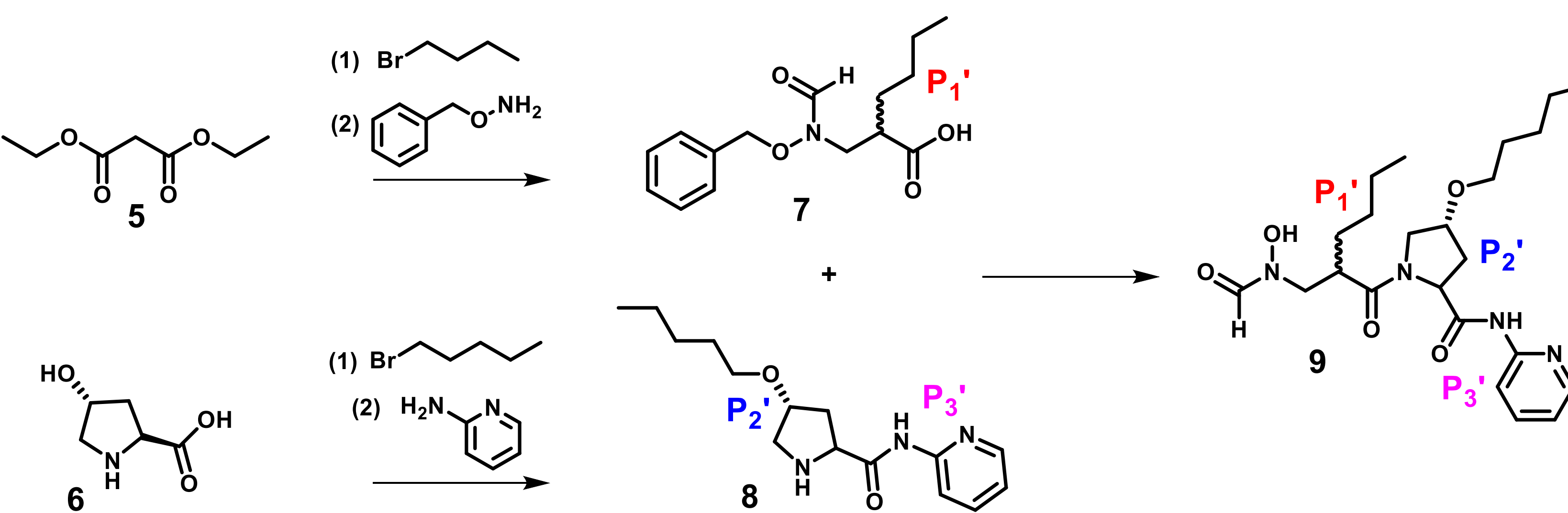
Introduction

Most PDFIs bear close resemblance to parent Actinonin and have been further optimized to improve antibacterial profiles. British Biotech BB83698 (**2**) and Novartis's LBM415 (**3**) candidates progressed to phase I clinical trial but were not further developed.^{6,7} While the reasons for not pursuing further are unclear, concerns about unexpected safety issues with the scaffold were reported.⁸ Glaxo Smith Kline later developed a novel hydrazide class of PDF inhibitors.

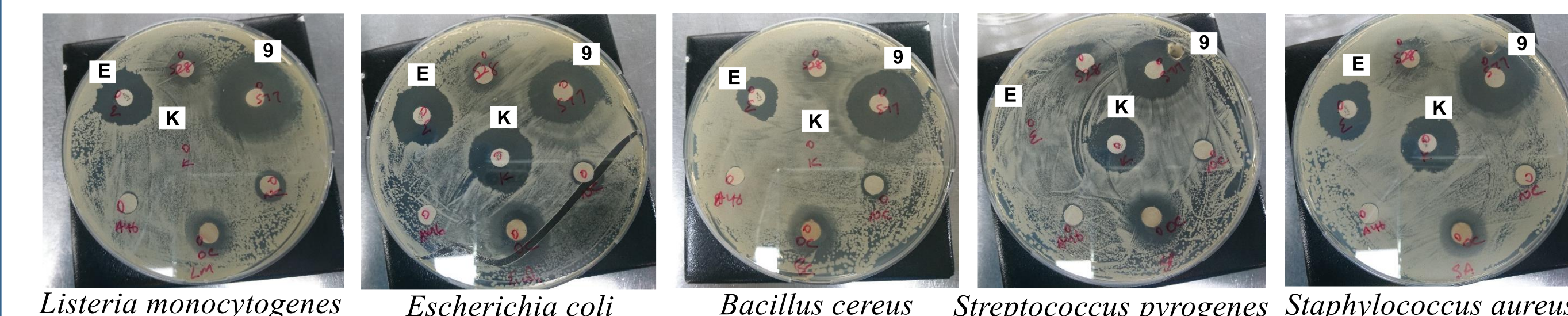


Their compound, GSK1322322 (**4**), showed promising safety and pharmacokinetic properties in phase I clinical trial; but it was discontinued after phase II trials.⁹ However, these previous investigations provided a suitable platform to compare, design, and develop new peptide deformylase inhibitors.

Experimental



Antibacterial Evaluation



Pathogens	MIC ($\mu\text{g/mL}$)		
	9	Kanamycin	Erythromycin
<i>Haemophilus influenzae</i>	0.97	0.97	< 0.48
<i>Klebsiella oxytoca</i>	> 250	23.44	250
<i>Listeria monocytogenes</i>	< 0.48	0.97	0.97
Methicillin-resistant <i>Staphylococcus aureus</i>	< 0.48	1.95	0.97
<i>Pseudomonas aeruginosa</i>	> 250	< 0.48	0.48
<i>Streptococcus pyogenes</i>	< 0.48	15.63	0.73

Conclusion

Compound **9** was successfully designed and synthesized via a multistep protocol. This synthetic effort aimed at the elaboration of the P_1' , P_2' , and P_3' moieties showed impressive potency against *L. monocytogenes*, Methicillin-resistant *S. aureus*, *S. pyogenes*, and *H. influenzae*.

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