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Development of Quinoline based NDM-1 Inhibitors

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Abstract

More than half a century ago, scientists found penicillin and sulfonamide as the cure for treating bacterial infections. They have continued to put a significant effort into screening soil samples and natural products for the new classes of antibiotics. However, resistance to the corresponding antibiotics was quickly found after discovery of these antibiotics.[1] One of the major antibiotic resistance mechanisms is the overproduction of β-lactamases. New Delhi Metallo-β-lactamase-1 (NDM-1) is considered the most worrisome β-lactamases due to its broad-spectrum effect on all clinically available β-lactam antibiotics, including the last resort antibiotics.[2] Until now, no NDM-1 inhibitor has been approved on the market. Therefore, there is a need to develop effective NDM-1 inhibitors. Recently, we have designed several quinoline based NDM-1 inhibitors that showed good MIC results against NDM-1 producing *E. coli* when synergistically applied with meropenem.

Introduction

β-lactamases are enzymes that hydrolyze the β-lactam ring of the commonly used β-lactam antibiotics. β-lactamases are generally classified into four classes (A, B, C and D) by Ambler's classification. Class A, C and D are serine β-lactamases, while class B refers to Metallo-β-lactamase. Class B is the most concerned β-lactamases as these β-lactamases can hydrolyze the majority of β-lactam antibiotics. Besides, several serine β-lactamases inhibitors are already available for clinical usage. However, there is no inhibitor for Metallo-β-lactamase available in therapy. One of the most common class B β-lactamase is the New Delhi Metallo-β-lactamase-1 (NDM-1). NDM-1 has a broad-spectrum effect on all types of β-lactam antibiotics. Moreover, a plasmid that codes NDM-1 is highly transferable. Therefore, there is a need for the development of NDM-1 inhibitors.

The active site of NDM-1

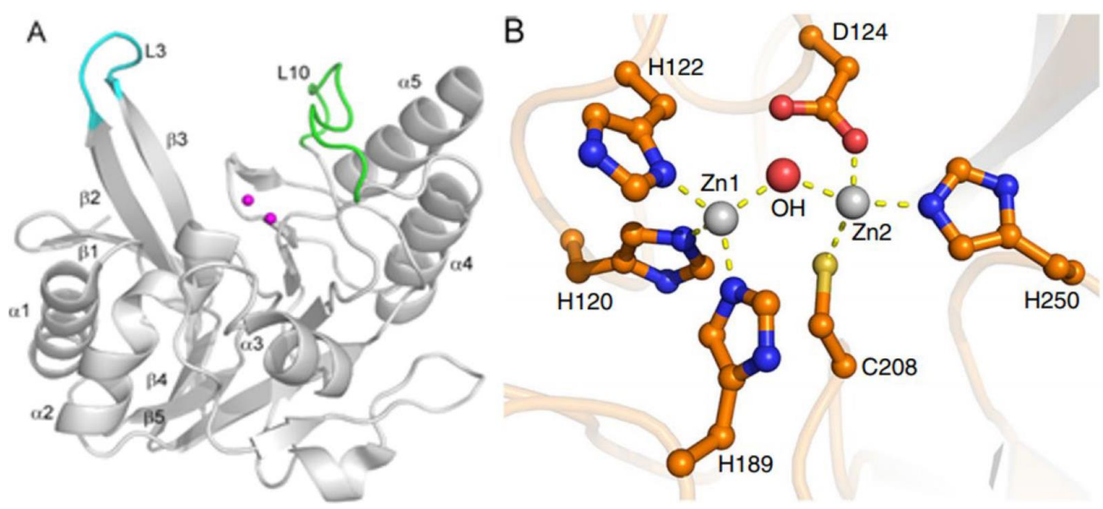

Figure 1. X-ray crystal structure of NDM-1.[3] (A) Overall folding of NDM-1. (B) The active site structure of NDM-1

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Species	Strain ID	β-lactamase content	Compounds	Meropenem MIC (μM)	Meropenem + Compound MIC (μM)
E. coli	ATCC BAA 2469	NDM-1	DPA	>64	1
			S-1	>64	64
			P-1	>64	1
			Q-1	>64	32
			Q-2	>64	64
			Q-3	>64	64
			Q-4	>64	64
			Q-5	>64	1

From the MIC results, the compounds P-1, Q-1 and Q-5 can lower the MIC value of meropenem against NDM-1 producing *E. coli* from 64 μM to 1 μM. It is suggested that the pyridine ring plays an essential role in binding with the active site of NDM-1. Once the pyridine ring was substituted with the thiophene (S-1) ring, the synergistic effect was lost. The quinoline derivatives (Q-1 and Q-5) can also lower the MIC value from 64 μM to 1 μM. However, adding the hydroxyl group at the 3-position would completely remove the synergistic effect. This may suggest that a hydrophilic group at the 3-position is not favour the binding of the quinoline derivatives to the active site. Therefore, we will try to introduce hydrophobic groups at the 3-position in the next step.

Structural Design of Quinoline Derivatives

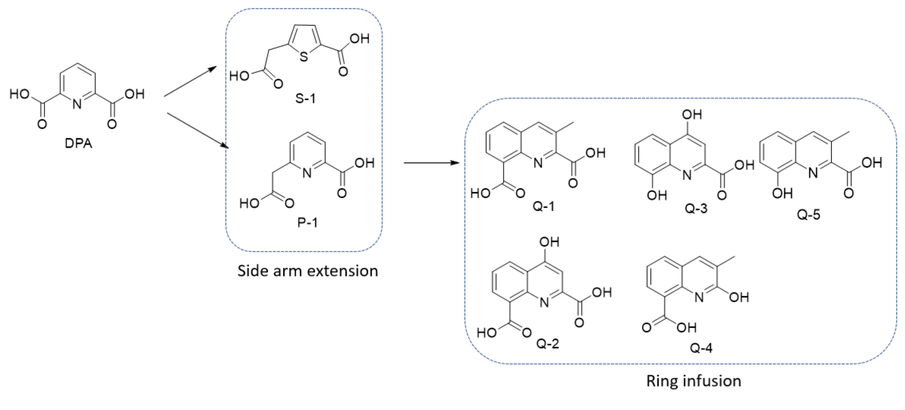

Figure 2. Modification of quinoline derivatives based on DPA

References

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