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Targeting DsbD from Neisseria meningitidis for the development of new anti-Neisserial agents

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The lack of antibiotic development coupled with the rapid increase of resistance to antibiotics in bacteria, has led to a situation described as an 'alarming public health crisis'(1). Multi-drug resistant (MDR) bacteria are becoming a significant problem because some bacterial strains cannot be treated with our current strongest and last resort antibiotics. There is an urgent need to develop alternative strategies to combat bacterial infections. Two MDR bacteria are Neisseria meningitidis, the causative agent of meningitis, and Neisseria gonorrhoeae, the causative agent of gonorrhoea. The overall aim of this work is to develop a narrow spectrum antibiotic against N. meningitidis. The biological target: NmDsbD, is a disulfide bond (Dsb) reductase that is required for the viability of N. meningitidis (2). NmDsbD is membrane bound and consists of three redox active domains: two are periplasmic domains, n-NmDsbD and c-NmDsbD, which flank the transmembrane domain, t-NmDsbD. In this work we solved the crystal structures of n-NmDsbD and c-NmDsbD, and have briefly investigated the interaction between these two domains. A fragment-based drug design approach was also used to identify small molecules that bind both n-NmDsbD and c-NmDsbD.

1. Boucher, H. W., et al. (2009) Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 48, 1-12
2. Kumar, P., et al. (2011) Characterization of DsbD in Neisseria meningitidis. Molecular microbiology 79, 1557-1573

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Summary

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