

Miracle Drugs for Superbugs: the Development of Dual Action Antibacterial Agents

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Abstract

With the ever-pressing threat of deadly “superbugs”, which are resistant to all known antibacterial agents, comes the need to design new and potent antibacterial drugs. One of the clinically relevant mechanisms by which bacterial multidrug resistance manifests itself is through efflux pumps.¹ These membrane bound proteins have the ability to detect a wide range of antibacterial agents (e.g. penicillin, ciprofloxacin) and reduce the intracellular concentration to sub-lethal levels.

An exciting concept to tackle the problem of bacterial multidrug resistance is a dual-action based approach.² Dual action drugs are compounds that contain two active moieties which are connected via a non-cleavable linkage, whilst dual action prodrugs contain a cleavable linker group. This presentation will cover the design, synthesis and biological evaluation of a series of inhibitors of the NorA efflux pump³ and a number of dual action drugs containing and an established antibacterial agent (the fluoroquinolone ciprofloxacin) linked to inhibitors of bacterial efflux pumps. Evidence for their dual mode of action will also be discussed.

¹ Lomovskaya, O., *et al.*, *Nat. Rev. Drug Discov.*, **2007**, 7 (7), 56-65

² Bremner, J. B.; Ambrus, J. I.; Samosorn, S. *Curr. Med. Chem.*, **2007**, 14 (13), 1459-1477

³ Ambrus, J. I.; Kelso, M. J.; Bremner, J. B.; Ball, A. R.; Casadai, G.; Lewis, K. *Bioorg. Med. Chem. Lett.*, **2008**, 18 (15), 4294-4297