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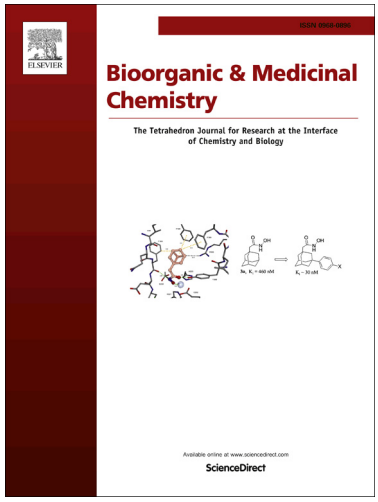

The relationship between target-class and the physicochemical properties of antibacterial drugs

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The relationship between target-class and the physicochemical properties of antibacterial drugs.

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Abstract

The discovery of novel mechanism of action (MOA) antibacterials has been associated with the concept that antibacterial drugs occupy a differentiated region of physicochemical space compared to human-targeted drugs. With, in broad terms, antibacterials having higher molecular weight, lower logP and higher polar surface area (PSA). By analysing the physicochemical properties of about 1,700 approved drugs listed in the ChEMBL database, we show, that antibacterials for whose targets are riboproteins (i.e. composed of a complex of RNA and protein) fall outside the conventional human 'drug-like' chemical space; whereas antibacterials that modulate bacterial protein targets, generally comply with the 'rule-of-five' guidelines for classical oral human drugs. Our analysis suggests a strong target-class association for antibacterials – either protein-targeted or riboprotein-targeted. There is much discussion in the literature on the failure of screening approaches to deliver novel antibacterial lead series, and linkage of this poor success rate for antibacterials with the chemical space properties of screening collections. Our analysis suggests that consideration of target-class may be an underappreciated factor in antibacterial lead discovery, and that in fact bacterial protein-targets may well have similar binding site characteristics to human protein targets, and questions the assumption that larger, more polar compounds are a key part of successful future antibacterial discovery.

Key words: Antibacterials, Physicochemical properties, Drug targets, Ribosome.