

Accepted Manuscript

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

Grace Mugumbate, John P. Overington

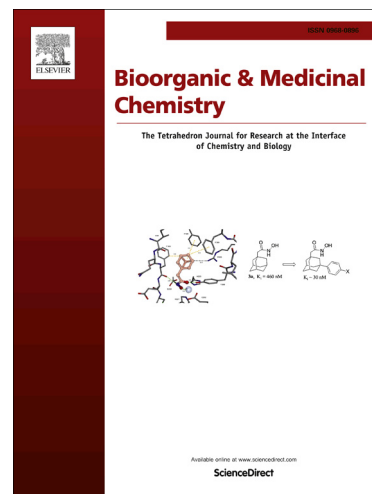
PII: S0968-0896(15)00371-5
DOI: <http://dx.doi.org/10.1016/j.bmc.2015.04.063>
Reference: BMC 12275

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 30 January 2015
Revised Date: 20 April 2015
Accepted Date: 22 April 2015

Please cite this article as: Mugumbate, G., Overington, J.P., The relationship between target-class and the physicochemical properties of antibacterial drugs, *Bioorganic & Medicinal Chemistry* (2015), doi: <http://dx.doi.org/10.1016/j.bmc.2015.04.063>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



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

3 Grace Mugumbate and John P. Overington*

4 European Molecular Biology Laboratory – European Bioinformatics Institute
5 (EMBL-EBI), Wellcome Trust Genome Campus, Hinxton, CB10 1SD, United
6 Kingdom

7 *Corresponding author: jpo@ebi.ac.uk, Tel: 00 44 (0) 1223 494467

8

9 **Abstract**

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

28

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

Download English Version:

<https://daneshyari.com/en/article/10583233>

Download Persian Version:

<https://daneshyari.com/article/10583233>

[Daneshyari.com](https://daneshyari.com)