A novel scoring profile for the design of antibacterials active against gram-negative bacteria

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Introduction

The increasing occurrence of multidrug-resistant bacteria is one of the major global threats to human health. Design of new antibacterials is challenging because new compound classes often do not possess the unique physicochemical properties required to penetrate the gram-negative cell wall. It is accepted that the physicochemical properties of many drugs are similar and attempts have been made to characterise these 'drug-like' properties, such as Lipinski's 'rule of five' for orally dosed drugs. However, antibiotics are a known exception to these rules. We compared antibiotics active against gram-negative bacteria with other classes of drug and compounds considered in medicinal chemistry projects to determine criteria for selection of compounds with a higher chance of success as a gram-negative antibacterial. These criteria are based on calculated properties, so can help to guide the design and selection of compounds in discovery projects.

Methods

Patient Rule Induction Method

The Patient Rule Induction Method (PRIM) [1] was applied in StarDrop's MPO Explorer module [2], to identify rules for determining the properties which distinguish antibiotics active against gram-negative bacteria from other 'drug-like' compounds. PRIM finds regions in a high-dimensional property space which contain a higher proportion of 'good' compounds for a specified objective. In this case, we use this approach to identify regions that have a higher proportion of gram-negative antibacterials relative to other 'drug-like' classes of compounds.

Figure 1: An illustration of how MPO Explorer uses the PRIM algorithm to identify boxes with a high proportion of 'good' compounds and represents these as rules for the selection of compounds with a high chance of achieving a desired objective. This is illustrated here in 2 dimensions for ease of visualisation.

Data sets

- 80 antibiotics active against gram-negative bacteria
- Data set of approved drugs from the ChEMBL database [3]
- Random selection of 8000 compounds from the full ChEMBL database [3]
- All calculated properties were generated with the StarDrop software [2]

Results

- MPO Explorer was used to find rules which differentiate 80 gram-negative antibacterials from approved small molecule drugs in the ChEMBL database.

Property	Identified cut-off
TPSA	> 65.68
Flexibility	< 0.3656
LogS	> 0.8232
LogD	< 1.793
hERG pIC50	< 4.938
MW	> 237.1
BBB category	negative

Table 1: The properties and desirability cut-offs identified by MPO Explorer as the rules which gram-negative antibacterials follow. The properties are listed in order of their importance with the most important at the top.

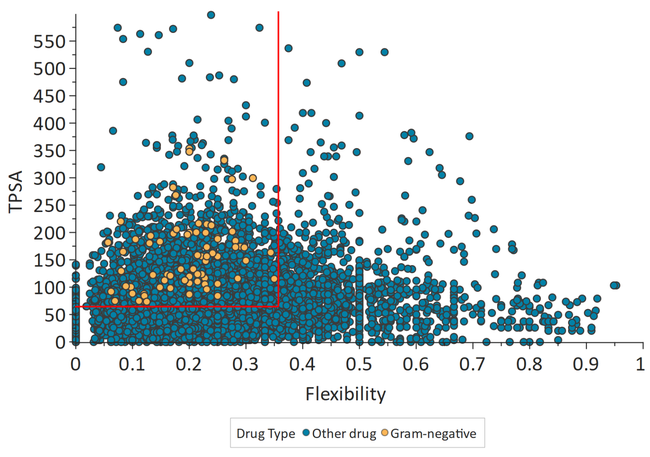

Figure 2: A scatter plot showing flexibility against TPSA, the two most important properties identified by MPO Explorer. The red lines indicate the desirability cut-offs for these properties.

- This analysis identified known properties which have previously been identified as unique to this group of antibiotics such as high topological polar surface area (TPSA) and low LogD [4, 5].
- Other properties were identified which, as far as we are aware, have not been previously noted as defining characteristics of gram-negative antibacterials, such as flexibility and logS.

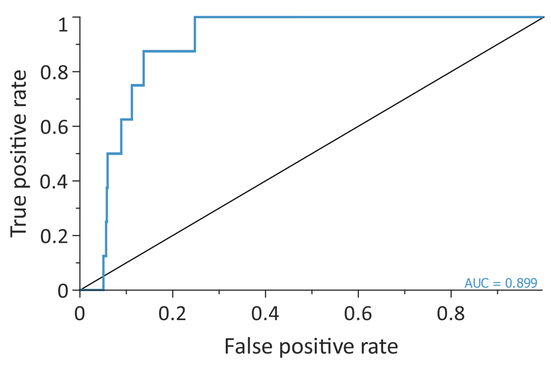

Figure 3: ROC curve showing the scoring profile created by MPO Explorer as a predictor of success as a gram-negative antibacterial for an independent test set.

To improve the predictive power of the scoring profile, the gram-negative antibiotics were compared with a wider diversity of compounds to see if there are any further properties that distinguish them from a broader diversity of drug-like compounds. MPO Explorer was again used to identify defining properties of the gram-negative antibacterials compared with compounds from the full ChEMBL database.

This secondary analysis indicated that **plasma protein binding** and number of **hydrogen bond acceptors** could be added to the scoring profile to better classify gram-negative antibacterials.

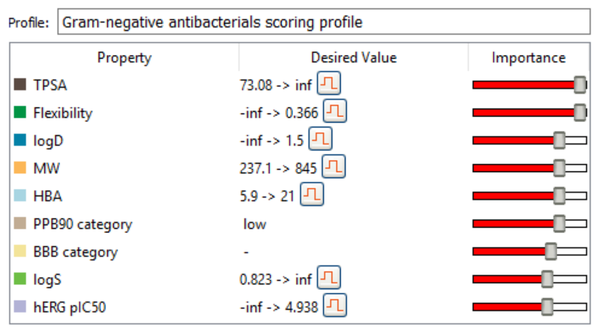

Figure 4: The proposed scoring profile showing property criteria which distinguish gram-negative antibacterials from other 'drug like' compounds.

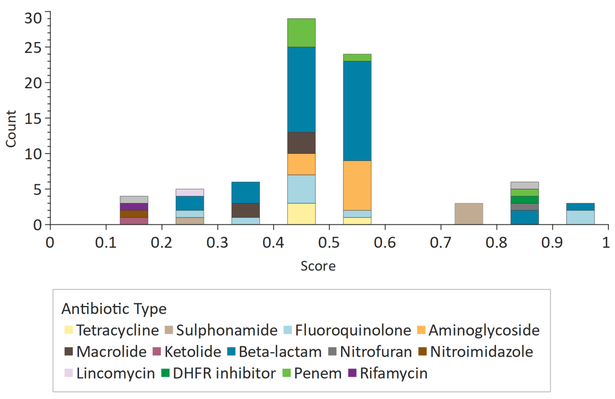

Figure 5: Plot showing the distribution of scores for the gram-negative antibacterials, coloured by the type of antibiotic.

The scoring profile was applied to novel compounds that showed activity in enzymatic assays against bacterial targets, but are not active against gram-negative isolates [7-12]. The resulting scores indicate that these compounds have a low chance of penetrating the gram-negative cell wall due to their size, flexibility or polarity, in agreement with the experimental observation. Although the range of scores for the inactive compounds overlapped with the lowest-scoring gram-negative antibacterials to a small extent (Figure 6), this confirms the ability of the scoring profile to identify compounds with a low chance of achieving gram-negative antibactierial activity.

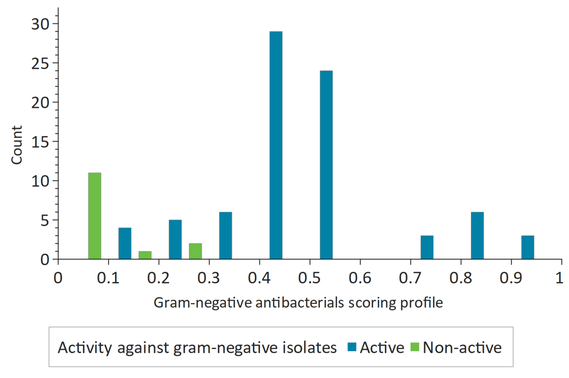

Figure 6: Histogram showing the distribution of scores for the gram-negative antibacterials and compounds which are not active against gram-negative isolates.

When applying the scoring profile, it is also important to consider **affinity to the target** as this is another key parameter which will greatly affect the success of the compounds. This parameter can be added to the scoring profile and the criterion for this parameter should be determine by the project's objectives.

The scoring profile was further modified, such that the scoring profile desirability cut-offs favoured sensitivity over selectivity. This is preferable for the purpose of the scoring profile, because we do not want the scoring profile to exclude potential gram-negative antibacterials, even if this comes at the cost of some additional false positives.

The final scoring profile (Figure 4) was applied to the gram-negative antibacterials data set using the Probabilistic Scoring approach [6], resulting in a score for each compound that indicates the likelihood of the compound achieving the ideal property criteria. The properties of antibiotics can heavily depend on their target and antibiotics can be grouped into types based on these target(s). The scoring profile would not be very useful if it favoured one class of antibiotic, therefore the scores were compared for the different types of antibiotic and, as Figure 5 illustrates, there is no bias towards a particular class.

Conclusions

- Using a rule induction method, we have defined a multi-parameter scoring profile to guide the generation of novel antibacterials active against gram-negative bacteria.
- Compounds which are inactive against gram-negative isolates did not score highly, indicating that the scoring profile can be used to deprioritise compounds that are unlikely to show gram-negative antibacterial activity.

References

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