# Applying QED to antibacterials – development of QEA, a quantitative estimate of antibacterial drug-likeness



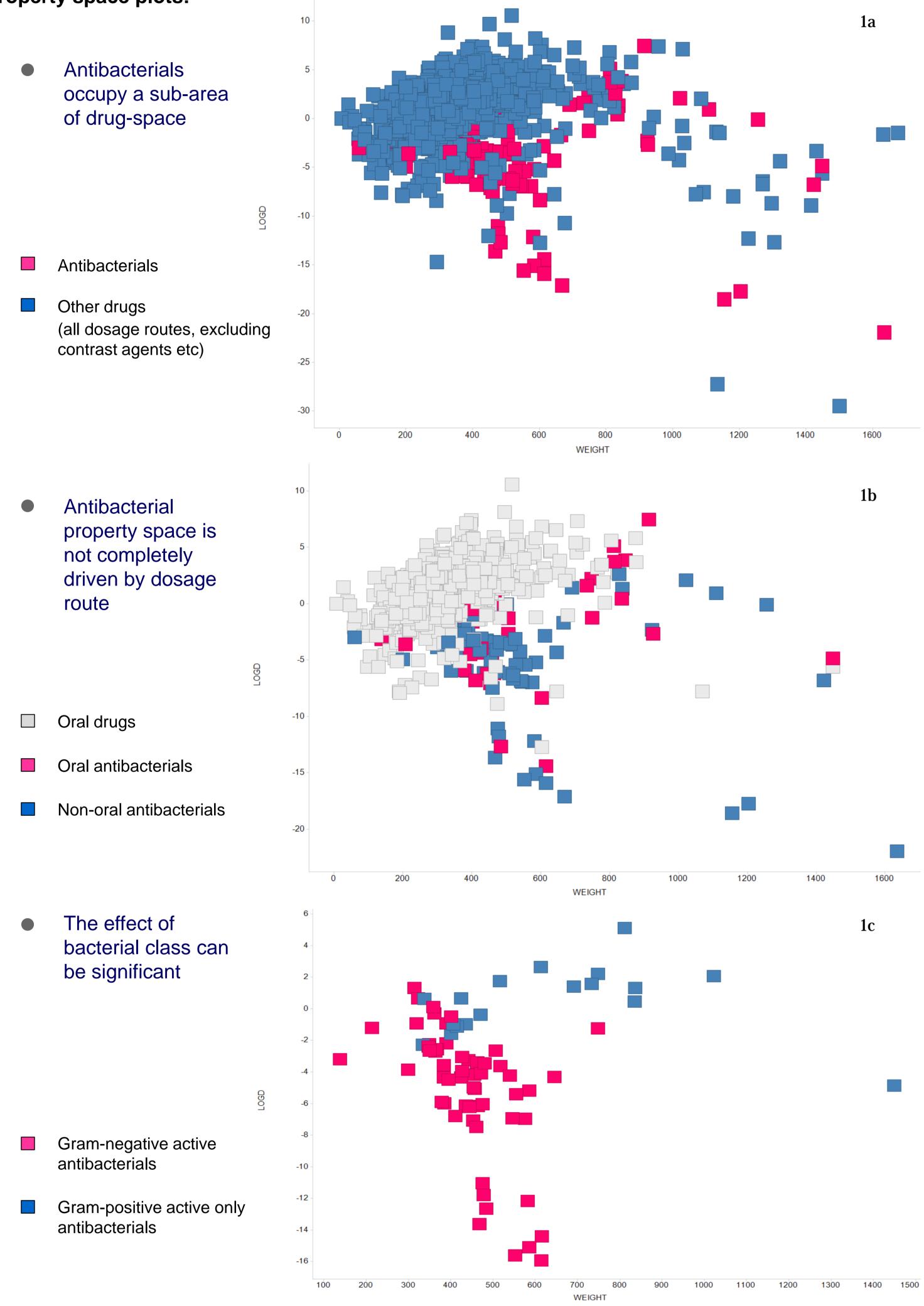
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#### How do antibacterial compounds compare with other approved drugs?

Drug-likeness is a key consideration in the selection of compounds during the early stages of drug discovery, and a new measure, quantitative estimate of drug-likeness (QED), has recently been proposed.<sup>1)</sup> Assessing a compound using QED provides a value from 0 to 1, with 1 being most desirable for oral drug-likeness. For antibacterial drug discovery, however, such general rules may not be applicable.2) With a view to developing a tool for assessing compounds for antibacterial druglikeness, we have examined the feasibility of applying the QED methodology to generate a quantitative estimate of antibacterial drug-likeness (QEA). To begin with a set of approved drugs from DrugBank<sup>4)</sup> was examined in 2D property space, plotting molecular weight vs logD, to assess the applicability of the published QED measure to antibacterial drugs.

#### **Property space plots:**

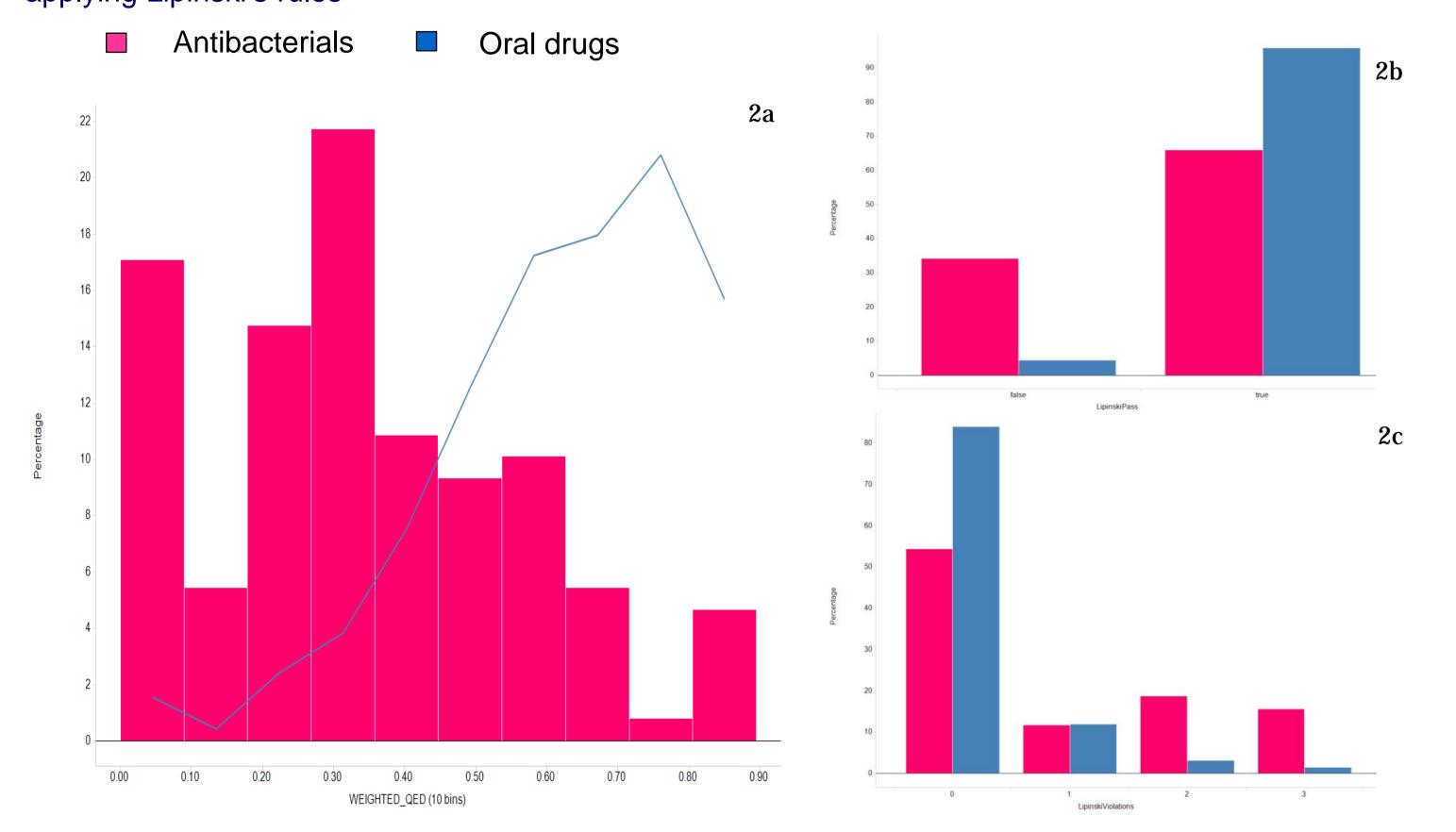


# Assessing 'oral drug-likeness' of antibacterial drugs

The set of approved drugs was further assessed using the published QED measure<sup>1)</sup> and also by applying Lipinski's rules<sup>3)</sup>

**Figure 1:** Molecular weight vs logD plots for approved drugs. (a) sorting for antibacterials and other

classes (b) sorting for dosage route (c) sorting for drugs targeting Gram +ve and Gram –ve bacteria

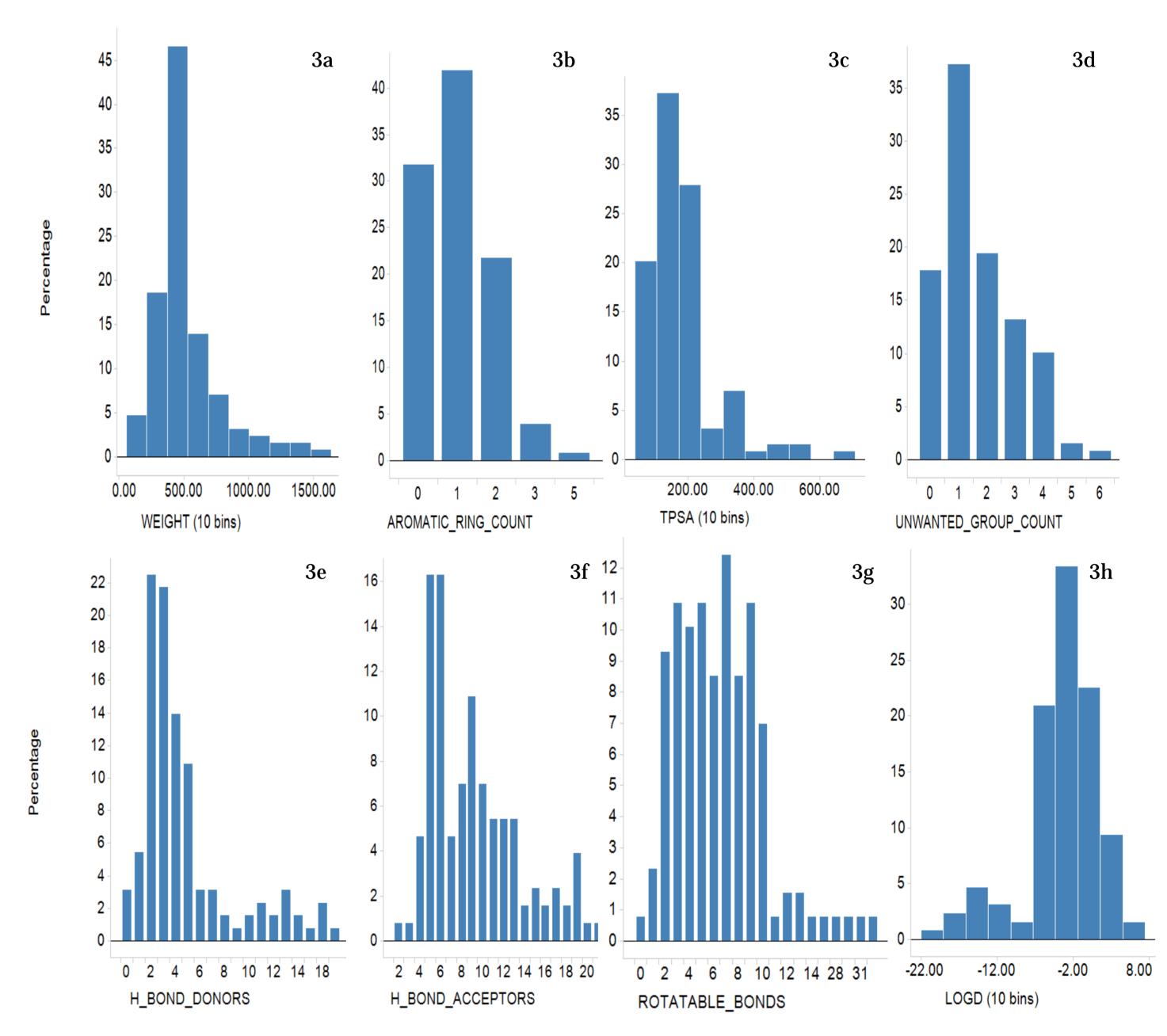


**Figure 2:** Assessment of oral drug-likeness of antibacterials (a) applying QED measure (b and c) applying Lipinski's rules

Many antibacterials have low oral drug-likeness according to the QED measure

#### Adapting the QED method for approved antibacterial drugs

Property distributions were defined using 129 published antibacterial drugs (cf 771 oral drugs used for QED). Distributions were fitted to a variety of functional forms, including the asymmetric double sigmoidal equation used in the QED publication, as well as simpler curves where appropriate. Fits were calculated using the nonlinear least-squares solver in the statistical package R.

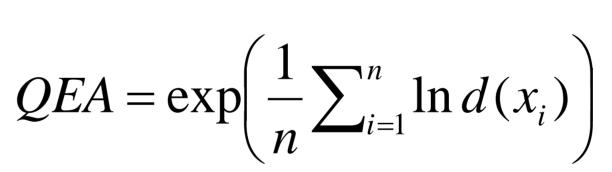


**Figure 3:** Property distributions for antibacterial drugs. Functional forms were fitted as follows: Asymmetric double sigmoidal — Molecular Weight (3a), H-bond Donors (3e), H-bond Acceptors (3f) and Rotatable Bond Count (3g); Simple single exponential - Aromatic Ring Count (3b); Double exponential – logD (3h); Polynomial – TPSA (3c) and Unwanted Group Count (3d)

# **Defining antibacterial space**

A measure of quantitative estimate of antibacterial drug-likeness (QEA) was then defined.

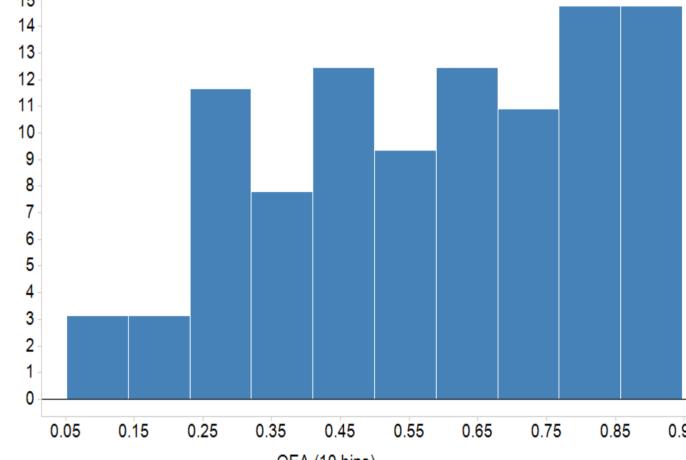
 Quantitative score (0->1) based on fitted distributions approved property compounds:



•  $x_i = MW$ , HBA, HBD, logD (pH 7.4), TPSA, aromatic ring count, rotatable bond count, unwanted group (structural alert) count.



- Partial enrichment for high QEA scores, not as distinct as for oral drugs.
- 50% of antibacterials have QEA ≥ 0.62.



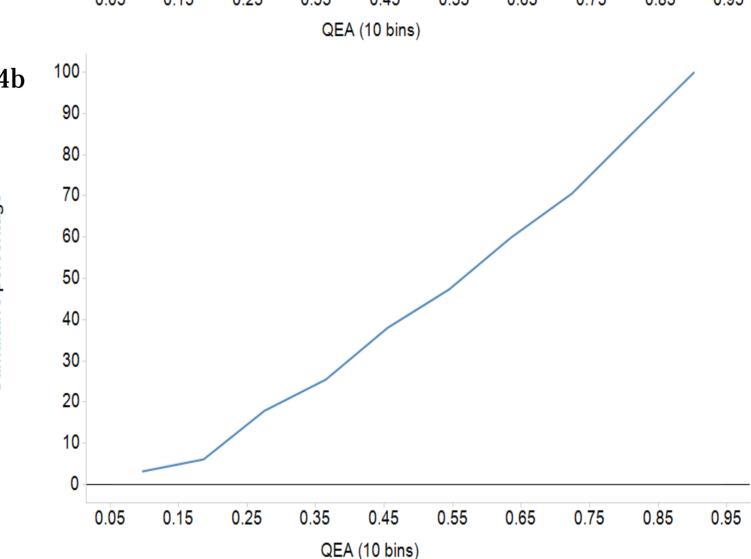


Figure 4: Applying QEA to antibacterial drugs. (a) % of antibacterials in each of 10 QEA bins (b) cumulative % of antibacterials starting with low QEA bin.

# **Conclusions**

- The property space inhabited by antibacterial compounds differs markedly from that considered to be desirable for oral drug-likeness in other drug classes.
- Therefore a specific computational measure for antibacterial drug-likeness is desirable.
- Whilst an improvement on QED, the current version of the QEA scoring developed by Evotec is only partially successful, with a significant proportion of approved antibacterials having a score <0.5.
- A larger data set and development of separate measures for Gram +ve and Gram -ve antibacterials may be necessary to improve the predictiveness of the scoring function.

# References

- 1. Bickerton, G.R., Paolini, G.V., Besnard, J., Muresan, S., Hopkins, A.L., Nature Chemistry, 2012, 4, 90-98
- O'Shea, R., Moser, H.E., Journal of Medicinal Chemistry, 2008, 51, 2871-2878
- Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., Advanced Drug Delivery Reviews, 1997, 23, 3-25.
- 4. http://www.drugbank.ca/