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.[1)] 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 drug-likeness, 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[4)] 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:

- Antibacterials occupy a sub-area of drug-space

- Antibacterial property space is not completely driven by dosage route

- The effect of bacterial class can be significant

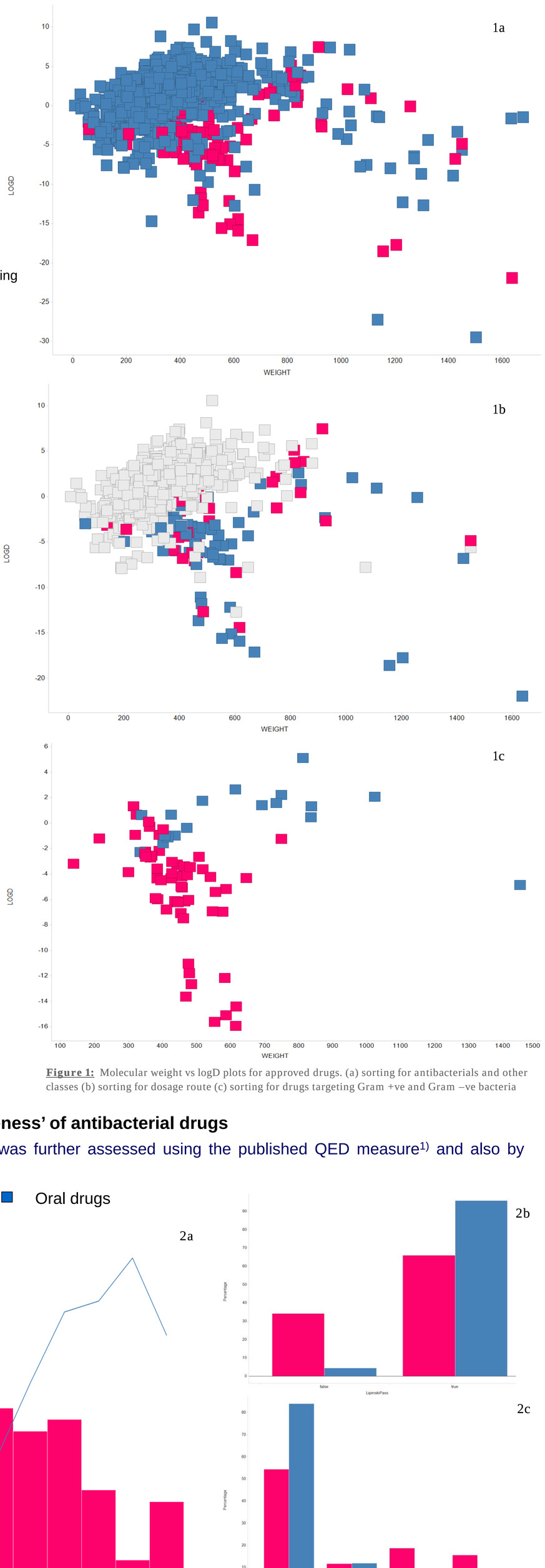

Figure 1: Molecular weight vs logD plots for approved drugs. (a) sorting for antibacterials and other classes (b) sorting for dosage route (c) sorting for drugs targeting Gram +ve and Gram –ve bacteria

Assessing 'oral drug-likeness' of antibacterial drugs

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

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.

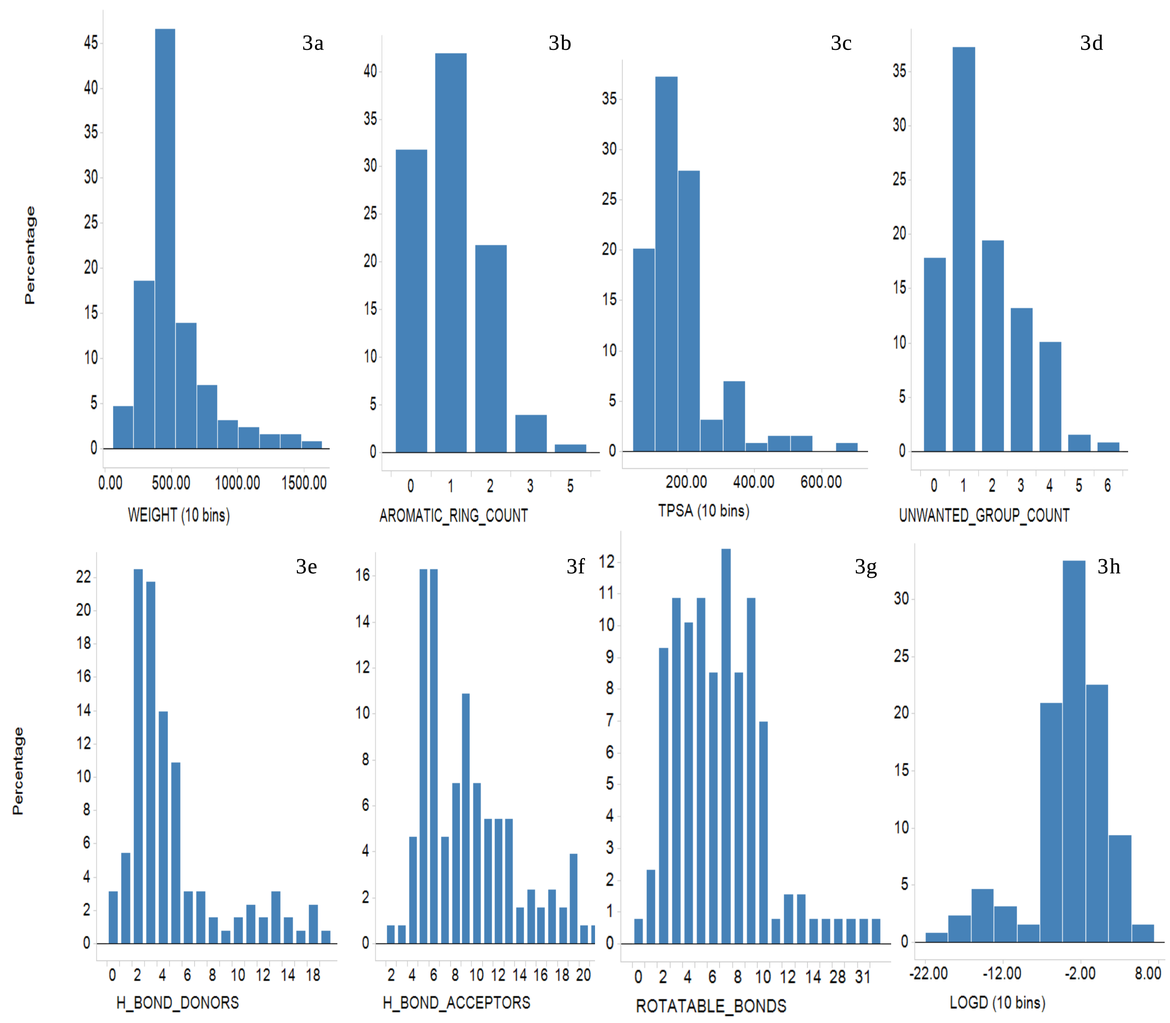

Figure 3: Property distributions for antibacterial drugs. Functional forms were fitted as follows: Asymmetric double sigmoidal – Molecular Weight (3a), H-bond Donors (3e), H-bond Acceptors (3f) and Rotatable Bond Count (3g); Simple single exponential - Aromatic Ring Count (3b); Double exponential – logD (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 property distributions of approved compounds :

$$QEA = \exp\left(\frac{1}{n}\sum_{i=1}^{n} \ln d(x_i)\right)$$

- x_i = MW, HBA, HBD, logD (pH 7.4), TPSA, aromatic ring count, rotatable bond count, unwanted group (structural alert) count.
- 129 compounds give reasonable distributions, but a larger sample would be preferable.
- Partial enrichment for high QEA scores, not as distinct as for oral drugs.
- 50% of antibacterials have QEA ≥ 0.62.

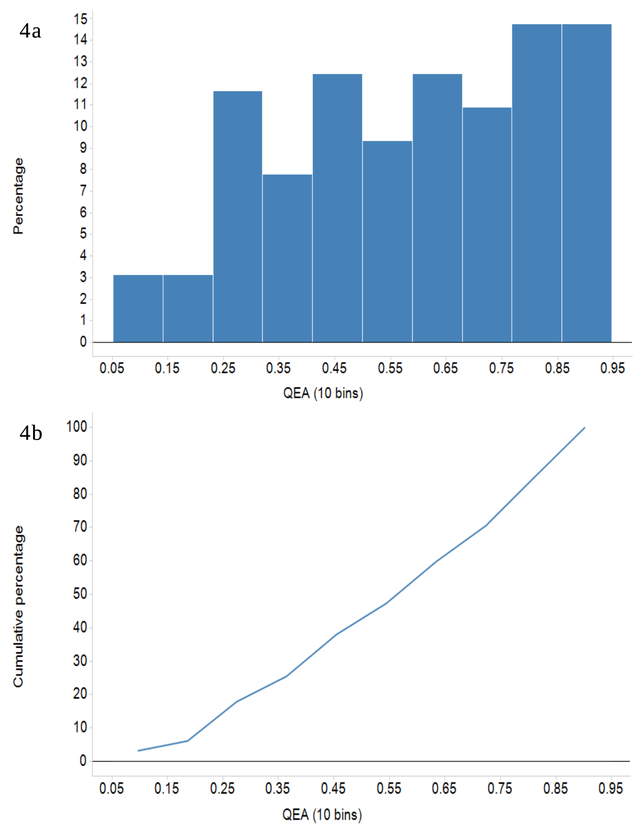

Figure 4: Applying QEA to antibacterial drugs. (a) % of antibacterials in each of 10 QEA bins (b) cumulative % of antibacterials starting with low QEA bin.

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

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3. Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., *Advanced Drug Delivery Reviews*, 1997, 23, 3-25.
4. http://www.drugbank.ca/