



QSAR of hERG potassium channel inhibition

John Dearden

QSAR & Molecular Modelling Group

School of Pharmacy & Chemistry

Liverpool John Moores University

E-mail: j.c.dearden@livjm.ac.uk



QT Interval Prolongation

Many non-antiarrhythmic drugs associated with prolongation of QT interval of the electrocardiogram.

Leads to adverse effects such as bradycardia, electrolyte imbalance, impaired hepatic and renal function.

Some drugs (e.g. astemizole, cisapride, terfenadine) withdrawn from market because of QT interval prolongation problems.



hERG

(human Ether-a-go-go-Related Gene)

The hERG potassium channel is expressed in the human heart.

Major contributor to cardiac repolarisation.

Contributes to QT interval.



Review

Safety of Non-Antiarrhythmic Drugs that Prolong the QT Interval or Induce Torsade de Pointes

De Ponti, F. et al, *Drug Safety* **25** (2002) 263.



Binding site determination

Mitcheson et al, *Proc. Nat. Acad. Sci. USA* **97**
(2000) 12329.

Used alanine-scanning mutagenesis and
homology modelling for hERG potassium
channel inhibition by MK-499.

Binding site comprises amino acids located on
S6 transmembrane domain and pore helix of
hERG channel subunit.



A pharmacophore model and 3-D QSAR CoMFA study

Cavalli et al, *J. Med. Chem.* **45** (2002) 3844.

Pharmacophore comprises three aromatic moieties connected through a nitrogen function.

CoMFA model, based on 31 compounds, gives $r^2 = 0.952$, $Q^2 = 0.767$, $s = 0.336$; $r^2_{\text{pred}} = 0.744$



3-D QSAR using Catalyst

Ekins et al, *J. Pharmacol. Exptl. Therap.* **301**
(2002) 427.

Pharmacophore comprises four hydrophobes
and one ionisable feature.

3-D QSAR with 15 compounds gave $r^2 =$
0.90; a 22-compound test-set gave $r^2 = 0.83$.



A pharmacophore model and 3-D QSAR CoMSiA study

Pearlstein et al, *Bioorg. Med. Chem. Lett.* **13**
(2003) 1829.

Pharmacophore comprises two aromatic hydrophobes and a basic nitrogen.

CoMSiA 3-D QSAR on 28 compounds gave $r^2 = 0.9$, $Q^2 = 0.6$ (estimated from graph).



Low-Dimensional QSAR

Various comparisons between 3D QSAR and low (0-2D) dimensional QSAR have indicated that the latter is generally as good as the former.

So we tried it!



Our approach

- Use as large and diverse a training set as possible
- Use hERG data obtained only from mammalian cell lines (mostly HEK and CHO)
- Use a wide range of descriptors, including MO, hydrogen bonding and topological



Our data

We collected 64 compounds for which hERG K^+ channel inhibition values in mammalian cells were available.

We generated 200 descriptors using ACD, QsarIS, TSAR and MOLPRO software.

We carried out statistical analysis in MINITAB using step-wise regression.



QSAR using full data-set

$$\begin{aligned}\log IC_{50} = & 0.411 \text{ nO} - 1.20 \text{ Ed}_{\max} \\ & - 0.683 ({}^3\chi_c - {}^4\chi_{pc}) + 0.000148 \text{ PMI}_z \\ & + 0.000635 \text{ TME} + 2.12\end{aligned}$$

$$n = 60 \quad r^2 = 0.842 \quad Q^2 = 0.797 \quad s = 0.614 \quad F = 57.5$$

There were three outliers: glibenclamide, verapamil and loratadine. Also one sertindole derivative was excluded because its IC_{50} value was considered unreliable.



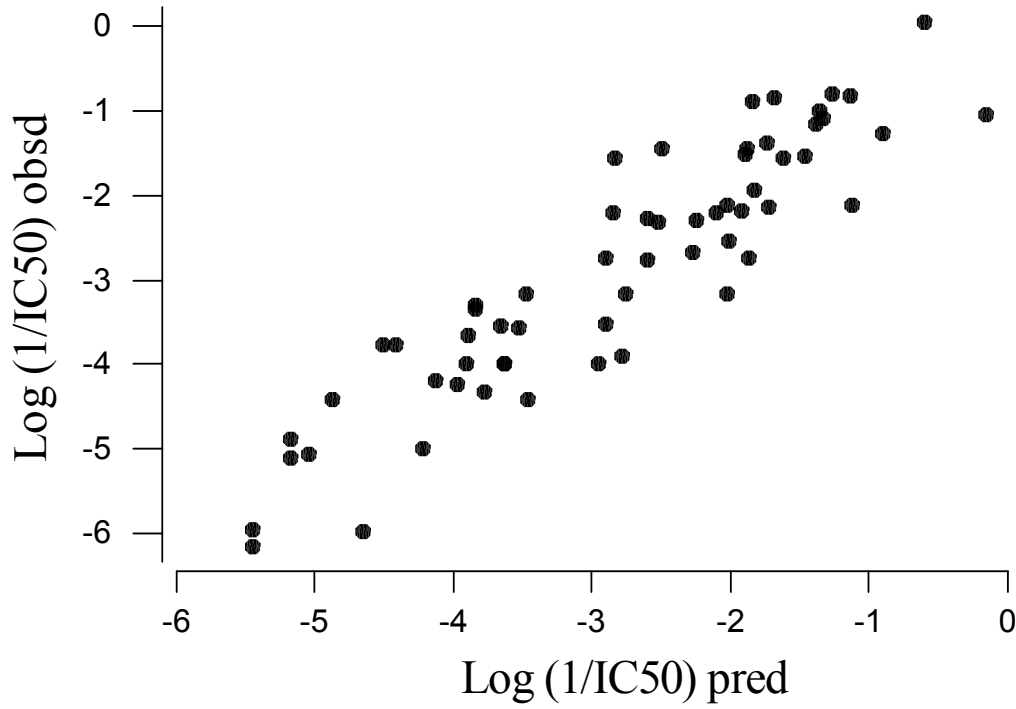
Validation

We removed 20% of the compounds from the training set, re-ran the QSAR and used it to predict the excluded compounds. This was repeated a further four times.

The correlation between predicted and observed $\log IC_{50}$ values was: $r^2 = 0.806$



Predicted vs. observed log 1/IC₅₀





QSAR of sertindole derivatives

$$\log IC_{50} = -1.12 Ca_{\max} - 0.570 Ed_{\max} + 0.0504 Q_{XX} + 4.03$$

$$n = 22 \quad r^2 = 0.902 \quad Q^2 = 0.858 \quad s = 0.419 \quad F = 55.0$$

One compound omitted because IC_{50} value considered unreliable



QSAR with sertindoles omitted

$$\begin{aligned}\log IC_{50} = & -0.843 E_{a_{\max}} * E_{d_{\max}} - 0.0175 MV \\ & - 0.615 nF + 0.388 ABSQ \\ & + 0.248 \log(P/D) - 0.326 E_{HOMO} \\ & - 0.078\end{aligned}$$

$$n = 41 \quad r^2 = 0.815 \quad Q^2 = 0.736 \quad s = 0.730 \quad F = 25.0$$



QSAR of compounds tested on CHO

$$\log IC_{50} = -0.104 \alpha - 1.55 Ed_{\max} + 0.471 \log (P/D) \\ - 0.192 S_{ssNH} + 0.0364 Q_{xx} + 3.47$$

$$n = 42 \quad r^2 = 0.885 \quad Q^2 = 0.818 \quad s = 0.562 \quad F = 55.5$$

One compound omitted because IC_{50} value considered unreliable



QSAR of compounds tested on HEK

$$\log IC_{50} = -0.985 E_{a_{\max}} * E_{d_{\max}} - 0.0151 MV \\ + 0.824 ABSQ + d^6 \chi^v_p - 0.126$$

$$n = 25 \quad r^2 = 0.812 \quad Q^2 = 0.702 \quad s = 0.614 \quad F = 21.6$$



Conclusions

- Good correlations can be obtained for hERG K^+ channel inhibition using 0-2D QSAR
- Possibly better results obtained if data using only one type of cell
- A combination of pharmacophore modelling, 3D QSAR and 0-2D QSAR should enable useful predictions to be made regarding the molecular features that will minimise hERG K^+ channel inhibition









