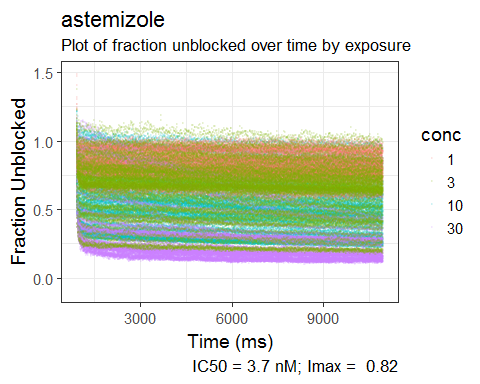
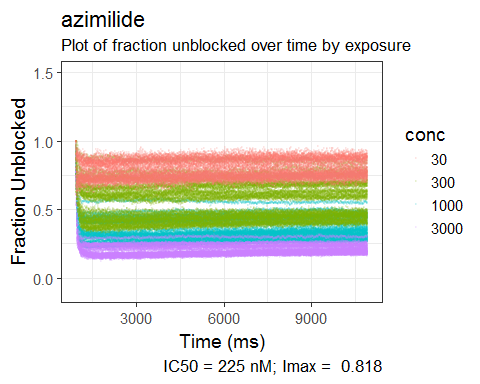
**Analysis of 28 CiPA compounds**

Figures 1 to 28 below show the plots of the raw kinetic data used by CiPA in their most recent study (Li et al., 2018). The data was obtained from their GitHub site: <https://github.com/FDA/CiPA/tree/Brad-Sandbox/hERG_fitting> . For each figure there is an estimated IC50 and maximal inhibition, Imax, value based on analyzing the end of the experiment i.e. when it reaches steady state, using:

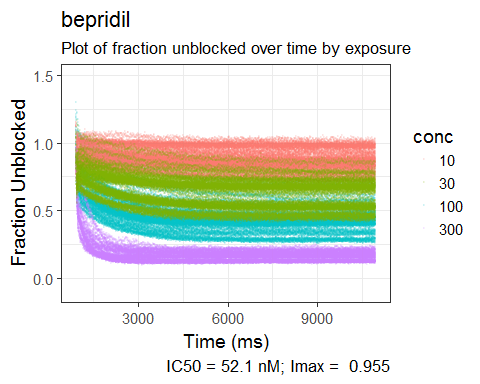
A comparison of these dynamic IC50 values to the original static IC50s is shown in Figure 29, they appear to be similar. However, when deriving the dynamic IC50 it’s noticeable that for certain compounds the Imax value is very different to the standard value of 1 which is used when deriving the static IC50 value, see Figures 9 and 11 as an example. Therefore, when we calculate the fraction of block at the free Cmax value we find that static block (Bkr-static) does not necessarily correlate strongly with dynamic block (Bkr-dynamic) for all compounds, see Figure 30.



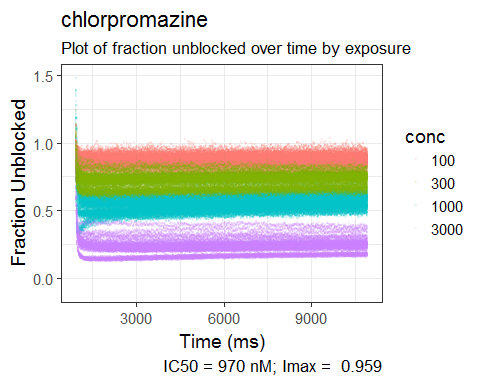
**Figure 1:** Fraction unblocked over time for increasing concentrations of astemizole.



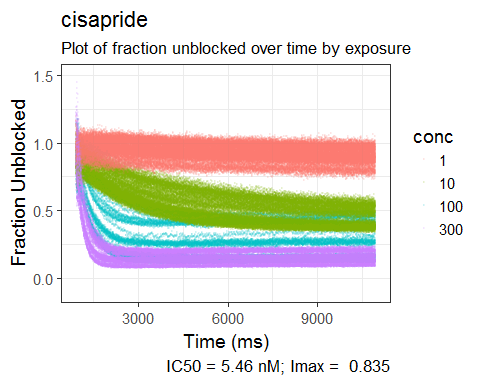
**Figure 2:** Fraction unblocked over time for increasing concentrations of azimilide.



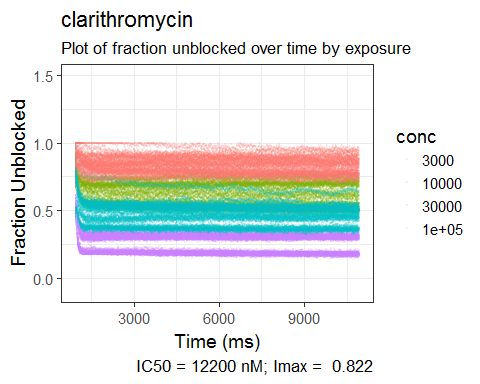
**Figure 3:** Fraction unblocked over time for increasing concentrations of bepridil.



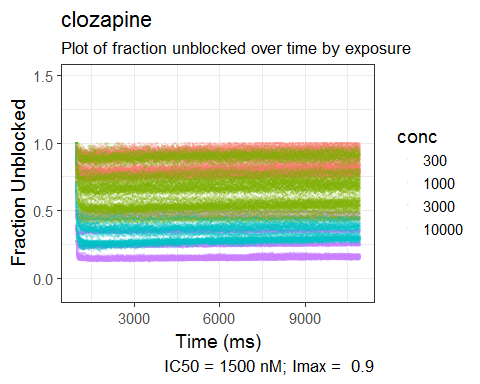
**Figure 4:** Fraction unblocked over time for increasing concentrations of chlorpromazine.



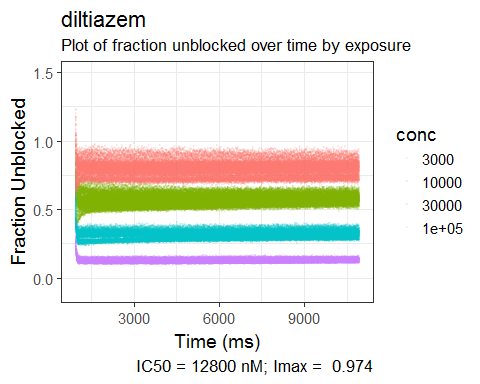
**Figure 5:** Fraction unblocked over time for increasing concentrations of cisapride.



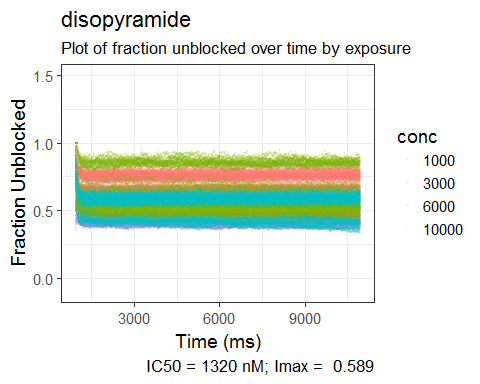
**Figure 6:** Fraction unblocked over time for increasing concentrations of clarithromycin.



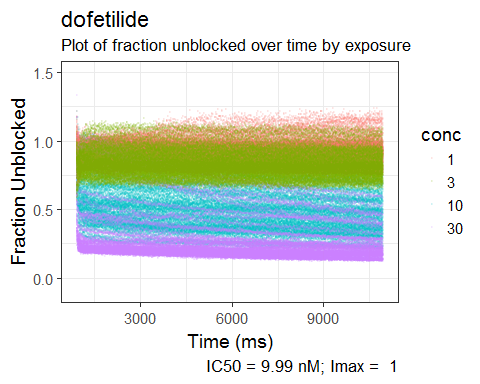
**Figure 7:** Fraction unblocked over time for increasing concentrations of clozapine.



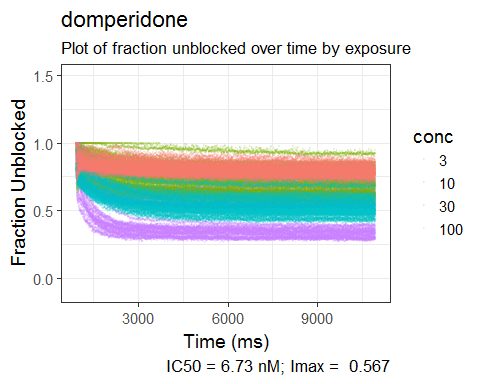
**Figure 8:** Fraction unblocked over time for increasing concentrations of diltiazem.



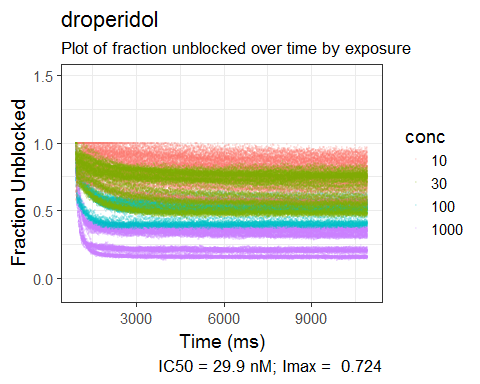
**Figure 9:** Fraction unblocked over time for increasing concentrations of disopyramide.



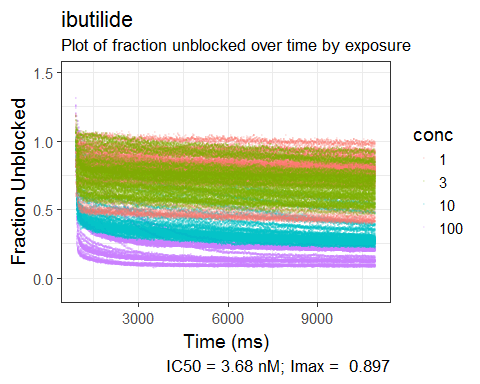
**Figure 10:** Fraction unblocked over time for increasing concentrations of dofetilide.



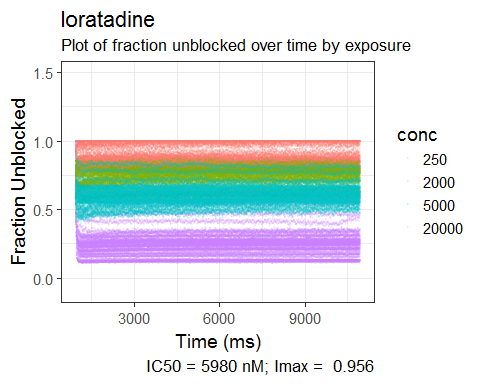
**Figure 11:** Fraction unblocked over time for increasing concentrations of domperidone.



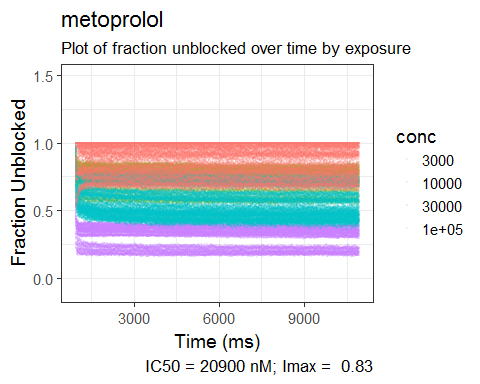
**Figure 12:** Fraction unblocked over time for increasing concentrations of droperidol.



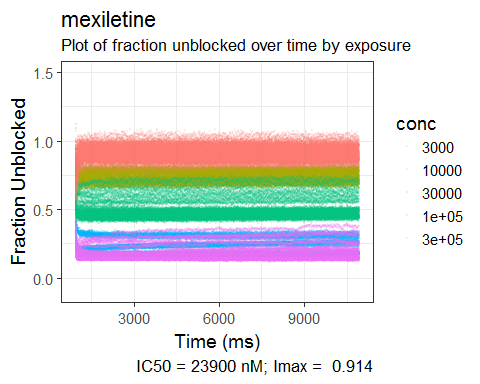
**Figure 13:** Fraction unblocked over time for increasing concentrations of ibutilide.



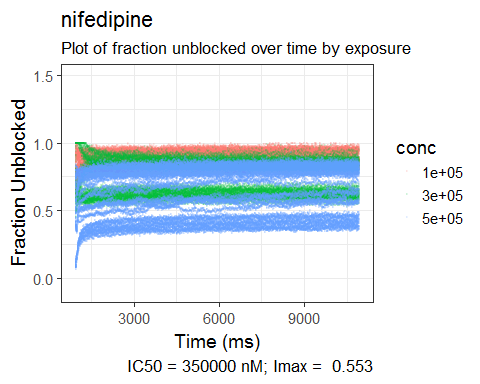
**Figure 14:** Fraction unblocked over time for increasing concentrations of loratadine.



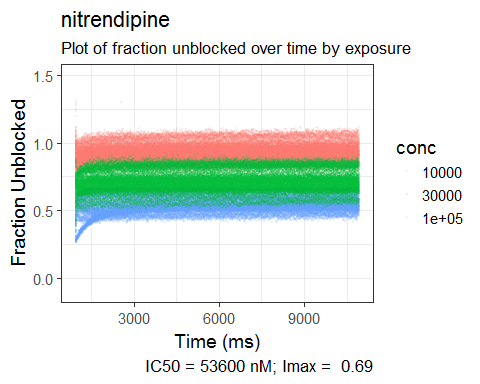
**Figure 15:** Fraction unblocked over time for increasing concentrations of metroprolol.



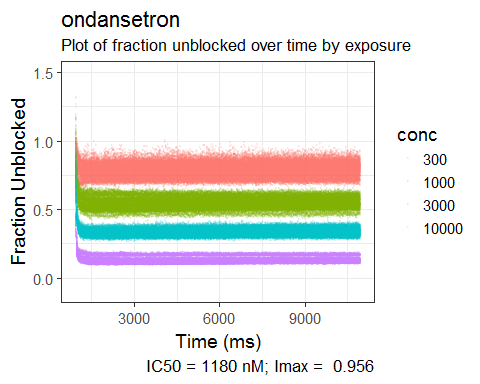
**Figure 16:** Fraction unblocked over time for increasing concentrations of mexiletine.



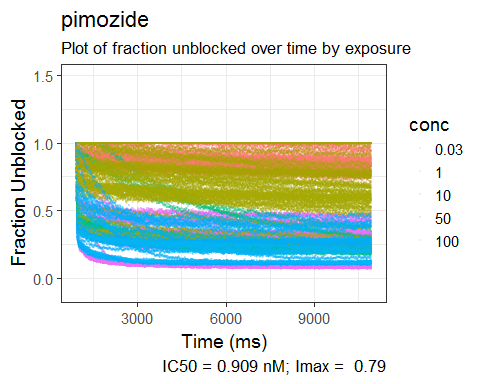
**Figure 17:** Fraction unblocked over time for increasing concentrations of nifedipine.



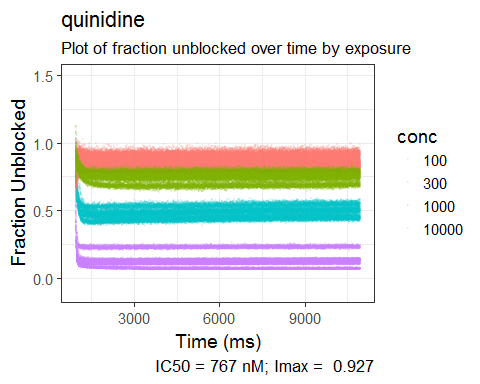
**Figure 18:** Fraction unblocked over time for increasing concentrations of nitrendipine.



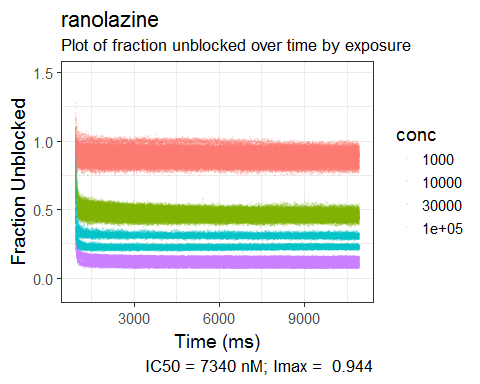
**Figure 19:** Fraction unblocked over time for increasing concentrations of ondansetron.



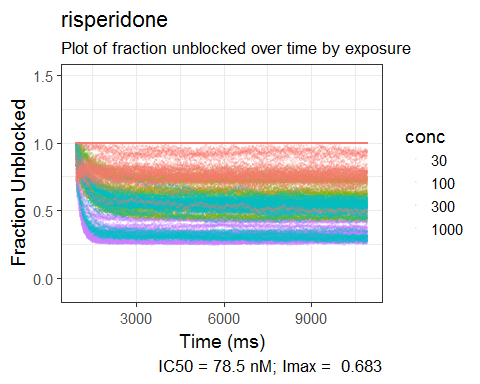
**Figure 20:** Fraction unblocked over time for increasing concentrations of pimozide.



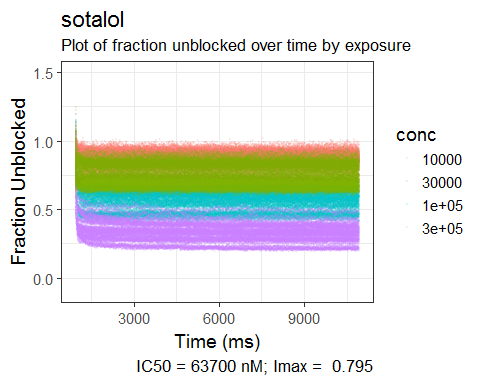
**Figure 21:** Fraction unblocked over time for increasing concentrations of quinidine.



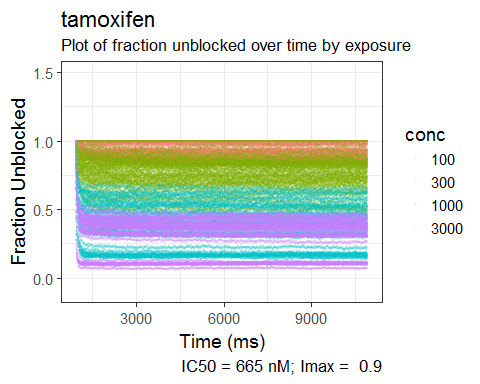
**Figure 22:** Fraction unblocked over time for increasing concentrations of ranolazine.



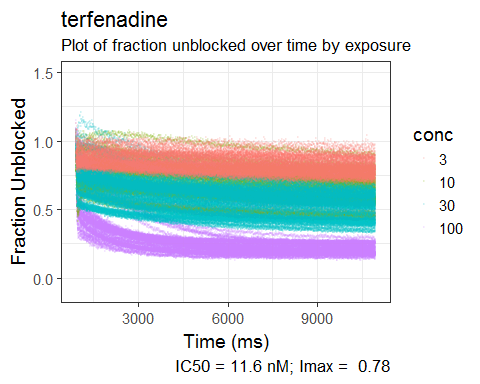
**Figure 23:** Fraction unblocked over time for increasing concentrations of risperidone.



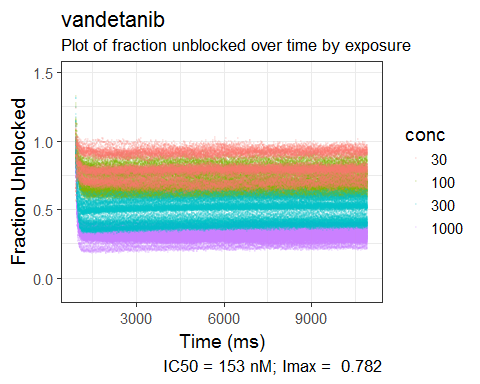
**Figure 24:** Fraction unblocked over time for increasing concentrations of sotalol.



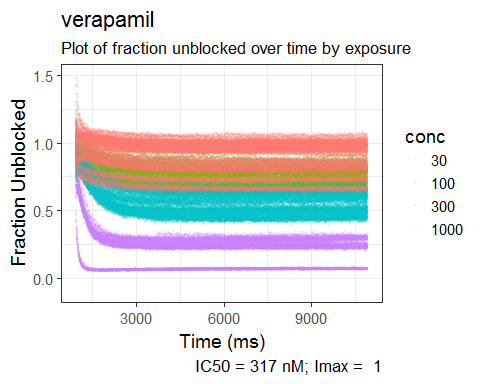
**Figure 25:** Fraction unblocked over time for increasing concentrations of tamoxifen.



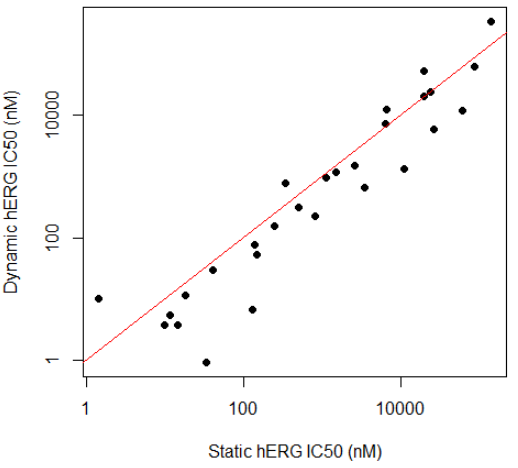
**Figure 26:** Fraction unblocked over time for increasing concentrations of terfenadine.



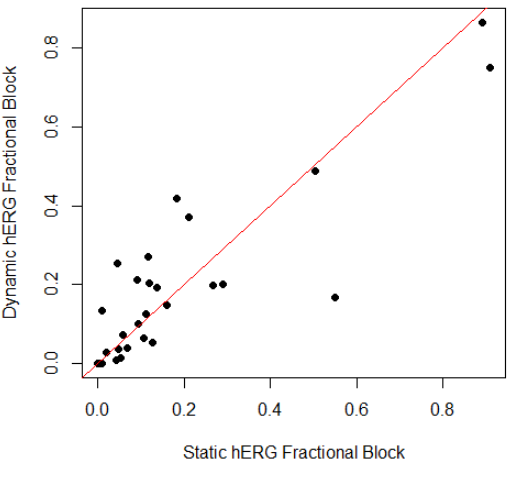
**Figure 27:** Fraction unblocked over time for increasing concentrations of vandetanib.



**Figure 28:** Fraction unblocked over time for increasing concentrations of verapamil.



**Figure 29:** Plot comparing the static to dynamic IC50 values for the hERG channel.



**Figure 30:** Plot comparing the static to dynamic fractional block at free Cmax.

**References**

Li, Z., Ridder, B.J., Han, X., Wu, W.W., Sheng, J., Tran, P.N., Wu, M., Randolph, A., Johnstone, R.H., Mirams, G.R., Kuryshev, Y., Kramer, J., Wu, C., Crumb, W.J., Strauss, D.G., 2018. Assessment of an In Silico Mechanistic Model for Proarrhythmia Risk Prediction Under the CiPA Initiative. Clin. Pharmacol. Ther. https://doi.org/10.1002/cpt.1184