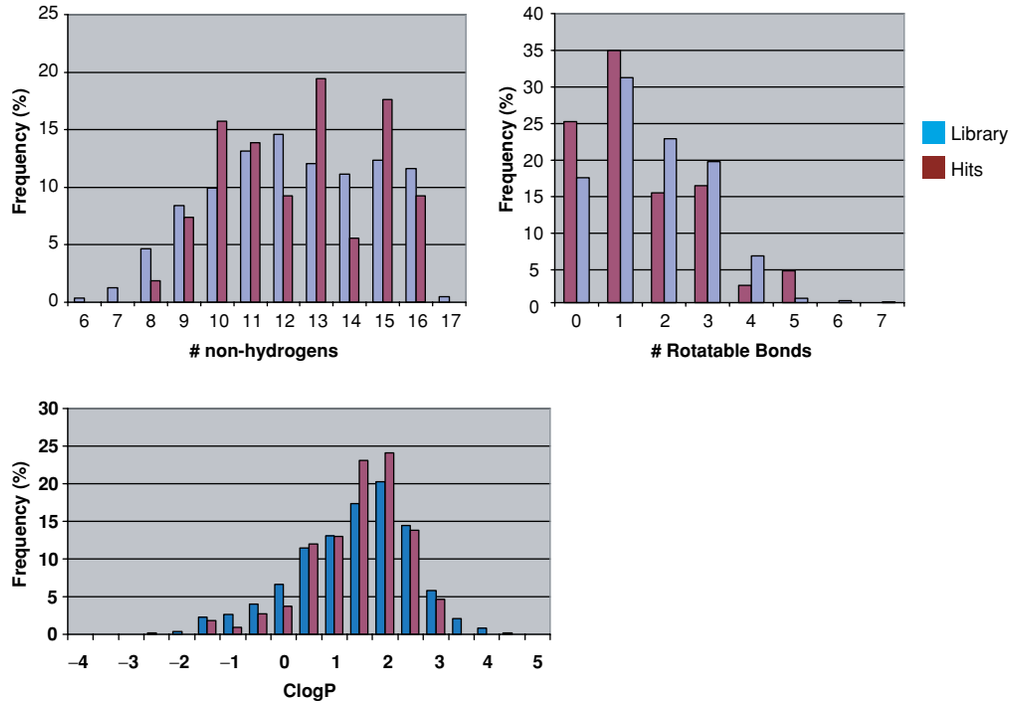

Figure 3.4. Comparison of selected properties of fragment hits versus those of the SGX core fragment library.

Lesson 3: Fragment optimization potential is not correlated with binding affinity

Figure 3.6 summarizes our experience with initial synthetic optimization of various fragments for some protein kinase targets. For each fragment we have plotted the relationship between the initially measured binding affinity of the fragment itself and the results of elaboration at one chemical handle. These data conclusively demonstrate that there is no correlation between the strength of initial binding and the optimization potential of a fragment. There is, therefore, no rational basis for preferentially devoting synthetic chemistry resources to fragment hits with higher affinities versus those that bind the target more weakly. Ligand efficiency is the issue, not affinity.

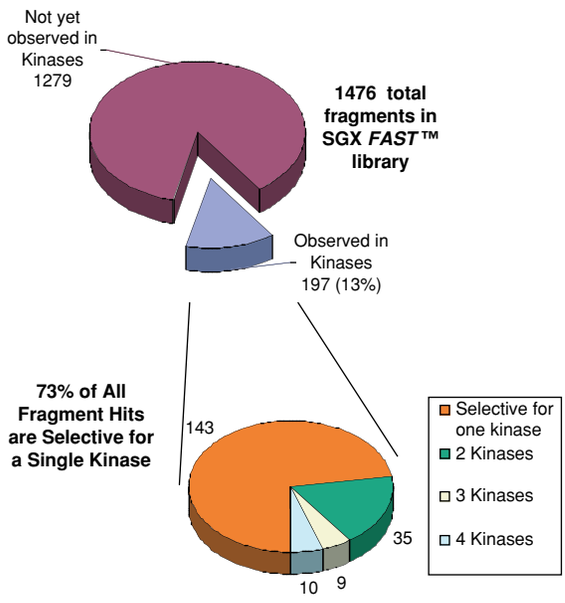

Figure 3.5. Most x-ray screening fragment hits are selective for a single protein kinase.

Future prospects

Notwithstanding the flurry of activity in fragment-based approaches since 2004, practitioners of this new strategy for drug discovery would appear to have only scratched the surface. There are many more target classes that should be pursued with fragment screening. Of particular interest

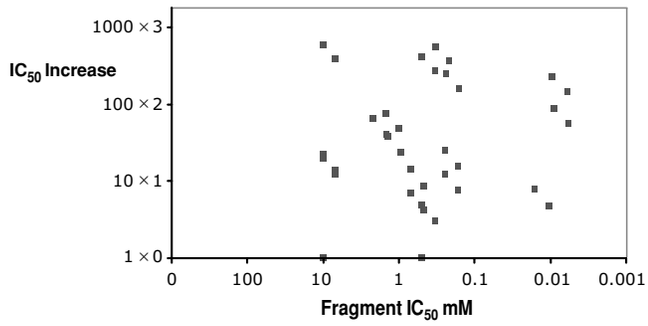

Figure 3.6. Relationship between initial binding affinity (IC_{50}) and increase in potency following elaboration at individual chemical handles for fragment hits obtained with five targets.