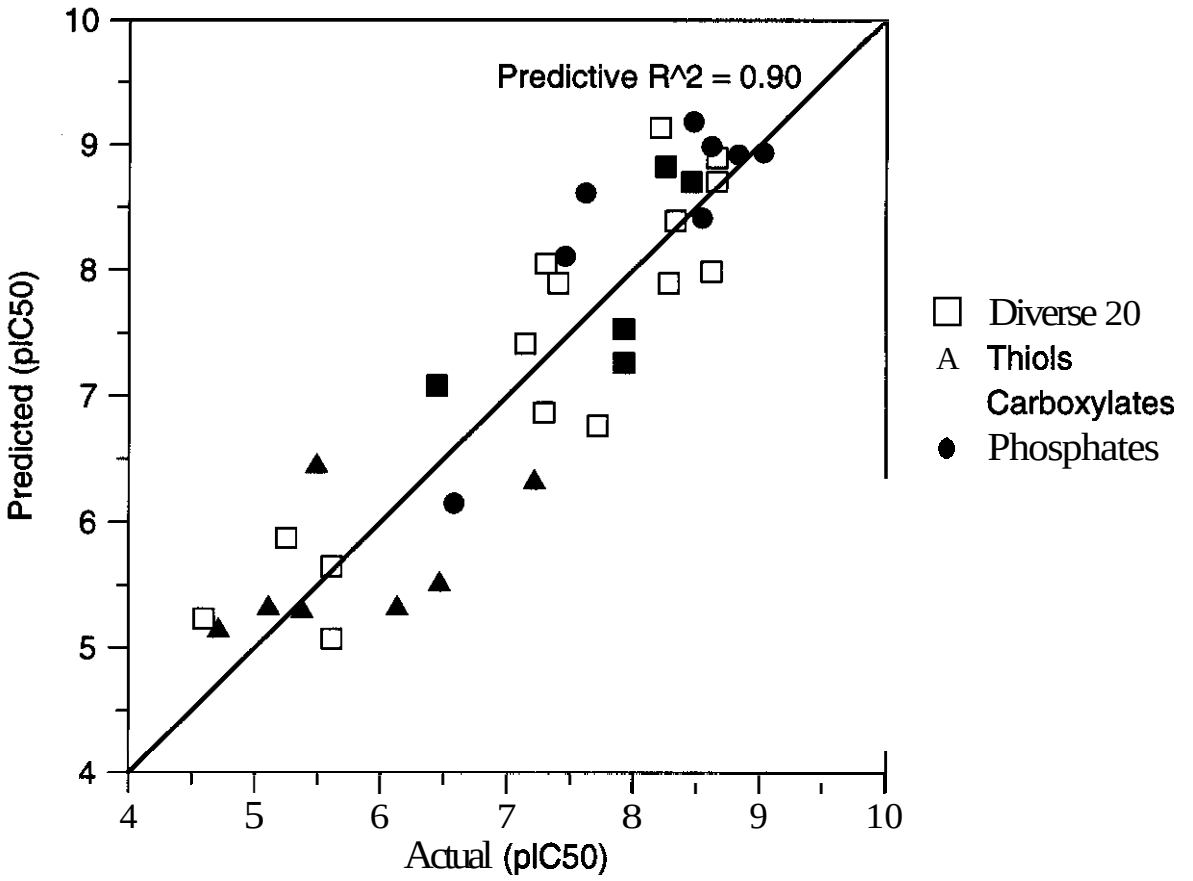

Figure 3.51. Plot of experimental versus predicted inhibition constants for 35 ACE inhibitors not used in derivation of CoMFA model (484). This plot indicates the predictability of the model. Used with permission.

(486) used two enzymes (thermolysin and renin) as well as antiviral activity against human rhinovirus, where the coat-protein receptor is known, to calibrate CoMFA methodology. They concluded that only enthalpies of binding and not binding affinities were predicted by CoMFA. Waller et al. (264) developed a predictive CoMFA model for the binding affinities of HIV-protease inhibitors based on crystal structures of complexes. Initial analysis of the 59 molecules in the training set representing five structurally diverse classes (hydroxyethylamine, statine, norstatine, ketoamide, and dihydroxyethylene) of transition-state protease inhibitors yielded a correlation with a cross-validated r^2 value of 0.786. To evaluate the predictive ability of this model, a test set of 18 additional inhibitors (487) was used that represented another class of transition-state isostere, hydroxyethylurea. The model expressed good predictive ability for the test set of hydroxyethylurea compounds ($r^2_{pred} = 0.624$) with all compounds predicted within 1.06 log unit (1.4 kcal/mol in binding affinity) of their actual activities, with an average absolute error of 0.58 log units (0.8 kcal/mol) across a range of 3.03 log units (Fig. 3.52). Predictions from this CoMFA model of HIV protease are being used to prioritize synthesis of *de* novo-designed HIV-protease inhibitors not included in development of the model.

Crippen developed a method (488) to objectively model the binding of small ligands to receptors, given the experimentally determined affinities of a set of ligands. The procedure, Vorom, used Voronoi polyhedra to generate the simplest geometrical model of the binding site. In a recent application to DHFR inhibitors (489), only eight analogs were used in the training set to derive the model and the affinities of 23/39 of the test set molecules were correctly predicted, with an average relative error of 0.83 kcal/mol for the remaining compounds.

5 CONCLUSIONS

Rapid advances in molecular and structural biology have provided ample therapeutic targets characterized in three dimensions. Tools to exploit this information are being rapidly developed and several strategies for *de* novo design of ligands, given an active site, are un-