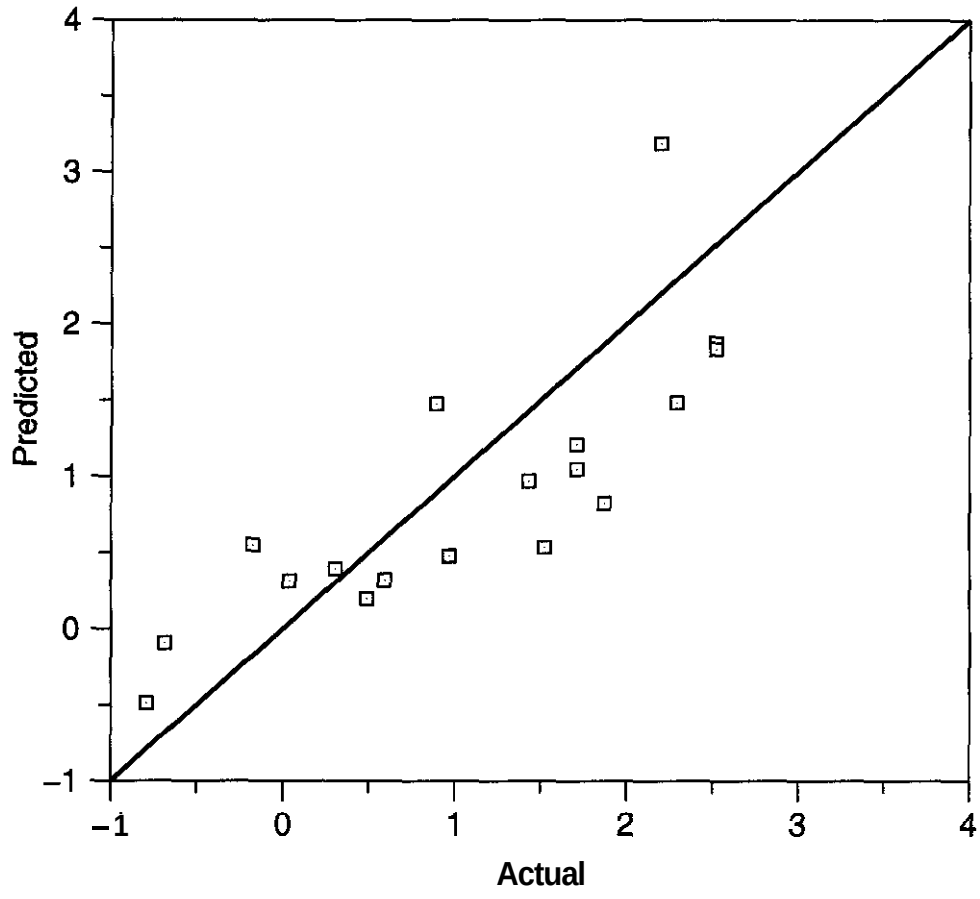

Figure 3.52. Plot of experimental versus predicted inhibition constants for 18 HIV-1 protease inhibitors not used in derivation of CoMFA model (264). This plot indicates the predictability of the model.

der investigation. It is already clear, however, that iterative approaches are necessary because of the lack of precision in predicting affinities for bound ligands. Molecular mechanics and computer graphics are essential components for design of novel ligands, and rapid progress in evolving a useful set of tools is apparent.

The ultimate goal in comparison of molecules with respect to their biological activity is insight into the receptor and its requirements for recognition and activation. Conjecture regarding the receptor is often a necessary part of rationalizing a set of structure-activity data. Although the problem of characterizing the active site of an unknown macromolecule indirectly is certainly challenging, the analysis of structure-activity data of a set of ligands, especially if their structural variety is wide, allows useful models of active sites to be developed. There are numerous caveats that must be acknowledged, however, such as flexibility of the receptor, multiple binding modes for ligands, and lack of uniqueness of most models because of limited experimental observations. Success in using these methods would appear to be increasing. This reflects both technological advances as well as insight into the problem and algorithmic improvements in our analytical approaches.

The game of 20 questions with receptors has progressed with experience. Ambiguity in interpretation of results and multiple models clearly reflect the uncertainties inherent in this indirect approach. Nevertheless, the absence of direct experimental data in many biological systems of intense therapeutic interest make this the only game available for many. It is hoped that the next decade will see further progress in our ability to extract three-dimensional information from structure-activity studies on unknown receptors.

This perspective has examined the approaches to molecular modeling and drug design and emphasized their limitations. The reader should be aware. however. that these tools are daily used on many problems of therapeutic interest with increasing success. This is clearly witnessed by publications of such studies in almost every issue of current major journals. For specific application areas, such as RNA (490, 491), DNA (492–496), membrane (497–507), or peptidomimetic modeling (382, 508–513), the reader is referred to the literature. The prediction of molecular properties, such as log P and correlation between substructures and metabolism. has led to a dramatic increase in efforts to correlate adsorption, distribution (514), metabolism (515–517), and elimination (ADME) with chemical