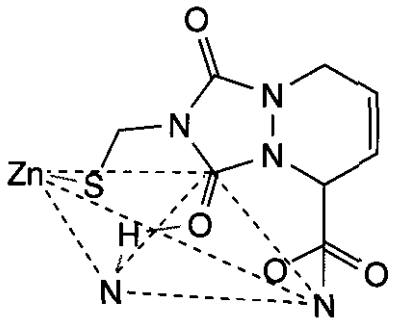

Figure 3.29. The use of active-site models in the Active Analog Approach. The structure shown is one of a series of ACE inhibitors analyzed. The thick gray lines are noncovalent interactions between the inhibitor and active-site points in the enzyme. The dashed lines correspond to the six interatomic distances monitored for each of the inhibitors analyzed.

this hypothesis by determining whether one or more geometrical arrangements of the postulated groups of site points is common to the set of active compounds. Such a geometrical arrangement of receptor groups becomes a candidate binding-site model, which can be evaluated for predictive merit.

In the study of the active site of angiotensin converting enzyme (ACE) by Mayer et al. (397), a binding site model (Fig. 3.29) was used by incorporating the active-site components as parts of each compound undergoing analysis. As an example, the sulfhydryl portion of captopril was extended to include a zinc bound at the experimentally optimal bond length and bond angle for zinc-sulfur complexes (Fig. 3.29). The orientation map (OMAP) (398), which is a multidimensional representation of the interatomic distances between pharmacophoric groups (Fig. 3.30), was based on the distances between binding-site points such as the zinc atom with the introduction of more degrees of torsional freedom to accommodate

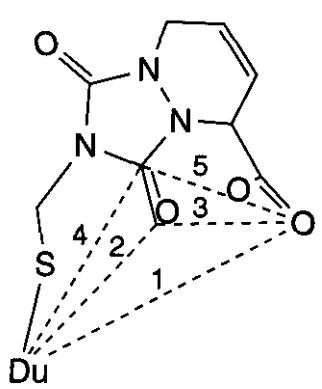

Figure 3.30. Distances used in five-dimensional OMAP used in analysis of ACE inhibitors.

the possible positioning of the zinc relative to ACE inhibitors such as captopril. Analyses of nearly 30 different chemical classes (Fig. 3.31) of ACE inhibitors led to a unique arrangement of the components of the active site postulated to be responsible for binding of the inhibitors. The displacement of the zinc atom in ACE to a location more distant from the carboxyl-binding Arg seen in carboxypeptidase A is compatible with the fact that ACE cleaves dipeptides from the C-terminus of peptides, whereas carboxypeptidase A cleaves single amino acid residues.

Visualization of the OMAP is useful to judge the additional information introduced as each new compound is added (Fig. 3.32). Computationally, it is much more efficient to treat the set of noncongeneric compounds simultaneously (111,399), as we shall see, but reassuring when identical results are obtained if one uses the sequential procedure introducing each molecule in turn, where intermediate results may be visually verified. The use of computer graphics to confirm intermediate processing of data in convenient display modes becomes increasingly more important as the individual computations and numbers of molecules under consideration increase.

4.1.4 Activity versus Affinity. Given a consistent model of either type, a limitation is that one can only ask whether the compound under consideration can present the three-dimensional electronic pattern (pharmacophore) that is the current candidate. In other words, one is limited to predicting the presence or absence of activity, a binary choice. Even the presence of the appropriate pattern is insufficient to ensure biological activity. For example, competition with the receptor for *occupied* space by other parts of the molecule can inhibit binding and preclude activity. We can thus postulate the following conditions for activity:

1. The compound must be metabolically stable and capable of transport to the site for receptor interaction (interpretation of inactive compounds may be flawed by problems with bioavailability).