



Figure 3.46. The flow of information in the Active Analog Approach (111,399). Sterically allowed conformations (represented by filled circles on the ω_1, ω_2 torsional grid) of a molecule are determined and the distances (d_1, d_2 , etc.) between pharmacophore elements are recorded for each. The resulting OMAP is used to constrain the next molecule in the series. Ideally, once all of the molecules have been evaluated, only a single point or cluster of points remains in the OMAP.

hyperspace of the set of the inhibitors, but rather the three-dimensional patterns common to the total set of inhibitors. Many conformations of a molecule often map into one three-dimensional pattern. Transformation of the multidimensional conformational hyperspace in a smaller-dimensioned OMAP space reduces the number of objects for comparison. If one starts with the most constrained inhibitor (fewest torsional degrees of freedom) and determined an OMAP for it, then one can use the upper and lower distance bounds as constraints for searches for the next molecule. In other words, one looks only where there are possible solutions to the problem. A more advanced approach simply exam-

ines each candidate solution from the initial OMAP to see whether all the other molecules are capable of presenting the same pattern. By changing the focus to the hypothesis of a common three-dimensional pattern, a more efficient approach has been devised (Fig. 3.46) (399). Clearly, the algorithms that one chooses to do the problem are important.

Table 3.1 Degrees of Torsional Freedom to Specify ACE Active Site Geometry

Degrees of Freedom (n)	Number of Molecules	Total
3	6	18
5	7	35
6	3	18
7	5	35
8	6	48
9	1	9
Totals	28	163

4.4.4 Alternative Approaches. A conceptually similar approach to receptor mapping has been taken by Ghose and Crippen (446–449), who used the distance geometry method to analyze site points and drug interactions. A site model was postulated with some initial estimates of force constants between the appropriate portion of the ligand and the site point. The binding energy for a particular binding mode can be calculated:

$$E_{\text{calcd}} = cE_c + Sx_{ti,tm}$$

where E_c is the conformational energy, c is a coefficient to be fit, x is the interaction of a site point i with the bound ligand point m , which depends on their types. The novel aspect of