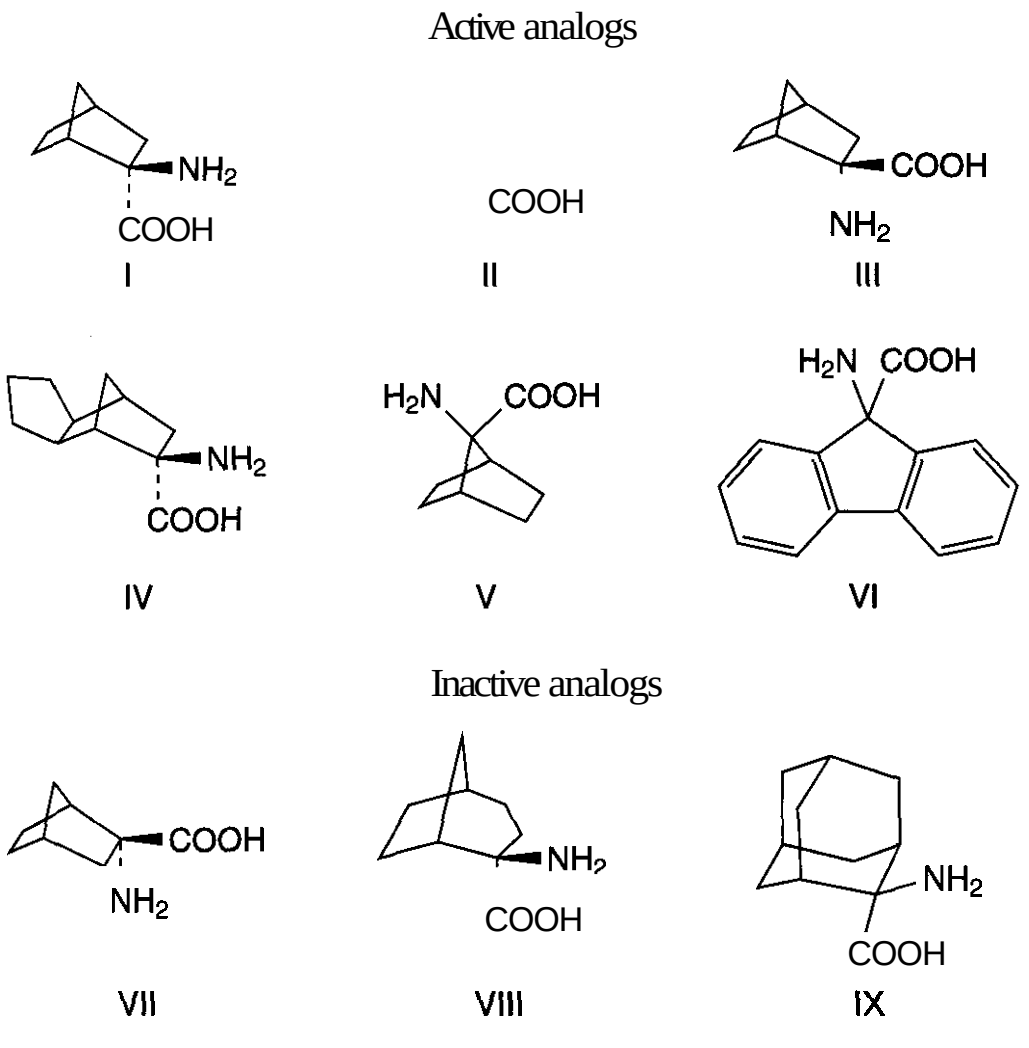

Figure 3.48. Example of receptor mapping of set of enzyme inhibitors that **can** be aligned on common amino acid framework. Set of inactive compounds all require common novel volume when compared with active compounds (402). Used with permission.

mapping of two different chemical classes of ligands to support the hypothesis that they bound to the same site. Calder et al. (460) argued that a successful correlative CoMFA model for 36 compounds of six chemical classes of GABA inhibitors indicated that the alignments used were significant. In some cases, comparison of volume maps for two receptors have allowed optimization of activity at one receptor with respect to the other. The work of Hibert et al. (461, 462), through the use of receptor mapping to increase the selectivity of a lead compound for the 5-HT_{1A} receptor over the a,-adrenoreceptor, has resulted in clinical trials for a novel chemical class. This steric-mapping approach has become relatively popular, and numerous examples appear in current journals (463) on a regular basis.

Although there are several feasible algorithms to deal with unions of molecular volumes, the use of pseudoelectron density functions calibrated to reproduce VDW radii (424) with three-dimensional contouring to represent the surface has allowed mathematical manipulation of the density associated with each lattice point to allow for union, intersection, and subtraction of volumes. Analytical representation of molecular volumes by Connolly (464, 465) and solvent-accessible surfaces by Kundrot et al. (466) may be an alternative that would allow optimization of volume overlap, for example, by minimizing the difference in volume between two structures. The solvent-accessible surface area can be used to approximate the free energy of hydration and a rapid, numerical procedure for its calculation has been reported (467).

4.4.6 Model Receptor Sites. One of the first visualizations of a receptor model is that of Beckett and Casey (468) for the opiate receptor published in 1954. Because morphine and many other compounds active at this receptor are essentially rigid, the model did not have to address the interaction of myriad numbers of flexible, naturally occurring opioid ligands, such as endorphins and enkephalin, which were only subsequently discovered. The model receptor had an anionic site to bind the charged nitrogen, a hydrophobic flat surface with a cleft to bind the phenyl ring, and a hydrophobic hydrocarbon bridge seen in morphine. Kier (469) published a number of pa-