for biological activity. Indeed, the deficiencies of conventional CoMFA routine mentioned earlier may be effectively dealt with by eliminating from the analyses those areas of three-dimensional space where changes in steric and electrostatic fields do not correlate with changes in biological activity. The q^2-GRS routine was devised (75) to eliminate those areas from the analysis based on the (low) value of the q^2 obtained for such regions individually. The major feature of this routine is that it optimizes the region selection for the final PLS analysis. In this regard, it is intellectually analogous to the GOLPE approach (74).

3D-QSAR remains an active area of research and method development. Several recent approaches such as COMSiA (45), QSiAR (46), and GRIND (122) address the most notorious CoMFA problems dealing with the grid artifacts. However, it should be kept in mind that 3D-QSAR modeling is a difficult process. It is reasonably successful when underlying molecules are relatively rigid and similar, so that the identification of the 3D pharmacophore is straightforward. With the increased complexity and flexibility of molecules and a possibility of multiple mechanisms of binding with the receptor, the derivation of unambiguous pharmacophore and unique alignment is sometimes practically impossible (as shown above in the case of AchE inhibitors), and extreme care is important in trying to obtain reproducible and validated QSAR models.

3.2 The Descriptor Pharmacophore Concept and Variable Selection QSAR

The termpharmacophore, introduced by Ehrlich in the early 1900s (123), was originally referred to the molecular framework that carries (*phoros*) the essential features responsible for a drug's (*pharmacon*) activity. Nowadays, this term has almost the opposite meaning as applied to three-dimensional (3D) molecular structure. A 3D pharmacophore is defined as a collection of particular chemical features (functional groups) and their spatial arrangement, which define pharmacological specificity of a series of compounds (124). The pharmacophore concept assumes that structurally diverse molecules bind to their receptor site in a similar way, with their pharmacophoric elements interacting with the same functional groups of the receptor.

The pharmacophore concept plays a very important role in guiding the drug discovery process. Pharmacophore models help medicinal chemists gain an insight into the key interactions between ligand and receptor when the receptor structure has not been determined experimentally. A pharmacophore can be used as a basis for the alignment rules in 3D-QSAR analysis for the lead compound optimization (125). Furthermore, a pharmacophore can be directly used as the search query for 3D database mining, which is a common and efficient approach for discovery of lead compounds (126).

Pharmacophore identification refers to the computational way of identifying the essential 3D structural features and configurations that are responsible for the biological activity of a series of compounds. It is computationally intensive, requiring searching two huge spaces: the available conformations for each compound and the possible correspondence (alignment) between different compounds. A number of approaches and computer programs have been specifically developed for pharmacophore identification including, for example, Active Analog Approach, AAA (108, 127, 128), Ensemble distance geometry (129), DISCO (116), Chem-X (130), Catalyst/Hypo (131, 132), Catalyst/HipHop (133, 134), and Apex-3D (135).

An obvious parallel can be established between the identification of descriptors contributing the most to the correlation with biological activity, and search for pharmacophoric elements, which are mainly responsible for the specificity of drug action. Indeed, individual pharmacophoric elements are typically identified in the course of experimental structure-activity studies. Considering molecules as a collection of substructures, pharmacophoric elements can also be viewed as specific chemical features selected from all chemical fragments present in a molecular data set. Thus, the selection of specific pharmacophoric features responsible for biological activity is directly analogous to the selection of specific chemical descriptors contributing to the most explanatory QSAR model. Frequently, the