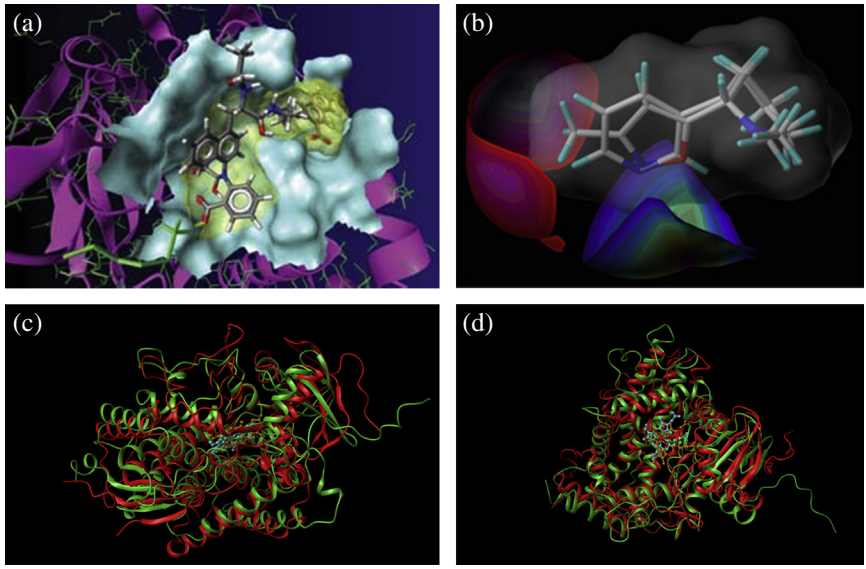

FIGURE 2.14 Tripos, the first independent company focused on the use of computer aided drug design, was founded in 1979. One of its products, Benchware 3D Explorer, provides drug discovery scientists with the ability to visualize and manipulate protein-ligand structures on a desktop computer. Ligands can be modified within the context of a protein in order to gain insight into the impact of structural changes on the potential binding energy of a new proposed ligand. Image (a) shows the PDB structure of protein tyrosine phosphatase 1B (RCSB 1NNY) with a potent inhibitor, which can be readily visualized and manipulated by non-experts in molecular modeling using the Tripos Benchware 3D Explorer software. Important aspects of binding, such as hydrogen bonding, hydrophobic interactions, and structural compatibility between the ligand and protein are readily identified. The surface of the binding site, highlighted in light blue (Connolly surfaces), enables the user to see the shape complementarity of the ligand and the protein. The Sybyl-X software system, also a product of Tripos, offers more advanced capabilities, such as virtual high throughput screening in which potentially millions of compounds are docked into a target protein's binding site and scored to provide an estimate of their relative binding energy at the target of interest. Pharmacophore-based virtual high throughput screening, a method of overlaying and comparing a compound of interest with potentially millions of compounds to determine their similarity, and therefore, potential for binding at a macromolecular target, is also possible with Sybyl-X. Image (b) shows an overlay of nicotine and an oxazole derivative, comparing their overall molecular architecture. The grey, translucent surface provides visualization of the molecular volume of the aligned molecules, the red area represents significant differences in hydrophobic surfaces between the two compounds, and the blue/green surface indicates a high degree of electrostatic potential overlap in the two structures. Comparisons of this type can be automated, scored, and sorted in order to facilitate the identification of potentially interesting molecules based on their similarity to known compounds of interest using Sybyl-X. Comparison of macromolecular structures is also facilitated with Sybyl-X. Panels (c) and (d) provide different views of an overlay of steroid 17-alpha-monooxygenase (Cyp17A1, RCSB 3RUK), a key enzyme in steroidogenesis, and cholesterol 7-alpha-monooxygenase (CYP7a1, RCSB 3DAX), the rate limiting enzyme in the synthesis of bile acid from cholesterol. Key differences in the binding sites in the two related enzymes can be exploited by drug discovery scientists to create compounds that are highly selective for one enzyme over the other.