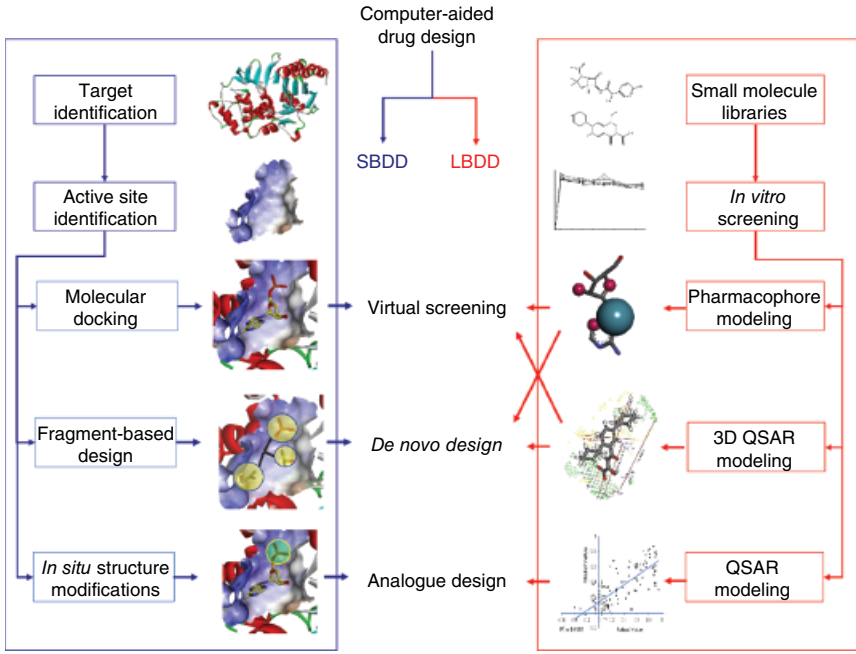

Figure 13.2 Overview of the methods used in the computer-aided design of antibiotics and inhibitors of antibiotic resistance mechanisms (SBDD, structure-based drug design; LBDD, ligand-based drug design; QSAR, quantitative structure–activity relationship; 3D, three-dimensional). *(See insert for color representation of the figure.)*

A knowledge of the three-dimensional (3D) structure of a biomolecule enables a structure-based drug design (SBDD) of candidates for the development of new therapeutic agents. These macromolecules should be validated as drug targets by proving that modulation of the target results in changing the disease states. A first stop source of 3D structures of biomolecules complexed with either drugs or active ligands is Protein Data Bank (PDB) website (Berman et al. 2000) that currently contains over 83 000 structures of bacterial macromolecules obtained by X-ray crystallography or NMR spectroscopy. Most of these entries provide information about the static structure of biomolecules with druggable sites or mutated active sites. For some proteins, there are multiple entries of the same biomolecule complexed with different ligands that can provide additional information about conformational flexibility of the site and the ability of target biomolecule to accommodate ligands of different sizes and shape. In the absence of the multiple entries, conformational flexibility of proteins and binding of different ligands can be explored using molecular dynamics simulation. Furthermore, homology modeling can be employed to predict the 3D structures of proteins without experimental structures. Once