production of damaged proteins involved in carcinogenesis. In the antisense oligonucleotides approach, the mRNA translation is interfered by inhibiting the translation of the information at the ribosome, whereas in the anti-gene therapy, a direct binding to the DNA double strand inhibits transcription.[36]

The knowledge of the three-dimensional (3D) structure of these new target macromolecules, which are normally proteins, by using X-ray crystallography, permits the rational design of small molecules that mimic the stereochemical features of the macromolecule functional domains. The principal steps in structure-based drug design using X-ray techniques are summarized in Figure 1.2.

In the absence of a 3D structure of a target protein, homology criteria may be applied by using the experimental structure of similar proteins, which is especially useful in the case of individual subfamilies. The knowledge of the 3D structure of a target also permits to design and generate virtual libraries of potential drug molecules to be used for *in silico* screening.

Many targets have different subtypes and functions, which makes finding therapeutically interesting inhibitors difficult. For instance, because matrix metalloproteases (MMPs) are involved in the cleavage of some bioactive molecules besides of extracelular matrix proteins, elimination of some of them in *knockout* animals—especially MMP-3, −8, and −9—has led to the development and metastasis of tumors. For this reason, only specific MMPs must be selected as anticancer targets. An example among ligands with multiple functions is transforming growth factor-β (TGF-β). This cytokine received that name based on its ability to induce fibroblast malignancy and favor metastasis by avoiding the immune system action in the last steps of a cancer, but it has been compared to the main character in "The strange case of Dr. Jekyll and Mr. Hyde" because it may also eliminate tumors in early

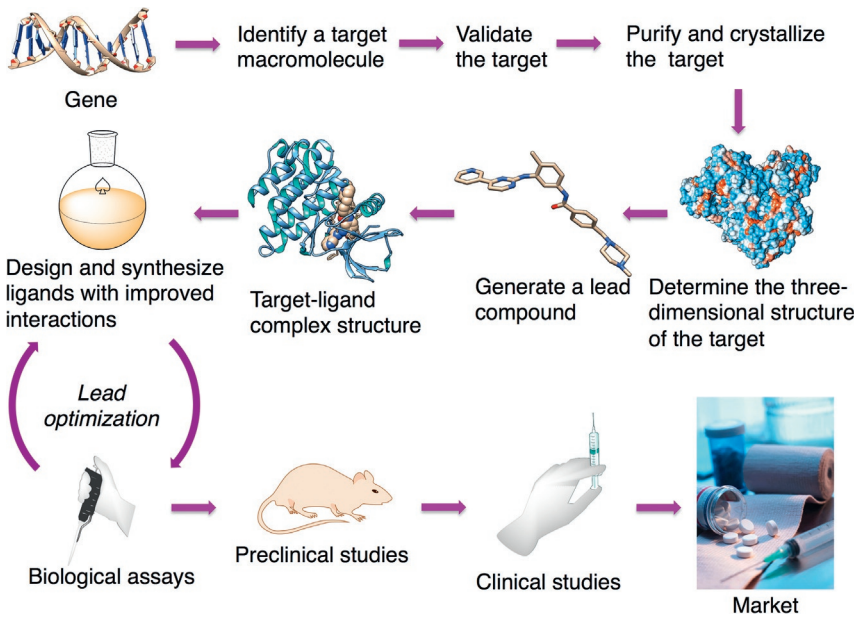

FIGURE 1.2

Structure-based drug design.