Multidrug resistance (MDR) is the dominant cause of the failure of cancer chemotherapy. Further investigation and progress in the abovementioned strategies will provide significant advances in the rational combat against cancer MDR. Other modalities to combat MDR are described in this review, including the pharmaco-modulation of acridine, which is a well-known scaffold in the development of bioactive compounds, the use of natural compounds as means to reverse MDR, and the conjugation of anticancer drugs with carriers that target specific tumor-cell components. The recently resolved X-ray structure of human P-gp can help predict the interaction sites of designed compounds, providing insight into their binding mode and directing possible rational modifications to prevent them from becoming P-gp drug substrates. In fact, hybrid compounds that are produced by covalently attaching NO-donors and antitumor drugs have been shown to elicit a synergistic cytotoxic effect in a variety of drug resistant cancer cell lines. This strategy is based on the design of hybrid compounds that are obtained either by merging the structural features of separate drugs, or by conjugating two drugs or pharmacophores via cleavable/non-cleavable linkers. Appropriate NO donors have been shown to reverse drug resistance via nitration of ABC transporters and by interfering with a number of metabolic enzymes and signaling pathways. Structure-based design methods, which utilize 3D structural data of proteins and their complexes with ligands, are the most effective of the in silico methods available, as they provide a prediction regarding the interaction between transport proteins and their substrates and inhibitors. The conjugation of anticancer agents with nitric oxide (NO) donors has recently been developed, creating a particular class of hybrid that can combat tumor drug resistance. Their pharmacokinetics are governed by the nanoparticle or polymer carrier and make use of the enhanced permeation and retention (EPR) effect, which can increase selective delivery to cancer cells. These systems are usually internalized by cancer cells via endocytosis and accumulate in endosomes and lysosomes, thus preventing rapid efflux. The use of hybrid molecules that are able to simultaneously interact with two or more cancer cell targets is currently being explored as a means to circumvent drug resistance. The design of antitumor drugs that are able to evade MDR is rapidly evolving, showing that this area of biomedical research attracts great interest in the scientific community. Encouraging results have been obtained in the investigation of the MDR-modulating properties of various classes of natural compounds and their analogues. The approach is highly promising due to the pharmacokinetic and pharmacodynamic advantages that can be achieved over the independent administration of the two individual components. Another strategy to circumvent MDR is based on nanocarrier-mediated transport and the controlled release of chemotherapeutic drugs and P-gp inhibitors. Finally, the outstanding potential of in silico structure-based methods as a means to evaluate the ability of antitumor drugs to interact with drug transporters is also highlighted in this review. In summary, although major efforts were invested in the search for new tools to combat drug resistant tumors, they all require further implementation and methodological development. The current review explores promising recent approaches that have been developed with the aim of circumventing or overcoming MDR. Inhibition of P-gp or downregulation of its expression have proven to be the main mechanisms by which MDR can be surmounted. However, it .should be stressed that the task of obtaining successful multivalent drugs is a very challenging one