other regions of the body (e.g., blood), drug concentrations are generally well below the concentrations required for transporter saturation.[29]

As mentioned earlier, P-glycoproteins (also referred to as multidrug resistant protein 1 (MDR1)) have been extensively studied as a result of their impact on the drug concentrations, especially with respect to the blood–brain barrier, but there are a number of other transporters that have an impact on compound distribution.[30a,b] The breast cancer resistant protein (BCRP) was originally identified as a key mechanism for the development of chemotherapeutically resistant breast tumor cells as the name implies, but it has been subsequently identified in normal hepatocytes, the placenta, and other tissues.[31] Additional examples of transporters include the organic anion transporters (OATs),[32] organic cation transporters (OATs),[33] di/tri peptide transporters,[34a,b] organic anion-transporting polypeptides (OATPs),[35] and monocarboxylic acid transporter.[36]

The impact of a transporter system on a compound's distribution can be either positive or negative depending on the desired outcome. If, for example, one is attempting to develop a compound that is directed towards a target in the brain, high Pgp activity would be a significant barrier to success. On the other hand, if entry into the brain would produce an undesired side effect, then high Pgp activity would be a positive outcome, as distribution into the brain would be limited. In a similar manner, compounds that are substrates for uptake transporters on specific organs can increase compound concentration in these organs, leading to either a positive or negative result, depending on the outcome. If high concentrations created by transporter activity enhance a compound's ability to reach its intended target, then *in vivo* activity may be higher than anticipated by pharmacokinetic studies. On the other hand, if an off-target activity or toxicity is driven by concentration of the compound in a particular organ or tissue type, transporter activity leading to increased concentration in the organ or tissue type can enhance undesired activity or lower the threshold required for toxicity.

It is also worth noting that drugs can be substrates for more than one transporter protein, which further complicates the picture. Expression levels of functional transporter proteins are variable across tissue types, and of course, compound affinities/rates of transport are different for each protein. Crestor® (rosuvastatin), for example, is a substrate for MDR1, multidrug resistance-associated protein 4 (MRP4), and OATP-1B3, as well as several others. Similarly, Gleevec® (imatinib) is a substrate for at least six different transporter proteins, each of which influences its tissue distribution (Figure 6.21).[37] It should be clear from these examples that a complete understanding of the impact of transporter protein on drug distribution requires knowledge of the role of multiple members of this important family of macromolecules. Given the wide variety of transporter proteins, there is no single set of structural changes that can be used as a guide for altering transporter-mediated drug transport. Removing or augmenting