keted by Pfizer as Viracept, the mesylate salt of nelfinavir. In both (42) and (**43**), the scientists involved used iterative SBDD methods to alter the physicochemical properties of the drug molecule while maintaining potency by optimizing interactions with the active site of the enzyme. An important feature shared by these compounds is the fact that the bound inhibitors appear to be in low energy conformers, so that minimal conformational energy costs must be paid upon binding to the enzyme.

2.4.3 Thrombin. Thromboembolic diseases such as stroke and heart attack are major health problems, especially in many Western countries. This has led to searches for drugs that are effective inhibitors of various serine endoproteases in the blood-clotting cascade, such as factor Xa and thrombin. Existing therapeutic agents such as the coumarins (like warfarin), heparin, and hirudin have problems related to their absorption or unpredictable metabolism and clearance. Recently, new small molecule inhibitors of thrombin have become available for human use in the United States, including (44) (argatroban, MD-805, developed by Mitsubishi) and (45) (melagatran, developed by AstraZeneca) (110, 111). These nanomolar inhibitors of human thrombin were optimized by classical medicinal chemistry, starting with peptidomimeticssimilar to the thrombin cleavage site in fibrinogen (see Fig. 10.14a). Poor absorption by an oral route requires that they must be administered intravenously or at best subcutaneously. At present, the only direct inhibitor of thrombin suitable for oral administration is ximelagatran, a prodrug form of melagatran in late development for various cardiovascular indications by AstraZeneca as of mid-2002. The therapeutic need and the availability of high quality crystal structures for human thrombin bound to inhibitors such as (44) make this an attractive target for SBDD (112). The significant efforts at Merck to use SBDD approaches to develop orally available inhibitors of thrombin, which have yielded compounds that have entered clinical trials, have been reviewed (113,114). For a good overview of this area, see the review by Babine and Bender (9).

Compound (46) [NAPAP, N-alpha-(2-naphthylsulfonylglycyl)-4-amidinophenylalanine piperidide] is a moderately potent inhibitor of human thrombin, but was found to have an unacceptably short plasma half-life in animals (115). However, (46) has been a useful experimental tool and a variety of analogs have been made. The structures of (44) and (46) bound to human thrombin show that they bind somewhat differently, as shown in Figure 10.14b (112,116). However, both form hydrogen bonds with the backbone at Gly216 (part of the oxyanion hole), and both fill the S_1 specificity pocket with a permanent cation attached to an extended hydrophobic group. Compound (46) was the starting point at Boehringer Ingelheim for the development of the orally bioavailable prodrug (47) (BIBR-1048) that generates in *vivo* a potent inhibitor of human thrombin (117). Compound (47) is currently in human clinical trials.

Scientists at Boehringer Ingelheim used the crystal structure of the complex between (**46**) and human thrombin to design a replacement for the central bridging glycine moiety. The hypothesis that a trisubstituted benzimidazole could correctly place groups into the S_1, S_3, and S_4 pockets was confirmed. The first such compound made was (48). The IC_{50} for thrombin inhibition by (48) was only 1.5 μM, but the compound had an improved serum half-life in rats. Determination of the crystal structure of the thrombin–(48) complex showed that (48) binds in a similar fashion to (**46**). The N-methyl on the benzimidazole fit into the P_1 pocket, and the phenylsulfonyl group extended into S_4. The low affinity is likely attributable to the fact that (48) forms no hydrogen bonds with the backbone of Gly216. An iterative optimization process (Fig. 10.15) was used to regain the lost affinity, eventually surpassing the thrombin affinity of the starting point (46) (0.2 μM).

Surprisingly, the N-methyl group could not be replaced with larger alkyl substituents, despite what appeared to be room for them in the P_1 pocket. However, replacing phenyl with larger aryl groups such as naphthyl or quinolinyl on the sulfonamide provided favorable interactions in the P_4 pocket. The crystal structure suggested that the increased lipophilicity of such aryl groups could be balanced by appending charged substituents to