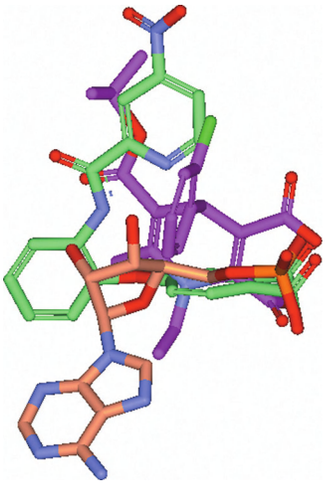

Figure 17.6. Comparison of docked compound **1a** with crystal structure of W1807 and AMP. Compound **1a** (carbons in green), W1807 (carbons in magenta, PDB entry 3AMV), and AMP (carbons in orange, PDB entry 8GPB) are shown in stick model with noncarbon atoms in standard colors. Hydrogen atoms have been omitted for clarity.

compound **1a** is almost perpendicular to that observed with W1807.

Characterization of the binding pocket

Grid-based surfaces were calculated by FLOG[18] using the docking model to further characterize the binding pocket. Each grid was visualized as a series of isoenergetic surfaces that describe the binding pocket by its polar (hydrogen bond donor and acceptor) and hydrophobic nature. The hydrophobic contour and hydrogen bond contour maps are shown in Figure 17.7. For clarity, the docked compound **1a** is shown, whereas the nearby residues in the binding pocket are omitted in the picture.

In the hydrogen bond contour map, the red area shows that the residues in the binding pocket would favor interaction with a hydrogen bond acceptor on the ligand. For example, the large red grid around the diacid on the A ring indicates that the surrounding residues, a cluster of arginines, would prefer to interact with a hydrogen bond donor that is a diacid functional group on the ligand. Similarly, the small red grid around the nitro group on the C ring shows that the residues in this region favor interaction with a hydrogen bond acceptor. In this region, the residue is Arg193 while the hydrogen bond group on the ligand is a nitro group.

In the hydrophobic contour map, the green area around compound **1a** denotes the regions in the binding pocket that would favor interaction with a hydrophobic group on the ligand. For example, the green region near the pyridine (C ring) suggests that activity can be enhanced with appropriate hydrophobic substitutions on the pyridine. This is in good agreement with the SAR in which compounds unsubstituted on the C ring (i.e., compound **1g**) have the least activity while potency increases more than tenfold with hydrophobic substitutions at the meta position, for example compounds **1e** and **1f** (Table 17.1).

Similarly, there is a large area near the central phenyl ring B that is unfilled by compound **1a** and for which SAR was unavailable. As was the case with the pyridine, this visually suggests that additional hydrophobic groups attached to the central phenyl B ring could fill this space and make favorable interactions with the residues that line this region of the binding pocket, thereby improving the binding and thus the potency.

Design and synthesis

One possible modification was to fuse a hydrophobic ring onto the central phenyl ring B to provide access to the putative hydrophobic region. Both saturated and unsaturated five- and six-member rings were considered. The designed compounds were obtained by modifying compound **1a**. Energy evaluation was carried out by fully optimizing each virtual ligand within the flexible binding pocket, as described before.

The interaction energy between each of the designed compounds and the enzyme was about 5–6 kcal/mol more favorable than that for the parent phenyl compound (Table 17.2). The fused ring moieties are nicely located among the aliphatic portion of the Gln72 side chain, the phenyl ring of Tyr75, and the side chain of Val45′ and make favorable interactions with the hydrophobic pocket. Based on synthetic considerations, compounds fused with an unsaturated six-member ring (naphthyl compounds) were synthesized.

The synthesis of naphthyl compounds was described by Z. Lu et al. in 2003.[28] The potencies of naphthyl analogs

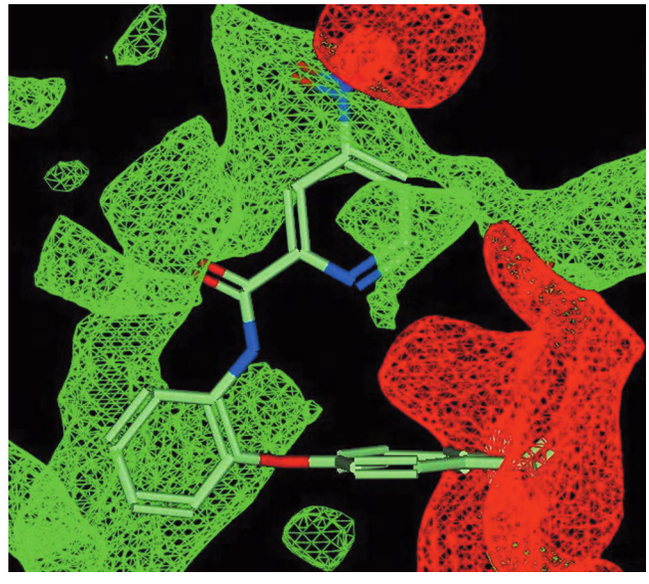

Figure 17.7. Hydrophobic and hydrogen bond acceptor contours from grid-based calculations on the docking model. The hydrophobic surface is shown as a green grid and the hydrogen bond acceptor surface is shown as a red grid. Compound **1a** is shown in stick model with carbons in green and noncarbon atoms in standard colors. Hydrogen atoms have been omitted for clarity.