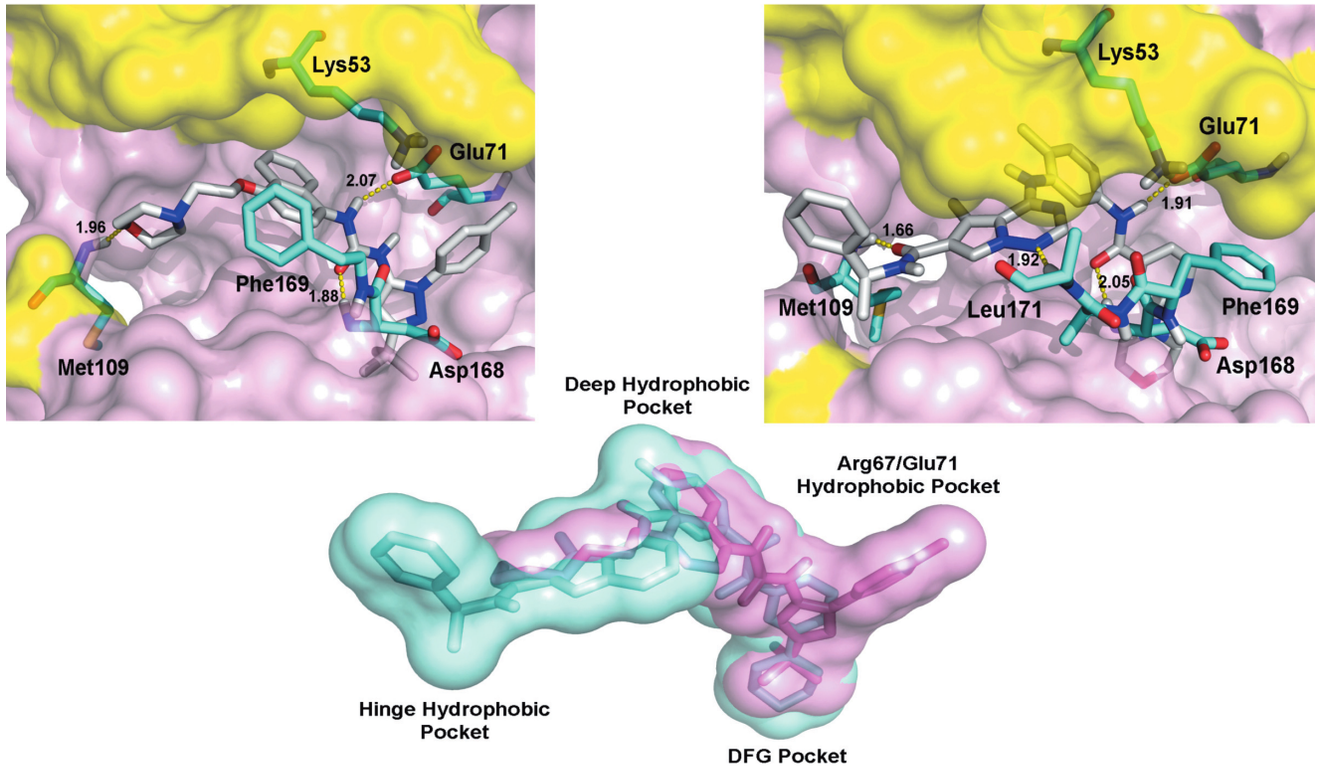

Figure 13.4. (Top left) The BIRB-796 x-ray structure in p38α illustrates the DFG-out motif, wherein a *t*-butyl group occupies the Phe169 pocket while the pendant morpholino O H-bonds to backbone NH at Met109 (1KV2.pdb). (Top right) Pyrrolotriazine **5** occupies the same Phe169 pocket while the displaced activation loop adopts a different pose with Leu171 backbone NH engaged in an H-bond to pyrrolotriazine N1 (3BV2.pdb). (Center) A comparison of overall shape between BIRB-796 and **5** illustrating similar occupation of the deep hydrophobic and DFG-out pockets.

3-morpholinobenzamide in combination with a C6-(S)-α-methylbenzylamide (**5**) exhibited a p38α K_i of 0.44 nM and a LPS/TNFα IC_{50} of 18 nM.[27] The x-ray crystal structure of the p38α complex of **5** confirmed the DFG-out configuration (Figure 13.4). The binding mode of **5** is similar to that of **4** in that the H-bonding patterns to Met109, Glu71, and backbone NH at Asp168 are conserved. The notable distinction here is that the pendant morpholinobenzamide group is found deep within the hydrophobic Phe169 pocket. In addition, part of the activation loop has relocated itself along the outer rim of the ATP-binding site so as to form a seal, as evidenced by the H-bond between pyrrolotriazine N1 and backbone NH at Leu171. This feature is distinct from that reported for BIRB-796. A further comparison between BIRB-796 and **5** is shown in Figure 13.4, wherein the molecular volume overlap between the two inhibitors is highlighted. Although BIRB-796 does not make use of the hinge hydrophobic pocket, both inhibitors occupy the deep hydrophobic pocket and the Phe169 pocket in similar ways. It is clear that relatively large inhibitors can be accommodated by the DFG-out version of p38α.

PYRAZOLOPYRIMIDINES

A further elaboration of the pyrimidine chemotype exemplified by **2** led to the discovery of the pyrazolopyrimidine core (Scheme 13.5). The presumption was that presentation of an H-bond acceptor at roughly the same location and trajectory as the cyano group in **2** could lead to a novel series of inhibitors that retain the Met109 NH interaction thought to be a key H-bonding interaction for nearly all kinase inhibitors. This was achieved by conceptually cyclizing the 5-cyano to the 6-aminoalkyl function, yielding a pyrazolopyrimidine core, which was further elaborated both at the N1 and the 4-methyl-3-benzamido aniline head group to more fully develop an SAR.[28] The x-ray crystal structure of the unphosphorylated p38α complex of **6**, shown in Figure 13.5, confirms that the N2 acceptor in the pyrazolopyrimidine core forms an H-bond with Met109 and the pendant methyl amide forms the usual H-bonding complex with Glu71 and Asp168. Additionally, the N1-phenyl is located along the hinge region hydrophobic pocket. Although **6** exhibited a good inhibition profile (p38α IC_{50} 14 nM, LPS/TNFα IC_{50} 513 nM), further SAR exploration identified the 1,2-oxazolamide (same as in **2**) as superior (p38α IC_{50} 5 nM, LPS/TNFα IC_{50} 6 nM).

THIAZOLES

The discovery of an active thiazole central core represents an unobvious elaboration of the pyrrolotriazine motif. Focused deck screening identified a C2-alkylaminothiazole