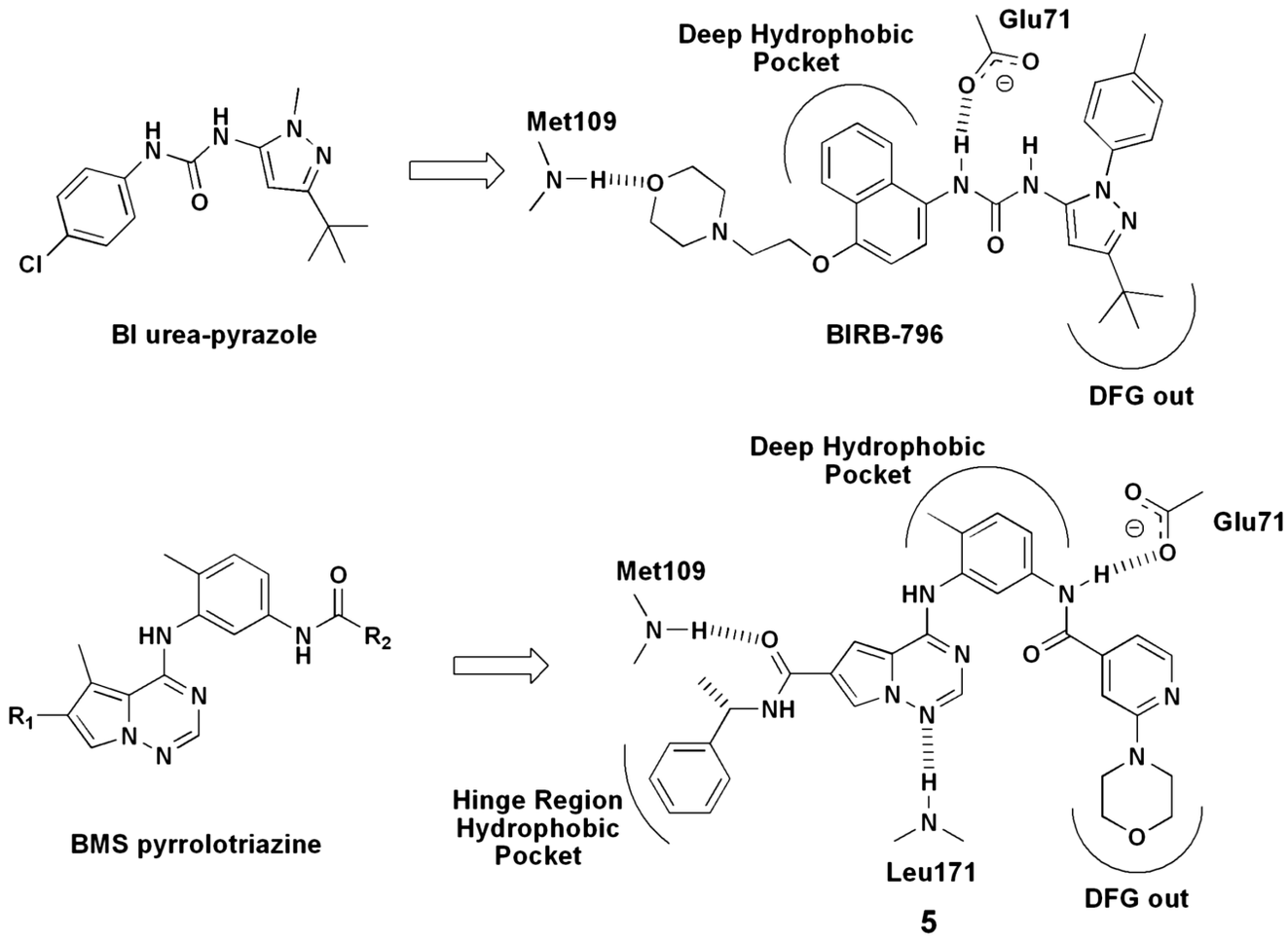

Scheme 13.4. The structures of the Boehringer Ingelheim "allosteric" inhibitors (BI urea-pyrazole and BIRB-796) are shown at top along with an indication of BIRB-796 interactions with p38α. The DFG-out conformation of p38α refers to the displacement of several residues along the activation loop (Asp168-Phe169-Gly170) providing for a hydrophobic pocket as an extension of the ATP binding site. The BMS pyrrolotriazines were further developed to include a structure (3-morpholinobenzamide, **5**) that was found to occupy the same DFG-out pocket.

4-methyl-3-benzamido aniline while the ethyl of **3** (not shown) and the (S)-α-methylbenzyl of **4** rested in the outer hinge pocket.

ACCESSING THE DFG-OUT BINDING POCKET

In 2002 researchers at Boehringer Ingelheim reported a limited set of inhibitors that used a novel p38 MAP kinase allosteric binding site.[26] The urea-pyrazole and the more elaborate BIRB-796 are illustrated in Scheme 13.4. The x-ray crystal structure for BIRB-796 (1KV2.pdb) is shown in Figure 13.4. Although part of the inhibitor is located in the ATP-binding site and H-bonds with Met109, the opposite end locates itself in a pocket created by the displacement of part of the activation loop, namely Asp168-Phe169-Gly170 (or DFG). This relocation of the DFG loop (sometimes referred to as DFG-out) vacates a hydrophobic pocket formerly occupied by Phe169. The DFG-out configuration of p38 results in an extended ATP-binding site. Its reference as an allosteric site may be somewhat misleading, as the inhibitory effect of binding a small molecule to Phe169 site is not allosteric in the classical sense. When a molecule binds to this newly formed site located adjacent to the ATP binding pocket, it directly interferes with ATP binding by providing a steric block. Normally, allosteric interactions are relegated to those requiring indirect communication between isolated sites. The remaining interactions observed in the x-ray structure for BIRB-796 entail those that have been seen before, namely hinge region Met109 H-bonding to pendant morpholino O and an H-bonding matrix among urea, Glu71, and Asp168 backbone NH.

Accessing the DFG-out conformation of p38 was accomplished through an extension of the pyrrolotriazines exemplified by **3** and **4**. It was found that the installation of larger amide groups off the 4-methyl-3-benzamido aniline head group led to congeners with potent p38α inhibition (Scheme 13.4). For example, the use of a