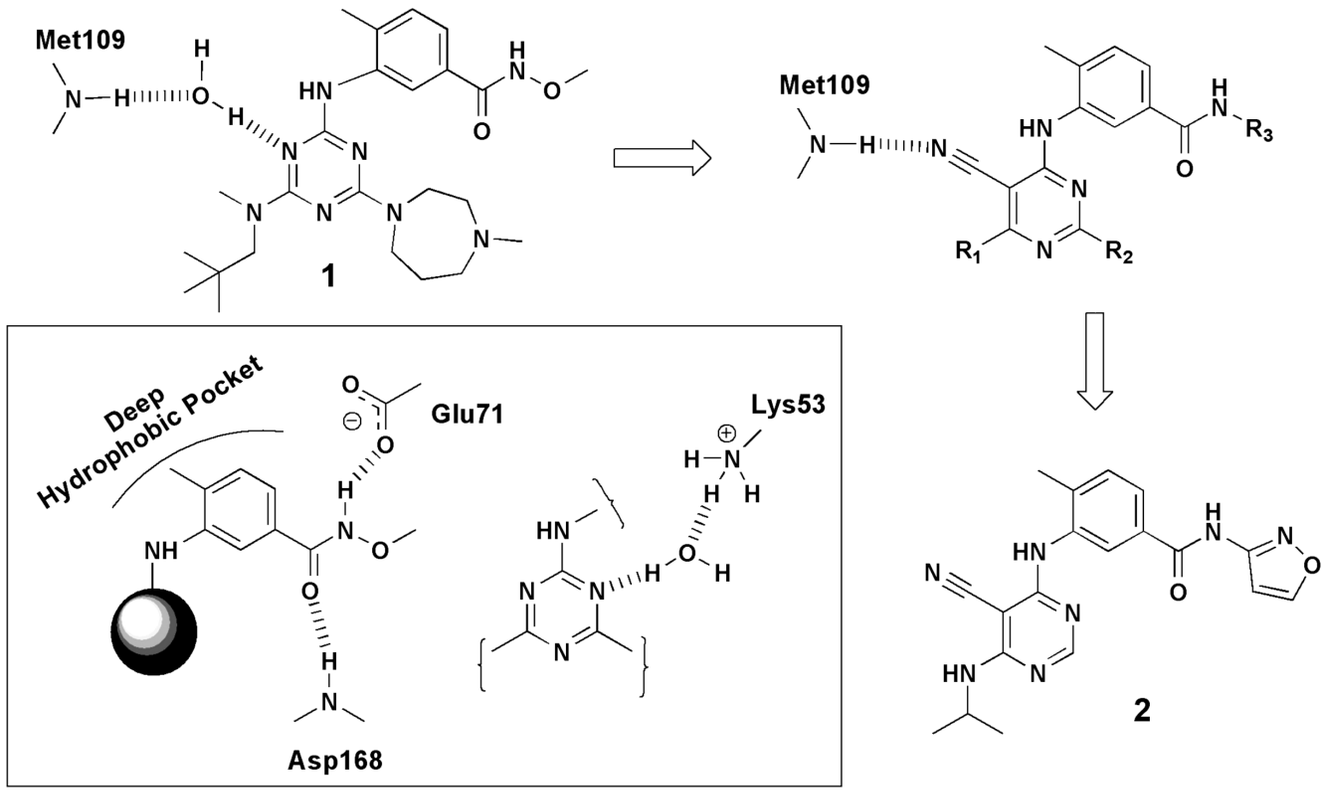

Scheme 13.2. The x-ray crystal structure of 1 revealed the presence of a key water molecule providing an H-bonding interaction between backbone NH at Met109 and triazine N3. The pryimidine scaffold (upper right) provided a means to replace that water molecule with a 5-cyano. Further synthesis identified **2** as a potent p38α inhibitor. The inset illustrates the major hydrophobic and H-bonding interactions observed at the 4-methyl-3-benzamido aniline head group and points to a possible water-mediated H-bonding interaction between triazine N1 and Lys53 (not observed).

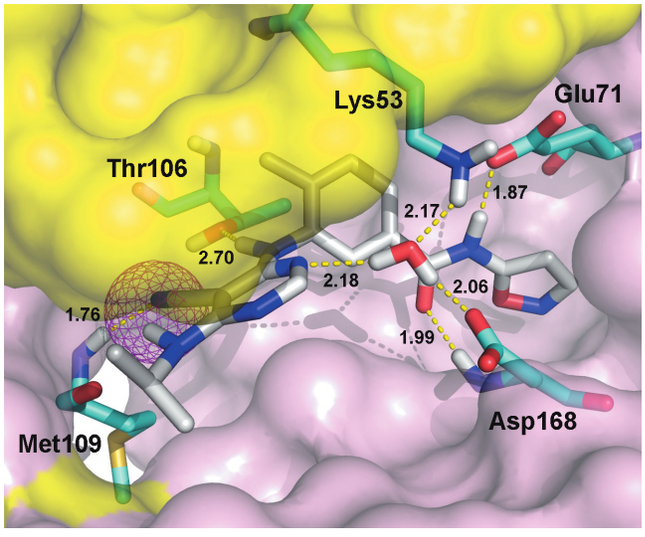

Figure 13.2. The complex between **2** and p38α confirms that the 5-cyano group that makes a key H-bonding interaction between inhibitor and p38α is located in the same position as the water molecule in **1**. A water molecule was observed in an H-bonding position among pyridyl N1, Asp168, and Lys53, while backbone NH at Asp168 and Glu71 anchor the pendant amide.

(IC_{50} 8.7 nM) is consistent with the number of strong interactions observed in the p38α ATP binding site, despite the absence of a substituent at the 2-position (6-position in the triazine). As the overall binding affinity for either the triazines or the pyrimidines is significantly affected by the combination and type of substituents it is difficult to directly assess the binding contribution due to a specific substituent. However, in this series, the best combinations included an amine at the 2-position and a branched alkylamine at the 4-position. The ultimate choice of best amine relies not only on observed p38α binding affinity but on cytotoxicity screens and cellular activity.

FUSED HETEROCYCLICS

A novel structural class of p38α MAP kinase inhibitors was developed as a result of the high-throughput screening (HTS) hit, pyrrolo[2,1-*f*][1,2,4]triazine oxindoles, shown in Scheme 13.3, which exhibited p38α IC_{50} values in the 60- to 80-nM range.[24] Substituted phenylaminopyrrolo[2,1-*f*][1,2,4]triazines had been used previously as a template for kinase inhibitor design,[25] and it was envisioned that the incorporation of a 4-methyl-3-benzamido aniline (as