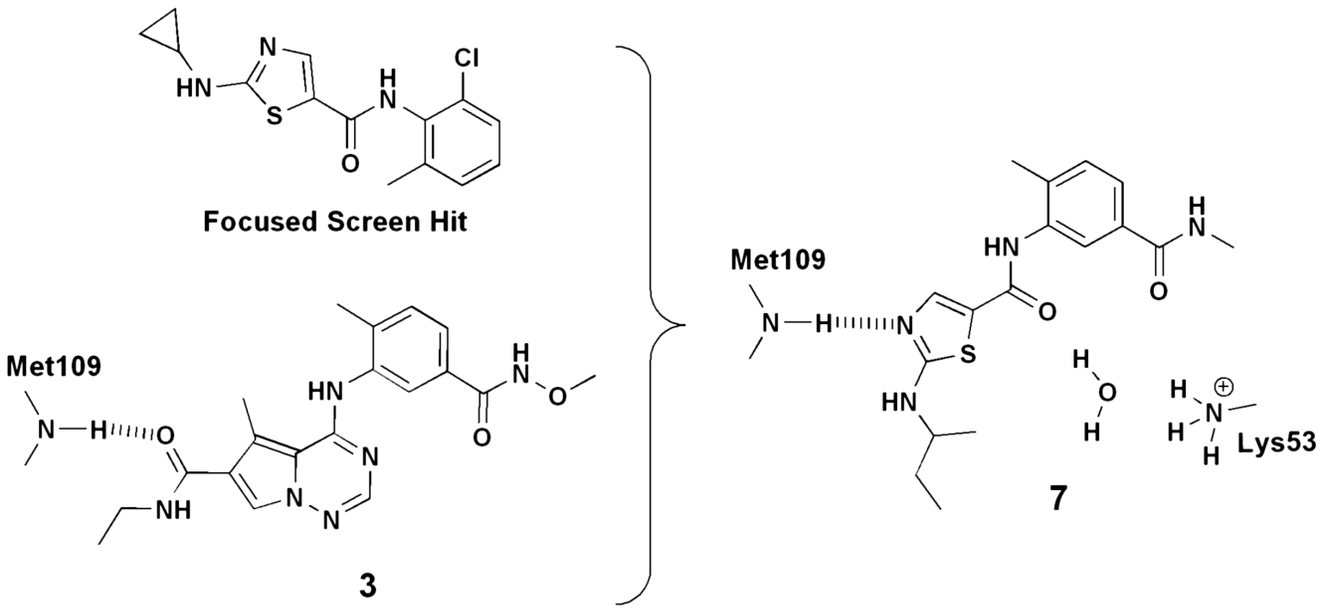

Scheme 13.6. The thiazole pictured at top was identified through focused deck screening with modest p38α activity. Coupling this observation with the structure of the pyrrolotriazine, **3**, led to the synthesis of **7**. Conceptually, the strategy was to replace the pendant amido carbonyl O–Met109 interaction with the thiazolyl N and incorporate a possible H-bond acceptor replacement (potential for H-bonding to Lys53/water) for the triazinyl N1 with the central carboxamido O.

sufficiently to the binding site to engage in productive H-bonding not only to Met109, Glu71, and Asp168 but also to Thr106 and backbone C=O at Met109 as well. This observation also reflects previous analyses highlighting the flexibility of p38α, specifically regarding the variation in the width of the ATP pocket as determined by a comparison of available x-ray structures.[11]

INDOLES

Scios recently reported the synthesis and SAR of indole-based heterocyclic inhibitors of p38α shown in Scheme 13.7.[30] The authors found that rigidifying the piperidine linker in **Scios 1** led to a significant increase in binding affinity (~fourteenfold, **Scios 2**). Further modifications eventually led to Scios's first p38 clinical compound, **Scios-469** (p38α IC_{50} 9 nM). These observations suggested that a similar conformational restraint might be achieved through the incorporation of a fused ring system, specifically, a connection between the benzyl methylene position and a proximal piperazine or piperidine ring (as illustrated in Scheme 13.7). A number of such analogs were synthesized and found to exhibit double-digit nanomolar p38α inhibition.[31] The binding mode of **8** (p38α IC_{50} 13 nM) was determined by x-ray crystallography (Figure 13.7). Several key H-bonding interactions are evident and consistent with previous observations: through-water Lys53/Asp168 H-bond to the exposed imidazo N and Met109 backbone NH H-bonding to the central carboxamide O. The major hydrophobic interaction occurs through the pendant difluorophenyl occupancy of the deep pocket created by Thr106 (not shown) and the aliphatic chain of Lys53. Curiously, the oxalamide portion extends upward and out along the hinge region, making no direct interactions with protein. It would appear that the occupancy of the deep hydrophobic pocket is critical in this series and that the Scios design, incorporating a conformationally constrained linker, directs the pendant benzyl group into that pocket.

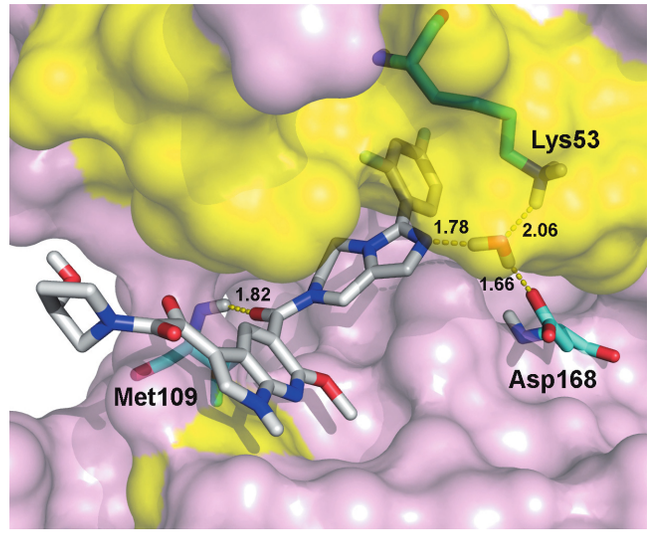

Figure 13.7. The x-ray structure of the complex between p38α and an analog of Scios-469 using a conformational constraint in the form of a fused ring system (imidazopyrazine, **8**) illustrates several key interactions: central amido carbonyl O H-bonding to Met109 and water molecule H-bonding among imidazo N, Asp168, and Lys53. The deep hydrophobic pocket created between Thr106 (not shown) and Lys53 is occupied by the pendant difluorophenyl. (2QD9.pdb)