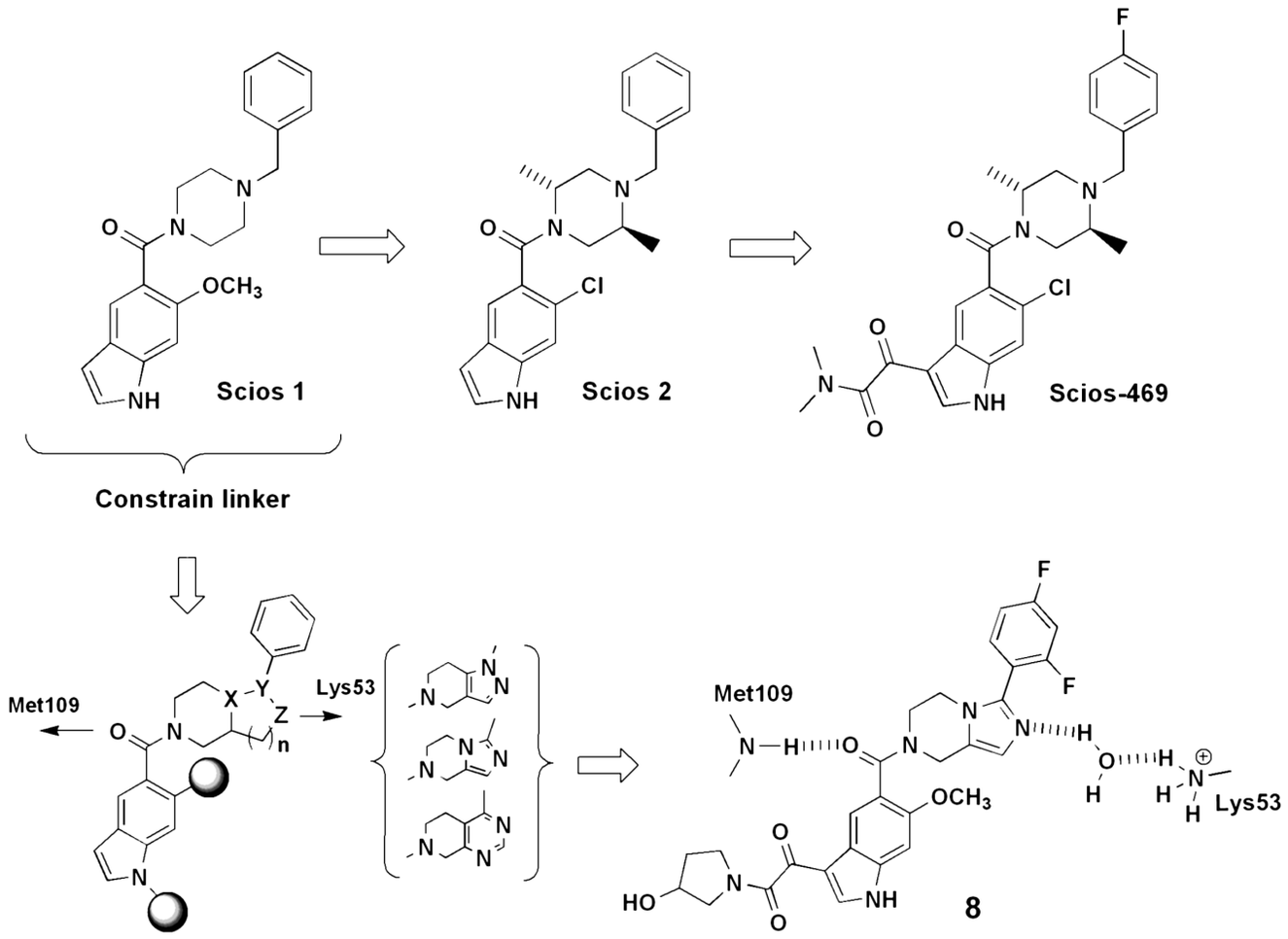

Scheme 13.7. Scios reported enhanced p38α inhibition through the incorporation of conformational constraints in their series (**Scios 1**, **Scios 2**, and **Scios-469**). The installation of a fused ring system (such as shown in parentheses) was considered as an alternate approach to conformational constraint, culminating in the potent p38α inhibitor, **8**.

THE 5-MEMBERED HETEROCYCLIC CORE

A very popular p38α inhibitor design is based on the early work of SmithKline Beecham (SKB) that described the trisubstituted imidazole, SB-203580 (Scheme 13.8).[1,32] Much effort has been expended on the successful replacement of the central imidazole core with other five-membered ring systems. Recent efforts have expanded the approach by focusing on fused ring systems as central cores. Examples in this regard include the Roche pyrrolopyridine.[33] Replacement of the Met109-targeting moiety has also been pursued, exemplified by the two Pfizer structures shown in Scheme 13.8.[34,35] Parallel efforts at Bristol-Myers Squibb (BMS) yielded the benzothiazole series that included the use of oxazoles and imidazoles as central cores.[36] An example oxazole, **9** (p38α IC_{50} 6.4 nM, LPS/TNFα IC_{50} 40 nM), was successfully crystallized with p38α (Figure 13.8). As expected, the fluorophenyl moiety is located in the deep hydrophobic pocket. Interestingly, the hinge region Met109 is engaged in two H-bonds to the ligand 2-aminothiazole system. Lys53 is found close enough to the oxazole N to consider a possible additional H-bond at that location. Unexpectedly, the P-loop of p38α is collapsed on the inhibitor in such a way that Tyr35 makes a tight van der Waals contact with the thiazole sulfur. This may represent a unique hydrophobic interaction scheme not typically used by p38 inhibitors. Finally, there is the subtle, yet important, hydrophobic interaction engaged by the 2-isopropylamine at the hinge entry. Small alkyl substituents at this position were observed to modulate the binding affinity (ethyl-butyl, 1.6–16 nM).

In summary, a number of structure-based design strategies were highlighted that focused on the use of novel ligand head groups to access the deep hydrophobic pocket (most notably, the 3-methyl-5-benzamide system), the incorporation of H-bond acceptor atoms in the core that target both the hinge region Met109 interaction as well as Lys53/Glu71/Asp168 deeper in the binding site, the exploitation of the Tyr169 pocket available in the DFG-out configuration, the subtle effect of alkyl/aryl group occupancy of the hinge region hydrophobic channel, and unique interactions such as the Tyr35 van der Waals interaction