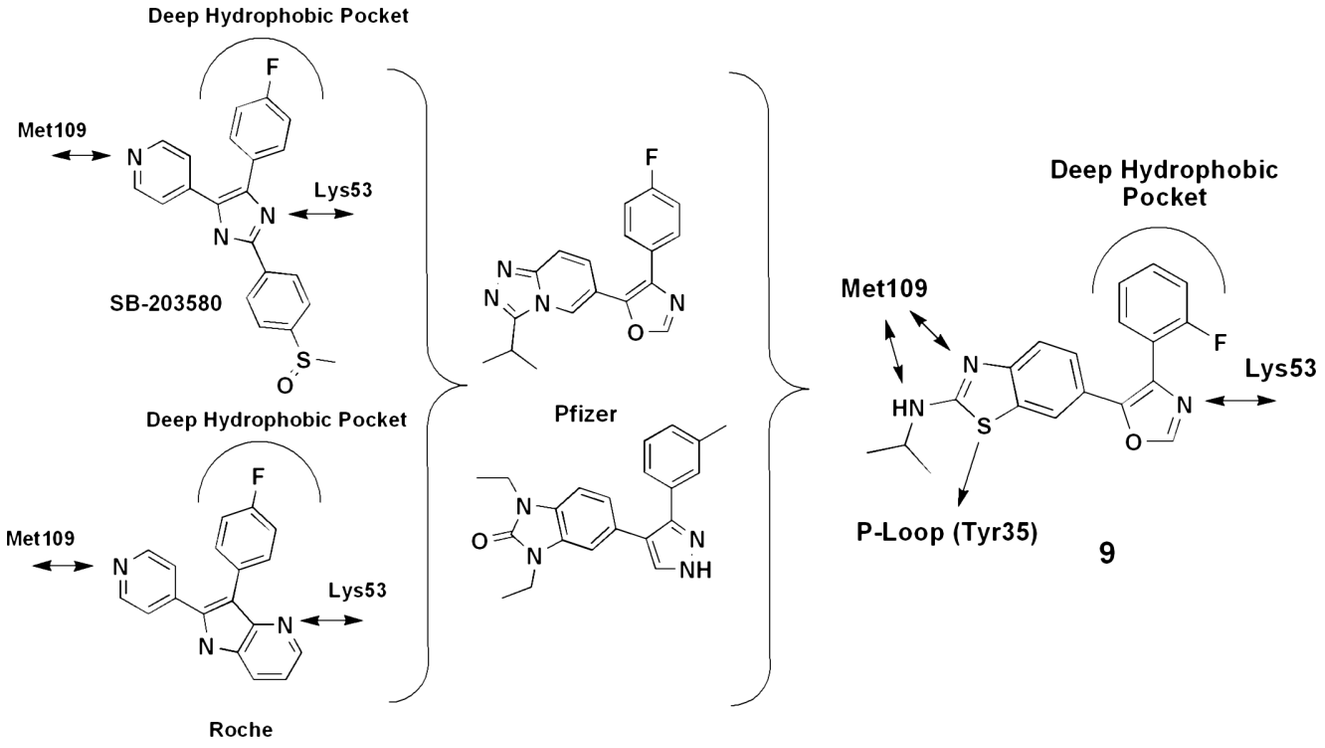

Scheme 13.8. The early work of SKB led to the synthesis of SB-203580 whose p38α x-ray structure revealed key interactions with Met109, Lys53, and the deep hydrophobic pocket. Subsequent efforts by Roche and Pfizer represent just a few of the variations around the SKB theme that led to potent inhibitors. The use of a fused heterocycle to access the backbone Met109 NH H-bond was successfully realized with **9**. In addition to the usual interactions, **9** exhibited a unique P-loop collapse that included a tight van der Waals contact between thiazolyl S and the ring face of Tyr35.

with thiazole sulfur. All of these approaches have led to the development of leads currently being investigated as potential drug candidates, testifying to the value and impact of a structure-based design approach in modern drug discovery.

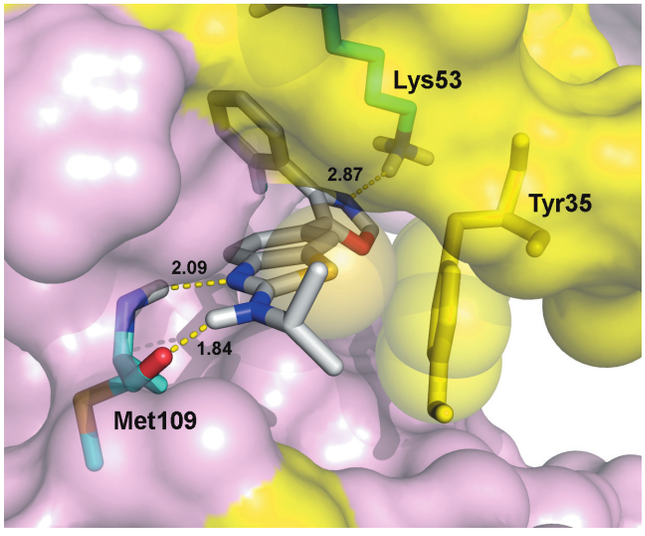

Figure 13.8. The x-ray crystal structure of the p38α complex with benzothiazole-oxazole, **9**, illustrates the expected H-bonding interactions at Met109 and Lys53. In addition, the collapse of the P-loop unto the inhibitor is evident, along with a tight van der Waals contact between thiazolyl S and Tyr35. (3C5U.pdb)

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