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Structure-based Design, Synthesis, and Biological Evaluation of Imidazo[1,2-*b*] Pyridazine- based p38 MAP Kinase Inhibitors

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We have identified a novel series of potent p38 MAP kinase inhibitors through structure-based design strategy. In the X-ray co-crystal structure of p38 MAP kinase with **TAK-715** (**1**), Phe169 adopts two conformations that one interacts with **1** and the other shows no interaction with **1**. Our structure-based design strategy is that these two conformations converge on one conformation by enhancement of the protein-ligand hydrophobic interaction. Scaffold transformation was conducted to enhance the protein-ligand hydrophobic interaction to resulting in the identification of imidazo[1,2-*b*]pyridazine derivatives as a lead series of potent p38 MAP kinase inhibitors, followed by investigation of structure and DMPK profile relationship. We provide a rational design, synthesis, SAR studies, and biological studies of imidazo[1,2-*b*]pyridazine derivatives.