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Abstract

The kinase PIM-1 plays a pivotal role in cytokine signaling and is implicated in the development of a number of tumors. The three-dimensional structure of PIM-1 is characterized by an unique hinge region which lacks a second hydrogen bond donor and makes it particularly important to determine how inhibitors bind to this kinase. We determined the structures of PIM-1 in complex with bisindolylmaleimide (BIM-1) and established the structure–activity relationship (SAR) for this inhibitor class. In addition, we screened a kinase targeted library and identified a number of high affinity inhibitors of PIM-1 such as imidazo[1,2-b]pyridazines, pyrazolo[1,5-a]pyrimidines, and members of the flavonoid family. In this paper we present an initial SAR of the identified scaffolds determined on the basis of a thermostability shift assay, calorimetric binding data, and biochemical assays which may find applications for the treatment of PIM-1 dependent cancer types.