Discovery of conformational control inhibitors switching off the activated c-KIT and targeting a broad range of clinically relevant c-KIT mutants

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Abstract

Drug resistance due to acquired mutations that constitutively activate c-KIT is a significant challenge in the treatment of patients with gastrointestinal stromal tumors (GISTs). Herein, we identified compound (**10a**) as a potent inhibitor against unactivated and activated c-KIT. The binding of **10a** induced rearrangements of the DFG motif, αC-helix, juxtamembrane domain, and the activation loop to switch the activated c-KIT back to its structurally inactive state. To the best of our knowledge, it is the first structural evidence demonstrating how a compound can inhibit the activated c-KIT by switching back to its inactive state through a sequence of conformational changes. Moreover, **10a** can effectively inhibit various c-KIT mutants and the proliferation of several GIST cell lines. The distinct binding features and superior inhibitory potency of **10a,** together with its excellent efficacy in the xenograft model, establish **10a** as worthy of further clinical evaluation in the advanced GISTs.