

Design and preclinical profile of CH5183284/Debio 1347, a novel orally available and selective FGFR inhibitor acting on a gatekeeper mutant of FGFR2.

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The fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases (RTKs) comprises four members (FGFR1-4). FGFRs regulate multiple biological processes, such as cell proliferation, migration, apoptosis, and differentiation. Various genetic alterations, as well as overexpression, drive activation of both kinase activity of the receptors and the pathway signaling, which is associated with tumor growth and survival. Therefore, the FGFR family represents an attractive therapeutic target for treating cancer. Here, we report the discovery and the pharmacological profiles of CH5183284/Debio 1347, an orally available and selective inhibitor of FGFR1, 2, and 3. The lead compound CH5183284/Debio 1347 was identified from our original compound library by a high throughput screening program. Chemical modifications, which were guided by 3D-modeling analyses of the lead series and FGFRs, led to identifying an inhibitor that is selective to FGFR1, FGFR2, and FGFR3 (IC₅₀: 9.3 nM, 7.6 nM, and 22 nM), but does not effectively inhibit FGFR4 (IC₅₀: 290 nM), KDR (IC₅₀: 2,100 nM) nor other 34 kinases. To evaluate kinase selectivity further, we used a KINOMEScan panel consisting of 442 kinases including some mutated forms of kinases. At 100 nM, CH5183284/Debio 1347 only bound to 5 kinases in the panel including FGFR1, FGFR2, and FGFR3 (over 80% inhibition to an ATP analog binding). An X-ray crystal structure analysis showed CH5183284/Debio 1347 binding to the ATP-binding site of FGFR1 in DFG-in mode and its interaction with both the hinge region and the backpocket of the protein. CH5183284/Debio 1347 also showed antitumor activity against cancer cell lines harboring genetic alterations in FGFRs in vitro and in xenograft models in mice.

In addition, the unique ability of CH5183284/Debio 1347 to inhibit a relevant FGFR2 gatekeeper mutant (V564F) was documented in cellular phosphorylation assays, in vitro cell proliferation assays, and in vivo efficacy studies in a xenograft mouse model. The X-ray crystal structure analysis and modeling studies of the inhibitors, including NVP-BGJ398 and AZD4547, with FGFRs that were used to guide the SAR strategy in the optimization program will be presented and discussed, together with the unique susceptibility of CH5183284/Debio 1347 against a gatekeeper

mutant of FGFR2. These findings underline the therapeutic potential of CH5183284/Debio 1347 in patients with FGFR genetic alterations and are the basis for an ongoing early clinical trial in several cancer types