Discovery of JDQ443, a structurally novel, potent and selective covalent oral inhibitor of KRASG12C

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RAS is the most frequently mutated oncogene in cancer, with *KRASG12C* mutations most commonly found in lung adenocarcinoma, colorectal cancer, and other solid tumor malignancies. Covalent inhibitors of KRAS*G12C* have shown antitumor activity against advanced/metastatic *KRAS G12C*-mutated cancers. Here we report the identification of a new class of pyrazole based KRAS*G12C* inhibitors discovered by structure based *de-novo* design. The compounds bind to the KRAS*G12C* switch II pocket with a novel binding mode, exploiting unique interactions with the GDP-bound form of the KRAS*G12C* protein. We describe the hit to lead and lead optimization by structure-based design of the novel chemical series leading to the discovery of NVP-JDQ443 (JDQ443), a novel, potent and selective, orally bioavailable KRAS*G12C* covalent inhibitor. We will share some aspects on the development of a feasible synthetic routes for fast SAR exploration and scale up of drug substance. JDQ443 showed dose dependent antitumor efficacy in *KRAS G12C*-mutated cell-derived models and is currently in clinical development as monotherapy as well as in combination.