KRAS Therapeutics: Identification of novel scaffolds for Dynamic Drugging Pockets of Oncogenic G12D Mutant Kirsten Rat Sarcoma protein

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As a proto-oncogene, Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) mutations can cause prolonged activation, leading to abnormal cell proliferation and subsequently development of a variety of human cancers. Therefore, the continuous efforts dedicated to fight against cancer through the discovery of anticancer leads is very significant. We report the identification of 2 novel scaffolds and their derivatives against KRAS G12D mutant protein. We used an integrated pharmacophore-based scaffold screening approach to select the optimum feature quintessential for scaffold stability. The scaffold nucleus was computationally grown using in-house tools. The library is screened, simulated, and analyzed. Intensive PCA analysis was performed, and conformational abundance was analyzed against the full-scale pharmacophore and molecular free states. We report five novel molecules with scores at par with the known FDA approved molecule. These molecules show preferential binding to the GDP-bound state of K-Ras and block the carboxylic group of the aspartatesp at 12th position. Compared to the retrospective analysis of the proposed molecules with the 12G variant, the leads show a considerable conformational density and Gibbs free energy difference. Overall, the reported novel molecules performed significantly ascompared to the known drug reference molecule of KRAS-G12D.