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Discovery of New Inhibitors for Colorectal Cancer Treatment

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Abstract : Colorectal cancer (CRC) is one of the main causes of cancer death in the world. Although several drugs have been developed to treat colorectal cancer, such as Regorafenib and 5-FU, their efficacy is often limited by the development of drug resistance. Therefore, development of new drugs with new scaffolds is necessary to treat CRC. Here, we used site-moiety maps to identify inhibitors against PIM1, LIMK1, SRC, and mTOR, which are often overexpressed in CRC. A site-moiety map represents physicochemical properties and moiety preferences of a binding site through anchors. An anchor contains three elements: (1) conserved interacting residues of a binding pocket; (2) moiety preference of the binding pocket; and (3) the type (e.g., hydrogen-bonding or van der Waals interactions) of interaction between the moieties and the binding pocket. Then, we performed a structure-based virtual screening of ~260,000 compounds and selected compound candidates with high site-moiety map scores for bioassays. Among these candidates, compound 1 and compound 2 inhibited the growth of CRC cells with IC50 values of <10 μM. The experimental result of enzyme-based assays indicated that compound 1 is a dual inhibitor against PIM1 (IC50 6 μM) and LIMK1(IC50 11 μM). Compound 2 was predicted as a SRC inhibitor and will be further validated. The compounds inhibited different protein targets compared to the current drugs. We believe that the compounds provide a starting point to design new drugs for CRC treatment.

Keywords : colorectal cancer, drug discovery, site-moiety map, virtual screening, PIM1, LIMK1
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