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Development of Protein Kinase Inhibitors as Anticaner agent & Therapeutics for Neurodegenerative Diseases

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The understanding of molecular mechanism for cancer has directed us that it is mainly caused by abnormal increased expression or activation of oncogenes and the corresponding proteins, it is rational to target a protein that is a key component of the oncogenic pathway as protein-targeted cancer therapies. As one of the interesting taget, the most frequent mutation of Raf protein, V600E shows a 500-fold increase in catalytic activity, providing cancer cells with both proliferation and survival signals. We started from imidazolopyrazole bicyclic ring scaffold11 based on binding mode of Sorafenib, which is a potent inhibitor of preactivated C-Raf, V600E B-Raf holding a unique binding mode, namely type II inhibitor. Afterwards, we found imidazolopyrazole bicyclic ring is a novel effective chemotype for both Raf kinases, and to develop more effective hydrogen bonding and hydrophobic interaction, we modified the bicyclic ring into aminopyrazole amide scaffold. We found that they were all potent and selective inhibitors of B-Raf (V600E) and C-Raf as well. In our docking studies, the aminopyrazole amide scaffold is supposed to have two hydrogen bonds in the hinge region and one intramolecular hydrogen bond between the hydrogen of the 5-amino group and the carbonyl oxygen in the 4-amide group in binding mode. Therefore, we decided to continue this work by introducing a 7-memebered ring mimicking intramolecular hydrogen bond next to pyrazole ring as a namely “conformation-restricted analogues”. The scaffold evolution of Raf-inhibitors are achived, and it is still going on.