ACS Medicinal Chemistry Letters

IN THIS ISSUE

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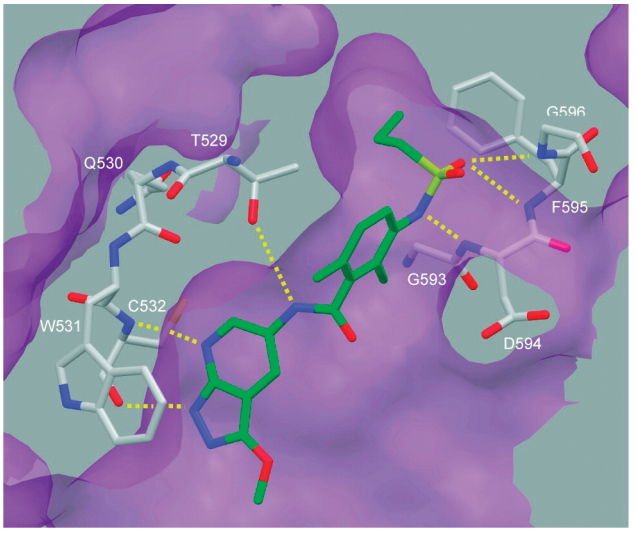
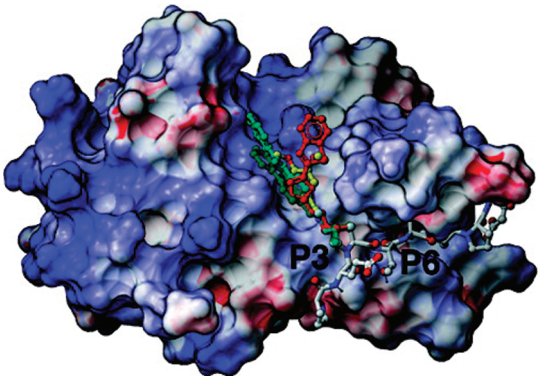
## Targeting MAP Kinase Signaling




Targeted molecular therapies are increasingly being explored as viable options for cancer drug discovery. A mutation resulting in the change of a specific valine to a glutamate residue in B-Raf kinase is associated with almost 7% of cancers and most commonly in melanomas. Wenglowsky et al. (DOI: 10.1021/ml200025q) used a structure-based design approach to derive a new series of pyrazolopyridine inhibitors of this aberrant kinase.

The authors optimized an inhibitor that showed selectivity against a broad panel of kinases. This compound is orally available. In addition, the compound exhibited significant antitumor activity in an in vivo cancer model, indicating that it might be a useful lead in the development of melanomas and other cancers possessing this driver mutation.

## Toward Inhibiting Binding Interactions




An interaction between the p6-terminal domain of the nascent HIV-1 Gag protein and the Tsg101 protein encoded by tumor susceptibility gene 101 is required for viral assembly and budding. Therefore, the development of Tsg101-binding inhibitors has potential as a new class of antiviral compounds. Toward this goal, Kim et al. (DOI: 10.1021/ml1002579) have solved the crystal structures of Tsg101 in complex with two peptides structurally derived from a four-residue binding region.

The structures describe new interactions that might prove to be useful in the design of high-affinity antagonists of Tsg101, which impact retroviral budding. On a broader level, targeting of protein−protein interactions represents a new paradigm in drug discovery.





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