Development of mechanism-based femtomolar inhibitors with anticancer properties

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Abstract:

Enzymes are good targets for the design of anticancer drugs. For example, many kinases, epigenetic enzymes, post-translational modifying enzymes etc. have been targeted for developing anticancer drugs. Enzymes are biochemical catalysts that increase the rate of their reactions by stabilizing their transition states. The active sites of enzymes bind tightly, with sub-attomolar dissociation constants, to their transition states. Therefore, studying enzymatic transition states are important for developing tight binding therapeutics. Despite their usefulness in developing tight binding inhibitors, enzymatic transition state structures are difficult to obtain experimentally because they exist for less than a single bond vibration or less than a picosecond. In this work, we used experimental methods based on kinetic isotope effect and computational tools of quantum chemistry to obtain geometric and electrostatic structures of the transition state of enzymes implicated in head and neck, and lung cancers. We then used the transition state structures to develop a chemical library that incorporated the properties of the transition states. These drug candidates bound to the target enzymes with dissociation constants in the low femtomolar range. These drug candidates showed strong anticancer properties against the head and neck and lung cancers in rodent xenograft models. They are currently in clinical development.

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