Design of a CLIPTAC Probe Molecule for the Treatment of EGFR Mutated Adenocarcinoma

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In-cell click-formed proteolysis targeting chimera molecules (CLIPTACs) were developed to allow both the inhibition and ubiquitination (degradation) of mutated proteins causing various diseases, including cancer. A CLIPTAC has two precursor molecule parts: the protein binding section and the E3 binding section, that link through click chemistry after delivery to the cell. No known CLIPTAC molecules have been developed for the treatment of EGFR mutated cancers. Mutated EGFR is correlated with uncontrolled cancer growth and cell division. The development of a CLIPTAC molecule for EGFR would prevent developed drug resistance while treating these cancers. This project computationally identified a potential CLIPTAC protein binding probe molecule for drug treatment of EGFR mutated cancer based on the structure of Dacomitinib, and established EGFR inhibitor, using Schrodinger Maestro. The identified molecule was then synthesized up through 3 of the 4 steps of its proposed synthesis. Computational design and synthesis procedure indicate that the entire molecule can be effectively synthesized and combined with an established E3 binding precursor molecule to form a successful CLIPTAC.

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