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Peptoid Linked Fragments as PIP Box Antagonists

A novel computational and experimental screening method successfully identifies small molecule compounds that disrupt key protein-protein interactions, yielding potential first-in-class cancer drug candidates.

Fragment-based drug discovery is a popular method used to design molecules that bind to protein targets. In this method, many small compounds are screened for their binding to a target protein. Subsequently, steps are undertaken to combine more than one of the small compounds found to bind weakly into a larger, stronger-binding, drug-like compound. Fragment-based drug discovery presents a significant challenge; information must be known about the binding sites of the fragments so that they can be combined in a way that does not disrupt the binding of the individual fragments. In addition, many important drug target proteins participate in protein-protein interactions. Disrupting such interactions is critical to disrupting the chemical signals that drive cancer and other diseases.

To overcome the challenges of traditional fragment-based drug design, researchers at Purdue University used a combination of computational and experimental technique to discover novel inhibitors of the interaction between proliferating cell nuclear antigen (PCNA) and a peptide that binds to a site on PCNA responsible for multiple protein-protein interactions relevant to its cellular function. Specifically, thousands of tripeptoids (peptide-like molecules with three chemically distinct sites) were screened in silico, facilitating the selection of a small number of tripeptoids for in vitro testing. Several of the selected tripeptoids show a good ability to disrupt the PCNA-peptide interaction. This method of drug discovery successfully identified a small number of hit compounds that disrupt a protein-protein interaction involving PCNA, an important cancer target.

Advantages:

-Potential first-in-class cancer drug

-Fewer compounds synthesized

Technology ID

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Category

Biotechnology & Life Sciences/Bioinformatics & Computational Biology

Pharmaceuticals/Small Molecule Therapeutics

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-Less structural information needed than in traditional fragment-based drug discovery

-Well-suited to targeting protein-protein interactions

Potential Applications:

-Drug discovery

-Cancer therapy

TRL: 3

Intellectual Property:

Provisional-Patent, 2015-12-07, United States | PCT-Patent, 2016-12-06, WO | NATL-Patent, 2018-06-06, United States | CON-Gov. Funding, 2020-08-12, United States

Keywords: Fragment-based drug discovery, tripeptoids, PCNA inhibitors, protein-protein interaction inhibitors, cancer target, drug discovery, computational screening, in silico screening, novel inhibitors, cancer therapy

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