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Synthesis & Evaluation of Dual Tyrosyl-DNA Phosphodiesterase (Tdp1) and Topoisomerase I (Top1) Inhibitors

Novel low molecular-weight compounds act as the first dual inhibitors of TOP1 and TDP1, offering a potentially more potent and simplified chemotherapy agent for cancer treatment.

Topoisomerase 1 (TOP1) is an enzyme involved in the replication of DNA. Molecules displaying TOP1 inhibitory function have found clinical applications as well as the frequent subject of research. Another enzyme functioning alongside TOP1 is tyrosyl-DNA phosphodiesterase 1 (TDP1), which repairs DNA lesions. Observations of this enzyme suggest mediating its activity could potentiate the cytotoxic effect of TOP1 inhibitors. TDP1 inhibitory activity has been seen to a limited extent in a handful of compounds, though their potencies, specificities, and pharmacokinetic properties leave much to be desired.

Purdue University researchers have developed a series of novel, low molecular-weight compounds that can act as dual inhibitors of both TOP1 and TDP1. A dual inhibitor of this type would offer significant advantages over individual TOP1 and TDP1inhibitors alone such as simplification of delivery and bioavailability. In lab tests, the dual inhibitor is an equally potent TOP1 inhibitor as the commercially available camptothecin. These molecules are thought to function by stalling the DNA synthesis phase of the cell cycle, thereby inducing apoptosis, and effectively killing the cell. This drug could work in combination with other chemotherapies to effectively eliminate highly proliferative cell growth in the body.

Advantages:

-First dual inhibitor of TOP1 and TDP1

-Shown to be as cytotoxic to TOP1 as camptothecin

-A potentially more potent chemotherapy agent

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Category
Pharmaceuticals/Small Molecule Therapeutics

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Potential Applications:

-Medical/Healthcare

-Pharmaceuticals

-Cancer Treatment

TRL: 3

Intellectual Property:

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