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5/6-5/6-Bisaryl Substituted with Saturated Cyclic Heterocycles as TAK1 Inhibitors

A novel, potent (nanomolar) transforming growth factor-beta activated kinase 1 inhibitor has been developed as a therapeutic candidate for treating multiple myeloma.

Researchers at Purdue University have developed a novel transforming growth factor-beta activated kinase 1 (TAK1) inhibitor therapeutic for multiple myeloma. Multiple myeloma, a blood cancer, is characterized by dysregulated and proliferative plasma cells, which facilitate bone destruction. Multiple myeloma cells have been found to overexpress phosphorylatedTAK1. TAK1 is important for cell growth, differentiation, and apoptosis and is emerging as a promising therapeutic target for the treatment of multiple myeloma. However, current therapeutics targeting TAK1 do so in the micromolar range making it difficult to achieve effective concentrations in blood without encountering dose-limiting toxicities. There is a dire need for discovering novel inhibitors of TAK1 in a nanomolar range to achieve effective concentrations in blood without encountering dose-limiting toxicities.

Purdue researchers have identified a molecule has a half maximal inhibitory concentration of 55 nanomolar. Aside from the increased activity compared to known TAK1 inhibitors, the compound demonstrated in cellulo activity in MPC-11 cells with a concentration that reduces total cell growth by 50% at 43 nanomolar. As phosphorylated TAK1 has been shown to be overexpressed in multiple myeloma, researchers demonstrated that there is a significant reduction of the phosphorylation of TAK1 at 100 nanomolar. This technology can be used to treat multiple myeloma.

Technology Validation: This technology has been validated with ADP Glo kinase assay, CellTiter-Blue cell viability assay, and western blot. These methods demonstrated that these compounds can inhibit phosphorylation of TAK1 and inhibit growth of MPC-11 cells.

Advantages:

Technology ID
2024-SINT-70377

Category
Biotechnology & Life Sciences/Biomarker Discovery & Diagnostics
Pharmaceuticals/Drug Discovery & Development
Biotechnology & Life Sciences/Analytical & Diagnostic Instrumentation
Pharmaceuticals/Small Molecule Therapeutics
Pharmaceuticals/Research Tools & Assays

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-Nanomolar activity

-Inhibits growth of multiple myeloma cells

-Reduces phosphorylation of TAK1

Applications:

-Multiple myeloma

TRL: 3

Intellectual Property:

Provisional-Patent, 2023-09-28, United States | PCT-Patent, 2024-09-25, WO

Keywords: TAK1 inhibitor, multiple myeloma, blood cancer treatment, transforming growth factor-beta activated kinase 1, nanomolar activity, plasma cell proliferative disorder, oncology therapeutic, TAK1 phosphorylation reduction, MPC-11 cells, novel therapeutic target