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Design and Synthesis of bi-aryl Methylated Lactam Derivatives to Inhibit the BRD7 Bromodomain Function in Prostate Cancer

Potent 3CLprotease inhibitors have been developed that block SARS-CoV-2 replication and exhibit superior antiviral activity compared to current approved COVID-19 therapies.

Researchers at Purdue have synthesized a novel small molecule inhibitor (dubbed 2-77) specific to Bromodomain-containing protein 7 (BRD7). Compound 2-77 was found to reduce the cell viability of prostate cancer cell lines LNCaP and PC-3 in a dose-dependent manner. Prostate cancer (PC), the most diagnosed cancer for men in the US, can be treated in several different ways. Hormone-responsive PC is treated using androgen depravation therapy. Unfortunately, patients eventually become resistant to this treatment, leading to development of castration-resistant prostate cancer (CRPC) after which, the prognosis is grim. Further development of novel small molecule inhibitors targeting BRD7, a protein implicated in the progression of PC, is a promising path for new treatments of PC. While some dual inhibitors of BRD7 and BRD9 exist, none target only BRD7, limiting their efficacy.

The researchers developed a series of possible hit compounds through an in silico virtual high-throughput screening. Using the best hit compounds, compound 2-77 was identified as the best at binding specifically to BRD7, and not BRD9 through a thermal shift assay. The anti-PC ability of 2-77 was quantified using an in vitro assay with PC cell lines that are androgen receptor positive and negative. It was found that compound 2-77 reduced the cell viability of androgen responsive PC cells in a dose-dependent manner, with a ~63 % reduction in viability at 5 uM compound 2-77. Furthermore, it was found that compound 2-77 reduced the cell viability of androgen nonresponsive CRPC cells by ~40 % at 5 uM.

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Based on the assumption that a protein bound to a well-shaped ligand becomes more stable, it should increase the temperature at which the sample melts (Tm). Upon measuring the Tm of BRD7 protein alone, BRD7 with compound 2-77, BRD9 alone, and BRD9 with compound 2-77, (n=4) with differential scanning fluorimetry, it was found that the sample containing BRD7 with compound 2-77 had a significantly higher Tm shift than BRD9 with compound 2-77, indicating that 2-77 binds specifically to BRD7 and not BRD9. Anti-PC effectiveness of 2-77 evaluated by treating LNCaP cells (androgen responsive) and PC-3 cells (androgen nonresponsive CRPC cells) with 0.1, 1, and 5 uM 2-77 after 4 days of incubation. Cell viability measured using CellTiter-GloÂ® Luminescent Cell Viability Assay.

Advantages:

- Specific to BRD7 over BRD9

- More potent than previously described BRD7 inhibitor BI7273

Applications:

- Prostate cancer treatment and diagnostics

- Biological investigation of role of BRD7 protein

Publications:

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