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Selective bromodomain protein inhibitors that reduce cancer cell viability

Small molecules systematically designed as highly selective bromodomain inhibitors for development as cancer and inflammatory disease therapeutics.

Technology No. 2019-343

IP Status: Pending US Patent; **Application #:** 16/892,072

Applications

- Anti-cancer therapeutic
- Inflammation treatment
- Basic research of bromodomains

Key Benefits & Differentiators

- **Minimal off-target effects:** Detailed structure-activity studies led to compounds selective for bromodomain protein 4 domain 1 (BRD4-BD1), with minimal binding to other proteins (including other BET bromodomains).
- **Reduced cancer viability:** Compound leads to inhibition of BRD4-BD1 and decreased viability of c-Myc dependent cancer cells (such as multiple myeloma).
- **Increased cell permeability:** Compounds designed to penetrate the membrane, increasing intracellular target engagement and facilitating the desired inhibition in cancer cells.

Making specific inhibitors to BET proteins

Bromodomain and extraterminal domain (BET) proteins have been repeatedly implicated in inflammation, heart disease, diabetes, and cancer, making them enticing targets for the development of potential therapeutics. However, it has been challenging to develop inhibitors selective enough to pass clinical trials due to dose limiting toxic side effects. Researchers at the University of Minnesota carried out detailed structure-activity relationship studies resulting in the development of compounds that specifically inhibit BRD4-BD1, and avoid off-target interactions with other proteins (including bromodomain-containing proteins).

Finding success in systematic design

BET proteins function as “readers” of epigenetic modifications on the genome modulating transcription and regulating cellular processes including cell proliferation and cell differentiation. For example the BET protein BRD4 interacts with super-enhancer regions, regulating c-Myc expression, a protein that is implicated in as many as 50% of all cancers. A previously identified BET inhibitor also inhibited other bromodomain containing proteins and p38α kinase. Based off of crystal structures of inhibitors bound to the kinase or BRD4, researchers modified the compound to enhance BET activity while reducing kinase activity >90,000 fold. Further modifications increased cell permeability of the molecule. Therapeutic potential of the compound was demonstrated through verifying activity against cancer cells (MM.1S cells), which was further supported by reduced c-Myc expression.

Phase of Development

In vitro proof of concept. Molecules have been systematically designed and optimized for selective inhibition of BET proteins (specifically BRD4-BD1), and shown to have activity against cancer cells, reducing c-Myc expression in tissue culture.

Researchers

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Publications

Systematically mitigating the p38α activity of triazole-based BET inhibitors
ACS Med. Chem, Lett, 2019, 10, 1296-1301
Molecular Basis for the N-Terminal Bromodomain and Extra Terminal (BET) Family Selectivity of a Dual Kinase-Bromodomain Inhibitor
J. Med. Chem., 2018, 61, 9316

Ready for Licensing

This technology is now available for license! The University is excited to partner with industry to see this innovation reach its potential. Please contact us to share your business’ needs and your licensing interests in this technology. The license is for the sale, manufacture or use of products claimed by the patents.

References

Huarui Cui et al(2021), https://doi.org/10.1021/acs.jmedchem.1c00933, J. Med Chem.

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