Selective N-Terminal BET-Family Bromodomain Inhibitor Development by Targeting the ZA-Channel of Brd4

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Background

- Proteins that contain bromodomains have been implicated in a large variety of diseases, including inflammation, neurological disorders, and cancer.\(^1\)
- A large interest in regulating bromodomain function has emerged for their ease of druggability and possible epigenetic intervention.\(^2\)
- Of the Bromodomains and Extra-Terminal (BET) family of proteins, domain one of Brd4 (Brd4-D1) engages several DNA-binding transcription factors to influence disease-relevant functions.\(^3\)
- Molecules such as (±)-JQ1 are highly potent (Brd4-D1 \(K_d = 49 \text{nM}\)) but are pan-BET family inhibitors.\(^4\)
- HU-10 developed by the Pomerantz lab, inhibits Brd4-D1 selectively over the C-terminal bromodomain (Brd4-D2).\(^5\)

Methods

- The Brd4-D1 co-crystal structure with HU-10 shows room in the protein for molecule expansion. Modifications to the amino-pyrimidine group may access the ZA-Channel and improve binding affinity.
- Possible modifications including triazoles, amides & thiazoles were considered, ensuring high structural rigidity.
- Over 150 HU-10 analogs were designed and computationally docked in Brd4-D1 using Maestro Schrodinger.\(^6\) The predicted binding energies are summarized as docking scores (kcal/mol).
- The best new variations of the HU-10 molecule were chosen for synthesis.
- The imidazole scaffold of HU-10 was originally synthesized in 10 steps, so a shorter alternative synthesis was used to make a triazole derivative requiring 6 steps (UT-1/LR-1-35).
- The synthesized HU-10 triazole will serve as a scaffold for the synthesis of new ZA-channel accessing analogs.

Results

- Amides were considered due to their ease of synthesis and commercial availability of reagents.
- Thiazoles provide a synthetic alternative to triazoles while producing consistent docking results in contrast to amides.
- The new diol showed the greatest predicted improvement in binding affinity to Brd4-D1, with a score of \(-12.8\) kcal/mol. This is likely due to an additional hydrogen bond to Proline-86 in the protein.

Discussion

- The new HU-10 analogs have improved predicted binding affinity to the Brd4-D1 protein.
- Synthesis of best predicted 1,5-substituted triazole molecules is ongoing. Evaluation for binding to Brd4-D1 using fluorescence anisotropy assays will be conducted afterwards.
- Epigenetic mechanisms have long been known to be involved in cancer and are also linked to neuropsychiatric disorders, inflammation, and metabolic disorders.\(^2\)
- Domain-selective inhibition represents "a new frontier of drug discovery that has huge potential for the development of future therapeutics."\(^2\)

Summary

- Novel triazoles improved docking scores by \(2 - 4\) kcal/mol compared to HU-10 (\(-8.0\) kcal/mol). The range of scores is between \(-10\) and \(-12\) kcal/mol.
- Triazoles were selected as candidates for synthesis based on their docking scores and their ability to extend into the open ZA-channel.
- The 1,5-triazoles provided greater scores than the 1,4 isomers.

References


Project Goals

- Design and synthesize HU-10 analogs, testing for improved Brd4-D1 inhibition.

Discussion

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