1-Benzoyl 4-Phenoxypiperidines Small-Molecule Inhibitors of the β-Catenin/BCL9 Protein-Protein Interaction

Aberrant Wnt pathway signaling is thought to be important for the growth of triple negative breast cancer stem cells and bulk cancer cells. The β-catenin/BCL9 protein-protein interaction (PPI) is thought to be near the end of the Wnt pathway and is therefore considered to be a good target with minimal side effects. Drug-like and selective β-catenin/BCL9 PPI inhibitors have been developed with an IC_{50} as low as 0.74 uM (K_i=0.5). Cell-based studies showed that the inhibitors selectively suppressed transactivation of Wnt/β-catenin signaling, regulated transcription and expression of Wnt target genes, and inhibited growth of Wnt/β-catenin-dependent cancer cells.

COMMERCIAL OPPORTUNITY

- There were estimated to be about 279,100 new cases of breast cancer in 2020. Triple negative breast cancer is found in about 10–20% of breast cancer patients. TNBC is highly metastatic, less responsive to standard treatment, and associated with a high rate of cancer recurrence. Data have indicated dramatic hyperactivation of canonical Wnt signaling in TNBC.
- Compelling basic and clinical studies demonstrate that hyperactivation of β-catenin signaling promotes hallmark characteristics of metastases in several cancers including triple negative breast cancer (TNBC). WNT/β-catenin signaling is also emerging as a key pathway that promotes immune evasion and resistance to immunotherapies.
- The inhibitors of the upstream effectors of the Wnt/β-catenin signaling pathway are less desirable, because those inhibitors have no efficacy for cancer cells harboring more downstream APC and Axin loss-of-function mutations, and β-catenin activation mutations. The upstream inhibitors also disturb noncanonical Wnt signaling pathways.
- BCL9/BCL9L provides the structure for scaffolding the 'WNT enhanceosome' and couples β-catenin and Pygos to the T-cell factor (Tcf) and lymphoid enhancer-binding factor (Lef) family of transcriptional factors to transcribe downstream target genes. Many studies have recognized the β-catenin-BCL9-Pygo axis is the key driver of malignancy, facilitating the switch from non-invasive to invasive cancer, provoking cancer progression and metastasis, and promoting immune suppression.

TECHNOLOGY

Structure-based design and optimization was performed to develop new β-catenin/B-cell lymphoma 9 (BCL9) inhibitors and improve their inhibitory activities. Compound 43 with a novel 1-benzoyl 4-phenoxypiperidine scaffold was discovered to disrupt the β-catenin/BCL9 protein–protein interaction (PPI) with a K_i of 0.96 μM in AlphaScreen competitive inhibition assays and displayed good selectivity for β-catenin/BCL9 over β-catenin/E-cadherin PPIs. Protein pull-down assays demonstrated that this series of compounds directly bound with β-catenin. Cell-based target engagement and coimmunoprecipitation experiments indicated that 43 bound with β-catenin and disrupted the β-catenin/BCL9 interaction without affecting β-catenin/E-cadherin interaction.

PUBLICATION/PATENT

- To be published in the Journal of Medicinal Chemistry 2021
- Provisional patent application filed April 19, 2021 for Dr. Ji.

CONTACT

Haskell Adler PhD MBA
Senior Licensing Manager
Haskell.Adler@Moffitt.org
(813) 745-6596

LICENSING OPPORTUNITY

MOFFITT CANCER CENTER