

Direct Inhibition of NF- κ B Subunits by 9-chloro-8-(hexyloxy)-2H-chromeno[2,3-d] pyrimidine-2,4(3H)-dione (IT-848)

Rateshwar, Janice (School: Jericho High School)

Aberrant Nuclear Factor-kappa B (NF- κ B) activation is observed in autoimmune, inflammatory, and malignant disorders. Current therapeutics targeting NF- κ B inhibit upstream NF- κ B activators, allowing for broad-spectrum toxicity and alternative mechanisms of NF- κ B activation. To address these limitations, 9-chloro-8-(hexyloxy)-2H-chromeno[2,3-d]pyrimidine-2,4(3H)-dione (IT-848) was developed as a direct NF- κ B inhibitor. This study analyzed the unknown molecular mechanisms of action of IT-848 based on molecular docking and gene expression analyses to elucidate the candidacy of IT-848 as a therapeutic for diseases with constitutive NF- κ B activation. Molecular docking analysis on PyRx revealed IT-848 demonstrates a strong binding affinity (binding energy <-6 kcal/mol) and non-covalent interactions with amino acid residues in the REL Homology Domain of all NF- κ B subunits: RelA, RelB, c-Rel, p50, and p52. Therefore, IT-848 is a competitive and reversible inhibitor of DNA binding for all NF- κ B dimers. Using Multiple Myeloma (MM) as proof of concept, differentially expressed genes induced by IT-848 in MM1S MM cell line were identified on BasePair and mapped for overlap on Venny with the target genes of RelA, RelB, c-Rel, p50, and p52 listed in the Harmonizome Database. IT-848 downregulated ($\log_2\text{foldchange} <-1.5$) target genes of each NF- κ B subunit. Thus, IT-848 is a potential therapeutic candidate for disorders with constitutive NF- κ B activation by inhibiting various NF- κ B-mediated pathways implicated in disease progression in a reversible, and therefore tumor-cell toxicity specific, manner. Further research should investigate IT-848 in autoimmune and inflammatory disorders and test the synergy of IT-848 with other MM therapeutics.