Design, Synthesis, and Testing of Novel Small Molecule Interleukin-6 Inhibitors for the Amelioration of Inflammatory Bowel Disease

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Inflammatory Bowel Disease (IBD) is a prevalent autoimmune condition that affects 2.39 million Americans and is characterized by an excess of inflammatory cytokines. Interleukins, a class of cytokines, regulate immune cell differentiation and response. Specifically, Interleukin-6 (IL-6) is key in IBD, binding to membrane bound receptors, phosphorylating downstream targets and activating inflammatory pathways such as JAK-STAT and MAPK. IL-6 induced inflammation can be suppressed by reducing IL-6 production or blocking IL-6-mediated signal transduction. The only FDA approved IL-6 inhibitor is tocilizumab, a monoclonal antibody. However, there are no small molecule inhibitors on the market that directly target IL-6. Small molecules are attractive due to their lower immunogenicity, lower production costs, and oral administrability in comparison to monoclonal antibodies. This project aims to computationally design, synthesize, and test novel small molecule drugs that have the ability to inhibit the IL-6 cytokine signaling cascade. The drug discovery platform Schrödinger Maestro was utilized to design these drugs, employing the natural compound curcumin as a template structure. More than 350 compounds were designed and a scoring profile was developed to identify the most optimal small molecules. Two compounds, Curcumin Derivative 1 (C1) and Curcumin Derivative 2 (C2) emerged as the most promising candidates due to their ideal binding affinity and high absorption through the gut-blood barrier; these compounds were chemically synthesized and characterized. Based on in-vivo testing in model organism Drosophila melanogaster, C1 and C2 are both highly effective in ameliorating IBD. Subsequent investigations will focus on conducting in-vitro cellular IL-6 inhibition assays.

Awards Won:
Second Award of $2,000
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Associated Technologies Association (DCAT): DCAT First Prize