Design, Synthesis, and Testing of a Novel 3,5-Dimethoxycinnamic Acid-based Cathepsin C Inhibitor for the Treatment of Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD), which encompasses Crohn's disease and ulcerative colitis, affects about 5 million people worldwide and is caused by the inflammation of the gastrointestinal tract. Current treatments, including surgery, anti-inflammatory medications, and cytokine inhibitors, often fall short because of their limited efficacy, side effects, or narrow cytokine targeting. To address this need, this project focused on developing a novel small-molecule inhibitor for Cathepsin C (CTSC), a cysteine protease that activates serine proteases. Serine proteases are responsible for activating multiple pro-inflammatory cytokines, which induce inflammation and further elevate IBD. 3,5-dimethoxycinnamic acid was chosen as the starting scaffold, and through computational modeling in Schrödinger Maestro, over 200 different variants of 3,5-dimethoxycinnamic acid were docked to the CTSC protein and screened for docking scores and ADME pharmacokinetic properties. Structure 228 (S228) was selected as the ideal candidate, was synthesized, and evaluated in Drosophila melanogaster via the SMURF assay, which was given DSS-induced IBD to test S228's efficacy in vivo. S228 demonstrated significant measurable improvements in gut integrity and survival. These results suggest that upstream inhibition of CTSC may offer a new therapeutic strategy for IBD by significantly reducing cytokine-driven inflammation.

Awards Won:
Third Award of $1,200