ORGANIC SEMINAR

DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF NOVEL HIV-1 PROTEASE INHIBITORS CONTAINING SEMI-PRINS/PINACOL MEDIATED, ARYL SUBSTITUTED, OXASPIROCYCLIC P2 LIGANDS

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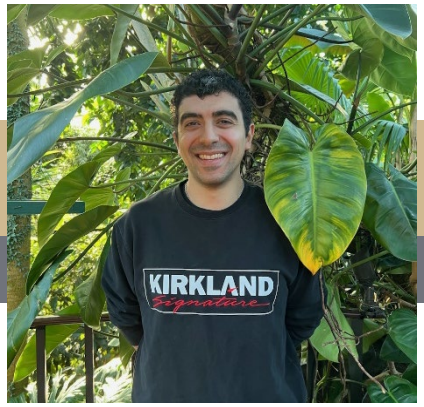

Abstract: Since the first officially reported cases of AIDS during the start of the epidemic in 1981, no cure exists for either AIDS or its causative infection, HIV-1. Among current treatment regiments, protease inhibitors remain an integral part of the most effective options for HIV-1 infected patients. This treatment, known as combination antiretroviral therapy (cART), is incredibly effective at reducing patient viral loads to virtually undetectable levels. However, current treatments are contending with the emergence of multi-drug-resistant strains of HIV-1. Even darunavir, which has been wildly implemented since its FDA approval in 2006 due to its remarkable activity against drug-resistant strains, has been stymied by this issue. Herein, we report the design, synthesis, stereochemical analysis, and biological evaluation of novel HIV-1 protease inhibitors featuring an oxaspirocyclic P2 ligand. These inhibitors were designed to promote hydrogen bonding with the HIV-1 backbone via methoxy dialed, aryl oxaspirocycles while also exploring the effects of stereochemistry on binding affinity. Currently, inhibitors displayed low nanomolar binding affinities with further results underway. This research contributes to the ongoing quest for innovative HIV-1 therapies underscoring the significance of stereochemical investigations and modifications in the development of potent and selective protease inhibitors.

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