Project: Development of Covalent Inhibitors for Understudied Protein Kinases

Short description: Although many successful and historical drugs such as aspirin, penicillin and omeprazole act inhibiting covalently their molecular targets, for a long time the design of drugs with a covalent mechanism of action has been avoided by pharmaceutical industries due to concerns about safety and selectivity. However, with the advent of structure-based approaches and the "omics" era, pharma-companies and academic labs have recently revival the design of covalent inhibitors in a rational manner, with outstanding results demonstrated by recent approvals of covalent drugs exemplified by Sotorasib, a mutant-KRASG12C inhibitor, and Nirmatrelvir, a SARS-CoV2 Mpro inhibitor (see https://doi.org/10.1021/acs.jmedchem.3c01825). Protein kinases are among the most important human drug target, being responsible for regulating cellular cycle and many others crucial physiological events. Overexpression of these proteins implies in several diseases, such as different types of cancers. Currently, we have 88 approved drugs as protein kinase inhibitors, however, there is still a substantial fraction of the so-called "kinome" with an unknown biological function, which is an enormous potential source for the developing of new drugs (see https://doi.org/10.1021/acs.jmedchem.1c00980).

Objective: We are seeking very motivated students to participate in a project to illuminate the chemically unexplored fraction of the kinome through the design and synthesis of covalent inhibitors for understudied protein kinases. If you want to be involved in a "hot topic" research in Drug Discovery with partners worldwide, just send an email!

Technical skills: Fundamental practical knowledge in synthetic organic chemistry and structural characterization of small-molecules (NMR, MS, HPLC, TLC...).

Openings offered: 1 Master thesis

Language: English

Director MS thesis: *Prof. Dr. Ricardo A. M. Serafim* (ricardo.serafim@iqs.url.edu)

Location: *IQS Synthesis Laboratory*