Structure-Based Design and In Silico Evaluation of Multi-Target Drug Candidates for Inflammatory and Cardiometabolic Diseases

Christos T. Chasapis
Assistant Professor
Organic Chemistry Laboratory, Department of Chemistry
NKUA

Abstract

Drug discovery for complex, multifactorial diseases increasingly moves beyond the classical “one drug–one target” paradigm toward multi-target drug candidates. Such molecules are designed to modulate several predefined targets within the same pathological network, with the aim of improving efficacy and reducing the need for polypharmacy. The first part of the seminar introduces the basic logic of rational drug design and simple structural strategies for constructing multi-target ligands, including linked, fused and merged architectures.

As an anti-inflammatory paradigm, dual inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) within the arachidonic-acid pathway is then discussed. A recent survey of dual COX-2/5-LOX inhibitors (2020–2024) relates biological context, active-site topographies and structure–activity relationships, leading to a concise “Rule of Four for Inflammation” that captures four recurrent structural features associated with potent, balanced dual inhibition. The second case study shifts to cardiometabolic disease and reviews protein–ligand interactions for six key therapeutic targets: GLP-1R, GIPR, FGFR1/β-Klotho, PCSK9, NF-κB and the NLRP3 inflammasome. Structural analysis across curated complexes highlights complementary aromatic, hydrophobic and polar motifs that govern ligand efficacy and specificity, and outlines how these shared features can guide the rational design of next-generation multi-target ligands with integrated effects on weight loss, glycaemic control and cardioprotection.