P3 – Pereira, Ana Catarina

Molecular docking reveals CDK1 as a therapeutic target of novel purine derivatives in triple negative breast cancer

Ana Catarina Pereira[1,2], Soraia P. Fernandes[2], Bruna Leite[2], Rafael Vieira[3], Cátia Santos-Pereira[1,5], Débora Ferreira[1,5], Sérgio F. Sousa[3,4], Alice Dias2 and Lígia Rodrigues[1,5]

[1] CEB - Centre of Biological Engineering, University of Minho, 4710-057 Braga, Portugal
[2] CQUM - Centre of Chemistry, University of Minho, 4710-057, Braga, Portugal
[3] LAQV/REQUIMTE BioSIM – Department of Biomedicine, Faculty of Medicine, University of Porto, 4200-319 Porto, Portugal
[4] Department of Chemical Engineering, FCTUC, University of Coimbra
[5] LABBELS – Associate Laboratory, Braga, Guimarães, Portugal

Abstract:
Triple negative breast cancer (TNBC) accounts for about 15% of the more than two million breast cancer cases diagnosed annually. Defined by the lack of estrogen (ER), progesterone (PR), and epidermal growth factor receptor 2 (HER2) expression, TNBC is highly aggressive, exhibits rapid proliferation, and shows poor response to conventional and hormonal therapies, highlighting the urgent need for new therapeutic strategies. Given the emerging anticancer potential of purine scaffolds, newly synthesized 6-cycloalkylaminoadenine derivatives were investigated for their therapeutic potential. These purine-based molecules were evaluated for antiproliferative activity in TNBC cells. Among them, one compound (3.2a) displayed notable growth-inhibitory effects and reduced motility and invasiveness of the TNBC MDA-MB-231 cell line. Further analyses indicated that this compound promotes cytoskeletal alterations and triggers apoptotic pathways. Computational docking was performed against a panel of signaling proteins associated with cell cycle regulation and oncogenic survival pathways. A validated molecular docking pipeline was established through redocking assays using GOLD with PLP and GoldScore scoring functions. Compound 3.2a showed a favorable docking score against CDK1, a key regulator of cell cycle progression, forming hydrogen bonds and hydrophobic interactions characteristic of high-affinity ATP-competitive inhibitors. Taken together, these results highlight the 6-cycloalkylaminoadenine scaffold as a promising lead structure for the rational design of selective CDK1 inhibitors for TNBC therapy.