**MEDICINAL CHEMISTRY SECTION**

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**OVERVIEW**

Medicinal Chemistry (MedChem) is a scientific discipline concerned with the design and synthesis of bioactive molecules to address unmet medical needs or to improve existing drugs. The discipline combines expertise in organic chemistry with knowledge of ligand-receptor interactions and pharmacology to design and modify the structure and properties of molecules, to improve potency and drug-like properties.

The Medicinal Chemistry Section is part of the multidisciplinary Experimental Therapeutics Programme (ETP), which focuses on early drug discovery activities. The ETP is integrated into the CNIO's structure, and acts as a bridge between basic research groups in cancer biology, which identify innovative targets that play a relevant role in cancer, and the pharmaceutical industry. Our goal is to generate molecules against these cancer targets and to demonstrate their efficacy and mechanism of action in animal models (in vivo proof of concept). This allows us to translate the results obtained in basic research laboratories into potential drugs that contribute to the understanding of cancer biology, as well as to increase the interest of the pharmaceutical industry to develop new therapies (FIGURE 1).

“We have licensed several hit compounds (Foxo activators) to Refoxy Pharmaceuticals GmbH as a result of a collaboration with them.”
RESEARCH HIGHLIGHTS

Our MedChem activities focus mainly on the following projects:

Telomeric repeat binding factor 1 (TRF1) inhibitors

This project is carried out in collaboration with María A. Blasco (CNIO Telomeres and Telomerase Group). The ETP Biology Section previously developed an assay to measure the binding of TRF1 to telomeric DNA. This assay allowed us to identify several inhibitors that did not interfere with the assay system and did not bind to ds-TelDNA. After validating some of the hits, in 2023 we focused on generating structure-activity relationships (SARs) by synthesising analogues. These compounds were further characterised in a non-radioactive EMSA assay and will be tested in additional assays to ultimately demonstrate their efficacy against TRF1.

Microtubule-associated serine/threonine protein kinase-like (MASTL) inhibitors

This project is undertaken in collaboration with Marcos Malamburg (CNIO Cell Division and Cancer Group). We envisaged 2 different approaches in this project: the search for small molecule inhibitors and for degraders. For the inhibitors, we continued to refine and characterise our lead compounds and generated back-up series to strengthen the search for SETD8 inhibitors is the result of a collaboration with Óscar Fernández Capetillo (CNIO Genomic Instability Group) and the Macromolecular Complexes in DNA Damage Response Group. Several assays were set up in the Biology Section (i.e., a biochemical assay with full-length SETD8 in the absence or presence of nucleosomes, and a cellular assay based on the determination of H4K20 monomethylation) to identify and characterise hit compounds. To date, the hits identified in initial biochemical screening campaigns have not yet been validated in the entire panel of assays. Moreover, we continued to refine and characterise our lead degraders by exploring different linkers, linking functional groups and scaffolds on drug-like properties. In terms of degraders, we focused our activities on optimising our lead degraders by identifying different linkers, linking functional groups and several E3 ligase ligands. So far, we have identified several PROTACS with good degradation profiles in different cell lines. The final goal of the project is to achieve degraders.

NUDT5 inhibition

Project under a strategic alliance with the CRG/UCIC (R. Wright) to optimise a hit that inhibits the ATP generating activity of NUDT5 in a biochemical assay. Several analogues have been acquired, and their quality assessed internally. Currently, an initial SAR has been generated.

Synthesis of reference or tool compounds

Apart from the drug discovery activities in the above-mentioned projects, we give support to several groups by synthesising reference or tool compounds. During 2023, we carried out this work for the following CNIO Groups: Brain Metastasis, Genomic Instability, Metabolism and Cell Signalling, Telomeres and DNA Breaks, and Growth Factors, Nutrients and Cancer.

Histone H4-Lysine 20 N-methyltransferase (SETD8) inhibitors

The search for SETD8 inhibitors is the result of a collaboration with Óscar Fernández Capetillo (CNIO Genomic Instability Group) and the Macromolecular Complexes in DNA Damage Response Group. Several assays were set up in the Biology Section (i.e., a biochemical assay with full-length SETD8 in the absence or presence of nucleosomes, and a cellular assay based on the determination of H4K20 monomethylation) to identify and characterise hit compounds. To date, the hits identified in initial biochemical screening campaigns have not yet been validated in the entire panel of assays. Moreover, we conducted a chemical exploration around the hits without significant success.

RANK antagonists as a novel therapeutic approach for the treatment of TNBC patients

We are collaborating with Eva González-Suárez (CNIO Transformation and Metastasis Group) to develop small molecules that specifically target the RANK receptor. The group of X. Barié (Universitat de Barcelona) conducted a second virtual screening of our ETP library of compounds. We supported the hit validation activities (i.e., SPR by the CNIO Spectroscopy and NMR Unit, and cell experiments by the Transformation and Metastasis Group), supervising the acquisition of hits and assessing their quality.