The Medicinal Chemistry Section is part of the Experimental Therapeutics Interdisciplinary Programme that is dedicated to early Drug Discovery activities in the oncology field. Medicinal Chemistry activities start with the identification of hits through high throughput screening campaigns from targeted or phenotypic assays, and lead on to further activities related to the design, synthesis and optimisation of the compounds in order to obtain novel lead compounds with in vivo activity in appropriate animal models. For hits obtained from phenotypic screenings we introduce an additional target identification step in order to decipher the mechanism of action responsible for the observed phenotype. Our Group has experience in the design and synthesis of affinity probes for target deconvolution studies. These molecules enable the detection of the cellular localisation of the target of interest through imaging techniques and enable its isolation through pull-down experiments. Additionally, as a complementary alternative, we are developing proteolysis targeting chimeras (PROTACs) as promoters of cellular protein degradation in order to establish their applicability across diverse drug discovery projects.

“We developed first generation HASPIN-selective inhibitors as chemical probes through the application of structure-based design strategies in order to determine the therapeutic potential of the pharmacological inhibition of this mitotic and epigenetic kinase.”
RESEARCH HIGHLIGHTS

Inhibition of Cancer Stem Cell (CSC) proliferation

During 2017, we were involved in the optimisation of ETP-27, a lead compound identified and developed in our programme, with demonstrated in vivo proof-of-concept in the acute myeloid leukaemia model, MOLM-13 xenograft. Fine tuning optimisation has been done and we have identified ETP-93, an orally bioavailable compound with longer half-life than ETP-27. ETP-93 showed oral levels in both plasma and tumour, biomarker modulation (pSTAT1) up to 8 hours after oral administration in PK/PD studies, and a significant tumour growth inhibition of 50% in a 10 day short-term study at 50 mpk P.O. in MOLM-13. The compound is rather selective (S(35): 0.08) in a 468 kinase panel (KINOMEscan™ platform) and only 1 main off-target has been identified. Currently, we are evaluating the positive contribution of this activity to the antiproliferative profile of the compound. Additionally, in this series we have identified very selective Cdk8 inhibitors with good in vivo PK, for example ETP-18, which has been selected for further in vivo efficacy studies.

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

Two different hits were identified from an HTS campaign with active full length human MASTL protein. About 100 analogues have been synthesised around them to establish Structure-Activity-Relationships (SAR), identifying compounds in the single digit nanomolar range from both chemical series. Selected compounds have been profiled in a small set of kinases to determine their selectivity and we have identified some main off-targets in the compounds. Currently, we are focussing our efforts on trying to obtain high quality selective chemical probes that will be used in pharmacological inhibition studies to decipher the whole therapeutic potential of MASTL.

HASPIN inhibitors

During the exploration of 2 chemical series we were able to obtain very potent biochemical and cellular low nanomolar haspin inhibitors, while removing the off-target activities present in the original hits. After the synthesis of about 90 compounds, we profiled the selectivity of 2 representative molecules from each chemical series, ETP-949 and ETP-945, in a 468 kinase panel (KINOMEscan™) obtaining a high level of selectivity for both of them (S(35) of 0.025 and 0.007). Currently, one of these chemical series is under in vivo characterisation with the aim of identifying a high quality Haspin inhibitor for pharmacological target validation studies. Additionally, a third chemical series was generated in 2017, including intellectual property in the design.

Telomeric repeat binding factor 1 (TRF1) inhibitors

This is a collaborative project undertaken with the CNIO Telomerases and Telomerase Group. During 2017, we focused on the synthesis of different affinity probes of hit compound ETP-946 in order to identify the putative molecular target responsible for the observed TRF1 modulation. Among them, the ETP-455 affinity probe showed similar TRF1 modulation to the hit compound and was selected for deconvolution studies. ETP-455 contains a reversible linker with a terminal alkyne reactive group that helps in cell localisation and pull down experiments by using a click chemistry reaction with functionalised (azide reactive group) fluorophores and or biotinylated derivatives. Preliminary cell localisation experiments using imaging techniques have been performed, demonstrating a rather specific localisation of the chemical probe that can be removed by competition with ETP-946.

Cyclin-dependent protein kinase 8 inhibitors (Cdk8i) project

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