Case Study

bio:ascent

Lead generation: discovery of novel KLK6 Inhibitors as novel anti-cancer drugs

A collaboration between the European Screening Centre of the European Lead Factory (now part of BioAscent) and the German Cancer Research Center (DKFZ)

BioAscent scientists working with teams at Pivot Park Screening Centre and the German Cancer Research Center as part of the European Lead Factory discovered potent and selective inhibitors of Kallikrein-related peptidase 6 aimed at potential new treatments for cancer.

Background

The European Lead Factory (ELF) is a project funded by the Innovative Medicines Initiative to identify high quality hit series using High Throughput Screening (HTS) for drug discovery projects. A consortium comprising of universities, SMEs and major pharma companies assembled the infrastructure, expertise and processes to identify these hit series for academic groups and small companies.

The German Cancer Research Center (DKFZ) is the largest biomedical research institute in Germany and a member of the Helmholtz Association of National research Centers. With over 90 divisions and research groups, DKFZ employs over 1,200 scientists who work on understanding the mechanisms of cancer, identifying cancer risk factors, and developing strategies to prevent people from getting cancer.

The BioAscent scientists, working closely with the group at DKFZ, used their expertise in biophysical and biochemical assays and medicinal chemistry to develop hits identified from a high throughput screen carried out at PPSC. This work has recently been published in ChemMedChem.

Challenge:

Identifying high quality chemical starting points is a key challenge for drug discovery. Whilst HTS is an important approach, historically the infrastructure and expertise to carry out successful campaigns has resided in major pharma companies and been less accessible to academic groups and small companies. DKFZ proposed a role for Kallikrein-related peptidase 6 (KLK6) in cancer and wanted to identify potent and selective inhibitors to advance their hypothesis and identify starting points for a drug discovery project.

Solution:

A high throughput screen of the 350,000 compound collection assembled for the ELF, led to the discovery of a validated hit cluster of N-(4-benzamidino)-oxazolidinones that showed

consistent inhibitory activity against KLK6. Re-synthesis of hits demonstrated that activity resided in a single stereoisomer. Docking-guided optimization of this scaffold, with a focus on potency against KLK6 and selectivity against up to six different related proteases resulted in compounds with single digit nanomolar potency and good to excellent selectivity.

Compounds were prepared as single enantiomers using either chiral synthesis of building blocks or separation of diastereomers derived from commercially available homochiral starting materials. Two chemists over a 9 month period prepared more than 90 final compounds and these were tested for bioactivity and selectivity. This work was performed by the team which is now part of BioAscent. ADME profiling of one compound showed that it has suitable properties for pre-clinical biological experiments and was found to reduce invasion of HCT116 cells in a dose-dependent manner. A control substance from the inactive enantiomeric series showed no such effect even at the highest tested concentrations.

Impact:

Identification of potent and selective KLK6 inhibitors with properties which make them suitable for further biological experiments enables key questions about the role of this enzyme in disease biology to be addressed. The availability of an inactive enantiomer increases the value of these tools. This programme demonstrates how the experienced ELF team working collaboratively with the DKFZ team could apply a variety of medicinal chemistry, biochemical and biophysical techniques to prosecute an HTS and then validate and optimise the resultant hits.

> *"Our scientists really enjoyed working with the DKFZ to help generate high quality hit series for this target. I think this project really demonstrates the strengths of the BioAscent drug discovery team – in this case working with the wider ELF team and the programme owner DKFZ to create results which can help advance drug discovery in this area and ultimately to benefit patients."* Dr Phil Jones, Chief Scientific Officer at BioAscent.

"Working with the ELF scientists was a real pleasure. They performed their work with a high level of quality and professionalism. More importantly, the scientists (now at BioAscent) who were involved in the hit development stage, were fully committed to the success of the project, bringing their own ideas and solutions, which made my role as project owner very comfortable. I would be very happy to work with them again." Dr Aubry Miller, Cancer Drug Discovery/Wirkstoffforschung Group Leader, German Cancer Research Center (DKFZ).

To find out more please get in touch.
Read the paper online here.

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