From idea to library

Design and implementation of a process to deliver 40,000 unique lead-like compounds

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SYGNATURE discovery

European Lead Factory

European Lead Factory (ELF)

The ELF is a €200M project (supported by the Innovative Medicines Initiative and European Federation of Pharmaceutical Industries and Associations (EFPIA)) that aims to promote drug discovery in Europe by producing a new collection of **500,000** drug-like compounds for high-throughput screening (HTS) by the public sector in a variety of therapeutic areas.

- **300,000** compounds have been donated by EFPIA partners.
- **200,000** compounds are being designed, generated and synthesised equally by Sygnature Discovery and four other SMEs in collaboration with academia.

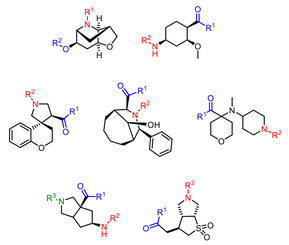
The new libraries being synthesised will focus on: **novelty**, **shape** (eg. sp^3-rich cores), **diversity potential** and **innovative library design** and will complement classical compound collections.

Idea Generation

An idea is designed around a chemical core which is then modified to produce several diverse scaffolds.

Scaffold criteria:

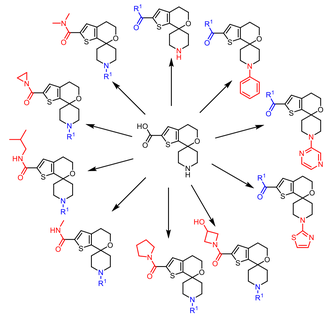
- 2 or 3 points of diversity
- Short and efficient synthetic route
- 5-6 steps
- Scalable chemistry
- Non-commercial
- cLogP <3
- MW <300
- 3D shape required
- Preferably amine, acid or alcohol handle
- No reactive groups in final compounds (e.g. imine, Michael acceptor…)



A selection of cores generated at Sygnature Discovery

Validation

Before full production can start the idea must be validated including scaffold preparation, library synthesis, purification and analysis in order to identify any possible issues.



Scaffolds produced for one idea. Typically 10 mmol of each is required

Key factors to identify:

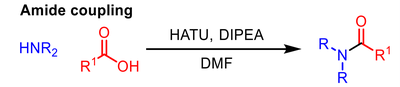
- Most robust synthesis of scaffold
- Possible issues for scale-up
- Library success rate

Compound properties validated:

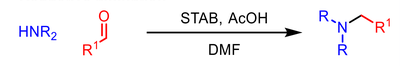
- Solubility
- Stability
- Ionisation
- Absorbency
- Reactivity
- Isolation
- Purification
- Recovery

Scaffolds → Final compounds

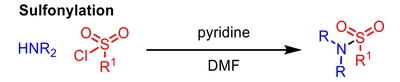
Amide coupling



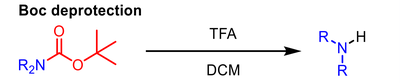
Reductive amination



Sulfonylation



Boc deprotection



Example library reactions tested during validation

Production and Dispatch

Reagent set

Waters UPLC

Analysis plate

Analysis plate
Samples diluted with DMSO into an analysis plate using the liquid handler

UPLC analysis
Plate stacker enables us to queue up to 9 plates

Analysis results
Focussed gradients for purification automatically generated from UPLC retention times

Starting materials
8-10 Scaffolds per idea

Reagent sets are stored as stock solutions in DMA in barcoded 48 well plates

Plate up
Reaction mixtures prepared using liquid handler or manual pipette

Reaction plate
- 96 Well reaction plate
- 96 Reactions per scaffold
- 0.1 mmol scale
- ~800 Reactions total
- Shake at ambient temperature overnight

Filter plate
Reaction mixtures filtered prior to purification

Purification
Semi-prep HPLC can purify >100 samples a day

Barcoded tubes
Fractions collected by semi-prep HPLC into barcoded tubes and dried by centrifugal evaporation

Reformat
Liquid handler

Barcoded tubes

Analysis plate

UPLC analysis, weighing

Submission vials
Dry compounds re-dissolved in MeOH/$CHCl_3$ on the liquid handler and transferred to vials for ELF and for Sygnature Discovery

Compounds dried for a final time

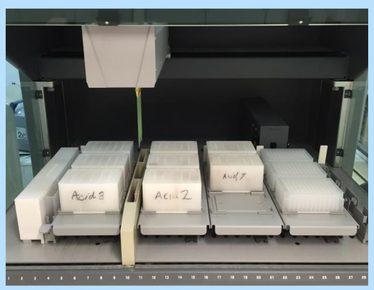
Submission vial

QC pass criteria
Purity >85% by UPLC
Quantity 5-50 µmol

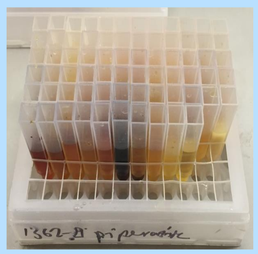
GeneVac HT6 centrifugal evaporator

Dispatch
Compounds passing QC are delivered to Bioascent, Scotland

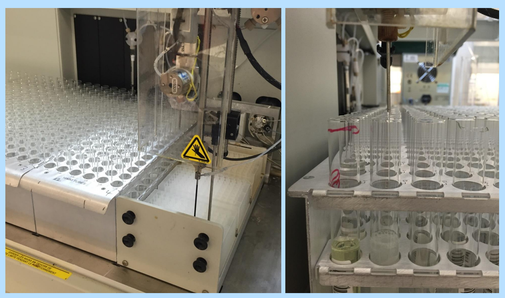
Compound hub
Compounds made into 10 mM solutions in DMSO and added to screening collection



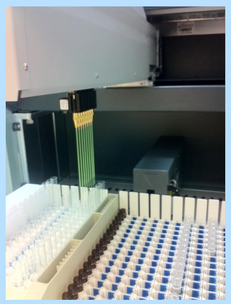
Plating up using reagent sets



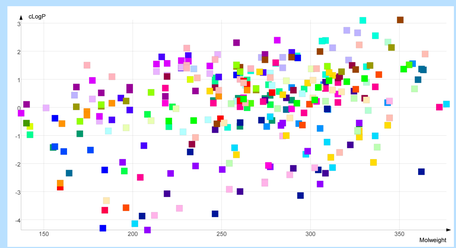
Reaction plate



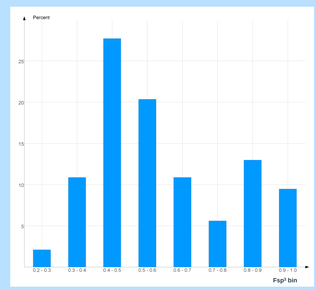
Waters semi-preparative HPLC



Tecan liquid handler



MW v cLogP of scaffolds for first 20,000 compounds



Fsp³ distribution of scaffolds

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