10 YEARS OF BREAKTHROUGHS A HEALTHIER FUTURE

European Lead Factory

55

FSP^3-RICH SPIROCYCLES TO ACCESS NOVEL COMPOUND LIBRARIES

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Facts & Figures

Start date:	01/01/2013
End date:	31/05/2018
Contributions	
IMI funding:	79 999 157 €
EFPIA in kind:	91 657 070 €
Other::	24 922 388 €
Total Cost:	196 578 615 €
Project website:	www.europeanleadfactory.eu

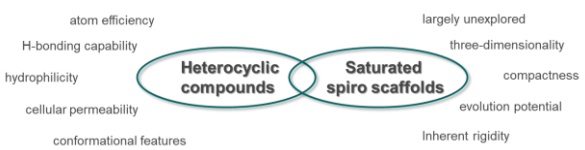
Social media:
de.linkedin.com/company/european-lead-factory
twitter.com/euleadfactory?lang=de

Challenge

The European Lead Factory (ELF), a collaborative public private partnership established in 2013, provides high-quality compound libraries and the opportunity to screen those compounds against potential drug targets to a broader community. Taros Chemicals, a privately owned CRO company, is leading the chemistry consortium and have contributed with 40 000 compounds into the Public Compound Collection (PCC) covering more than 65 scaffolds with a very high dissimilarity.

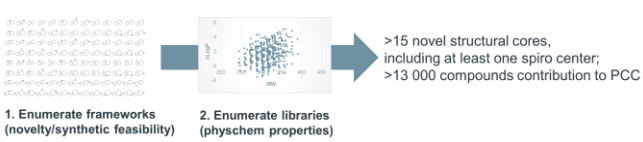
The distinctive characteristic of the Taros' screening compounds is their high level of structural complexity and three-dimensionality, two features that are regarded as attractive in drug discovery application. The three dimensional core structures are further expanded by the decoration of a diverse in-house collection of final diversification reagents. The substitution pattern and unsaturated character provide versatile starting points and ample opportunities for further chemical exploration and growth during the hit-to-lead phase.

Spirocycles in particular are attractive structural frameworks for drug discovery due to the peculiar shape and conformational features. Taros' screening compounds are unique unsaturated ring systems with an overall high percentage of sp^3 hybridized carbon. Important properties of these scaffolds include their inherent rigidity, structural novelty, reduced lipophilicity, and greatly increased potential for the precise presentation of pendant functional groups in three-dimensional space.



Approach & Methodology

The design of the attractive libraries starts with the enumeration of underrepresented 3-5-membered ring containing spirocycles scaffolds. The synthetic feasibility dictates the set of highly compact, three-dimensional cores targeting unusual scaffold topology that is further diversified to yield compounds with the desired physchem properties with interesting substitution patterns.



Results

Within the ELF project, Taros has contributed to the PCC of ELF a wide range of novel scaffolds, including >15 libraries, featuring at least one spiro center. On Fig.1 are presented few examples of the produced libraries and some of their physicochemical properties.

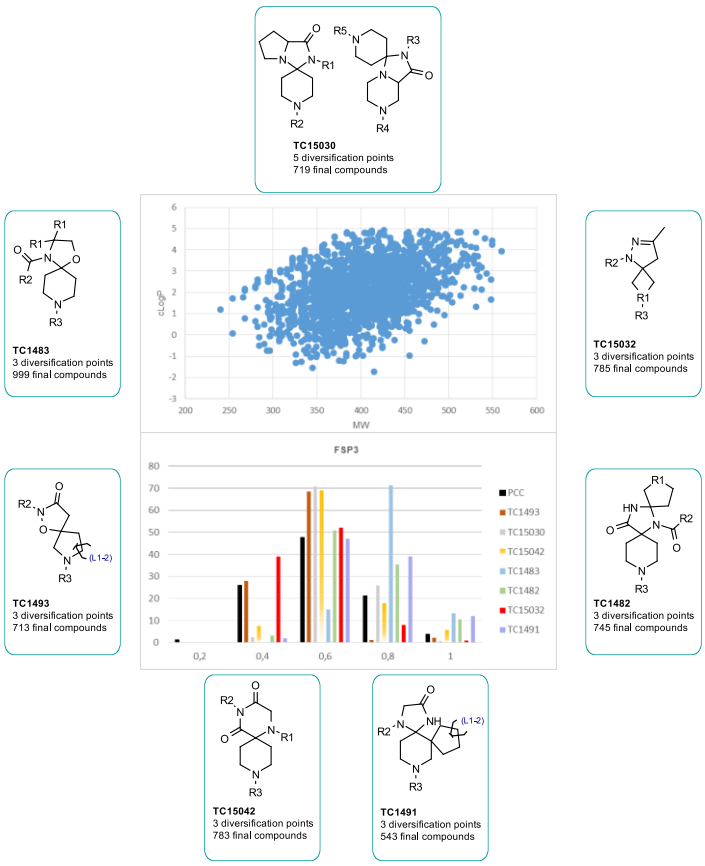


Fig 1. Examples of spirocyclic libraries produced in Taros Chemicals and graphical representation of their molecular weight, clogP and Fsp^3

Through careful design and thorough consideration and choice of the diversification reagents, all produced compounds exhibit ´drug-like´ character in correspondence to Lipinski's rule concerning molecular weight, clogP, number of rotatable bonds, hydrogen bond acceptors and donors, etc. Moreover, the rich Fsp^3 character of the presented libraries ensure high three-dimensionality, providing the opportunity to target challenging hot spots. The substitution pattern on the other hand, in combination with the well established, robust synthetic 'know-how' offers a wide range of opportunities for further structural elaborations.

Value of IMI Collaboration

The exploration of chemical space remains one of the most critical steps towards identification of novel chemical matters for drug discovery applications. Thus, populating areas of chemical space with biological relevance is of great importance. Fsp^3-rich, spirocyclic compounds show many attractive features, such as molecular compactness, structural complexity and three-dimentional character. The inclusion of such libraries in PCC of ELF and their exposure to >100 HTSs during the ELF project life cycle will provide an important test to evaluate their biological relevance, target class propensity and overall suitability in a drug discovery setting.

Impact & Take Home message

The primary goal of ELF was to deliver hit compounds that in turn can be translated into patents and drug candidates with the ultimate goal to improve patients' lives. ELF is the perfect instrument to address this challenge, through providing the early drug discovery community with the resources required to identify and better potential drug candidates with the potential to move faster into the clinic.

imi innovative medicines initiative efpia

This work has received support from the EU/EFPIA/Innovative Medicines Initiative [2] Joint Undertaking ([EUC²LID] grant no [115489]'.