

### Discovering leads from natural products

Natural products have long been a major source of new medicines. About 50% of the drugs introduced to the market in the last 20 years trace their origin to compounds derived from nature. A similar impact has been experienced in animal health and agrochemical discovery.

BioFocus DPI offers the latest technologies to discover promising hit and lead molecules from fungal and bacterial sources of natural products. Natural product-based compounds offer chemical structures unavailable in synthetic chemistry collections. The compounds in our natural products collection display:

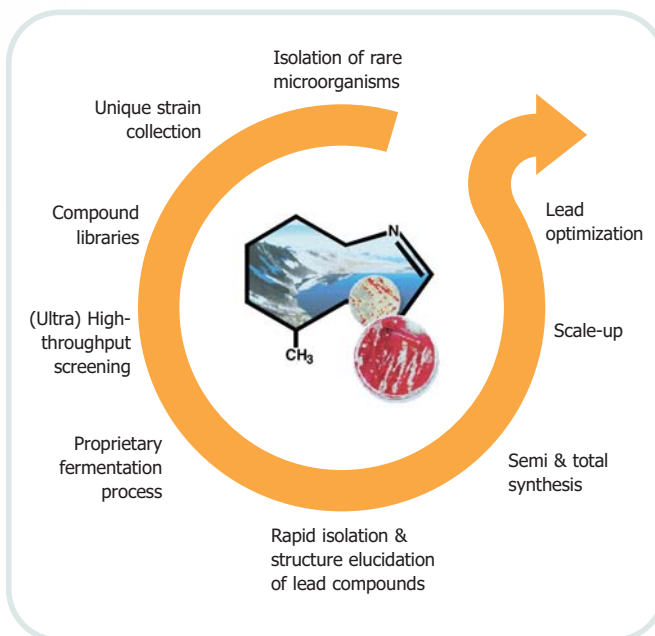
- Potent pharmacological activities over a broad range of biological targets
- High chemical and functional diversity
- Desirable physicochemical properties

BioFocus DPI has an advanced, comprehensive suite of technologies that greatly simplify natural product-based drug discovery:

- Access to ~140,000 highly diverse pre-purified natural compound subfractions
- Over 700 pure natural compounds
- Preparation and screening of focused libraries based on natural product scaffolds
- High-throughput screening against a broad range of target classes
- Large-scale isolation of active compounds
- Rapid structure elucidation
- Chemical synthesis and derivatization
- Lead optimization including profiling studies

### Subfraction library

BioFocus DPI has an exclusive collection of over 45,000 actinomycetes and 8,000 fungi. Using a proprietary fermentation process, excellent expression of secondary metabolites is obtained from the strains of our collection. We then apply a unique subfractionation process to obtain pre-purified natural compound samples that are suitable for (ultra)high-throughput screening. Approximately 140,000 subfractions (each containing approximately 10 to 15 compounds) are currently available for screening.



### Natural compounds

BioFocus DPI offers a collection of natural compounds and derivatives covering a broad range of biological activities. The collection includes compounds acting on specific target classes, such as inhibitors of HSP90, kinases and proton-ATPases; natural compounds interacting with specific pathways, such as apoptosis, angiogenesis and immunosuppression; as well as compounds with cytotoxic or antimicrobial activities. We also offer a collection of 245 pure natural compounds which are, to the best of our knowledge, not commercially available elsewhere.

Our **NatFocus** Libraries are small focused compound collections based on natural product scaffolds with attractive biological activity, physicochemical properties and structural features.



# Natural products screening

## Assay development and hit identification

At BioFocus DPI, we have experience in developing robust, reliable assays suitable for HTS of natural product subfractions for a broad range of target classes - notably GPCRs, kinases, proteases and ion channels. With a track record of performing hundreds of drug discovery projects on a wide range of target classes, we have accumulated significant expertise in various therapeutic areas using a number of assay formats. These formats include enzyme activity, receptor binding and functional receptor assays as well as protein-protein interaction studies and eukaryotic and prokaryotic cell-based assays. Once a suitable assay has been established, subfractions or pure natural compounds are screened using high throughput and ultra-high throughput technologies. After data is processed by state-of-the-art tools, hits are ranked according to activity, selectivity, sample polarity and microbial source. This robust screening approach results in primary hits with a high confidence level, generating quality compounds for hit follow-up and lead finding.

## Fine fractionation and dereplication

Selected subfractions undergo one additional fine fractionation step, which delivers samples suitable for dereplication. Active fine fractions are analyzed by LC-MS and the analytical data is used to identify known compounds by comparison with our extensive in-house as well as external databases.

## Refermentation, isolation, structure elucidation and profiling

New compounds selected after dereplication are re-fermented and isolated in mg amounts for structure elucidation and biological profiling. Using NMR and other analytical procedures, we determine the structure of hit molecules generated from a natural compound screen within a few days. Our natural product isolation group is

able to (re)supply gram amounts of pure, active compounds for profiling, animal studies and semi-synthetic derivatization. Using our production-scale fermentation capacity and preparative HPLC equipment, we are able to purify tens of grams of natural compounds.

## Chemical synthesis

Our synthesis team is particularly skilled in the semi-synthetic modification and optimization of natural product leads (solution and solid phase parallel synthesis) including the generation of focused libraries around natural scaffolds through parallel synthesis.

## Case studies

### Hit identification from natural product subfractions

A Ser/Thr-kinase screen of 10,000 subfractions delivered 330 hits. After hit validation and selectivity testing, 40 subfractions were fine fractionated. The program resulted in new and known compounds from several structural classes, which are currently in the hit-to-lead phase, e.g. a known compound that has not yet been described as kinase inhibitor and a new kinase inhibitor scaffold.

### Lead optimization of natural compounds

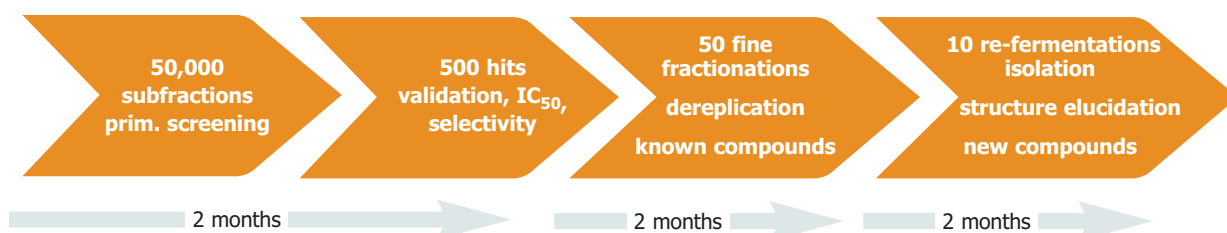
Fredericamycin A (FMA) from *Streptomyces griseus* was identified as a starting point for a novel anti-tumor agent.

Following strain optimization and production of the starting material, the compound was converted into 300 derivatives through a semi-synthetic process. Screening against an appropriate tumor cell line panel yielded 17 compounds with improved potency and cell line selectivity.

## Contact

To learn more about our natural product offering, please contact us at [biofocusdpi@glpg.com](mailto:biofocusdpi@glpg.com)

Typical hit finding process and timelines:



[biofocusdpi.com](http://biofocusdpi.com)

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