

# CHEMISTRY



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We understand that each partner has different needs, internal capabilities and capacities. Evotec prides itself in being able to provide flexible, innovative and efficient solutions. Evotec's experienced scientists can support your aspirations in a variety of ways. The capabilities listed below can be accessed individually where required or brought together to form complete project solutions:

- ▶ Cutting-edge molecular design
- ▶ Rapid synthetic execution
- ▶ Expert advice on overall project strategy
- ▶ Developing strategy for and securing IP protection
- ▶ Scale-up chemistry
- ▶ Preparative chromatography
- ▶ Project management

## SYNTHESIS

At the foundation of Evotec's medicinal chemistry group is a talented and industry-experienced team of >175 synthetic organic chemists. Their skills are utilised during medicinal chemistry-driven projects, focused-library preparation, scale-up synthesis and when preparing chemical building blocks or literature compounds.

Synthetic execution is one of the most cost- and time-consuming parts of the early discovery process. We understand that where synthesis is concerned, speed is paramount. The faster our teams can deliver molecules into bioassays, the faster the project teams can obtain new knowledge.

Our approach is to employ, educate and retain talented chemists and to enable them with the latest technology and equipment.

- ▶ More than 60% of our chemists are educated to PhD level
- ▶ >40% of our chemists have >8 years' experience at major pharmaceutical and biotech companies prior to joining Evotec
- ▶ Our chemists utilise state-of-the-art equipment known to accelerate productivity: microwave reactors, automated purification systems, parallel synthesisers

These facets enable Evotec to provide superior synthetic chemistry and problem-solving capabilities to our partners and to efficiently deliver compounds in a shorter timeframe than our competitors.

Good molecular design often leads to complex syntheses (e.g. densely functionalised heterocycles, multiple chiral centres). Projects are successfully executed at Evotec that involve highly challenging syntheses and isolation procedures, for example:

- ▶ Natural products
- ▶ Steroids
- ▶ Macrocycles
- ▶ Nucleosides
- ▶ Carbohydrates
- ▶ Peptidomimetics

The origin of the chemistry department in Abingdon was in asymmetric synthesis and Evotec routinely develops enantioselective synthetic

methods and has a full range of chiral separation technologies including SFC to deliver single isomers.

## MEDICINAL CHEMISTRY

Evotec has a powerful core of experienced, industry-seasoned drug hunters who drive the molecular design process. Our teams in Abingdon, UK and Toulouse, France have co-located group of medicinal chemists, computational chemists, structural biologists and DMPK scientists that have made significant contributions to discovery projects throughout their careers:

- ▶ >100 development candidates
- ▶ Named inventors and authors on >860 patents and publications

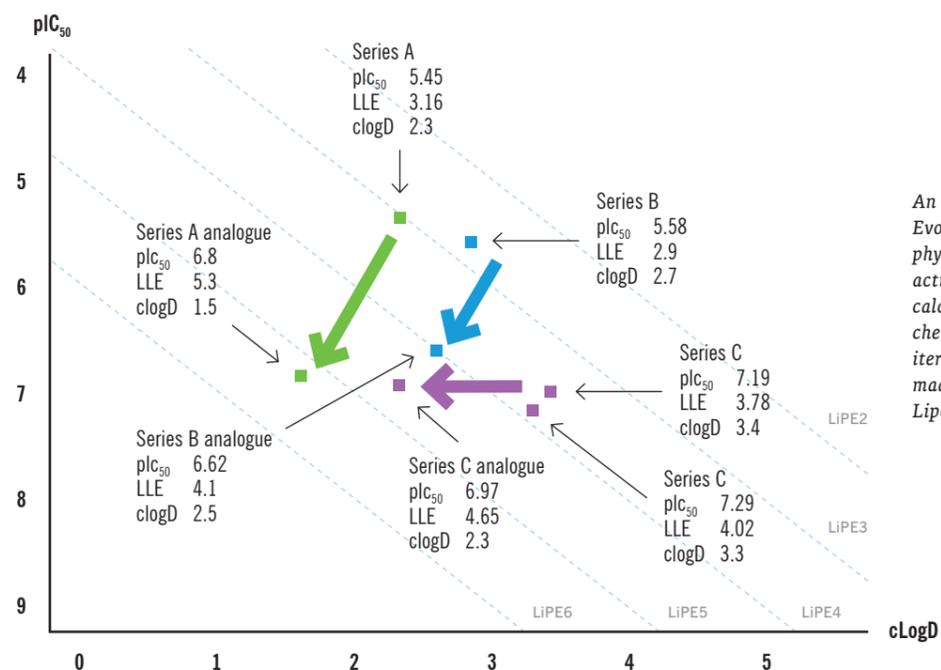
Our scientists are drawn from a variety of backgrounds and have been successful in all major therapeutic areas and target classes. We have a particularly strong track record in prosecuting ion channel modulators, enzyme inhibitors and protein-protein interaction inhibitors, with several compounds progressing to pre-clinical development and beyond.

Our teams are fluent and expert in both protein structure-guided and ligand-based design, utilising internal knowledge and experience as well as a wealth of supporting computational models.

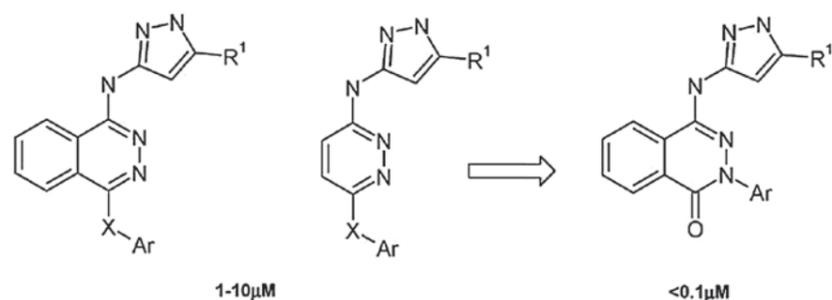


## OFFERING

Small molecule drug discovery requires a deep understanding of biological context coupled to knowledge and experience of the property space required to produce safe, efficacious drugs. Over the past 20 years, Evotec has developed expertise in numerous therapeutic areas including diseases of the central nervous system ("CNS"), oncology, diabetes and metabolic diseases, pain, cardiovascular and thrombosis diseases, inflammation and anti-infectives.



An example of multiparameter optimisation. Evotec's design teams simultaneously improve physicochemical properties as well as biological activity. The plot above (-log<sub>10</sub>IC<sub>50</sub> versus calculated LogD) highlights three different chemotypes from the same project. Over 2 iterations, the arrows indicate the improvements made to each series as seen from the improved Lipophilic Ligand Efficiency (LLE) scores



Selected templates investigated as Aurora kinase inhibitors, Phthalazinone Pyrazoles as Potent, Selective, and Orally Bioavailable Inhibitors of Aurora-A Kinase, *J. Med. Chem.* 2011, 54, 312–319

The focus of our medicinal chemistry teams is on high-quality design and crisp decision making. The process at Evotec is enabled by widespread availability of visualisation, analysis and design software tools. Our medicinal chemists target analogues within defined property space to answer specific structure-property and structure-activity questions – the emphasis is always on making the right compounds with optimisation of biological activity and properties in parallel. We firmly believe that the co-location and interaction of synthetic and medicinal chemistry, computational science, structural biology and DMPK enhances the overall design, analysis and communication process.

We continually review our internal processes (analysis, compound management, registration, dispatch etc.) to ensure that our discovery teams are working in the most efficient manner possible with the implementation of lean processes wherever possible. We have implemented a companywide electronic lab

notebook system and internal LIMS system for compound submissions. In addition we have project specific databases and workflows to enable rapid data sharing within teams and with our clients.

Our focus is to ensure the shortest possible “design-make-test-analyse” cycle with typically one complete cycle per month. With this in place we can achieve;

- ▶ Key project decision points in a shorter timeframe
- ▶ Increased knowledge and experience due to more learning cycles per time unit
- ▶ Better quality output/product
- ▶ Less waste due to more informed decisions
- ▶ Effective, efficient teams

#### SCALE-UP CHEMISTRY

Evotec can supply large quantities of molecules of interest through a team of very experienced chemists originating from chemical development that has contributed to:

- ▶ Late development synthesis of > 20 pre-clinical and clinical candidates

- ▶ Large scale synthesis of > 140 compounds for advanced pharmaceutical profiling

Their expertise allows them to cover areas such as:

- ▶ Large scale synthesis of API, intermediates (up to 100-200g)
- ▶ Route scouting for IND process
- ▶ Optimisation of synthetic routes
- ▶ Crystalline Salt selections
- ▶ Full technical package for transfer to larger scales for GMP batches synthesis

We ensure that synthetic processes match the safety requirements of large scale synthesis by using state-of-the-art equipments for calorimetric studies and in-process controls.

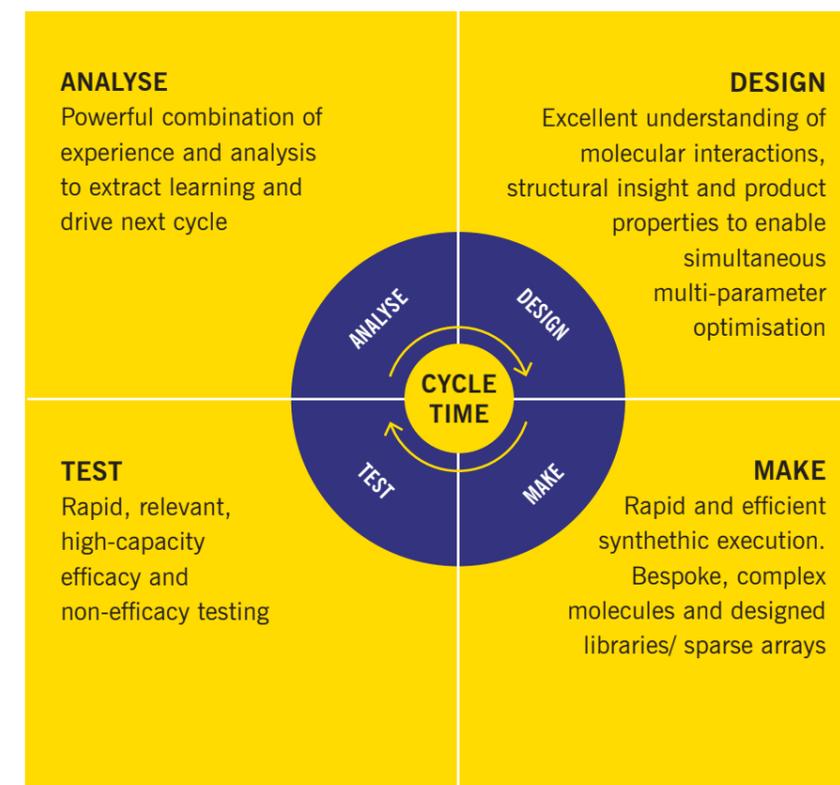
#### PREPARATIVE CHROMATOGRAPHY

Evotec has established a high quality preparative chromatography service catering from milligram to kilogram scales. The highly experienced group utilises complementary analytical and preparative HPLC and SFC separation techniques to provide:

- ▶ Separation of chiral compounds at the preparative scale (intermediates or final compounds)
- ▶ Successful purifications when higher resolution techniques are needed (peptides, vitamins, steroids, macrolides, amino-acid derivatives)
- ▶ Impurity isolation for structural identification
- ▶ Chiral analysis for asymmetric synthesis follow-up
- ▶ Evaluation of chiral stability of final molecules or development candidates

The group has also developed unique biomimetic oxidation models mimicking P450 monooxygenases for the synthesis, purification and structural identification of real and putative metabolites of active compounds.

Design, synthesis and structure-activity relationships of a novel class of sulfonylpyridine inhibitors of Interleukin-2 inducible T-cell kinase (ITK), *Bioorg. Med. Chem. Lett.* 2014, 24, 5818-5823



#### ANALYSE

Powerful combination of experience and analysis to extract learning and drive next cycle

#### DESIGN

Excellent understanding of molecular interactions, structural insight and product properties to enable simultaneous multi-parameter optimisation

#### TEST

Rapid, relevant, high-capacity efficacy and non-efficacy testing

#### MAKE

Rapid and efficient synthetic execution. Bespoke, complex molecules and designed libraries/ sparse arrays

#### EVOTEC TRACK RECORD

- ▶ Over the last 15 years, Evotec chemists have supported >125 hit-to-lead and/or lead optimisation projects
- ▶ Evotec scientists are named inventors on >200 client patents and have helped identify >30 pre-clinical candidates
- ▶ Our project teams have made major contributions to the identification of >20 compounds that have been approved for clinical trials

