

MEDICINAL CHEMISTRY AND EARLY DEVELOPMENT

OUR CAPABILITIES, SKILLS AND EXPERTISE

HIT-TO-LEAD AND LEAD OPTIMISATION TRACK RECORD

Through scientific know-how, proven project management and a value-driven, delivery orientated culture, Evotec has established a strong track record in drug discovery:

- 125 hit-to-lead and lead optimisation projects
- 100 lead series identified
- 20 preclinical candidates
- Supporting the identification of 15 compounds that have been approved for clinical trials

THERAPEUTIC AREA EXPERTISE

Evotec has a considerable depth of disease area understanding based on the successful completion of multiple hit-to-candidate projects, including:

- Over 10 projects in cardiovascular and metabolic disease areas
- Over 20 projects in CNS, Oncology, infectious and inflammatory disease areas

TARGET CLASS EXPERTISE

- Significant biology and chemistry expertise in all major target classes resulting in more than 120 client patents with Evotec medicinal chemists as named inventors
- Efficient and successful drug disco-

very via an unrivalled range of solutions from ligand design to delivery of clinical candidates

STRUCTURAL BIOLOGY

- Proprietary high throughput platform incorporates parallel construct design, molecular biology, protein expression and protein purification
- *De novo* X-ray crystallographic structure elucidation and repeat ligand complexes, providing structural information for structure-based drug design
- NMR team experienced in labeling studies such as use of ¹⁵N plus licence to Abbott's SAR-by-NMR™ screening technology

COMPUTATIONAL CHEMISTRY

- Computational and medicinal chemists working closely together applying structure and ligand-based design technologies: homology modelling, scaffold hopping, pharmacophore studies and quantitative structure activity relationship (QSAR)
- Working with the best available commercial and in-house developed software tools, rational design is applied for each project and used in our hypothesis-driven, multiparameter optimisation process

Evotec's expertise in medicinal chemistry has enabled it to successfully execute collaborations with leading pharmaceutical and biotechnology companies integrating core capabilities in synthetic chemistry, structural biology, computational chemistry and ADMET/Pharmacokinetic profiling.

Evotec has expertise in numerous therapeutic areas including oncology, CNS, respiratory, metabolic disease, inflammation, antibacterial and virology. As a result we have developed a strong understanding and technologies that can be utilised for drug discovery against all of the major target classes (GPCRs, kinases, ion channels, etc) and our scientists have experience of progressing compounds from screening into the clinic.

SYNTHETIC ORGANIC CHEMISTRY PROBLEM SOLVING

- Evotec's expertise in synthetic organic synthesis encompasses all major chemotypes, thus providing powerful problem solving abilities and greater flexibility. Chemotypes include:
 - ▶ Heterocyclic synthesis
 - ▶ Nucleosides
 - ▶ Steroids & triterpenes
 - ▶ Amino acids, peptides and peptidomimetics
 - ▶ Macrocycles

COMPOUND LIBRARY SYNTHESIS

- Lead finding and focused library design and synthesis
- Profiling of all virtual libraries using proprietary software to select compounds for synthesis
- *In silico* ADMET tools for compound selection
- Automated purification of compound libraries

EARLY DEVELOPMENT CHEMISTRY

- Custom synthesis of key intermediates
- Expertise in oxetanone building block synthesis with over 70 derivatives available
- Process research and development, scale up and API supply up to 25 kg

Case study – Screen to development candidate in 18 months: Hedgehog signalling pathway inhibitors

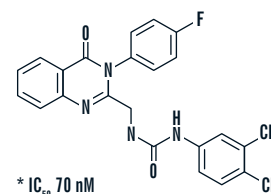
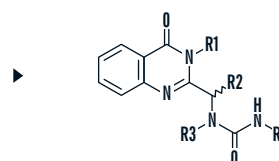


— Evotec carried out initial high throughput, high content screen. Following the successful completion of the screen, Evotec medicinal chemists carried out hit to lead and lead optimisation activities

— SAR developed via a high content assay
 — Agonist and antagonist focused optimisation programmes
 — Compound developed as part of this collaboration progressed into the clinic

— For further details on this project, please read: *Journal of Medicinal Chemistry*, 2008, 51, 1108-1110

Cmpd	R1	R2	R3	R4	IC ₅₀ , nM
3	H	H	methyl	3-F ₃ C phenyl	> 10000
4	4-fluorophenyl	methyl	methyl	3-F ₃ C phenyl	1400 ± 300
5	4-fluorophenyl	methyl	H	3-F ₃ C phenyl	4700
6	isopropyl	H	H	3-F ₃ C phenyl	4300
7	4-fluorophenyl	H	H	3-F ₃ C phenyl	700
8	4-fluorophenyl	H	H	3-F ₃ C, 5-OMe phenyl	250
9	4-fluorophenyl	H	H	3,5-di Cl, 4-pyridyl	110
10*	4-fluorophenyl	H	H	3-F ₃ C, 4-Cl phenyl	70 ± 20



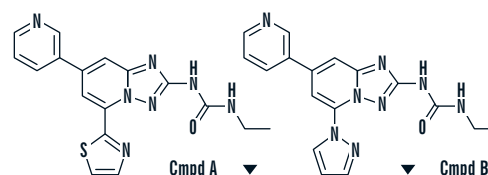
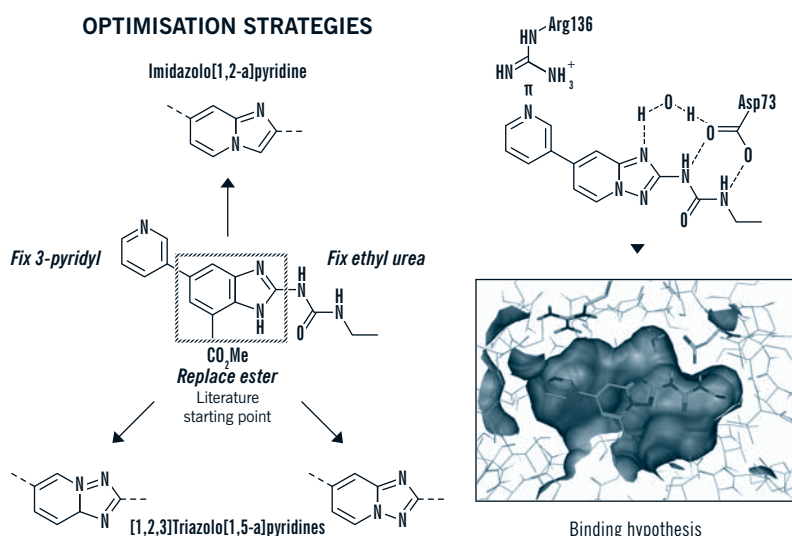
Case Study – Literature-to-lead programme in 12 months: Gyrase / Topoisomerase IV inhibitors



— Evotec conducted a structure-based drug design approach to identify and optimise inhibitors with activity against bacterial DNA gyrase B and topoisomerase IV ParE

— Dual inhibitors with good antibacterial activity against Gram positive pathogens were identified
 — Compounds progressed into *in vivo* models

— For further details on this project, please read: *Bioorganic and Medicinal Chemistry Letters*, 2009, 19, 894-899



	A	B
Gyrase B IC ₅₀	70 nM	54 nM
Par E IC ₅₀	11 µM	25 µM
<i>S. aureus</i> MIC	0.5-1 µg/ml	4 µg/ml
<i>S. pneumonia</i> MIC	1 µg/ml	2 µg/ml
<i>E. faecalis</i> MIC	1 µg/ml	4 µg/ml
<i>M. catarrhalis</i> MIC	0.5 µg/ml	1 µg/ml
<i>H. Influenzae</i> MIC	>128 µg/ml	16 µg/ml