

ASSAY DEVELOPMENT AND SCREENING



OUR CAPABILITIES, SKILLS AND EXPERTISE

ASSAY DEVELOPMENT

— Development of functional, cellular, biochemical, as well as radiochemical, NMR, SPR and LC-MS assays

— Support all standard readouts including fluorescence, absorbance, luminescence and radioactive

— Proven expertise in the adaptation and miniaturisation of client assays. Over 320 assays developed to date

— Labelling chemistry, protein and cell production performed in an integrated fashion to increase efficiency

— Complex cellular models including primary and stem cell applications

MEDIUM & HIGH THROUGHPUT SCREENING

— EVOscreen™: HTS conducted in 384 to 2080 well formats using, amongst others, our Insight™ single molecule reader

— Functional assays available in multiple formats including FLIPR® and ELISA assay systems

— Track record of success with over 170 high throughput screens carried out including challenging targets such as ion channels and protein:protein interactions

ION CHANNEL AND GPCR SCREENING

— Electrophysiology expertise from primary hit identification to safety pharmacology using automated and manual systems

— Access to DiscoverRx's PathHunter™ and HitHunter™ assay technologies

SCREENING LIBRARY

— High quality library consisting of 250,000 compounds, selected for diversity and containing over 90,000 non-commercially available compounds synthesised by Evotec

— Optimised compound storage for long term stability and regular analysis by LC-MS

— Continual addition of new high quality compounds

Evotec's proprietary screening platform, EVOscreen®, combines a highly sensitive detection technology with ultra high throughput. This facilitates assay miniaturisation and multiple read-out parameters thus reducing false positives and negatives. In addition, Evotec integrates other technologies to its screening platform, including nuclear magnetic resonance (NMR), surface plasmon resonance (SPR) and high content screening (HCS). Evotec has a strong track record in assay development and high throughput screening (HTS). As a result, it has developed in excess of 320 biochemical, cellular and functional assays and has completed over 170 screening campaigns. Evotec also provides access to its actively managed small molecule screening collection of 250,000 compounds, differentiated through its quality, novelty and diversity.

NMR AND LABEL-FREE SCREENING

— Protein observed NMR measurements (HSQC, TROSY) with license to Abbott's SAR-by-NMR™ technology

— Ligand observed NMR measurements (e.g. STD)

— Additional capabilities including SPR (Biacore™) and mass spectrometry

HIGH CONTENT SCREENING

— Opera™: State-of-the-art proprietary cellular imaging used for detailed intracellular analysis and pathway screening

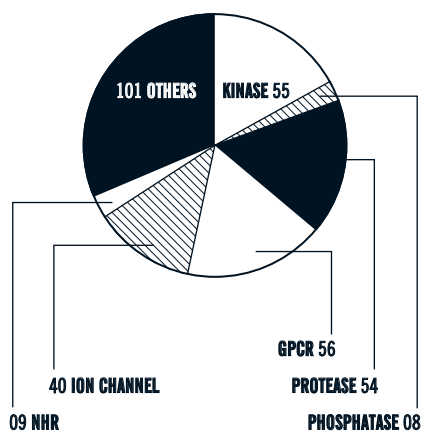
— Multi-colour and multi-parameter imaging with the distinct benefit of reducing false positives and, for instance, simultaneously measuring target activity and cytotoxicity / apoptosis

EVOscreen®: Evotec's proprietary HTS technology combining ultra high throughput, high sensitivity and multiple read-out parameters thus reducing false positives and negatives

Over 320 assays developed and 170 high throughput campaigns successfully completed

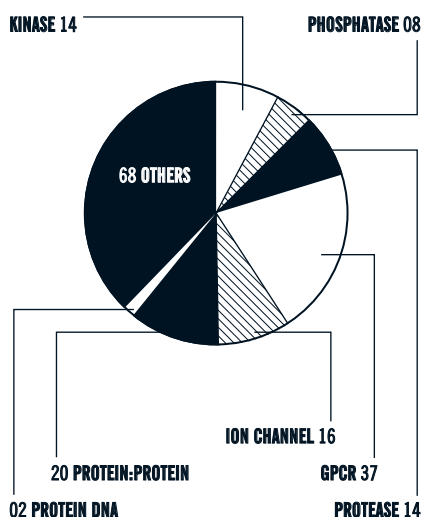
ASSAY DEVELOPMENT

— >320 assays developed
 — Increasing percentage of cellular assays



HIGH THROUGHPUT SCREENING

— >170 uHTS screens

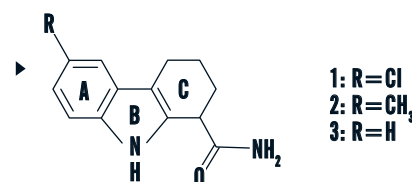


Case study: HTS delivers novel HDAC class III activators



— Evotec carried out reagent production, assay development, high throughput screening and medicinal chemistry
 — Biochemical assay technology performed on EVOscreen®, Evotec's proprietary fluorescent confocal spectroscopy platform, identified indoles that led to nM active compounds
 — Indoles 1, 2 and 3 were identified as hits following primary screening. These hits were further confirmed through an orthogonal radiometric assay
 — These compounds provide ideal chemical tools to study the biology of SIRT1 and to explore therapeutic uses for SIRT1 inhibitors

— A compound derived from this programme (SEN0014196, also known as EX-527), was in-licensed by Siena Biotech in 2009 and is currently undergoing Phase II clinical studies for the treatment of Huntington's Disease.
 — For further details on this project, please read: *J. Med. Chem.* 2005, 48, 8045-8054



IN VITRO SELECTIVITY

| Cmpd | IC ₅₀ (μM) | | | | | |
|------|-----------------------|-------|-------|------|-------|--------|
| | SIRT1 | SIRT2 | SIRT3 | HDAC | SIRT1 | NADase |
| 1 | 0.098 | 19.6 | 48.7 | >100 | 1.29 | >100 |
| 2 | 0.205 | 11.5 | >100 | >100 | 2.5 | >100 |
| 3 | 1.47 | 24.8 | >100 | >100 | 3.3 | >100 |

ADMET PROFILE

| Cmpd | % INHIBITION | | | | | | half-life (min) |
|------|--------------|--------|--------|---------|--------|---------------|----------------------|
| | AT 1 μM | | | | | AT 10 μM | |
| Cmpd | CYP3A4 | CYP2D6 | CYP2C9 | CYP2C19 | CYP1A2 | hERG blockade | rat liver microsomes |
| 1 | -26 | -5 | -5 | 6 | 11 | 0 | >60 |
| 2 | -16 | -3 | -9 | 9 | 7 | 0 | ND |
| 3 | -22 | -4 | -8 | 5 | 4 | 0 | ND |