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'RESEARCH NEVER STOPS'

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COMPUTATIONAL CHEMISTRY

Medicinal Chemistry and Early Development

OUR CAPABILITIES, SKILLS AND EXPERTISE

The experienced computational chemistry team at Evotec has a proven track record of helping medicinal chemistry and screening efforts to more efficiently find hits and reach lead and clinical candidate nominations. A range of tools enables us to guide activities from ligand-based, structure-based and cheminformatic / ADMET perspectives.
Combining a wide range of commercial software with proprietary code, such as those for GPCR and hERG modelling, and the expertise of the computational chemistry team, Evotec has developed superior methodologies to increase success and reduce timelines for hit finding, hit-to-lead, fragment-to-lead, and lead optimisation stages of the drug discovery process.

KEY CAPABILITIES

— Large team of PhD computational chemists with extensive experience gained at major pharmaceutical and academic / governmental institutions
— Access to a comprehensive suite of commercial software
— Development, validation and implementation of proprietary software with particular expertise on membrane protein modelling

NOVEL METHOD DEVELOPMENT

— Evotec is constantly developing new computational methods either to solve specific problems or as part of our continuing internal investment in computational chemistry technology: ▸ Hierarchical GPCR modelling ▸ hERG affinity modelling via electrostatic complementarity ▸ 3D pharmacophore tools ▸ Shape and pharmacophore combined searching tools ▸ *De novo* compound design tool based on Evotec chemistry ▸ Molecular dynamics methods for binding pocket expansion ▸ Fragment Molecular Orbital QM calculations

EVERY STAGE OF DISCOVERY

— Screening and fragment library design
— Hit finding (virtual screening)
— Hit expansion and hit-to-lead
— Fragment-to-lead
— Lead optimisation

VIRTUAL SCREENING

— Evotec has several methods for target / information specific design of initial hit finding or hit expansion virtual screening, including shape, pharmacophore, and docking on a distributed computer network

HIT AND FRAGMENT-TO-LEAD

— Fragment expansion and linking tools
— Pharmacophore analysis
— Homology modelling
— Structure-based design and *de novo* ligand design

LEAD OPTIMISATION

— Chemical descriptors
— 2D and 3D QSAR modelling
— ADMET property predictors
— hERG affinity modelling
— QM calculations

Whatever the target, Evotec accelerates your drug discovery programme through rational design, using proprietary computational chemistry methods and techniques

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Case study: GPCR modelling of B1, at the optimised similarity level, produced models that explained SAR and guided chemistry

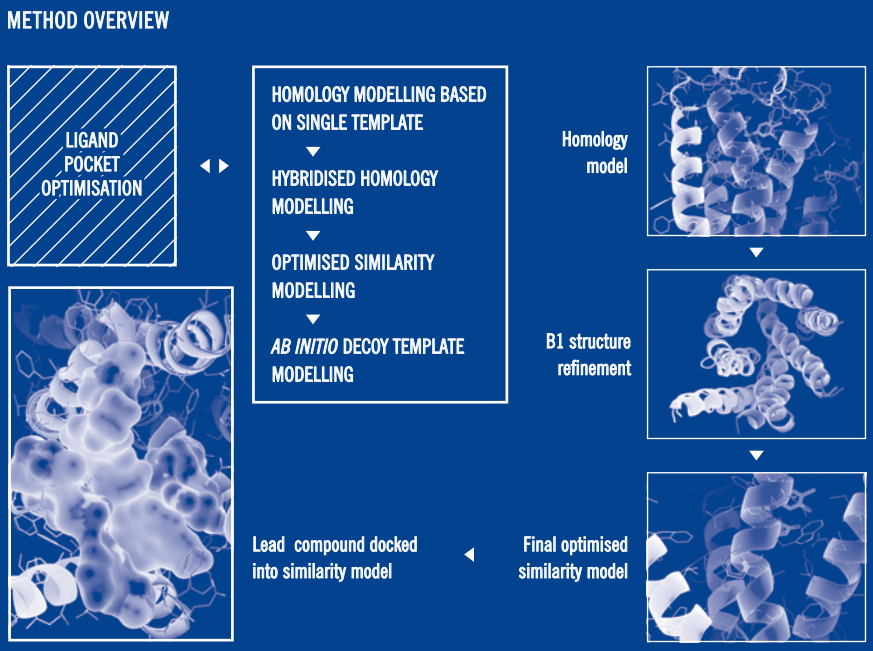
BRADYKININ B1: GPCR MODELING

— Evotec has developed a hierarchical scheme for GPCR modelling

— Whether or not the next stage is required to produce a predictive model is determined by multiple calculated descriptors

— A model of B1 was constructed at the optimised similarity level, as the many molecular dynamics optimisation scripts determined an unavoidable structural error in any simple homology models. The error relates to the transmembrane helix 2 of B1, which is kinked in the wrong direction, radically altering the residues placed in the ligand binding site

— The new B1 GPCR model was able to explain SAR for both rat and human B1 and has aided the design of more potent compounds



Case study: hERG inhibition modelling of B1 compounds guided chemists to abolish hERG inhibition

BRADYKININ B1: hERG INHIBITION MODELLING

— Evotec has developed a multi-stage hERG inhibition model

— 3D and 2D descriptors are used as part of a QSAR model

— Predicted or known actives are then submitted to structure-based electrostatic complementarity analysis

— Minor changes to the molecule were suggested to chemists based on this analysis that were predicted, and later proven, to have a dramatic (70-fold) effect on hERG inhibition, yet retaining target activity