This poster by Peter Hunt, Tamsin Mansley, Edmund Champness, Nicholas Foster & Matthew Segall was presented at the ACS Fall 2017 National Meeting & Exposition held in Washington DC, USA.

Abstract

Drug discovery is a multi-parameter optimisation (MPO) process, in which the goal is to simultaneously optimise target potency, selectivity and a broad range of Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties, prioritising those compounds most likely to succeed against a project's objectives. However, the ultimate goal is not simply to select from those compounds already available, but to design new compounds with an improved balance of properties.

De novo design approaches typically result in more in silico compound ideas than can reasonably be synthesised and tested. Assessment of these virtual compounds therefore requires development and use of in silico models which predict potency, or other properties, based upon information derived from the known structure-activity relationships (SAR). These predictive models can be used in an MPO assessment of selectivity, optimising for high potency at one receptor and low potency at others.

We present a truly MPO approach to de novo design, using Probabilistic Scoring and quantitative structure-activity relationship (QSAR) models to generate and prioritise high quality compounds ideas. This approach enables simultaneous optimisation of the virtual compounds for high potency with selectivity over multiple receptors, whilst also considering a balanced ADMET profile. It is exemplified with optimisation of selective dipeptidyl peptidase (DPP) inhibitors.

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