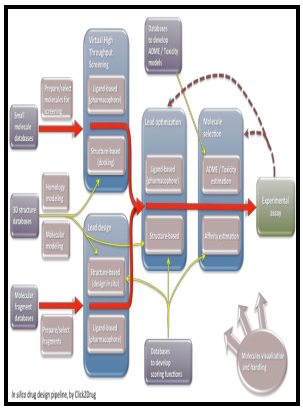
Chemogenomics - knowledge-based approaches to drug discovery

Imperial College Press - Knowledge



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Chemogenomic approaches to drug discovery: similar receptors bind similar ligands

Such papers paved the way for the recognition of lipophilicity and electronic properties as major determinants of PD and PK responses, as best illustrated by the epoch-making and still ongoing work of Corwin Hansch ; , a founding father of drug design.

Chemogenomics: Knowledge

Further methods such as agglomerative hierarchical clustering based on 2D structural similarity, recursive partitioning, Sammon maps, self-organising maps and generative topographic mapping could be used with computational predictions ; ; ;.

Knowledge

Common chemical scaffolds and three-dimensional 3D pharmacophores within the ligands of purinergic GPCRs were identified and chemical libraries comprising 2400 compounds around 5 chemical scaffolds were synthesized. Systematic virtual screening of a library consisting of 5000 random compounds and 78 known active ligands against 19 different protein structures representative of 10 nuclear receptors was also reported.

Chemogenomic approaches to drug discovery: similar receptors bind similar ligands

Insights from chemogenomics are used for the rational compilation of screening sets and for the rational design and synthesis of directed chemical libraries to accelerate drug discovery. Comprehensive computational assessment of ADME properties using mapping techniques. However, as ADMET is hard to predict for large data sets,115 because it is typically multi-mechanism related and the predictions get worse as more data accumulates, these methods are mostly descriptive and focus mainly on the prediction of absorption or bioavailability.

Knowledge

These efforts suggest that pharmacophore-based approaches may have considerable versatility and applicability to be used with difficult biological targets. Also, as the number of protein—ligand complexes available continues to grow, docking methods are beginning to incorporate all the

information derived from the conformation adopted by protein-bound ligands as a knowledge-based strategy to correct some of the limitations of current scoring functions and actively guide the orientation of the ligands into the protein cavity. Developing the optimal QSAR model for the chemical property or biological effect of interest, as well as defining its applicability domain within chemical space, is still very much an active area of investigation as described later.

Chemogenomics : Knowledge

Application of data mining approaches to drug delivery. Using alanine scans one can identify the key pharmacophore points; D-aminoacid or proline scans allow stabilization of β-turn structures; cyclic scans bias the peptide or portions of the peptide in a particular conformation α-helix, β-turn and so on ; other scans, like N-methyl-amino-acid scans and amide-bond-replacement depsi-peptides scans aim to improve the ADME properties.

Chemogenomic approaches to drug discovery: similar receptors bind similar ligands

Curr Opin Drug Discov Dev. Increasingly over the last decade however we have seen that computational in silico methods have been developed and applied to pharmacology hypothesis development and testing. Martin Slater from the for library design pioneering BioTech company Galapagos-Biofocus, Inc.

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