Kinase type II inhibitors

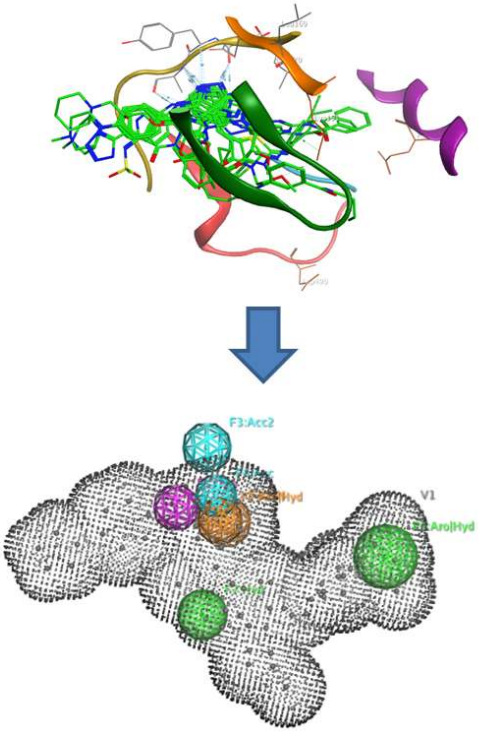
ASINEX

Using a proprietary computational algorithm [1,2], ASINEX has designed molecules that could act as Type-II Kinase ligands. To select this set, we have used crystals from PDB with DFG-Out conformations [1,2]. Several pharmacophore (ph4) queries have been constructed based on the ligands for each kinase family. All queries have 6 to 10 features in the pharmacophore definitions, some allow partial match. The resulting queries have been run against the conformers generated from Asinex Kinase Library and molecules matching the queries have been selected. 45 % of the hits match only one query, showing that each family has unique features in the ph4 definitions, ~35% match 2 or 3 queries.

Step 1
Extracting DGF-Out co-crystals

group-family	DFG-Out co-crystals
CMGC-MAPK	84
TK-ABL	73
TKL-RAF	41
TK-VEGFR	36
TK-SRC	35
STE-STE20	33
TK-PDGFR	24
TK-EGFR	19
OPK-NEK	14
TK-FAK	14
TK-FGFR	14
TK-MET	14
TK-DDR	12
TK-TRK	12
CAMK-CAMKL	11
OPK-AUR	11

Step 2
Based on ph4 consensus analysis a ph4 query has been defined



Step 3
ph4-based selection of molecules

group-family	Compounds selected
camk-camkl-melk	131
cmgc-mapk-p38	621
opk-aur-aur	909
ste-ste20-slk	525
tk-abl-abl	387
tk-ddr-ddr	110
tk-egfr-egfr	22
tk-fgfr-fgfr	242
tkl-raf-raf	373
tkl-vegfr-vegfr	91
tk-met-met	477
tk-pdgfr-pdgfr	770
tk-src-srca	907
tk-trk-trk	244

References:

1. J Med Chem. 2015 Jan 8; 58(1): 466–47; doi: 10.1021/jm501603h
2. J. Med. Chem., 2015, 58 (1), pp 183–196; doi: 10.1021/jm500480k