SPROUT is an effective tool for the design of drug-like, biologically active molecules. It is an interactive system that can assist in several stages of the structure-based rational drug design process.

The system is modularised and offers automatic methods for solving a number of problems in drug design. The user maintains control and is able to guide the operation of each module for maximum versatility.

FUNCTIONS

- **Binding pocket identification** in the solvent accessible surface of the protein complex
- **Identification** of favourable hydrogen bonding, metal bonding and hydrophobic regions or specification of user generated target sites within the binding pocket
- **Docking** of small fragments to target sites to form starting points for structure generation; alternatively importing of larger fragments (and if necessary structure modification e.g. deletion of a central core to allow replacement – scaffold hopping). Key step in “fragment based drug design” using NMR or crystallographically derived fragments.
- **Fragment joining** to build skeletons from the starting groups and/or imported fragments by incremental construction always satisfying the steric constraints of the binding pocket
- **Scoring** and sorting the solutions on estimated binding affinity and synthetic feasibility

VALIDATION

Our validation experiments show that SPROUT is able to regenerate structures of known drugs, and due to its exhaustive exploration of the search space it routinely suggests novel solutions with higher predicted binding affinity than the known inhibitors.

RECENT SUCCESS STORIES

- Structure-based design of inhibitors of class 2 dihydroorotate dehydrogenases (T.J. Heikkilä, M. Davies, M.R. Parsons, A.P. Johnson) *
- Design and Synthesis of New Dihydroorotate Dehydrogenase Inhibitors as Potent Antimalarials (Davies M., Heikkilä T.J., Fishwick C.W.G., and A.P Johnson) *

* see attached posters
A protein of \textit{p38 MAP kinase} is selected to illustrate SPROUT’s ability to design novel ligands with high predicted binding affinity.

The crystal structure of \textit{p38 MAP kinase} complex with \textit{Inhibitor1} is an entry of the Protein Data Bank (PDB code: 1KV1). \textit{Inhibitor1} has a binding affinity of -10.17 estimated by SPROUT.

SPROUT generates 5919 structures many of which have a higher binding affinity than -10. The best scored structure has a value of -13.67 (see chart).

Structures coloured blue:
Two hits after heteroatom substitution having highest predicted binding affinity.

Structure coloured gold:
\textit{Inhibitor1}