

SPROUT-LeadOpt: optimizing lead drug candidates by creating structurally similar, synthetically accessible, ligands.



SPROUT-LeadOpt is the latest release in the SPROUT product line. SPROUT-LeadOpt aims to solve the problem of optimizing lead drug candidates, within the constraints of the receptor, with synthetic considerations. SPROUT-LeadOpt allows the user to import and modify a core, typically known binding, structure into a receptor site. The program then identifies reactive functional groups as possible extension sites. At these sites, monomers from either a default or user-supplied library are systematically added, via synthetic reactions, to create structurally similar molecules. The new molecules can be further analyzed by a suite of analysis tools.

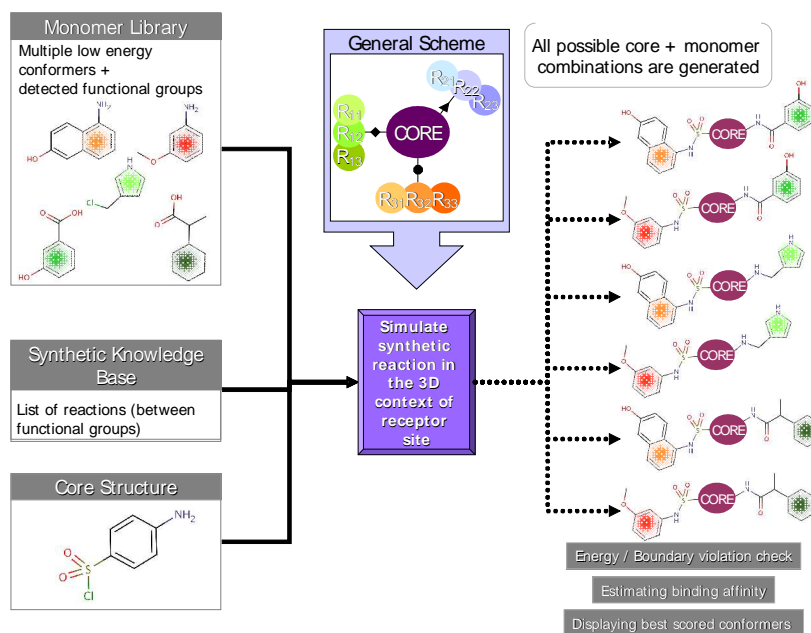


Figure 1: The lead optimization scheme of SPROUT-LeadOpt, via core modification.

HIV-1 Case Study (1EP4)

HIV-1 reverse transcriptase in complex with S-1153 (pdb code 1EP4) was chosen for this case study, to illustrate the ability of SPROUT-LeadOpt to optimize known binders. Figure 2 shows the 1EP4 receptor with S-1153 inhibitor. Here we can see that the inhibitor S-1153 forms two key hydrogen bond interactions with PRO-A236 and LYS-A103. These hydrogen bonds anchor the ligand and thus are kept as part of the selected core. The core structure, derived from the bound ligand, is depicted in Figure 3. Here we can see that the hydrophobic dichlorobenzene moiety has been removed. This is the area selected for optimization.

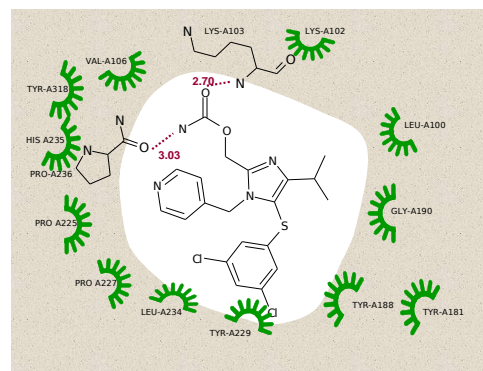


Figure 2: Schematic representation of the binding pocket of 1EP4 HIV-1 protease with the bound S-1153 inhibitor.

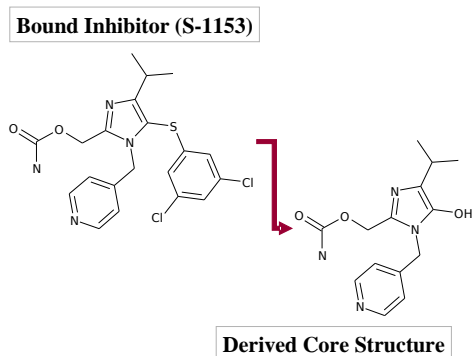


Figure 3: The bound inhibitor, S-1153, and the derived core structure selected for modification.

The sulfur atom in the inhibitor was changed to an oxygen atom in the derived core, as the created phenol functional group was used as a substitution point for the optimization.

The lead optimization scheme is shown in Figure 4 where an ether formation reaction (that takes place between the phenol of the core and aryl halide of the monomers) is applied to generate products.

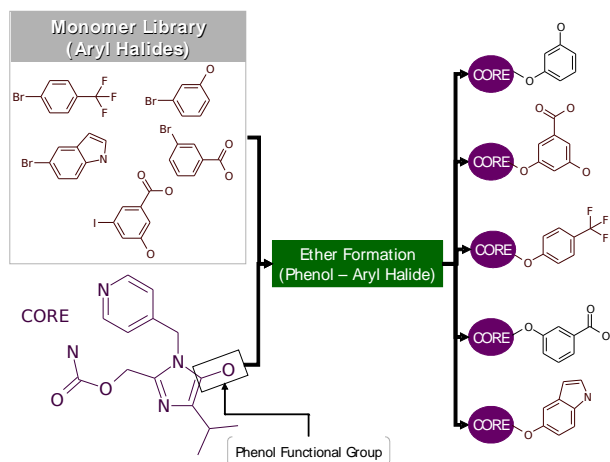


Figure 4: Lead optimization scheme of IEP4 case study.

Generating the Monomer Library

A monomer library was generated using a small, user-defined, synthetic knowledge base and available starting material databases.

SPROUT-LeadOpt does contain a set of ~30 synthetic reactions and associated functional group perceptions (see Figure 5), however for this example the synthetic

knowledge base used contained just two functional groups (Phenol, Aryl Halide) and one synthetic reaction that takes place between the functional groups (see Figure 6). This knowledge base is a user-editable text file, that can be easily modified to suit the user's problem.



Figure 5: Synthetic rules and functional groups of standard MDDR fragmentation library, default in SPROUT-LeadOpt.

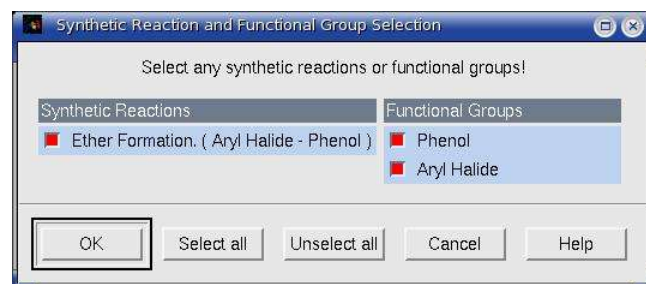


Figure 6: Synthetic rules and functional groups for IEP4 example.

The starting material databases from Aldrich, Maybridge, Acros, and Lancaster were used as input. The synthetic knowledge base was applied automatically perceived all the structures that

contained aryl halide functional groups. This generated a monomer library of 1510 structures (7413 conformers). NOTE, SPROUT-LeadOpt is able to link with 3D generation software such as CORINA or conformer generators such as ROTATE during the monomer generation process.

Results

During the lead optimization process, each core+monomer product is generated using all the low energy conformations of a monomer present in the library. In addition, the user is able to perform a more complete conformational search by allowing the program to slightly “twist” around rotatable bonds. Figure 7 illustrates the effect of this “twist” on the conformational space searched.

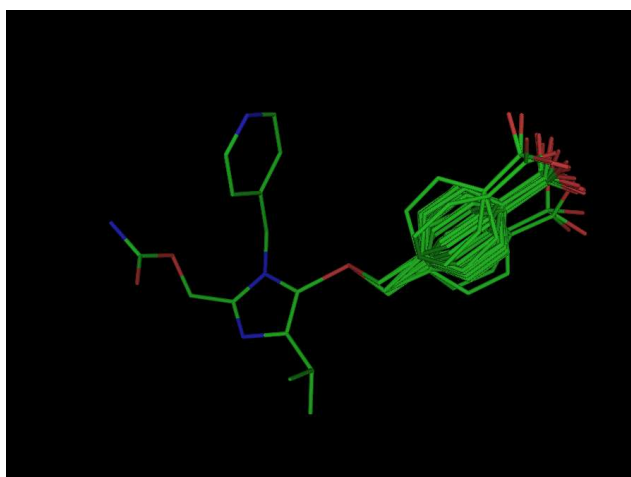


Figure 7: Generating slightly distorted, twisted conformations around local minima in order to explore conformational space.

The lead optimization process generated 256 products. The top two structures are shown in Figure 5 and 6. Both structures are very similar to the superimposed bound inhibitor (S-1153) and have a very strong predicted binding affinity (-12.05 and -12.01 respectively).

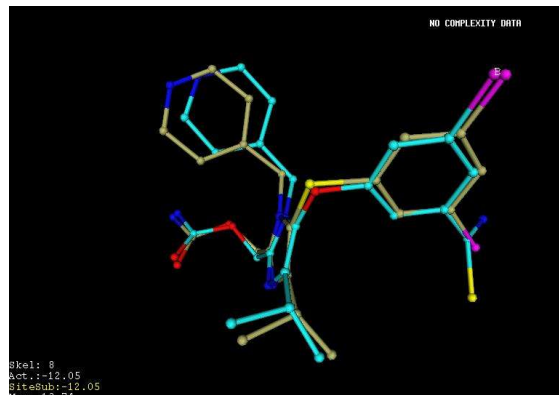


Figure 8: Top scoring structure generated, score: -12.05.

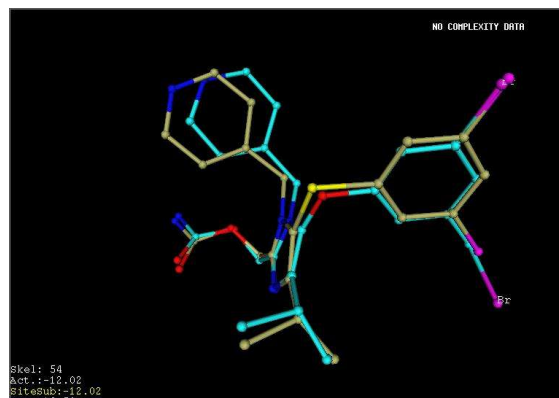


Figure 9: Structure ranked second in the lead optimization process, score: -12.01

Additional Information

SPROUT-LeadOpt is a great tool for optimizing known inhibitors. In addition to the core modification procedure described in the paper, SPROUT-LeadOpt also has a monomer replacement option, which takes a lead candidate and detects monomers within the inhibitor. These monomers are then replaced, using synthetic rules, with new monomers. The new molecules can then be scored and further analyzed in SPROUT-LeadOpt.

For more information about SPROUT-LeadOpt, or to obtain a free evaluation, please contact us at:

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