Scaffold Hopping into New DPP-IV Protease Inhibitors

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Abstract

Cresset's powerful scaffold hopping and fragment replacement software can be used to mimic an existing 'active' molecule's electrostatic patterns to quickly, and efficiently, generate new molecular designs. The outcome, based on 3D molecular electrostatic similarity, is more biologically relevant than that from other similarity metrics. Here, we show how Spark can be used to rapidly generate potentially valuable chemical ideas for new DPP-IV inhibitors.

Background

Two peptide hormones, GLP-1 and GIP, mediate lowering of blood glucose level through stimulation of insulin release and inhibition of Glucagon release. DPP-IV cleaves a dipeptide from the N-terminus of both GLP-1 and GIP hormones to give their inactive forms, thus abolishing their glucose lowering action. DPP-IV inhibitors have been shown to be important agents useful for treating type II diabetes.

Scaffold hopping methodology

The method involves:

An initial bioactive conformation: Preferably a potent target molecule of interest. This can either be extracted from an X-ray or modelled (e.g. from a pharmacophore or alignment / binding hypothesis).

Field pattern generation: Cresset's proprietary XED force field used to generate electrostatic properties.

Database of molecule fragments: Spark uses an internal database of fragments derived from ChEMBL and ZINC. Custom sets can be generated from proprietary chemistry.

Automated reconstruction of the new 3D molecules: Can specify linking chemistry and replacement sites (e.g. scaffold or decoration).

Aligns and scores output as full minimized molecules: Using 'field similarity' and shape similarity relative to the starting template(s).

Protein target can be used as excluded volume: Can take account of protein pocket by penalising examples with steric clashes.

Filter output on physiochemical properties

Experiment and results

Alogliptin (1), Omarigliptin (2) and the fluoro-olefin (3, PDB: 3C45) represent some of the most ligand efficient examples from these clusters. Two experiments were performed in Spark using (1) and (2) in a simple scaffold hopping exercise. A final experiment was a chemotype merging experiment: a truncated (2) was used, with (3) as a second template, to find molecules bridging the two series. Workflow as shown in Figure 2.

Example results (Table 1) shows the diverse range of output suggestions provided for new chemistry and validates the method by providing examples which already have precedents in patents and the literature.

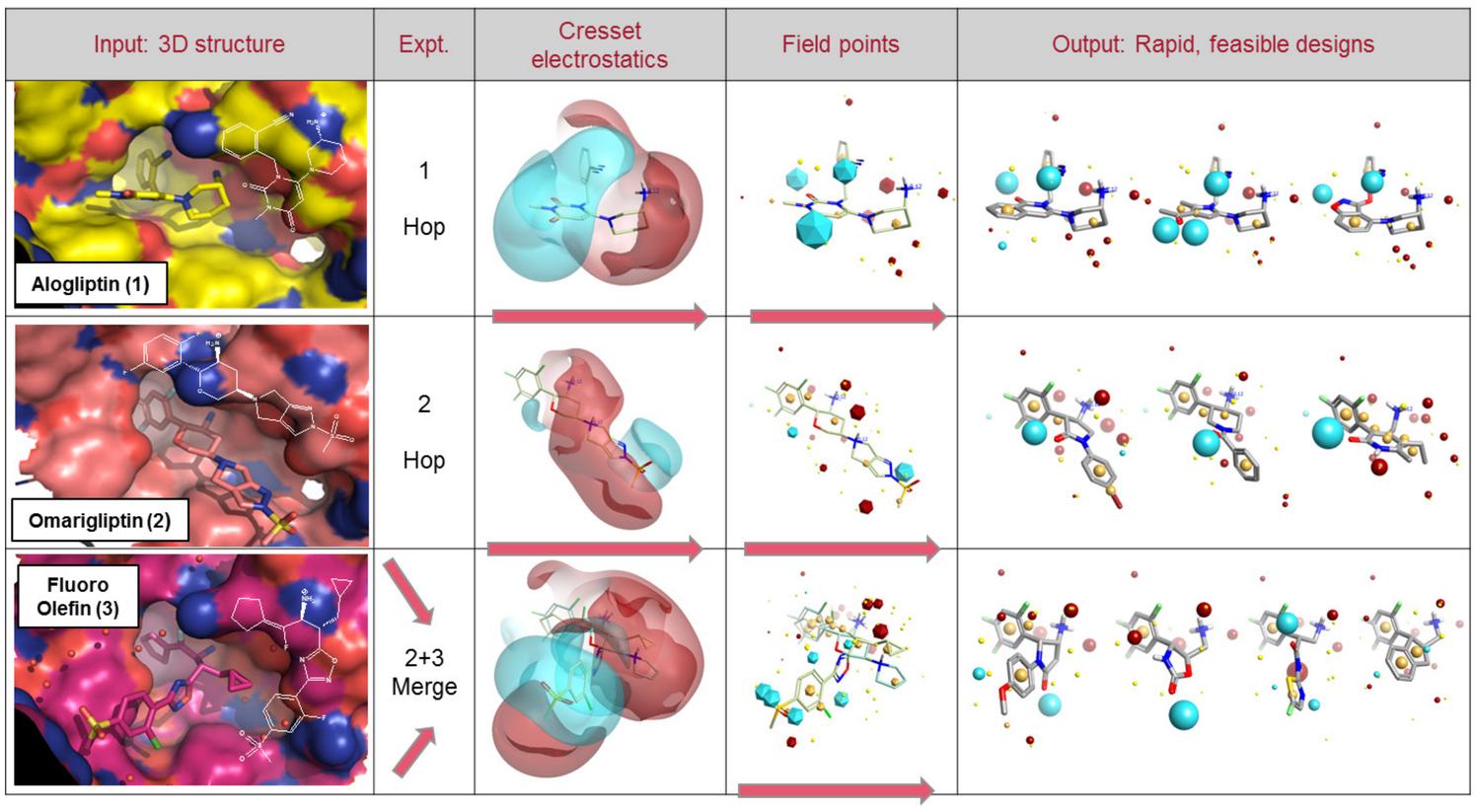
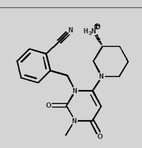
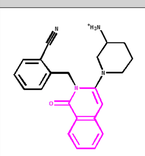
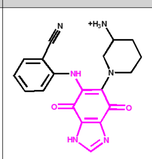
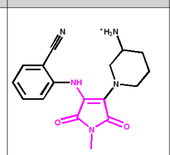
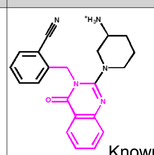
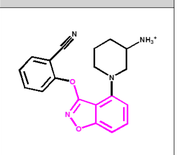
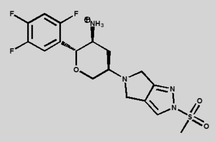
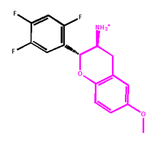
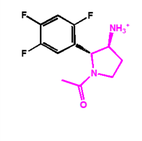
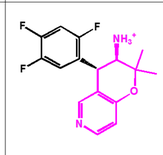
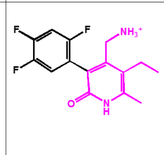
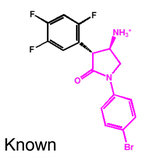
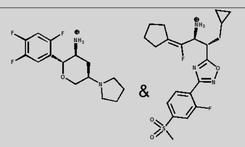
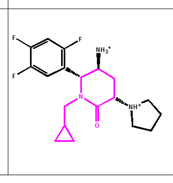
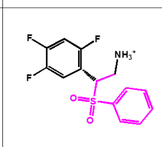
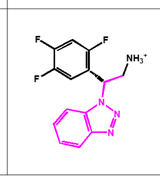
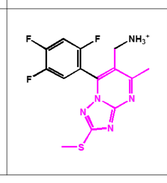
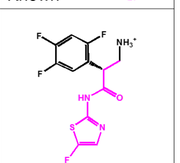


Figure 2. Scaffold hopping and merging – input structures, fields, field points and output examples.

Expt. tpsa logP	Search molecule(s) chosen	Entry Rank tpsa logP	Example structure	Entry Rank tpsa logP	Example structure	Entry Rank tpsa logP	Example structure	Entry Rank tpsa logP	Example structure	Entry Rank tpsa logP	Example structure
1 95.3 1.1		**1** 10 75 2.9		**2** 11 130 1.4		3 28 104 0.6		4 61 87 2.6	 Known	5 112 90 2.8	
2 93.3 2.1		**6** 42 46 3.9		**7** 60 48 2.5		**8** 84 50 3.9		**9** 175 57 3.4		**10** 332 48 4.2	 Known
3 As **2** & 100.7 4		**11** 14 52 3.4		**12** 40 62 3.4		**13** 43 58 3.2		**14** 85 71 3.5		15 132 70 3.5	

DPP-IV X-ray ligand electrostatic and shape similarity analysis

A plethora of molecules are already known which inhibit DPP-IV and have useful anti-diabetic properties.

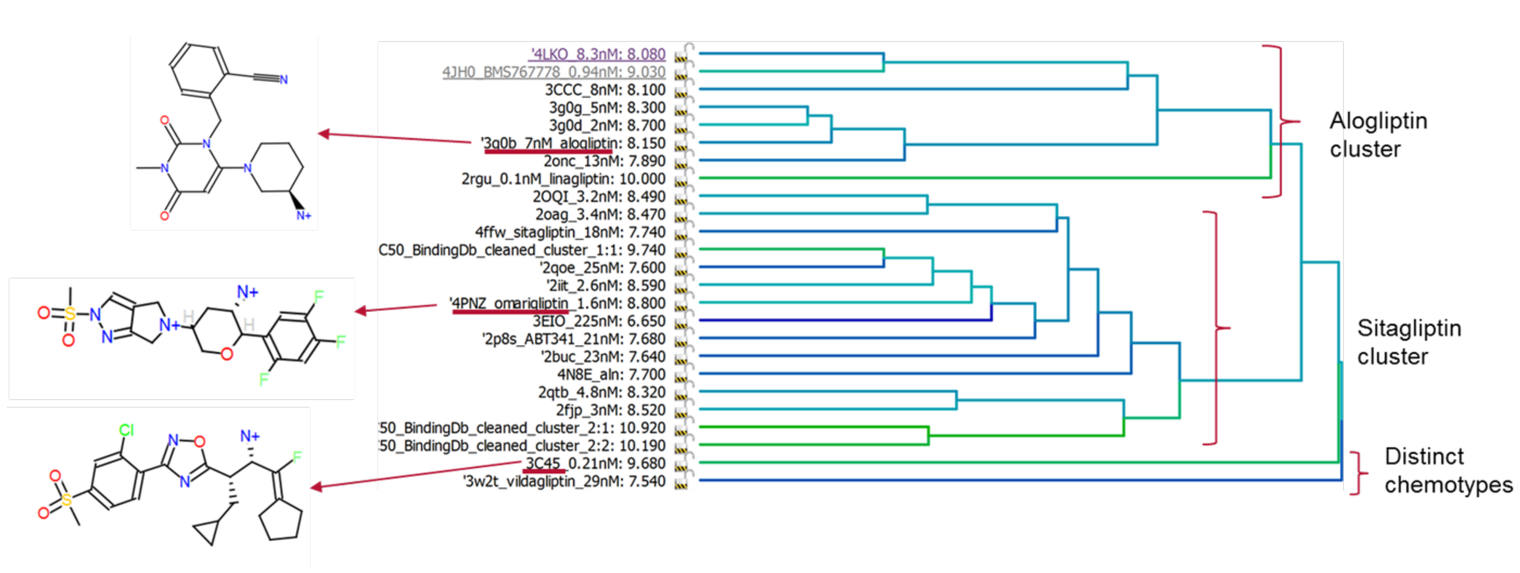


Figure 1. Hierarchical clustering of DPP-IV x-ray ligands by 'electrostatic and shape similarity'.

Superimposition of over 20 published x-ray crystal structures, followed by hierarchical clustering using all-by-all field similarity on the ligands, reveals two main clusters and a distinct mode of binding for a fluoro-olefin example (Figure 1). This unique clustering, performed in Cresset's ligand-focused workbench, Forge, allowed the selection of three distinct inhibitors for further scaffold hopping work.

Results

The Spark searches output a wide range of diverse chemotypes that included active or very close architectures to known active frameworks. A number of these had been discovered through HTS rather than through rational design. Tight control over the chemistry ensures that feasible chemistry is provided from known fragments whilst maintaining the features necessary for activity.

Summary

Spark is a powerful molecular modeling tool for the rapid virtual elaboration of scaffold ideas; either in scaffold hopping, merging, fragment growing or linking experiments. Applying Spark to chemotypes bound to the active site of DPP-IV provided a range of interesting and synthetically-feasible suggestions.

References

1. Green et al, *Diabetes and Vascular Disease Research* 2006, **3** No3, p159-65.

Protein pictures were rendered using open source Pymol from Delano Scientific.

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