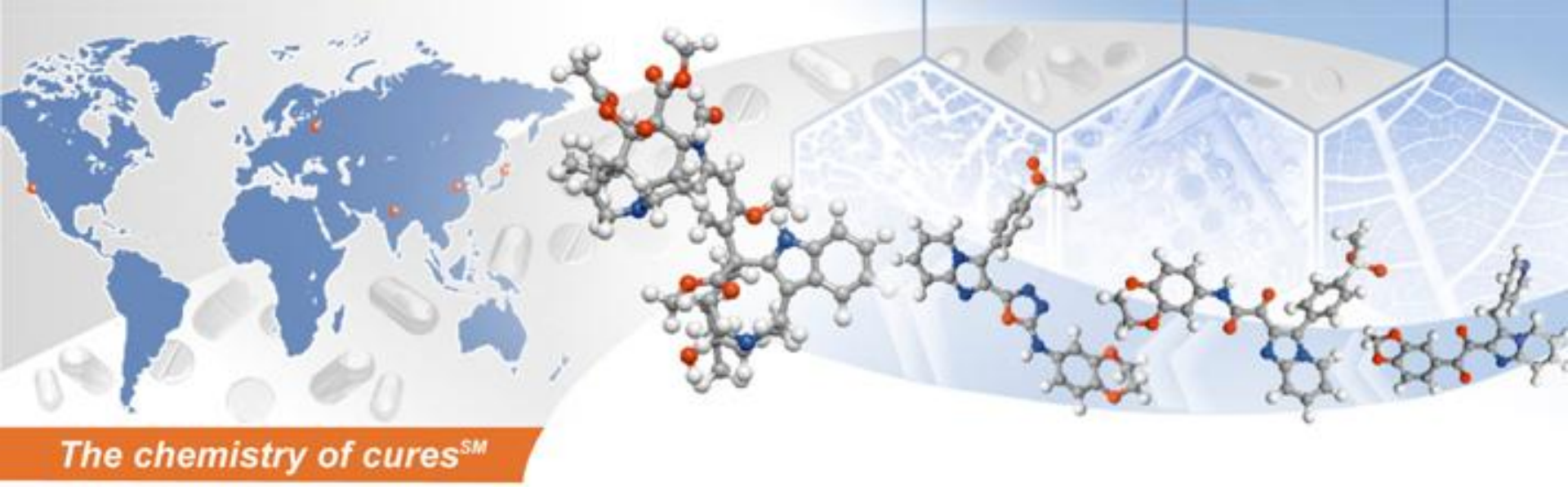


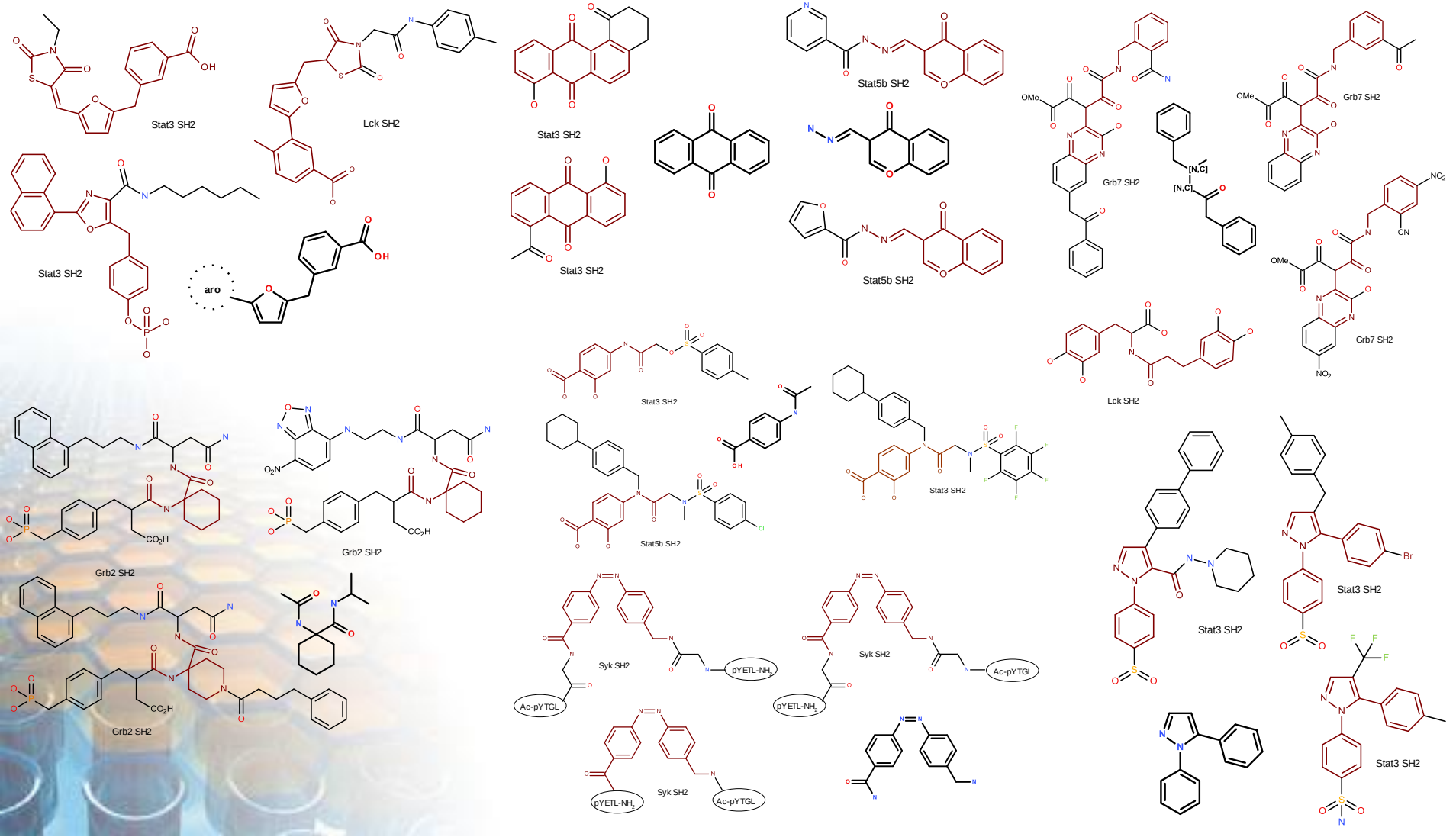
SH2 domain binders

targeted library

2014

A brief insight into the property space of the reported SH2 domain inhibitors

- Src homology 2 (SH2) domains are 100 amino acid modular units, which recognize and bind to tyrosyl-phosphorylated peptide sequences on their target proteins, and thereby mediate intracellular protein-protein interactions.

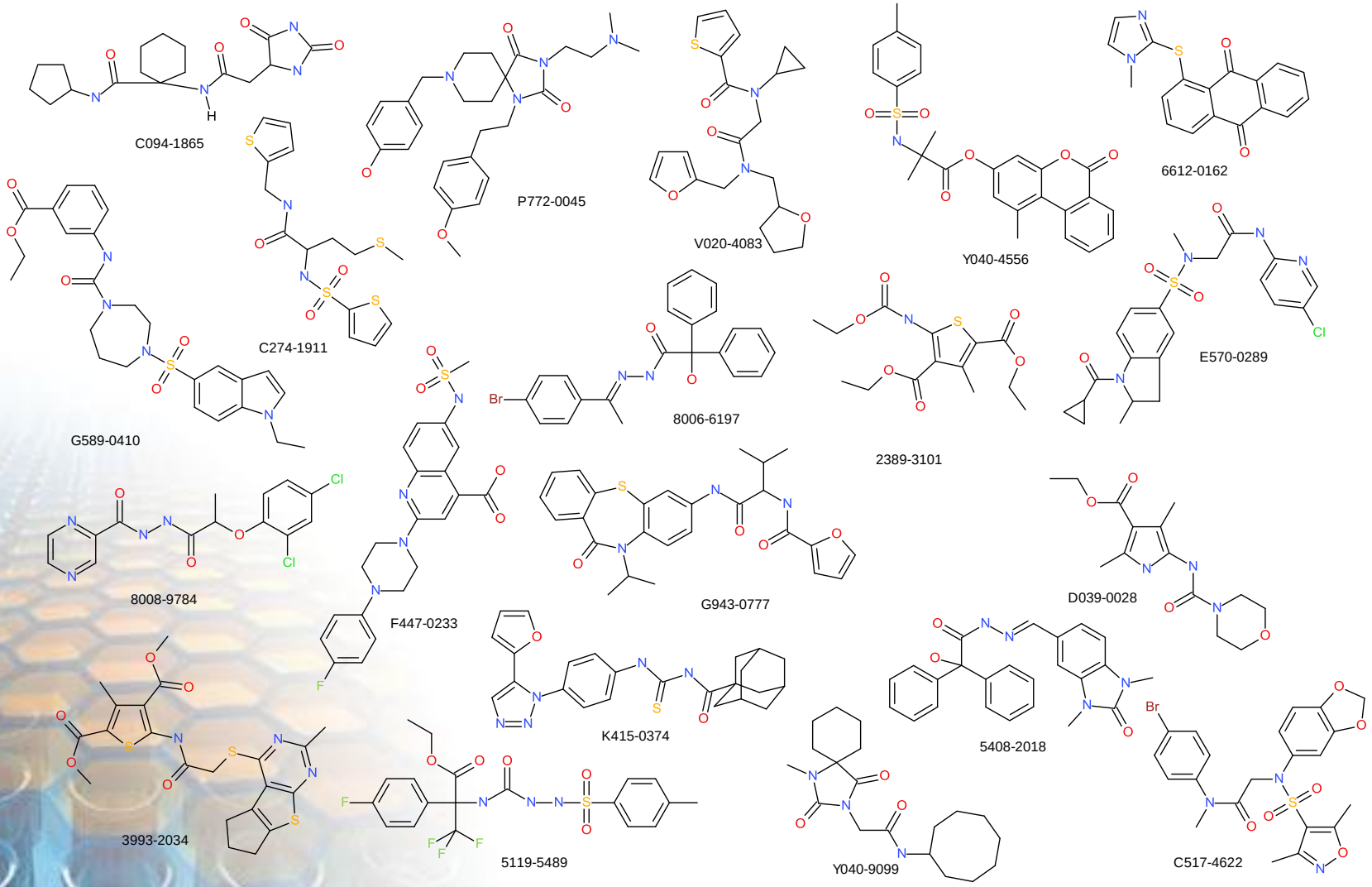


Library design

The core strategy:

- 3D/2D Structural Similarity
- 2D-topological analogues
- Privileged scaffold hopping
- Diversity set
- 3D Pharmacophore modeling

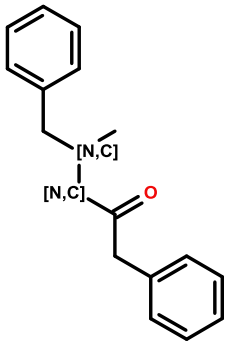
Representative examples from 15K library

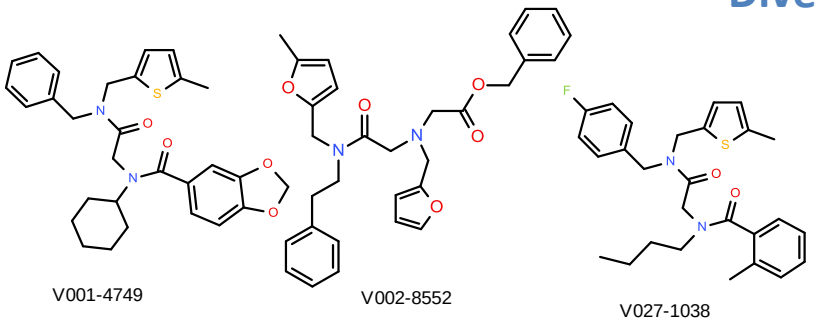


Examples

Diversity set

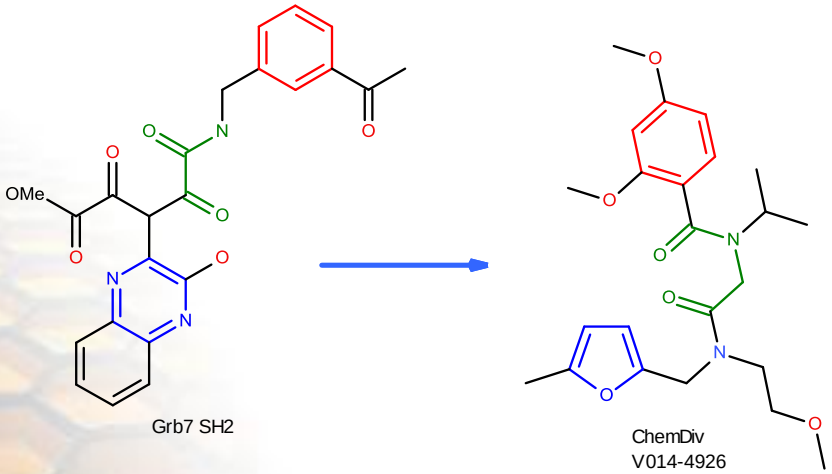
Scaffold





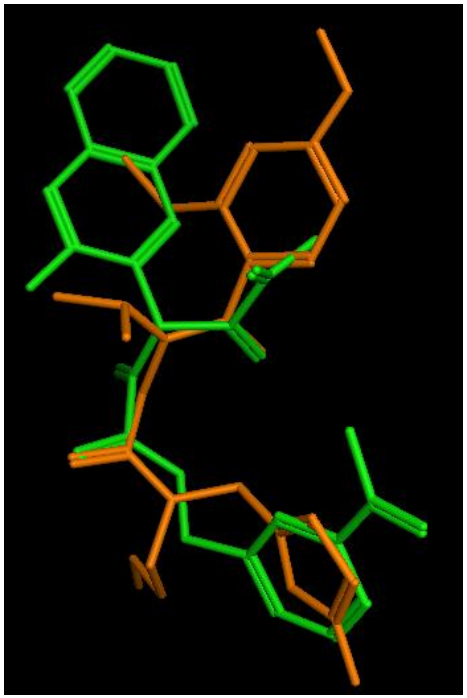
1236 cmpds per cluster

2D Structural Similarity



LogP:
PSA:
HBD:
HBA:
Sp³:

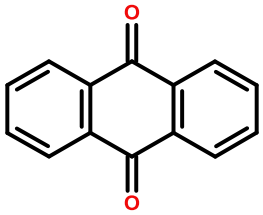
3D Structural Similarity



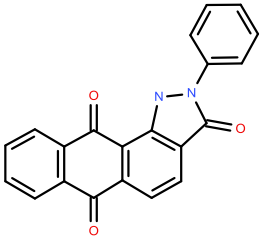
Green – Grb7 SH2 inhibitor;
Orange – ChemDiv cmpd

Examples

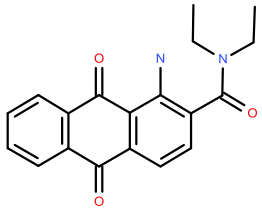
Scaffold



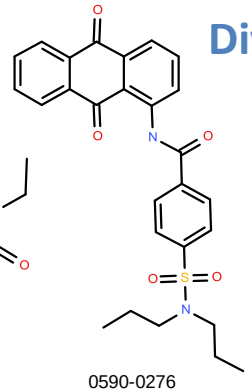
Diversity set



0310-0137



0310-0480



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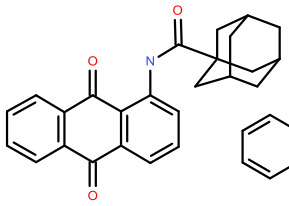

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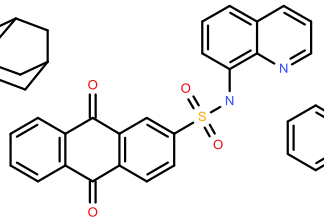
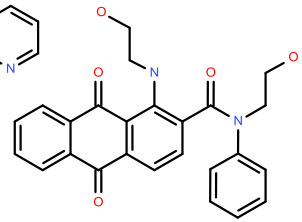


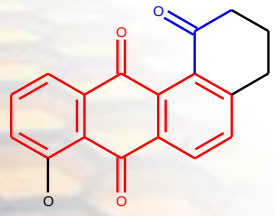
3039-0069



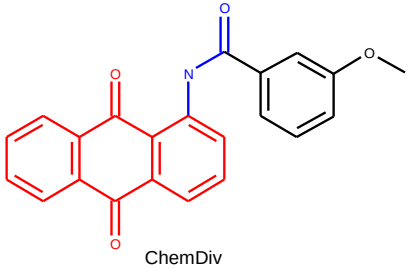
C092-0023

2D Structural Similarity

374 cmpds per cluster

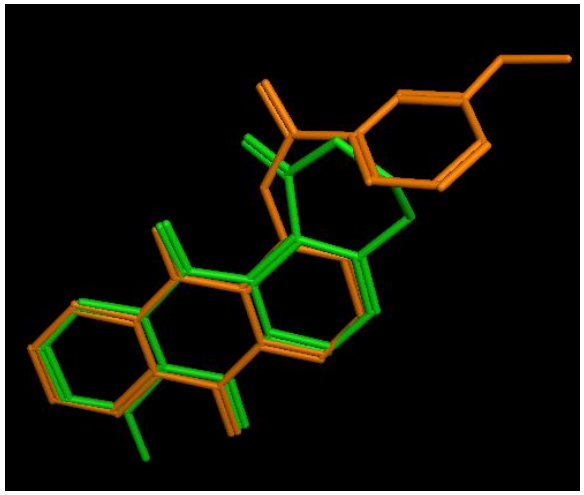


Stat3 SH2



ChemDiv
0163-0046

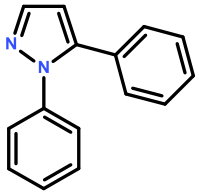
3D Structural Similarity



Green – Stat3 SH2 inhibitor;
Orange – ChemDiv cmpd

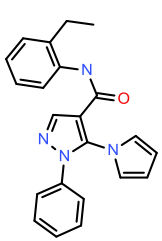
Examples

Scaffold

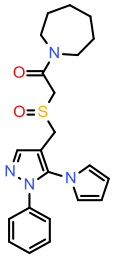


1626 cmpds per cluster

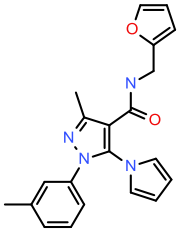
Diversity set



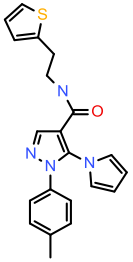
C883-0106



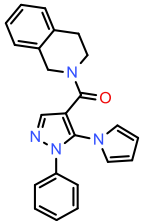
G819-0003



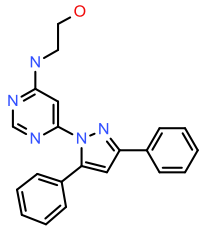
G011-0129



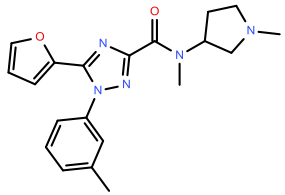
E751-3268



C883-0022

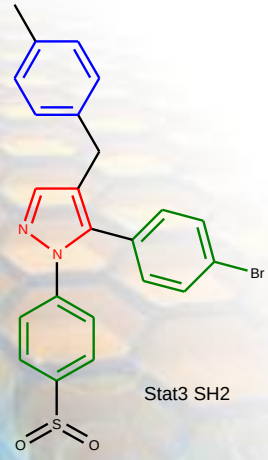


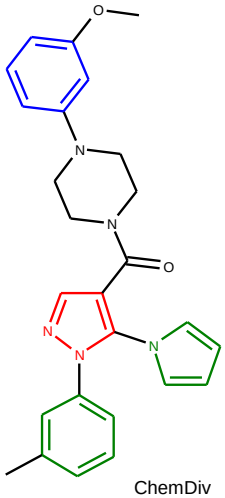
3454-2600



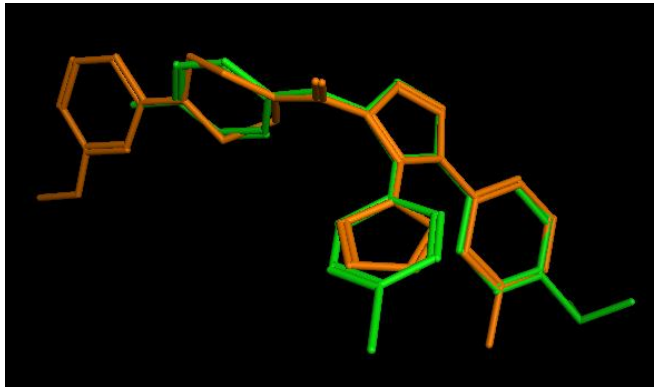
V002-5772

2D Structural Similarity





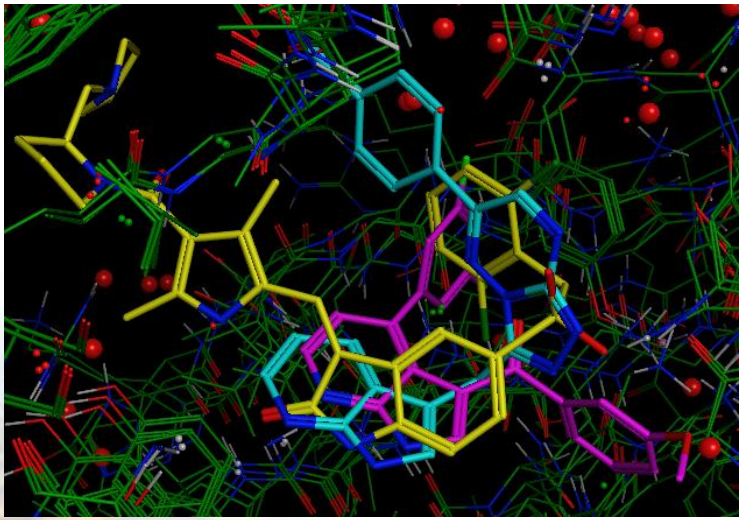
3D Structural Similarity



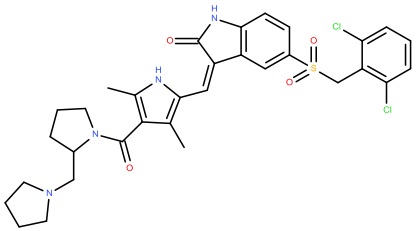
Green – Stat3 SH2 inhibitor;
Orange – ChemDiv cmpd

3D *in silico* modeling

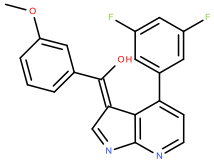
Currently, more than 50 crystallographic complexes obtained for various small-molecule SH2 domain inhibitors are available within PDB databank. The **4-centered pharmacophore model** was constructed based on the selected X-Ray data (2WKM, 3GQL and 4AOI). The reference compounds were then docked into the constructed model starting form 2D structures without any stereo assignment. The obtained results are well correlated with the RSA data used (av. RMSD=0.2)



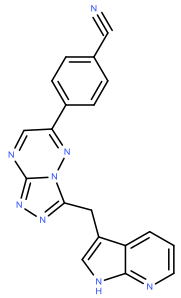
overlapping of cmpd 1 (*yellow*), cmpd 2 (cyan) and cmpd 3 (*violet*) in the SH2 domain binding site (*RSA data*)



2WKM
Cmpd 1
Pfizer

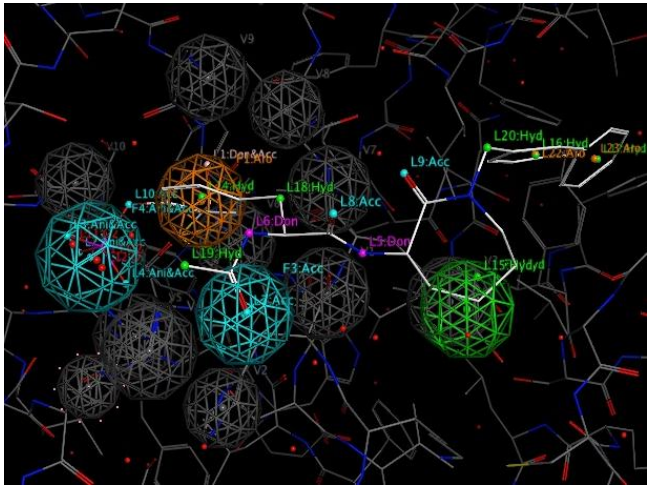


3GQL
Cmpd 2
Yale University School of Medicine



4AOI
Cmpd 3
Pfizer

SH2 domains inhibitors used for 3D model construction and self-validation



All the compounds from **SH2 domains library** were evaluated using the developed pharmacophore model. **High-score** molecules were included in the library (more than 50% of the total amount)