Sodium Dependent Glucose Transporter (SGLT) 1/2 - Elucidating Inhibitor SAR and Selectivity using Homology Modelling and 3D QSAR Studies

Susann Vorberg[+§], Ina Koch[+], Christian Buning[§]

[+] University Frankfurt, Institute for Computer Science, Department for Molecular Bioinformatics, 60325 Frankfurt a.M., Germany
[§] Sanofi-Aventis Deutschland GmbH, Industriepark Höchst, Building G838, 65926 Frankfurt a.M., Germany

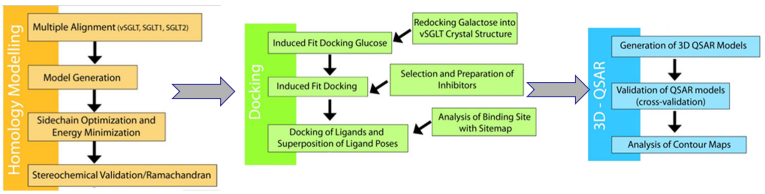
Motivation

Inhibiting sodium-dependent glucose transporters (SGLTs) has been proposed as a new therapy for the treatment of diabetes [1]. SGLT2 as the most prominent member of this family is mainly expressed in the kidney and responsible for the reabsorption of the vast majority of the filtered glucose. Therapeutic goals of SGLT2 inhibition are reduced plasma glucose levels and weight loss. Potential side effects in case of SGLT2 inhibition are expected to be mediated by a lack of selectivity towards SGLT1 that is mainly expressed in the intestine and responsible for glucose- and galactose absorption from food sources.

GOAL: inhibition of glucose resorption by SGLT2 while keeping the activity of SGLT1

Workflow & Tools

Homology Modelling – Template vSGLT crystal structure (PDB: 3DH4) Resolution: 2,7Å [2]. Protein modeling was accomplished with Maestro (Schroedinger,LLC, Portland, OR), 3D QSAR studies were performed using the Sybyl Molecular Modeling Package (Tripos, St.Louis, MO).

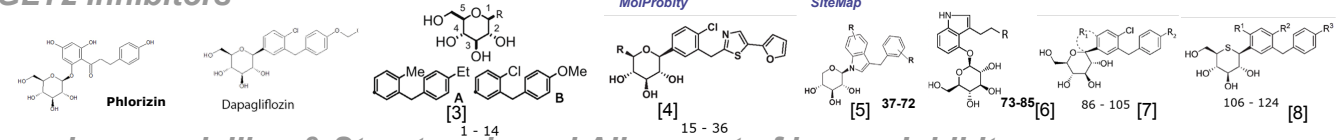


ClustalW
Prime
MolProbity

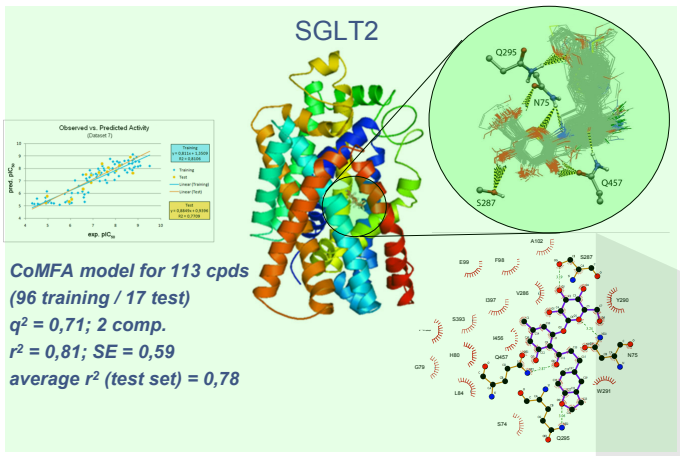
Induced Fit Docking Protocol
Glide
SiteMap

CoMFA

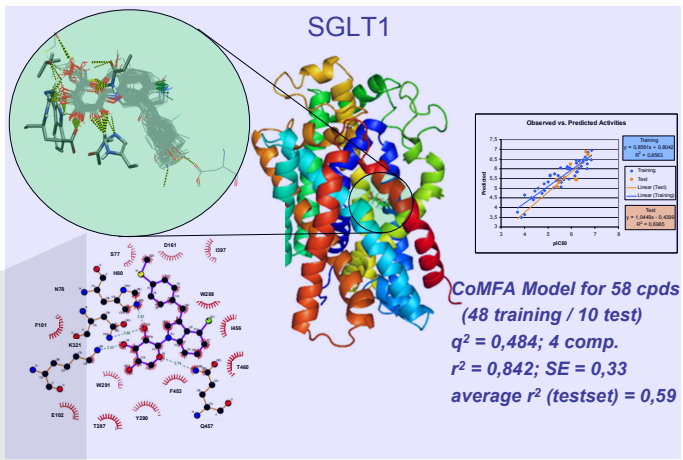
SGLT2 Inhibitors



Homology modelling & Structure-based Alignment of known Inhibitors



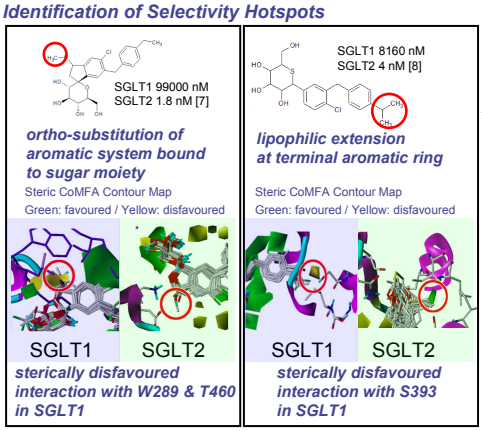
CoMFA model for 113 cpds
(96 training / 17 test)
q^2 = 0,71; 2 comp.
r^2 = 0,81; SE = 0,59
average r^2 (test set) = 0,78



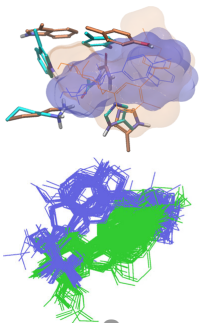
CoMFA Model for 58 cpds
(48 training / 10 test)
q^2 = 0,484; 4 comp.
r^2 = 0,842; SE = 0,33
average r^2 (testset) = 0,59

SGLT1/2 Inhibitor Selectivity

Identification of Selectivity Hotspots



Alignment of SGLT1/2 Binding Poses & Pockets based on Homology Models

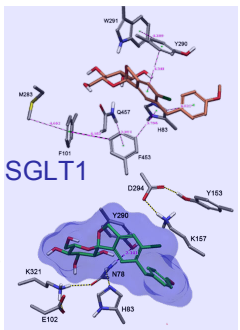


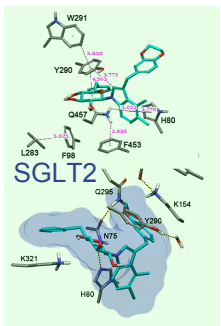
The binding pockets have different shapes
Brown: SGLT2
Blue: SGLT1

The binding modes differ significantly
Blue: SGLT1 binding poses
Green: SGLT2 binding poses

Comparison of SGLT1/2 Binding Pockets

Intersidechain contacts in the binding pockets differ between SGLT1 / 2





References

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Summary & Conclusion

- ***Homology models were generated for SGLT1 & SGLT2 using the vSGLT x-ray structure as template - 3D QSAR studies elucidate the inhibitor SAR for SGLT1/2***
- ***The generated models suggest different binding sites and modes for inhibitors despite of high sequence similarity between SGLT1 and SGLT2***
- ***Selectivity Hotspots have been identified***

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