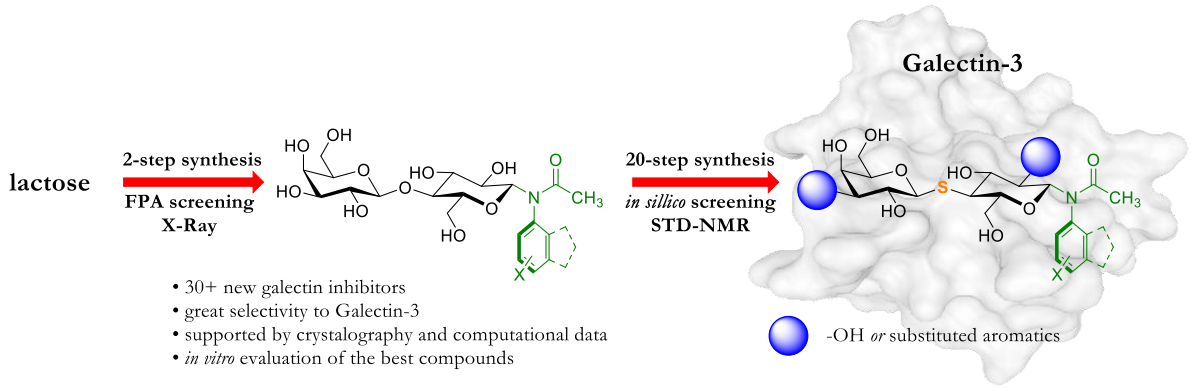
SYNTHESIS AND STRUCTURE-AFFINITY RELATIONSHIP OF A NEW CLASS OF LACTOSYLAMIDE GALECTIN INHIBITORS

Jakub Zýka[a], Jan Choutka[b], Nina Habanová[b], Jaroslav Kozák[b], Radek Pohl[b], Kamil Parkan[a]

[a] Department of Chemistry of Natural Compounds, University of Chemistry and Technology, Prague, Technická 5, 166 28, Prague, Czech Republic
zykaj@vscht.cz
[b] Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo náměstí 2, 160 00, Prague, Czech Republic

Galectins are proteins from the lectin family that selectively bind D-galactosides, such as glycosylated proteins bearing terminal lactose or LacNAc units. Over the years, interest in their inhibition has been growing, as they are responsible for several key cell functions [1] such as cell adhesion, communication and other functions, which influence pathological processes like cancer [2] and virus cell entry [3]. Recently, there have been several attempts to bring a glycomimetic drug targeting galectins to the market [4].
Building on previously developed synthesis of glycosylamines and amides [5], we employed a new two-step procedure to obtain a series of *N*-lactosylanilides. A new binding motif was identified based on fluorescence polarization/anisotropy (FPA) affinity measurements and protein-ligand crystal structure with galectin-3. Further investigation by thorough *in silico* screening and saturation transfer difference NMR provided valuable insight into the structure-affinity relationships between the newly prepared compounds and binding to galectins-3 and -1. These findings culminated in a multistep synthesis of highly decorated glycomimetics with single digit nanomolar affinity and high selectivity towards galectin-3. Further evaluation by means of cell-based assays showed promising results.



Acknowledgements: This work was supported by the Czech Science Foundation (№ 23-05805S) and the Specific University Research grant (№ A1_FPBT_2024_003).

References:
1. A. Gupta, G.S. Gupta in *Animal Lectins: Form, Function and Clinical Applications* (Eds.: G.S. Gupta), Springer, Vienna, **2012**, pp. 191-306.
2. H. Ghazarian, B. Idoni, S. B. Oppenheimer, *Acta Histochem.* **2011**, *113*, 236-247.
3. A. Sethi, S. Sanam, S. Munagalasetty, S. Jayanthi, M. Alvala, *RCS Advances* **2020**, *10*, 29873-29884.
4. A. Sethi, S. Sanam, R. Alvala, M. Alvala, *Expert Opin. Ther. Pat.* **2021**, *31*, 709-721.
5. J. Zýka, V. Prouza, N. Habanová, R. Pohl, K. Parkan, *Carbohydr. Res.* **2024**, *536*, 109023