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GalNAc mimetics: from synthesis to potential inhibitors in Alzheimer's Disease

João de Barros[1,2,*], David Evans[3], Nicolas Dreyfus[3], Gary Sharman[3], Amélia P. Rauter[1,2]

[1] Centro de Química e Bioquímica, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Ed. C8, Campo Grande, 1749-016 Lisboa, Portugal;

[2] Centro de Química Estrutural, Instituto Superior Técnico/Faculdade de Ciências, Universidade de Lisboa, Portugal;

[3] ELI LILLY AND COMPANY LIMITED, Lilly House, Priestley Road, Basingstoke, RG24 9NL, United Kingdom;

* Corresponding author: jmvbarros@fc.ul.pt

Carbohydrate Chemistry Group

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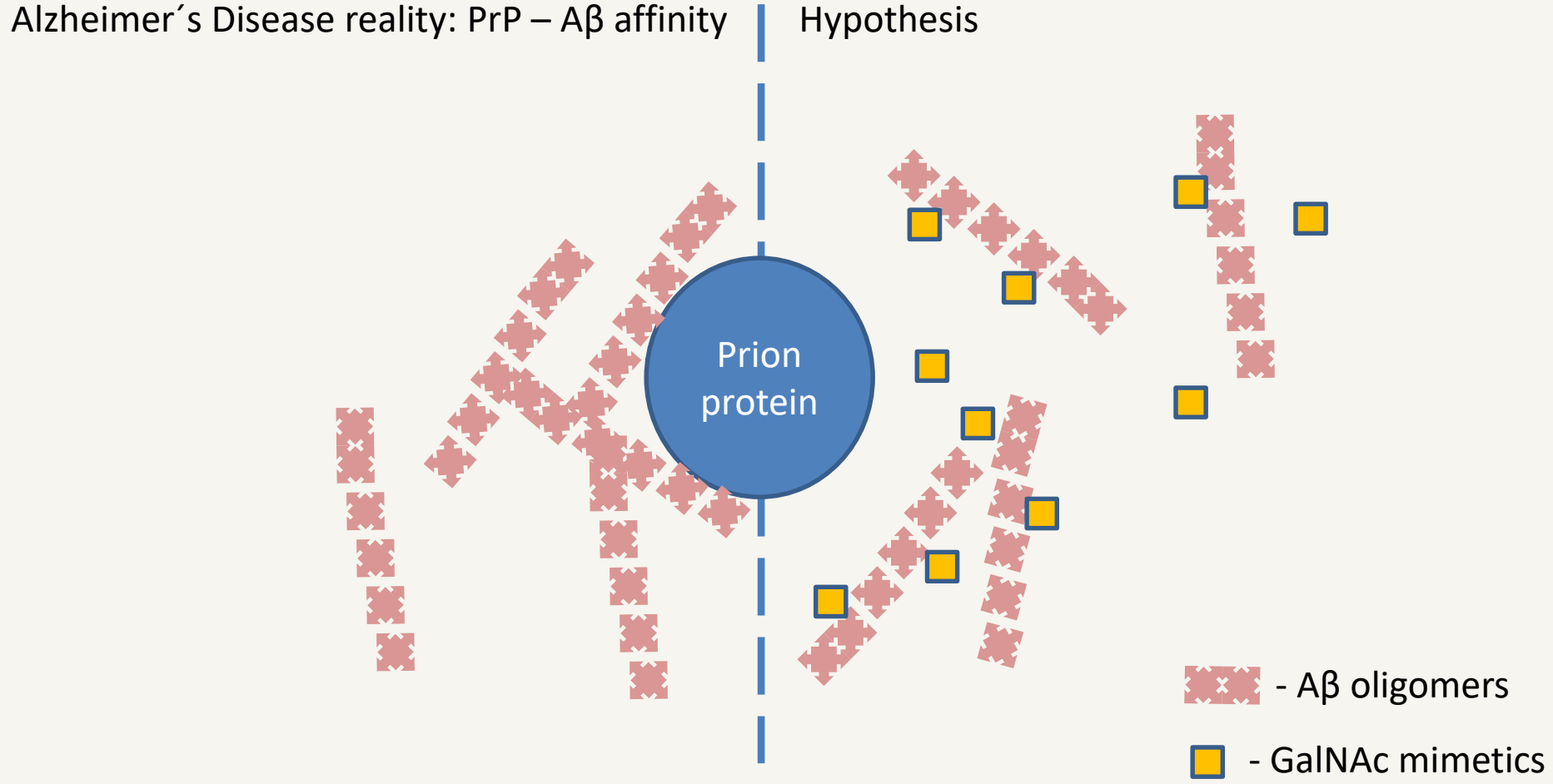
GalNAc mimetics: from synthesis to potential inhibitors in Alzheimer's Disease



Abstract:

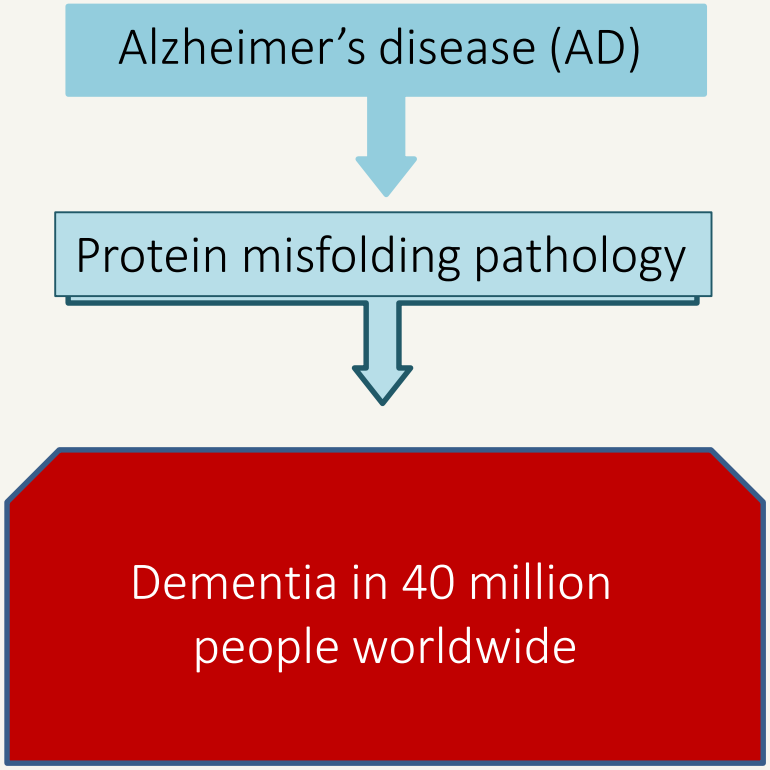
N-acetylgalactosamine(GalNAc) belongs to the group of 2-amino-2-deoxysugars which are found in a wide range of biological structures playing a role in in cell-cell interaction and receptor induced cell signaling.

Alzheimer's disease (AD) is a protein misfolding pathology, causing dementia in over 40 million people worldwide. Cellular prion protein (PrP) has a high-affinity binding with amyloid β (Aβ) oligomers, the most toxic species in Alzheimer's pathology. It has been demonstrated that *O*-glycosylated GalNAc, attached to Ser/Thr side chain of PrP via an α-glycosidic linkage, promotes the inhibition of amyloidogenesis in AD.

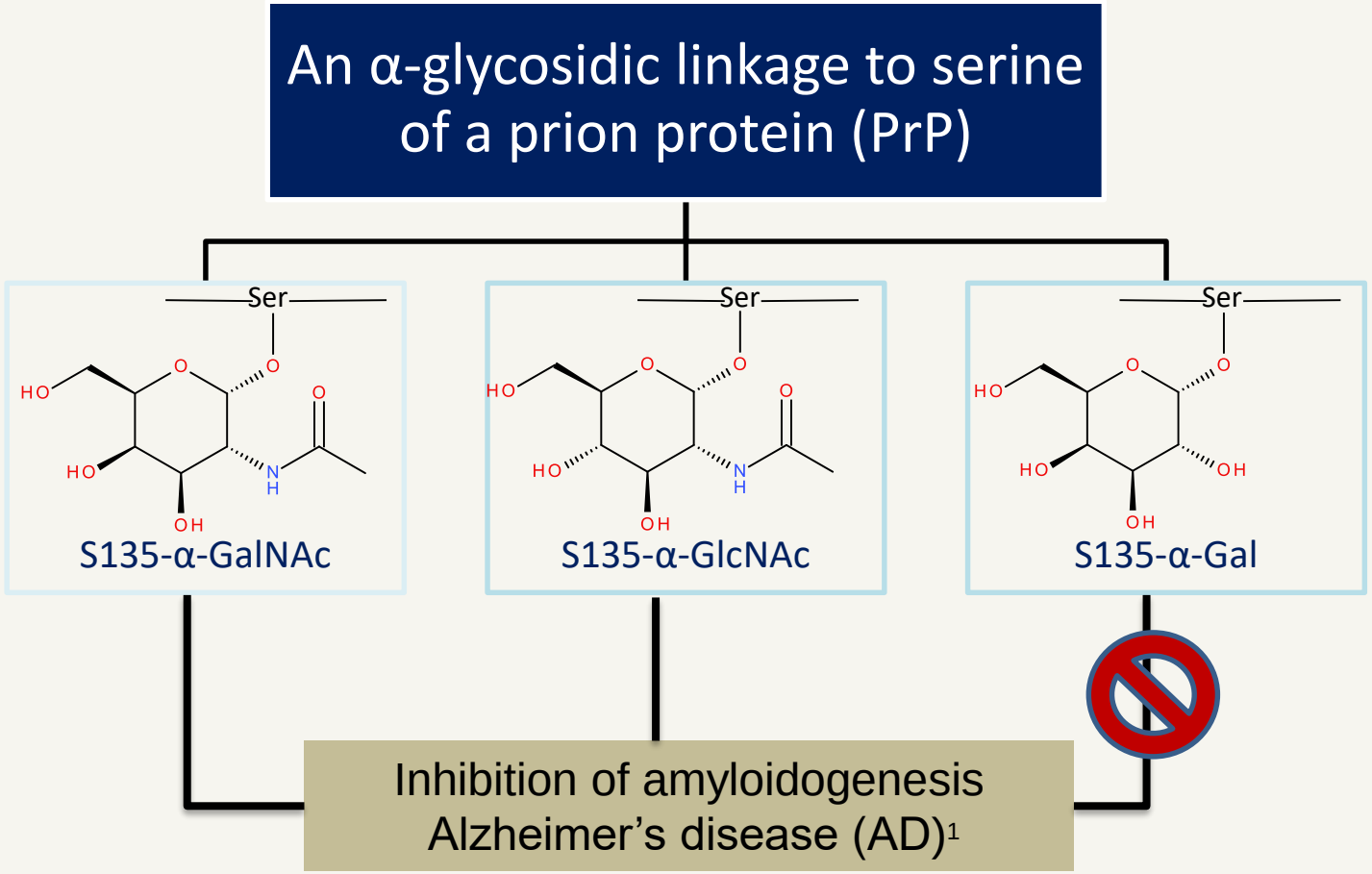
In this context, we have synthesized new GalNAc mimetics, with additional contacts in the GalNAc core structure, to improve the interactions with the prion peptide and to investigate the binding affinity with $A\beta_{1-42}$. The study of the intermolecular interactions of the new chemical structures and $A\beta_{1-42}$ oligomers was investigated by NMR methods, namely saturation transfer difference NMR (STD-NMR) and ^{19}Fluorine NMR (F-NMR) protocols. In this communication, synthetic approaches to the GalNAc mimetics will be presented and interaction results regarding C2 substitution and anomeric heteroatoms, such as O, S and Se with $A\beta_{1-42}$ oligomers will be discussed.

Keywords: Alzheimer's disease; GalNAc; Aβ oligomers.

Introduction

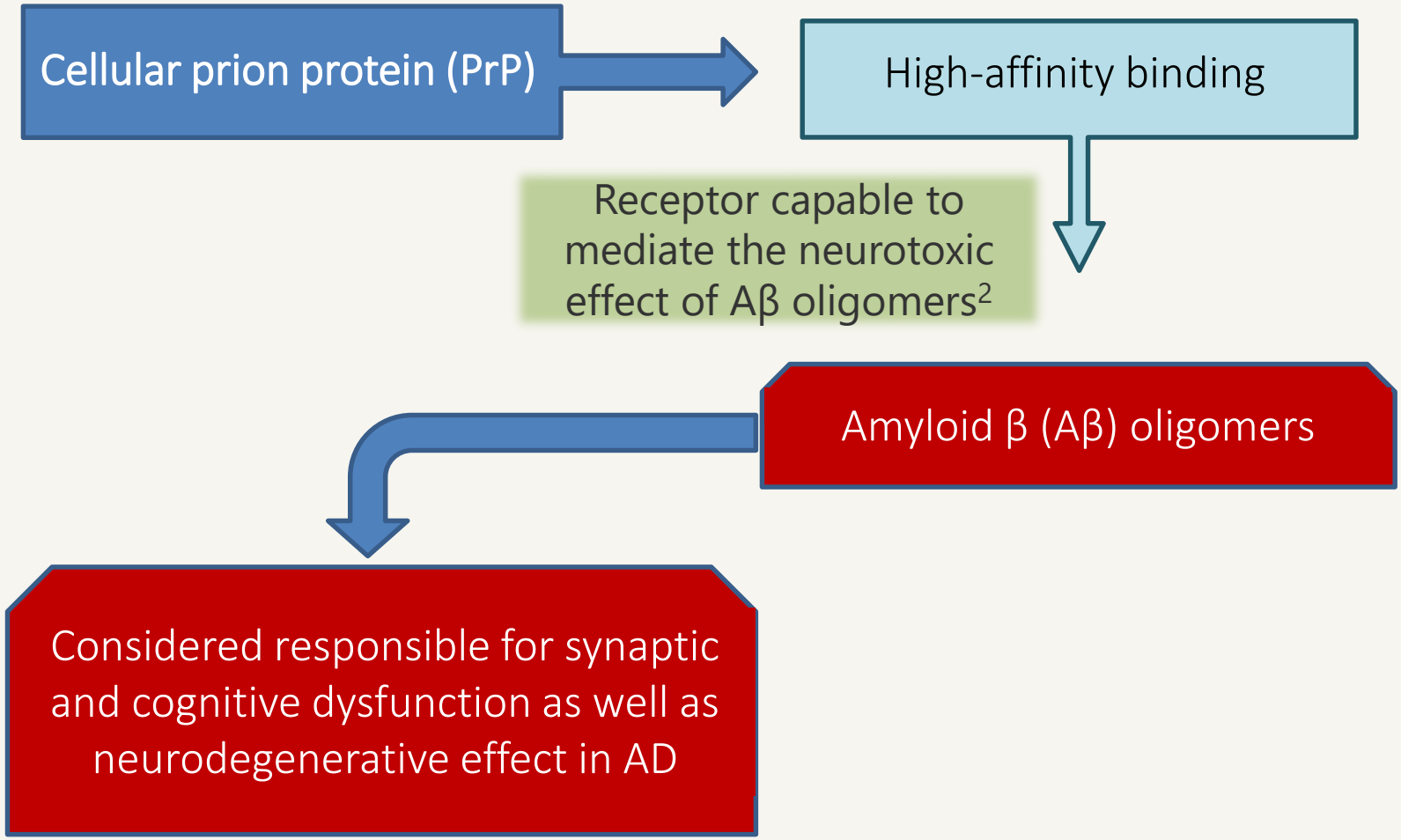


Introduction



[1] C. Lin, E. Chen, L. Lee, R. Hsu, F. Luh, L. Yang, C. Chou, L. Huang, C. Lin, R. Chen, *Carbohydr. Res*. 2014, 387, 46-53.

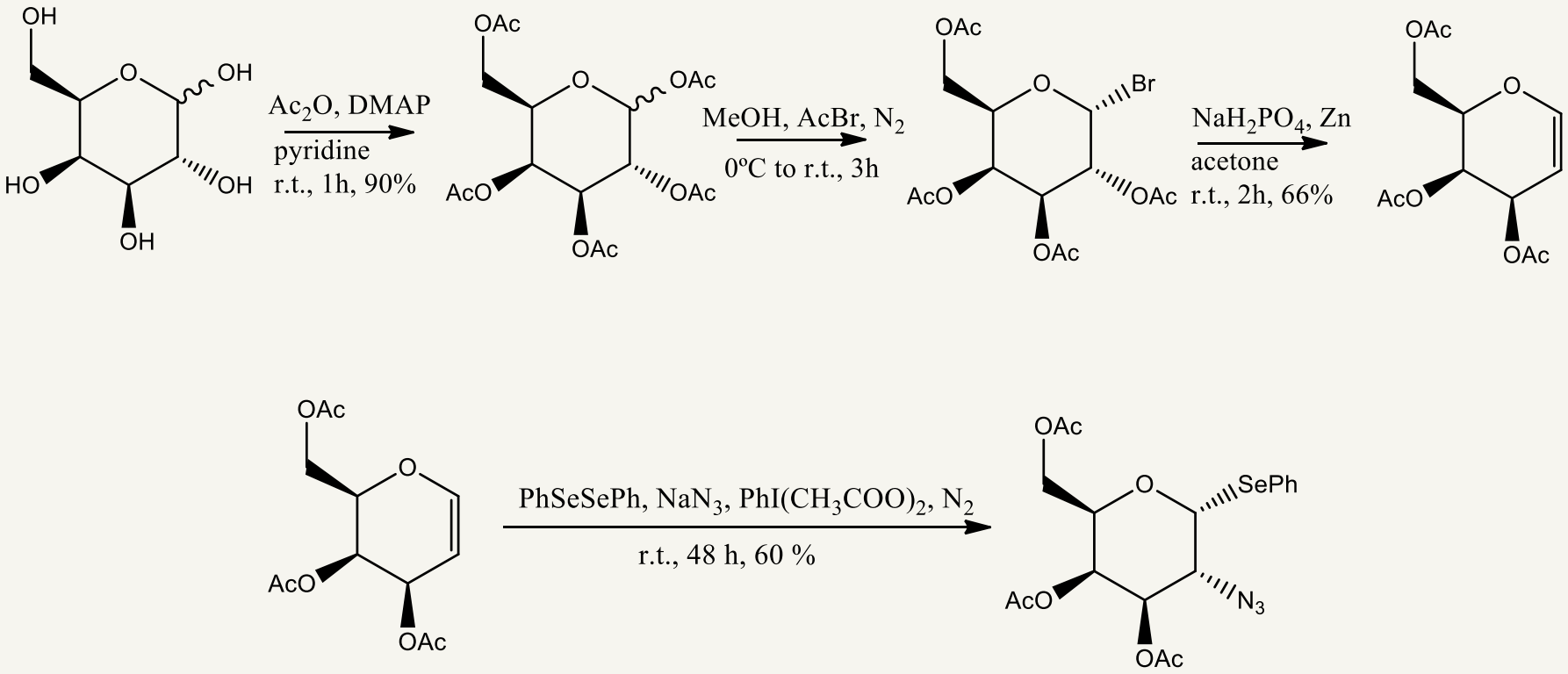
Introduction



[2]Laurén J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature 2009; 457:1128-32.

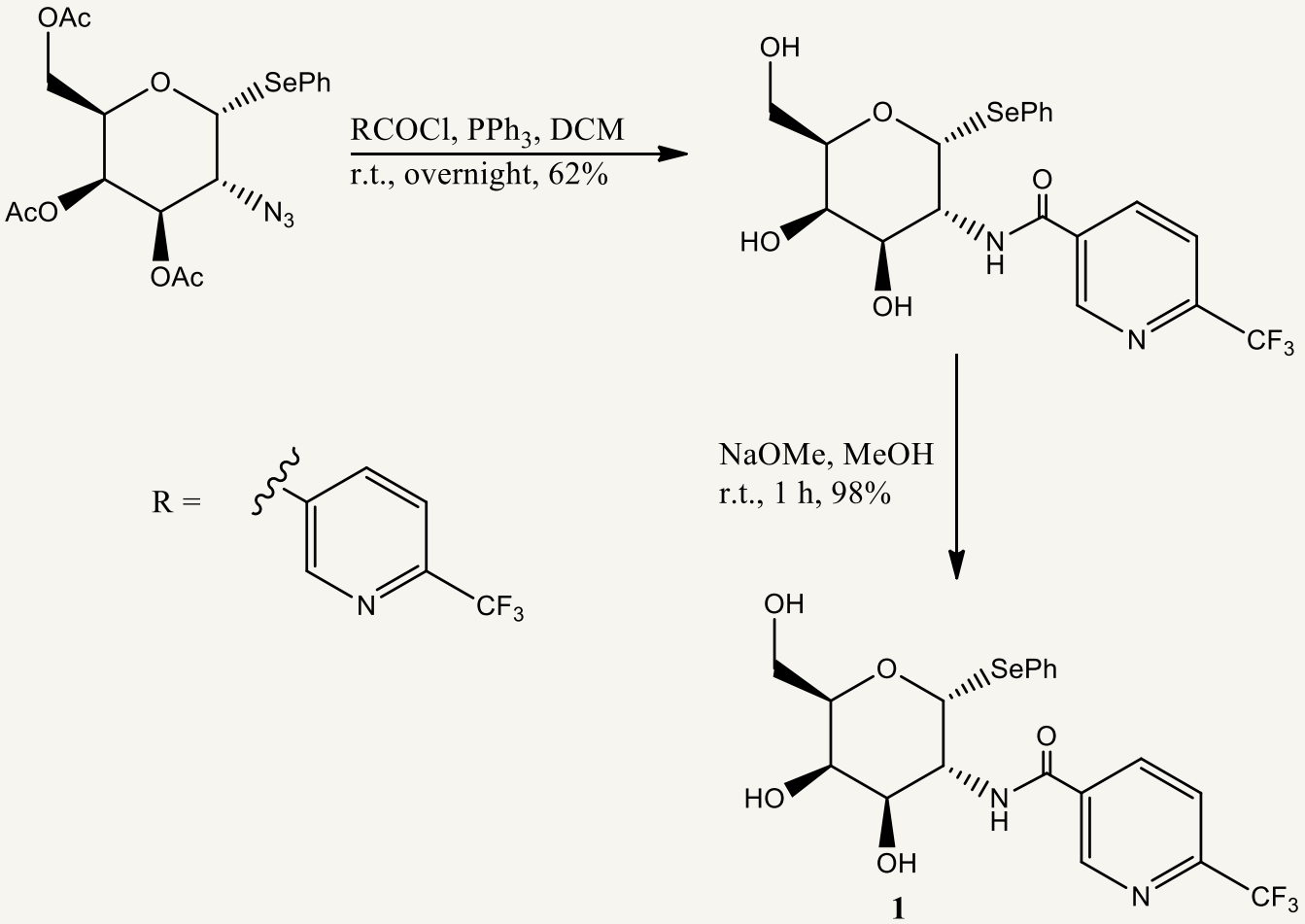
Results and discussion

Synthesis: SePh



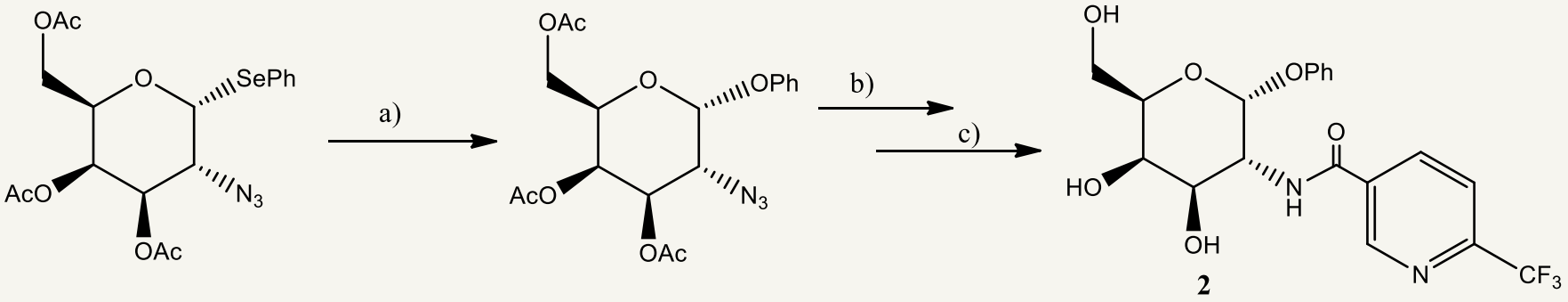
Results and discussion

Synthesis: SePh



Results and discussion

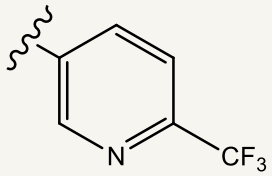
Synthesis: OPh



a) PhOH, I_2/DDQ, dioxane/toluene, r.t., overnight, 67%;

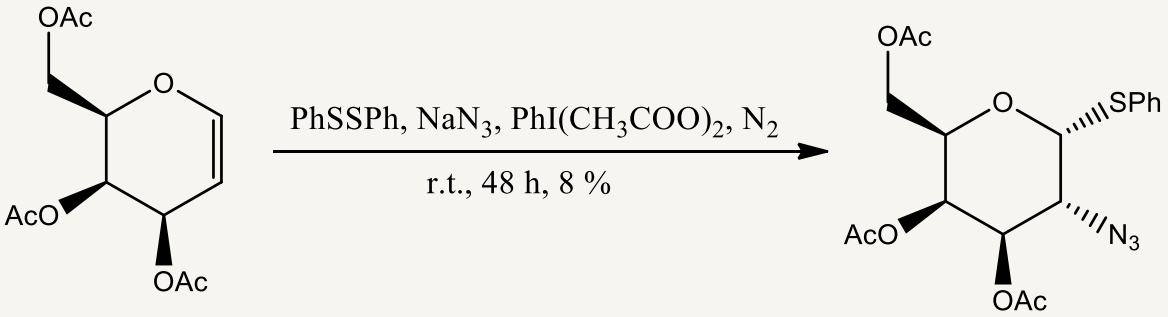
b) RCOCl, PPh_3, DCM ,r.t., overnight; 61 %;

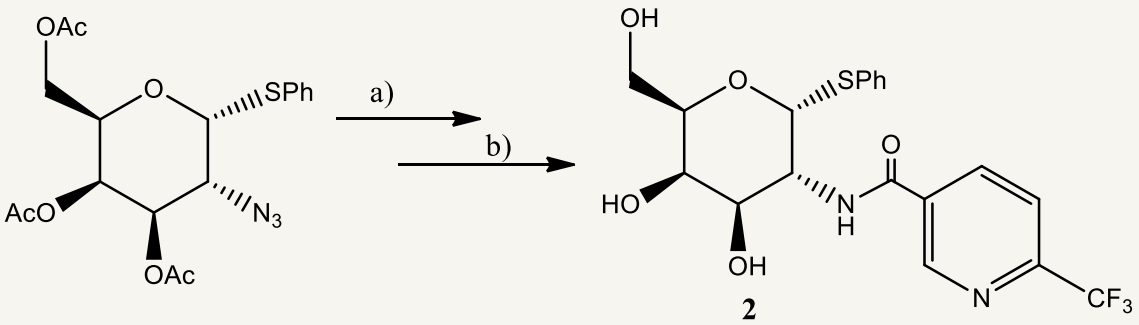
c) NaOMe, MeOH, r.t., 1h, 93%.

R = 

Results and discussion

Synthesis: SPh

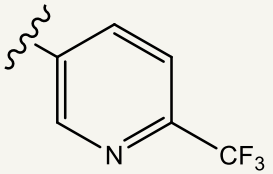




a) RCOCl, PPh_3, DCM ,r.t., overnight; 34 %;

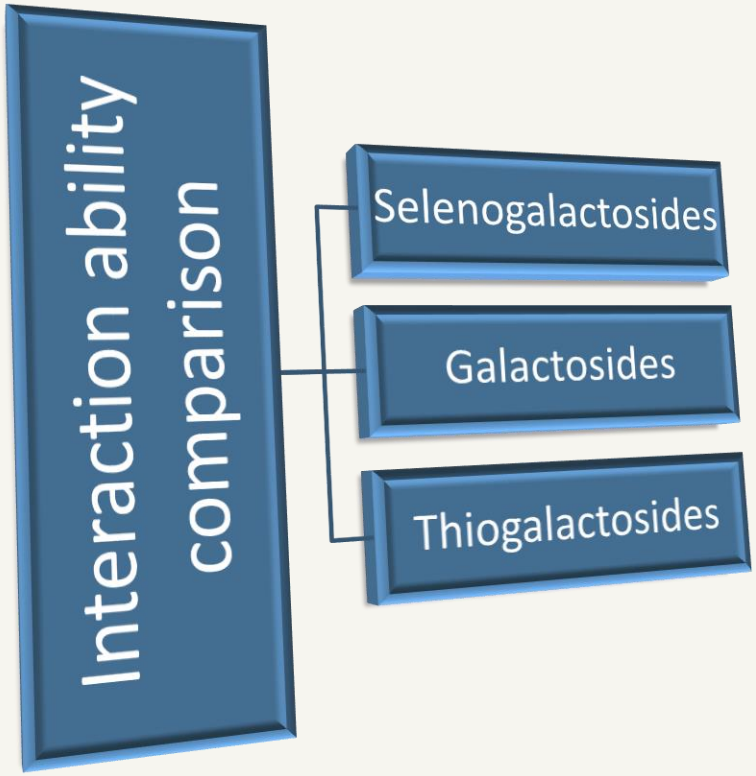
b) NaOMe, MeOH, r.t., 1h, 97%.

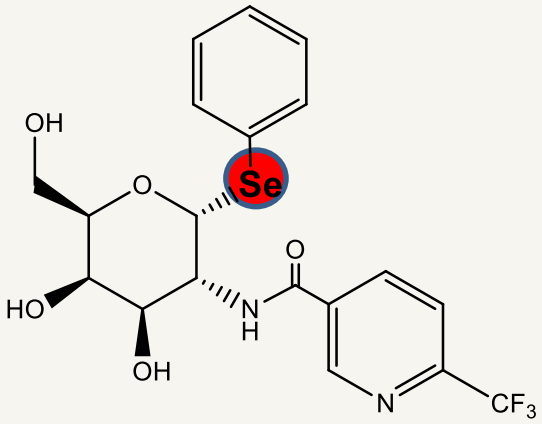
R =

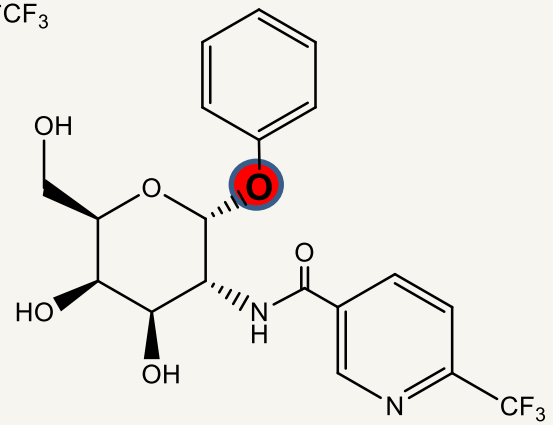


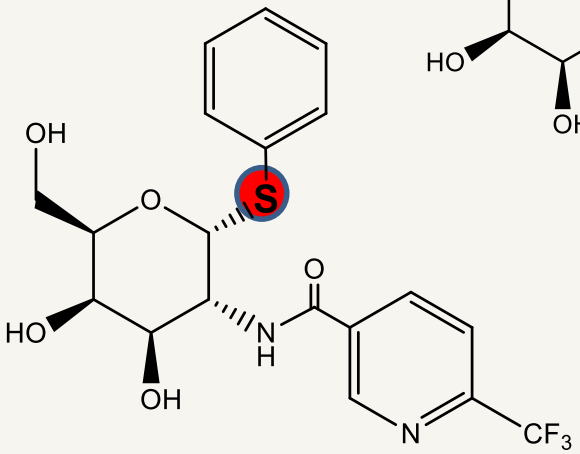
Results and discussion

Synthesis





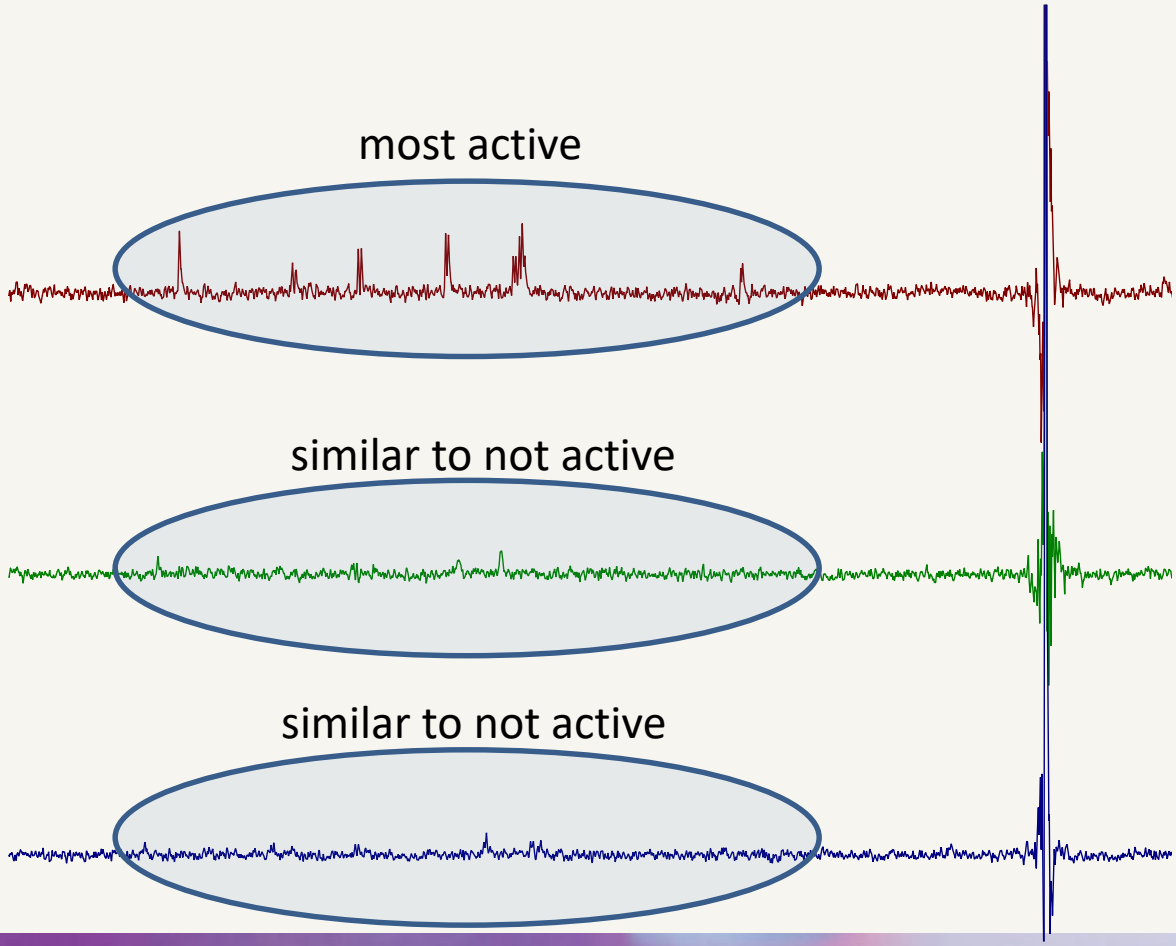


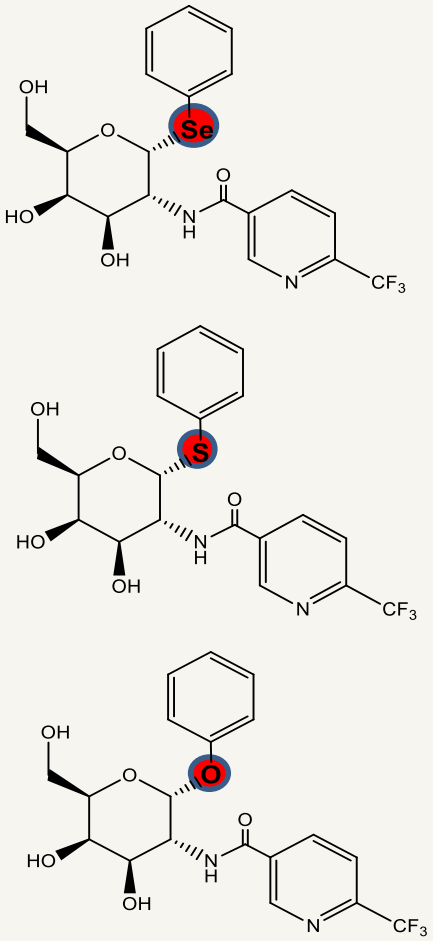


Results and discussion

STD-NMR

Compounds 1, 2 and 3 interactions with $A\beta_{1-42}$ oligomers





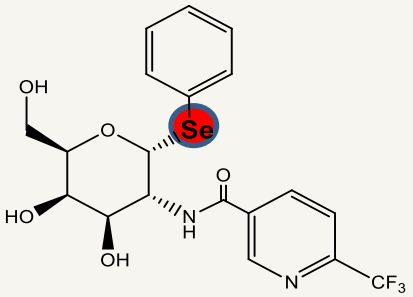
Results and discussion

^{19}F-NMR

Compound 1 interactions with $A\beta_{1-42}$ oligomers – <u>Positive result</u>

Blue – absence of Aβ

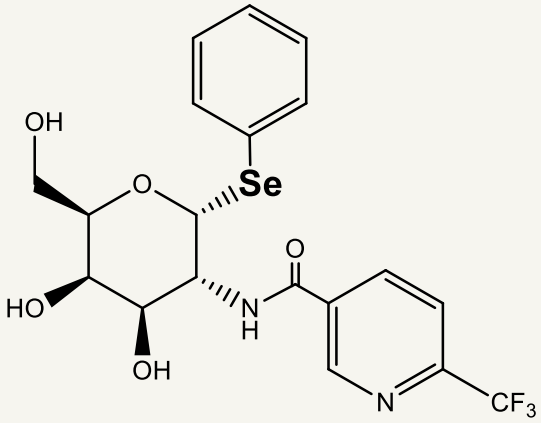
Red – presence of Aβ



Results and discussion

Toxicity Experiments

MTT experiments



revealed to be non toxic

> 75 % cell viability (50 µM)

Conclusions

New GalNAc mimetics

- Synthetic route aiming C2 *N*-functionalization;
- Anomeric substitution with stereochemical control.

$A\beta_{1-42}$ interaction (STD-NMR; ^{19}F-NMR) and toxicity results

STD –NMR and ^{19}F-NMR:

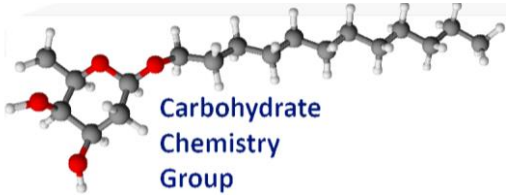
- require the presence of selenium atom, at the anomeric position;
- selenogalactoside interact with $A\beta_{1-42}$ oligomers, opening the possibility to inhibit the PrP-Aβ binding;

Compounds toxicity:

- selenoglactoside (active compound) is not toxic.

Acknowledgments

The European Union for the support of the project entitled "Diagnostic and Drug Discovery Initiative for Alzheimer's Diseases" (D3i4AD), FP7-PEOPLE-2013-IAPP, GA 612347.



Lilly

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D3i4AD
Diagnostic and Drug Discovery Initiative for Alzheimer's Disease