Alzheimer's disease: exploring GalNAc mimetics towards binding affinity to Aβ and Prion

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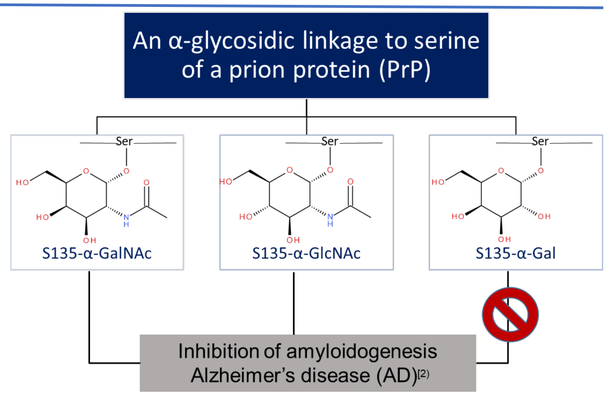
Introduction

Alzheimer's disease (AD) is a protein misfolding pathology which cause dementia in 40 million people worldwide[1].

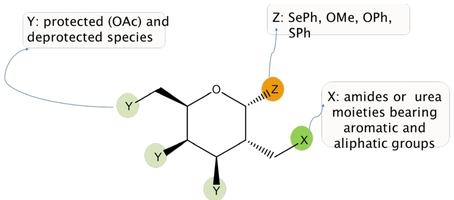
The multifactorial AD is associated to the formation of $A\beta_{1-42}$ toxic small oligomers, which lead to membrane damage and neuronal death.

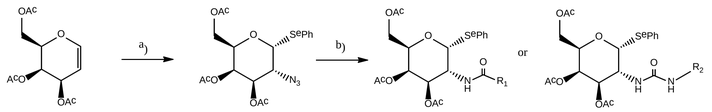
Amyloid β (Aβ) oligomers are the most toxic species in AD pathology and have a high affinity binding with PrP.



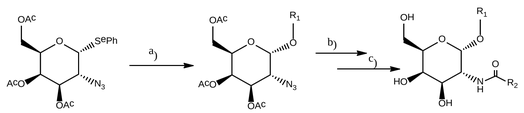
Methodology

✓ ***Synthesis of a library of mimetics:***

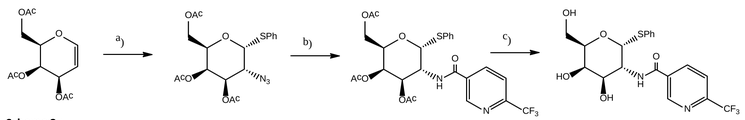




Scheme 1:
a) Ph_2Se_2, $TMSN_3$, $PhI(CH_3COO)_2$, DCM, -35ºC to r.t., 4h, 72 %;
b) One-pot: i) Et_3P (1M in THF), THF/H_2O (4:1), r.t., 30 min; ii) R_1COCl/R_2NCO, Et_3N, molecular sieves 4Å, DCM, r.t., 30min-1h, 35%-68%;



Scheme 2:
a) R_1OH, I_2/DDQ, dioxane/toluene (3:1), r.t., overnight(11.1:1 α:β); 61% - 92 %;
b) i) Et_3P (1M in THF), THF/H_2O (4:1), r.t., 30 min; ii) R_2COCl, Et_3N, molecular sieves 4Å, DCM, r.t., 30min-1h, 35% - 77% yield;
c) NaOMe (1.2 M in MeOH), MeOH, r.t., 10 min-30 min, 87% - 99% yield.



Scheme 3 :
a) PhSSPh, $TMSN_3$, (diacetoxyiodo)benzene, N_2, -30ºC to -10º C, 48 h, 8 % yield.
b) i) Et_3P (1M in THF), THF/H_2O (4:1), r.t., 30 min; ii) RCOCl, Et_3N, molecular sieves 4Å, DCM, r.t., 30min-1h, 34% yield;
c) NaOMe (1.2 M in MeOH), MeOH, r.t., 10 min-30 min, 97% yield.

✓ ***Binding studies by STD-NMR and F-NMR against Aβo for the establishment of Structure Activity Relationships***

✓ ***Metabolic biological assays with liver microsomes (human, mouse, rat and dog)***

[1]Matos, A.M., Macedo, M.P., Rauter, A.P., Bridging type 2 diabetes and Alzheimer's disease: assembling the puzzle pieces in the quest for the molecules with therapeutic and preventive potential., Med. Res. Rev., 2018, 38, 261-324;
[2]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.

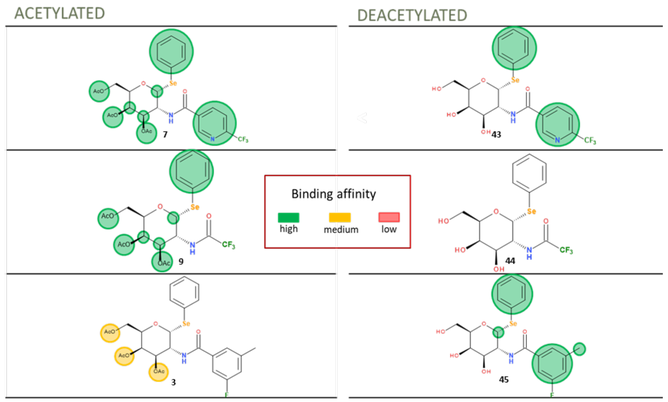
. The European Union is gratefully acknowledged for the support of the project entitled "Diagnostic and Drug Discovery Initiative for Alzheimer's Diseases" (D3i4AD), FP7-PEOPLE-2013-IAPP, GA 612347; .
The authors also thank Fundação para a Ciência e a Tecnologia for the financial support to Centro de Química Estrutural (project UIDB/00100/2020).

Results

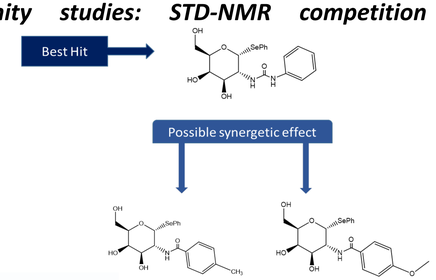
. Synthesis of a library of mimetics – more then 50 new compounds

. Binding affinity studies: STD-NMR and F-NMR against Aβo

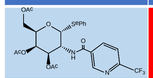
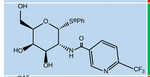
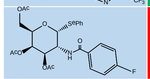
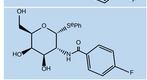
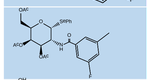
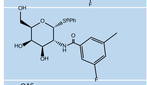
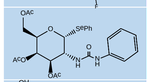
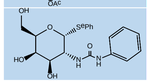
NMR experiments : acetylaled vs deacetylated (examples)



Binding affinity studies: STD-NMR competition experiments



. Metabolic biological assays with liver microsomes (human, mouse, rat and dog).

Compound	Human hepatic micrs.	Mouse hepatic micros.	Rat hepatic micros.	Dog hepatic micros.	Solubility (aqueous pH 7.4)
	100	100	95.4	100	21 µM
	5.7	9.5	49.2	9.3	> 100 µM
	99.8	100	96.6	88.9	11 µM
	0	13.8	12.5	0	> 100 µM
	100	100	100	100	11 µM
	6.8	25.8	21.1	15.5	41 µM
	100	100	98.6	100	21 µM
	3.8	14.9	12.9	0	> 100 µM

Conclusions

- Synthetic route improvement (C2 ***one-pot*** *N*-functionalization);
- Anomeric substitution with ***stereochemical control***;
- ***Lead series*** based on ***phenyl selenogalactosides*** bearing **amide** and **urea** functionalities
- on C2: Water soluble and are not metabolized by human liver microsomes – ***bioavailability***; ***Not toxic***;
  - Ability to ***bind to Aβ amyloid*** oligomers;
  - Better Aβo binders when compared to other galactosides;
  - Require ***aromatic moieties*** at anomeric and C2 positions;
  - Require the presence of ***electronegative atoms*** for binding enhancement.