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SYNTHESIS, DOCKING STUDIES AND ANTICHOLINESTERASE INHIBITION OF OPEN-CHAIN CARBOHYDRATE AMIDES

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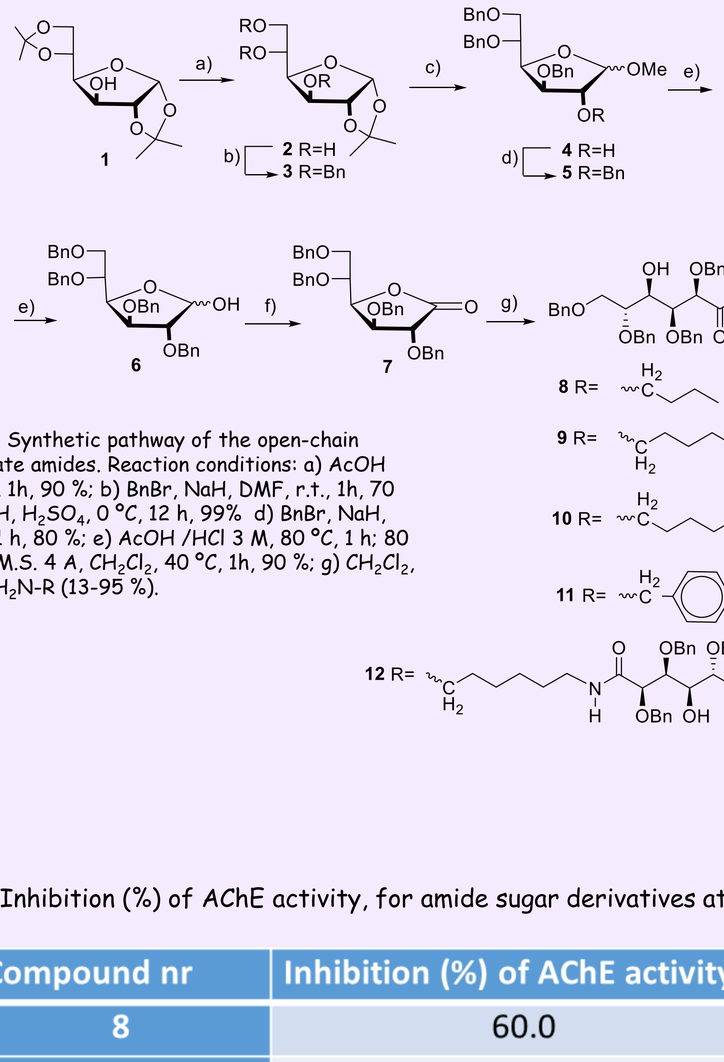
INTRODUCTION

According to the World Health Organization (WHO) in 2018, about 50 million people worldwide currently suffer from dementia, and two thirds of them have Alzheimer's disease (AD), a severe neurodegenerative disorder.[1,2]This number is expected to reach over 150 million by 2050[3] and the approved treatments only alleviate AD symptoms, being unable to stop disease progression[4]. The enzyme acetylcholinesterase (AChE) is involved in neurotransmission in the brain and its inhibition has an important role in the progression of the AD[4]. Hence, we have explored molecular diversity towards new agents to control disease progression targeting disease molecular mechanisms involved in neurotransmission based on open chain sugar amides.

RESULTS AND DISCUSSION

Synthesis of the new sugar amides is depicted in Scheme 1, covering the preparation of protected glucono-1,4-lactone **7** and reaction with the appropriate amines. Evaluation of AChE inhibition shows that compounds **10** and **11** are the most promising ones (63 and 63,4% inhibition activity). (Table 1).



Scheme 1. Synthetic pathway of the open-chain carbohydrate amides. Reaction conditions: a) AcOH 80%, 60°C, 1h, 90 %; b) BnBr, NaH, DMF, r.t., 1h, 70 %; c) MeOH, H_2SO_4, 0 °C, 12 h, 99% d) BnBr, NaH, DMF, r.t., 1 h, 80 %; e) AcOH /HCl 3 M, 80 °C, 1 h; 80 %; f) PCC, M.S. 4 A, CH_2Cl_2, 40 °C, 1h, 90 %; g) CH_2Cl_2, 40 °C, 1h, H_2N-R (13-95 %).

Table 1- Inhibition (%) of AChE activity, for amide sugar derivatives at 100 µg/mL:

Compound nr	Inhibition (%) of AChE activity
8	60.0
9	48.7
10	63.4
11	63.0
12	29.0
Rivastigmine	98.6

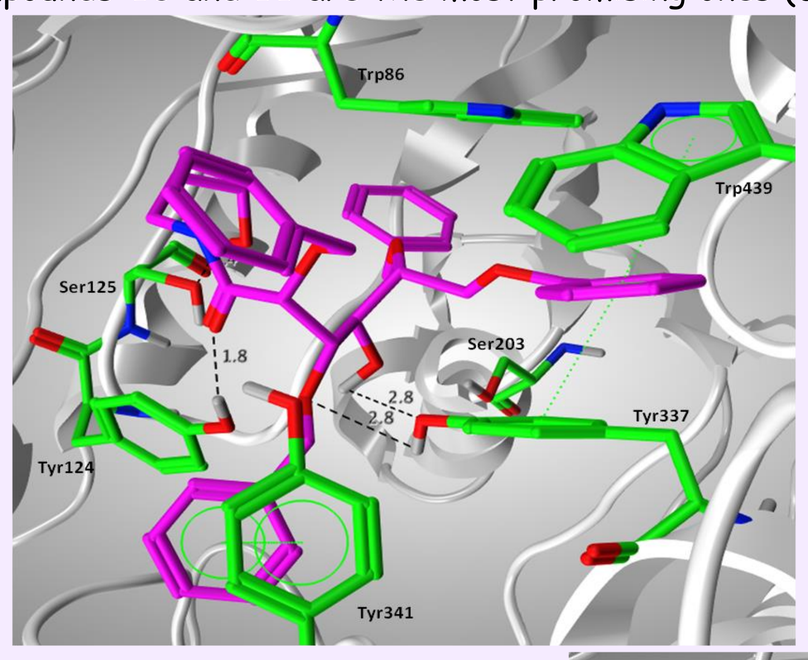


Figure 1 – Docking studies of compound **10** gave the interactions:
6-OBn π π stacking with residues Tyr 337 and Trp 439
3-OBn π π stacking with Tyr341.
O-3, OH-4 Tyr337.
Carbonyl H-bonding to the Tyr124
OH-primary H-donor toward Ser125-OH interaction.

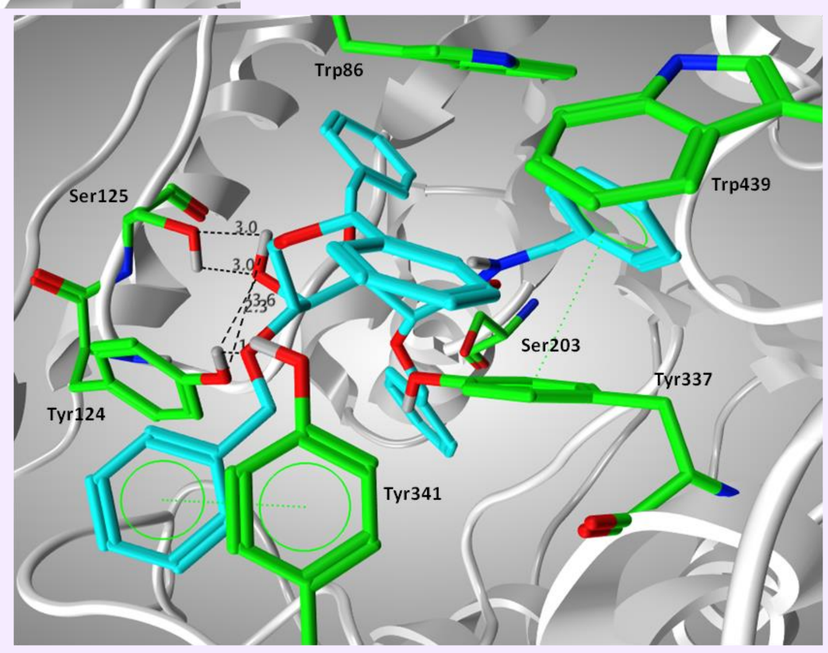


Figure 2 – Docking studies of compound **11** gave the interactions:
NH-Bn π π stacking with residues Tyr 337 blocking Ser 203
5-OBn π π stacking with Tyr341.
O-5, OH-4 Tyr124 and Ser125, strong H-bonding..

CONCLUSION

Docking studies with PDB code of AChE used was 4BDT, and have shown that aromatic groups as well as H-bond donor and acceptor groups as well as the flexibility associated with the open-chain form of these sugars are responsible for their activity.

The studied compounds inhibited acetylcholinesterase to some extent (29-63.4% inhibition). The most promising ones are compounds 10 and 11, bearing the amide functionality *N*-substituted with benzyl or hydroxypropyl groups.

The efficiency of the reactions makes the approach very well-suited for production of new molecular entities for structure-activity relationship studies, where both the configurational pattern and the nature of *N*-substituents can be systematically profiled.

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