Sociedade Brasileira de Química (SBQ)

Synthesis of 1,2,3-triazole-linked glycoconjugates as potential inhibitors of human galectin-3.

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Galectin-3, Triazole, Glycoconjugates, "Click chemistry", Surface Plasmon Resonance, Molecular Modeling

Introduction

Galectins constitute a family of carbohydrate-binding proteins defined by their ability to recognize β-galactosides containing glycoconjugates. Galectin-3 (Gal-3), for instance, is super-expressed in several tumor cells, being involved in essential cancer related functions, such as tumorigenesis, neoplastic transformation and angiogenesis. Moreover, it can help tumors to escape from immune surveillance through modulation of immune and inflammatory responses.[1] Therefore, synthetic galectin-3 inhibitors are of utmost relevance for development of new anti-tumor therapeutic strategies against different types of cancer. Within this context, this work presents the synthesis of the 1,2,3-triazole-linked glycoconjugates **1-7** by "click chemistry" as possible inhibitors of galectin-3 (Fig. 1).

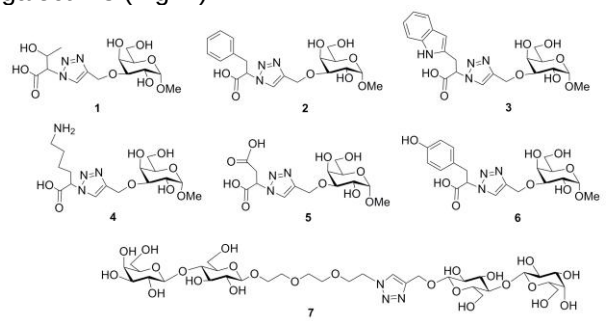

Figure 1. Chemical structures of 1,2,3-triazole-linked glycoconjugates **1-7**.

Results and Discussion

In general, the synthesis of compounds **1-7** was performed by Cu(I)-assisted 1,3-dipolar azide-alkyne cycloaddition reactions (CuAAC- "click chemistry") in a microwave reactor utilizing the catalytic system $CuSO_4$/ sodium ascorbate and DMF.[2] Firstly, CuAAC reactions of the previously prepared azido-derived amino acids N_3-L-ThrOBn **8**, N_3-L-PheOBn **9**, N_3-L-N-Boc-TrpOBn **10**, N_3-L-N-Boc-LysOBn **11**, N_3-L-O-tBu-AspOBn **12** or N_3-L-TyrOH **13** with the sugar 3-*O*-propynyl-GalOMe **14** afforded the protected amino acids-derived glycoconjugates **15-20** in yields varying from 34% to 47%. Subsequently, deprotection reactions of **15-20** gave the final compounds **1-6** (30%-75%). Regarding the 1,2,3-triazole lactose-derived glycoconjugate **7**, it was synthesized by click chemistry reaction between the sugar azido-lactose **21** and 2-propynyl-lactose **22**, followed by deacetylation reaction, being obtained in 40% overall yield. The evaluation of the binding affinity of compounds **1-7** to Gal-3 was performed by surface plasmon resonance (SPR), which showed lower K_D values for compounds **2** (7.96 μM), **4** (4.56 μM) and **7** (K_{D1} 0.15 μM/ K_{D2} 19 μM). The theoretical capacity of glycoconjugates **1-7** to interact with Gal-3 was assessed by docking and molecular dynamics simulations, being verified effective interactions, such as specific cation-π (Arg144) and ionic (Asp148) interactions for **2** and **4**, and a non-covalent cross-link between two Gal-3 monomers created by **7** (Fig. 2).

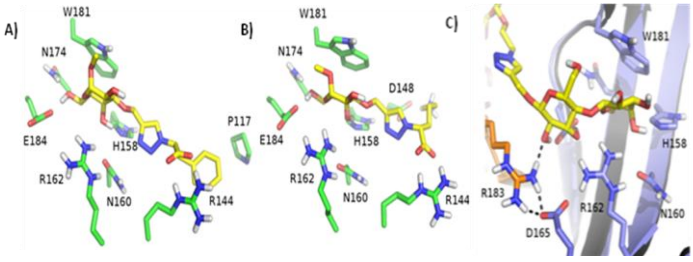

Figure 2. Representative binding modes between the most potent glycoconjugates: **2** (A), **4** (B) and **7** (C).

Conclusions

The 1,2,3-triazole-linked glycoconjugates **1-7** were successfully obtained by "click chemistry" reactions. SPR and molecular modeling data pointed out these compounds as potential Gal-3 inhibitors, with emphasis on the amino acids-derived glycoconjugates **2** and **4**, and the divalent lactoside **7**.

Acknowledgements

FAPESP, CAPES

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2 Aragão-Leoneti, V.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I. *Tetrahedron*. **2010**, *66*, 9475.