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

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. 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).

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 CuSO4/ sodium ascorbate and DMF. Firstly, CuAAC reactions of the previously prepared azido-derived amino acids N3-L-ThrOBn 8, N3-L-PheOBn 9, N3-L-N-Boc-TrpOBn 10, N3-L-N-Boc-LysOBn 11, N3-L-OtBu-AspOBn 12 or N3-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_D 0.15 µM/ K_D 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 (Arg148) interactions for 2 and 4, and a non-covalent cross-link between two Gal-3 monomers created by 7 (Fig. 2).

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.

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