Synthesis of glycopeptides mimetics of *T. cruzi* and tumor mucins as potential vaccines

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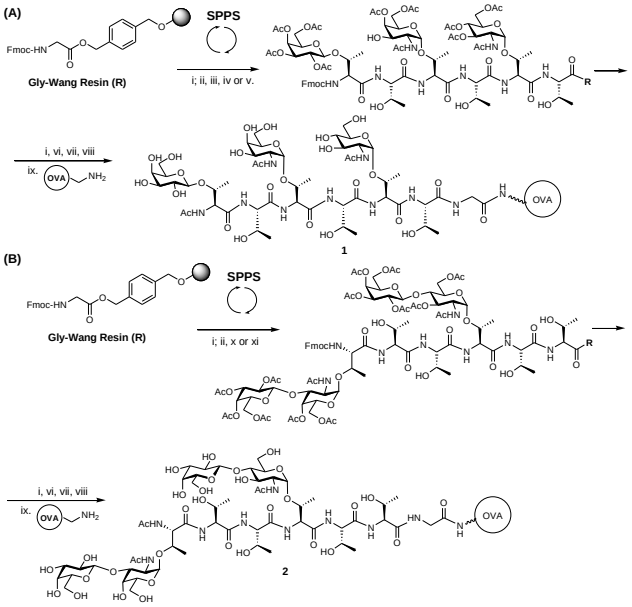
INTRODUCTION

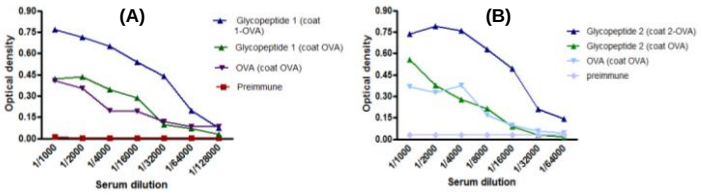
Mucins are highly *O*-glycosylated glycoproteins that are rich in serine (Ser) and threonine (Thr) repeating units, whose external oligosaccharides are linked to the protein via sugar units of α-*N*-acetylglucosamine (GlcNAc), in *T. cruzi*, or α-*N*-acetylgalactosamine (GalNAc), in mammals.[1] In *T. cruzi*, these structures help the parasite to interact with the infected cell, while in vertebrates the functions of mucins range from being protective barriers to providing lubrication for epithelial cells. In tumor-related mucins, however, altered glycosylation is a common feature, being verified the presence of mono- and disaccharide structures known as T_N and TF antigens, respectively.[1] Therefore, this work presents the synthesis and biological assays of the glycopeptides NHAc[βGal]-$(Thr)_2$-[αGalNAc]-$(Thr)_2$-[αGlcNAc] $(Thr)_2$Gly-OVA **1** and NHAc[βGal-αGalNAc]-$(Thr)_3$-[αLacNAc]-$(Thr)_3$-Gly-OVA **2** related to *T. cruzi* and tumor mucins, which can be useful for development of vaccines against infectious and tumoral processes.

RESULTS AND DISCUSSION

The synthesis of glycopeptides **1** and **2** in solid phase (SPPS-Gly-Wang resin) was performed by sequential coupling reactions of the amino acid FmocThrOH and the glycosyl-amino acids αGlcNAc-ThrOH **3**, αGalNAc-ThrOH (Tn) **4**, βGal-ThrOH **5**, αLacNAc-ThrOH **6** and βGal-αGalNAc-ThrOH (TF) **7**, in the presence of the coupling reactants PyBOP and HOBt, and the base DIPEA in DMF (Sheme 1),[2]. After cleavage from the resin with aqueous TFA, followed by *N*-acetylation (Py and Ac_2O) and *O*-deacetylation (NaOMe) reactions, glycopeptides **1** and **2** were purified by gel filtration chromatography, being obtained in the corresponding overall yields of 30% and 25%. Subsequently, glycopeptides **1** and **2** were conjugated to the carrier protein ovalbumin (OVA) and then submitted to immunization assays in murine models for evaluation of their capacity to stimulate an immune response against *T. cruzi* and breast tumor (MCF-7). For the detection of glycopeptides **1** and **2** specific antibodies, ELISA assays were performed, being verified high titers of 64000 and 32000 for glycopeptides **1** and **2**, respectively.



Scheme 1. Solid-phase synthesis of glycopeptides **1 (A)** and **2 (B)**. i. 20% piperidine-DMF; ii. FmocThrOH, PyBOP, HOBt, DIPEA, 3h; iii, iv or v. αGlcNAc-ThrOH **3**, αGalNAc-ThrOH **4** or βGal-ThrOH **5**, PyBOP, HOBt, DIPEA, 24h; vi. TFA 80%; vii. Py, Ac_2O; viii. NaOMe, MeOH; ix, EDCI, NHS, OVA, 72h; x or xi. αLacNAc-ThrOH **6** or βGal-αGalNAc-ThrOH **7**, PyBOP, HOBt, DIPEA, 72h.



Scheme 2. ELISA of the antisera induced by glycopeptides **1** (A) and **2** (B) conjugated to OVA.

CONCLUSION

Glycopeptides **1** and **2** were effectively obtained by SPPS, and according to the results obtained by ELISA, show potential for development of vaccines against *T. cruzi* and cancer.

ACKNOWLEDGEMENTS

CAPES

REFERENCES

[1] Brocke, C.; Kunz, H. *Bioorg. Med. Chem.* **2002**, *10*, 3085.
[2] Campo, V. L.; Carvalho, I.; Allman, S.; Davis, B. G.; Field, R. A. *Org. Biomol. Chem.* **2007**, *5*, 2645.