Chemical synthesis of glycopeptide related to *T. cruzi* and cancer mucins

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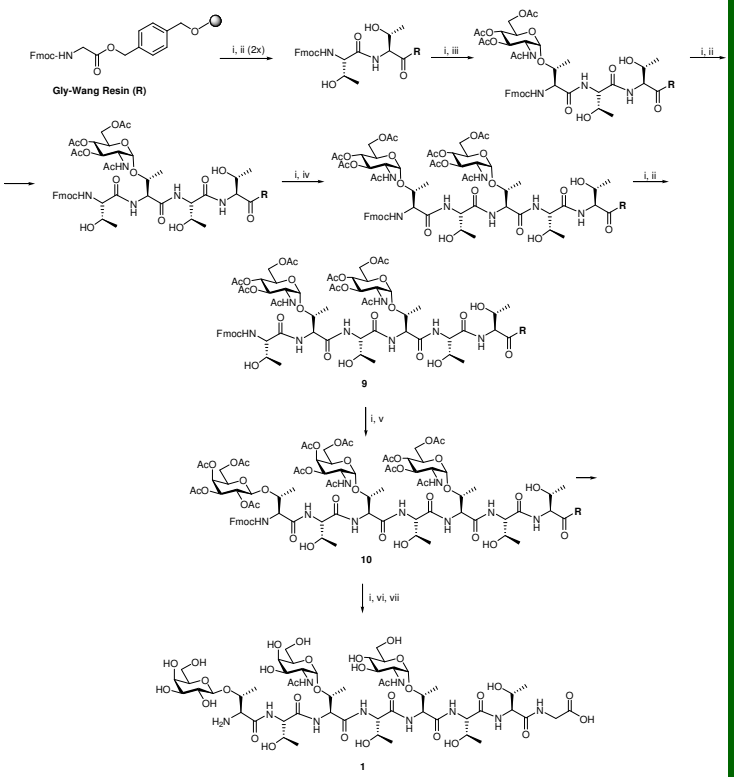
INTRODUCTION

Mucins are highly *O*-glycosylated (about 60% carbohydrate by weight), 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*-acetyl-glucosamine (GlcNAc), in *T. cruzi*, or α-*N*-acetylgalactosamine (GalNAc), in mammals.[1] In *T. cruzi*, these structures helps the parasite to interact with the infected host, while in vertebrates the functions of mucins range from being protective barriers to providing lubrication for epithelial cells. In cancer-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.[2] Therefore, this work presents the synthesis of the glycopeptide NH_2[βGal]-$(Thr)_2$-[αGalNAc]-$(Thr)_2$-[αGlcNAc]-$(Thr)_3$GlyOH **1**, related to *T. cruzi* and cancer mucins, which can be useful for development of new therapeutics, like vaccines, against infectious and tumoral processes.

RESULTS AND DISCUSSION

The synthesis of glycopeptide **1** involved the previous preparation of the glycosyl-amino acids αGlcNAc-ThrOH **2** (22%), αGalNAc-ThrOH **3** (54%), and βGal-ThrOH **4** (33%) by glycosylation reactions between the corresponding sugars αGlcNAcCl **5,** $\alpha GalN_3Cl$ **6** and αGalBr **7** with the amino acid FmocThrBn **8**, followed by reductive acetylation reaction (compound **6**) and removal of the benzyl ester groups by standard hydrogenation (10% Pd-C/H_2).[3] Subsequently, the synthesis of glycopeptide **1** in solid-phase was carried out in the presence of the coupling reactants benzotriazol-1-yloxytris-pyrrolidino phosphonium hexafluorophosphate (PyBOP) and 1-hydroxybenzotriazole (HOBt), and the base diisopropylethylamine (DIPEA) in DMF,[3] as outlined in Scheme 1. After cleavage from the resin with aqueous TFA and removal of the sugar acetate protecting groups with catalytic NaOMe in MeOH, the glycopeptide **1** was purified by reverse-phase HPLC, being obtained in 20% overall yield. The structure of compound **1** was confirmed by NMR spectroscopy, whereas ESI-MS analysis is being realized.



Scheme 1. Solid-phase synthesis of glycopeptide **1**. i. 20% piperidine-DMF ; ii. FmocThrOH, PyBOP, HOBt, DIPEA , 3h; iii, iv, and v. αGlcNAc-ThrOH **2**, αGalNAc-ThrOH **3** or βGal-ThrOH **4**, PyBOP, HOBt, DIPEA, 24 h; vi. TFA 80%, vii. NaOMe, MeOH.

CONCLUSION

The glycopeptide **1** was obtained in reasonable yield by combination of *in solution* and solid phase methods, and will be further attached to a carrier protein (BSA or KLH) in order to be evaluated as potential anti-parasite and anti-cancer vaccine.

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CAPES and FAPESP

REFERENCES

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