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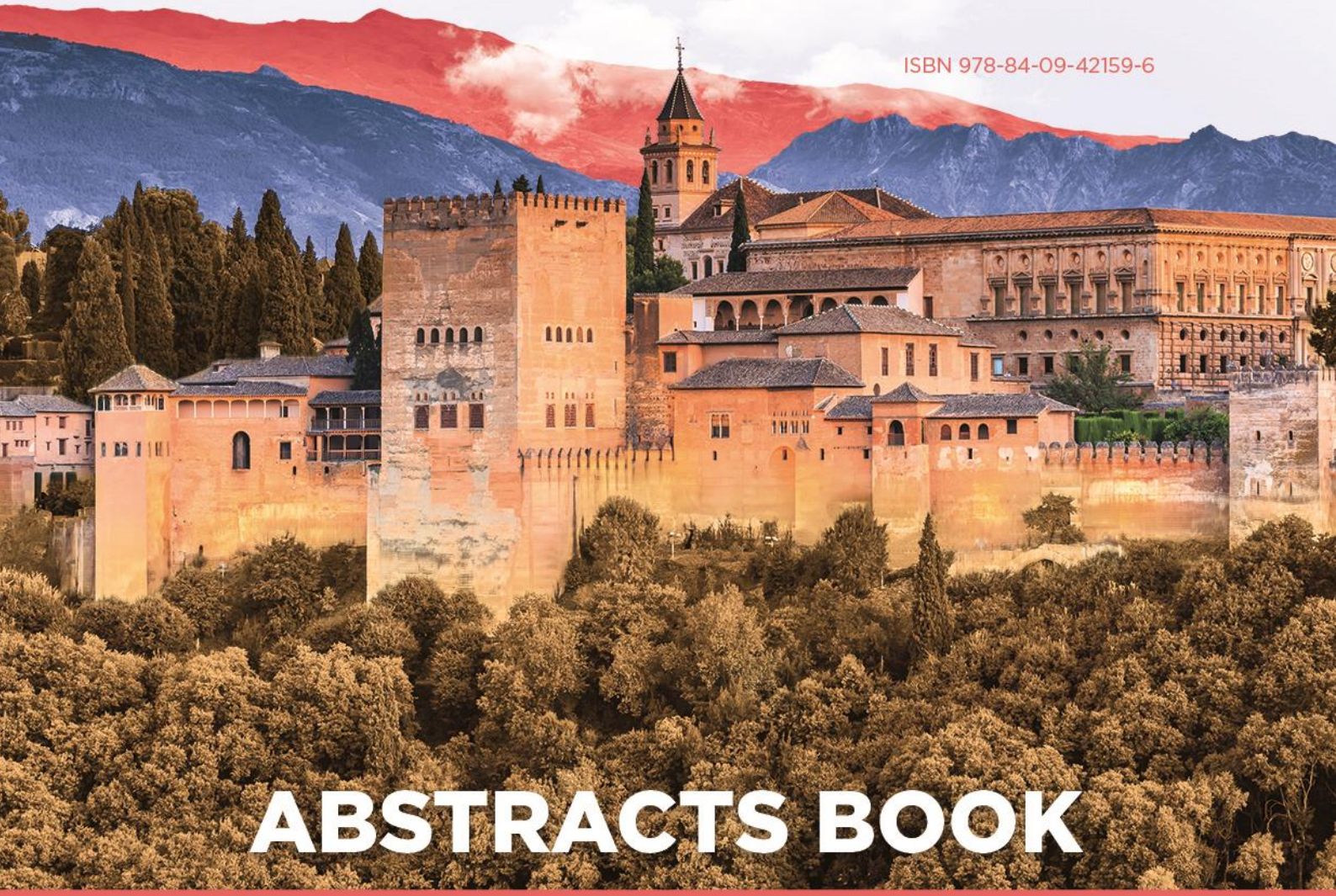

ABSTRACTS BOOK

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SYNTHESIS OF Tn ANTIGEN MIMETICS AND THEIR INCORPORATION INTO THE MUC1 GLYCOPROTEIN SEQUENCE

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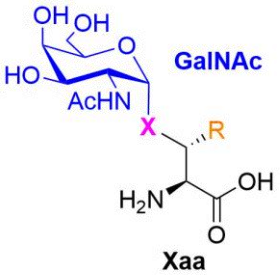
Cancer is a disease with one of the highest mortality rates in the first world countries and its treatment today is still invasive and often ineffective. To overcome these limitations, new treatment strategies are being developed, such as immunotherapy; the patient's immune system recognizes and eliminates tumor cells with high specificity and effectiveness. Moreover, the early detection of cancer is essential for effective treatment. However, the development of immunotherapy and these diagnostic tools requires the study of new biomarkers, as in the case of the MUC1 mucin. In cancer cells, unlike in healthy cells, alterations occur in its glycosylation, exposing different antigens that can trigger an immune response, such as the Tn antigen (GalNAc-α-*O*-Ser/Thr). Thus, the Tn antigen has been incorporated in peptides and used both to generate therapeutic vaccines against cancer and for its early detection. However, the therapeutic use of *O*-glycopeptides is sometimes limited since they are easily hydrolyzed in biological systems. Therefore, different mimetics of the Tn antigen are being developed, including those that involve changes in the *O*-glycosidic bond [1].

In this work, the oxygen atom of this bond has been replaced by a sulfur or selenium atom (Figure 1). These Tn antigen mimetics have been incorporated at position 16 of the MUC1 tandem repeat peptide sequence (HGVTSAPDTRPAPGST^{16}APPA) using SPPS (Solid-Phase Peptide Synthesis) methodology, replacing the natural Tn antigen [2]. A S_N2-type bimolecular nucleophilic substitution on the corresponding protected β-haloamino acid was the key step to obtain *S*- or *Se*-mimetics of the Tn antigen, using GalNAc-α-SH and a base or diselenide (GalNAc-α-Se)$_2$ and $NaBH_4$ as nucleophiles, respectively. Affinities (K_D) of all glycopeptides incorporating unnatural Tn mimetics to different anti-MUC1 antibodies were determined experimentally by ELISA tests and/or Surface Plasmon Resonance (SPR) experiments. The results obtained were explained in base of the conformational preferences deduced from NMR experiments combined to MD simulations. The best surrogates in terms of affinity will be the selected candidates to develop cancer therapy approaches in the future.



R = Me (threonine derivatives):
X = O, Xaa = **Thr** (threonine)
X = S, Xaa = ***S*Thr** (tiothreonine)
X = Se, Xaa = ***Se*Thr** (selenothreonine)

R = H (serine derivatives):
X = O, Xaa = **Ser** (serine)
X = S, Xaa = **Cys** (cysteine)
X = Se, Xaa = **Sec** (selenocysteine)

Figure 1: Structures of the different Tn antigens (naturals and unnatural mimetics) synthesized.

References

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