Amphipathic malonates as potential antiviral agents

Reinier Lemos,[1] **Luis Almagro,** [1] **Blanca I. Tolón,**[2] **Margarita Suárez** [1]

[1]Laboratorio de Síntesis Orgánica, Facultad de Química, Universidad de la Habana, Cuba e-mail: reylemos81@gmail.com

[2]Instituto Finlay de Vacunas, La Habana, Cuba

INTRODUCTION

Human immunodeficiency virus-1 (HIV-1) infection continues to be a major medical threat to humans. In anti-HIV therapies, HIV-1 protease (HIVP) is still one of the most important targets. It has been reported that sugar hybrids have the ability to interact with the HIVP. [1]

In this work we performed a study of the interactions with the active site of HIVP of hybrids which contain two sugar units across a malonate spacer (type I) through Molecular Docking simulations. Due to the ability of steroids to increase the biocompatibility of the hybrids,[2] was also performed the docking studies of carbohydrate-steroid conjugates (type II).

Herein, in the best of our knowledge, we report for first time the synthesis of two novel hybrids sugar-steroid conjugates through several steps that involves nucleophilic substitution reactions.

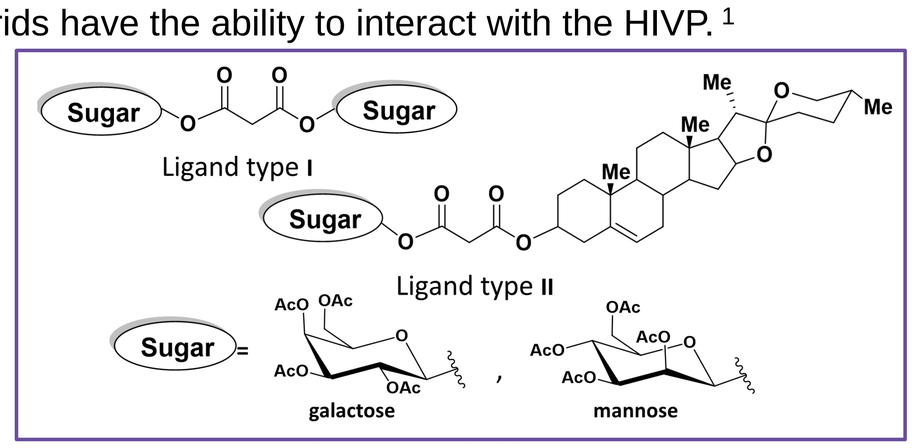


Figure 1. Hybrid structures

RESULTS

In order to analyze the binding interactions between the ligands and HIVP was employed the Autodock Vina 1.1.2 program. Each docking simulation produced a total of 20 different docked conformations, which were then grouped based upon Root Mean Square Deviation (RMSD) of the different bound poses. The binding free energy of every cluster was calculated as the mean binding free energy (MBFE) of all the conformations present in the same cluster. The group with the highest number of conformers and the lowest MBFE was selected as the representative binding mode for each complex.

- **Receptor:** Protease HIV-1 (PDB code: 5ULT)
- **Best two solutions**
- **Energy range:** -8 to -10 kcal/mol
- **Utmost solutions:** number of times repeated

All the studied derivatives presented affinity for the HIVP. However, the ligand type **II** occluded the active site of the protease with a major affinity than ligand type. The results suggested that type **II** hybrids could be used as potential inhibitors of HIVP.

Table 1. Binding free energies

Group		1		2		3		4	
Ligand		MBFE	C	MBFE	C	MBFE	C	MBFE	C
galactose	I	-8.50	8	-8.32	9	-	-	-	-
	II	-10.70	9	-10.42	6	-10.53	4	-	-
mannose	I	-8.43	8	-8.43	4	-8.30	3	-8.43	3
	II	-10.60	6	-10.48	6	-10.10	3	-10.18	4

* C represents the amount of conformations within a cluster

** MBFE is in kcal/mol

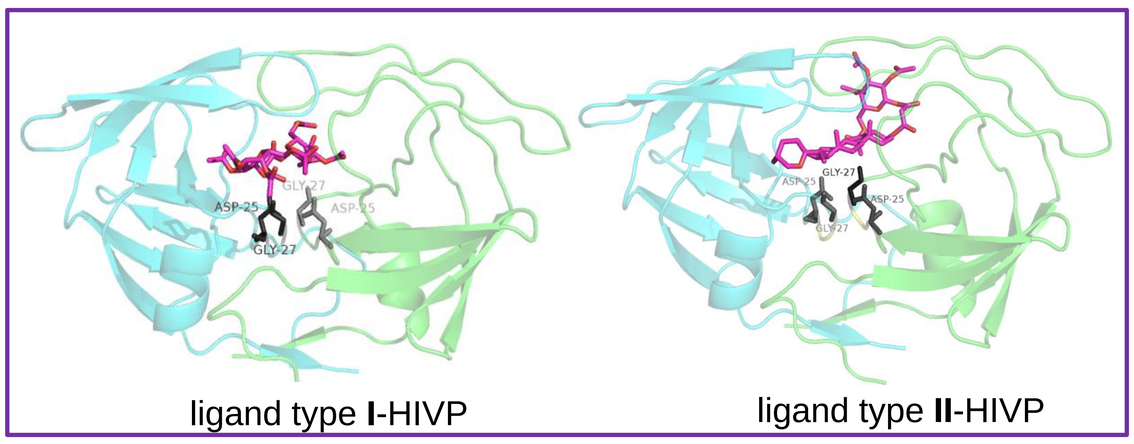
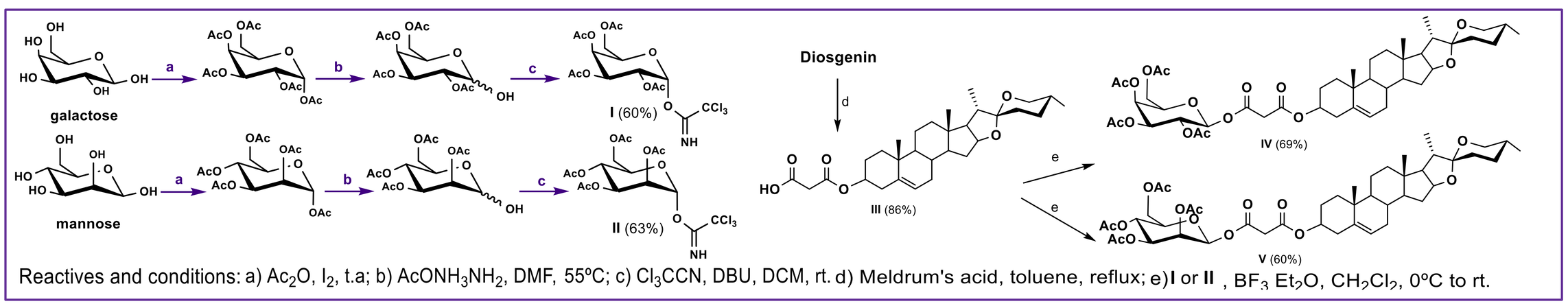


Figure 2. Representatives ligand-HIVP complexes

The synthetic strategy used consists of two steps (**Scheme 1**). Initially, the monosaccharides are selectively protected using standard methodologies and the chemical activation of the anomeric hydroxyl groups. Then, the chemical transformation of the hydroxyl group of diosgenin through an acyl nucleophilic substitution using Meldrum's acid is obtained to a steroidal acid (**III**). Finally, the glycosylation reaction between the corresponding trichloroacetomidates **I** or **II** and the steroidal acid steroidal acid **III** produce a corresponding hybrid carbohydrate-steroid **IV** and **V**.



Scheme 1. Synthetic strategy of amphiphatic malonates.

CONCLUSIONS

We have carried out the synthesis of a new type amphiphatic malonates bearing sugars and steroids wings. The 3-oxopropanoic acids were obtained through the reaction between the Meldrum′s acid and diosgenin. The galactose and mannose are functionalized with the trichloroacetimidate group allowed to obtain monosteroidal malonates with monosaccharide units. Moreover, *In silico* Molecular Docking methods allowed to determine that the potential inhibitors contain a steroidal frame and a monosaccharide.

References

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2. L. Almagro, D. Hernandez-Garcia, O. Ortiz, D. Alonso, A. Ruiz, J. Coro, M-A Herranz, D. Molero, R. Martinez-Alvarez, M. Suarez, N. Martin, *Eur. J. Org. Chem*. **2018**.