TRITERPENOID SAPONINS BEARING LEWIS-X AND QS-21 EPITOPES: ANTIVIRAL, TOXICOLOGICAL, AND IMMUNOLOGICAL EVALUATION

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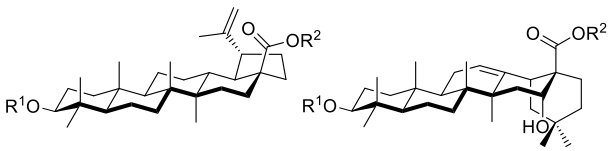
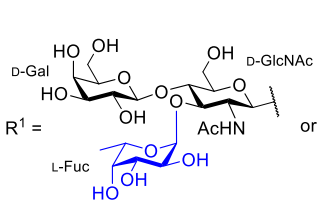
The syntheses of betulinic acid and echinocystic acid saponins bearing either a Lewis-X trisaccharide [1] or the minimal QS-21 trisaccharide epitopes required for adjuvant activity [2] are described (Figure 1). These chimeric triterpenoid saponins were synthesized using convergent, stereoselective, and efficient glycosylation strategies involving various glycosyl donors. We demonstrate that Lewis-X-containing triterpenoid saponins are among the most potent monovalent inhibitors reported to date of dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) and liver/lymph node-specific intercellular adhesion molecule-3-grabbing integrin (L-SIGN)-mediated transfer of human immunodeficiency virus 1 (HIV-1) infection to CD4-positive cells, with IC_{50} values in the low micromolar range (21-50 μM). These triterpenoid saponins, along with their rhamnose-modified analogs [3], were evaluated *in vivo* for their toxicological and immunological potential in both C57BL/6 and hDC-SIGN transgenic mice. Our findings reveal that, while the synthetic saponins exhibit low toxicity, replacing echinocystic acid with betulinic acid negatively impacts their immunogenicity profiles. This work provides a valuable foundation for the development of saponin-based antiviral agents and highlights the potential of these glycosylation strategies for synthesizing complex and unnatural glycoconjugates for therapeutic and prophylactic applications.

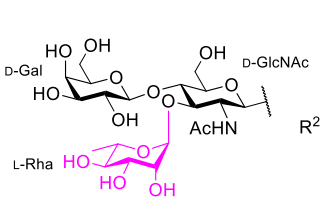


betulinic acid: $R^1 = R^2 = H$
R^1 = Lewis-X; R^2 = H
R^1 = RhaLewis-X; R^2 = H
R^1 = H; R^2 = QS-21 epitope

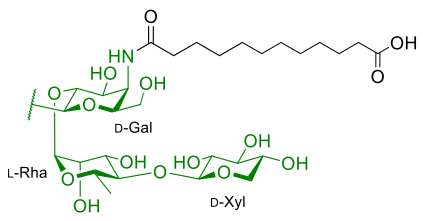
echinocystic acid: $R^1 = R^2 = H$
R^1 = Lewis-X; R^2 = H
R^1 = RhaLewis-X; R^2 = H
R^1 = H; R^2 = QS-21 epitope



Lewis-X
(*ref. 1*)



RhaLewis-X
(*ref. 2*)



QS-21 epitope
(*ref. 3*)

References:
1. O. J. Gamboa Marin, K. Ng, N. Verma, A. G. F. Yapi, R. Pantophlet, C. Gauthier, *Chem. Eur. J.* **2025**, submitted.
2. O. J. Gamboa Marin, N. Verma, M. Cloutier, C. Gauthier, *Eur. J. Org. Chem.* **2025**, submitted.
3. O. J. Gamboa Marin, Y. Adda-Bouchard, B. Sylla, N. Verma, T. Charpentier, A. Pichette, A. Lamarre, C. Gauthier, *Chem. Eur. J.* **2025**, submitted.