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Design, Synthesis and characterization of synthetic and natural derived TLR4 antagonists.

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TLR4 is an inflammatory receptor belonging to the class of Pattern Recognition Receptor (PRRs), whose function is to sense Pathogens or Damages Associated Molecular Patterns (PAMPs, DAMPs) and start the innate immune response.[1] The natural ligand of TLR4 is Lipopolysaccharide (LPS), an essential component of Gram-negative bacteria outer membrane.[1,2] The minimal portion of LPS required for immunogenicity is a glycolipid called Lipid A.[2] Through molecular simplification starting from Lipid A, our group developed two new compounds which showed promising TLR4 antagonism: FP7 (Fig. 1, **a**) and FP12 (Fig.1, **b**) (HEK-Blue hTLR4 IC_{50} = 2.0 and 0.63 µM; RAW-Blue TLR4 IC_{50} = 7.7 and 1.7 µM).[3,4]

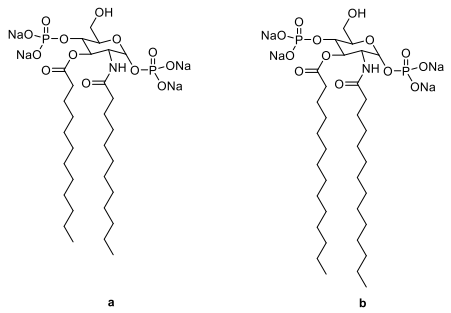

Figure 1: TLR4 antagonists developed by our group.

The aim of this work is to produce novel TLR4 antagonists. This goal will be achieved modifying the substituent on the anomeric position of FP7 and FP12 to increase stability for further functionalization of the C6 position. Furthermore, starting form promising natural compounds active as TLR4 antagonists, computer assisted docking will be applied to select new scaffolds to be synthetized and chemically modified.

References:

[1] Ruslan Medzhitov. Toll-like receptors and innate immunity. *NATURE REVIEWS* (2001).
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[3] Peri, F. & Piazza, M. Therapeutic targeting of innate immunity with Toll-like receptor 4 (TLR4) antagonists. *Biotechnology Advances* vol. 30 251–260 Preprint at https://doi.org/10.1016/j.biotechadv.2011.05.014 (2012).
[4] Facchini, F. A. *et al.* Structure-activity relationship in monosaccharide-based toll-like receptor 4 (TLR4) antagonists. *J Med Chem* **61**, 2895–2909 (2018).