NEW SMALL MOLECULES AS TLR4 MODULATORS: SYNTHESIS AND BIOLOGICAL CHARACTERIZATION

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Innate Immunity is a multicellular organism first defense against internal of external threats. It acts through inflammation, triggered by the recognition of specific Pathogen or Damage Associated Molecular Patterns (PAMPs or DAMPs) by specific protein receptors. Toll-Like Receptor 4 (TLR4) is one of the most important PAMPs receptors, as its role is to recognize bacterial presence by recognizing Lipopolisaccharide (LPS).[1]
TLR4 modulation is very attractive, as an inhibition can alleviate an excessive inflammation (which can lead to sepsis and various auto-immune diseases), while a mild, nontoxic activation can lead to vaccine adjuvants identification or cancer immunotherapy drugs.[2,3]
Thus, our aim is to chemically synthetize small molecules, simplifying LPS molecular formula but retaining the ability to bind TLR4. Great effort has been spent in designing a synthetic procedure to easily obtain this kind of compounds, focusing on both creating a branched synthesis -giving versatile intermediates- and reducing the number of steps required, in order to efficiently scale the synthesis up for industrial purposes.

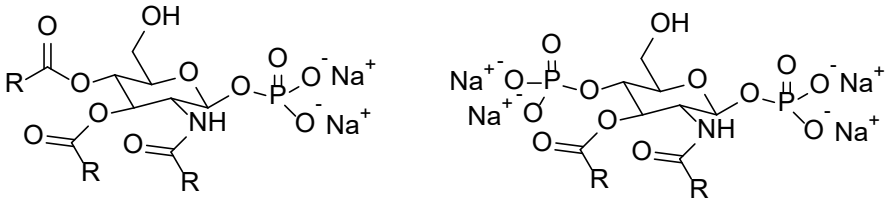

Figure 1: (A) general structure of agonist compound and (B) general structure of antagonist

1. Medzhitov, R. Toll-Like Receptors and Innate Immunity. *Nat. Rev. Immunol.* **1**, 135–145 (2001).
2. Leon, C. G., Tory, R., Jia, J., Sivak, O. & Wasan, K. M. Discovery and development of toll-like receptor 4 (TLR4) antagonists: A new paradigm for treating sepsis and other diseases. *Pharm. Res.* **25**, 1751–1761 (2008).
3. Casella, C. R. & Mitchell, T. C. Putting endotoxin to work for us: Monophosphoryl lipid a as a safe and effective vaccine adjuvant. *Cell. Mol. Life Sci.* **65**, 3231–3240 (2008).