Synthesis Optimization and Biological Characterization of New Toll-Like Receptor 4 (TLR4) Modulators

Alessio Romerio[1], Ana R. Franco[1], Nicolé Gotri[1], Valentina Artusa[1], Simona D'amato[1], Federico Lami[1], Francesco Peri[1]

E-mail: a.romerio1@campus.unimib.it

[1] Università di Milano-Bicocca, Department of Biotechnology and Bioscience, Milano

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Abstract:

Innate Immunity is the first defense line in multicellular organisms 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 pattern-recognition receptors (PRRs). Toll-Like Receptor 4 (TLR4) is one of the most important PRRs, and it responds to gram-negative bacteria lipopolysaccharide (LPS).[1]

TLR4 modulation is emerging as an important therapeutic approach in several clinical settings: TLR4 inhibition has a potent anti-inflammatory effect; on the other hand, TLR4 mild activation can be used to stimulate immunity in vaccine adjuvants or to develop cancer immunotherapeutic drugs.[2,3]

We present rationally designed lipid A analogues based on a monosaccharide structure that are active in binding MD-2/TLR4, thus activating or inhibiting LPS/TLR4 or DAMP/TLR4 signalling. We also present synthesis optimization of TLR4 modulators, with the aim of producing versatile synthetic intermediates and reducing the number of synthetic steps to efficiently scale the synthesis up for industrial purposes.