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Activity-guided Development of Potent and Selective Toll-like Receptor 9 Antagonists

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ABSTRACT

TLR9 is one of the major innate immune receptors expressed in the endosomes of pDCs and B cells in humans. Aberrant TLR9 activation is implicated in several autoimmune and metabolic disorders as well as in sepsis, making this receptor an important therapeutic target, though specific TLR9 antagonists are yet to be available for clinical use. Here we elucidate the importance of specific physiochemical properties through substitution patterns in quinazoline scaffold to achieve potent hTLR9 inhibition at < 50 nM as well as > 600 fold selectivity against hTLR7, another closely related TLR that shares downstream signaling with TLR9 but plays distinct roles in physiology and pathology. Assays were performed using hPBMC and reporter cell lines. Favorable in vitro ADME profile, pharmacokinetics as well as validation in a clinically relevant in vivo TLR9-inhibition efficacy model in mice establish these novel TLR9-antagonists as candidate therapeutic agents in relevant clinical contexts.

1. Introduction

Toll-like receptors (TLRs) are germline-encoded pattern recognition receptors critical for innate immunity in the body [1]. These innate receptors are involved in recognizing conserved pathogen-associated molecular patterns (PAMPs) and driving innate immune response in health and disease [2]. The group of TLRs (TLR7, TLR8 and TLR9) that are expressed in the endolysosomal compartment of immune cells are specialized for detecting nucleic acids of non-self origin which are acquired from phagocytosed microbes on their entry into the acidic (pH < 6.5) endolysosomal compartments [1,3,4].