Design and Synthesis of Pyrazole-based Inhibitors of Toll-like Receptor Signaling

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Activation of the Toll-like receptor (TLR) signaling pathway is an important step in initiating an immune response to pathogens. However, increased TLR-activation by lipopolysaccharides or peptidoglycans from the pathogen can lead to amplified, pathological inflammatory response resulting in host damage. Inhibition of TLR signaling pathways may provide a novel mechanism for moderating the immune response to these infections, diseases, and thus, there remains an unmet medical need for small molecule TLR signaling inhibitors. Using a high-throughput screening assay of a bioactive compound library, we have identified methyl-piperidino-pyrazole (MPP), a known estrogen receptor α antagonist, as a TLR signaling inhibitor. Based on these results, we have initiated studies on the design and synthesis of novel MPP-based TLR inhibitors. Our approach comprises modifications in the heterocyclic ring, installation of basic side chains, with the goals of enhancing their potency in TLR inhibition and minimizing their toxicity and estrogenic activity.

Rapid Injection NMR Reveals Pre-Transmetalation Intermediates in the Suzuki-Miyaura Reaction

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Despite numerous mechanistic studies on the Suzuki-Miyaura reaction, the observation of pre-transmetalation intermediates (Pd-O-B) has remained elusive. Under normal reaction conditions, the transmetalation step occurs rapidly, transferring the aryl group from boron to palladium. The use of rapid injection NMR (RI-NMR) has made it possible to prepare and characterize the proposed (Pd-O-B) intermediate. The ability to generate a pre-transmetalation species has provided a unique opportunity to interrogate aspects of this critical transmetalation step, specifically the formation of pre-reductive elimination intermediates ($L_2PdAryl_2$). The study of these reactive intermediates in the Suzuki-Miyaura reaction has led to new insights into the transmetalation event and the role of the phosphine ligands in this step.