

Selection, Preparation, and Evaluation of Inhibitors of Toll-Like Receptor 4

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ABSTRACT

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Selection, Preparation, and Evaluation of Inhibitors of Toll-Like Receptor 4

Thesis directed by Associate Professor Hang (Hubert) Yin

Toll-like receptor-4 (TLR4), a membrane spanning receptor that functions in complex with its accessory protein MD-2 is an intriguing target for therapeutic development. Here in we report the identification of a novel TLR4 inhibitor, T5342126, and the development of a robust synthesis using an unprecedented Mannich-type reaction to functionalize a pyrazole ring. We went on to make a number of analogs of T5342126 and tested them both *in silico* and *in vitro*. *In silico* and cellular assay results demonstrated that T5342126 and most analogs block TLR4 activation to varying degrees.

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