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

By

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The final copy of this thesis has been examined by the signatories, and we find that both content and form meet the acceptable presentation standards of scholarly work in the above mentioned discipline.

ABSTRACT

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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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