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Extended Abstract

Peptidomimetic 1-Benzyl-5-methyl-4-(*n*-octylamino)pyrimidin-2(1*H*)-one Showed Cardioprotection Effect in a Myocardial Ischemia (MI) Mouse Model †

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† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 14 August 2019

Keywords: peptidomimetics; cardioprotection; in silico modeling

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TLR4, a member of the toll-like receptors (TLRs) family, serves as a pattern recognition receptor in the innate immune response to different microbial pathogens. TLR4 also might be activated by endogenous factors produced by different stress stimuli or cell damage and regulates the inflammatory reaction to ischemic injury in the heart tissues. TRIF-related adaptor molecule (TRAM) serves as an adapter that recruits the Toll/interleukin 1 receptor (TIR) domain-containing adapter-inducing IFN-β (TRIF) to activate TLR4, following TRIF-dependent cytokine gene transcription. Based on a known TRAM-derived decoy, a nine-amino acid peptide [1], which corresponds to sequences from the TIR domain, the minimal effective sequence resultant in tetrapeptide was evaluated in cardiomyocytes. Then, a simplified peptidomimetic framework was designed, and ten peptidomimetics of this type were synthesized. One of them, namely 1-benzyl-5-methyl-4-(*n*-octylamino)pyrimidin-2(1*H*)-one (**1**), exhibited high potency and efficacy in vitro. Obtained in vitro data and in silico analysis provided evidences for a direct interaction of **1** with the TLR4 complex. Being administered in mice with MI, peptidomimetic **1** was able to block the pathophysiological manifestation of MI, resulting in normalization of CK, LDH, and troponin blood levels, restoration of the concomitant tissue damage, and a 100% survival rate. Inhibition of TLR4-mediated inflammation in post-ischemic myocardium might be used as a therapeutic approach for developing novel cardioprotective drugs [2].

References

1. Piao, W.; Vogel, S.N.; Toshchakov, V.Y. Inhibition of TLR4 signaling by TRAM-derived decoy peptides in vitro and in vivo. *J. Immunol.* **2013**, *190*, 2263–2272.

2. Trifonov, E.; Nudelman, V.; Zhenin, M.; Matsree, E.; Afri, M.; Schmerling, B.; Cohen, G.; Jozwiak, K.; Weitman, M.; Korshin, E.; et al. A peptidomimetic: 1-benzyl-5-methyl-4-(octylamino)pyrimidin-2(1H)-one designed based on the structure of in TLR4 related TRIF-related adaptor molecule (TRAM)—Decoy peptide, showed cardio protective effect in myocardial ischemia mouse model. *J. Med. Chem*. **2018**, *61*, 11309–11326.