Effects of 3-(2-Hydroxyphenyl)-1-(5-methyl-furan-2-y-l) propenone (HMP) upon signalling pathways of lipopolysaccharide-induced iNOS synthesis in RAW 264.7 cells.

ABSTRACT

NO synthesis in the RAW 264.7 murine macrophage line. The inhibition of NO synthesis was related to inhibition of p38 phosphorylation and kinase activity that led to significant inhibition of phosphorylation of ATF-2. This effect in turn caused inhibition of AP-1-DNA binding which partially explains the inhibitory effect upon the synthesis of iNOS. HMP had no effect upon phosphorylation of JNK, ERK1/2 and STAT-1. Kinase activity of JNK and ERK1/2 was also not affected by HMP as determined by levels of phosphorylated c-jun and phosphorylated elk-1. Furthermore HMP failed to block phosphorylation of IκBα, and subsequent nuclear translocation and DNA-binding activity of p65 NF-κB in IFN-γ/LPS-induced RAW 264.7 cells. Molecular docking experiments confirmed that HMP fits well in the highly conserved hydrophobic pocket of p38 MAP kinase. We conclude that the synthetic HMP is a chalcone analogue that selectively inhibits the p38/ATF-2 and AP-1 signaling pathways in the NO synthesis by the macrophage RAW 264.7.

Keyword: Hydroxypropenone; Nitric oxide; iNOS; MAPK; NF-κB.