Suppression of PGE2 production via disruption of MAPK phosphorylation by unsymmetrical dicarbonyl curcumin derivatives

ABSTRACT

Curcumin is an important molecule found in turmeric plants and has been reported to exhibit some profound anti-inflammatory activities by interacting with several important molecular targets found in the mitogen-activated protein kinase and NF-κβ pathways. As part of our continuing effort to search for new anti-inflammatory agents with better in vitro and in vivo efficacies, we have synthesized a series of new unsymmetrical dicarbonyl curcumin derivatives and tested their effects on prostaglandin E2 secretion level in interferon-γ/lipopolysaccharide-activated macrophage cells. Among those, five compounds exhibited remarkable suppression on prostaglandin E2 production with IC50 values ranging from 0.87 to 18.41 μM. The most potent compound 17f was found to down-regulate the expression of cyclooxygenase-2 mRNA suggesting that this series of compounds could possibly target the mitogen-activated protein kinase signal transduction pathway. Whilst the compound did not affect the expression of the conventional mitogen-activated protein kinases, the results suggest that it could disrupt the phosphorylation and activation of the proteins particularly the c-Jun N-terminal kinases. Finally, the binding interactions were examined using the molecular docking and dynamics simulation approaches.

Keyword: Prostaglandin E2; COX-2 mRNA expression; MAPK phosphorylation; Molecular; Dynamic simulation; Unsymmetrical dicarbonyl curcumin derivatives