Synthesis of unsymmetrical monocarbonyl curcumin analogues with potent inhibition on prostaglandin E_2 production in LPS-induced murine and human macrophages cell lines

ABSTRACT

The syntheses and bioactivities of symmetrical curcumin and its analogues have been the subject of interest by many medicinal chemists and pharmacologists over the years. To improve our understanding, we have synthesized a series of unsymmetrical monocarbonyl curcumin analogues and evaluated their effects on prostaglandin E_2 production in lipopolysaccharide-induced RAW264.7 and U937 cells. Initially, compounds **8b** and **8c** exhibited strong inhibition on the production of PGE_2 in both LPS-stimulated RAW264.7 (**8b**, IC_{50} = 12.01 μM and **8c**, IC_{50} = 4.86 μM) and U937 (**8b**, IC_{50} = 3.44 μM and **8c**, IC_{50} = 1.65 μM) cells. Placing vanillin at position Ar_2 further improved the potency when both compounds **15a** and **15b** significantly lowered the PGE_2 secretion level (RAW264.7: **15a**, IC_{50} = 0.78 μM and **15b**, IC_{50} = 1.9 μM while U937: **15a**, IC_{50} = 0.95 μM and **15b**, IC_{50} = 0.92 μM). Further experiment showed that compounds **8b**, **8c**, **15a** and **15b** did not target the activity of downstream inflammatory COX-2 mediator. Finally, docking simulation on protein targets COX-2, IKK-β, ERK, JNK2, p38α and p38β were performed using the conformation of **15a** determined by single-crystal XRD.

Keyword: Unsymmetrical curcumin analogues; Prostaglandin E_2; RAW264.7; U937; Single-crystal XRD; Cyclooxygenase-2

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