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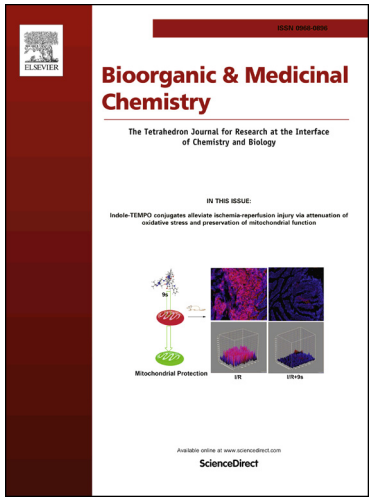

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Synthesis of benzoxazole derivatives as interleukin-6 antagonists

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Abstract

A growing number of studies have demonstrated that interleukin (IL)-6 plays pathological roles in the development of chronic inflammatory disease and autoimmune disease by activating innate immune cells and by stimulating adaptive inflammatory T cells. So, suppression of IL-6 function may be beneficial for prevention and treatment of chronic inflammatory disease. This study reports that a series of synthetic derivatives of benzoxazole have suppressive effects on IL-6-mediated signaling. Among 16 synthetic derivatives of benzoxazole, the compounds **4**, **6**, **11**, **15**, **17**, and **19** showed a strong suppressive activity against IL-6-induced phosphorylation of signal transducer and activator of transcription (STAT) 3 by 80-90%. While the cell viability was strongly decreased by compounds **11**, **17**, **19**, the compounds **4**, **6**, and **15** revealed less cytotoxicity. We then examined the effects of the compounds on inflammatory cytokine production by CD4+ T cells. CD4+ T cells were induced to differentiate into interferon (IFN)-γ-, IL-17-, or IL-4-producing effector T cells in the presence of either the compound **4** or the compound **7**. While the inactive compound **7** had no significant effect on the cytokine production by effector T cells, the active compound **4** strongly suppressed the production of inflammatory cytokines IFN-γ and IL-17, and also inhibited allergic inflammatory cytokines IL-4, IL-5, and IL-13 produced by effector Th2 cells. These results suggest that a benzoxazole derivative, compound **4** effectively suppresses IL-6-STAT3 signaling and inflammatory cytokine production by T cells and provides a beneficial effect for treating chronic inflammatory and autoimmune disease.