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Synthesis, in vitro anti-inflammatory and cytotoxic evaluation, and mechanism of action studies of 1-benzoyl-β-carboline and 1-benzoyl-3-carboxy-β-carboline derivatives

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ABSTRACT

In the present study, various 1-substituted and 1,3-disubstituted β-carboline derivatives were synthesized by a modified single-step Pictet–Spengler reaction. The compounds were examined for cytotoxicity and anti-inflammatory activity, as measured by the inhibition of prostaglandin E_2 (PGE_2) production and nitric oxide (NO) production. While only two compounds (**28** and **31**) showed marginal cytotoxicity against four human cancer cell lines, most of the tested compounds exhibited potent inhibitory activity of both NO and PGE_2 production. Moreover, compounds **6** and **16** significantly reduced the expression of inducible nitric oxide synthase (*i*NOS) and cyclooxygenase 2 (COX2), suggesting that β-carboline analogs can inhibit NO and PGE_2 production at the translational level. In addition, several of the β-carboline derivatives (**1**, **2**, **4–8**, **11**, **13**, **22**, **25**, **27**, **31**, and **41–43**) displayed significant inhibitory activity of superoxide anion (O_2^-) generation or elastase release compared to the reference compound, with **6** being the most potent. *N*-Formyl-L-methionyl-phenylalanine (FMLP)-induced phosphorylation of *c-Jun N*-terminal kinase (JNK) and protein kinase B (AKT) were also inhibited by **6**, suggesting that it suppresses human neutrophil functions by inhibiting the activation of JNK and AKT signaling pathways. Therefore, the synthetic 1-benzoyl-3-carboxy β-carboline analogs may have great potential to be developed as anti-inflammatory agents.

1. Introduction

Sustained nitric oxide (NO) release by inducible nitric oxide synthase (*i*NOS) and prostaglandin E_2 (PGE_2) production by cyclooxygenase 2 (COX2) have been implicated as mediators of inflammation and are induced by bacterial lipopolysaccharide (LPS) or immunological stimuli.[1,2] It has been reported that excess production of NO and PGE_2 by macrophages and other cells exposed to endotoxins may contribute to septic shock, cerebral injury, myocardical ischemia, diabetes, arteriosclerosis, and other local or systemic inflammatory disorders.[2,3] Thus, inhibition of NO synthesis and PGE_2 production stands as an important therapeutic goal. On the other hand, overwhelming activation of neutrophils is known to play important roles in the pathogenesis of various diseases, such as rheumatoid arthritis, ischemia, reperfusion injury, chronic obstructive pulmonary disease, and asthma.[4,5] In response to diverse stimuli, activated neutrophils secrete a series of cytotoxins, such as superoxide anion (O_2^-), a precursor of other reactive oxygen species, and elastase, a granule protease. Therefore, it is crucial to retain O_2^- production and elastase release in physiological conditions, while potentiating these functions in infected tissues and organs. Currently, only a few agents are available in clinical practice that can directly modulate neutrophil proinflammatory responses.

Natural and synthetic products containing a β-carboline pharmacophore exhibit a wide range of important bioactivities, particularly on the central nervous system.[6,7] Due to their unique rigid heterocyclic skeleton, many β-carbolines bind with high affinity to benzodiazepine,[8] serotonin,[6] and dopamine[9] receptor sites and inhibit monoamine oxidase A.[10] The reported biological effects of this class of compounds include sedative,[11] antithrombotic,[12] anti-HIV,[13] and DNA-targeting properties,[14] as well as suppression of CDK,[15,16] topoisomerase,[17] and IκK.[18] For example, flazin[19] and

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