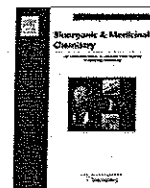




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Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

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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ARTICLE INFO

Article history:

Received 22 November 2010

Revised 6 January 2011

Accepted 16 January 2011

Available online 22 January 2011

Keywords:

β -Carboline derivatives

Anti-inflammatory activity

Nitric oxide production inhibition

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 E₂ (PGE₂) 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 PGE₂ production. Moreover, compounds **6** and **16** significantly reduced the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2), suggesting that β -carboline analogs can inhibit NO and PGE₂ 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 (O₂⁻) 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.

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1. Introduction

Sustained nitric oxide (NO) release by inducible nitric oxide synthase (iNOS) and prostaglandin E₂ (PGE₂) 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 PGE₂ by macrophages and other cells exposed to endotoxins may contribute to septic shock, cerebral injury, myocardial ischemia, diabetes, arteriosclerosis, and other local or systemic inflammatory disorders.^{2,3} Thus, inhibition of NO synthesis and PGE₂ 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 dis-

eases, 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 (O₂⁻), a precursor of other reactive oxygen species, and elastase, a granule protease. Therefore, it is crucial to retain O₂⁻ 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 dopamine⁹ 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 I κ B.¹⁸ For example, flazin¹⁹ and

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