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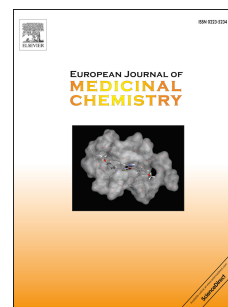
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Influence of the C-5 substitution in polysubstituted pyrimidines on inhibition of prostaglandin E₂ production

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Abstract: As a part of a broader structure-activity relationship study of substituted 2-aminopyrimidines the influence of the C-5 substitution on inhibition of prostaglandin E₂ (PGE₂) production was studied. Thirty compounds were prepared starting from the corresponding 2-amino-4,6-dichloropyrimidines using Suzuki cross-coupling. It was shown previously that 2-amino-4,6-dichloropyrimidines with smaller C-5 substituent (hydrogen and methyl) were devoid of significant activity, while 5-butyl derivatives exhibited prominent potency. In this study, on the other hand, both monoaryl- and bisarylpyrimidines were potent inhibitors of PGE₂ production regardless the length of the C-5 substituent (hydrogen, methyl, n-butyl). Moreover, the shorter the C-5 substituent the higher potency to inhibit PGE₂ production was observed. 2-Amino-4,6-diphenylpyrimidine was the best inhibitor of PGE₂ production with IC₅₀ = 3 nM and no cytotoxicity. The most potent inhibitors deserve further preclinical evaluation as potential anti-inflammatory agents.

Keywords: pyrimidines; Suzuki-Miyaura reaction; prostaglandin E₂; inhibitor

1. Introduction

Prostaglandins (PGs) are lipid mediators and end products of fatty acid metabolism, that are produced from the key precursor, arachidonic acid (AA), via the cyclooxygenase (COX)

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