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Viktor Kolman, Filip Kalčic, Petr Jansa, Zdeněk Zídek, Zlatko Janeba

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Influence of the C-5 substitution in polysubstituted pyrimidines on inhibition of prostaglandin E_2 production

Viktor Kolman[a], Filip Kalčic[a], Petr Jansa,[a,‡] Zdeněk Zídek[b,*], Zlatko Janeba[a,*]

[a] *Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic*

[b] *Institute of Experimental Medicine of the Czech Academy of Sciences, Vídeňská 1083, 142 20, Prague 4, Czech Republic*

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 E_2 (PGE_2) 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 PGE_2 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 PGE_2 production was observed. 2-Amino-4,6-diphenylpyrimidine was the best inhibitor of PGE_2 production with IC_{50} = 3 nM and no cytotoxicity. The most potent inhibitors deserve further preclinical evaluation as potential anti-inflammatory agents.

Keywords: pyrimidines; Suzuki-Miyaura reaction; prostaglandin E_2; 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)