NOVEL 4-AMINOPYRIMIDINE DERIVATIVES AS SELECTIVE COX-2 INHIBITORS

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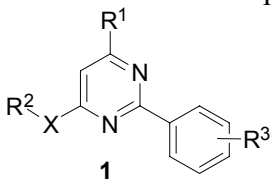
After some trisubstituted pyrimidines were described as selective COX-2 inhibitors [1], we have synthesized a series of pyrimidines **1**, which have shown also high selectivity as COX-2 inhibitors. In an effort to evaluate the influence of substituents on **1** regarding COX-2 inhibitory activity and selectivity, a new series of pyrimidines with different substituents on R^3 and X were prepared.



1

X = O, S, SO, SO_2, NH, NMe, NEt

R^3 = 4-SMe, 4-SOMe, 4-SO_2Me, 3-SO_2Me, 4-SO_2NH_2, 4-NO_2, 4-NH_2, 4-$NHSO_2$Me, 4-OSO_2Me

The synthesis of **1** has been carried out from commercially available starting materials following known synthetic methods.

Analysis of the *in vitro* COX-1 and COX-2 inhibitory activity data permitted to draw the following conclusions:

a) Potency widely varies with the chemical nature of X. When X = S, NH, NMe products with good to medium potency are obtained. On the other hand, linking R^2 through an oxy or aminoethyl bridge (X = O or NEt) led to compounds with no significant COX-2 inhibitory activity.
b) Introduction of a SO or SO_2 linking bridge dramatically decreases COX-2 inhibitory activity.
c) The presence of SO_2CH_3 or SO_2NH_2 at R^3 is essential for significant COX-2 inhibitory activity.
d) Location of the polar group SO_2Me at *meta* position of the 2-aryl moiety moderately affects activity. To the best of our knowledge this finding has no precedent in the literature.
e) When assayed *in vitro*, sulfamoyl substituted derivatives exhibited a substantial decrease in activity against human blood COX-2 compared to results of the assay against the commercial purified enzyme.

From this study, 4-aminopyrimidine **1e** ($R^1 = CF_3$, X = NH, R^3 = 4-SO_2CH_3, R^2 = Bn) was identified as a more potent and selective COX-2 inhibitor (COX-2 IC_{50} = 71.0 nM and selectivity index COX-1/COX-2 = 1,408) than rofecoxib. Further pharmacological evaluation and preliminary results of cytotoxicity will be presented somewhere else.

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[1] a) Carter M.C., Naylor A., Payne J. J., Pegg N. A., Glaxo Group LTD. PCT Int. Appl. WO 0158881 (2001); b) Hartley C. D., Naylor A., Payne J. J., Pegg N. A., Glaxo Group Ltd. PCT Int. Appl. WO 02096427 (2002); c) Naylor A., Payne J. J., Pegg N. A. Glaxo Group Ltd. PCT Int. Appl. WO 02096885 (2002).