Pharmacological evaluation of TP receptor antagonists characterized by differential activity on alpha and beta isoforms

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Thromboxane A_2 (TXA_2) is a mediator implicated in pathologies such as myocardial infarction and atherosclerosis. The TXA_2 receptor is a GPCR of which two alternative spliced isoforms, TPα and TPβ, have been described. In this study, we present the pharmacological evaluation on the individual TPα and TPβ isoforms of a series of original nitrobenzene sulfonylureas. We developed a model using cell lines expressing either TPα or TPβ, and measured the intracellular calcium mobilization triggered by TXA_2 agonist. In this screening, several compounds displayed interesting pharmacological profiles, many exhibiting greater antagonistic functional activity for either TPα or TPβ. For example, JH90 was characterized by a selectivity $TP\alpha IC_{50}/TP\beta IC_{50}$ ratio of ~10 ($TP\alpha IC_{50}$= 1590 nM ± 1320 nM; $TP\beta IC_{50}$= 151 nM ± 110 nM). In conclusion, we have pharmacologically defined several TP receptor antagonists characterized by differential activity on the TP isoforms receptors. Moreover, from our results, we can propose several structural moieties conferring isoform specificity. These agents could lead to development of pharmacological tools useful for the study of the specific role of TP isoform receptors.