Abstract

Their roles in maturation of dendritic cells, inhibition of TNF-α release, and in myocardial contractility are reasons for investigating $P2Y_{11}$ receptors. NF157 and NF340 are known nanomolar potency $P2Y_{11}$ antagonists containing naphthalene sulfonate groups. Further, non-nucleotide agonists were recently found for $P2Y_{11}$ receptors. However, the structure-activity relationships of naphthalene sulfonate urea derivatives are not fully understood. This prompted us to synthesize variations of known $P2Y_{11}$ ligands to understand structure-activity relationships. 25 New symmetrical ureas and their precursors were synthesized. Compounds were biologically tested at $P2Y_{11}$ receptors recombinantly expressed in 1321N1 astrocytoma cells by a fluorescence calcium assay. Results led to the discovery of new agonists and antagonists. The naphthalene trisulfonate urea derivatives 8c and 9c activate $P2Y_{11}$ receptors. The EC_{50} values were 3.73 µM and 2.10 µM, respectively. Hexasodium 7,7′- {carbonylbis[azanediyl(4-fluoro-3,1-phenylene) carbonylazanediyl]}bis(naphthalene-1,3,5-trisulfonate) (5c) was the most potent competitive antagonist in this study with an app. pK_i value of 7.55 ± 0.07 (K_i = 28.0 nM) and almost as potent as NF340 (app. pK_i 7.71 ± 0.04, K_i = 19.5 nM). Structure-activity relationships were further analysed. At least one phenylene-linker is needed in the naphthalene sulfonate ureas for activity at $P2Y_{11}$ receptors. Exchange of a meta against a para phenylene-linker turned the antagonist 5c into the agonist 8c. Extension of the agonist 8c with a second meta phenylene-linker increased the agonistic activity slightly (9c). Ureas like 5c with a meta position between a sulfonate group and the amido phenylene-linker showed the highest potency. Substitution of the 4-position in the phenylene-linker of 5c resulted in the following rank order of potency -F(5c) >-H >-CH_3 >-OCH_3. A symmetrical urea is not required for activity as some precursors showed which is in accordance with previous studies. The new non-nucleotide ligands 5c, 8c, and 9c are selective for $P2Y_{11}$ over $P2Y_1$, $P2Y_2$, and $P2Y_4$ receptors. In conclusion, structure-activity relationships of naphthalene sulfonate urea derivatives are better understood and will assist in the design of improved $P2Y_{11}$ ligands.

Curriculum Vitae

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