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From UTP to AR-C118925, the discovery of a potent non nucleotide antagonist of the $P2Y_2$ receptor

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ABSTRACT

The G protein-coupled $P2Y_2$ receptor, activated by ATP and UTP has been reported as a potential drug target for a wide range of important clinical conditions, such as tumor metastasis, kidney disorders, and in the treatment of inflammatory conditions. However, pharmacological studies on this receptor have been impeded by the limited reported availability of stable, potent and selective $P2Y_2R$ antagonists. This article describes the design and synthesis of AR-C118925, a potent and selective non-nucleotide antagonist of the $P2Y_2$ receptor discovered using the endogenous $P2Y_2R$ agonist UTP as the chemical starting point.
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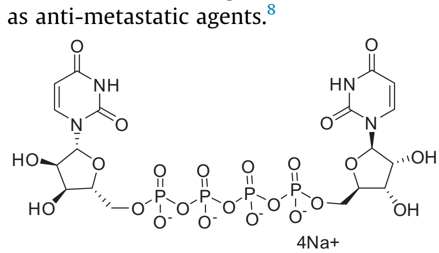
Purinergic receptors are divided into P1 (adenosine) and P2 (ATP, ADP) receptors,[1] with P2 subdivided into P2X (trimeric ion channels) and P2Y (metabotropic G-coupled receptors).[2] The eight members of the P2Y family of receptors, so far characterized, have been further subdivided based on their primary signaling through specific coupled G-proteins. The first subgroup $P2Y_{1,2,4,6,11}$ act through Gq and the second group, $P2Y_{12,13,14}$, through Gi.[3] The $P2Y_2$ receptor ($P2Y_2R$) has been found in a variety of different tissues and cell types. Cell types include: epithelial cells, endothelial cells, smooth muscles cells and leukocytes. A study using $P2Y_2$ knockout mice revealed that the receptor mediates 85–95% of nucleotide-stimulated chloride secretion in the trachea. This suggests that $P2Y_2R$ agonists have therapeutic potential as a treatment for cystic fibrosis (CF), as activation of this chloride secretion channel could compensate for the defective chloride secretion in the respiratory epithelium of CF patients.[4,5] Indeed, a $P2Y_2$ agonist, diquafosol **2**, mediating chloride secretion, has been approved in Japan for the topical treatment of dry eye disease.[6]

Agonism of the $P2Y_2R$ can also lead to keratinocyte proliferation and neutrophil migration, indicating that $P2Y_2$ antagonists have therapeutic potential as a treatment for psoriasis.[5,7] It has also been reported that ATP released from tumor-cell activated platelets, acting through the $P2Y_2R$, induce opening of the endothelial barrier, leading to migration of tumor cells and hence cancer proliferation. $P2Y_2R$ antagonists, therefore have therapeutic potential as anti-metastatic agents.[8]



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Despite the appeal of the $P2Y_2R$ as an important drug target, limited reports on $P2Y_2R$ antagonists have appeared to date[9–11] and indeed the only reported discovery of drug-like $P2Y_2R$ antagonists[12] is from an industrial research group within AstraZeneca, disclosed within a series of chemical patents.[13,14] One of the most potent and selective of these antagonists, AR-C118925, has been used as a tool for pharmacological studies on the $P2Y_2$ receptor.[15,16] More recently, its selectivity profile against a range of P2 receptors has been published. AR-C118925 was at least 50-fold selective against $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{14}$, $P2X_2$, $P2X_4$ and $P2X_7$, whilst ~40-fold against $P2X_1$ and ~15-fold against $P2X_3$.[17]

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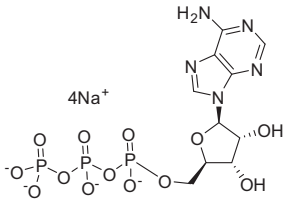

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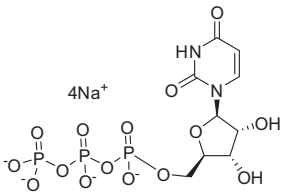

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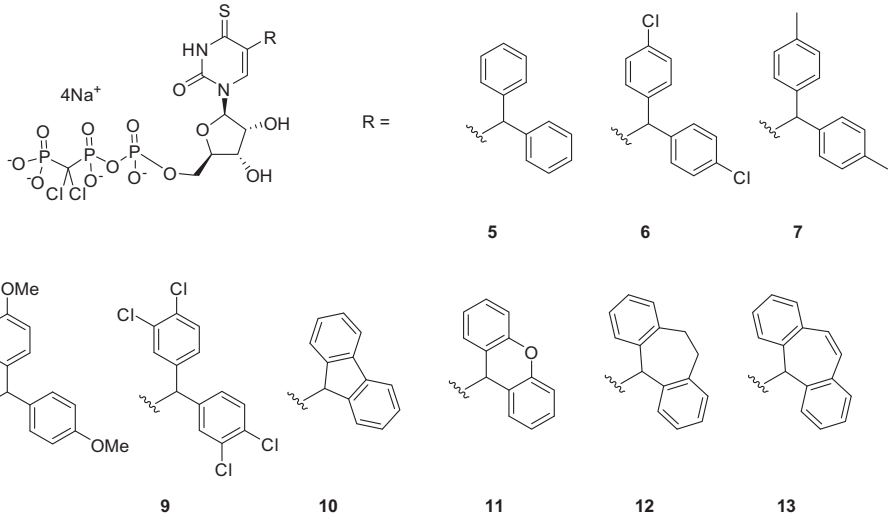
Herein we report the design and synthesis of $P2Y_2R$ antagonists, which led to the discovery of AR-C118925.

In the absence of a high throughput screening (HTS), the endogenous agonists, adenosine triphosphate (ATP) **3** and uridine triphosphate (UTP) **4** were considered as starting points for the research program. The greater selectivity of UTP for $P2Y_2R$ over the other P2 purinoceptors led to its selection as the chemical starting point. Replacing the βγ-oxygen of the triphosphate moiety of UTP with a dichloromethylene unit and substitution of the oxygen in the 4-position of the uracil with sulfur, gave enhanced metabolic stability, whilst maintaining agonist activity.[18–20] Interestingly, it was discovered that that $P2Y_2R$ antagonism could be achieved through substitution of the 5-position of the uracil ring with lipophilic substituents (Table 1). The introduction of a benzhydryl group into this position (**5**) gave a compound with a pA_2 for the $P2Y_2R$ of 6. $P2Y_2R$ activity was substantially increased by either symmetrically adding substituents to the benzhydryl group, compounds **6**, **7**, **8**, and **9**, or by linking the two phenyl rings of the benzhydryl to form a tricycle, compounds **10**, **11**, **12**, and **13**, with the highest activity achieved with the dibenzosuberenyl group, compound **13** (pA_2 8.5).

The $P2Y_2R$ antagonist program ultimately required the development of an oral drug-like compound.[21] This necessarily meant moving away from the high molecular weight, highly charged substituted nucleotides. Removing the triphosphate group gave the nucleoside analogue **14** (Table 2). Whilst this compound was substantially less potent than its parent triphosphate **13**, it did retain some antagonist activity (pA_2 4.7). Furthermore, it was discovered that the ribose ring could be replaced with the structurally less complex 3-methylenebenzoic acid to give **15**, with a slight gain in activity. The rationale for having the carboxylic acid was to mimic any binding interactions the alpha phosphate of UTP might have with the $P2Y_2R$.

Changing the linker between the carboxylic acid and phenyl ring from a direct bond to a one or two atom linker, potentially

Table 1
Exploration of the 5-position of the uracil ring.



Compound	$P2Y_2$ pA_2[a,b]
5	6.0± 0.2
6	7.9± 0.2
7	7.8± 0.2
8	7.1± 0.2
9	7.7± 0.2
10	7.2± 0.2
11	7.3± 0.2
12	8.0± 0.2
13	8.5 ± 0.2

[a] The assay used a human $P2Y_2R$ clone which was isolated from HL60 cells cDNA and then stably transfected into a Jurkat cell line. The cloned receptor mediates an increase in intracellular calcium in the cell line, which possesses no endogenous nucleotide receptor of its own. Inhibition of UTP mediated calcium responses were measured using 17 ktM fluo-3AM dye on a SPEX Fluomax using 508 nm excitation and 525 nm emission wavelengths at room temperature.

[b] n = ≥2 replicates.

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