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8-(2-Furyl)adenine derivatives as A_{2A} adenosine receptor ligands

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ABSTRACT

Selective adenosine receptor modulators are potential tools for numerous therapeutic applications, including cardiovascular, inflammatory, and neurodegenerative diseases. In this work, the synthesis and biological evaluation at the four human adenosine receptor subtypes of a series of 9-substituted 8-(2-furyl)adenine derivatives are reported. Results show that 8-(2-furyl)-9-methyladenine is endowed with high affinity at the A_{2A} subtype. Further modification of this compound with introduction of arylacetyl or arylcarbamoyl groups in N^6-position takes to different effects on the A_{2A} affinity and in particular on the selectivity versus the other three adenosine receptor subtypes. A molecular modelling analysis at three different A_{2A} receptor crystal structures provides an interpretation of the obtained biological results.

1. Introduction

Agonism and antagonism of adenosine receptors (ARs) are responsible of several effects in different organ systems suggesting that regulation of ARs has substantial therapeutic potential [1]. All ARs are G protein-coupled receptors (GPCRs), with four subtypes classified as A_1, A_{2A}, A_{2B}, and A_3 ARs [2–4], which exert their physiological role by activation or inhibition of different second messenger systems. In particular, the modulation of adenylyl cyclase activity could be considered as the principal signal mediated by these receptors [5,6]. Furthermore, ARs can be distinguished on the base of their tissue distribution and unique pharmacological profiles. In fact, a variety of physiological actions can be referred to adenosine, including effects on heart rate and atrial contractility, vascular smooth muscle tone, release of neurotransmitters, lipolysis, as well as renal, platelet, and white blood cell functions [7]. Hence, selective AR modulators are promising for numerous therapeutic applications, including cardiovascular, inflammatory, and neurodegenerative diseases [1].

The prototypical AR antagonists are the naturally occurring methylxanthines, whose modifications led to derivatives endowed with marked potency and selectivity for specific AR subtypes [8–10]. However, only a few xanthine antagonists such as caffeine and theophylline have been approved as drugs for their central nervous system (CNS) stimulating, diuretic, and bronchodilating effects [10,11]. Very recently, the A_{2A}AR antagonist istradefylline (KW-6002) has been approved for manufacturing and marketing in Japan for the treatment of Parkinson's disease [12]. Many different classes of compounds have been proposed as AR antagonists, with both good affinity and selectivity [13,14]. Among them, a series of AR antagonists have been obtained by removing the ribose moiety from the natural ligand adenosine and by modifying the adenine core. In fact, the introduction of different substituents in 2-, 8-, and 9-position of adenine resulted in high-affinity antagonists with distinct receptor selectivity profile [15–26]. In particular, some 8-substituted-9-ethyladenine derivatives were reported to ameliorate motor deficits in rat models of Parkinson's disease, suggesting potential therapeutic application for these compounds [27]. Among them, the 8-bromo-9-ethyladenine

Abbreviations: AR, adenosine receptor; GPCR, G protein-coupled receptor; CNS, central nervous system; DMF, dimethylformamide; NBS, *N*-bromosuccinimide; CHO, Chinese hamster ovary; pdb, protein data bank; EL, extracellular loop; IL, intracellular loop; MOE, molecular operating environment; RMSD, root mean square deviation; TM, transmembrane; TLC, thin-layer chromatography; IR, infrared; THF, tetrahydrofuran.

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(**1**; Fig. 1, Table 1) showed good affinity (K_i $A_{2A}AR$ = 52 nM) and moderate selectivity at $A_{2A}AR$ especially *vs* the A_1 receptor subtype (selectivity A_1/A_{2A} = 5). Substitution of the bromine atom with a 2-furyl ring in 8-position of this molecule led to 9-ethyl-8-furyl adenine (**2**), which showed increased affinity at all ARs and in particular at the A_{2A} subtype, but with still low selectivity *vs* the A_1AR (**2**; K_i $A_{2A}AR$ = 3.7 nM, selectivity A_1/A_{2A} = 6; Fig. 1, Table 1) [28]. In this work, aimed at modulating the affinity and selectivity at the A_{2A} subtype of compound **2**, its 9-ethyl group was replaced by small alkyl or hydroxyalkyl chains (**12**–**15**; Fig. 1, Scheme 1). The choice of the 9-substituents was made on the base of previously reported results indicating that the introduction of small alkyl or hydroxyalkyl chains in 9-position of 8-bromoadenine (**8**–**11**, Scheme 1, Table 1) leads to $A_{2A}AR$ ligands endowed with high affinity for the same subtype [22]. Among the newly synthesized 8-furyl derivatives **12**–**15**, the 8-(2-furyl)-9-methyladenine (**12**) was selected for further investigations since it showed the best $A_{2A}AR$ selectivity profile (Scheme 1, Table 1). Very recently, a trisubstituted adenosine derivative named UK-432097 (Fig. 1), bearing a large and lipophilic group at N^6-position, has been reported as a potent and selective $A_{2A}AR$ agonist [29]. Starting from this observation, in a second phase of the present work, large and lipophilic arylacetyl and arylcarbamoyl substituents, which are more flexible respect to the 2,2-diphenylethyl group present in UK-432097, were introduced at N^6-position of the selected compound **12** to give the newly trisubstituted adenine derivatives **16**–**22** (Fig. 1, Scheme 2).

2. Results and discussion

2.1. Chemistry

Desired compounds **12**–**22** were obtained as summarized in Schemes 1 and 2. Alkylation of commercially available adenine (**3**) with the suitable alkyl halide in dry dimethylformamide (DMF), employing potassium carbonate as base, led to a mixture (ratio 3:1) of the N9- and N7-isomers, **4**–**7** and **4a**–**7a**, respectively, which were separated by chromatography (Scheme 1).

Treatment of the N9 isomers **4**–**7** with *N*-bromosuccinimide (NBS) led to the 8-bromo derivatives **8**–**11** [22] that, after reaction with tributylstannylfurane in the presence of $(PPh_3)_2PdCl_2$ as a catalyst, gave the desired 8-furyl-9-substituted adenine derivatives **12**–**15**.

N^6-Substituted adenines **16**–**22** were prepared by reacting **12** with the appropriate isocyanate or acyl chloride in dioxane at reflux for 1–2 h in the presence of triethylamine (Scheme 2).

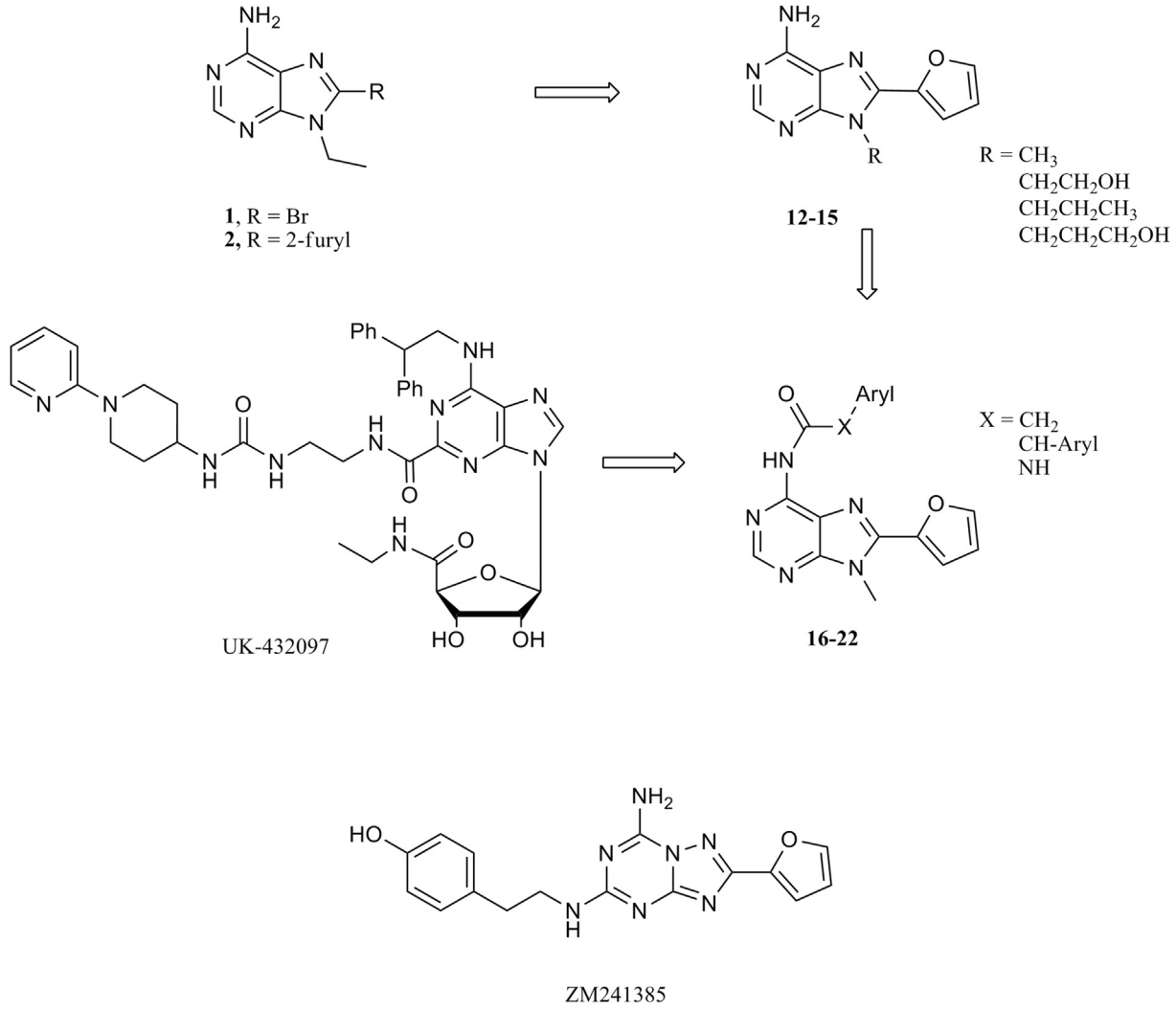

Fig. 1. Structure of known and newly synthesized AR ligands.