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Original article

Novel 8-(*p*-substituted-phenyl/benzyl)xanthines with selectivity for the A_{2A} adenosine receptor possess bronchospasmolytic activity

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ABSTRACT

A new series of 8-(*p*-substituted-phenyl/benzyl)xanthines has been synthesized and evaluated *in vitro* for adenosine receptor binding affinity and *in vivo* for bronchospasmolytic effects. It was observed that the nature of substituent at *para*-position of 8-phenyl/benzyl group on the xanthine scaffold remarkably affects the binding affinity and selectivity of xanthine derivatives for various adenosine receptor subtypes and also their bronchospasmolytic effects. Newly synthesized 8-phenylxanthines displayed potent binding affinity and significant selectivity for A_{2A} receptors and also produced potent bronchospasmolytic effects. Replacement of phenyl ring with benzyl moiety at C_8 of xanthine skeleton resulted in notable reduction in adenosine receptor affinity and broncholytic effects.

1. Introduction

Asthma remains one of the most common respiratory diseases with unmet medical needs. Enough evidence has accumulated in support of the role of adenosine in pathogenesis of asthma [1,2]. Selective agonists or antagonists of adenosine receptors are being explored by various research groups and pharmaceutical industry in an attempt to generate novel antiasthmatic agents. All four adenosine receptor (AR) subtypes (A_1, A_{2A}, A_{2B} and A_3) are expressed in lungs and in inflammatory cells involved in asthma. This has led to investigations into all AR subtypes as potential therapeutic targets for the treatment of asthma [3–5]. As binding studies in human lungs have indicated higher abundance of A_2 than other subtypes, therefore these receptors seem to play a more prominent role in mediating the bronchoconstriction and proinflammatory effects of adenosine in lungs [6].

Substituted xanthines constitute one of the most persuasive categories of adenosine receptor antagonists reported to date and are known for variable potency and selectivity for adenosine receptor subtypes [7–9]. 8-Phenyltheophylline is the parent member of a variety of potent adenosine receptor antagonists, e.g., MRS-1754 (**1**) (Fig. 1) [9,10]. Although 8-phenyl substitution exhibits maximum adenosine receptor antagonistic activity, it confers extremely limited water solubility to xanthines, which restricts their usefulness as *in vivo* research tools and their possible use as therapeutic agents [11]. The incorporation of polar substituents improves the otherwise extremely limited water solubility of 8-phenylxanthines and consequently increases their effectiveness as potential therapeutic agents. Furthermore, appropriate substitutions on the 8-phenyl ring greatly affects the potency and selectivity of xanthines towards AR subtypes and thus their pharmacological effects [10,12,13].

In the light of these observations, we decided to study the impact of substituting polar dialkylaminoethoxy substituents at *para* position of the 8-phenyl ring of xanthines on adenosine receptor binding affinity and selectivity. In order to examine specific structural features, which may be important for adenosine receptor binding, it was also appealing to introduce a methylene spacer between the aromatic unit and the C_8 of the xanthine nucleus and study the resulting effects on biological activity. As a continuation of our earlier xanthine based research [10,14,15], a new series of 8-(substituted-phenyl/benzyl)xanthines has been synthesized and evaluated for their binding affinity for various adenosine receptor subtypes and also for bronchospasmolytic effects.

2. Chemistry

The synthesis of various 8-(substituted-phenyl)xanthines has been depicted in Schemes 1 and 2.

Substituted aromatic aldehydes **3**–**9** [16] were prepared by treating 4-hydroxybenzaldehyde with hydrochloride of desired

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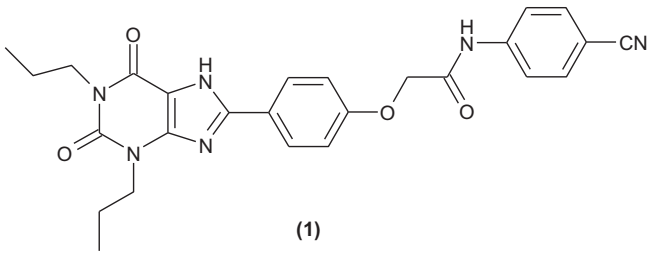


Fig. 1. Structure of xanthine based adenosine receptor antagonist MRS-1754 (**1**).

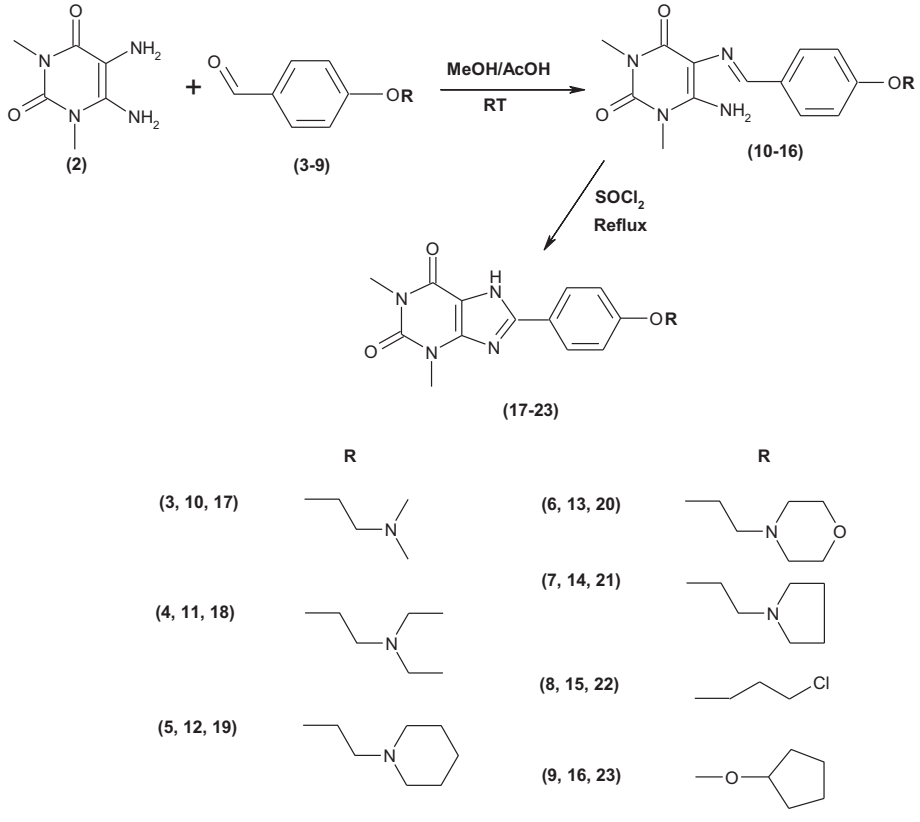
dialkylamino ethyl chloride, 1-bromo-3-chloropropane and cyclopentyl bromide, respectively, in refluxing ethyl methyl ketone in the presence of anhydrous potassium carbonate (Scheme-1).

Treatment of obtained aldehydes **3**–**9** with 5,6-diamino-1,3-dimethyluracil (**2**) [17,18] in MeOH-AcOH (4:1) at room temperature resulted in the formation of corresponding benzylidene adducts **10**–**16**, subsequent ring closure of which in refluxing thionyl chloride afforded the target compounds **17**–**23** as shown in Scheme-1. Characteristic NMR signals appeared at δ 2.93 [s, 6H, $-N(CH_3)_2$] for **17**, 1.32 [s, 6H, $-N(CH_2CH_3)_2$] for **18**, 2.98–3.06 (m, 4H, $-N(CH_2)_2$, piperidine) for **19**, 3.70 [t, 4H, O-$(CH_2)_2$, morpholine] for **20**, 2.88 [s, 4H, $-N(CH_2)_2$, pyrrolidine] for **21**, 3.77 ppm (t, 2H, $-CH_2Cl$) for **22** and a multiplet at 4.80–4.91 ppm for $-OCH$ of cyclopentyloxy ring substituted xanthine **23**. Further, two separate singlets for both methyl groups present at 1- and 3-position of purine nucleus were found at $\delta \sim$ 3.4 and 3.6, and $-OCH_2-$ protons resonated as a triplet around 4.3 ppm for all the compounds.

Keeping in mind the reported adenosine binding affinity of imidazole [15] derived xanthines and antihistaminic properties of aryl piperazine substituted 8-phenylxanthines, chloroalkoxy derivative **22** was thermally fused separately with powdered imidazole and 1-(2-chlorobenzyl)piperazine at 160 °C for 2 h to afford the corresponding xanthine congeners **24** and **25** (Scheme-2). Imidazolyl protons appeared at δ 6.97, 7.03 and 7.52 and *N*-methylene protons of $-CH_2-N<$ resonated downfield as a triplet at 3.99 for compound **24**, while an 8-proton multiplet of piperazinyl ring was seen at 2.56–2.60 ppm in the NMR spectrum of **25**.

For the preparation of target 8-[4-(aminopropoxy)benzyl]xanthines, attempts to synthesize the starting substituted acidic compound **29** by direct alkylation of 4-hydroxyphenylacetic acid with 1-bromo-3-chloropropane remained unsuccessful. Therefore an alternative synthetic route was adopted as shown in Scheme 3. 4-Hydroxyphenylacetic acid was esterified by heating under reflux in methanol in presence of a catalytic amount of sulfuric acid to afford an oily residue of methyl-4-hydroxyphenyl acetate (**27**). Alkylation of the compound **27** was carried out by treating with 1-bromo-3-chloropropane in ethyl methyl ketone using anhydrous potassium carbonate to give the oily residue methyl-[4-(3-chloropropoxy)phenyl]acetate (**28**). Alkaline hydrolysis of ester **28** led to the formation of the desired starting compound **29** as shown in Scheme 3.

4-Chloropropoxyphenylacetic acid (**29**) was condensed with 5,6-diamino-1,3-dimethyluracil (**2**) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) in methanol at room temperature to yield 6-amino-5-[{4-(3-chloropropoxy)phenyl} carboxacetamido]-1,3-dimethyluracil (**30**) as shown in Scheme 3. ^{1}H NMR spectrum of carboxamide derivative **30** displayed a characteristically downfield singlet integrating for two protons of NH–CO–CH_2–Ar group at δ 3.67, while protons of the free $-NH_2$ group resonated as a singlet at 5.87 ppm. Symmetric and asymmetric stretching bands of free $-NH_2$ group appeared at 3321 and 3200 cm^{-1} in the IR spectrum of the compound **30**.



Scheme 1. Synthetic route to 8-(*p*-substituted phenyl)xanthine derivatives **17**–**23**.