1,3,7,8-SUBSTITUTED XANTHINE DERIVATIVES AS POTENTIAL ANTIASTHMATIC AGENTS WHICH ACT ON ADENOSINE RECEPTOR

ABSTRACT

Asthma is one of the most common chronic diseases in modern society. There is a high prevalence of usage of complementary medicine for asthma. Xanthine derivatives which act on adenosine receptor have been cited as a most popular complementary treatment. This studys was undertaken to determine if there is any evidence for the clinical efficacy of xanthine derivatives for the treatment of asthma symptoms. This review highlights the more recent developments in the design and optimization of xanthine derivatives which act on A_2A and A_2B adenosine receptor. 1,3,8 and 1,3,7,8-substituted xanthine derivatives were found to be effetive. 1,3,7,8 Substituted xanthine derivative possess good affinity on A_2A and A_2B AR and are not selective for one particular receptor. This is benefitical for decreasing the side effects related to CVS.

Keywords: Asthma; Xanthine; Adenosine Receptor.

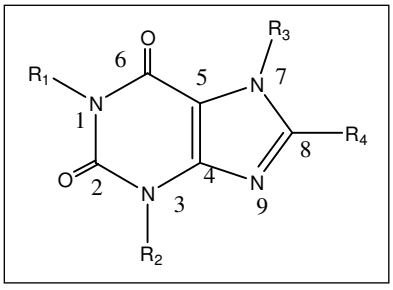
INTRODUCTION

Overview of Xanthine Derivatives and Adenosine Receptors (AR) used in therapy

Adenosine is an endogenous non-selective agonist that activates all four subtypes of adenosine receptors (AdoR): A_1, A_2A, A_2B and A_3[1]. Adenosine receptors have been recognized as playing an important role in chronic inflammatory airway conditions such as asthma, chronic obstructive pulmonary disease and fibrosis[2,3]. Experimental evidence, such as the increase in the adenosine concentration in hypoxia and cellular inflammation in the bronchoalveolar fluids of asthmatics and in plasma (upon contact with allergens), has highlighted the key role that adenosine and its A2B receptors play in asthma[4-6]. At least half of the population of the world uses tea-containing xanthine: caffeine, small amount of theophylline and theobromine, prepared from the leaves of *Thea sinensis.* First half of the last century confirmed that methylxanthines share many pharmacological actions and differ only in potency. They are CNS stimulants, predominantly caffeine, while theophylline has some CNS-stimulant properties, and theobromine possess only weak stimulant activity[7]. All these well known drugs are xanthine (2,6-dioxypurine) derivatives, easily chemically transformed to uric acid (2,6,8-trioxopurine). Theophylline is 1,3-dimethyl xanthine, theobromine 3,7-dimethylxanthine and caffeine 1,3,7-trimethyl xanthine[8].

Biochemical mechanism of action of xanthine derivatives:

The naturally occurring xanthine derivative, caffeine and theophylline, are the classical adenosine receptor antagonists[9]. Adenosine released under conditions of cellular stress as seen in asthmatic airways may bind to one of its four AR. A_1 AR activation has been implicated in several events including bronchoconstriction and mucus hypersecretion. Activation of A_2A AR on the inflammatory cells mostly suppresses oxidative stress and proinflammatory cytokines, and may also inhibit the release of leukotrienes (LTs) and histamine from the mast cells. Activation of A_2B AR leads to the release of LTs, histamine, proinflammatory cytokines and enzymes such as chymase and tryptase. LTs and histamine can directly cause smooth muscle contraction, while other mediators such as cytokines, LTs, tryptase and chymase may be chemoattractants for infiltration of leukocytes into the airway space, leading to airway inflammation. A_3 AR activation may be involved in vasopermeability changes, mucus hypersecretion, elastase and superoxide anion release, and recruitment of eosinophils to the airways[10].



(General structure of xanthine)

Xanthine derivatives are also therapeutically used as antiparkinson drugs, analeptics, vasodilators, antihypertensives and diuretics. Beside adenosine receptor antagonistic activities, other mechanism of action including inhibition of phosphodiesterases (PDE), Mobilization of the intracellular calcium ions (Ca^{2+}) via cell membrane hyperpolarization also plays a significant

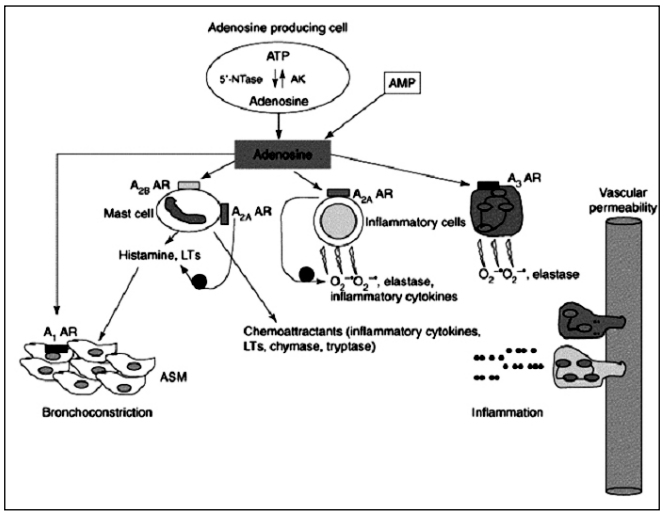


Fig. 1: Mechanism of AR

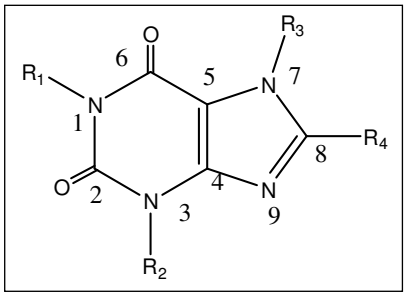
(⊗ in red denotes inhibition. AK, adenosine kinase; AR, adenosine receptor; ASM, airway smooth muscle; 5′-NTase, 5′-nucleotidase; LTs, leukotrienes; $O_2^{\cdot -}$, superoxide radical.).

role in their biological activity[8]. Inhibition of enzyme-phosphodiesterase leads to an increase of lipolysis and glycogenolysis as a result of elevated concentration of c AMP[11]. Inhibition of cyclic nucleotide phosphodiesterase causes accumulation of c-AMP, however an increase of intracellular c-AMP concentration may influence the movement of Ca^{2+} which is involved in smooth muscle contraction with the result that relaxation occurs. Theophylline stimulates the release of catecholamines from the adrenal medulla and also inhibits the enzyme catecholamine-O-methyl transferase (COMT) which contribute to its bronchodilatory effects[7,8,11].

1, 3, 7, 8-Substituted xanthine derivatives and their analogues

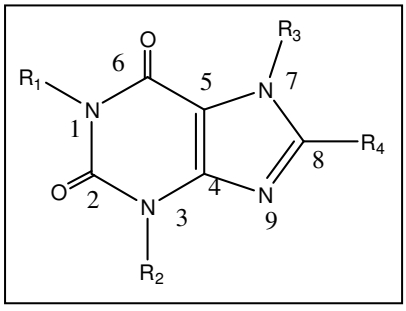
Extensive studies have been performed on the 1, 3, 7, 8-substituted xanthine derivatives including synthetic procedures and structure determination. In the present study, in an effort to better understand the structure-activity relationships (SAR) of ligands of the A_2A and A_2B AR, we have screened a variety of xanthine derivatives substituted at the 1-, 3-, 7- and 8-positions. it was found that anellation at 1, 3, 7, 8-position of xanthine changed the profile of its AR activity. The pharmacological evaluation of the series of novel xanthine derivatives with 1, 3, 7, 8-substitution generally demonstrated their antiasthmatic effect on AR.

It was found that 1,3,8-substituted xanthine derivatives have good selectivity for A_2B AR but low to moderate affinity on A_2A and A_2B AR. But 1,3,7,8-substituted xanthine derivative have good affinity on A_2A and A_2B receptors and decreased A_2B / A_2A selectivity[12].Selective activation of A_2A AR could be a possible therapeutic approach for the treatment of asthma, but direct delivery to the lung will be required to circumvent cardiovascular side effects, especially lowering of blood pressure[13]. Selective antagonism of A_2B AR may lead to adverse effects related to cystic fibrosis phenotype and cardiac preconditioning[14,15]. 1, 3, 8-Substituted xanthine derivative (e.g.1-ethyl-3,8-bis(thiophen-2-ylmethyl)xanthine) have affinity 5.40 and 6.86 % for A_2A and A_2B AR, respectively and 28.9 A_2B / A_2A, selectively.



R_1 - ethyl
R_2 and R_4 - thiophen-2-ylmethyl

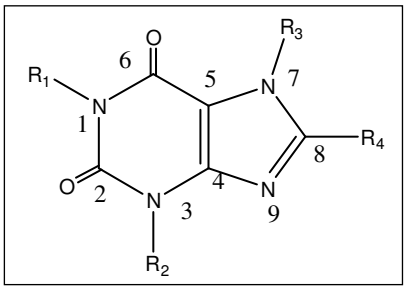
1, 3, 7, 8-substituted xanthine derivatives (e.g.1-ethyl-3-thiophen-2-ylmethyl-8-furfuryl-7- methyl xanthine) have affinity 6.66 and 7.57% for A_2A and A_2B AR, respectively and 8.1 A_2B / A_2A, selectively[12].



R_1 - ethyl
R_2 - thiophen-2-ylmethyl
R_3 – methyl and R_4 - furfuryl

A larger alkyl group at the 1-position than at the 3-position favored affinity at the human A2B receptor, as indicated by 1-allyl-3-methyl-8-phenylxanthine, with a *K*i value of 37 nM. Substitution on the 8-phenyl ring indicated that an electron-rich ring was preferred for A_2B[16] and A2A receptor binding[17]. Substitution of methyl group on N-7 favour A_2A and A_2B receptor affinity and decreases selectivity for A_2B receptor[12].

Above-described xanthine derivatives, containing 1-allyl-3,7-dimethyl-8-phenyl substitution on xanthine ring were also developed[16].



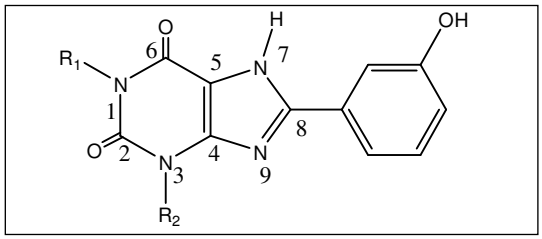
R_1 – Allyl, R_2 – Methyl

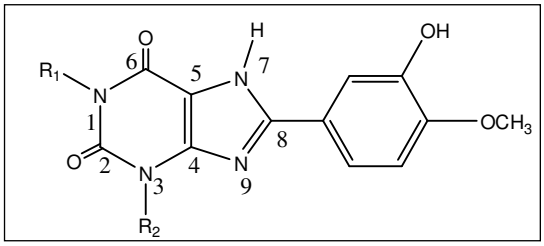
R_3 – Methyl, R_4 - Phenyl

K_i for A2A = 23500 nM

K_i for A2B = 11400 nM

8-Phenyltheophylline is the parent member of a variety of potent adenosine receptor antagonists. It has been reported that appropriate substituents on the 8-phenyl ring not only affects the potency and selectivity towards adenosine receptors but also the solubility properties[17]. On one side, monosubstituted 8-(p-hydroxyphenyl) xanthine has been chosen as a suitable lead compound to develop as a potent and selective A_2B receptor antagonist[18]. The incorporation of polar substituents has been shown to improve the otherwise extremely limited water solubility of 8-phenylxanthines and increase their usefulness as potential therapeutic agents[17,18].In view of the above observations, it was decided that substitution of -H on N-7 position and either polar group on benzene ring at meta position on C-8 position of xanthine or this polar group may be present at ortho position of methoxy group on benzene ring on C-8 position of xanthine. All these substituent favour A_2A receptor affinity[19].





In conclusion, new leads for the design of xanthines substituted in the 1-, 3-, 7-, and 8-positions which act on both A_2A and A_2B AR was studied.

Methods

Computerised literature searches were performed to identify all published articles on the subject. The following databases were used: on Science Direct, Pubmed, Elsevier, and Embase. Search terms used were “asthma”, adenosine receptor, xanthine derivative as well as any individual drug name cited in the asthma literature.The bibliographies of all papers thus located were searched for further relevant articles.

All articles were read in full and data. In this review, Immunological studies were not included. This paper concentrated on the adenosine receptor, xanthine derivative, affinity and selectivity of the compound on the AR and decrease the side effect on the basis of SAR.

RESULT

1,3,8 and 1,3,7,8-substituted xanthine derivatives were found. 1,3,7,8-substituted xanthine derivatives are more effective on A2A and A2B AR, because, 1,3,8-substituted xanthine derivatives have good selectivity for A2B AR but low to moderate affinity on A2A and A_2B AR. But 1,3,7,8-substituted xanthine derivative have good affinity on A_2A and A_2B receptor and decreased A2B / A2A selectivity. Selective antagonism of A2B AR may lead to adverse effects related to cystic fibrosis phenotype and cardiac preconditioning. Therefore, AR was selected as a target as it displays multiple actions i.e. leucotriene antagonistm, decrease inflammation, mast cell stabilization and inhibition of release of histamine and 1, 3, 7, 8 substituted xanthine derivatives as a lead compound to decrease the side effect on the basis of structure activity relationship. They have shown the activity on A2A and A2B AR with minimum side effects.

CONCLUSION

1,3,8-Substituted xantine derivatives exhibited good selectivity on A2B AR but low to moderate affinity on A2A and A2B AR. 1,3,7,8-Substituted xanthine derivatives exhibited good affinity on both receptors and were not selective for one particular receptors, particulary those which contained long alkyl chain at N-1 than N-3 position, only methyl group on N-7 position and electron rich ring on 8 position. In conclusion, 1,3,7,8 substituted xanthine derivative possess good affinity on A2A and A2B AR and are not selective for particular one receptor. This is benefitial for decreasing the side effects related to CVS. Several 1,3,7,8-substituted xanthine derivatives were compared to 1,3,7-substituted xanthine derivatives. 1,3,7,8-substituted xanthine derivatives gave the characteristic antiasthmatic

property; they have shown activity on A2A and A2B AR with decrease the CVS related side effect.

REFERENCES

1. Fredholm, B.N.; Ijzerman, A.P.; Jacobson, K.A.; Klotz, K.N.; Linden, **J. Int. Pharmacol. Rev**. 2001, 53, 527.
2. Berge, M.; Hylkeman, M.; Verslius, M.; Pastma, D. S. **Drugs R&D.** Rev. 2007, 8, 13.
3. Akkari, R.; Burbiel, J. C.; Hockemeyer, J.; Mueller, C. E. Neuroprotective mechanisms of adenosine action on CNS neurons. **Curr. Top. Med. Chem**. 2006, 6, 1375.
4. Zhong, H.; Bellardinelli, L.; Zeng, D. Purinergic Regulation of Respiratory Diseases. **J.Respir. Cell Mol. Biol.** 2004, 30, 118.
5. Zhong, H.; Bellardinelli, L.; Zeng, D. Adenosine A_{2B} receptors are highly expressed on murine type II alveolar epithelial cells. **J. Respir. Cell Mol. Biol.** 2006, 5, 587.
6. Holgate, S. T. Adenosine closes the K^+ channel $K_{Ca}3.1$ in human lung mast cells and inhibits their migration **via** the adenosine A_{2A} receptor **Br. J. Pharmacol. 2005,** 145, 1009.
7. Index Nominum. International Drug Directory 92/93. Med pharm Scientific Publishers, Stuttgart 1992.
8. Kumar, Y.; Sharda; Singh, M. Pandey, R. Electrochemical Study of Zn+2- Theophylline Complex. **Inter. J. Chem.** 2011, 1, 43-50.
9. Fhid, O.; Zeglam, T.; Alag, M.; Almog, T. Tri- and Tetra-Cyclic Theophylline Derivatives as a Potential Agents Acting on CNS and CVS. **Inter. J. Pharm. Biol.** 2012, 3, 507-512.
10. Nadeem, A.; Mustafa, S.J. Adenosine receptor antagonists and asthma. Drug Discovery Today: **Therapeutics Strategies.** 2006, Vol. 3, 3, 269-273.
11. Bialer, M.; Clinical pharmacology of valpromide. **Clin. Pharmacokinet**. 1991, 20, 114-122.
12. José, R.; María, C.B. Synthesis and pharmacological evaluation of novel 1,3,8- and 1,3,7,8-substituted xanthines as adenosine receptor antagonists. **Bioorg. Med. Chem**. 2010, 5, 2001–2009.
13. Spicuzza, L. Adenosine in the airways: implications and applications. **Eur. J. Pharmacol**. 2006, 533, 77–88.
14. Huang, P. Compartmentalized autocrine signaling to cystic fibrosis transmembrane conductance regulator at the apical membrane of airway epithelial cells. **Proc. Natl. Acad. Sci.** U S A. 2001, 98, 14120–14125.
15. Solenkova, N.V. Endogenous adenosine protects preconditioned heart during early minutes of reperfusion by activating Akt. **Am. J. Physiol. Heart Circ. Physiol**. 2006, 290, 441–449.
16. Soon, S.; Melissa, A.; Marshall, A.; Neli, M.; Christa, E. Structure activity relationships at human and rat A_2B adenosine receptors of xanthine derivatives substituted at the 1,3,7 and 8-positions. **J. Med. Chem.** 2002, 45, 2131-2138.
17. Shamim, M.T.; Ukena, D.; Padgett, W.L.; Hong, O.; Daly, J.W. 8-Substituted xanthine as antagonist at A1 and A2A adenosine receptor. **J. Med. Chem**. 1988, 31, 613–617.
18. Hayallah, A.M.; Sandoval-Ramirez, J.; Reith, U.; Schobert, U.; Preiss, B.; Schumacher, B.; Daly, J.W.; Muller, C.E. Progress in the discovery of selective, high affinity A_{2B} adenosine receptor antagonists as clinical candidates. **J. Med. Chem**. 2002, 45, 1500–1510.
19. Bansal, R.; Kumar, G.; Gandhi, D.; Louise, C.Y.; Alan, L.H. Synthesis of a series of 8-(substituted-phenyl)xanthenes and a study on the effects of substitution pattern of phenyl substituents on affinity for adenosine A1 and A2A receptors. **Eur. J.Chem**. 2009, 44, 2122-2127.

[a] B.R. Nahata College of Pharmacy, Mandsaur University, Mandsaur - 458 001, Madhya Pradesh, India

Shringi M.[a*] and Baregama C.[a]

***For Correspondence: E-mail: Chetnabaregama@gmail.com**

(Received 02 June 2018) (Accepted 12 December 2018)

https://doi.org/10.53879/id.56.07.11436