INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Research Article

SYNTHESIS OF NEW 1, 3, 7, 8-TETRASUBSTITUTED XANTHENES ANALOGUE

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Article Received on: 19/08/12 Revised on: 22/09/12 Approved for publication: 16/10/12

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ABSTRACT

Theophylline, a methyl xanthenes compound, is known as an efficient bronchodilator drug, having also anti-inflammatory and immunomodulatory effects. In order to improve its pharmacological profile and to reduce also the serious side effects that appear at high concentrations, new 1, 3, 7, 8-tetrasubstituted theophylline derivatives have been synthesized. The new compounds are obtained in two steps by the reaction of 8-substituted theophyllines with epoxy propyl acetaminophen. The chemical structure of the synthesized compounds has been elucidated by their 1H-NMR spectra. The potential bronchodilator effects of the synthesized compounds have been also established.

Key word: Theophylline derivatives, bronchodilator effect, mercapto xanthine, ethoxy propyl acetaminophen, 1, 3, 7, 8-tetrasubstituted xanthenes.

INTRODUCTION

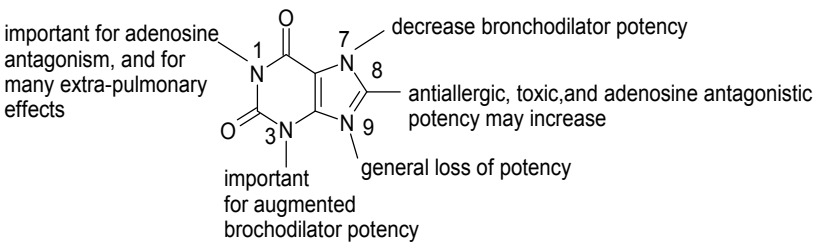
Xanthenes belong to the group of purine compounds they retained the methyl groups in 1-and 3-positions, various polar substitutions were introduced in the 7-position in an attempt of making more water-soluble compounds, they reported to be generally less potent than theophylline, the introduction of small alkyl groups in the 8-position will not reduce the bronchodilator potency. Also, many 1, 3, 8-derivatives exhibit potent and interesting ant allergic properties, A common metabolic pathway with xanthenes is oxidation in the 8-position to uric acids; 8-substituted xanthenes would therefore be predictably more stable compounds. The 1, 3, 7, 9-tetra alkyl derivatives are permanently charged xanthiniums that will not easily traverse lipid membranes.[1]

Useful findings and development On the basis of their molecular features for xanthenes compounds (**1**) were reported to contribute in the development of new molecules for studying the pharmacology of CFTR (cystic fibrosis transmembrane conductance regulator), 1, 3, 7, 8-tetrasubstitutions were absent .[2]

Assessing the influence of methylation of the nitrogen at position 7 of several substituted theophylline (**2**) (Table 1), indicated that it depend on the receptor, in the case of A2B and A2A receptors a significant increase in affinity level was obtained.[3] Also, it has been reported that theophylline derivatives (Table 1,**2**f and g) to show bronchodilator effects 6.5 and 2.5 times respectively more active than theophylline.[4] 8-substituted theophyline-7-riboside (**2**h) was synthesized in an almost quantitative yield [5], and show low efficacy agonist or antagonist for the adenosine receptor .[6]

Table 1

	R1	R2	R3	R4
a	Ethyl	Benzyl	Thiophen-2-ylmethyl	Methyl
b	Ethyl	Benzyl	Furfuryl	Methyl
c	Ethyl	Thiophen-2-ylmethyl	Thiophen-2-ylmethyl	Methyl
d	Ethyl	Thiophen-2-ylmethyl	Furfuryl	Methyl
e	Ethyl	Thiophen-2-ylmethyl	2,6-difluorobenzyl	Methyl
f	Methyl	Methyl	Bromo	Propyl acetaminophen
g	Methyl	Methyl	Imidazolyl	Propyl acetaminophen
h	Methyl	Methyl	Alkyl substitutions	Ribosyl
i	Ethyl	Ethyl	Methyl	Styryl substitutions



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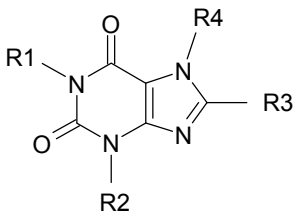

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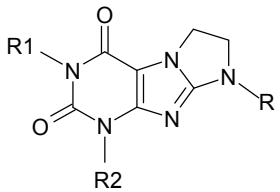


(3)

High affinity and selectivity for antagonist of A2A adenosine receptor have been achieved by introducing styryl substitution at the 8-position of the theophylline (**2i**) istradefylline.[7]Annelation of six or seven-member ring at 7-, and 8-position of theophylline (**3**) was reported to change the profile of its CNS activity (sedation, or neuroleptic- like properties) in comparison to the mother compound (stimulating activity).[8, 9]

An important challenge was carried out in our group to improve its pharmacological profile and aiming to reduce the serious side effects, new theophylline derivatives have been synthesized covering two tasks. Firstly, is by introducing different substituent at N-7(1, 3, 7-trialkyl-8-substituted phenyl xanthenes) scheme 1. Secondly, synthesis of some 8-mercaptotheophylline derivatives scheme 2.

RESULTS AND DISCUSSION

1,3-dimethyl-8-(4-carboxymethyloxy)phenylxanthine **6** was prepared by the reported procedure[10] (Scheme 1) starting from 5,6-diamino-1,3-dimethyluracil **4** to give the uncyclized 6-amino-1,3-dimethyl-5-(4-carboxymethyloxybenzyliden) aminouracil **5**, the later undergo cyclization upon treated with thionyl chloride to afford compound **3**. Alkylation of 6 was carried out using different alkyl iodide to give 1, 3, 7, 8-alkyl substituted xanthine **7** scheme 1.

The amide **8** was prepared [11] by conversion of compound **7** to its acid chloride using thionyl chloride, after distillation off the excess thionyl chloride, the acid chloride dissolved in anhydrous pyridine: dichloromethane as solvent then appropriate amine was added to give **8**.

Mercapto xanthine [12] **9** is exist in tautomeric form (thione-thiol tautomers) was reacted with methyl bromoacetate in the presence of sodium hydroxide at room temperature to give the ester,[13] the later undergo alkylation with alkyl halide in DMF afford the compound **10**.

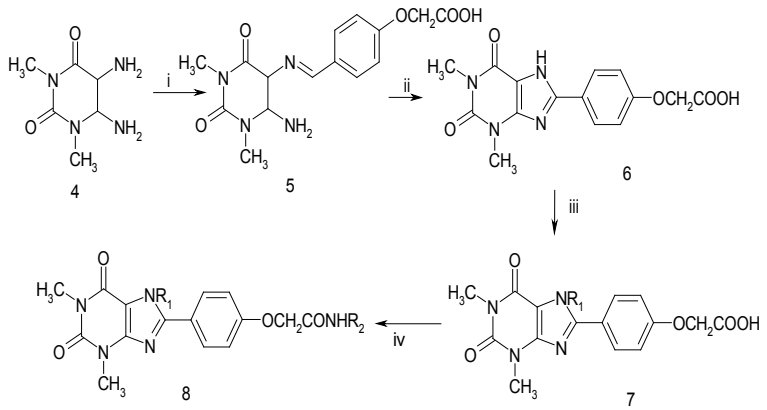
The ester **10** was treated with hydrazine hydrate 80% to obtained **11**, which reacted with different substituted aldehydes to give the Schiff base derivatives **12** (Table 3) Scheme 2.

Table 2

Comp.	R1	R2	R3	R4	% yield	M.P (°C)	NMR
7a	CH_3	CH_3	CH_3	$PhOCH_2COOH$	67.5	290-292	3.2, 3.4, 3.9, *s*, N1-, N3-, N7-CH_3 respectively, 4.7,*s*, -OCH_2, 7.1, 7.6, *d*, *p*-subs. phenyl group.
7b	CH_3	CH_3	C_2H_5	$PhOCH_2COOH$	46.5	306-307	3.2, 3.4,s, N1-, N3-CH_3, 1.4,*t*, N7-CH_2CH_3, 4.3,*q*, N7-CH_2CH_3, 4.7,*s*, -OCH2, 7.1, 7.6,*d, p*-subs. Phenyl group
7c	CH_3	CH_3	C_3H_7	$PhOCH_2COOH$	42	310-312	3.2, 3.4, N1-, N3-CH_3, 0.8, *t*, N7-$CH_2CH_2CH_3$, 1.7,*m*, N7-$CH_2CH_2CH_3$, 4.2, *t*, N7-$CH_2CH_2CH_3$, 4.7,*s*, -OCH_2, 7.1, 7.6, *d*, *p*-subs.phenyl group
7d	CH_3	CH_3	C_4H_9	$PhOCH_2COOH$	42	309-310	3.2, 3.4, N1-, N3—CH_3, 0.9, *t*, N7-$CH_2CH_2CH_2CH_3$, 1.3, *m*, N7-$CH_2CH_2CH_2CH_3$, 4.3, *t*, N7-$CH_2CH_2CH_2CH_3$, 4.7, *s*, -OCH_2, 7.1, 7.6, *d*, *p*-subs. Phenyl group.
8	CH_3	CH_3	CH_3	$phOCH_2CONHCH_2ph$	42	248-250	3.2, 3.4, *s*, N1-, N3-, N7-CH_3, 3.9, *s*, ph-CH_2-, 4.9, *s*, -OCH_2, 9.6, *s*, -NH-amide

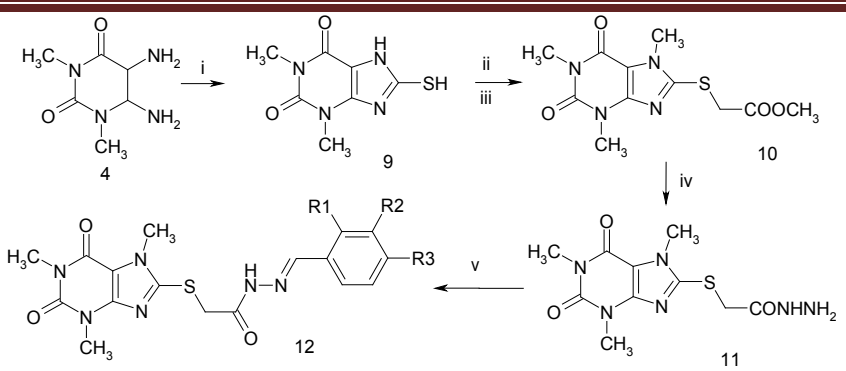
Table 3

Comp.	8-psition	R1	R2	R3	% yield	M.P (°C)	NMR
10	SCH_2COOCH_3				85.7	215-216	3.4, 3.6, *s*, N1-, N3-CH_3, 3.98, *s*, OCH_2, 4.47, *s*, -SCH_2, 14.4, broad *s*, N7-H
11	$SCH_2CONHNH_2$				92	279-283	3.2,3.4,3.7, *s*, N1-,N3-,N7-CH_3, 4.18, *s*, SCH_2, 7.6, *s*, $NHNH_2$
12a	SCH2CONHNCHPh	Cl	H	Cl	76.2	281-283	3.1,3.3,3.6, *s*, N1-, N3-, N7 CH_3, 4.4, *s*, -SCH_2, 7.4-7.9, *m*, substituted phenyl group, 8.3, *s*, N=CH, 11.8, *s*, -CONH-
12b		H	H	OH	83.6	265-267	
12c		H	CH3	H	81.5	246-248	
12d		H	OCH 3	OH	78	278-283	



i)4-formylphenoxyacetic acid in methanol/ acetic acid at r.t, 18hr, ii)SOCl2 30min reflux ,
iii) alkyl halide in DMF/K2CO3, iv) a.SOCl2 ,b.alkylamine in pyridine

Scheme1



i)KOH,DMF,CS2, ii) BrCH2COOCH3, NaOH 1%, iii) alkyl halide in DMF
iv) NH2NH2.H2O 80% / ethanol, v)Substituted benzaldehyde in ethanol

Scheme 2

EXPERIMENTAL

8-(4-carboxymethyloxy) pheny-1,3,7-trimethyl xanthine **7**.

1, 3-dimethyl-8-(4-carboxymethyloxy) phenyl xanthine **6** (0.229g, 0.69mmol) was dissolved in 10 ml DMF with gentle heating at 60oC. After cooling to room temperature, potassium carbonate (0.21g, 1.52mmol) was added and the reaction mixture was stirred for 2hr followed by the addition of CH_3I (0.98g, 6.9mmol) the reaction mixture was followed by TLC (CH_2Cl_2:CH_3OH, 9:1) and stirred at room temperature for 96hr. the precipitate was filtered and crystallized from DMF: H2O to give **7** in 67.5% yield.

Similar procedure was carried out using ethyl-, propyl-, and butyl iodide (Table 2).

8-(4-benzylamincarboxymethyloxyphenyl)1,3,7-trimethyl xanthine **8**.

8-(4-carboxymethyloxy) phenyl-1, 3, 7-trimethyl xanthine **7a** (0.3g, 0.87mmol) stirred in 40 ml thionyl chloride at 70^oC for 4hr. access thionyl chloride was distilled off, the resulted solid was dissolved in CH_2Cl_2 15ml followed by addition of benzyl amine (0.232g, 2.17mmol) then anhydrous pyridine was added 8ml, the mixture was stirred at 55^oC for 40hr, subsequently the solvent was removed under reduced pressure till dryness. The product was recrystallized from (CH_2Cl_2:CH_3OH, 1:1) to afford 8 in 42% yield.

General procedure for the preparation of 12a-d.

1.7 x 10^{-3} mol was added to a solution of compound 11 in absolute ethanol 20 ml, followed by 4-5 drops of acetic acid, the reaction mixture was refluxed for 8 hr. the precipitate resulted was filtered, washed with ethanol, dried, and crystallized from ethanol to give 12.

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Source of support: Nil, Conflict of interest: None Declared