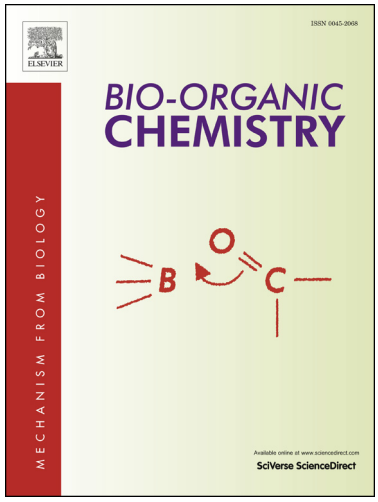

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PII: S0045-2068(16)30003-7
DOI: http://dx.doi.org/10.1016/j.bioorg.2016.01.003
Reference: YBIOO 1871

To appear in: *Bioorganic Chemistry*

Received Date: 27 October 2015
Revised Date: 15 January 2016
Accepted Date: 16 January 2016

Please cite this article as: R. Yadav, R. Bansal, S. Kachler, K-N. Klotz, Synthesis and pharmacological characterization of novel xanthine carboxylate amides as A_{2A} adenosine receptor ligands exhibiting bronchospasmolytic activity, *Bioorganic Chemistry* (2016), doi: http://dx.doi.org/10.1016/j.bioorg.2016.01.003

Synthesis and pharmacological characterization of novel xanthine carboxylate amides as A_{2A} adenosine receptor ligands exhibiting bronchospasmolytic activity

Rakesh Yadav[1], Ranju Bansal[1*], Sonja Kachler[2] and Karl-Norbert Klotz[2]

[1]University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh – 160014, India

[2]Institut für Pharmakologie und Toxikologie, Universität Würzburg, Germany

[*]**Corresponding author:**
Prof. Ranju Bansal
University Institute of Pharmaceutical Sciences
Panjab University, Chandigarh-160 014, India
Email: ranju29in@yahoo.co.in
Tel.: 0172-2541142; Fax: 0172-2543101

Abstract

The carboxylate amides of 8-phenyl-1,3-dimethylxanthine described herein represent a new series of selective ligands of the adenosine A_{2A} receptors exhibiting bronchospasmolytic activity. The effects of location of 8-phenyl substitutions on the adenosine receptor (AR) binding affinities of the newly synthesized xanthines have also been studied. The compounds displayed moderate to potent binding affinities towards various adenosine receptor subtypes when evaluated through radioligand binding studies. However, most of the compounds showed the maximum affinity for the A_{2A} subtype, some with high selectivity *versus* all other subtypes. Xanthine carboxylate amide **13b** with a diethylaminoethylamino moiety at the *para*-position of the 8-phenylxanthine scaffold was identified as the most potent A_{2A} adenosine receptor ligand with K_i = 0.06 µM. Similarly potent and highly A_{2A}-selective are the isovanillin derivatives **16a** and **16d**. In addition, the newly synthesized xanthine derivatives showed good *in vivo* bronchospasmolytic activity when tested in guinea pigs.

Keywords:

Adenosine receptor ligands, Bronchospasmolytic agents, 8-Phenylxanthine carboxylate amides, Partition coefficient

1. Introduction

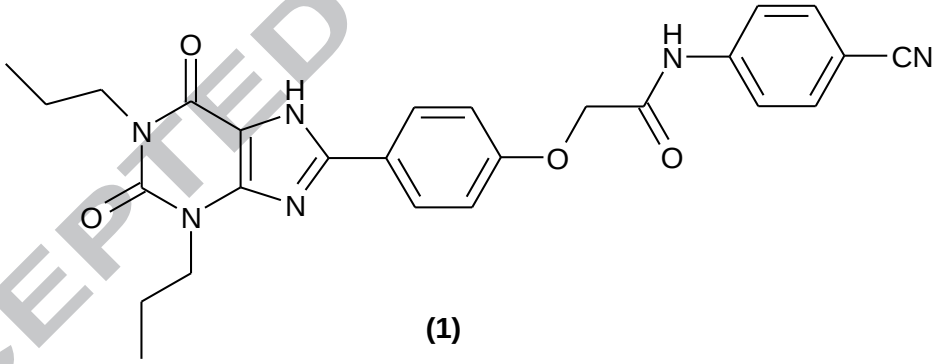
The development of potent and selective ligands of adenosine receptors (ARs) has been the subject of medicinal chemistry research for more than three decades. The expression and activation of the four adenosine receptor subtypes A_1, A_{2A}, A_{2B}, and A_3 are associated with the control of gene expression, cell growth, intestinal function, neurosecretion, vascular tone and asthma. Therefore all AR subtypes have been considered as potential targets for therapies of neurodegenerative, cardiac, immune and inflammatory disorders [1,2]. Although several adenosine receptor-specific compounds have entered clinical trials and an A_{2A} AR selective agonist Regadenosan® has gained approval from US Food and Drug Administration (FDA), in practice this goal remains elusive even today [3,4]. The possibility of side effects due to the ubiquitous nature of ARs suggests subtype selectivity to be of significance for numerous therapeutic applications [5].

A_{2A} receptor subtype represents a fascinating target for the development of small molecules as antiasthmatic agents as these receptors are expressed in lungs and in inflammatory cells involved in asthma. Therefore selective ligands of this subtype are being widely explored by a large number of research bodies to generate novel therapies for asthma and chronic obstructive pulmonary disease (COPD) [6,7].

Substituted xanthines represent the first potent class of adenosine receptor antagonists reported till date [8]. It has been established that appropriate substitutions as well as location of 8-phenyl substituents affects the potency and selectivity of xanthines towards ARs and thus their pharmacological effects [9,10]. The progressive studies on alkylxanthines led to the development of 8-phenylxanthine carboxylic acid congeners as potent and selective adenosine A_2 receptor antagonists. In particular, the derivative named MRS-1754 (**1**) has emerged as a potent and selective xanthine based A_{2B} adenosine receptor antagonist [11,12] (fig 1). Jacobson and co-workers demonstrated the increased affinity of xanthine amides at A_2 receptors with the introduction of an 8-phenyl group functionalized in the *para*-position with a carboxymethoxy chain [13]. However the effect of this moiety on other positions of the 8-phenyl group remains relatively unexplored. In continuation of our earlier

investigations [14-16] directed towards finding therapeutically useful molecules through the preparation of substituted xanthines, we considered it worthwhile to synthesize and study additional amide derivatives of xanthine carboxylates as represented by structure **2** in figure 1.

Taking into consideration the related interesting literature reports, an acetyloxy group linked through a nitrogen atom to a variety of cyclic and acyclic substituents was introduced on the 8-phenyl ring in this series of xanthine derivatives. Previous studies have indicated that suitable selection and positioning of aryl substituents lead to the development of potent and selective xanthine based AR ligands [14]. Shifting of *para* substituents to *meta* position of 8-phenyl ring resulted into xanthines with almost equal affinity for A_1 and A_{2A} subtypes while the former were more selective for A_{2A} receptors. Therefore, the effects of varying the location of 8-phenyl substituent in the current series of xanthine carboxylate amides on the biological properties were also examined. It is also anticipated that coupling of a carboxylic group with various polar groups such as amines may improve the water solubility of xanthines, so one of the series was also selected randomly to evaluate the hydrophobicity of the synthesized compounds [17,18].



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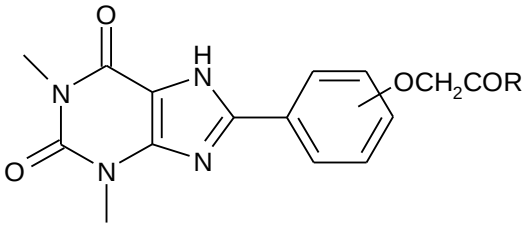


(2)

Figure 1: Structures of potent xanthine based A_{2B} adenosine receptor antagonist MRS-1754 (**1**) and general structure (**2**) of proposed xanthine derivatives

The synthesized compounds have been biologically evaluated using radioligand binding to membranes prepared fom CHO cells transfected with human A_1, A_{2A}, A_{2B} and A_3 adenosine receptor subtypes [19,20]. *In vivo* experiment using a histamine chamber was also performed to study the bronchospasmolytic activity of the new compounds using theophylline as a standard drug [21].

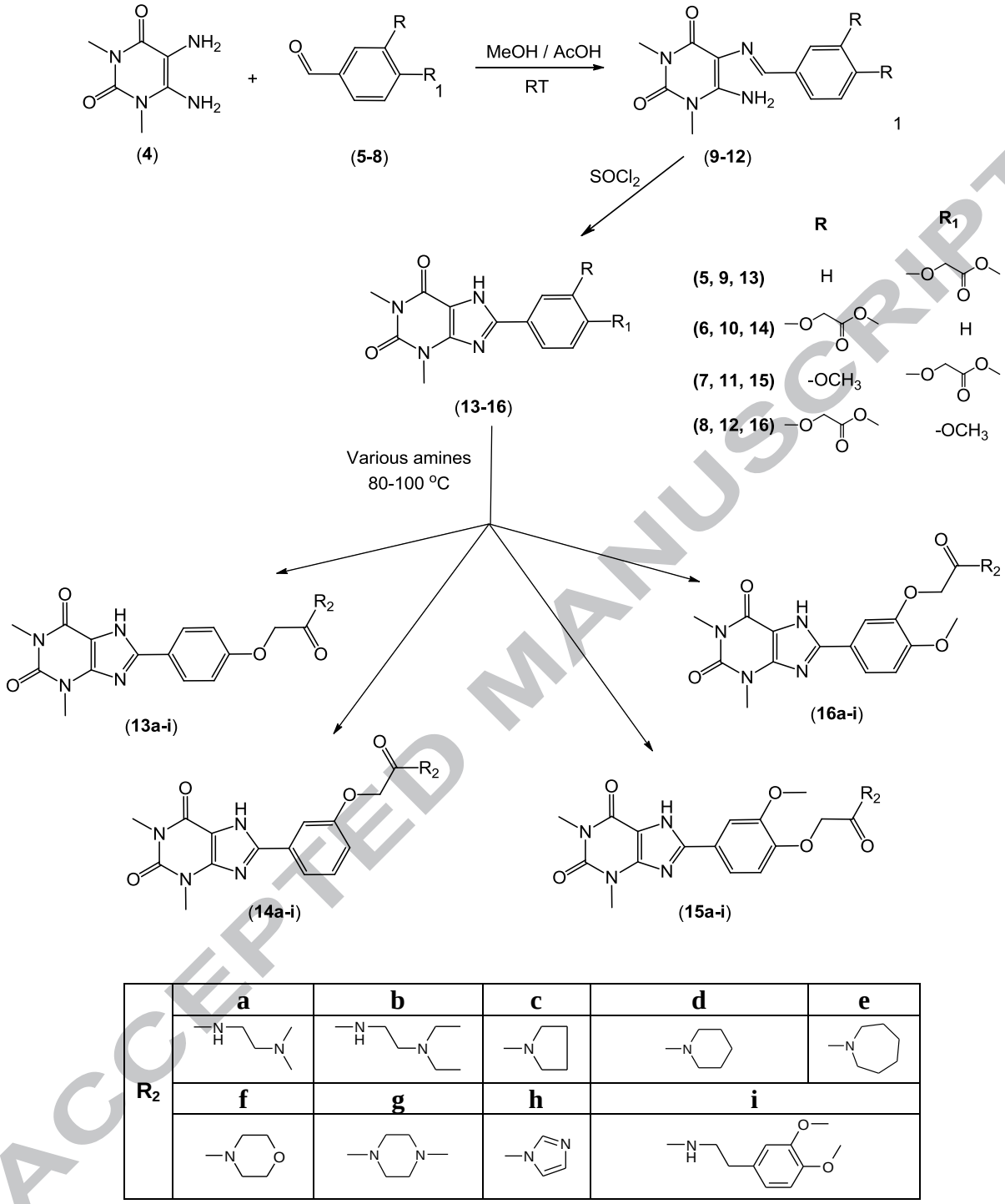
2. Results and Discussion

2.1. Chemistry

5,6-Diaminouracil (**4**), the intermediate used for the preparation of new xanthine derivatives was prepared according to the reported method [22,23]. Synthesis of substituted aldehydes **5-8**, Schiff bases **9-12** and xanthine carboxylate esters **13-16** is presented in scheme 1. The starting aldehydes such as 4-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, vanillin and isovanillin, possessing a vulnerable *para* or *meta* hydroxy group on the 8-phenyl ring for derivatization, were selected to study the effect of such substitution pattern on affinity and selectivity of xanthine derivatives for various adenosine receptor subtypes. This choice is not only characterized by ease of substitution but also helped to evaluate the impact of various substituting groups in *para* or *meta* positions of the 8-phenyl ring, with or without an *ortho* methoxy group, on adenosine binding affinity and selectivity.

Condensation of various substituted aldehydes **5-8** with 5,6-diaminouracil (**4**) in the presence of MeOH:AcOH (4:1) at room temperature afforded Schiff bases **9-12**, oxidative cyclization of which in refluxing thionyl chloride formed xanthine carboxylates **13-16** as shown in scheme 1. A singlet integrating for one proton appeared at ~ δ 9.7 ppm for N=C*H* in ^{1}H NMR all the benzylidene derivatives **9-12.**

Amide derivatives **13a-i**–**16a-i** of parent xanthine carboxylate esters **13-16** were prepared according to scheme 1 by fusing them with appropriate acyclic and cyclic amines. A prominent singlet for -OCH_2- ranging from δ 4.5 to 4.8 and presence of two *N*-methyl of xanthine ring at ~ 3.40 and ~ 3.50 ppm were observed in the nuclear magnetic resonance spectra of all the amide derivatives **13a-i**–**16a-i**. Three *N*-methylenes of –CH_2-N(CH_2CH_3)$_2$ moiety appeared together as a multiplet at δ 2.5-2.6 for diethylamino derivatives **13b-16b**, whereas protons of –CH_2-N of dimethylamino



Scheme-1- Synthetic route to the synthesis of xanthine carboxylate amides **13a-i, 14a-i, 15a-i** and **16a-i**

derivatives **13a-16a** resonated separately at ~ 2.5 ppm. Two *N*-methylenes of the heterocyclic ring for pyrrolidino xanthines **13c-16c** were found a little upfield than those of piperidino derivatives **13d-16d**. The compounds **13-16** were also fused with

homoveratrylamine to observe the effect of such functionality on the pharmacological profile of xanthines since this type of moiety form an integral part of a potent and selective A_{2B} adenosine receptor antagonist, MRE-2028F20 [18].

2.2. Partition Coefficient

The partition coefficient values of xanthine carboxylate ester **14** and its amidic congeners **14a-i** belonging to 3-hydroxybenzaldehyde series were measured using the shake flask method and an *in silico* (ChemDraw Ultra 8.0.3 and Biotage Path Finder) method [18]. Partition coefficient data (Log PC) of various xanthine derivatives have been compiled in *table 1*. In general, the compounds displayed good hydrophobicity except the compounds **14a-b** and **14h**.

Table 1: *Partition coefficient values of some 8-substituted-phenylxanthine derivatives*

Comp. No. (Code)	**Partition Coefficient (Log PC)**			
	Calculated		**Measured**	
	Biotage	**Chem Draw**	**$LogPC_{CH}$**	**$LogPC_{OC}$**
14 (RB-374)	1.06	0.27	0.865	1.051
14a (RB-379)	1.08	0.26	-0.094	0.064
14b (RB-378)	0.39	-0.41	-1.144	-0.396
14c (RB-381)	0.99	0.14	1.776	1.509
14d (RB-382)	1.38	0.56	2.339	1.506
14e (RB-376)	1.78	0.97	1.710	2
14f (RB-375)	0.32	-0.58	1.094	0.526
14g (RB-380)	0.46	-0.42	0.240	0.655
14h (RB-445)	0.94	-0.41	-1.037	-1.735
14i (RB-377)	1.94	1.35	1.82	0.089

There is also a significant correlation between chloroform/phosphate buffer and *n*-octanol/phosphate buffer partition coefficient values of these derivatives (r^2 = 0.64; $p < 0.05$) as shown in *figure 2*. The regression line (solid line) was calculated by the least-

squares method. The dotted lines indicate 95% confidence limits for the regression line. The three xanthine amides **14c-e**, substituted with 5-, 6-, and 7-membered heterocyclic ring, respectively, exhibited higher partition coefficient values, which indicate their preferential distribution to hydrophobic compartments such as the lipid bilayers of cells. The ideal not too hydrophobic nor too hydrophilic character of the new xanthines predicts their good bioavailability. It is assumed that these compounds might produce good bronchodilating effects as the potency of relaxant effects of xanthines depends on the cell membrane permeability based on their hydrophobic property. The hydrophobicity may also be the major factor for the molecules to bind to the receptors.

2.3. Radioligand binding assays

Table 2 summarizes the observed binding affinities of newly synthesized 8-(carboxymethyloxyphenyl)xanthine derivatives towards the four human adenosine receptor subtypes (A_1, A_{2A}, A_{2B} and A_3). In general, the 8-phenylsubstituted xanthine carboxylate esters **13-16** and their amidic congeners **13a-i–16a-i** displayed moderate to potent binding affinities towards various adenosine receptor subtypes, however, augmented affinity and thus resulting in selectivity was markedly present for the A_{2A} subtype in the majority of the cases. Overall the binding selectivity for A_{2A} is somewhat more pronounced *versus* A_3 receptors (up to > 400 fold) as compared to the A_1 (maximally about 60 fold) and A_{2B} (up to > 130 fold) subtypes. Monosubstituted 8-phenylxanthine carboxylate esters **13** and **14** with a polar side chain present at *para* or *meta* positions of the 8-phenyl ring, respectively, displayed higher binding affinity for all AR subtypes and more notably for A_{2A} receptors in comparison to disubstituted analogues **15** and **16**, which possess an additional methoxy group *ortho* to the methoxycarbonylmethoxy side chain. Incorporation of a methoxy substituent significantly improves the A_{2A} selectivity of disubstituted xanthines **15** and **16** *versus* A_1 subtype in comparison to their monosubstituted counterparts, however reduced selectivity is observed *versus* A_{2B} and A_3 adenosine receptors. The results are in agreement with the adenosine binding affinity data of a series of 8-(4-aminoethoxy)phenylxanthines previously reported from our

laboratory [14]. Conversion of xanthine carboxylates into amides enhances the A_{2A} binding affinity in general, but the selectivity pattern remains the same as seen with their precursors. While comparing the two series of monosubstituted 8-phenylxanthine derivatives **13a-i** and **14a-i**, it was observed that both *para* and *meta* substituted 8-phenylxanthines showed pronounced affinity for A_{2A} receptors. However, the *meta* substituted products **14a-i** exhibited markedly decreased affinity for A_{2B} receptors in comparison to their *para* phenyl substituted counterparts **13a-i**. 1,3-Dimethyl-8-[4-{2-(diethylaminoethylamino)-2-oxoethoxy}phenyl]xanthine (**13b**) with the K_i = 63 nM at A_{2A} receptors remains the most potent compound of the two series.

The binding affinity of disubstituted 8-phenylxanthine analogues **15a-i** possessing a methoxy group *ortho* to the *meta* substituted polar side chain was found to be lower for A_{2A} in comparison to monosubstituted compounds. The isovanilloid based compounds **16a-i** with the rearrangement of the side substitutions of the 8-phenyl ring so that methoxy is at 4-position and polar substituents are at 3-position on the 8-phenyl ring, showed high affinity for A_{2A} receptors. This resulted in a higher level of selectivity for A_{2A} *versus* other receptor subtypes compared to the vanilloid series **15a-i**.1,3-Dimethyl-8-[4-methoxy-3-{2-(-(dimethylaminoethylamino)-2-oxoethoxy}phenyl]xanthine (**16a**) emerged as the most potent compound of the disubstituted series with a K_i = 75 nM. No systematic differences were observed in binding affinity of 8-(carboxymethyloxyphenyl) substituted xanthines bearing open (**13a-b**–**16a-b**) and cyclisized heterocyclic ring systems (**13c-i**–**16c-i**) in their side chains for individual adenosine receptors. In contrast to earlier reported xanthine carboxylate amides such as MRS-1754 with high A_{2B} receptor selectivity [11], the new compounds depicted higher affinity for A_{2A} AR *versus* the other human adenosine receptor subtypes.

Table. 2 *Binding profile of various xanthine derivatives at adenosine receptors (A_1, A_2, A_{2B} and A_3)*

COMP. NO. (CODE)	K_i (μM)				A_{2A} selectivity		
	$(A_1)^a$	$(A_{2A})^b$	$(A_{2B})^c$	$(A_3)^d$	A_1/A_{2A}	A_{2B}/A_{2A}	A_3/A_{2A}
13 (RB-419)	0.319 (0.273-0.374)	0.170 (0.124-0.233)	0.980 (0.866-1.11)	5.86 (5.01-6.85)	1.9	5.8	34

COMP. NO. (CODE)	K_i (μM)				A_{2A} selectivity		
	$(A_1)^a$	$(A_{2A})^b$	$(A_{2B})^c$	$(A_3)^d$	A_1/A_{2A}	A_{2B}/A_{2A}	A_3/A_{2A}
14 (RB-374)	3.95 (2.36-6.63)	0.375 (0.236-0.597)	>10	3.81 (2.90-5.00)	11	>26	10
15 (RB-384)	>30	4.38 (2.35-8.15)	>10	>10	>6.8	>2.3	>2.3
16 (RB-410)	11.8 (7.76-18.0)	0.717 (0.547-0.939)	>10	10.7 (8.62-13.4)	16	>14	15
13a (RB-420)	0.220 (0.194-0.249)	0.100 (0.046-0.216)	0.903 (0,760+1,07)	10.5 (6.59-16.8)	2.2	9.0	105
13b (RB-421)	0.298 (0.233-0.380)	0.063 (0.042-0.096)	0.968 (0.851-1.10)	8.35 (7.25-9.61)	4.7	15	132
13c (RB-426)	0.796 (0.622-1.02)	0.122 (0.082-0.182)	1.49 (1.25-1.78)	5.68 (3.91-8.24)	6.5	12	47
13d (RB-427)	0.419 (0.369-0.476)	0.178 (0.101-0.313)	0.401 (0,232-0,696)	13.0 (11.8-14.4)	2.4	1.5	73
13e (RB-424)	0.609 (0.456-0.813)	0.273 (0.196-0.381)	0.443 (0.406-0.486)	4.15 (2.61-6.59)	2.2	1.6	15
13f (RB-423)	1.25 (0.996-1.62)	0.283 (0.195-0.411)	2.29 (1.85-2.83)	7.11 (5.62-8.99)	4.4	8.1	25
13g (RB-425)	0.499 (0.450-0.553)	0.193 (0.098-0.378)	0.954 (0,645-1,41)	10.1 (9.83-10.3)	2.6	4.9	52
13h (RB-447)	3.99 (2.83-5.63)	2.69 (1.71-4.21)	6.38 (4.75-8.58)	>30	1.5	2.4	>11
13i (RB-422)	1.68 (1.34-2.10)	0.128 (0.102-0.161)	0.516 (0.468-0.571)	6,0 (5.46-6.58)	13	4.0	47
14a (RB-379)	0.683 (0.627-0.744)	0.163 (0.079-0.339)	2.83 (1,78-4,50)	8.97 (5.73-14.0)	4.2	17	55
14b (RB-378)	1.22 (0.983-1.52)	0.179 (0.143-0.223)	4.91 (3.32-7.30)	8.39 (6.58-10.70)	6.8	27	47
14c (RB-381)	3.29 (3.10-3.49)	0.237 (0.167-0.338)	>10	4.64 (4.27-5.04)	14	>42	20
14d (RB-382)	1.52 (1.37-1.69)	0.209 (0.102-0.430)	4.04 (2,00-6,51)	4.16 (2.90-5.00)	7.3	19	20
14e (RB-376)	2.43 (2.20-2.69)	0.226 (0.133-0.384)	6.28 (3.49-11.3)	3.69 (2.85-4.78)	11	28	16
14f (RB-375)	5.37 (4.89-5.89)	0.679 (0.657-0.702)	>10	7.90 (5.81-10.70)	7.9	>15	12
14g (RB-380)	1.90 (1.75-2.06)	0.561 (0.296-1.07)	8.21 (1,80-14,0)	5.67 (6.12-14.4)	3.4	15	10
14h (RB-445)	>30	0.509 (0.310-0.836)	>30	4.89 (4.35-5.49)	>59	>59	9.6

COMP. NO. (CODE)	K_i (μM)				A_{2A} selectivity		
	$(A_1)^a$	$(A_{2A})^b$	$(A_{2B})^c$	$(A_3)^d$	A_1/A_{2A}	A_{2B}/A_{2A}	A_3/A_{2A}
14i (RB-377)	5.98 (4.27-8.38)	1.39 (0.80-2.41)	>10	9.25 (6.95-12.3)	4.3	>7.2	6.7
15a (RB-386)	9.25 (6.66-12.8)	0.821 (0.462-1.46)	10.0 (8,93-11,3)	>10	11	12	>12
15b (RB-388)	>10	0.692 (0.582-0.823)	>10	>30	>14	>14	>43
15c (RB-392)	>30	4.57 (3.48-6.00)	>30	>30	>6.6	>6.6	>6.6
15d (RB-391)	>30	3.35 (1.66-6.73)	>10	>10	>8.9	>3,0	>3.0
15e (RB-387)	>10	2.41 (1.49-3.90)	7.82 (4.38-13.9)	9.01 (4.76-17.0)	>4.1	3.2	3.7
15f (RB-385)	>30	2.74 (2.05-3.67)	>30	>30	>11	>11	>11
15g (RB-446)	>30	4.21 (2.77-6.39)	>10	>30	>7.1	>2.4	>7.1
15h (RB-390)	>30	7.74 (7.17-8.35)	>30	>30	>3.9	>3.9	>3.9
15i (RB-389)	>30	0.843 (0.559-1.27)	>30	>30	>36	>36	>36
16a (RB-413)	0.847 (0.605-1.18)	0.075 (0.042-0.132)	4.80 (3,72-6,19)	>30	11	64	>400
16b (RB-411)	1.97 (1.68-2.30)	0.126 (0.076-0.208)	8.05 (6.43-10.0)	>30	16	64	>240
16c (RB-414)	5.94 (4.17-8.45)	0.259 (0.194-0.345)	>10	8.98 (7.25-11.1)	23	>39	35
16d (RB-417)	1.62 (1.48-1.77)	0.076 (0.040-0.145)	>10	1.97 (1.49-2.61)	21	>130	26
16e (RB-449)	1.91 (1.55-2.34)	0.094 (0.057-0.156)	3.94 (3.00-5.16)	0.797 (0.790-0.836)	20	42	8.5
16f (RB-415)	3.51 (2.48-4.96)	0.466 (0.348-0.624)	>10	14.30 (8.60-23.8)	7.5	>21	31
16g (RB-416)	3.64 (3.41-3.89)	0.685 (0.428-1.10)	6.54 (4,62-9,27)	>10	5.3	9.5	>15
16h (RB-450)	>30	1.12 (0.91-1.38)	>30	4.10 (3.70-4.55)	>27	>27	3.7
16i (RB-412)	>30	0.772 (0.607-0.981)	>30	>30	>39	>39	>39

Shown values are geometric means from 3–5 experiments in μM with 95% confidence intervals in parentheses, where:-

[a]Displacement of specific (^{3}H)CCPA binding in CHO cells, stably transfected with human recombinant A_1 adenosine receptor, expressed as K_i (nM).

[b]Displacement of specific (^{3}H)NECA binding in CHO cells, stably transfected with human recombinant A_{2A} adenosine receptor, expressed as K_i (nM).

[c]Antagonist affinities were determined by inhibition of NECA-stimulated adenylyl cyclase activity in membrane preparations.

[d]Displacement of specific (^{3}H)HEMADO binding in CHO cells, stably transfected with human recombinant A_3 adenosine receptor, expressed as K_i (nM).

2.4. Bronchospasmolytic activity

All the newly synthesized 8-(carboxymethyloxyphenyl) derived xanthine amides **13a-i–16a-i** displayed significant protection against histamine aerosol induced bronchospasm in guinea pigs (*Table 3*). Many compounds showed more bronchospasmolytic potency in comparison to the standard drug theophylline as apparent from enhanced time of onset of bronchospasm in case of test compounds compared to theophylline. In the 4-hydroxybenzaldehyde series the most effective compounds with negligible jerks, least severity of bronchospasm and 100% survival of animals were xanthenes **13b**, **13c** and **13f**. The compounds **14d**, **14g** and **14h** from the 3-hydroxybenzaldehyde series displayed a similar pattern of bronchospasmolytic activity along with markedly increased time for onset of bronchospasm. In the vanillin substituted series **(15a-15i)** comparable bronchospasmolytic effects as that of standard theophylline were observed, but the survival of animals was reduced to 60%. Only the imidazole substituted compound **15h** of this series showed a 100% survival of animals with onset of bronchospasm equivalent to theophylline. The **16d** and **16g** of the isovanillin series showed prominent protection against histamine induced bronchospasm with 100% survival of animals.

Table 3: Protection by newly synthesized xanthine derivatives against bronchospasm induced by histamine aerosol (5 ml of 1% w/v aerosoled in 1 min) in guinea pigs

Comp. No. (Code)	**Mean time in seconds for onset of bronchospasm Mean ± S.E.M**	**Duration of jerks in seconds Mean ± S.E.M**	**Severity of bronchospasm**	**Survival (%)**
Control	67±2*	172±4*	+++	0
Theophylline	92±3	89±7	+	100

Comp. No. (Code)	**Mean time in seconds for onset of bronchospasm Mean ± S.E.M**	**Duration of jerks in seconds Mean ± S.E.M**	**Severity of bronchospasm**	**Survival (%)**
13a (RB-420)	76±5	17±4*	++	40
13b (RB-421)	95±3	32±5*	+	100
13c (RB-426)	131±4*	32±3*	+	100
13d (RB-427)	74±4	34±6*	++	40
13e (RB-424)	92±2	41±2*	+	80
13f (RB-423)	86±3	38±3*	+	100
13g (RB-425)	80±2	38±4*	++	40
13h (RB-447)	79±5	26±3*	++	60
13i (RB-422)	86±5	115±5*	++	40
14a (RB-379)	71±4	24±5*	++	60
14b (RB-378)	98±4	74±2	+	80
14c (RB-381)	71±5	33±2*	++	40
14d (RB-382)	121±6*	38±3*	+	100
14e (RB-376)	120±5*	60±5*	+	80
14f (RB-375)	94±4	46±3*	+	80
14g (RB-380)	102±3	42±2*	+	100

Comp. No. (Code)	**Mean time in seconds for onset of bronchospasm Mean ± S.E.M**	**Duration of jerks in seconds Mean ± S.E.M**	**Severity of bronchospasm**	**Survival (%)**
14h (RB-445)	130±5*	30±4*	+	100
14i (RB-377)	100±4	68±2*	+	80
15a (RB-386)	110±4	90±4	++	60
15b (RB-388)	81±4	34±6*	++	60
15c (RB-392)	84±4	38±2*	++	60
15d (RB-391)	112±4	65±2*	++	40
15e (RB-387)	99±3	34±2*	++	60
15f (RB-385)	92±2	82±2	++	60
15g (RB-446)	126±3*	66±4*	++	60
15h (RB-390)	97±4	20±3*	+	100
15i (RB-389)	86±4	19±1*	++	40
16a (RB-413)	84±5	80±3	++	40
16b (RB-411)	72±3	50±2*	++	40
16c (RB-414)	68±2	53±4*	++	60
16d (RB-417)	103±5	60±3*	+	100
16e (RB-449)	64±4*	41±3*	++	40

Comp. No. (Code)	Mean time in seconds for onset of bronchospasm Mean ± S.E.M	Duration of jerks in seconds Mean ± S.E.M	Severity of bronchospasm	Survival (%)
16f (RB-415)	96±5	113±3*	++	60
16g (RB-416)	116±5*	59±2*	+	100
16h (RB-450)	73±3	42±4*	+	40
16i (RB-412)	71±2	51±2*	++	60

Number of animals in each group (N) = 4
Dose of standard and tested compounds = 50 mg/kg
****Tukey's test; p<0.05***

All compounds exhibited A_{2A} AR binding affinity ranging from about 60 nM to 8 µM along with prominent bronchospasmolytic effects. Imidazole substituted 8-(carboxymethyloxyphenyl) xanthine **15h** shows the lowest affinity for A_{2A} but the bronchospasmolytic effects are prominent. Although a causal relationship between A_{2A} antagonism and broncholysis seems very likely other contributing mechanisms cannot be ruled out in this case.

3. Conclusions

The newly synthesized 8-(carboxymethyloxyphenyl)xanthine amides display significant binding affinity for adenosine receptors with maximum potency for A_{2A} receptors and varying degree of selectivity *versus* other AR subtypes. The effects of varying substituents and their location on the 8-phenyl ring are clearly visible in the pharmacological characteristics of these novel xanthine derivatives. Suitable introduction of 8-phenyl substituents on the xanthine scaffold results in potent and selective binding with A_{2A} adenosine receptors, which seems to be an important trait for potent bronchospasmolytic effects. Further the partition coefficient values predict the ideal not too hydrophobic nor too hydrophilic character of the new xanthines for good bioavailability.

4. Experimental section

4.1. Chemistry

All melting points were obtained using glass capillary tubes on Veego melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on Perkin-Elmer RX1 Fourier Transform-Infrared spectrophotometer using potassium bromide pellets (υ_{max} in cm^{-1}). Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance spectroscopy were performed using a Bruker AC-400F, 400 MHz spectrometer for solutions in deuteriochloroform ($CDCl_3$), deuterated dimethylsulfoxide (DMSO-d_6) and mixture of $CDCl_3$-DMSO-d_6 (2:1) and are reported in parts per million (ppm) downfield from tetramethylsilane (Me_4Si) as internal standard. The spin multiplicities are indicated by the symbols, s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), br (broad) and the coupling constants (*J*) are given in Hertz (Hz). Elemental analyses were carried out on a Thermo-Flash EA-1112 CHNS-O analyzer. The results are within 0.4% of the theoretical values. Precoated plates with silica gel G (E. Merck 60 F_{254}, 0.25 mm) were used for thin layer chromatography (TLC). Chromatographic spots were visualized by ultra-violet light in the UV cabinet (Perfit, India). Anhydrous sodium sulfate was utilized as drying agent. All solvents were freshly distilled and dried prior to use according to standard procedures. Synthesis of substituted aldehydes **5-8** by a two step method is reported in literature [24], however we performed the reaction in a single step.

4.1.1. General method for the synthesis of compounds 5-8

Methyl chloroacetate (4.0 ml) was added to a stirred and refluxing suspension of desired aromatic aldehyde [4-hydroxybenzaldehyde (1.0 g, 8.19 mmol) / 3-hydroxybenzaldehyde (1.0 g, 8.19 mmol) / vanillin (1.0 g, 6.57 mmol) / isovanillin (1.0 g, 6.57 mmol] and anhydrous potassium carbonate (2.0 g) in ethyl methyl ketone (40 ml). The reaction mixture was further refluxed for 4 h with continuous stirring until the reaction was complete. (monitored by TLC). The reaction mixture was cooled, filtered and solvent was removed under reduced pressure to obtain the corresponding oily residues **5-8**, which were used as such for subsequent reaction.

4.1.2. General method for the synthesis of various benzylidene derivatives 9-12

To a stirred solution of 5,6-diamino-1,3-dimethyluracil (**4**) (1.0 g, 5.87 mmol) in MeOH–AcOH (4:1, 40 mL) was slowly added the solution of above obtained oily residues of requisite substituted aldehydes **5-8** in methanol (24 ml). Yellow colored precipitate appeared during addition. The reaction mixture was further stirred overnight at room temperature and the completion of reaction was monitored by thin layer chromatography. The precipitate obtained was filtered off, washed with methanol and dried to obtain corresponding benzylidene derivatives **9-12**.

4.1.2.1. 6-Amino-5-[{4-(2-methoxy-2-oxoethoxy)benzylidene}amino]-1,3-dimethyluracil (**9**) (1.2 g; 65 %), mp: 236-238 °C; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 3.33 (s, 3H, N-CH_3), 3.51 (s, 3H, N-CH_3), 3.81 (s, 3H, -OCH$_2$COOCH_3), 4.71 (s, 2H, -OCH_2), 6.87 (s(br), 2H, -NH_2), 6.92 (d, 2H, 2-C*H* and 6-C*H*, aromatic, J_o = 8.68 Hz), 7.73 (d, 2H, 3-C*H* and 5-C*H*, aromatic, J_o = 8.68 Hz) and 9.71 ppm (s, 1H, N=C*H*); FT-IR (KBr): υ_{max} = 3331, 2955, 1755, 1696, 1627, 1510, 1437, 1301, 1230, 1080, 965, 830 and 755 cm^{-1}; Anal. calcd. for $C_{16}H_{18}N_4O_5$: C, 55.49; H, 5.24; N, 16.18. Found: C, 55.60; H, 5.25; N, 16.29.

4.1.2.2. 6-Amino-5-[{3-(2-methoxy-2-oxoethoxy)benzylidene}amino]-1,3-dimethyluracil (**10**) (0.76 g; 75 %), mp: 198-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 3.34 (s, 3H, N-CH_3), 3.51 (s, 3H, N-CH_3), 3.81 (s, 3H, -OCH$_2$COOCH_3), 4.71 (s, 2H, -OCH_2-), 6.85 (s, 2H, -NH_2), 6.88 (d, 1H, 4-C*H*, aromatic, J_o = 7.68 Hz), 7.31 (t, 1H, 5-C*H*, aromatic, J_o = 7.96 Hz), 7.36 (m, 2H, 2-C*H* and 6-C*H*, aromatic) and 9.72 ppm (s, 1H, N=C*H*); FT-IR (KBr): υ_{max} = 3312, 2957, 1772, 1738, 1692, 1588, 1438 and 860 cm^{-1}; Anal. calcd. for $C_{16}H_{18}N_4O_5$: C, 55.49; H, 5.24; N, 16.18. Found: C, 55.65; H, 5.31; N, 16.08.

4.1.2.3. 6-Amino-5-[{(4-(2-methoxy-2-oxoethoxy)-3-methoxy)benzylidene}amino]-1,3-dimethyl- uracil (**11**) (1.1 g, 99 %), mp: 218-220 °C; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 3.27 (s, 3H, N-CH_3), 3.48 (s, 3H, N-CH_3), 3.77 (s, 3H, -OCH$_2$COOCH_3), 3.93 (s, 3H, -OCH_3), 4.75 (s, 2H, -OCH_2-), 6.85 (d, 1H, 5-C*H*, aromatic, J_o = 8.28 Hz), 7.07 (s,

2H, -N*H*$_2$), 7.24 (d, 1H, 6-C*H*, aromatic, J_o = 8.24 Hz), 7.48 (s, 1H, 2-C*H*, aromatic) and 9.68 ppm (s, 1H, N=C*H*); FT-IR (KBr): υ_{max} = 3329, 2922, 2851, 1763, 1691, 1621, 1507, 1438, 1221 and 758 cm^{-1}; Anal. calcd. for $C_{17}H_{20}N_4O_6$: C, 54.25; H, 5.36; N, 14.89. Found: C, 55.12; H, 5.16; N, 15.25.

4.1.2.4. 6-Amino-5-[{(3-(2-methoxy-2-oxoethoxy)-4-methoxy)benzylidene}amino]-1,3-dimethyluracil (**12**) (0.74 g, 67 %), mp: 208-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.30 (s, 3H, N-C*H*$_3$), 3.50 (s, 3H, N-C*H*$_3$), 3.78 (s, 3H, -OCH$_2$COOC*H*$_3$), 3.90 (s, 3H, -OC*H*$_3$), 4.80 (s, 2H, -OC*H*$_2$-), 6.95 (d, 1H, 5-C*H*, aromatic, J_o = 8.32 Hz), 7.00 (s(br), 2H, -N*H*$_2$), 7.29 (dd, 1H, 6-C*H*, aromatic, J_m = 1.80 Hz; J_o = 8.22 Hz), 7.42 (d, 1H, 2-C*H*, aromatic, J_m = 1.60 Hz) and 9.65 ppm (s, 1H, N=C*H*); FT-IR (KBr): υ_{max} = 3318, 2942, 1762, 1677, 1620, 1507, 1432, 1262, 1219, 1135, 1065, 868 and 761 cm^{-1}; Anal. Calcd. for $C_{17}H_{20}N_4O_6$: C, 54.25; H, 5.36; N, 14.89. Found: C, 54.27; H, 5.27; N, 14.74.

4.1.3. General method for synthesis of various 8-(substitutedphenyl)xanthine derivatives 13-16

Benzylidene derivatives **9-12** (1.0 g, 2.88 mmol) thus obtained were refluxed individually in thionyl chloride (20 ml) for 30-40 min to affect cyclization. The excess thionyl chloride was removed under reduced pressure to obtain a solid product. Ice cold water was added to it and resultant suspension was neutralized with ammonium hydroxide solution. The precipitate obtained was collected by filtration, dried and crystallized from a mixture of methanol and chloroform to afford the desired products **13-16**, respectively.

4.1.3.1. 1,3-Dimethyl-8-[4-(2-methoxy-2-oxoethoxy)-phenyl]xanthine (**13**) (0.94 g, 94 %), mp: 260 ºC (decomp.); ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.42 (s, 3H, N-C*H*$_3$), 3.64 (s, 3H, N-C*H*$_3$), 3.82 (s, 3H, -OCH$_2$COOC*H*$_3$), 4.72 (s, 2H, -OC*H*$_2$-), 6.98 (s, 2H, 2-C*H* and 6-C*H*, aromatic) and 8.13 ppm (s, 2H, 3-C*H* and 5-C*H*, aromatic); FT-IR (KBr): υ_{max} = 3165, 2953, 1749, 1691, 1647, 1479, 1232, 1065, 988, 839 and 747 cm^{-1}; Anal. calcd. for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.79; H, 4.71; N, 16.12.

4.1.3.2. 1,3-Dimethyl-8-[3-(2-methoxy-2-oxoethoxy)-phenyl]xanthine (**14**) (0.92 g, 92 %), mp: 280 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.43 (s, 3H, N-C*H*$_3$), 3.66 (s, 3H, N-C*H*$_3$), 3.82 (s, 3H, -OCH$_2$COOC*H*$_3$), 4.77 (s, 2H, -OC*H*$_2$-), 7.02 (dd, 1H, 4-C*H*, aromatic, J_m = 2.74 Hz; J_o = 7.44 Hz), 7.38 (m, 1H, 5-C*H*, aromatic), 7.76 (s, 1H, 2-C*H*, aromatic) and 7.82 ppm (d, 1H, 6-C*H*, aromatic, J_o = 7.44 Hz); FT-IR (KBr): υ_{max} = 3183, 1760, 1703, 1655, 1594, 1522, 1481 and 1297 cm^{-1}; Anal calcd. for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.76; H, 4.55; N, 16.32.

4.1.3.3. 1,3-Dimethyl-8-[{4-(2-methoxy-2-oxoethoxy)-3-methoxy}-phenyl]xanthine (**15**) (0.95 g, 95 %), mp: 212-214 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.39 (s, 3H, N-C*H*$_3$), 3.61 (s, 3H, N-C*H*$_3$), 3.80 (s, 3H, -OCH$_2$COOC*H*$_3$), 3.93 (s, 3H, -OC*H*$_3$), 4.80 (s, 2H, -OC*H*$_2$-), 6.98 (s, 1H, 5-C*H*, aromatic), 7.36 (s, 1H, 6-C*H*, aromatic), 7.81 (s, 1H, 2-C*H*, aromatic) and 13.36 ppm (s, 1H, N-*H*); FT-IR (KBr): υ_{max} = 2960, 1757, 1694, 1649, 1488, 1266, 1080, 992, 879, 760 and 746 cm^{-1}; Anal. calcd. for $C_{17}H_{18}N_4O_6$: C, 54.54; H, 4.85; N, 14.97. Found: C, 54.35; H, 4.95; N, 14.79.

4.1.3.4. 1,3-Dimethyl-8-[{3-(2-methoxy-2-oxoethoxy)-4-methoxy}-phenyl]xanthine (**16**) (0.97 g, 97 %), mp: 238-240 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (s, 3H, N-C*H*$_3$), 3.60 (s, 3H, N-C*H*$_3$), 3.80 (s, 3H, -OCH$_2$COOC*H*$_3$), 3.92 (s, 3H, -OC*H*$_3$), 4.83 (s, 2H, -OC*H*$_2$-), 7.01 (d, 1H, 5-C*H*, aromatic, J_o = 8.56 Hz), 7.74 (d, 1H, 2-C*H*, aromatic, J_m = 2.00 Hz) and 7.82 ppm (dd, 1H, 6-C*H*, aromatic, J_o = 8.56 Hz; J_m = 1.96 Hz); FT-IR (KBr): υ_{max} = 3159, 2952, 1757, 1697, 1645, 1557, 1486, 1438, 1372, 1274, 1108, 983, 867, and 753 cm^{-1}; Anal. Calcd. for $C_{17}H_{18}N_4O_6$: C, 54.54; H, 4.85; N, 14.97. Found: C, 54.74; H, 4.77; N, 14.84.

4.1.4. General method for the synthesis of 8-(carboxymethyloxyphenyl)xanthine amides 13a-i–16a-i

The mixtures of cyclized xanthine esters **13-16** (1.0 g, 2.90 mmol) with appropriate amines **a-i** (in excess) were heated at 80-100 ºC for 30-40 min. The completion of reaction was monitored by TLC. The excess of amine was removed under vacuum and

residue so obtained was washed thoroughly with diethyl ether. The solid so obtained was filtered, and dried to afford the respective products **13a-i–16a-i**, which were crystallized in methanol.

4.1.4.1. 1,3-Dimethyl-8-[4-{2-(dimethylaminoethylamino)-2-oxoethoxy}-phenyl]xanthine (**13a**) (0.62 g, 53 %), mp: 270-272 ºC; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 2.41 (s, 6H, -N(CH_3)$_2$), 2.58-2.60 (m, 2H, -CH_2-N<), 3.49-3.52 (s, 3H, N-CH_3), 3.48-3.52 (m, 2H, -CONHCH_2), 3.65 (s, 3H, N-CH_3), 4.57 (s, 2H, -OCH_2-), 7.04 (d, 2H, 2-C*H* and 6-C*H*, aromatic, J_o = 8.96 Hz) and 8.13 ppm (d, 2H, 3-C*H* and 5-C*H*, aromatic, J_o = 8.88 Hz); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 27.61 (N-**C**H$_3$), 29.57 (N-**C**H$_3$), 35.93 (HN-**C**H$_2$), 44.60 (2×N-**C**H$_3$), 57.52 (N-**C**H$_2$), 66.87 (O-**C**H$_2$), 107.23 (Ar**C**), 114.86 (2×Ar**C**H), 121.90 (Ar**C**), 127.91 (2×Ar**C**H), 148.39 (Ar**C**), 149.70 (Ar**C**), 151.08 (Ar**C**), 153.99 (**C**=O), 159.00 (**C**=O), 167.28 (**C**=O); FT-IR (KBr): υ_{max} = 3152, 2947, 1693, 1650, 1477, 1250, 1049, 839 and 744 cm^{-1}.; Anal. calcd. for $C_{19}H_{24}N_6O_4$: C, 56.99; H, 6.04; N, 20.99. Found: C, 56.93; H, 6.17; N, 21.06.

4.1.4.2. 8-[4-{2-(Diethylaminoethylamino)-2-oxoethoxy}-phenyl]-1,3-dimethylxanthine (**13b**) (0.22 g, 17 %), mp: 258-260 ºC; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 1.03 (t, 6H, -N(CH$_2$CH_3)$_2$; *J* = 7.06 Hz), 2.56-2.62 (m, 6H, -N(CH_2CH$_3$)$_2$ and -CH_2N<), 3.38 (s(br), 5H, -CONHCH_2 and N-CH_3), 3.57 (s, 3H, N-CH_3), 4.54 (s, 2H, -OCH_2-), 7.03 (d, 2H, 2-C*H* and 6-C*H*, aromatic, J_o = 8.44 Hz), 7.81 (s, 1H, -CON*H*CH$_2$-), 8.11 ppm (d, 2H, 3-C*H* and 5-C*H*, aromatic, J_o = 8.68 Hz) and 13.38 ppm (s, 1H, N-*H*); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 11.47 (2×**C**H$_3$), 27.59 (N-**C**H$_3$), 29.55 (N-**C**H$_3$), 36.23 (HN-**C**H$_2$), 46.51 (2×N-**C**H$_2$), 51.10 (N-**C**H$_2$), 66.89 (O-**C**H$_2$), 107.25 (Ar**C**), 114.79 (2×Ar**C**H), 121.95 (Ar**C**), 127.89 (2×Ar**C**H), 148.35 (Ar**C**), 149.67 (Ar**C**), 151.05 (Ar**C**), 153.97 (**C**=O), 158.91 (**C**=O), 167.15 (**C**=O); FT-IR (KBr): υ_{max} = 3187, 2964, 1695, 1656, 1477, 1253, 1049, 983, 842 and 738 cm^{-1}; Anal. calcd. for $C_{21}H_{28}N_6O_4$: C, 58.86; H, 6.59; N, 19.61. Found: C, 58.98; H, 6.48; N, 19.73.

4.1.4.3. 1,3-Dimethyl-8-[4-{2-(pyrrolidin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**13c**) (0.9 g, 80 %), mp: 215-217 ºC; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 1.88 (p, 2H, -CH_2-,

pyrrolidine), 2.01 (p, 2H, -C*H*$_2$-, pyrrolidine), 3.37 (s, 3H, N-C*H*$_3$), 3.47 (t, 2H, N-C*H*$_2$, pyrrolidine, *J* = 6.76 Hz), 3.53 (t, 2H, N-C*H*$_2$, pyrrolidine, *J* = 6.9 Hz), 3.59 (s, 3H, N-C*H*$_3$), 4.73 (s, 2H, -OC*H*$_2$-), 7.00 (d, 1H, 2-C*H* and 6-C*H*, aromatic, J_o = 8.92 Hz), 8.09 (d, 1H, 3-C*H* and 5-C*H*, aromatic, J_o = 8.92 Hz) and 13.43 ppm (s, 1H, N-*H*); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 23.46 (2×**C**H$_2$), 25.67 (HN-**C**H$_2$), 27.60 (N-**C**H$_3$), 29.58 (N-**C**H$_3$), 44.73 (N-**C**H$_2$), 45.53 (2×N-**C**H$_2$), 66.15 (O-**C**H$_2$), 107.18 (Ar**C**), 114.72 (2×Ar**C**H), 121.52 (Ar**C**), 127.82 (2×Ar**C**H), 148.43 (Ar**C**), 149.85 (Ar**C**), 151.10 (Ar**C**), 153.99 (**C**=O), 159.56 (**C**=O), 165.23 (**C**=O); FT-IR (KBr): υ_{max} = 3168, 2954, 2881, 1687, 1647, 1481, 1357, 1189, 1080 and 984 cm^{-1}; Anal. calcd. for $C_{19}H_{21}N_5O_4$: C, 59.52; H, 5.52; N, 18.27. Found: C, 59.61; H, 5.61; N, 18.12.

4.1.4.4. 1,3-Dimethyl-8-[4-{2-(piperidin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**13d**) (0.70 g, 61 %), mp: 288-290 ºC; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 1.55-1.68 (m, 6H, 3 x -C*H*$_2$-, piperidine), 3.40 (s, 3H, N-C*H*$_3$), 3.49 (t, 2H, N-C*H*$_2$, piperidine, *J* = 5.2 Hz), 3.54 (t, 2H, N-C*H*$_2$, piperidine, *J* = 5.34 Hz), 3.63 (s, 3H, N-C*H*$_3$), 4.78 (s, 2H, -OC*H*$_2$-), 7.02 (d, 2H, 2-C*H* and 6-C*H*, aromatic, J_o = 8.68 Hz) and 8.11 ppm (d, 2H, 3-C*H* and 5-C*H*, aromatic, J_o = 8.68 Hz); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 23.93 (**C**H$_2$), 25.22 (2×**C**H$_2$), 25.91 (HN-**C**H$_2$), 27.66 (N-**C**H$_3$), 29.64 (N-**C**H$_3$), 42.19 (N-**C**H$_2$), 45.17 (2×N-**C**H$_2$), 65.99 (O-**C**H$_2$), 107.21 (Ar**C**), 114.81 (2×Ar**C**H), 121.51 (Ar**C**), 127.86 (2×Ar**C**H), 148.48 (Ar**C**), 149.86 (Ar**C**), 151.14 (Ar**C**), 154.04 (**C**=O), 159.60 (**C**=O), 165.01 (**C**=O); FT-IR (KBr): υ_{max} = 3165, 2939, 2861, 1680, 1649, 1479, 1240, 1188, 1062, 841 and 749 cm^{-1}; Anal. calcd. for $C_{20}H_{23}N_5O_4$: C, 60.44; H, 5.83; N, 17.62. Found: C, 60.57; H, 5.72; N, 17.76.

4.1.4.5. 1,3-Dimethyl-8-[4-{2-(hexamethyleneimin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**13e**) (0.6 g, 50 %), mp: 196-198 ºC; ^{1}H NMR (400 MHz,$CDCl_3$-DMSO-d_6): δ 1.52 (p, 4H, 2 x -C*H*$_2$-, hexamethyleneimine), 1.64 (p, 2H, -C*H*$_2$-, hexamethyleneimine), 1.72 (p, 2H, -C*H*$_2$-, hexamethyleneimine), 3.30 (s, 3H, N-C*H*$_3$), 3.45 (t, 4H, N-(C*H*$_2$)$_2$, hexamethylene imine, *J* = 5.84 Hz), 3.52 (s, 3H, N-C*H*$_3$), 4.75 (s, 2H, -OC*H*$_2$-), 6.94 (d, 2H, 2-C*H* and 6-C*H*, aromatic, J_o = 8.84 Hz), 8.05 (d, 2H, 3-C*H* and 5-C*H*, aromatic, J_o = 8.84 Hz) and 13.42 ppm (s, 1H, N-*H*); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 26.09 (**C**H$_2$), 26.89 (**C**H$_2$), 26.95 (HN-**C**H$_2$), 27.58 (N-**C**H$_3$), 28.51 (2×**C**H$_2$), 29.55 (N-**C**H$_3$), 45.34 (N-

CH_2), 46.33 (2×N-**C**H_2), 65.88 (O-**C**H_2), 107.18 (Ar**C**), 114.65 (2×Ar**C**H), 121.53 (Ar**C**), 127.82 (2×Ar**C**H), 148.41 (Ar**C**), 149.84 (Ar**C**),151.10 (Ar**C**), 153.99 (**C**=O), 159.53 (**C**=O), 166.24 (**C**=O); FT-IR (KBr): υ_{max} = 3170, 2931, 1691, 1650, 1480, 1244, 1064 and 839 cm^{-1}; Anal. calcd. for $C_{21}H_{25}N_5O_4$: C, 61.30; H, 6.12; N, 17.02.Found: C, 61.38; H, 6.20; N, 16.91.

4.1.4.6. 1,3-Dimethyl-8-[4-{2-(morpholin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**13f**) (0.84 g, 72 %), mp: 262-264 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 3.32 (s, 3H, N-CH_3), 3.50-3.55 (m, 7H, N-(CH_2)$_2$, morpholine and N-CH_3), 3.60-3.67 (m, 4H, O-(CH_2)$_2$, morpholine), 4.86 (s, 2H, -OCH_2-), 7.01 (d, 2H, 2-C*H* and 6-C*H*, aromatic, J_o = 8.88 Hz) and 8.08 ppm (d, 2H, 3-C*H* and 5-C*H*, aromatic, J_o = 8.88 Hz); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 27.66 (N-**C**H_3), 29.64 (N-**C**H_3), 41.56 (N-**C**H_2), 44.66 (N-**C**H_2), 65.69 (2×O-**C**H_2), 66.03 (O-**C**H_2), 107.22 (Ar**C**), 114.67 (Ar**C**H), 114.86 (Ar**C**H), 121.58 (Ar**C**), 127.84 (2×Ar**C**H), 148.47 (Ar**C**), 149.82 (Ar**C**), 151.11 (Ar**C**), 154.03 (**C**=O), 159.51 (**C**=O), 165.63 (**C**=O); FT-IR (KBr): υ_{max} = 3172, 2956, 1690, 1649, 1481, 1237, 1111, 1031, 984, 846 and 754 cm^{-1}; Anal. Calcd. for $C_{19}H_{21}N_5O_5$: C, 57.14; H, 5.30; N, 17.53. Found: C, 57.29; H, 5.23; N, 17.46.

4.1.4.7. 1,3-Dimethyl-8-[4-{2-(1-methylpiperazin-4-yl)-2-oxoethoxy}-phenyl]xanthine (**13g**) (0.80 g, 66 %), mp: 230 ºC (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 2.28 (s, 3H, >N-CH_3, *N*-methylpiperazine), 2.36 (t(br), 2H, N-CH_2, *N*-methylpiperazine), 2.42 (t(br), 2H, N-CH_2, *N*-methylpiperazine), 3.35 (s, 3H, N-CH_3), 3.57 (s(br), 7H, N-CH_3 and -N(CH_2)$_2$, *N*-methylpiperazine), 4.84 (s, 2H, -OCH_2-), 7.0 (d, 2H, 2-C*H* and 6-C*H*, aromatic, J_o = 8.88 Hz), 8.09 (d, 2H, 3-C*H* and 5-C*H*, aromatic, J_o = 8.84 Hz) and 13.46 ppm (s, 1H, N-*H*); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 27.64 (N-**C**H_3), 29.61 (N-**C**H_3), 41.10 (N-**C**H_3), 43.96 (N-**C**H_2), 45.58 (N-**C**H_2), 54.15 (N-**C**H_2), 54.53 (N-**C**H_2), 65.77 (O-**C**H_2), 107.17 (Ar**C**), 114.79 (2×Ar**C**H), 121.51 (Ar**C**), 127.81 (2×Ar**C**H), 148.39 (Ar**C**), 149.78 (Ar**C**), 151.07 (Ar**C**), 153.97 (**C**=O), 159.49 (**C**=O), 165.37 (**C**=O); FT-IR (KBr): υ_{max} = 3170, 2946, 1680, 1648, 1560, 1481, 1292, 1187, 1032, 987, 841 and 753 cm^{-1}; Anal. Calcd. for $C_{20}H_{24}N_6O_4$: C, 58.24; H, 5.87; N, 20.38. Found: C, 58.44; H, 5.78; N, 20.41.

4.1.4.8. 1,3-Dimethyl-8-[4-{2-(imidazol-1-yl)-2-oxoethoxy}-phenyl]xanthine (**13h**) (0.4 g, 36 %), mp: 250 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 3.42 (s, 3H, N-C*H*$_3$), 3.69 (s, 3H, N-C*H*$_3$), 4.65 (s, 2H, -OC*H*$_2$-), 6.99 (d, 2H, 2-C*H* and 6-C*H*, aromatic, J_o = 8.88 Hz), 7.32 (s(br), 2H, C*H*, imidazole), 8.11 (d, 2H, 3-C*H* and 5-C*H*, aromatic, J_o = 8.88 Hz), 8.69 (s(br), 1H, C*H*, imidazole) and 13.32 ppm (s, 1H, N-*H*); ^{13}C NMR (DMSO-d_6): δ = 27.75 (N-**C**H$_3$), 29.73 (N-**C**H$_3$), 56.83 (O-**C**H$_2$), 99.49 (2×Ar**C**H), 107.23 (Ar**C**), 114.84 (2×Ar**C**H), 121.52 (Ar**C**), 127.95 (3×Ar**C**H), 148.51 (Ar**C**), 149.80 (2×Ar**C**), 151.16 (**C**=O), 154.07 (**C**=O), 159.40 (**C**=O); FT-IR (KBr): υ_{max} = 3179, 2951, 2562, 1685, 1648, 1481, 1306, 1244, 1189, 1058, 987, 840 and 754 cm^{-1}; Anal. calcd. for $C_{18}H_{16}N_6O_4$: C, 56.84; H, 4.24; N, 22.10. Found: C, 56.70; H, 4.16; N, 21.94.

4.1.4.9. 1,3-Dimethyl-8-[4-{2-(homoveratrylamino)-2-oxoethoxy}-phenyl]xanthine (**13i**) (0.92 g, 64 %), mp: 283-285 ºC; ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 2.77 (t, 2H, -CONHCH$_2$C*H*$_2$-), 3.36 (s, 3H, N-C*H*$_3$), 3.47 (q, 2H, -CONHC*H*$_2$CH$_2$-), 3.59 (s, 3H, N-C*H*$_3$), 3.80 (s, 6H, 2 x OC*H*$_3$), 4.52 (s, 2H, -OC*H*$_2$-), 6.70 (dd, 1H, 5-C*H*, aromatic, J_m = 1.74 Hz, homoveratrylamine), 6.76-6.80 (m, 2H, 2-C*H* and 6-C*H*, aromatic, homoveratrylamine), 6.99 (d, 2H, 2-C*H* and 6-C*H*, aromatic, J_o = 8.84 Hz), 7.74 (s, 1H, -CON*H*CH$_2$CH$_2$-), 8.11 (d, 2H, 3-C*H* and 5-C*H*, aromatic, J_o = 8.88 Hz) and 13.49 ppm (s, 1H, N-*H*); ^{13}C NMR (DMSO-d_6): δ = 27.72 (N-**C**H$_3$), 29.70 (N-**C**H$_3$), 34.58 (**C**H$_2$), 40.07 (HN-**C**H$_2$), 55.29 (O-**C**H$_3$), 55.40 (O-**C**H$_3$), 66.91 (O-**C**H$_2$), 107.34 (Ar**C**), 111.73 (Ar**C**H), 112.34 (Ar**C**H), 115.02 (2×Ar**CH**), 120.39 (Ar**C**), 121.87 (Ar**C**H), 127.92 (2×Ar**C**H), 131.61 (Ar**C**), 147.16 (Ar**C**), 148.49 (Ar**C**), 148.55 (Ar**C**), 149.74 (Ar**C**), 151.13 (Ar**C**), 154.08 (**C**=O), 159.15 (**C**=O), 167.13 (**C**=O); FT-IR (KBr): υ_{max} = 3171, 2940, 1702, 1654, 1478, 1235, 839 and 744 cm^{-1}; Anal. calcd. for $C_{25}H_{27}N_5O_6$: C, 60.84; H, 5.51; N, 14.19. Found: C, 60.81; H, 5.66; N, 14.26.

4.1.4.10. 1,3-Dimethyl-8-[3-{2-(dimethylaminoethylamino)-2-oxoethoxy}-phenyl]xanthine (**14a**) (0.86 g, 69 %), mp: 215-217 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.33 (s, 6H, -N(C*H*$_3$)$_2$), 2.58 (s, 2H, -C*H*$_2$N<), 3.39 (s, 3H, N-C*H*$_3$), 3.44 (q, 2H, -CONHC*H*$_2$CH$_2$-), 3.62 (s, 3H, N-C*H*$_3$), 4.60 (s, 2H, -OC*H*$_2$-), 7.05 (dd, 1H, 4-C*H*, aromatic, J_m = 1.88 Hz; J_o = 8.00 Hz), 7.38 (t, 1H, 5-C*H*, aromatic, J_o = 7.96 Hz), 7.61 (s(br), 1H, N-*H*), 7.73 (d,

1H, 2-C*H*, aromatic, J_m = 2.08 Hz) and 7.81 ppm (dd, 1H, 6-C*H*, aromatic, J_m = 2.20 Hz; J_o = 8.40 Hz); ^{13}C NMR (DMSO-d_6): δ = 27.78 (N-**C**H$_3$), 29.78 (N-**C**H$_3$), 35.86 (HN-**C**H$_2$), 44.59 (2×N-**C**H$_3$), 57.56 (**N**-**C**H$_2$), 66.95 (O-**C**H$_2$), 107.82 (Ar**C**), 112.14 (Ar**C**H), 116.83 (Ar**C**H), 119.30 (Ar**C**), 129.96 (Ar**C**H), 130.14 (Ar**C**H), 148.34 (Ar**C**), 149.31 (Ar**C**), 151.16 (Ar**C**), 154.23 (**C**=O), 157.91 (**C**=O) and 167.44 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3170, 2947, 1699, 1661, 1521, 1446, 1279, 1225, 1054, 792 and 724 cm^{-1}; Anal. calcd. for $C_{19}H_{24}N_6O_4$: C, 56.99; H, 6.04; N, 20.99. Found: C, 56.80; H, 6.10; N, 21.03.

4.1.4.11. 8-[3-{2-(Diethylaminoethylamino)-2-oxoethoxy}-phenyl]-1,3-dimethylxanthine (**14b**) (0.6 g, 51 %), mp: 240 ºC (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.0 (t, 6H, -N(CH$_2$C*H*$_3$)$_2$, J = 7.01 Hz), 2.51-2.61 (m, 6H, -N(C*H*$_2$CH$_3$)$_2$ and -C*H*$_2$N<), 3.34 (q, 2H, -CONHC*H*$_2$CH$_2$-), 3.40 (s, 3H, N-C*H*$_3$), 3.62 (s, 3H, N-C*H*$_3$), 4.58 (s, 2H, -OC*H*$_2$-), 7.03 (dd, 1H, 4-C*H*, aromatic, J_m = 1.74 Hz; J_o = 8.22 Hz), 7.39 (t, 1H, 5-C*H*, aromatic, J_o = 8.16 Hz), 7.50 (s(br), 1H, N-*H*) and 7.82-7.84 ppm (m, 2H, 2-C*H* and 6-C*H*, aromatic); ^{13}C NMR (DMSO-d_6): δ = 11.65 (2×**C**H$_3$), 27.69 (N-**C**H$_3$), 29.67 (N-**C**H$_3$), 36.34 (HN-**C**H$_2$), 46.55 (2×N-**C**H$_2$), 51.17 (**N**-**C**H$_2$), 66.94 (O-**C**H$_2$), 108.04 (Ar**C**), 111.88 (Ar**C**H), 116.56 (Ar**C**H), 119.23 (Ar**C**), 129.96 (Ar**C**H), 130.22 (Ar**C**H), 148.28 (Ar**C**), 149.41 (Ar**C**), 151.07 (Ar**C**), 154.23 (**C**=O), 157.77 (**C**=O) and 167.24 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3178, 2968, 1700, 1669, 1523, 1479 and 1216 cm^{-1}; Anal. calcd. for $C_{21}H_{28}N_6O_4$: C, 58.86; H, 6.59; N, 19.61. Found: C, 58.98; H, 6.72; N, 19.52.

4.1.4.12. 1,3-Dimethyl-8-[3-{2-(pyrrolidin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**14c**) (0.79 g, 70 %), mp: 280 ºC (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.87 (p, 2H, -C*H*$_2$-, pyrrolidine), 2.00 (p, 2H, -C*H*$_2$-, pyrrolidine), 3.35 (s, 3H, N-C*H*$_3$), 3.45 (t, 2H, N-C*H*$_2$, pyrrolidine, J = 6.94 Hz), 3.56 (t, 2H, N-C*H*$_2$, pyrrolidine, J = 6.84 Hz), 3.58 (s, 3H, N-C*H*$_3$), 4.75 (s, 2H, -OC*H*$_2$-), 7.00 (dd, 1H, 4-C*H*, aromatic, J_m = 2.26 Hz; J_o = 8.22 Hz), 7.36 (t, 1H, 5-C*H*, aromatic, J_o = 7.96 Hz), 7.75 (d, 1H, 2-C*H*, aromatic, J_m = 2.16 Hz), 7.77 (d, 1H, 6-C*H*, aromatic, J_o = 7.88 Hz) and 13.63 ppm (s, 1H, N-*H*); ^{13}C NMR (DMSO-d_6): δ = 23.49 (**C**H$_2$), 25.67 (**C**H$_2$), 27.78 (N-**C**H$_3$), 29.76 (N-**C**H$_3$), 44.77 (N-**C**H$_2$), 45.57 (N-**C**H$_2$), 66.17 (O-**C**H$_2$), 107.64 (Ar**C**), 112.26 (Ar**C**H), 116.48 (Ar**C**H), 118.99 (Ar**C**), 129.99 (2×Ar**C**H), 144.99 (Ar**C**), 149.61 (Ar**C**), 151.17 (Ar**C**), 154.30 (**C**=O), 158.44 (**C**=O) and 165.41 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3154, 2953, 1699,

1653, 1520, 1476 and 1218 cm^{-1}; Anal. calcd. for $C_{19}H_{21}N_5O_4$: C, 59.52; H, 5.52; N, 18.27. Found: C, 59.66; H, 5.45; N, 18.44.

4.1.4.13. 1,3-Dimethyl-8-[3-{2-(piperidin-1-yl)]-2-oxoethoxy}-phenyl]xanthine (**14d**) (0.72 g, 62 %), mp: 240 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 1.57 (t(br), 2H, -CH_2, piperidine), 1.67 (p(br), 4H, -(CH_2)$_2$, piperidine), 3.42 (s, 3H, N-CH_3), 3.50 (t, 2H, -N-CH_2, piperidine, J = 4.94 Hz), 3.57 (t, 2H, -N-CH_2, piperidine, J = 5.44 Hz), 3.64 (s, 3H, N-CH_3), 4.79 (s, 2H, -OCH_2-), 7.03 (dd, 1H, 4-CH, aromatic, J_m = 2.50 Hz; J_o = 7.54 Hz), 7.37 (t, 1H, 5-CH, aromatic, J_o = 7.96 Hz), 7.78 (d, 1H, 2-CH, aromatic, J_m = 2.88 Hz) and 7.80 ppm (d, 1H, 6-CH, aromatic, J_o = 7.84 Hz); ^{13}C NMR (DMSO-d_6): **δ =** 23.95 (**C**H_2), 25.29 (**C**H_2), 25.98 (**C**H_2), 27.75 (N-**C**H_3), 29.68 (N-**C**H_3), 42.18 (N-**C**H_2), 45.23 (N-**C**H_2), 65.92 (O-**C**H_2), 107.73 (Ar**C**), 112.10 (Ar**C**H), 116.48 (Ar**C**H), 118.91 (Ar**C**), 129.82 (Ar**C**H), 129.96 (Ar**C**H), 148.30 (Ar**C**), 149.40 (Ar**C**), 151.10 (Ar**C**), 154.19 (**C**=O), 158.36 (**C**=O) and 165.11 ppm (**C**=O); FT-IRυ_{max} (KBr): 3164, 2936, 1695, 1647, 1522, 1450, 985 and 791 cm^{-1}; Anal. calcd. for $C_{20}H_{23}N_5O_4$: C, 60.44; H, 5.83; N, 17.62. Found: C, 60.34; H, 5.76; N, 17.79.

4.1.4.14. 1,3-Dimethyl-8-[3-{2-(hexamethyleneimin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**14e**) (0.6 g, 50 %), mp: 210 ºC (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 1.60 (p, 4H, 2 x -CH_2-, hexamethyleneimine), 1.73 (p, 2H, -CH_2-, hexamethyleneimine), 1.82 (p, 2H, -CH_2-, hexamethyleneimine), 3.40 (s, 3H, N-CH_3), 3.55 (t, 4H, -N-(CH_2)$_2$, hexamethyleneimine), 3.63 (s, 3H, N-CH_3), 4.81 (s, 2H, -OCH_2-), 7.02 (dd, 1H, 4-CH, aromatic, J_m = 2.20 Hz; J_o = 8.16 Hz), 7.37 (t, 1H, 5-CH, aromatic, J_o = 7.98 Hz), 7.76 (d, 1H, 2-CH, aromatic, J_m = 2.08 Hz), 7.79 (d, 1H, 6-CH, aromatic, J_o = 7.80 Hz) and 13.52 ppm (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): **δ =** 26.11 (**C**H_2), 26.83 (**C**H_2), 27.03 (**C**H_2), 27.75 (**C**H_2), 28.48 (N-**C**H_3), 29.67 (N-**C**H_3), 45.21 (N-**C**H_2), 46.24 (N-**C**H_2), 65.71 (O-**C**H_2), 107.82 (Ar**C**), 112.00 (Ar**C**H), 116.48 (Ar**C**H), 118.83 (Ar**C**), 129.90 (2×Ar**C**H), 148.32 (Ar**C**), 149.47 (Ar**C**), 151.11 (Ar**C**), 154.22 (**C**=O), 158.42 (**C**=O) and 166.37 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3160, 2928, 1698, 1649, 1477, 1288, 1223 and 752 cm^{-1}. Anal. calcd. for $C_{21}H_{25}N_5O_4$: C, 61.30; H, 6.12; N, 17.02. Found: C, 61.53; H, 5.99; N, 17.18.

4.1.4.15. 1,3-Dimethyl-8-[3-{2-(morpholin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**14f**) (0.78 g, 67 %), mp 250 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ 3.43 (s, 3H, N-CH_3), 3.65 (s, merged with multiplet, 7H, -N-(CH_2)$_2$, morpholine and N-CH_3), 3.70-3.73 (m, 4H, O-(CH_2)$_2$, morpholine), 4.81 (s, 2H, -OCH_2-), 7.35 (dd, 1H, 4-C*H*, aromatic, J_m = 2.12 Hz; J_o = 7.88 Hz), 7.38 (t, 1H, 5-C*H*, aromatic, J_o = 7.96 Hz), 7.79-7.83 (m, 2H, 2-C*H* and 6-C*H*, aromatic) and 9.98 ppm (s, 1H, N-*H*); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 27.76 (N-**C**H$_3$), 29.75 (N-**C**H$_3$), 41.63 (N-**C**H$_2$), 44.80 (N-**C**H$_2$), 57.63 (O-**C**H$_2$), 65.70 (O-**C**H$_2$), 66.07 (O-**C**H$_2$), 108.44 (Ar**C**), 112.18 (Ar**C**H), 116.20 (Ar**C**H), 118.97 (Ar**C**), 129.93 (Ar**C**H), 130.48 (Ar**C**H), 148.52 (Ar**C**), 149.79 (Ar**C**), 151.20 (Ar**C**), 154.47 (**C**=O), 158.27 (**C**=O) and 165.79 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3148, 2926, 1699, 1652, 1519, 1478, 1211 and 795 cm^{-1}; Anal. calcd. for $C_{19}H_{21}N_5O_5$: C, 57.14; H, 5.30; N, 17.53. Found: C, 57.24; H, 5.35; N, 17.60.

4.1.4.16. 1,3-Dimethyl-8-[3-{2-(1-methylpiperazin-4-yl)-2-oxoethoxy}-phenyl]xanthine (**14g**) (0.6 g, 50 %), mp: 218-220 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, >N-CH_3, *N*-methylpiperazine), 2.37 (t(br), 2H, N-CH_2, *N*-methylpiperazine J_o = 4.0 Hz), 2.44 (t(br), 2H, N-CH_2, *N*-methylpiperazine), 3.36 (s, 3H, N-CH_3), 3.59 (s(br), 7H, N-CH_3 and -N-(CH_2)$_2$, *N*-methylpiperazine), 4.83 (s, 2H, -OCH_2-), 7.01 (dd, 1H, 4-C*H*, aromatic, J_m = 2.04 Hz; J_o = 8.16 Hz), 7.36 (t, 1H, 5-C*H*, aromatic, J_o = 7.98 Hz), 7.75-7.79 (m, 2H, 2-C*H* and 6-C*H*, aromatic) and 13.62 ppm (s, 1H, N-*H*); ^{13}C NMR (DMSO-d_6): δ = 27.78 (N-**C**H$_3$), 29.77 (N-**C**H$_3$), 41.15 (N-**C**H$_3$), 45.52 (2×N-**C**H$_2$), 54.55 (2×N-**C**H$_2$), 65.78 (O-**C**H$_2$), 107.76 (Ar**C**), 112.24 (Ar**C**H), 116.52 (Ar**C**H), 119.02 (Ar**C**), 129.75 (Ar**C**H), 130.04 (Ar**C**H), 148.27 (Ar**C**), 149.38 (Ar**C**), 151.16 (Ar**C**), 154.22 (**C**=O), 158.37 (**C**=O) and 165.53 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3163, 2938, 1695, 1648, 1522, 1478, 1221 and 717 cm^{-1}; Anal. calcd. for $C_{20}H_{24}N_6O_4$: C, 58.24; H, 5.87; N, 20.38. Found: C, 58.14; H, 5.97; N, 20.14.

4.1.4.17. 1,3-Dimethyl-8-[3-{2-(imidazol-1-yl)-2-oxoethoxy}-phenyl]xanthine (**14h**) (0.720 g, 65 %), mp: 250 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 3.40 (s, 3H, N-CH_3), 3.63 (s, 3H, N-CH_3), 4.71 (s, 2H, -OCH_2-), 7.01 (dd, 1H, 4-C*H*, aromatic, J_m = 2.04 Hz; J_o = 8.00 Hz), 7.27 (s, 1H, C*H*, imidazole), 7.37 (t, 1H, 5-C*H*, aromatic, J_o =

7.94 Hz), 7.78 (d, 2H, 2-C*H* and 6-C*H*, aromatic, J_m = 2.44 Hz), 7.82 (s, 1H, C*H*, imidazole), 8.42 (s, 1H, C*H*, imidazole) and 13.56 ppm (s, 1H, N-*H*); ^{13}C NMR (DMSO-d_6): δ = 27.78 (N-**C**H$_3$), 29.77 (N-**C**H$_3$), 64.56 (O-**C**H$_2$), 105.64 (Ar**C**H), 105.96 (Ar**C**H), 107.71 (Ar**C**), 111.48 (Ar**C**H), 116.81 (Ar**C**H), 119.16 (Ar**C**), 129.80 (2×Ar**C**H), 130.12 (Ar**C**H), 148.33 (Ar**C**), 149.32 (Ar**C**), 151.16 (Ar**C**), 154.22 (**C**=O), 158.13 (**C**=O) and 170.03 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3161, 2950, 1692, 1647, 1523, 1479, 1364, 1289, 984 and 754 cm^{-1}; Anal. calcd. for $C_{18}H_{16}N_6O_4$: C, 56.84; H, 4.24; N, 22.10. Found: C, 56.98; H, 4.32; N, 22.00.

4.1.4.18. 1,3-Dimethyl-8-[3-{2-(homoveratrylamino)-2-oxoethoxy}-phenyl]xanthine (**14i**) (0.91 g, 63 %), mp: 220 ºC (decomp.); ^{1}H NMR (400 MHz, CDCl$_3$-DMSO-d_6): δ = 2.97 (t, 2H, -CONHCH$_2$C*H*$_2$-), 3.40 (s, 3H, N-C*H*$_3$), 3.53 (q, 2H, -CONHC*H*$_2$CH$_2$-), 3.63 (s, 3H, N-C*H*$_3$), 3.81 (s, 3H, -OC*H*$_3$), 3.82 (s, 3H, -OC*H*$_3$), 4.57 (s, 2H, -OC*H*$_2$-), 6.69-6.78 (m, 3H, C*H*, aromatic, homoveratrylamine), 6.99 (dd, 1H, 4-C*H*, aromatic, J_m = 2.06 Hz; J_o = 8.22 Hz), 7.38 (t merged with br(s), 2H, 5-C*H*, aromatic, J_o = 8.00 Hz and N-*H*) and 7.81-7.84 ppm (m, 2H, 2-C*H* and 6-C*H*, aromatic); ^{13}C NMR (DMSO-d_6): δ = 27.75 (N-**C**H$_3$), 29.76 (N-**C**H$_3$), 34.63 (**C**H$_2$), 40.08 (HN-**C**H$_2$), 55.28 (O-**C**H$_3$), 55.40 (O-**C**H$_3$), 66.97 (O-**C**H$_2$), 111.74 (Ar**C**), 112.11 (Ar**C**H), 112.33 (2×Ar**C**H), 116.43 (Ar**C**H), 119.20 (2×Ar**C**), 120.37 (Ar**C**H), 130.02 (Ar**C**H), 131.65 (Ar**C**H), 147.15 (Ar**C**), 148.51 (Ar**C**), 148.55 (Ar**C**), 149.72 (Ar**C**), 151.20 (Ar**C**), 154.46 (**C**=O), 157.95 (**C**=O) and 167.25 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3184, 3096, 2933, 1704, 1668, 1518, 1448 and 1264 cm^{-1}; Anal. calcd. for $C_{25}H_{27}N_5O_6$: C, 60.84; H, 5.51; N, 14.19. Found: C, 60.71; H, 5.61; N, 14.11.

4.1.4.19. 1,3-Dimethyl-8-[{4-(2-(dimethylaminoethylamino)-2-oxoethoxy)-3-methoxy}-phenyl]-xanthine (**15a**) (0.44 g, 38 %), mp: 190 ºC (decomp.); ^{1}H NMR (400 MHz, CDCl$_3$-DMSO-d_6): δ = 2.30 (s, 6H, -N(C*H*$_3$)$_2$), 2.51-2.54 (m, 2H, -C*H*$_2$N<), 3.45 (s merged with triplet, 5H, -CONHC*H*$_2$- and N-C*H*$_3$), 3.67 (s, 3H, N-C*H*$_3$), 3.96 (s, 3H, -OC*H*$_3$), 4.57 (s, 2H, -OC*H*$_2$-), 6.98 (s, 1H, 5-C*H*, aromatic), 7.35 (s, 1H, 2-C*H*, aromatic), 7.37 (s(br), 1H, N-*H*) and 7.55 ppm (s, 1H, 6-C*H*, aromatic); ^{13}C NMR (CDCl$_3$-DMSO-d_6): δ = 27.70 (N-**C**H$_3$), 29.74 (N-**C**H$_3$), 36.09 (HN-**C**H$_2$), 44.80 (2×N-**C**H$_3$), 55.93 (N-**C**H$_2$), 57.60 (O-CH$_3$), 67.95 (O-**C**H$_2$), 107.45 (Ar**C**), 114.13 (Ar**C**H), 115.56 (Ar**C**H),

121.12 (Ar**C**), 123.37 (Ar**C**H), 147.69 (Ar**C**), 147.74 (Ar**C**), 147.88 (Ar**C**), 148.78 (Ar**C**), 151.11 (**C**=O), 154.23 (**C**=O) and 166.96 ppm (**C**=O); FT-IR (KBr): υ_{max} = 2939, 2820, 2775, 1694, 1655, 1526, 1491, 1262, 1047, 824 and 747 cm^{-1}; Anal. calcd. for $C_{20}H_{26}N_6O_5$: C, 55.80; H, 6.09; N, 19.52. Found: C, 55.97; H, 5.97; N, 19.66.

4.1.4.20. 8-[{4-(2-(Diethylaminoethylamino)-2-oxoethoxy)-3-methoxy}-phenyl]-1,3-dimethyl- xanthine (**15b**) (0.62 g, 50.65%), mp: 188-190 ºC; ^{1}H NMR ($CDCl_3$): δ = 1.00 (t, 6H, -N(CH_2CH_3)$_2$, *J* = 7.14 Hz), 2.54 (q, 4H, -N(CH_2CH_3)$_2$), 2.59 (t, 2H, -CH_2N<, *J* = 6.0 Hz), 3.39-3.42 (m, 2H, -CONHCH_2CH_2-), 3.45 (s, 3H, N-CH_3), 3.68 (s, 3H, N-CH_3), 3.98 (s, 2H, -OCH_3), 4.57 (s, 2H, -OCH_2-), 6.93 (s, 1H, 5-C*H*, aromatic), 7.27 (s, 1H, 2-C*H*, aromatic), 7.36 (s, 1H, N-*H*) and 7.82 ppm (s, 1H, 6-C*H*, aromatic); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 11.66 (2×**C**H_3), 27.72 (N-**C**H_3), 29.76 (N-**C**H_3), 36.39 (HN-**C**H_2), 46.48 (2×N-**C**H_2), 51.12 (N-CH_2), 55.92 (O-**C**H_3), 67.94 (O-**C**H_2), 107.59 (Ar**C**), 114.08 (Ar**C**H), 115.46 (Ar**C**H), 121.24 (Ar**C**), 123.46 (Ar**C**H), 147.73 (Ar**C**), 147.77 (Ar**C**), 147.94 (Ar**C**), 148.59 (Ar**C**), 151.17 (**C**=O), 154.29 (**C**=O) and 166.81 ppm (**C**=O); FT-IR (KBr): υ_{max} = 2976, 2822, 1693, 1653, 1537, 1486, 1387, 1236, 1041, 880 and 750 cm^{-1}; Anal. calcd. for $C_{22}H_{30}N_6O_5$: C, 57.63; H, 6.59; N, 18.33. Found: C, 57.86; H, 6.47; N, 18.22.

4.1.4.21. 1,3-Dimethyl-8-[3-methoxy-4-{2-(pyrrolidin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**15c**) (0.6 g, 54 %), mp: 215-217 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (p, 2H, -CH_2-, pyrrolidine), 2.01 (p, 2H, -CH_2-, pyrrolidine), 3.39 (s, 3H, N-CH_3), 3.47 (t, 2H, N-CH_2, pyrrolidine, *J* = 6.92 Hz), 3.53 (t, 2H, N-CH_2, pyrrolidine, *J* = 6.80 Hz), 3.62 (s, 3H, N-CH_3), 3.92 (s, 3H, -OCH_3), 4.77 (s, 2H, -OCH_2-), 7.02 (s, 1H, 5-C*H*, aromatic), 7.35 (s, 1H, 2-C*H*, aromatic) and 7.80 ppm (s, 1H, 6-C*H*, aromatic); ^{13}C NMR (DMSO-d_6): δ = 23.49 (**C**H_2), 25.60 (**C**H_2), 27.79 (N-**C**H_3), 29.84 (N-**C**H_3), 44.55 (N-**C**H_2), 45.55 (N-**C**H_2), 55.95 (O-**C**H_3), 66.47 (O-**C**H_2), 107.35 (Ar**C**), 114.09 (Ar**C**H), 114.73 (Ar**C**H), 120.32 (Ar**C**), 123.25 (Ar**C**H), 147.48 (2×Ar**C**), 147.92 (Ar**C**), 149.33 (Ar**C**), 151.15 (**C=**O), 154.28 (**C**=O) and 164.94 ppm (**C**=O); FT-IR (KBr): υ_{max} = 2953, 1706, 1663, 1550, 1484, 1178, 1073 and 988 cm^{-1}; Anal. calcd. for $C_{20}H_{23}N_5O_5$: C, 58.10; H, 5.61; N, 16.94. Found: C, 57.97; H, 5.73; N, 16.86.

4.1.4.22. 1,3-Dimethyl-8-[3-methoxy-4-{2-(piperidin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**15d**)

(0.32 g, 28 %), mp: 218-220 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57-1.67 (m, 6H, 3 x -C*H*$_2$-, piperidine), 3.45 (s, 3H, N-C*H*$_3$), 3.48 (t, 2H, N-C*H*$_2$, piperidine, *J* = 5.22 Hz), 3.58 (t, 2H, N-C*H*$_2$, piperidine, *J* = 5.42 Hz), 3.68 (s, 3H, N-C*H*$_3$), 3.97 (s, 3H, -OC*H*$_3$), 4.82 (s, 2H, -OC*H*$_2$-), 6.97 (s, 1H, 5-C*H*, aromatic), 7.27 (s, 1H, 2-C*H*, aromatic) and 7.79 ppm (s, 1H, 6-C*H*, aromatic); FT-IR (KBr): υ_{max} = 2937, 1705, 1659, 1551, 1486, 1259, 1065 and 990 cm^{-1}; Anal. calcd. for $C_{21}H_{25}N_5O_5$: C, 59.01; H, 5.90; N, 16.38. Found: C, 58.90; H, 5.85; N, 16.25.

4.1.4.23. 1,3-Dimethyl-8-[{4-(2-(hexamethyleneimin-1-yl)-2-oxoethoxy)-3-methoxy}-phenyl]-xanthine (**15e**) (0.5 g, 42 %), mp 114 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58-1.60 (m, 4H, 2 x -C*H*$_2$-, hexamethyleneimine), 1.72-1.76 (m, 2H, -C*H*$_2$-, hexamethyleneimine), 1.79 (m, 2H, -C*H*$_2$-, hexamethyleneimine), 3.46 (s, 3H, N-C*H*$_3$), 3.51 (t, 2H, N-C*H*$_2$, hexamethyleneimine, *J* = 6.06 Hz), 3.57 (t, 2H, N-C*H*$_2$, hexamethyleneimine, *J* = 5.96 Hz), 3.68 (s, 3H, N-C*H*$_3$), 3.95 (s, 2H, -OC*H*$_3$), 4.85 (s, 2H, -OC*H*$_2$-), 6.94 (s, 1H, 5-C*H*, aromatic), 7.26 (s, 1H, 2-C*H*, aromatic) and 7.79 ppm (s, 1H, 6-C*H*, aromatic); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ 26.04 (**C**H$_2$), 26.82 (**C**H$_2$), 27.05 (**C**H$_2$), 27.77 (N-**C**H$_3$), 28.31 (**C**H$_2$), 29.83 (N-**C**H$_3$), 45.21 (N-**C**H$_2$), 46.15 (N-**C**H$_2$), 55.93 (O-**C**H$_3$), 66.10 (O-**C**H$_2$), 107.61 (Ar**C**), 114.07 (Ar**C**), 114.63 (Ar**C**H), 120.42 (Ar**C**), 123.17 (Ar**C**H), 147.46 (Ar**C**), 147.96 (Ar**C**), 148.02 (Ar**C**), 149.23 (Ar**C**), 151.15 (**C=**O), 154.33 (**C**=O) and 165.94 ppm (**C**=O); FT-IR (KBr): υ_{max} = 2926, 2855, 1706, 1653, 1551, 1487, 1263, 1058, 877 and 744 cm^{-1}; Anal. calcd. for $C_{22}H_{27}N_5O_5$: C, 59.85; H, 6.16; N, 15.86. Found: C, 59.72; H, 6.26; N, 15.72.

4.1.4.24. 1,3-Dimethyl-8-[3-methoxy-4-{2-(morpholin-1-yl)-2-oxoethoxy}-phenyl]xanthine **(15f)** (0.78 g, 68 %), mp: 238-240 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.43 (s, 3H, N-C*H*$_3$), 3.59-3.63 (m, 4H, N-(C*H*$_2$)$_2$, morpholine), 3.65 (s, 3H, N-C*H*$_3$), 3.68-3.70 (m, 4H, O-(C*H*$_2$)$_2$, morpholine), 3.93 (s, 3H, -OC*H*$_3$), 4.84 (s, 2H, -OC*H*$_2$-), 7.04 (s, 1H, 5-C*H*, aromatic), 7.41 (s, 1H, 2-C*H*, aromatic), 7.56 (s, 1H, 6-C*H*, aromatic) and 13.09 ppm (s, 1H, N-*H*); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 27.79 (N-**C**H$_3$), 29.83 (N-**C**H$_3$), 41.59 (N-**C**H$_2$), 44.64 (N-**C**H$_2$), 55.98 (O-**C**H$_3$), 65.97 (O-**C**H$_2$), 66.06 (O-**C**H$_2$), 66.12 (O-**C**H$_2$),

107.32 (Ar**C**), 114.14 (Ar**C**H), 114.80 (Ar**C**H), 120.37 (Ar**C**), 123.28 (Ar**C**H), 147.53 (Ar**C**), 147.83 (Ar**C**), 147.94 (Ar**C**), 149.20 (Ar**C**), 151.13 (**C=**O), 154.24 (**C**=O) and 165.34 ppm (**C**=O); FT-IR (KBr): υ_{max} = 2946, 1704, 1664, 1649, 1603, 1554, 1487, 1210, 1042, 822 and 749 cm^{-1}; Calcd. for $C_{20}H_{23}N_5O_6$: C, 55.94; H, 5.40; N, 16.31. Found: C, 55.85; H, 5.30; N, 16.37.

4.1.4.25. 1,3-Dimethyl-8-[3-methoxy-4-{2-(1-methylpiperazin-4-yl)-2-oxoethoxy}-phenyl]-xanthine (**15g**) (0.34 g, 29 %), mp: 240 ºC (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 2.33 (s, 3H, >N-CH_3, *N*-methylpiperazine), 2.43-2.47 (m, 4H, N-(CH_2)$_2$, *N*-methylpiperazine), 3.41 (s, 3H, N-CH_3), 3.61 (s merged with a multiplet, 7H, N-CH_3 and -CON-(CH_2)$_2$, *N*-methylpiperazine), 3.92 (s, 3H, -OCH_3), 4.83 (s, 2H, -OCH_2-), 7.02 (s, 1H, 5-C*H*, aromatic), 7.37 (s, 1H, 2-C*H*, aromatic) and 7.63 ppm (s, 1H, 6-C*H*, aromatic); ^{13}C NMR (DMSO-d_6): δ 27.77 (N-**C**H$_3$), 29.82 (N-**C**H$_3$), 40.99 (N-**C**H$_3$), 43.78 (N-**C**H$_2$), 45.43 (N-**C**H$_2$), 54.11 (N-**C**H$_2$), 54.43 (N-**C**H$_2$), 55.96 (O-**C**H$_3$), 66.15 (O-**C**H$_2$), 107.31 (Ar**C**), 114.11 (Ar**C**H), 114.74 (Ar**C**H), 120.30 (Ar**C**), 123.25 (Ar**C**H), 147.50 (Ar**C**), 147.80 (Ar**C**), 147.88 (Ar**C**), 149.20 (Ar**C**), 151.11 (**C=**O) and 154.21 ppm (**C**=O), 165.10 (**C**=O); FT-IR (KBr): υ_{max} = 3387, 2941, 2795, 1665, 1548, 1482, 1384, 1259, 1213, 1036, 992, 873 and 743 cm^{-1}; Anal. calcd. for $C_{21}H_{26}N_6O_5$: C, 57.00; H, 5.92; N, 18.99. Found: C, 59.93; H, 5.81; N, 19.07.

4.1.4.26. 1,3-Dimethyl-8-[{4-(2-(imidazol-1-yl)-2-oxoethoxy)-3-methoxy}-phenyl]xanthine (**15h**) (0.5 g, 46 %), mp: 240 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 3.41 (s, 3H, N-CH_3), 3.63 (s, 3H, N-CH_3), 3.93 (s, 3H, -OCH_3), 4.70 (s, 2H, -OCH_2-), 6.94 (s, 1H, 5-C*H*, aromatic), 7.01 (s, 1H, 2-C*H*, aromatic), 7.11 (s(br), 2H, C*H*, imidazole), 7.36 (s, 1H, 6-C*H*, aromatic) and 7.88 ppm (s(br), 1H, C*H*, imidazole); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 27.66 (N-**C**H$_3$), 29.69 (N-**C**H$_3$), 55.87 (O-**C**H$_3$), 67.57 (O-**C**H$_2$), 107.38 (Ar**C**), 114.03 (Ar**C**H), 114.58 (Ar**C**H), 115.29 (Ar**C**H), 120.49 (Ar**C**H), 120.93 (Ar**C**), 123.36 (Ar**C**H), 123.39 (Ar**C**H), 147.49 (Ar**C**), 147.64 (Ar**C**), 148.79 (Ar**C**), 148.88 (Ar**C**), 151.09 (**C=**O), 154.17 (**C**=O) and 169.20 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3144, 2946, 2838, 1695, 1649, 1486, 1385, 1233, 1050, 989, 866 and 755 cm^{-1}; Anal calcd. for $C_{19}H_{18}N_6O_5$: C, 55.61; H, 4.42; N, 20.48. Found: C, 55.47; H, 4.36; N, 20.70.

4.1.4.27. 1,3-Dimethyl-8-[{4-(2-(homoveratrylamino)-2-oxoethoxy)-3-methoxy}-phenyl]-xanthine (**15i**) (0.72 g, 51 %), mp: 197 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.81 (t, 2H, -CONHCH$_2$C*H*$_2$-), 3.46 (s, 3H, N-C*H*$_3$), 3.61(q, 2H, -CONHC*H*$_2$CH$_2$-), 3.68 (s, 3H, N-C*H*$_3$), 3.79 (s, 3H, -OC*H*$_3$), 3.87 (s, 3H, -OC*H*$_3$), 3.88 (s, 3H, -OC*H*$_3$), 4.55 (s, 2H, -OC*H*$_2$-), 6.65-6.80 (m, 4H, C*H*, aromatic, homoveratrylamine and N-*H*), 6.86 (s, 1H, 5-C*H*, aromatic), 7.26 (s, 1H, 2-C*H*, aromatic), 7.71 (s, 1H, 6-C*H*, aromatic) and 11.00 ppm (s, 1H, N-*H*); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ = 27.73 (N-**C**H$_3$), 29.74 (N-**C**H$_3$), 34.69 (HN-**C**H$_2$), 55.34 (**C**H$_2$), 55.46 (O-**C**H$_3$), 55.89 (O-**C**H$_3$), 55.92 (O-**C**H$_3$), 68.11 (O-**C**H$_2$), 107.35 (Ar**C**), 111.63 (Ar**C**H), 112.24 (2×Ar**C**H), 115.64 (Ar**C**H), 120.44 (Ar**C**), 123.65 (Ar**C**H), 128.02 (Ar**C**H), 131.52 (Ar**C**), 147.19 (Ar**C**), 147.79 (Ar**C**), 148.58 (Ar**C**), 148.80 (Ar**C**), 150.87 (Ar**C**), 151.18 (Ar**C**), 152.96 (**C=**O), 157.84 (**C**=O) and 166.88 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3201, 2991, 2935, 1703, 1662, 1606, 1548, 1482, 1232, 1051, 851 and 760 cm^{-1}; Anal. calcd. for $C_{26}H_{29}N_5O_7$: C, 59.65; H, 5.58; N, 13.38. Found: C, 59.88; H, 5.65; N, 13.25.

4.1.4.28. 1,3-Dimethyl-8-[{3-(2-(dimethylaminoethylamino)-2-oxoetho-xy)-4-methoxy}-phenyl]- xanthine (**16a**) (0.8 g, 70 %), mp: 230 ºC (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.29 (s, 6H, -N(C*H*$_3$)$_2$), 2.53 (t, 2H, -C*H*$_2$N<), 3.45 (s, 5H, -CONHC*H*$_2$CH$_2$- and N-C*H*$_3$), 3.63 (s, 3H, N-C*H*$_3$), 3.94 (s, 3H, -OC*H*$_3$), 4.65 (s, 2H, -OC*H*$_2$-), 6.98 (d, 1H, 5-C*H*, aromatic, J_o = 8.40 Hz), 7.53 (s(br), 1H, N-*H*) and 7.80-7.82 ppm (m, 2H, 2-C*H* and 6-C*H*, aromatic); ^{13}C NMR (DMSO-d_6): δ = 27.69 (N-**C**H$_3$), 29.72 (N-**C**H$_3$), 36.15 (HN-**C**H$_2$), 44.91 (2×N-**C**H$_3$), 55.71 (O-**C**H$_3$), 57.69 (N-**C**H$_2$), 68.05 (O-**C**H$_2$), 107.25 (Ar**C**), 111.87 (Ar**C**H), 112.15 (Ar**C**H), 120.67 (Ar**C**H), 121.16 (Ar**C**), 147.10 (Ar**C**), 148.40 (Ar**C**), 149.70 (Ar**C**), 150.70 (Ar**C**), 151.11 (**C=**O), 154.02 (**C**=O) and 167.33 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3178, 2947, 1702, 1695, 1594, 1529, 1489, 1444, 1273, 1159, 1051, 984 and 752 cm^{-1}; Anal. calcd. for $C_{20}H_{26}N_6O_5$: C, 55.80; H, 6.09; N, 19.52. Found: C, 55.71; H, 6.17; N, 19.41.

4.1.4.29. 8-[{3-(2-(Diethylaminoethylamino)-2-oxoethoxy)-4-methoxy}phenyl]-1,3-dimethylxanthine (**16b**) (0.88 g, 72 %), mp: 198-200 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.0 (t, 6H, -N(CH$_2$C*H*$_3$)$_2$, *J* = 6.72 Hz), 2.52-2.59 (m, 6H, N(C*H*$_2$CH$_3$)$_2$ and -C*H*$_2$N<),

3.38-3.43 (m, 2H, -CONHC*H*$_2$CH$_2$-), 3.43 (s, 3H, N-C*H*$_3$), 3.65 (s, 3H, N-C*H*$_3$), 3.93 (s, 3H, -OC*H*$_3$), 4.65 (s, 2H, -OC*H*$_2$-), 6.98 (d, 1H, 5-C*H*, aromatic, J_o = 8.16 Hz), 7.43 (s(br), 1H, N-*H*) and 7.83-7.86 ppm (m, 2H, 2-C*H* and 6-C*H*, aromatic); ^{13}C NMR (DMSO-d_6): δ = 11.65 (2×**C**H$_3$), 27.71 (N-**C**H$_3$), 29.73 (N-**C**H$_3$), 36.25 (HN-**C**H$_2$), 46.40 (2×N-**C**H$_2$), 51.02 (N-**C**H$_2$), 55.68 (O-**C**H$_3$), 67.84 (O-**C**H$_2$), 107.30 (Ar**C**), 111.51 (Ar**C**H), 112.14 (Ar**C**H), 120.61 (Ar**C**H), 121.19 (Ar**C**), 147.00 (Ar**C**), 148.44 (Ar**C**), 149.74 (Ar**C**), 150.61 (Ar**C**), 151.14 (**C=**O), 154.06 (**C**=O) and 167.20 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3176, 2964, 1701, 1655, 1490, 1272, 1221, 1054, 985, 874 and 754 cm^{-1}; Anal. calcd. for $C_{22}H_{30}N_6O_5$: C, 57.63; H, 6.59; N, 18.33. Found: C, 57.48; H, 6.47; N, 18.45.

4.1.4.30. 1,3-Dimethyl-8-[4-methoxy-3-{2-(pyrrolidin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**16c**) (0.74 g, 67 %), mp: 250 ºC (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.89 (p, 2H, -C*H*$_2$-, pyrrolidine), 2.02 (p, 2H, -C*H*$_2$-, pyrrolidine), 3.39 (s, 3H, N-C*H*$_3$), 3.49 (t, 2H, N-C*H*$_2$, pyrrolidine), 3.58-3.62 (m, 5H, N-C*H*$_2$, pyrrolidine and N-C*H*$_3$), 3.92 (s, 3H, -OC*H*$_3$), 4.78 (s, 2H, -OC*H*$_2$-), 6.98 (d, 1H, 5-C*H*, aromatic, J_o = 8.40 Hz), 7.76 (s, 1H, 2-C*H*, aromatic), 7.80 (s, 1H, 6-C*H*, aromatic, J_o = 8.32 Hz) and 13.32 ppm (s, 1H, N-*H*); ^{13}C NMR (DMSO-d_6): δ = 23.50 (**C**H$_2$), 25.70 (CH$_2$), 27.73 (N-**C**H$_3$), 29.71 (N-**C**H$_3$), 44.96 (N-**C**H$_2$), 45.60 (N-**C**H$_2$), 55.66 (O-**C**H$_3$), 66.85 (O-**C**H$_2$), 107.19 (Ar**C**), 111.01 (Ar**C**H), 112.08 (Ar**C**H), 120.12 (Ar**C**H), 120.99 (Ar**C**), 147.51 (Ar**C**), 148.48 (Ar**C**), 149.93 (Ar**C**), 150.63 (Ar**C**), 151.13 (**C=**O), 154.07 (**C**=O) and 165.38 ppm (**C**=O); FT-IR (KBr): υ_{max} = 2955, 2886, 1696, 1657, 1624, 1564, 1491, 1259, 1220, 1022, 988, 816 and 746 cm^{-1}. Anal. calcd. for $C_{20}H_{23}N_5O_5$: C, 58.10; H, 5.61; N, 16.94. Found: C, 58.04; H, 5.79; N, 17.05.

4.1.4.31. 1,3-Dimethyl-8-[4-methoxy-3-{2-(piperidin-1-yl)-2-oxoethoxy}-phenyl]xanthine (**16d**) (0.30 g, 26 %), mp: 240 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 1.57 (s, 2H, -C*H*$_2$-, piperidine), 1.68 (s, 4H, 2 x -C*H*$_2$-, piperidine), 3.40 (s, 3H, N-C*H*$_3$), 3.51 (t, 2H, N-C*H*$_2$, piperidine), 3.55 (t, 2H, N-C*H*$_2$, piperidine), 3.63 (s, 3H, N-C*H*$_3$), 3.92 (s, 3H, -OC*H*$_3$), 4.83 (s, 2H, -OC*H*$_2$-), 6.98 (d, 1H, 5-C*H*, aromatic, J_o = 8.52 Hz), 7.76 (d, 1H, 2-C*H*, aromatic, J_m = 1.84 Hz) 7.80 (d, 1H, 6-C*H*, aromatic, J_o = 8.44 Hz), and 13.35 ppm (s, 1H, N-*H*); ^{13}C NMR (DMSO-d_6): δ = 24.01 (**C**H$_2$), 25.35 (**C**H$_2$), 26.02 (**C**H$_2$), 27.75 (N-**C**H$_3$), 29.66 (N-**C**H$_3$), 42.24 (N-**C**H$_2$), 45.41 (N-**C**H$_2$), 55.68 (O-**C**H$_3$),

66.47 (O-**C**H_2), 107.27 (Ar**C**), 111.04 (Ar**C**H), 112.08 (Ar**C**H), 119.93 (Ar**C**H), 121.04 (Ar**C**), 147.46 (Ar**C**), 148.50 (Ar**C**), 149.96 (Ar**C**), 150.61 (Ar**C**), 151.16 (**C=**O), 154.10 (**C**=O) and 165.01 ppm (**C**=O); FT-IR (KBr): υ_{max} = 2940, 2857, 1692, 1655, 1561, 1490, 1256, 1221, 1022, 789 and 746 cm^{-1}; Anal. calcd. for $C_{21}H_{25}N_5O_5$: C, 59.01; H, 5.90; N, 16.38. Found: C, 58.89; H, 5.85; N, 16.40.

4.1.4.32. 1,3-Dimethyl-8-[{3-(2-(hexamethyleneimin-1-yl)-2-oxoethoxy)-4-methoxy}-phenyl]xanthine (**16e**) (0.56 g, 47 %), mp: 180 ºC (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.61 (s, 4H, 2 x -CH_2-, hexamethyleneimine), 1.73 (s, 2H, -CH_2-, hexamethylene -imine), 1.83 (s, 2H, -CH_2-, hexamethyl-eneimine), 3.41 (s, 3H, N-CH_3), 3.55 (t, 4H, N-(CH_2)$_2$, hexamethyleneimine, J_o = 5.52 Hz), 3.64 (s, 3H, N-CH_3), 3.92 (s, 2H, -OCH_3), 4.86 (s, 2H, -OCH_2-), 6.98 (d, 1H, 5-C*H*, aromatic, J_o = 8.40 Hz), 7.73 (s, 1H, 2-C*H*, aromatic) and 7.84 ppm (d, 1H, 6-C*H*, aromatic, J_o = 8.40 Hz); ^{13}C NMR (DMSO-d_6): δ = 26.08 (**C**H_2), 26.79 (**C**H_2), 26.99 (**C**H_2), 27.76 (N-**C**H_3), 28.53 (**C**H_2), 29.65 (N-**C**H_3), 45.31 (N-**C**H_2), 46.33 (N-**C**H_2), 55.66 (O-**C**H_3), 66.20 (O-**C**H_2), 107.24 (Ar**C**), 110.91 (Ar**C**H), 112.05 (Ar**C**H), 119.80 (Ar**C**H), 121.05 (Ar**C**), 146.81 (Ar**C**), 147.58 (Ar**C**), 150.05 (Ar**C**), 150.59 (Ar**C**), 151.17 (**C=**O), 154.03 (**C**=O) and 166.26 ppm (**C**=O); FT-IR (KBr): υ_{max} = 2933, 1703, 1644, 1560, 1487, 1349, 1272, 1156, 1017, 982, 914 and 748 cm^{-1}; Anal. calcd. for $C_{22}H_{27}N_5O_5$: C, 59.85; H, 6.16; N, 15.86. Found: C, 59.62; H, 6.25; N, 15.91.

4.1.4.33. 1,3-Dimethyl-8-[4-methoxy-3-{(2-(morpholin-1-yl)-2-oxoethoxy}-phenyl]-xanthine (**16f**) (0.64 g, 56 %), mp: 245 ºC (decomp); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.40 (s, 3H, N-CH_3), 3.63 (s, 7H, N-(CH_2)$_2$, morpholine and N-CH_3), 3.68-3.73 (m, 2H, O-(CH_2)$_2$, morpholine), 3.92 (s, 3H, -OCH_3), 4.85 (s, 2H, -OCH_2-), 6.99 (d, 1H, 5-C*H*, aromatic, J_o = 8.52 Hz), 7.78 (d, 1H, 2-C*H*, aromatic, J_m = 1.92 Hz) and 7.82 ppm (dd, 1H, 6-C*H*, aromatic, J_m = 1.96 Hz; J_o = 8.48 Hz); ^{13}C NMR (DMSO-d_6): δ = 27.75 (N-**C**H_3), 29.69 (N-**C**H_3), 45.08 (2×N-**C**H_2), 55.70 (O-**C**H_3), 66.15 (2×O-**C**H_2), 66.42 (O-**C**H_2), 107.22 (Ar**C**), 111.27 (Ar**C**H), 112.15 (Ar**C**H), 120.14 (Ar**C**H), 120.99 (Ar**C**), 147.32 (Ar**C**), 148.49 (Ar**C**), 149.87 (Ar**C**), 150.68 (Ar**C**), 151.15 (**C=**O), 154.08 (**C**=O) and 165.65 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3156, 2961, 1707, 1648, 1530, 1490, 1273,

1220, 1111, 1013, 984 and 744 cm^{-1}; Anal. calcd. for $C_{20}H_{23}N_5O_6$: C, 55.94; H, 5.40; N, 16.31. Found: C, 55.86; H, 5.41; N, 16.43.

4.1.4.34. 1,3-Dimethyl-8-[4-methoxy-3-{2-(1-methylpiperazin-4-yl)-2-oxo-ethoxy}-phenyl]xanthine (**16g**) (0.66 g, 56 %), mp: 220 ºC (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.30 (s, 3H, >N-CH_3, *N*-methylpiperazine), 2.39 (s, 2H, N-CH_2, *N*-methylpiperazine), 2.46 (s, 2H, N-CH_2, *N*-methyl piperazine), 3.37 (s, 3H, N-CH_3), 3.60 (s, 7H, N-CH_3 and –CON-(CH_2)$_2$, *N*-methylpiperazine), 3.90 (s, 3H, -OCH_3), 4.84 (s, 2H, -OCH_2-), 6.99 (d, 1H, 5-C*H*, aromatic, J_o = 8.52 Hz), 7.80 (dd, 1H, 6-C*H*, aromatic, J_m = 1.60 Hz; J_o = 8.44 Hz) and 7.87 ppm (s, 1H, 2-C*H*, aromatic); ^{13}C NMR (DMSO-d_6): δ = 27.69 (N-**C**H$_3$), 29.73 (N-**C**H$_3$), 41.12 (N-**C**H$_3$), 44.20 (N-**C**H$_2$), 45.54 (N-**C**H$_2$), 54.22 (N-**C**H$_2$), 54.62 (N-**C**H$_2$), 55.65 (O-**C**H$_3$), 66.51 (O-**C**H$_2$), 107.15 (Ar**C**), 111.16 (Ar**C**H), 112.02 (Ar**C**H), 120.08 (Ar**C**H), 120.95 (Ar**C**), 147.30 (Ar**C**), 148.39 (Ar**C**), 149.82 (Ar**C**), 150.62 (Ar**C**), 151.08 (**C=**O), 154.00 (**C**=O) and 165.42 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3201, 2947, 1701, 1650, 1591, 1490, 1271, 1216, 1151, 1015, 870 and 746 cm^{-1}; Anal. calcd. for $C_{21}H_{26}N_6O_5$: C, 57.00; H, 5.92; N, 18.99. Found: C, 57.14; H, 5.94; N, 19.10.

4.1.4.35. 1,3-Dimethyl-8-[{3-(2-(imidazol-1-yl)-2-oxoethoxy)-4-methoxy}-phenyl]xanthine (**16h**) (0.76 g, 69 %), mp: 240 ºC (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ = 3.42 (s, 3H, N-CH_3), 3.67 (s, 3H, N-CH_3), 3.94 (s, 3H, -OCH_3), 4.80 (s, 2H, -OCH_2-), 6.98 (d, 1H, 5-C*H*, aromatic, J_o = 8.40 Hz), 7.34 (s, 2H, C*H*, imidazole), 7.78 (s, 1H, 2-C*H*, aromatic), 7.85 (d, 1H, 6-C*H*, aromatic, J_o = 8.08 Hz) and 8.76 ppm (s, 1H, C*H*, imidazole) and 14.92 ppm (s, 1H, N-*H*); ^{13}C NMR (DMSO-d_6): δ = 27.72 (N-**C**H$_3$), 29.75 (N-**C**H$_3$), 55.60 (O-**C**H$_3$), 64.86 (O-**C**H$_2$), 107.18 (Ar**C**), 110.31 (Ar**C**H), 112.09 (Ar**C**H), 120.08 (Ar**C**H), 120.90 (2×Ar**C**H), 121.52 (Ar**C**), 135.07 (Ar**C**H), 147.26 (Ar**C**), 148.45 (Ar**C**), 149.82 (Ar**C**), 150.43 (Ar**C**), 151.15 (**C=**O), 154.05 (**C**=O) and 170.02 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3121, 2966, 1968, 1699, 1658, 1560, 1482, 1323, 1266, 1216, 1131, 1028, 982, 863 and 754 cm^{-1}; Anal. calcd. for $C_{19}H_{18}N_6O_5$: C, 55.61; H, 4.42; N, 20.48. Found: C, 55.70; H, 4.50; N, 20.52.

4.1.4.36. 1,3-Dimethyl-8-[{3-(2-(homoveratrylamino)-2-oxoethoxy)-4-methoxy}-phenyl]xanthine (**16i**) (0.82 g, 59 %), mp: 242-244 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ

= 2.81 (t, 2H, -CONHCH$_2$C*H*$_2$-, *J* = 6.86 Hz), 3.43 (s, 3H, N-C*H*$_3$), 3.58 (q, 2H, -CONHC*H*$_2$CH$_2$-), 3.65 (s, 3H, N-C*H*$_3$), 3.82 (s, 3H, -OC*H*$_3$), 3.85 (s, 6H, 2 x OC*H*$_3$), 4.64 (s, 2H, -OC*H*$_2$-), 6.73-6.78 (m, 3H, C*H*, aromatic, homoveratrylamine), 6.96 (d, 1H, 5-C*H*, aromatic, J_o = 8.36 Hz), 7.06 (s(br), 1H, N-*H*) and 7.82-7.87 ppm (m, 2H, 2-C*H* and 6-C*H*, aromatic); ^{13}C NMR (DMSO-d_6): δ = 27.75 (N-**C**H$_3$), 29.75 (N-**C**H$_3$), 34.57 (HN-**C**H$_2$), 40.00 (**C**H$_2$), 55.23 (O-**C**H$_3$), 55.37 (O-**C**H$_3$), 55.68 (O-**C**H$_3$), 68.08 (O-**C**H$_2$), 111.67 (Ar**C**), 112.27 (2×Ar**C**H), 120.34 (Ar**C**), 128.89 (2×Ar**C**H), 131.53 (Ar**C**), 147.20 (2×Ar**C**H), 148.54 (Ar**C**), 149.74 (Ar**C**), 150.69 (Ar**C**), 151.19 (Ar**C**), 152.38 (Ar**C**), 154.07 (Ar**C**), 158.80 (**C=**O), 161.19 (**C**=O) and 167.34 ppm (**C**=O); FT-IR (KBr): υ_{max} = 3165, 2936, 1700, 1661, 1554, 1487, 1267, 1148, 1022, 985, 870 and 746 cm^{-1}; Anal. calcd. for $C_{26}H_{29}N_5O_7$: C, 59.65; H, 5.58; N, 13.38. Found: C, 59.77; H, 5.49; N, 13.31.

4.2. Partition Coefficient

4.2.1. Materials

The hydrophobicity of 8-phenylxanthine derivatives **14** and **14a-i** was observed by partition coefficient method.

4.2.2. Experimental protocol

The compounds **14** and **14a-14i** were dissolved separately in phosphate-buffered saline (PBS) of pH 7.4 to obtain 10 µg/ml solutions. Five ml of the PBS solution was added to an equal volume of *n*-octanol and chloroform, which was then equilibrated at 25 °C by continuous shaking for 2 h [16]. After the separation of phases, concentration of each compound in the aqueous phase or organic phase was determined using ultra-violet spectrophotometer at 315 nm wavelength. Partition coefficient of each compound was estimated as the ratio of the concentration in the organic phase to that in the aqueous phase and was expressed as logarithmic partition coefficient. *In silico* log P were also determined using ChemDraw and Biotage softwares.

4.3. Biological methods

4.3.1. Radioligand binding assays

4.3.1.1. Materials

[^{3}H]CCPA (2-chloro-*N*^{6}-cyclopentyladenosine) was from PerkinElmer, Boston, MA, U.S.A., [^{3}H]NECA (5'-N-ethylcarboxamidoadenosine) and [α-^{32}P]ATP were from

Hartmann, Braunschweig, Germany, [^{3}H]HEMADO (2-hexyn-1-yl-N^6-methyladenosine) was from Tocris, Bristol, UK. The 96-well microplate filtration system (Multiscreen MAFC) was obtained from Millipore, Eschborn, Germany. Cell culture media and fetal calf serum were purchased from Pan Systems, Aidenbach, Germany. Penicillin (100 U/ml), streptomycin (100 mg/ml), L-glutamine and G418 were from Gibco-Life Technologies, Eggenstein, Germany.

4.3.1.2. Cell culture

The cells were grown adherently and maintained in Dulbecco's Modified Eagles Medium with nutrient mixture F12 (DMEM/F12) without nucleosides, containing 10% fetal calf serum, penicillin (100 U/ml), streptomycin (100 mg/ml), L-glutamine (2 mM) and Geneticin (G418, 0.2 mg/ml; A_{2B}, 0.5 mg/ml) at 37 °C in 5% CO_2/95% air. Cells were split 2 or 3 times weekly at a ratio between 1:5 and 1:20. For binding assays the culture medium was removed, cells were washed with PBS and frozen in the dishes until preparation of membranes. The cells utilized for cAMP determinations had a viability > 95%, as assessed by the exclusion of tryptan blue.

4.3.1.3. Membrane preparation

Crude membranes for radioligand binding experiments were prepared by thawing frozen cells followed by scraping them off the petridishes in ice-cold hypotonic buffer (5 mM Tris/HCl, 2 mM EDTA, pH 7.4). The cell suspension was homogenized on ice (Ultra-Turrax, 2 x 15 s at full speed) and the homogenate was spun for 10 min (4° C) at 1,000 g. The supernatant was then centrifuged for 30 min at 100,000 g. The membrane pellet was resuspended in 50 mM Tris/HCl buffer pH 7.4 (for A_3 adenosine receptors: 50 mM Tris/HCl, 10 mM $MgCl_2$, 1 mM EDTA, pH 8.25), frozen in liquid nitrogen at a protein concentration of 1-3 mg/ml and stored at -80 °C. For the measurement of adenylyl cyclase activity a slightly modified protocol with only one centrifugation step was used. Fresh cells were homogenized and the homogenate was sedimented for 30 min at 54,000 g. The resulting pellet was resuspended in 50 mM Tris/HCl pH 7.4 and used for the adenylyl cyclase assay immediately.

4.3.1.4. Radioligand binding

Dissociation constants at *A_1, A_{2A} and A_3 receptors* (K_i-values) were determined in radioligand competition experiments as reported earlier [17,18]. All binding experiments were done in a microplate format utilizing a 96-well microplate filtration system (Millipore Multiscreen MAFC). As radioligands the agonists [^{3}H]CCPA (1 nM) for A_1, [^{3}H]NECA (10 nM) for A_{2A}, and [^{3}H]HEMADO (1 nM) for A_3 receptors were used. Samples were incubated with 10 µg of membrane protein for 3 h at 25 °C, filtered through the built-in filter at the bottom of the wells and washed three times with 200 ml of ice-cold binding buffer. After addition of 20 µl of scintillator to the dried filter plates samples were counted in a Wallac Micro-Beta counter. Nonspecific binding was determined in the presence of 1 mM theophylline ([^{3}H]CCPA) or 100 mM R-PIA (*N*^{6}-phenylisopropyladenosine; [^{3}H]NECA and [^{3}H]HEMADO). All binding data were calculated by non-linear curve fitting with the program SCTFIT [17].

4.3.1.5. Adenylyl cyclase activity

Due to the lack of a suitable radioligand the affinity of ligands for A_{2B} adenosine receptors was determined in adenylyl cyclase experiments [17]. Membranes were incubated with about 150,000 cpm of [α-^{32}P]ATP for 20 min in the incubation mixture as described without EGTA and NaCl. IC_{50}-values for concentration-dependent inhibition of NECA-stimulated adenylyl cyclase caused by antagonists were calculated using the Hill equation. IC_{50}-values for antagonist were then converted to K_i values with the Cheng and Prusoff equation [17].

4.3.1.6. Cell culture and membrane preparation

Cell culture of CHO cells stably transfected with human adenosine receptors was carried out as described before [17]. In brief, cells were grown adherently and maintained in Dulbecco's Modified Eagles Medium at 37 °C in 5% CO_2/95% air with nutrient mixture F12 (DMEM/F12) without nucleosides, containing 10% fetal calf serum, penicillin (100 U/ml), streptomycin (100 µg/ml), L-glutamine (2 mM) and Geneticin (G-418, 0.2 mg/ml). Crude membrane fractions for radioligand binding studies were prepared as before [17].

4.3.2. Bronchospasmolytic activity

The newly synthesized xanthine derivatives **13-16, 13a-i–16a-i** were evaluated for bronchoprotective effects against histamine aerosol induced bronchospasm in guinea pigs according to the method of Zabeer *et al* [19].

4.3.2.1. Animals

Male guinea-pigs (Dunkin Hartley) of 250±30 g, bred in the disease free small animal house of Chaudhary Charan Singh Haryana Agriculture University (Hisar, Haryana) were obtained. The animals were housed under standard laboratory conditions, maintained on a 12 hour light and dark cycle and had free access to food (carrots, cucumbers, leafy vegetables etc) and water. The experimental protocols were approved by the Institutional Animal Ethics Committee of the Panjab University, Chandigarh (CAH/1476 dated 14.09.2009), and conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals.

4.3.2.2. Drugs

Histamine hydrochloride (Himedia, India), theophylline, carboxymethyl cellulose (CMC) and test compounds.

4.3.2.3. Experimental protocol

Three groups of animal (4 in each) were made and designated as I, II and III for control (CMC + distilled water), standard (CMC + theophylline + distilled water) and test drug (CMC + test drug + distilled water), respectively. The grouped animals were kept for overnight fasting and pretreated with the test drug (50 mg/kg), theophylline (50 mg/kg), and CMC (control) per oral 1 h before exposure to aerosol. Each group of the animals were kept in the histamine chamber (M/s Inco, Ambala) separately and exposed to histamine aerosol. Five ml of 1% solution of histamine was aerosoled in 1 min to each animal of each group. The onset of bronchospasm, duration of jerks, severity of bronchospasm and death or survival of the animals was recorded for each group. The animals remained in the chamber for 8 min after which they were removed in fresh air and fed with proper water and food.

Acknowledgments

The financial support provided by the Indian Council of Medical Research, New Delhi, India is gratefully acknowledged.

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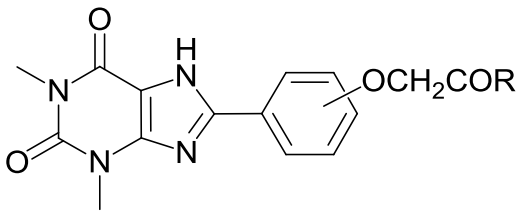
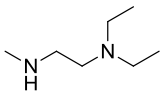
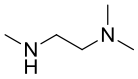
Graphical abstract

Novel xanthine carboxylate amides as potent A_{2A} adenosine receptor ligands exhibiting bronchospasmolytic activity are reported



R = various alkyl amines

(13b)  K_i = 0.06 μM

(16a)  K_i = 0.075 μM

(16d)  K_i = 0.076 μM

Highlights

- ✓ Thirty six novel xanthine carboxylate amides were synthesized
- ✓ Many compounds showed high affinity for the A_{2A} receptors in nM range along with good selectivity *versus* all other subtypes
- ✓ All the xanthine derivatives displayed good bronchospasmolytic activity against histamine aerosol induced bronchospasm
- ✓ Partition coefficient studies indicate Log P values between -0.41 and 2.0