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Full Paper

Structure–5-HT Receptor Affinity Relationship in a New Group of 7-Arylpiperazynylalkyl and 7-Tetrahydroisoquinolinylalkyl Derivatives of 8-Amino-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

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In our previous paper, we have reported that some 8-alkoxy-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione derivatives possessed high affinity and displayed agonistic activity for the serotonin 5-HT_{1A} receptor. In order to examine the influence of the substituent in the position 8 of the purine moiety on the affinity for the serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors, a series of 7-arylpiperazynylalkyl and 7-tetrahydroisoquinolinylalkyl (THIQ) derivatives of 8-amino-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione were synthesized. All the final compounds were investigated in *in vitro* competition binding experiments for serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors. The structure–affinity relationships for this group of compounds were discussed. For selected compounds, functional assays for the 5-HT_{1A} receptor were carried out. The results of the assays indicated that these groups of derivatives possessed antagonistic activity for this receptor.

Keywords: 5-HT_{1A} / 5-HT_{2A} / 5-HT_7 / LCAPs / Theophylline

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Introduction

It is well known that the serotoninergic receptors 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 present in central nervous system are involved in such psychiatric disorders as anxiety, depression, and schizophrenia. Big group of compounds acting on these receptors are derivatives possessing arylpiperazine moiety connected to cyclic amide core with linker, so called long-chain arylpiperazines (LCAPs).

For several years, we have been interested in developing new series of LCAPs with different xanthine moieties playing the role of cyclic amides. In our previous paper, we have described a series of derivatives possessing 8-alkoxy-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione core, which proved to be 5-HT_{1A} receptor agonists with moderate-to-high affinity for these receptors [1]. One of them, shown in Fig. 1, displayed antidepressant and anxiolytic activity in *in vivo* tests.

The aim of our study was to investigate the influence of further modifications of the substituent in position 8 of xanthine core. In this purpose, we have designed a new series of 1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione derivatives possessing in position 8 differently substituted amine moiety, i.e., dibenzylamine, *N*-ethylbenzylamine, *N*-methylbenzylamine, ethylamine, methylamine, or unsubstituted amine moiety. This gave us opportunity to investigate a relationship between lipophilicity and size of the substituent and affinity to different serotoninergic receptors. The influence of the structural modifications was investigated in classic arylpiperazine (R = H, 2-OCH_3, 3-Cl, and 4-F) or 1,2,3,4-tetrahydroisoquinolie (THIQ) derivatives with three to five methylene group linkers. All the new compounds were tested for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7

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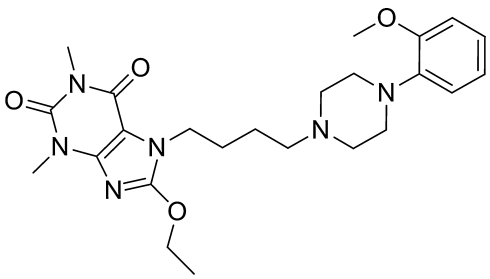


Fig. 1. 8-Alkoxytheophylline derivative with agonistic activity for 5-HT_{1A} receptor, $K_i = 11$ nM [1].

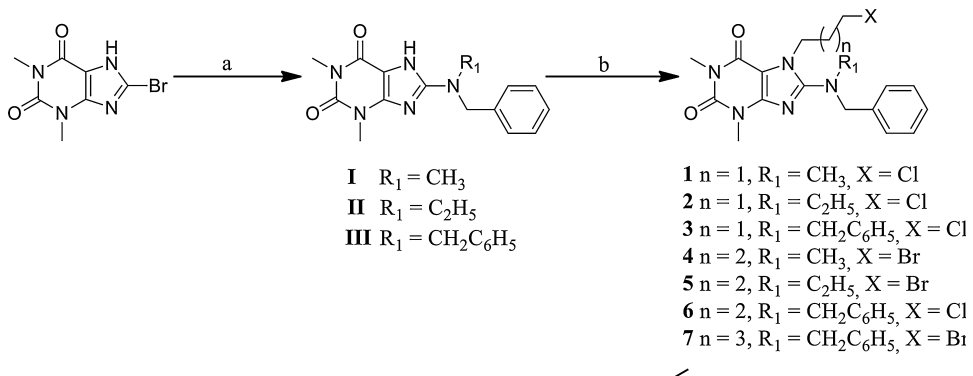
receptor affinity. For selected compounds, the functional assays for 5-HT_{1A} receptor were carried out.

Results and discussion

Chemistry

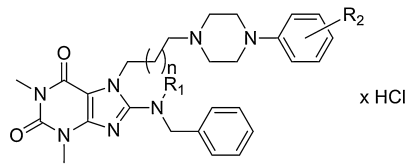
Structures of the investigated compounds and their syntheses are presented in Schemes 1 and 2.

The starting 8-(*N*-alkylbenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-diones (**I** and **II**) and 8-(dibenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**III**) were prepared in a reaction of 8-bromo-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione with the appropriate *N*-alkylbenzylamine (*N*-methylbenzylamine or *N*-ethylbenzylamine, respectively) or dibenzylamine



I $R_1 = CH_3$
II $R_1 = C_2H_5$
III $R_1 = CH_2C_6H_5$

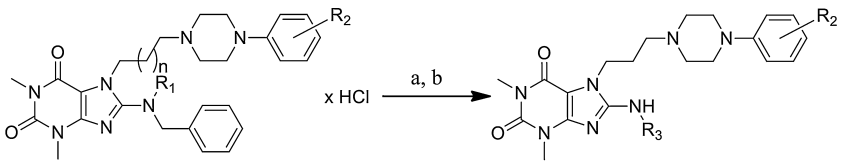
1 n = 1, $R_1 = CH_3$, X = Cl
2 n = 1, $R_1 = C_2H_5$, X = Cl
3 n = 1, $R_1 = CH_2C_6H_5$, X = Cl
4 n = 2, $R_1 = CH_3$, X = Br
5 n = 2, $R_1 = C_2H_5$, X = Br
6 n = 2, $R_1 = CH_2C_6H_5$, X = Cl
7 n = 3, $R_1 = CH_2C_6H_5$, X = Br



x HCl

8 n = 1, $R_1 = CH_3$, R_2 = H
9 n = 1, $R_1 = CH_3$, R_2 = 2-OCH_3
10 n = 1, $R_1 = CH_3$, R_2 = 3-Cl
11 n = 1, $R_1 = C_2H_5$, R_2 = H
12 n = 1, $R_1 = C_2H_5$, R_2 = 2-OCH_3
13 n = 1, $R_1 = CH_2C_6H_5$, R_2 = H
14 n = 1, $R_1 = CH_2C_6H_5$, R_2 = 2-OCH_3
15 n = 1, $R_1 = CH_2C_6H_5$, R_2 = 3-Cl
16 n = 1, $R_1 = CH_2C_6H_5$, R_2 = 4-F
17 n = 1, $R_1 = CH_2C_6H_5$, R_2 = THIQ
18 n = 2, $R_1 = CH_3$, R_2 = H
19 n = 2, $R_1 = CH_3$, R_2 = 2-OCH_3
20 n = 2, $R_1 = CH_3$, R_2 = THIQ
21 n = 2, $R_1 = C_2H_5$, R_2 = H
22 n = 2, $R_1 = C_2H_5$, R_2 = 2-OCH_3
23 n = 2, $R_1 = C_2H_5$, R_2 = THIQ
24 n = 2, $R_1 = CH_2C_6H_5$, R_2 = H
25 n = 2, $R_1 = CH_2C_6H_5$, R_2 = 2-OCH_3
26 n = 2, $R_1 = CH_2C_6H_5$, R_2 = 3-Cl
27 n = 2, $R_1 = CH_2C_6H_5$, R_2 = 4-F
28 n = 2, $R_1 = CH_2C_6H_5$, R_2 = THIQ
29 n = 3, $R_1 = CH_2C_6H_5$, R_2 = H
30 n = 3, $R_1 = CH_2C_6H_5$, R_2 = 2-OCH_3
31 n = 3, $R_1 = CH_2C_6H_5$, R_2 = 3-Cl
32 n = 3, $R_1 = CH_2C_6H_5$, R_2 = 4-F
33 n = 3, $R_1 = CH_2C_6H_5$, R_2 = THIQ

Scheme 1. Reagents and conditions: (a) *N*-Methylbenzylamine or *N*-ethylbenzylamine or dibenzylamine, 2-(2-methoxyethoxy)-ethanol, reflux; (b) 1-bromo-3-chloropropane or 1-bromo-4-chlorobutane or 1,4-dibromobutane or 1,5-dibromopentane, K_2CO_3, TEBA, acetone, reflux; (c) arylpiperazine or THIQ, K_2CO_3, 1-propanol, reflux; (d) conc. HCl, anhydrous ethanol.



34 n = 1, R_3 = H, R_2 = H
35 n = 1, R_3 = H, R_2 = 2-OCH_3
36 n = 1, R_3 = H, R_2 = 3-Cl
37 n = 1, R_3 = H, R_2 = 4-F
38 n = 1, R_3 = H, R_2 = THIQ
39 n = 1, R_3 = CH_3, R_2 = H
40 n = 1, R_3 = CH_3, R_2 = 2-OCH_3
41 n = 1, R_3 = CH_3, R_2 = 3-Cl
42 n = 1, R_3 = C_2H_5, R_2 = H
43 n = 1, R_3 = C_2H_5, R_2 = 2-OCH_3
44 n = 2, R_3 = H, R_2 = H
45 n = 2, R_3 = H, R_2 = 2-OCH_3
46 n = 2, R_3 = H, R_2 = 3-Cl
47 n = 2, R_3 = H, R_2 = 4-F
48 n = 2, R_3 = H, R_2 = THIQ
49 n = 2, R_3 = C_2H_5, R_2 = H
50 n = 2, R_3 = C_2H_5, R_2 = 2-OCH_3
51 n = 2, R_3 = C_2H_5, R_2 = THIQ
52 n = 3, R_3 = H, R_2 = H
53 n = 3, R_3 = H, R_2 = 2-OCH_3
54 n = 3, R_3 = H, R_2 = 3-Cl
55 n = 3, R_3 = H, R_2 = 4-F

Scheme 2. Reagents and conditions: (a) 90% H_2SO_4, rt; (b) 30% NaOH.

according to the previously described method [2–4]. 7-ω-Haloalkyl-8-(*N*-alkylbenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-diones (**1**, **2**, **4**, and **5**) and 7-ω-haloalkyl-8-(dibenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-diones (**3**, **6**, and **7**) were prepared in a reaction of **I–III** with an appropriate dihaloalkane (1-bromo-3-chloropropane, 1-bromo-4-chlorobutane, 1,4-dibromobutane, or 1,5-dibromobutane) in presence of K_2CO_3 and TEBA (*N*,*N*,*N*-triethylbenzylammonium chloride) in acetone. The designed 7-(ω-(4-arylpiperazin-1-yl)-alkyl)-8-(*N*-alkylbenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-diones (**8–12**, **18**, **19**, **21**, and **22**), 7-(ω-(4-arylpiperazin-1-yl)alkyl)-8-(dibenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-diones (**13–16**, **24–27**, and **29–32**) and their 7-(ω-(3,4-dihydroisoquinolin-2(1*H*)-yl)alkyl counterparts (**17**, **20**, **23**, **28**, and **33**) were synthesized by nucleophilic substitution of **1–7** with the appropriate arylpiperazines or 1,2,3,4-tetrahydroisoquinoline (THIQ) in the presence of K_2CO_3. The compounds **8–33** were isolated from the reaction mixtures as hydrochloric salts. The designed 7-(ω-(4-arylpiperazin-1-yl)alkyl)-8-(alkylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-diones (**39–43**, **49**, and **50**), 7-(ω-(4-arylpiperazin-1-yl)alkyl)-8-amino-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-diones (**34–37**, **44–47**, and **52–55**), as well as their 7-(ω-(3,4-dihydroisoquinolin-2(1*H*)-yl)alkyl counterparts (**38**, **48**, and **51**) were prepared by debenzylation of compounds **8–33** with 90% H_2SO_4 in room temperature. Resulting compounds were isolated from the reaction mixtures as free bases and then converted into hydrochloric salts in a reaction with conc. HCl in dry ethanol.

The structures of the newly synthesized compounds **1–55** were confirmed by ^{1}H NMR spectra, LC/MS, and elemental analysis. The investigated compounds were pharmacologically tested as hydrochloride salts.

Pharmacology

The compounds were tested in competition binding experiments for rats' serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors. The affinity data are shown in Tables 1 and 2.

In order to determine the influence of the structure of the substituent in the position 8 of 1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione on the functional profile for 5-HT_{1A} receptor compounds possessing moderate-to-high affinity for this receptor and preference for binding to 5-HT_{1A} receptor (compounds **9**, **14**, and **23**) or 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors (compounds **26** and **54**) were selected. For the selected compounds, the functional assays for 5-HT_{1A} receptor were carried out. The results are presented in Table 3.

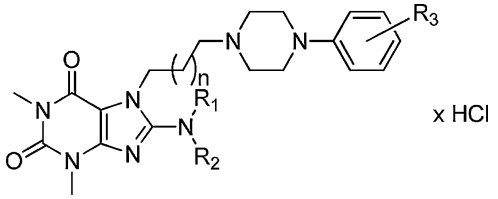
The newly synthesized derivatives of 8-amino-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione showed diversified level of affinity for 5-HT_{1A} ranging from 14 to 5332 nM, for 5-HT_{2A} from 18 to 22,880 nM, and for 5-HT_7 receptors from 20 to 12,750 nM.

Influence of the linker length on the affinity for these receptors was evident: elongation of the linker caused augmentation of affinity, although strength of this influence depended on the receptor type. For 5-HT_{1A} and especially 5-HT_7 receptors, this influence was strong, while for 5-HT_{2A} receptors weaker. For example, comparison between **34**, with three methylene groups in linker, and its higher homolog **52**, with five methylene groups, showed, that elongation of the linker caused almost 16-fold increase for 5-HT_7, over 3.6-fold increase of affinity for 5-HT_{1A} receptors and less than 3-fold increase for 5-HT_{2A} receptors.

Analysis of the results of affinity for 5-HT_{1A} receptors showed, that the derivatives with (2-methoxyphenyl)piperazine moiety possessed the highest affinity for these receptors. Derivatives possessing (3-chlorophenyl)piperazine moiety generally had lower, 1.39- to 8.09-fold (**14** vs. **15** and **40** vs. **41**, respectively), or even comparative affinity, as for **45** and **46**. (4-Fluorophenyl)piperazine moiety caused great diminution of affinity for these receptors, e.g., affinity of **16** was over 72-fold lower than **14**. Generally, the affinity of investigated derivatives for 5-HT_{1A} receptors changed according to the scheme:

(2-Methoxyphenyl)piperazines > (3-chlorophenyl)piperazines > phenylpiperazines ≫ (4-fluorophenyl)piperazines

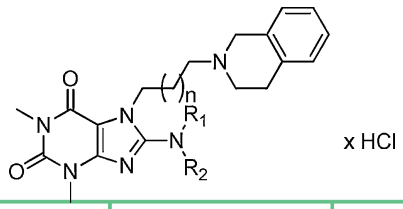
Table 1. Structure and binding affinity data on serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors of the investigated 7-(ω-(4-arylpiperazin-1-yl)alkyl)-8-amino-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione derivatives.



Comp.	*n*	R_1	R_2	R_3	K_i (nM) 5-HT_{1A}	K_i (nM) 5-HT_{2A}	K_i (nM) 5-HT_7
8	1	$CH_2C_6H_5$	CH_3	H	243	182	109
9	1	$CH_2C_6H_5$	CH_3	2-OCH_3	25	239	243
10	1	$CH_2C_6H_5$	CH_3	3-Cl	141	55	163
11	1	$CH_2C_6H_5$	C_2H_5	H	98	18	298
12	1	$CH_2C_6H_5$	C_2H_5	2-OCH_3	14	588	105
13	1	$CH_2C_6H_5$	$CH_2C_6H_5$	H	329	230	492
14	1	$CH_2C_6H_5$	$CH_2C_6H_5$	2-OCH_3	33	1239	135
15	1	$CH_2C_6H_5$	$CH_2C_6H_5$	3-Cl	267	280	335
16	1	$CH_2C_6H_5$	$CH_2C_6H_5$	4-F	2403	255	1178
18	2	$CH_2C_6H_5$	CH_3	H	78	241	47
19	2	$CH_2C_6H_5$	CH_3	2-OCH_3	45	202	152
21	2	$CH_2C_6H_5$	C_2H_5	H	72	102	149
22	2	$CH_2C_6H_5$	C_2H_5	2-OCH_3	77	121	114
24	2	$CH_2C_6H_5$	$CH_2C_6H_5$	H	246	790	493
25	2	$CH_2C_6H_5$	$CH_2C_6H_5$	2-OCH_3	120	288	88
26	2	$CH_2C_6H_5$	$CH_2C_6H_5$	3-Cl	176	119	116
27	2	$CH_2C_6H_5$	$CH_2C_6H_5$	4-F	678	115	478
29	3	$CH_2C_6H_5$	$CH_2C_6H_5$	H	226	700	84
30	3	$CH_2C_6H_5$	$CH_2C_6H_5$	2-OCH_3	42	856	20
31	3	$CH_2C_6H_5$	$CH_2C_6H_5$	3-Cl	169	264	78
32	3	$CH_2C_6H_5$	$CH_2C_6H_5$	4-F	555	198	228
34	1	H	H	H	887	871	5721
35	1	H	H	2-OCH_3	272	372	3258
36	1	H	H	3-Cl	590	186	2609
37	1	H	H	4-F	1269	48	1604
39	1	H	CH_3	H	108	134	335
40	1	H	CH_3	2-OCH_3	51	1766	814
41	1	H	CH_3	3-Cl	71	128	347
42	1	H	C_2H_5	H	226	88	157
43	1	H	C_2H_5	2-OCH_3	73	937	659
44	2	H	H	H	60	613	3274
45	2	H	H	2-OCH_3	29	705	504
46	2	H	H	3-Cl	25	184	211
47	2	H	H	4-F	130	284	1384
49	2	H	C_2H_5	H	485	67	233
50	2	H	C_2H_5	2-OCH_3	109	221	109
52	3	H	H	H	240	291	359
53	3	H	H	2-OCH_3	111	253	140
54	3	H	H	3-Cl	98	25	77
55	3	H	H	4-F	757	360	131

Influence of THIQ moiety strongly depended on the structure of 8-amino substituent: derivatives with lipophilic substituents, such as *N*-methylbenzylamine (**20**), *N*-ethylbenzylamine (**23**), had K_i below 60 nM, while those with unsubstituted amine group (**48**) or alkylamine moiety (**51**) had K_i over 1000 nM. In case of the derivatives with dibenzylamine moiety, affinity for 5-HT_{1A} receptors was between earlier described groups and depended on length of the linker between THIQ moiety and purine: elongation of the linker caused augmentation of affinity, e.g., compound **33** with five methylene

Table 2. Structure and binding affinity data on serotonin 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_7$ receptors of the investigated 8-amino-7-(ω-(3,4-dihydroisoquinolin-2(1H)-yl)alkyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione derivatives.



x HCl

Comp.	*n*	R_1	R_2	K_i (nM) 5-HT$_{1A}$	K_i (nM) 5-HT$_{2A}$	K_i (nM) 5-HT$_7$
17	1	$CH_2C_6H_5$	$CH_2C_6H_5$	841	22,880	1926
20	2	$CH_2C_6H_5$	CH_3	59	1050	72
23	2	$CH_2C_6H_5$	C_2H_5	21	1102	72
28	2	$CH_2C_6H_5$	$CH_2C_6H_5$	161	5036	56
33	3	$CH_2C_6H_5$	$CH_2C_6H_5$	47	2609	94
38	1	H	H	5332	2666	12,750
48	2	H	H	1320	309	639
51	2	H	C_2H_5	1579	963	207

groups in linker showed over 17-fold higher affinity than its lower homolog **17**, possessing three methylene groups.

Analysis of the influence of the structure of the substituent in the position 8 of purine moiety showed, that the affinity for 5-HT$_{1A}$ receptors changed according to the scheme:

N-Ethylbenzylamine > *N*-methylbenzylamine > methylamine > ethylamine > amine ≈ dibenzylamine

For example, affinity of **12** (*N*-ethylbenzylamine) was almost 2-fold higher than **9** (*N*-methylbenzylamine), over 3.5-fold higher than **40** (methylamine), over 5-fold higher than **43** (ethylamine), 23.5-fold higher than **13** (dibenzylamine) and over 63-fold higher than **34** (amine).

The lowest affinity of the derivatives with 8-dibenzylamine moiety might suggest, that although lipophilic substituent was preferred for interaction with the 5-HT$_{1A}$ receptors, its size was also important – substituents larger than *N*-ethylbenzylamine were not preferred.

Analysis of the results of affinity for 5-HT$_{2A}$ receptors showed, that the derivatives with (3-chlorophenyl)piperazine moiety possessed the highest affinity for these receptors. Derivatives possessing (4-fluorophenyl)piperazine moiety generally had lower or comparable affinity, e.g., **54** versus **55** and **15** versus **16**, respectively. Derivatives with (2-methoxyphenyl)piperazine moiety generally had low affinity for these receptors, e.g., affinity of **40** was over 10-fold lower than **39**, possessing phenylpiperazine moiety, and **41**, possessing (3-chlorophenyl)piperazine moiety. Derivatives with THIQ moiety possessed the lowest affinity for 5-HT$_{2A}$ receptors among the investigated compounds. The affinity of the investigated derivatives for 5-HT$_{2A}$ receptors changed according to the scheme:

(3-Chlorophenyl)piperazines ≈ (4-fluorophenyl)piperazines > phenylpiperazines ≈ (2-methoxyphenyl)piperazines > THIQ

Influence of the structure of the substituent in the position 8 of purine moiety on affinity for 5-HT$_{2A}$ receptors was analogical to that described for 5-HT$_{1A}$ receptors, except for the derivatives with unsubstituted 8-amine moiety, which possessed the lowest affinity for these receptors. The affinity

Table 3. Functional assay results for the tested compounds.

Concentration of compounds	Agonist mode[a)]						Antagonist mode[b)]					
	10^{-5} M			10^{-6} M			10^{-5} M			10^{-6} M		
Comp.	**Mean**	**SD**	**SEM**	**Mean**	**SD**	**SEM**	**Mean**	**SD**	**SEM**	**Mean**	**SD**	**SEM**
9	4.0	1.8	0.9	5.5	0.6	0.3	98.3	1.0	0.5	78.0	0.8	0.4
14	4.0	2.3	1.2	6.5	1.3	0.6	97.5	0.6	0.3	89.8	1.3	0.6
23	101.8	5.3	2.7	76.5	7.0	3.5	99.5	0.6	0.3	99.8	0.5	0.3
26	3.8	2.1	1.0	7.0	0.8	0.4	99.5	0.6	0.3	90.3	1.5	0.8
54	18.8	9.1	4.5	18.8	3.0	1.5	99.8	0.5	0.3	86.3	1.5	0.8

[a)] Percent of maximal agonist response (serotonin 10^{-6} M).
[b)] Percent of inhibition of reference agonist signal (serotonin 10^{-7} M corresponding to the EC_{80}).

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for 5-HT_{2A} receptors changed according to the scheme:

N-Ethylbenzylamine > *N*-methylbenzylamine > ethylamine > methylamine > dibenzylamine > amine

Analysis of the results of affinity for 5-HT_7 receptors indicated, that the influence of the arylpiperazine or THIQ moiety for the derivatives with substituted 8-amine moiety was similar to that observed for 5-HT_{1A} receptors. In case of derivatives with unsubstituted 8-amine moiety affinity for 5-HT_7 receptors changed according to the scheme:

(3-Chlorophenyl)piperazines > (2-methoxyphenyl)piperazines > (4-fluorophenyl)piperazines > phenylpiperazines > THIQ

The influence of the structure of the substituent in the position 8 of purine moiety was also comparable to that observed for 5-HT_{2A} receptors.

Further analysis of the results of the competition binding experiments let us to divide the compounds according to their preference for binding the investigated receptors:

- compounds with preference for binding to 5-HT_{1A} receptors: **9**, **12**, **14**, **19**, **20**, **23**, **43**, **44**, **45**, and **46**,
- compounds with preference for binding to 5-HT_{2A} receptors: **10**, **11**, **37**, **42**, and **49**,
- compound with preference for binding to 5-HT_7 receptors: **28**,
- compound with preference for binding to 5-HT_{1A} and 5-HT_{2A} receptors: **39**,
- compounds with preference for binding to 5-HT_{1A} and 5-HT_7 receptors: **18**, **20**, **25**, and **30**,
- compounds with preference for binding to 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors: **21**, **22**, **26**, and **54**.

The results of the functional assays for 5-HT_{1A} receptor showed, that all the arylpiperazine derivatives were antagonists of the receptor, regardless of the structure of the substituent in the position 8 of purine moiety or the linker length. The compound **23** displayed partial agonist properties, what might be the result of the substitution of the arylpiperazine moiety with THIQ. Comparison of the results with the results presented in our previous paper for 8-alkoxy derivatives [1] may suggest that the oxygen atom in close vicinity to the 8 position of purine moiety was needed for the agonistic activity of the derivatives.

Experimental

Chemistry

Melting points (m.p.) were determined with a Büchi Melting Point B-545 apparatus and were uncorrected.

^{1}H NMR spectra were taken with a Varian Mercury-VX (300 MHz) spectrometer in $CDCl_3$ (**1–7**, **41–43**, and **49–50**) or DMSO-d_6 (**8–40**, **44–48**, and **51–55**) solutions, using signal of solvent's residual ^{1}H atoms as internal standard ($\delta = 7.26$ and 2.48 ppm, respectively). Chemical shifts were expressed in δ (ppm) and the coupling constants *J* in Hertz (Hz). For compounds **8–55**, spectra were taken for hydrochloric salts if not described differently.

LC/MS analyses were performed on Waters Acquity TQD apparatus with eλ DAD detector. For mass spectrometry ESI+ (electrospray positive) ionization mode was used. UV spectra were taken in 200–700 nm range. For establishing the purity of compounds UV chromatograms were used. All the investigated final compounds had purity over 95%.

All the compounds were routinely checked by TLC using Merck Kieselgel 60 F_{254} sheets with the following eluents: A: methylene chloride/methanol = 95:5, B: methylene chloride/methanol = 90:10. Spots were detected by UV absorption.

Elemental analyses were taken with Elementar Vario EL III apparatus. All analyses were within ±0.4% of the theoretical values. The results of the analyses are presented in the Supporting Information.

*General procedure for preparing 7-ω-haloalkyl-8-(N-alkylbenzylamino)-1,3-dimethyl-1H-purine-2,6(3H,7H)-diones (**1**, **2**, **4**, and **5**) and 7-ω-haloalkyl-8-(dibenzylamino)-1,3-dimethyl-1H-purine-2,6(3H,7H)-diones (**3**, **6**, and **7**)*

Mixture of 1 eq. (0.1 mol) of 8-(*N*-methylbenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**I**), 8-(*N*-ethylbenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**II**) or 8-(dibenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**III**), 2 eq. of appropriate alkylating agent dihaloalkane (1-bromo-3-chloropropane, 1-bromo-4-chlorobutane, 1,4-dibromobutane or 1,5-dibromobutane), 2 eq. of K_2CO_3 and 0.1 eq. of TEBA in acetone (50 mL) was refluxed for 10 h. Then the mixture was filtered off and the filtrate was evaporated under reduced pressure. The residue was crystallized from methanol.

*8-(N-Methylbenzylamino)-7-(3-chloropropyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**1**)*

From **I** in 60% yield: m.p. 114–116°C, $R_f = 0.67$ (A), 0.81 (B), ^{1}H NMR δ 2.25–2.35 (m, 2H, $CH_2C\underline{H_2}CH_2$), 2.91 (s, 3H, $NC\underline{H_3}$), 3.38 (s, 3H, N(1)$C\underline{H_3}$), 3.51 (t, $^3J = 6.0$ Hz, 2H, $C\underline{H_2}Cl$), 3.54 (s, 3H, N(3)$C\underline{H_3}$), 4.30 (t, $^3J = 7.4$ Hz, 2H, N(7)$C\underline{H_2}$), 4.44 (s, 2H, $C\underline{H_2}C_6H_5$), 7.26–7.36 (m, 5H, $C_6\underline{H_5}$). LC/MS: 86%, *m/z* calc. 376.15, found 376.26. Anal. ($C_{18}H_{22}ClN_5O_2$) C, H, N.

*8-(N-Ethylbenzylamino)-7-(3-chloropropyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**2**)*

From **II** in 62% yield: m.p. 85–87°C, $R_f = 0.71$ (A), 0.81 (B), ^{1}H NMR δ 1.17 (t, $^3J = 7.0$ Hz, 3H, $NCH_2C\underline{H_3}$), 2.19–2.28 (m, 2H, $CH_2C\underline{H_2}CH_2$), 3.26 (q, $^3J = 7.0$ Hz, 2H, $NC\underline{H_2}CH_3$), 3.36 (s, 3H, N(1)$C\underline{H_3}$), 3.46 (t, $^3J = 6.5$ Hz, 2H, $C\underline{H_2}Cl$), 3.53 (s, 3H, N(3)$C\underline{H_3}$), 4.24 (t, $^3J = 7.4$ Hz, 2H, N(7)$C\underline{H_2}$), 4.40 (s, 2H, $C\underline{H_2}C_6H_5$), 7.27–7.36 (m, 5H, $C_6\underline{H_5}$). LC/MS: 91%, *m/z* calc. 390.17, found 390.31. Anal. ($C_{19}H_{24}ClN_5O_2$) C, H, N.

*8-(Dibenzylamino)-7-(3-chloropropyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**3**)*

From **III** in 82% yield: m.p. 118–120°C, $R_f = 0.77$ (A), 0.87 (B), ^{1}H NMR δ 2.09–2.18 (m, 2H, $CH_2C\underline{H_2}CH_2$), 3.37 (s, 3H, N(1)$C\underline{H_3}$), 3.44 (t, $^3J = 6.0$ Hz, 2H, $C\underline{H_2}Cl$), 3.55 (s, 3H, N(3)$C\underline{H_3}$), 4.22 (t,

$^3J = 7.6$ Hz, 2H, N(7)C$\underline{H_2}$), 4.35 (s, 4H, N(C$\underline{H_2}$C$_6$H$_5$)$_2$), 7.26–7.36 (m, 10H, N(CH$_2$C$_6\underline{H_5}$)$_2$). LC/MS: 95%, *m/z* calc. 452.18, found 452.28. Anal. ($C_{24}H_{26}ClN_5O_2$) C, H, N.

*8-(N-Methylbenzylamino)-7-(4-bromobutyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**4**)*
From **I** in 75% yield: m.p. 75–77°C, $R_f = 0.67$ (A), 0.81 (B), ^{1}H NMR δ 1.74–1.81 (m, 2H, CH$_2$CH$_2$C$\underline{H_2}$CH$_2$Br), 1.89–1.99 (m, 2H, CH$_2$C$\underline{H_2}$CH$_2$CH$_2$Br), 2.90 (s, 3H, NC$\underline{H_3}$), 3.36 (t, $^3J = 4.0$ Hz, 2H, C$\underline{H_2}$Br), 3.38 (s, 3H, N(1)C$\underline{H_3}$), 3.54 (s, 3H, N(3)C$\underline{H_3}$), 4.15 (t, $^3J = 7.3$ Hz, 2H, N(7)C$\underline{H_2}$), 4.42 (s, 2H, C$\underline{H_2}$C$_6$H$_5$), 7.26–7.36 (m, 5H, C$_6\underline{H_5}$). LC/MS: 83%, *m/z* calc. 434.11, found 434.25. Anal. ($C_{19}H_{24}BrN_5O_2$) C, H, N.

*8-(N-Ethylbenzylamino)-7-(4-bromobutyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**5**)*
From **II** in 64% yield: m.p. 67–69°C, $R_f = 0.73$ (A), 0.81 (B), ^{1}H NMR δ 1.16 (t, $^3J = 7.1$ Hz, 3H, NCH$_2$C$\underline{H_3}$), 1.71–1.79 (m, 2H, CH$_2$CH$_2$C$\underline{H_2}$CH$_2$Br), 1.84–1.92 (m, 2H, CH$_2$C$\underline{H_2}$CH$_2$CH$_2$Br), 3.26 (q, $^3J = 7.1$ Hz, 2H, NC$\underline{H_2}$CH$_3$), 3.33 (t, $^3J = 7.0$ Hz, 2H, C$\underline{H_2}$Br), 3.37 (s, 3H, N(1)C$\underline{H_3}$), 3.54 (s, 3H, N(3)C$\underline{H_3}$), 4.11 (t, $^3J = 7.3$ Hz, 2H, N(7)C$\underline{H_2}$), 4.39 (s, 2H, C$\underline{H_2}$C$_6$H$_5$), 7.24–7.34 (m, 5H, C$_6\underline{H_5}$). LC/MS: 84%, *m/z* calc. 448.13, found 448.25. Anal. ($C_{20}H_{26}BrN_5O_2$) C, H, N.

*8-(Dibenzylamino)-7-(4-chlorobutyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**6**)*
From **III** in 74% yield: m.p. 108–110°C, $R_f = 0.77$ (A), 0.87 (B), ^{1}H NMR δ 1.56–1.65 (m, 2H, CH$_2$CH$_2$C$\underline{H_2}$CH$_2$Cl), 1.75–1.85 (m, 2H, CH$_2$C$\underline{H_2}$CH$_2$CH$_2$Cl), 3.37 (s, 3H, N(1)C$\underline{H_3}$), 3.42 (t, $^3J = 6.4$ Hz, 2H, C$\underline{H_2}$Cl), 3.56 (s, 3H, N(3)C$\underline{H_3}$), 4.08 (t, $^3J = 7.6$ Hz, 2H, N(7)C$\underline{H_2}$), 4.35 (s, 4H, N(C$\underline{H_2}$C$_6$H$_5$)$_2$), 7.26–7.36 (m, 10H, N(CH$_2$C$_6\underline{H_5}$)$_2$). LC/MS: 89%, *m/z* calc. 466.20, found 466.32. Anal. ($C_{25}H_{28}ClN_5O_2$) C, H, N.

*8-(Dibenzylamino)-7-(5-chloropentyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**7**)*
From **III** in 58% yield: m.p. 102–104°C, $R_f = 0.77$ (A), 0.87 (B), ^{1}H NMR δ 1.28–1.36 (m, 2H, CH$_2$CH$_2$C$\underline{H_2}$CH$_2$CH$_2$Br), 1.59–1.69 (m, 2H, CH$_2$CH$_2$CH$_2$C$\underline{H_2}$CH$_2$Br), 1.71–1.81 (m, 2H, CH$_2$C$\underline{H_2}$CH$_2$CH$_2$CH$_2$Br), 3.32 (t, $^3J = 6.7$ Hz, 2H, C$\underline{H_2}$Br), 3.37 (s, 3H, N(1)C$\underline{H_3}$), 3.56 (s, 3H, N(3)C$\underline{H_3}$), 4.05 (t, $^3J = 7.6$ Hz, 2H, N(7)C$\underline{H_2}$), 4.34 (s, 4H, N-(C$\underline{H_2}$C$_6$H$_5$)$_2$), 7.26–7.36 (m, 10H, N(CH$_2$C$_6\underline{H_5}$)$_2$). LC/MS: 79%, *m/z* calc. 524.16, found 524.22. Anal. ($C_{26}H_{30}BrN_5O_2$) C, H, N.

*General procedure for preparing 7-(ω-(4-arylpiperazin-1-yl)-alkyl)-8-(N-alkylbenzylamino)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione hydrochlorides (**8–12**, **18**, **19**, **21**, and **22**), 7-(ω-(4-arylpiperazin-1-yl)alkyl)-8-(dibenzylamino)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione hydrochlorides (**13–16**, **24–27**, and **29–32**) and their 7-(ω-(3,4-dihydroisoquinolin-2(1H)-yl)alkyl counterparts (**17**, **20**, **23**, **28**, and **33**)*
Mixture of 1 eq. (10 mmol) of the appropriate 7-ω-haloalkyl-8-(*N*-alkylbenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione derivative (**1**, **2**, **4**, or **5**) or 7-ω-haloalkyl-8-(dibenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione derivative (**3**, **6**, or **7**), 1 eq. of the appropriate arylpiperazine (1-phenylpiperazine, 1-(2-methoxyphenyl)piperazine, 1-(3-chlorophenyl)-piperazine or 1-(4-fluorophenyl)piperazine) or 1,2,3,4-tetrahydroisoquinoline, 2 eq. of K_2CO_3 in 1-propanol (20 mL) was refluxed for 40 h. Then the mixture was filtered off and the filtrate was reduced under reduced pressure. The residue was dissolved in small volume of dry ethanol (ca. 10 mL), acidified with conc. HCl to pH ca. 3 and cooled. Precipitate was filtered off and purified by crystallization from ethanol.

*8-(N-Methylbenzylamino)-1,3-dimethyl-7-(3-(4-phenylpiperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**8**)*
From **1** in 75% yield: m.p. 237–239°C, $R_f = 0.27$ (A), 0.65 (B), ^{1}H NMR δ 2.10–2.30 (m, 2H, CH$_2$C$\underline{H_2}$CH$_2$), 2.89 (s, 3H, NC$\underline{H_3}$), 3.00–3.19 (m, 6H, C$\underline{H_2}$NH$^+$(CH$_2$C$\underline{H_2}$)$_2$N), 3.21 (s, 3H, N(1)C$\underline{H_3}$), 3.38 (s, 3H, N(3)C$\underline{H_3}$), 3.48–3.55 (m, 2H, CH$_2$NH$^+$(C$\underline{H_2}$CH$_2$)$_2$N), 3.76–3.80 (m, 2H, CH$_2$NH$^+$(C$\underline{H_2}$CH$_2$)$_2$N), 4.20 (t, $^3J = 7.0$ Hz, 2H, N(7)C$\underline{H_2}$), 4.48 (s, 2H, C$\underline{H_2}$C$_6$H$_5$), 6.84 (t, $^3J = 7.2$ Hz, 1H, *p*-NC$_6\underline{H_5}$), 6.97 (d, $^3J = 8.0$ Hz, 2H, *o*-NC$_6\underline{H_5}$), 7.24 (t, $^3J = 8.0$ Hz, 2H, *m*-NC$_6\underline{H_5}$), 7.24–7.37 (m, 5H, CH$_2$C$_6\underline{H_5}$), 10.50–10.60 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 502.29, found 502.41. Anal. ($C_{28}H_{36}ClN_7O_2$) C, H, N.

*8-(N-Methylbenzylamino)-1,3-dimethyl-7-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**9**)*
From **1** in 92% yield: m.p. 238–240°C, $R_f = 0.19$ (A), 0.58 (B), ^{1}H NMR δ 2.15–2.25 (m, 2H, CH$_2$C$\underline{H_2}$CH$_2$), 2.89 (s, 3H, NC$\underline{H_3}$), 3.04–3.15 (m, 6H, C$\underline{H_2}$NH$^+$(CH$_2$C$\underline{H_2}$)$_2$N), 3.20 (s, 3H, N(1)C$\underline{H_3}$), 3.38 (s, 3H, N(3)C$\underline{H_3}$), 3.44–3.47 (m, 2H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 3.77 (s, 3H, OC$\underline{H_3}$), 3.80–3.90 (m, 2H, CH$_2$NH$^+$(C$\underline{H_2}$CH$_2$)$_2$N), 4.20 (t, $^3J = 7.0$ Hz, 2H, N(7)C$\underline{H_2}$), 4.48 (s, 2H, C$\underline{H_2}$C$_6$H$_5$), 6.85–7.04 (m, 4H, NC$_6\underline{H_4}$OCH$_3$), 7.24–7.37 (m, 5H, CH$_2$C$_6\underline{H_5}$), 10.80–10.95 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 532.03, found 532.11. Anal. ($C_{29}H_{38}ClN_7O_3$) C, H, N.

*8-(N-Methylbenzylamino)-1,3-dimethyl-7-(3-(4-(3-chlorophenyl)piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**10**)*
From **1** in 66% yield: m.p. 221–223°C, $R_f = 0.40$ (A), 0.71 (B), ^{1}H NMR δ 2.10–2.25 (m, 2H, CH$_2$C$\underline{H_2}$CH$_2$), 2.89 (s, 3H, NC$\underline{H_3}$), 3.05–3.19 (m, 6H, C$\underline{H_2}$NH$^+$(CH$_2$C$\underline{H_2}$)$_2$N), 3.20 (s, 3H, N(1)C$\underline{H_3}$), 3.38 (s, 3H, N(3)C$\underline{H_3}$), 3.45–3.53 (m, 2H, CH$_2$NH$^+$(C$\underline{H_2}$CH$_2$)$_2$N), 3.75–3.80 (m, 2H, CH$_2$NH$^+$(C$\underline{H_2}$CH$_2$)$_2$N), 4.22 (t, $^3J = 7.0$ Hz, 2H, N(7)C$\underline{H_2}$), 4.48 (s, 2H, C$\underline{H_2}$C$_6$H$_5$), 6.86 (d, $^3J = 7.1$ Hz, 1H, 6-NC$_6\underline{H_4}$Cl), 6.95 (d, $^3J = 7.9$ Hz, 1H, 4-NC$_6\underline{H_4}$Cl), 7.04 (s, 1H, 2-NC$_6\underline{H_4}$Cl), 7.22–7.37 (m, 6H, 5-NC$_6\underline{H_4}$Cl, CH$_2$C$_6\underline{H_5}$), 10.70–10.80 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 536.25, found 536.29. Anal. ($C_{28}H_{35}Cl_2N_7O_2$) C, H, N.

*8-(N-Ethylbenzylamino)-1,3-dimethyl-7-(3-(4-phenylpiperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**11**)*
From **2** in 72% yield: m.p. 189–191°C, $R_f = 0.35$ (A), 0.69 (B), ^{1}H NMR δ 1.10 (t, $^3J = 7.0$ Hz, 3H, NCH$_2$C$\underline{H_3}$), 2.10–2.25 (m, 2H,

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$CH_2C\underline{H_2}CH_2$), 2.95–3.15 (m, 6H, $C\underline{H_2}NH^+(CH_2C\underline{H_2})_2N$), 3.20 (s, 3H, N(1)$C\underline{H_3}$), 3.23 (q, $^3J = 7.1$ Hz, 2H, $NC\underline{H_2}CH_3$), 3.38 (s, 3H, N(3)$C\underline{H_3}$), 3.40–3.50 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 3.75–3.85 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 4.14 (t, $^3J = 7.0$ Hz, 2H, N(7)$C\underline{H_2}$), 4.43 (s, 2H, $C\underline{H_2}C_6H_5$), 6.84 (t, $^3J = 7.3$ Hz, 1H, *p*-$NC_6\underline{H_5}$), 6.97 (d, $^3J = 8.5$ Hz, 2H, *o*-$NC_6\underline{H_5}$), 7.24 (t, $^3J = 8.0$ Hz, 2H, *m*-$NC_6\underline{H_5}$), 7.27–7.38 (m, 5H, $CH_2C_6\underline{H_5}$), 10.75–10.85 (s, 1H, $N\underline{H}^+$). LC/MS: *m/z* calc. 516.31, found 516.45. Anal. ($C_{29}H_{38}ClN_7O_2$) C, H, N.

*8-(N-Ethylbenzylamino)-1,3-dimethyl-7-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**12**)*
From **2** in 53% yield: m.p. 178–180°C, $R_f = 0.27$ (A), 0.65 (B), ^{1}H NMR δ 1.10 (t, $^3J = 7.0$ Hz, 3H, $NCH_2C\underline{H_3}$), 2.10–2.20 (m, 2H, $CH_2C\underline{H_2}CH_2$), 2.90–3.15 (m, 6H, $C\underline{H_2}NH^+(CH_2C\underline{H_2})_2N$), 3.20 (s, 3H, N(1)$C\underline{H_3}$), 3.23 (q, $^3J = 7.1$ Hz, 2H, $NC\underline{H_2}CH_3$), 3.30–3.35 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 3.39 (s, 3H, N(3)$C\underline{H_3}$), 3.43–3.46 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 3.77 (s, 3H, $OC\underline{H_3}$), 4.13 (t, $^3J = 7.0$ Hz, 2H, N(7)$C\underline{H_2}$), 4.43 (s, 2H, $C\underline{H_2}C_6H_5$), 6.88–7.00 (m, 4H, $NC_6\underline{H_4}OCH_3$), 7.25–7.38 (m, 5H, $CH_2C_6\underline{H_5}$), 10.20–10.40 (s, 1H, $N\underline{H}^+$). LC/MS: *m/z* calc. 546.32, found 546.36. Anal. ($C_{30}H_{40}ClN_7O_3$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(3-(4-phenylpiperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**13**)*
From **3** in 95% yield: m.p. 158–160°C, $R_f = 0.40$ (A), 0.74 (B), ^{1}H NMR δ 2.00–2.18 (m, 2H, $CH_2C\underline{H_2}CH_2$), 2.88–3.10 (m, 6H, $C\underline{H_2}NH^+(CH_2C\underline{H_2})_2N$), 3.19 (s, 3H, N(1)$C\underline{H_3}$), 3.35–3.50 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 3.37 (s, 3H, N(3)$C\underline{H_3}$), 3.75–3.85 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 4.15 (t, $^3J = 6.4$ Hz, 2H, N(7)$C\underline{H_2}$), 4.38 (s, 4H, $N(C\underline{H_2}C_6H_5)_2$), 6.85 (t, $^3J = 7.0$ Hz, 1H, *p*-$NC_6\underline{H_5}$), 6.98 (d, $^3J = 6.0$ Hz, 2H, *o*-$NC_6\underline{H_5}$), 7.26–7.36 (m, 12H, *m*-$NC_6\underline{H_5}$, N-$(CH_2C_6\underline{H_5})_2$), 9.80–10.05 (s, 1H, $N\underline{H}^+$). LC/MS: *m/z* calc. 578.32, found 578.43. Anal. ($C_{34}H_{40}ClN_7O_2$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**14**)*
From **3** in 94% yield: m.p. 145–147°C, $R_f = 0.33$ (A), 0.68 (B), ^{1}H NMR δ 2.00–2.20 (m, 2H, $CH_2C\underline{H_2}CH_2$), 2.89–3.15 (m, 6H, $C\underline{H_2}NH^+(CH_2C\underline{H_2})_2N$), 3.19 (s, 3H, N(1)$C\underline{H_3}$), 3.30–3.41 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 3.38 (s, 3H, N(3)$C\underline{H_3}$), 3.43–3.55 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 3.78 (s, 3H, $OC\underline{H_3}$), 4.16 (t, $^3J = 6.8$ Hz, 2H, N(7)$C\underline{H_2}$), 4.39 (s, 4H, $N(C\underline{H_2}C_6H_5)_2$), 6.86–7.00 (m, 4H, $NC_6\underline{H_4}OCH_3$), 7.25–7.38 (m, 5H, $CH_2C_6\underline{H_5}$), 10.15–10.30 (s, 1H, $N\underline{H}^+$). LC/MS: *m/z* calc. 608.33, found 608.48. Anal. ($C_{35}H_{42}ClN_7O_2$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(3-(4-(3-chlorophenyl)-piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**15**)*
From **3** in 93% yield: m.p. 191–192°C, $R_f = 0.46$ (A), 0.77 (B), ^{1}H NMR δ 2.00–2.15 (m, 2H, $CH_2C\underline{H_2}CH_2$), 2.90–3.10 (m, 6H, $C\underline{H_2}NH^+(CH_2C\underline{H_2})_2N$), 3.19 (s, 3H, N(1)$C\underline{H_3}$), 3.32–3.42 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 3.37 (s, 3H, N(3)$C\underline{H_3}$), 3.86–3.90 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 4.15 (t, $^3J = 6.9$ Hz, 2H, N(7)$C\underline{H_2}$), 4.38 (s, 4H, $N(C\underline{H_2}C_6H_5)_2$), 6.86 (d, $^3J = 7.1$ Hz, 1H, 6-$NC_6\underline{H_4}Cl$), 6.95 (d, $^3J = 7.8$ Hz, 1H, 4-$NC_6\underline{H_4}Cl$), 7.04 (s, 1H, 2-$NC_6\underline{H_4}Cl$), 7.22–7.38 (m, 6H, 5-$NC_6\underline{H_4}Cl$, $CH_2C_6\underline{H_5}$), 10.00–10.20 (s, 1H, $N\underline{H}^+$). LC/MS: *m/z* calc. 612.28, found 612.44. Anal. ($C_{34}H_{39}Cl_2N_7O_2$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(3-(4-(4-fluorophenyl)-piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**16**)*
From **3** in 91% yield: m.p. 183–185°C, $R_f = 0.37$ (A), 0.74 (B), ^{1}H NMR δ 2.00–2.15 (m, 2H, $CH_2C\underline{H_2}CH_2$), 2.85–3.15 (m, 6H, $C\underline{H_2}NH^+(CH_2C\underline{H_2})_2N$), 3.19 (s, 3H, N(1)$C\underline{H_3}$), 3.37 (s, 3H, N(3)$C\underline{H_3}$), 3.39–3.50 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 3.70–3.80 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 4.14 (t, $^3J = 7.0$ Hz, 2H, N(7)$C\underline{H_2}$), 4.38 (s, 4H, $N(C\underline{H_2}C_6H_5)_2$), 6.95–7.15 (m, 4H, $NC_6\underline{H_4}F$), 7.28–7.40 (m, 5H, $CH_2C_6\underline{H_5}$), 9.60–9.75 (s, 1H, $N\underline{H}^+$). LC/MS: *m/z* calc. 596.31, found 596.42. Anal. ($C_{34}H_{39}ClFN_7O_2$) C, H, N.

*8-(Dibenzylamino)-7-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-propyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione hydrochloride (**17**)*
From **3** in 85% yield: m.p. 209–210°C, $R_f = 0.35$ (A), 0.68 (B), ^{1}H NMR δ 2.10–2.25 (m, 2H, $CH_2C\underline{H_2}CH_2$), 2.88–3.20 (m, 4H, $C\underline{H_2}NH^+$THIQ, 4,4-THIQ), 3.19 (s, 3H, N(1)$C\underline{H_3}$), 3.37 (s, 3H, N(3)$C\underline{H_3}$), 3.50–3.60 (m, 2H, 3,3-THIQ), 4.10–4.20 (m, 1H, 1-THIQ), 4.19 (t, $^3J = 7.0$ Hz, 2H, N(7)$C\underline{H_2}$), 4.39 (s, 4H, $N(C\underline{H_2}C_6H_5)_2$), 4.40–4.50 (m, 1H, 1-THIQ), 7.10–7.36 (m, 14H, 5,6,7,8-THIQ, $N(CH_2C_6\underline{H_5})_2$), 10.30–10.50 (s, 1H, $N\underline{H}^+$). LC/MS: *m/z* calc. 549.30, found 549.47. Anal. ($C_{33}H_{37}ClN_6O_2$) C, H, N.

*8-(N-Methylbenzylamino)-1,3-dimethyl-7-(4-(4-phenylpiperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**18**)*
From **4** in 73% yield: m.p. 210–212°C, $R_f = 0.25$ (A), 0.65 (B), ^{1}H NMR δ 1.55–1.70 (m, 2H, N(7)$CH_2CH_2C\underline{H_2}CH_2$), 1.70–1.80 (m, 2H, N(7)$CH_2C\underline{H_2}CH_2CH_2$), 2.88 (s, 3H, $NC\underline{H_3}$), 3.00–3.15 (m, 6H, $C\underline{H_2}NH^+(CH_2C\underline{H_2})_2N$), 3.20 (s, 3H, N(1)$C\underline{H_3}$), 3.37 (s, 3H, N(3)$C\underline{H_3}$), 3.40–3.50 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 3.70–3.85 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 4.15 (t, $^3J = 6.9$ Hz, 2H, N(7)$C\underline{H_2}$), 4.47 (s, 2H, $C\underline{H_2}C_6H_5$), 6.84 (t, $^3J = 7.2$ Hz, 1H, *p*-$NC_6\underline{H_5}$), 6.98 (d, $^3J = 8.0$ Hz, 2H, *o*-$NC_6\underline{H_5}$), 7.24 (t, $^3J = 8.0$ Hz, 2H, *m*-$NC_6\underline{H_5}$), 7.24–7.37 (m, 5H, $CH_2C_6\underline{H_5}$), 10.00–10.15 (s, 1H, $N\underline{H}^+$). LC/MS: *m/z* calc. 516.31, found 516.49. Anal. ($C_{29}H_{38}ClN_7O_2$) C, H, N.

*8-(N-Methylbenzylamino)-1,3-dimethyl-7-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**19**)*
From **4** in 77% yield: m.p. 170–172°C, $R_f = 0.42$ (A), 0.77 (B), ^{1}H NMR δ 1.50–1.65 (m, 2H, N(7)$CH_2CH_2C\underline{H_2}CH_2$), 1.70–1.80 (m, 2H, N(7)$CH_2C\underline{H_2}CH_2CH_2$), 2.85 (s, 3H, $NC\underline{H_3}$), 3.05–3.15 (m, 6H, $C\underline{H_2}NH^+(CH_2C\underline{H_2})_2N$), 3.22 (s, 3H, N(1)$C\underline{H_3}$), 3.39 (s, 3H, N(3)$C\underline{H_3}$), 3.40–3.47 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 3.73 (s, 3H, $OC\underline{H_3}$), 3.75–3.85 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2N$), 4.17 (t, $^3J = 7.0$ Hz, 2H, N(7)$C\underline{H_2}$), 4.48 (s, 2H, $C\underline{H_2}C_6H_5$), 6.85–7.00 (m, 4H, $NC_6\underline{H_4}OCH_3$), 7.24–7.36 (m, 5H, $CH_2C_6\underline{H_5}$), 10.20–10.40 (s, 1H, $N\underline{H}^+$). LC/MS: *m/z* calc. 546.32, found 546.45. Anal. ($C_{30}H_{40}ClN_7O_3$) C, H, N.

*8-(N-Methylbenzylamino)-7-(4-(3,4-dihydroisoquinolin-2(1H)-yl)butyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione hydrochloride (**20**)*
From **4** in 78% yield: m.p. 174–176°C, $R_f = 0.40$ (A), 0.73 (B), ^{1}H NMR δ 1.80–1.90 (m, 4H, N(7)CH_2C$\underline{H_2}$C$\underline{H_2}$$CH_2$), 2.88 (s, 3H, NC$\underline{H_3}$), 3.05–3.20 (m, 4H, C$\underline{H_2}$$NH^+$THIQ, 4,4-THIQ), 3.19 (s, 3H, N(1)C$\underline{H_3}$), 3.37 (s, 3H, N(3)C$\underline{H_3}$), 3.55–3.65 (m, 2H, 3,3-THIQ), 4.15 (t, $^3J = 7.0$ Hz, 2H, N(7)C$\underline{H_2}$), 4.15–4.25 (m, 1H, 1-THIQ), 4.39–4.47 (m, 1H, 1-THIQ), 4.47 (s, 2H, C$\underline{H_2}$$C_6H_5$), 7.15–7.40 (m, 9H, 5,6,7,8-THIQ, $CH_2C_6\underline{H_5}$), 10.30–10.50 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 487.28, found 487.38. Anal. ($C_{28}H_{35}ClN_6O_2$) C, H, N.

*8-(N-Ethylbenzylamino)-1,3-dimethyl-7-(4-(4-phenylpiperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**21**)*
From **5** in 67% yield: m.p. 195–197°C, $R_f = 0.45$ (A), 0.81 (B), ^{1}H NMR δ 1.14 (t, $^3J = 7.1$ Hz, 3H, $NCH_2C\underline{H_3}$), 1.70–1.75 (m, 2H, N(7)$CH_2CH_2C\underline{H_2}CH_2$), 1.80–1.90 (m, 2H, N(7)$CH_2C\underline{H_2}CH_2CH_2$), 3.05–3.15 (m, 6H, C$\underline{H_2}$$NH^+(CH_2C\underline{H_2})_2$N), 3.22 (s, 3H, N(1)C$\underline{H_3}$), 3.24 (q, $^3J = 7.1$ Hz, 2H, $NC\underline{H_2}CH_3$), 3.35 (s, 3H, N(3)C$\underline{H_3}$), 3.35–3.45 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2$N), 3.70–3.80 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2$N), 4.20 (t, $^3J = 6.9$ Hz, 2H, N(7)C$\underline{H_2}$), 4.43 (s, 2H, C$\underline{H_2}$$C_6H_5$), 6.84 (t, $^3J = 7.2$ Hz, 1H, *p*-$NC_6\underline{H_5}$), 6.98 (d, $^3J = 8.0$ Hz, 2H, *o*-$NC_6\underline{H_5}$), 7.24 (t, $^3J = 8.0$ Hz, 2H, *m*-$NC_6\underline{H_5}$), 7.24–7.37 (m, 5H, $CH_2C_6\underline{H_5}$), 10.20–10.30 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 530.32, found 530.44. Anal. ($C_{30}H_{40}ClN_7O_2$) C, H, N.

*8-(N-Ethylbenzylamino)-1,3-dimethyl-7-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**22**)*
From **5** in 75% yield: m.p. 185–187°C, $R_f = 0.42$ (A), 0.77 (B), ^{1}H NMR δ 1.16 (t, $^3J = 7.0$ Hz, 3H, $NCH_2C\underline{H_3}$), 1.75–1.80 (m, 2H, N(7)$CH_2CH_2C\underline{H_2}CH_2$), 1.80–1.90 (m, 2H, N(7)$CH_2C\underline{H_2}CH_2CH_2$), 3.00–3.20 (m, 6H, C$\underline{H_2}$$NH^+(CH_2C\underline{H_2})_2$N), 3.22 (s, 3H, N(1)C$\underline{H_3}$), 3.24 (q, $^3J = 7.1$ Hz, 2H, $NC\underline{H_2}CH_3$), 3.35 (s, 3H, N(3)C$\underline{H_3}$), 3.40–3.45 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2$N), 3.72 (s, 3H, OC$\underline{H_3}$), 3.75–3.80 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2$N), 4.18 (t, $^3J = 7.0$ Hz, 2H, N(7)C$\underline{H_2}$), 4.47 (s, 2H, C$\underline{H_2}$$C_6H_5$), 6.85–7.05 (m, 4H, $NC_6\underline{H_4}OCH_3$), 7.24–7.36 (m, 5H, $CH_2C_6\underline{H_5}$), 10.20–10.40 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 560.33, found 560.39. Anal. ($C_{31}H_{42}ClN_7O_3$) C, H, N.

*8-(N-Ethylbenzylamino)-7-(4-(3,4-dihydroisoquinolin-2(1H)-yl)butyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione hydrochloride (**23**)*
From **5** in 86% yield: m.p. 195–197°C, $R_f = 0.13$ (A), 0.50 (B), ^{1}H NMR δ 1.09 (t, $^3J = 7.0$ Hz, 3H, $NCH_2C\underline{H_3}$), 1.65–1.80 (m, 4H, N(7)$CH_2C\underline{H_2}C\underline{H_2}CH_2$), 3.05–3.20 (m, 4H, C$\underline{H_2}$$NH^+$THIQ, 4,4-THIQ), 3.18 (s, 3H, N(1)C$\underline{H_3}$), 3.23 (q, $^3J = 7.2$ Hz, 2H, $NC\underline{H_2}CH_3$), 3.37 (s, 3H, N(3)C$\underline{H_3}$), 3.50–3.65 (m, 2H, 3,3-THIQ), 4.07–4.13 (m, 2H, N(7)C$\underline{H_2}$), 4.20–4.25 (m, 1H, 1-THIQ), 4.35–4.45 (m, 1H, 1-THIQ), 4.42 (s, 2H, C$\underline{H_2}$$C_6H_5$), 7.15–7.35 (m, 9H, 5,6,7,8-THIQ, $CH_2C_6\underline{H_5}$), 10.80–10.90 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 501.30, found 501.44. Anal. ($C_{29}H_{37}ClN_6O_2$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(4-(4-phenylpiperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**24**)*
From **6** in 97% yield: m.p. 187–189°C, $R_f = 0.27$ (A), 0.64 (B), ^{1}H NMR δ 1.40–1.70 (m, 4H, N(7)$CH_2C\underline{H_2}C\underline{H_2}CH_2$), 2.95–3.20 (m, 6H, C$\underline{H_2}$$NH^+(CH_2C\underline{H_2})_2$N), 3.19 (s, 3H, N(1)C$\underline{H_3}$), 3.37 (s, 3H, N(3)C$\underline{H_3}$), 3.35–3.50 (m, 4H, $CH_2NH^+(C\underline{H_2}CH_2)_2$N), 4.07–4.13 (m, 2H, N(7)C$\underline{H_2}$), 4.39 (s, 4H, N(C$\underline{H_2}$$C_6H_5)_2$), 6.84 (t, $^3J = 7.0$ Hz, 1H, *p*-$NC_6\underline{H_5}$), 6.98 (d, $^3J = 6.0$ Hz, 2H, *o*-$NC_6\underline{H_5}$), 7.26–7.35 (m, 12H, *m*-$NC_6\underline{H_5}$, N($CH_2C_6\underline{H_5})_2$), 9.90–10.10 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 592.34, found 592.47. Anal. ($C_{35}H_{42}ClN_7O_2$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**25**)*
From **6** in 90% yield: m.p. 210–212°C, $R_f = 0.25$ (A), 0.58 (B), ^{1}H NMR δ 1.45–1.70 (m, 4H, N(7)$CH_2C\underline{H_2}C\underline{H_2}CH_2$), 2.80–3.20 (m, 6H, C$\underline{H_2}$$NH^+(CH_2C\underline{H_2})_2$N), 3.18 (s, 3H, N(1)C$\underline{H_3}$), 3.37 (s, 3H, N(3)C$\underline{H_3}$), 3.35–3.50 (m, 4H, $CH_2NH^+(C\underline{H_2}CH_2)_2$N), 3.78 (s, 3H, OC$\underline{H_3}$), 4.06–4.11 (m, 2H, N(7)C$\underline{H_2}$), 4.39 (s, 4H, N(C$\underline{H_2}$$C_6H_5)_2$), 6.91–7.05 (m, 4H, $NC_6\underline{H_4}OCH_3$), 7.25–7.37 (m, 10H, N($CH_2C_6\underline{H_5})_2$), 10.20–10.40 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 622.35, found 622.52. Anal. ($C_{36}H_{44}ClN_7O_3$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(4-(4-(3-chlorophenyl)-piperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**26**)*
From **6** in 97% yield: m.p. 124–125°C, $R_f = 0.35$ (A), 0.74 (B), ^{1}H NMR δ 1.50–1.70 (m, 4H, N(7)$CH_2C\underline{H_2}C\underline{H_2}CH_2$), 3.00–3.16 (m, 6H, C$\underline{H_2}$$NH^+(CH_2C\underline{H_2})_2$N), 3.18 (s, 3H, N(1)C$\underline{H_3}$), 3.37 (s, 3H, N(3)C$\underline{H_3}$), 3.37–3.49 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2$N), 3.84–3.88 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2$N), 4.07–4.11 (m, 2H, N(7)C$\underline{H_2}$), 4.39 (s, 4H, N(C$\underline{H_2}$$C_6H_5)_2$), 6.88 (d, $^3J = 9.0$ Hz, 1H, 6-$NC_6\underline{H_4}$Cl), 6.96 (d, $^3J = 7.9$ Hz, 1H, 4-$NC_6\underline{H_4}$Cl), 7.04 (s, 1H, 2-$NC_6\underline{H_4}$Cl), 7.22–7.38 (m, 11H, 5-$NC_6\underline{H_4}$Cl, N($CH_2C_6\underline{H_5})_2$), 10.20–10.40 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 626.30, found 626.47. Anal. ($C_{35}H_{41}Cl_2N_7O_2$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(4-(4-(4-fluorophenyl)-piperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**27**)*
From **6** in 95% yield: m.p. 155–157°C, $R_f = 0.27$ (A), 0.72 (B), ^{1}H NMR δ 1.45–1.70 (m, 4H, N(7)$CH_2C\underline{H_2}C\underline{H_2}CH_2$), 2.90–3.17 (m, 6H, C$\underline{H_2}$$NH^+(CH_2C\underline{H_2})_2$N), 3.18 (s, 3H, N(1)C$\underline{H_3}$), 3.37 (s, 3H, N(3)C$\underline{H_3}$), 3.37–3.43 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2$N), 3.69–3.73 (m, 2H, $CH_2NH^+(C\underline{H_2}CH_2)_2$N), 4.06–4.12 (m, 2H, N(7)C$\underline{H_2}$), 4.39 (s, 4H, N(C$\underline{H_2}$$C_6H_5)_2$), 6.95–7.15 (m, 4H, $NC_6\underline{H_4}$F), 7.25–7.38 (m, 10H, N($CH_2C_6\underline{H_5})_2$), 9.80–10.00 (s, 1H, N$\underline{H}^+$). LC/MS: *m/z* calc. 610.33, found 610.46. Anal. ($C_{35}H_{41}ClFN_7O_2$) C, H, N.

*8-(Dibenzylamino)-7-(4-(3,4-dihydroisoquinolin-2(1H)-yl)-butyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione hydrochloride (**28**)*
From **6** in 92% yield: m.p. 182–184°C, $R_f = 0.28$ (A), 0.66 (B), ^{1}H NMR δ 1.60–1.75 (m, 4H, N(7)$CH_2C\underline{H_2}C\underline{H_2}CH_2$), 2.90–3.10 (m, 4H, C$\underline{H_2}$$NH^+$THIQ, 4,4-THIQ), 3.17 (s, 3H, N(1)C$\underline{H_3}$), 3.32 (s, 3H, N(3)C$\underline{H_3}$), 3.55–3.65 (m, 2H, 3,3-THIQ), 4.07–4.11 (m, 2H, N(7)

CH_2), 4.20–4.25 (m, 1H, 1-THIQ), 4.39 (s, 4H, $N(CH_2C_6H_5)_2$), 4.40–4.45 (m, 1H, 1-THIQ), 7.15–7.37 (m, 14H, 5,6,7,8-THIQ, $N(CH_2C_6H_5)_2$), 10.60–10.80 (s, 1H, NH^+). LC/MS: *m/z* calc. 563.31, found 563.44. Anal. ($C_{34}H_{39}ClN_6O_2$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(5-(4-phenylpiperazin-1-yl)pentyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**29**)*
From **7** in 91% yield: m.p. 154–156°C, $R_f = 0.32$ (A), 0.68 (B), ^{1}H NMR δ 1.00–1.10 (m, 2H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 1.50–1.70 (m, 4H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 2.90–3.10 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.17 (s, 3H, $N(1)CH_3$), 3.37 (s, 3H, $N(3)CH_3$), 3.46–3.49 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.76–3.80 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 4.07 (t, $^3J = 7.6$ Hz, 2H, $N(7)CH_2$), 4.39 (s, 4H, $N(CH_2C_6H_5)_2$), 6.85 (t, $^3J = 7.3$ Hz, 1H, *p*-NC_6H_5), 6.98 (d, $^3J = 7.9$ Hz, 2H, *o*-NC_6H_5), 7.22–7.40 (m, 12H, *m*-NC_6H_5, $N(CH_2C_6H_5)_2$), 10.60–10.80 (s, 1H, NH^+). LC/MS: *m/z* calc. 606.36, found 606.50. Anal. ($C_{36}H_{44}ClN_7O_2$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(5-(4-(2-methoxyphenyl)piperazin-1-yl)pentyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**30**)*
From **7** in 81% yield: m.p. 106–107°C, $R_f = 0.26$ (A), 0.60 (B), ^{1}H NMR δ 1.00–1.15 (m, 2H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 1.50–1.70 (m, 4H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 2.90–3.15 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.18 (s, 3H, $N(1)CH_3$), 3.37 (s, 3H, $N(3)CH_3$), 3.45–3.49 (m, 4H, $CH_2NH^+(CH_2CH_2)_2N$), 3.78 (s, 3H, OCH_3), 4.08 (t, $^3J = 7.2$ Hz, 2H, $N(7)CH_2$), 4.40 (s, 4H, $N(CH_2C_6H_5)_2$), 6.89–7.02 (m, 4H, $NC_6H_4OCH_3$), 7.20–7.37 (m, 10H, $N(CH_2C_6H_5)_2$), 9.90–10.10 (s, 1H, NH^+). LC/MS: *m/z* calc. 636.36, found 636.55. Anal. ($C_{37}H_{46}ClN_7O_3$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(5-(4-(3-chlorophenyl)-piperazin-1-yl)pentyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**31**)*
From **7** in 92% yield: m.p. 167–168°C, $R_f = 0.40$ (A), 0.72 (B), ^{1}H NMR δ 1.00–1.15 (m, 2H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 1.50–1.70 (m, 4H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 2.90–3.15 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.17 (s, 3H, $N(1)CH_3$), 3.37 (s, 3H, $N(3)CH_3$), 3.45–3.48 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.84–3.88 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 4.06–4.09 (m, 2H, $N(7)CH_2$), 4.39 (s, 4H, $N(CH_2C_6H_5)_2$), 6.86 (d, $^3J = 7.6$ Hz, 1H, 6-NC_6H_4Cl), 6.95 (d, $^3J = 8.4$ Hz, 1H, 4-NC_6H_4Cl), 7.04 (s, 1H, 2-NC_6H_4Cl), 7.22–7.37 (m, 11H, 5-NC_6H_4Cl, $N(CH_2C_6H_5)_2$), 10.30–10.50 (s, 1H, NH^+). LC/MS: *m/z* calc. 640.32, found 640.51. Anal. ($C_{36}H_{43}Cl_2N_7O_2$) C, H, N.

*8-(Dibenzylamino)-1,3-dimethyl-7-(5-(4-(4-fluorophenyl)-piperazin-1-yl)pentyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**32**)*
From **7** in 94% yield: m.p. 164–166°C, $R_f = 0.30$ (A), 0.66 (B), ^{1}H NMR δ 1.00–1.10 (m, 2H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 1.50–1.70 (m, 4H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 2.90–3.15 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.17 (s, 3H, $N(1)CH_3$), 3.37 (s, 3H, $N(3)CH_3$), 3.46–3.48 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.68–3.71 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 4.07 (t, $^3J = 7.2$ Hz, 2H, $N(7)CH_2$), 4.39 (s, 4H, $N(CH_2C_6H_5)_2$), 6.98–7.12 (m, 4H, NC_6H_4F), 7.19–7.37 (m, 10H, $N(CH_2C_6H_5)_2$), 10.60–10.70 (s, 1H, NH^+). LC/MS: *m/z* calc. 624.34, found 624.49. Anal. ($C_{36}H_{43}ClFN_7O_2$) C, H, N.

*8-(Dibenzylamino)-7-(5-(3,4-dihydroisoquinolin-2(1H)-yl)-pentyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione hydrochloride (**33**)*
From **7** in 84% yield: m.p. 158–160°C, $R_f = 0.26$ (A), 0.60 (B), ^{1}H NMR δ 1.00–1.15 (m, 2H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 1.55–1.70 (m, 4H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 2.95–3.15 (m, 4H, CH_2NH^+THIQ, 4,4-THIQ), 3.17 (s, 3H, $N(1)CH_3$), 3.31 (s, 3H, $N(3)CH_3$), 3.60–3.67 (m, 2H, 3,3-THIQ), 4.06–4.11 (m, 2H, $N(7)CH_2$), 4.20–4.25 (m, 1H, 1-THIQ), 4.38 (s, 4H, $N(CH_2C_6H_5)_2$), 4.40–4.45 (m, 1H, 1-THIQ), 7.17–7.37 (m, 14H, 5,6,7,8-THIQ, $N(CH_2C_6H_5)_2$), 10.30–10.40 (s, 1H, NH^+). LC/MS: *m/z* calc. 577.33, found 577.43. Anal. ($C_{35}H_{41}ClN_6O_2$) C, H, N.

*General procedure for preparing 7-(ω-(4-arylpiperazin-1-yl)-alkyl)-8-amino-1,3-dimethyl-1H-purine-2,6(3H,7H)-diones (**34–37, 44–47,** and **52–55**), 7-(ω-(4-arylpiperazin-1-yl)alkyl)-8-(N-alkylamino)-1,3-dimethyl-1H-purine-2,6(3H,7H)-diones (**39–43, 49,** and **50**) and their 7-(ω-(3,4-dihydroisoquinolin-2(1H)-yl)alkyl counterparts (**38, 48,** and **51**)*
Five millimoles of appropriate 7-(ω-(4-arylpiperazin-1-yl)alkyl) or 7-(ω-(3,4-dihydroisoquinolin-2(1*H*)-yl)alkyl derivative of 8-(*N*-alkylbenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione or 8-(dibenzylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione was dissolved in 10 mL of 90% H_2SO_4 and left in room temperature for 24 h. Afterwards 20 mL of water was added and mixture was filtered off. Filtrate was alkalized with 30% NaOH and extracted with chloroform (2×10 mL). Organic layer was evaporated under reduced pressure and residue was dissolved in dry ethanol and acidified with conc. HCl to pH ca. 3 and cooled. Precipitate was filtered off and purified by crystallization from ethanol.

*8-Amino-1,3-dimethyl-7-(3-(4-phenylpiperazin-1-yl)-propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**34**)*
From **13** in 91% yield: m.p. 317–319°C, $R_f = 0.19$ (A), 0.46 (B), ^{1}H NMR δ 2.00–2.18 (m, 2H, $CH_2CH_2CH_2$), 2.99–3.13 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.17 (s, 3H, $N(1)CH_3$), 3.32 (s, 3H, $N(3)CH_3$), 3.54–3.58 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.78–3.83 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 4.10 (t, $^3J = 6.7$ Hz, 2H, $N(7)CH_2$), 6.84 (t, $^3J = 7.2$ Hz, 1H, *p*-NC_6H_5), 6.98 (d, $^3J = 7.9$ Hz, 2H, *o*-NC_6H_5), 7.07 (s, 2H, NH_2), 7.24 (t, $^3J = 8.0$ Hz, 2H, *m*-NC_6H_5), 9.80–10.00 (s, 1H, NH^+). LC/MS: *m/z* calc. 398.23, found 398.33. Anal. ($C_{20}H_{28}ClN_7O_2$) C, H, N.

*8-Amino-1,3-dimethyl-7-(3-(4-(2-methoxyphenyl)-piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**35**)*
From **14** in 61% yield: m.p. 298–300°C, $R_f = 0.13$ (A), 0.42 (B), ^{1}H NMR δ 2.00–2.15 (m, 2H, $CH_2CH_2CH_2$), 2.90–3.15 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.18 (s, 3H, $N(1)CH_3$), 3.32 (s, 3H, $N(3)CH_3$), 3.50–3.60 (m, 4H, $CH_2NH^+(CH_2CH_2)_2N$), 3.77 (s, 3H, OCH_3), 4.10 (t, $^3J = 6.7$ Hz, 2H, $N(7)CH_2$), 6.84–7.00 (m, 4H,

$NC_6H_4OCH_3$), 7.07 (s, 2H, NH_2), 9.90–10.10 (s, 1H, NH^+). LC/MS: *m/z* calc. 428.24, found 428.36. Anal. ($C_{21}H_{28}ClN_7O_3$) C, H, N.

*8-Amino-1,3-dimethyl-7-(3-(4-(3-chlorophenyl)piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**36**)*
From **15** in 93% yield: m.p. 290–292°C, $R_f = 0.22$ (A), 0.52 (B), ^{1}H NMR δ 2.00–2.15 (m, 2H, $CH_2CH_2CH_2$), 3.00–3.17 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.17 (s, 3H, N(1)CH_3), 3.32 (s, 3H, N(3)CH_3), 3.53–3.60 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.86–3.89 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 4.10 (t, $^3J = 6.7$ Hz, 2H, N(7)CH_2), 6.85 (dd, $^3J = 7.7$ Hz, $^4J = 1.8$ Hz, 1H, 6-NC_6H_4Cl), 6.94 (dd, $^3J = 8.4$ Hz, $^4J = 1.9$ Hz, 1H, 4-NC_6H_4Cl), 7.03 (t, $^4J = 2.2$ Hz, 1H, 2-NC_6H_4Cl), 7.07 (s, 2H, NH_2), 7.24 (t, $^3J = 8.2$ Hz, 1H, 5-NC_6H_4Cl), 10.00–10.20 (s, 1H, NH^+). LC/MS: *m/z* calc. 432.19, found 432.24. Anal. ($C_{20}H_{27}Cl_2N_7O_2$) C, H, N.

*8-Amino-1,3-dimethyl-7-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**37**)*
From **16** in 93% yield: m.p. 292–294°C, $R_f = 0.21$ (A), 0.48 (B), ^{1}H NMR δ 2.00–2.15 (m, 2H, $CH_2CH_2CH_2$), 2.96 (t, $^3J = 12.2$ Hz, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.05–3.17 (m, 4H, $CH_2NH^+(CH_2CH_2)_2N$), 3.17 (s, 3H, N(1)CH_3), 3.33 (s, 3H, N(3)CH_3), 3.54–3.58 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.70–3.74 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 4.10 (t, $^3J = 6.5$ Hz, 2H, N(7)CH_2), 6.97–7.11 (m, 6H, NC_6H_4F, NH_2), 9.08–10.00 (s, 1H, NH^+). LC/MS: *m/z* calc. 416.22, found 416.32. Anal. ($C_{20}H_{27}ClFN_7O_2$) C, H, N.

*8-Amino-7-(3-(3,4-dihydroisoquinolin-2(1H)-yl)propyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione hydrochloride (**38**)*
From **17** in 56% yield: m.p. 266–268°C, $R_f = 0.19$ (A), 0.46 (B), ^{1}H NMR δ 2.05–2.20 (m, 2H, $CH_2CH_2CH_2$), 2.85–3.19 (m, 4H, CH_2NH^+THIQ, 4,4-THIQ), 3.18 (s, 3H, N(1)CH_3), 3.35 (s, 3H, N(3)CH_3), 3.45–3.60 (m, 2H, 3,3-THIQ), 4.10–4.20 (m, 1H, 1-THIQ), 4.14 (t, $^3J = 7.1$ Hz, 2H, N(7)CH_2), 4.40–4.50 (m, 1H, 1-THIQ), 7.08 (s, 2H, NH_2), 7.10–7.26 (m, 4H, 5,6,7,8-THIQ), 10.00–10.20 (s, 1H, NH^+). LC/MS: *m/z* calc. 396.20, found 369.37. Anal. ($C_{19}H_{25}ClN_6O_2$) C, H, N.

*1,3-Dimethyl-8-(methylamino)-7-(3-(4-phenylpiperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**39**)*
From **8** in 60% yield: m.p. 281–283°C, $R_f = 0.17$ (A), 0.54 (B), ^{1}H NMR δ 2.00–2.15 (m, 2H, $CH_2CH_2CH_2$), 2.89 (s, 3H, NHCH_3), 3.08–3.17 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.18 (s, 3H, N(1)CH_3), 3.36 (s, 3H, N(3)CH_3), 3.54–3.56 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.76–3.79 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 4.13 (t, $^3J = 7.0$ Hz, 2H, N(7)CH_2), 6.84 (t, $^3J = 7.2$ Hz, 1H, *p*-NC_6H_5), 6.98 (d, $^3J = 7.0$ Hz, 2H, *o*-NC_6H_5), 7.24 (t, $^3J = 8.0$ Hz, 2H, *m*-NC_6H_5), 7.35 (s, 1H, NHCH$_3$), 10.50–10.70 (s, 1H, NH^+). LC/MS: *m/z* calc. 412.24, found 412.35. Anal. ($C_{21}H_{30}ClN_7O_2$) C, H, N.

*1,3-Dimethyl-8-(methylamino)-7-(3-(4-(2-methoxyphenyl)-piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**40**)*
From **9** in 50% yield: m.p. 287–289°C, $R_f = 0.13$ (A), 0.44 (B), ^{1}H NMR δ 2.00–2.20 (m, 2H, $CH_2CH_2CH_2$), 2.89 (s, 3H, NHCH_3), 3.02–3.17 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.17 (s, 3H, N(1)CH_3), 3.38 (s, 3H, N(3)CH_3), 3.44–3.48 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.51–3.55 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.77 (s, 3H, OCH_3), 4.14 (t, $^3J = 7.0$ Hz, 2H, N(7)CH_2), 6.85–7.03 (m, 4H, $NC_6H_4OCH_3$), 7.20 (s, 1H, NHCH$_3$), 10.80–10.95 (s, 1H, NH^+). LC/MS: *m/z* calc. 442.26, found 442.34. Anal. ($C_{22}H_{32}ClN_7O_3$) C, H, N.

*1,3-Dimethyl-8-(methylamino)-7-(3-(4-(3-chlorophenyl)-piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**41**)*
From **10** in 76% yield: m.p. 301–303°C, $R_f = 0.19$ (A), 0.54 (B), ^{1}H NMR (base) δ 2.05–2.15 (m, 2H, $CH_2CH_2CH_2$), 2.37 (t, $^3J = 6.2$ Hz, 2H, $CH_2N(CH_2CH_2)_2N$), 2.62 (t, $^3J = 4.9$ Hz, 4H, $CH_2N(CH_2CH_2)_2N$), 3.03 (d, $^3J = 4.9$ Hz, 3H, NHCH_3), 3.26 (t, $^3J = 4.9$ Hz, 4H, $CH_2N(CH_2CH_2)_2N$), 3.37 (s, 3H, N(1)CH_3), 3.54 (s, 3H, N(3)CH_3), 4.04 (t, $^3J = 5.6$ Hz, 2H, N(7)CH_2), 6.81 (ddd, $^3J = 8.5$ Hz, $^4J = 2.4$ Hz, $^5J = 0.8$ Hz, 1H, 6-NC_6H_4Cl), 6.86 (ddd, $^3J = 8.0$ Hz, $^4J = 2.0$ Hz, $^5J = 0.8$ Hz, 1H, 4-NC_6H_4Cl), 6.90 (t, $^4J = 2.0$ Hz, 1H, 2-NC_6H_4Cl), 7.14–7.18 (m, 1H, NHCH$_3$), 7.17 (t, $^3J = 8.1$ Hz, 1H, 5-NC_6H_4Cl). LC/MS: *m/z* calc. 446.21, found 446.35. Anal. ($C_{21}H_{29}Cl_2N_7O_2$) C, H, N.

*8-(Ethylamino)-1,3-dimethyl-7-(3-(4-phenylpiperazin-1-yl)-propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**42**)*
From **11** in 69% yield: m.p. 286–287°C, $R_f = 0.17$ (A), 0.50 (B), ^{1}H NMR (base) δ 1.19 (t, $^3J = 7.0$ Hz, 3H, NHCH$_2$CH_3), 2.05–2.15 (m, 2H, $CH_2CH_2CH_2$), 2.38 (t, $^3J = 6.1$ Hz, 2H, $CH_2N(CH_2CH_2)_2N$), 2.62 (m, 4H, $CH_2N(CH_2CH_2)_2N$), 3.14 (m, 4H, $CH_2N(CH_2CH_2)_2N$), 3.36 (s, 3H, N(1)CH_3), 3.47 (q, $^3J = 7.0$ Hz, 2H, NHCH_2CH$_3$), 3.53 (s, 3H, N(3)CH_3), 4.06 (t, $^3J = 7.0$ Hz, 2H, N(7)CH_2), 6.83 (t, $^3J = 7.0$ Hz, 1H, *p*-NC_6H_5), 6.96 (d, $^3J = 8.5$ Hz, 2H, *o*-NC_6H_5), 7.25 (t, $^3J = 8.0$ Hz, 2H, *m*-NC_6H_5), 7.26 (t, $^3J = 6.0$ Hz, 1H, NH CH$_2$CH$_3$). LC/MS: *m/z* calc. 426.26, found 426.38. Anal. ($C_{22}H_{32}ClN_7O_2$) C, H, N.

*8-(Ethylamino)-1,3-dimethyl-7-(3-(4-(2-methoxyphenyl)-piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**43**)*
From **12** in 65% yield: m.p. 286–287°C, $R_f = 0.13$ (A), 0.48 (B), ^{1}H NMR (base) δ 1.26 (t, $^3J = 7.2$ Hz, 3H, NHCH$_2$CH_3), 2.09–2.16 (m, 2H, $CH_2CH_2CH_2$), 2.39 (t, $^3J = 6.0$ Hz, 2H, $CH_2N(CH_2CH_2)_2N$), 2.68 (m, 4H, $CH_2N(CH_2CH_2)_2N$), 3.15 (m, 4H, $CH_2N(CH_2CH_2)_2N$), 3.38 (s, 3H, N(1)CH_3), 3.47 (q, $^3J = 7.0$ Hz, 2H, NHCH_2CH$_3$), 3.53 (s, 3H, N(3)CH_3), 3.88 (s, 3H, OCH_3), 4.04 (t, $^3J = 5.7$ Hz, 2H, N(7)CH_2), 6.88–7.08 (m, 4H, $NC_6H_4OCH_3$), 7.23 (t, $^3J = 5.3$ Hz, 1H, NHCH$_2$CH$_3$). LC/MS: *m/z* calc. 456.27, found 456.38. Anal. ($C_{23}H_{34}ClN_7O_3$) C, H, N.

*8-Amino-1,3-dimethyl-7-(4-(4-phenylpiperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**44**)*
From **24** in 94% yield: m.p. 252–254°C, $R_f = 0.06$ (A), 0.26 (B), ^{1}H NMR δ 1.60–1.80 (m, 4H, N(7)$CH_2CH_2CH_2CH_2$), 3.05–3.15 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.16 (s, 3H, N(1)CH_3), 3.31 (s, 3H, N(3)CH_3), 3.48–3.50 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.77–3.80 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 4.00–4.05 (m, 2H, N(7)CH_2), 6.84 (t, $^3J = 7.3$ Hz, 1H, *p*-NC_6H_5), 6.98 (d, $^3J = 7.7$ Hz, 2H, *o*-NC_6H_5), 7.24 (t, $^3J = 8.0$ Hz, 2H, *m*-NC_6H_5), 6.90–7.30 (s, 2H, NH_2), 10.60–

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10.70 (s, 1H, NH$^+$). LC/MS: *m/z* calc. 412.24, found 412.37. Anal. ($C_{21}H_{30}ClN_7O_2$) C, H, N.

*8-Amino-1,3-dimethyl-7-(4-(4-(2-methoxyphenyl)-piperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**45**)*
From **25** in 61% yield: m.p. 234–235°C, $R_f = 0.14$ (B), ^{1}H NMR δ 1.60–1.80 (m, 4H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 3.00–3.15 (m, 6H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 3.17 (s, 3H, N(1)CH$_3$), 3.32 (s, 3H, N(3)CH$_3$), 3.45–3.48 (m, 4H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 3.77 (s, 3H, OCH$_3$), 4.04 (m, 2H, N(7)CH$_2$), 6.85–7.05 (m, 4H, NC$_6$H$_4$OCH$_3$), 6.90–7.30 (s, 2H, NH$_2$), 10.40–10.60 (s, 1H, NH$^+$). LC/MS: *m/z* calc. 442.26, found 442.35. Anal. ($C_{22}H_{32}ClN_7O_3$) C, H, N.

*8-Amino-1,3-dimethyl-7-(4-(4-(3-chlorophenyl)piperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**46**)*
From **26** in 93% yield: m.p. 201–203°C, $R_f = 0.04$ (A), 0.24 (B), ^{1}H NMR δ 1.55–1.75 (m, 4H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 3.00–3.20 (m, 6H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 3.16 (s, 3H, N(1)CH$_3$), 3.31 (s, 3H, N(3)CH$_3$), 3.46–3.49 (m, 2H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 3.83–3.87 (m, 2H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 4.03 (t, $^3J = 6.4$Hz, 2H, N(7)CH$_2$), 6.84 (dd, $^3J = 7.9$ Hz, $^4J = 1.3$ Hz, 1H, 6-NC$_6$H$_4$Cl), 6.90–7.30 (s, 2H, NH$_2$), 6.93 (dd, $^3J = 8.2$ Hz, $^4J = 2.1$ Hz, 1H, 4-NC$_6$H$_4$Cl), 7.03 (t, $^4J = 2.2$ Hz, 1H, 2-NC$_6$H$_4$Cl), 7.24 (t, $^3J = 8.1$Hz, 1H, 5-NC$_6$H$_4$Cl), 10.60–10.70 (s, 1H, NH$^+$). LC/MS: *m/z* calc. 446.21, found 446.37. Anal. ($C_{21}H_{29}Cl_2N_7O_2$) C, H, N.

*8-Amino-1,3-dimethyl-7-(4-(4-(4-fluorophenyl)piperazin-1-yl)butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**47**)*
From **27** in 87% yield: m.p. 200–202°C, $R_f = 0.02$ (A), 0.18 (B), ^{1}H NMR δ 1.60–1.80 (m, 4H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 3.00–3.15 (m, 6H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 3.16 (s, 3H, N(1)CH$_3$), 3.32 (s, 3H, N(3)CH$_3$), 3.48–3.50 (m, 2H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 3.67–3.71 (m, 2H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 4.04 (t, $^3J = 8.7$ Hz, 2H, N(7)CH$_2$), 6.97–7.12 (m, 2H, NC$_6$H$_4$F, NH$_2$), 10.70–10.80 (s, 1H, NH$^+$). LC/MS: *m/z* calc. 430.24, found 430.36. Anal. ($C_{21}H_{29}ClFN_7O_2$) C, H, N.

*8-Amino-7-(4-(3,4-dihydroisoquinolin-2(1H)-yl)butyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione hydrochloride (**48**)*
From **28** in 65% yield: m.p. 232–234°C, $R_f = 0.16$ (B), ^{1}H NMR (base) δ 1.40–1.55 (m, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 1.60–1.70 (m, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 2.41 (t, $^3J = 7.2$ Hz, 2H, CH$_2$NTHIQ), 2.58 (t, $^3J = 5.9$ Hz, 2H, 3,3-THIQ), 2.75 (t, $^3J = 5.6$ Hz, 2H, 4,4-THIQ), 3.14 (s, 3H, N(1)CH$_3$), 3.30 (s, 3H, N(3)CH$_3$), 3.46 (s, 2H, 1,1-THIQ), 3.99 (t, $^3J = 7.1$ Hz, 2H, N(7)CH$_2$), 6.88 (s, 2H, NH$_2$), 6.97–6.99 (m, 1H, 8-THIQ), 7.04–7.09 (m, 3H, 5,6,7-THIQ). LC/MS: *m/z* calc. 383.22, found 383.34. Anal. ($C_{20}H_{27}ClN_6O_2$) C, H, N.

*8-(Ethylamino)-1,3-dimethyl-7-(4-(4-phenylpiperazin-1-yl)-butyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**49**)*
From **21** in 68% yield: m.p. 181–183°C, $R_f = 0.06$ (A), 0.37 (B), ^{1}H NMR (base) δ 1.26 (t, $^3J = 7.2$ Hz, 3H, NHCH$_2$CH$_3$), 1.61 (quin, $^3J = 7.1$ Hz, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 1.80 (quin, $^3J = 7.2$ Hz, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 2.46 (t, $^3J = 7.1$ Hz, 2H, CH$_2$N(CH$_2$CH$_2$)$_2$N), 2.59–2.63 (m, 2H, CH$_2$N(CH$_2$CH$_2$)$_2$N), 3.18–3.22 (m, 2H, CH$_2$N-(CH$_2$CH$_2$)$_2$N), 3.37 (s, 3H, N(1)CH$_3$), 3.51 (q, $^3J = 7.2$ Hz, 2H, NHCH$_2$CH$_3$), 3.52 (s, 3H, N(3)CH$_3$), 4.07 (t, $^3J = 7.4$ Hz, 2H, N(7)CH$_2$), 6.85 (t, $^3J = 7.7$ Hz, 1H, *p*-NC$_6$H$_5$), 6.90 (d, $^3J = 6.6$ Hz, 2H, *o*-NC$_6$H$_5$), 6.94 (s, 1H, NHCH$_2$CH$_3$), 7.26 (t, $^3J = 7.8$ Hz, 2H, *m*-NC$_6$H$_5$). LC/MS: *m/z* calc. 440.28, found 440.36. Anal. ($C_{23}H_{34}ClN_7O_2$) C, H, N.

*8-(Ethylamino)-1,3-dimethyl-7-(4-(4-(2-methoxyphenyl)-piperazin-1-yl)propyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**50**)*
From **22** in 49% yield: m.p. 192–194°C, $R_f = 0.04$ (A), 0.33 (B), ^{1}H NMR (base) δ 1.28 (t, $^3J = 7.2$ Hz, 3H, NHCH$_2$CH$_3$), 1.60–1.75 (m, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 1.75–1.90 (m, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 2.51 (t, $^3J = 6.9$ Hz, 2H, CH$_2$N(CH$_2$CH$_2$)$_2$N), 2.55–2.70 (m, 2H, CH$_2$N(CH$_2$CH$_2$)$_2$N), 2.95–3.15 (m, 2H, CH$_2$N(CH$_2$CH$_2$)$_2$N), 3.38 (s, 3H, N(1)CH$_3$), 3.40–3.60 (m, 2H, NHCH$_2$CH$_3$), 3.52 (s, 3H, N(3)CH$_3$), 3.87 (s, 3H, OCH$_3$), 4.07 (t, $^3J = 7.6$ Hz, 2H, N(7)CH$_2$), 6.86–7.20 (m, 5H, NC$_6$H$_4$OCH$_3$, NHCH$_2$CH$_3$). LC/MS: *m/z* calc. 470.29, found 470.41. Anal. ($C_{24}H_{36}ClN_7O_3$) C, H, N.

*7-(4-(3,4-Dihydroisoquinolin-2(1H)-yl)butyl)-8-(ethylamino)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione hydrochloride (**51**)*
From **23** in 35% yield: m.p. 178–180°C, $R_f = 0.06$ (A), 0.35 (B), ^{1}H NMR (base) δ 1.12 (t, $^3J = 7.2$ Hz, 3H, NHCH$_2$CH$_3$), 1.35–1.48 (m, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 1,58–1.68 (m, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$), 2.41 (t, $^3J = 7.1$ Hz, 2H, CH$_2$NTHIQ), 2.58 (t, $^3J = 5.8$ Hz, 2H, 3,3-THIQ), 2.75 (t, $^3J = 5.6$ Hz, 2H, 4,4-THIQ), 3.14 (s, 3H, N(1)CH$_3$), 3.30–3.40 (m, 2H, NHCH$_2$CH$_3$), 3.32 (s, 3H, N(3)CH$_3$), 3.46 (s, 2H, 1,1-THIQ), 4.01 (t, $^3J = 7.1$ Hz, 2H, N(7)CH$_2$), 6.93–7.01 (m, 2H, 8-THIQ, NHCH$_2$CH$_3$), 7.04–7.09 (m, 3H, 5,6,7-THIQ). LC/MS: *m/z* calc. 411.25, found 411.38. Anal. ($C_{22}H_{31}ClN_6O_2$) C, H, N.

*8-Amino-1,3-dimethyl-7-(5-(4-phenylpiperazin-1-yl)-pentyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**52**)*
From **29** in 74% yield: m.p. 267–269°C, $R_f = 0.20$ (B), ^{1}H NMR δ 1.27 (quin, $^3J = 7.2$ Hz, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 1.65 (quin, $^3J = 7.2$ Hz, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 1.74 (quin, $^3J = 7.7$ Hz, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 3.00–3.11 (m, 6H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 3.18 (s, 3H, N(1)CH$_3$), 3.30 (s, 3H, N(3)CH$_3$), 3.46–3.52 (m, 2H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 3.75–3.79 (m, 2H, CH$_2$NH$^+$(CH$_2$CH$_2$)$_2$N), 4.01 (t, $^3J = 6.9$ Hz, 2H, N(7)CH$_2$), 6.84 (t, $^3J = 7.3$ Hz, 1H, *p*-NC$_6$H$_5$), 6.85–7.00 (s, 2H, NH$_2$), 6.98 (d, $^3J = 8.0$ Hz, 2H, *o*-NC$_6$H$_5$), 7.23 (t, $^3J = 8.0$ Hz, 2H, *m*-NC$_6$H$_5$), 10.70–10.90 (s, 1H, NH$^+$). LC/MS: *m/z* calc. 426.26, found 426.40. Anal. ($C_{22}H_{32}ClN_7O_2$) C, H, N.

*8-Amino-1,3-dimethyl-7-(5-(4-(2-methoxyphenyl)-piperazin-1-yl)pentyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**53**)*
From **30** in 66% yield: m.p. 253–255°C, $R_f = 0.18$ (B), ^{1}H NMR (base) δ 1.24 (quin, $^3J = 7.6$ Hz, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 1.43 (quin, $^3J = 7.3$ Hz, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 1.63 (quin, $^3J = 7.3$ Hz, 2H, N(7)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 2.25 (t, $^3J = 7.3$ Hz, 2H, CH$_2$N(CH$_2$CH$_2$)$_2$N), 2.48 (m, 4H, CH$_2$N(CH$_2$CH$_2$)$_2$N), 2.90 (m, 4H, CH$_2$N(CH$_2$CH$_2$)$_2$N), 3.15 (s, 3H, N(1)CH$_3$), 3.30 (s, 3H, N(3)CH$_3$), 3.74 (s, 3H, OCH$_3$), 3.97 (t, $^3J = 7.2$ Hz, 2H, N(7)CH$_2$), 6.83–6.95

(m, 6H, $NC_6H_4OCH_3$, NH_2). LC/MS: *m/z* calc. 456.27, found 456.45. Anal. ($C_{23}H_{34}ClN_7O_3$) C, H, N.

*8-Amino-1,3-dimethyl-7-(5-(4-(3-chlorophenyl)piperazin-1-yl)pentyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**54**)*
From **31** in 84% yield: m.p. 259–261°C, $R_f = 0.02$ (A), 0.29 (B), ^{1}H NMR δ 1.27 (quin, $^3J = 6.9$ Hz, 2H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 1.58–1.78 (m, 4H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 2.98–3.11 (m, 6H, $CH_2NH^+(CH_2CH_2)_2N$), 3.17 (s, 3H, $N(1)CH_3$), 3.30 (s, 3H, $N(3)CH_3$), 3.48–3.52 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 3.82–3.88 (m, 2H, $CH_2NH^+(CH_2CH_2)_2N$), 4.00 (t, $^3J = 7.1$ Hz, 2H, $N(7)CH_2$), 6.80-7.10 (s, 2H, NH_2), 6.85 (dd, $^3J = 8.0$ Hz, $^4J = 1.7$ Hz, 1H, 6-NC_6H_4Cl), 6.94 (dd, $^3J = 8.2$ Hz, $^4J = 2.3$ Hz, 1H, 4-NC_6H_4Cl), 7.03 (t, $^4J = 2.2$ Hz, 1H, 2-NC_6H_4Cl), 7.24 (t, $^3J = 8.1$ Hz, 1H, 5-NC_6H_4Cl), 10.50–10.70 (s, 1H, NH^+). LC/MS: *m/z* calc. 460.22, found 460.41. Anal. ($C_{22}H_{31}Cl_2N_7O_2$) C, H, N.

*8-Amino-1,3-dimethyl-7-(5-(4-(4-fluorophenyl)piperazin-1-yl)pentyl)-1H-purine-2,6(3H,7H)-dione hydrochloride (**55**)*
From **32** in 95% yield: m.p. 265–267°C, $R_f = 0.21$ (B), ^{1}H NMR δ 1.24 (quin, $^3J = 7.2$ Hz, 2H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 1.43 (quin, $^3J = 7.2$ Hz, 2H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 1.62 (quin, $^3J = 6.8$ Hz, 2H, $N(7)CH_2CH_2CH_2CH_2CH_2$), 2.25 (t, $^3J = 7.3$ Hz, 2H, $CH_2N(CH_2CH_2)_2N$), 2.43 (t, $^3J = 4.9$ Hz, 4H, $CH_2N(CH_2CH_2)_2N$), 3.00 (t, $^3J = 4.9$ Hz, 4H, $CH_2N(CH_2CH_2)_2N$), 3.15 (s, 3H, $N(1)CH_3$), 3.29 (s, 3H, $N(3)CH_3$), 3.97 (t, $^3J = 7.2$ Hz, 2H, $N(7)CH_2$), 6.87 (s, 2H, NH_2), 6.87–7.04 (m, 4H, NC_6H_4F). LC/MS: *m/z* calc. 444.25, found 444.40. Anal. ($C_{22}H_{31}ClFN_7O_2$) C, H, N.

Pharmacology

In vitro radioligand binding assays
In vitro radioligand binding assays for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors were carried out using methods published by Zajdel et al. [5].

Functional assays for the 5-HT_{1A} receptor
The functional assays for the selected compounds were carried out according to the methods published by Kołaczkowski et al. [6]. The compounds were tested in concentrations 10^{-5} and 10^{-6} M.

The competition binding experiments were financed by project of Polish-Norwegian Research Fund "Creating an academia-based platform to discover substances acting on serotonergic and glutamatergic systems as potential new antidepressant or anxiolytic drugs".

The authors have declared no conflict of interest.

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