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N-(4-Arylpiperazinoalkyl)acetamide derivatives of 1,3- and 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-diones and their 5-HT$_6$, 5-HT$_7$, and D$_2$ receptors affinity

Abstract: A series of *N*-(arylpiperazinyl)acetamide derivatives of 1,3- and 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione was synthesized and biologically evaluated in *in vitro* competition binding experiments for serotonin 5-HT$_6$, 5-HT$_7$, and dopamine D$_2$ receptors. The structure-affinity relationships for this group of compounds allowed for determination of structural features responsible for receptor affinity. Among the investigated derivatives, compounds **5** and **12** with (2,3-dichlorophenyl)piperazine moiety were classified as potent dual 5-HT$_6$/D$_2$ receptors ligands, whereas compound **4**, with 4-(benzo[*d*]isothiazol-3-yl)piperazine moiety, and compounds **8** and **15**, with (2,3-dichlorophenyl)piperazine moiety, were classified as potent D$_2$ receptor ligands.

Keywords: 5-HT$_6$ receptor ligands; 5-HT$_7$ receptor ligands; D$_2$ receptor ligands; long-chain arylpiperazines; theobromine; theophylline.

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Introduction

Compounds with affinity for serotoninergic (5-HT$_6$, 5-HT$_7$) and dopaminergic type 2 receptors (D$_2$Rs) exhibit potential for the treatment of diverse central nervous system disorders, e.g., depression [1, 2], schizophrenia [3], as well as dementia [4] and Alzheimer disease [5]. Importantly, derivatives with mixed receptor binding profile, often called serotonin/dopamine modulators, may attenuate both negative, positive symptoms of schizophrenia, as well as improve cognitive deficits [6, 7].

A vast group of compounds with mixed serotonin/dopamine receptor binding profile belongs to a class of long-chain arylpiperazines (LCAPs). Typically, in such derivatives, the arylpiperazine moiety is connected *via* an alkyl linker to the terminal fragment. For several years, we have been interested in developing of LCAPs with different xanthine moieties playing a role of a cyclic amide core in the terminal fragment. 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 behaved as 5-HT$_{1A}$ receptors agonists [8].

The aim of our study was to investigate structure-affinity relationships for the 5-HT$_6$, 5-HT$_7$, and D$_2$ receptors in a group of LCAPs with xanthine moieties in the terminal fragment and an additional amide bond in the linker. For this purpose, we have designed a series of new *N*-(arylpiperazinylalkyl)acetamide derivatives of 1,3- and 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione with a different length polymethylene spacer between the amide moiety and the basic nitrogen atom. Structural modifications in the amine fragment comprised introduction of 1-(2,3-dichlorophenyl)piperazine and 1-(benzo[*d*]isothiazol-3-yl)piperazine, as substructures related to aripiprazole and ziprasidone (Figure 1), respectively. To further examine an impact of replacement of sulfur atom with oxygen atom on affinity, the analogues with 1-(benzo[*d*]isoxazol-3-yl)piperazine moiety were also synthesized.

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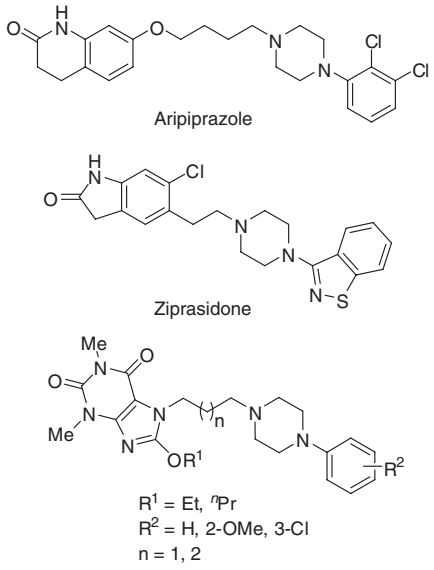
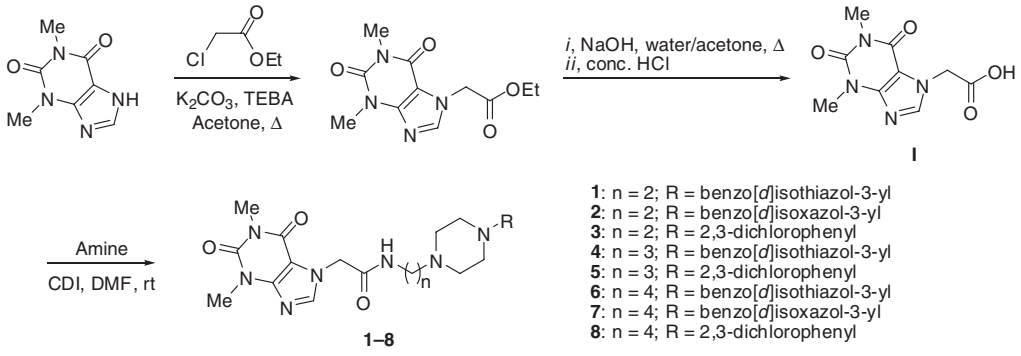


Figure 1 Aripiprazole, ziprasidone, and a general structure of 8-alkoxy-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione derivatives [8].

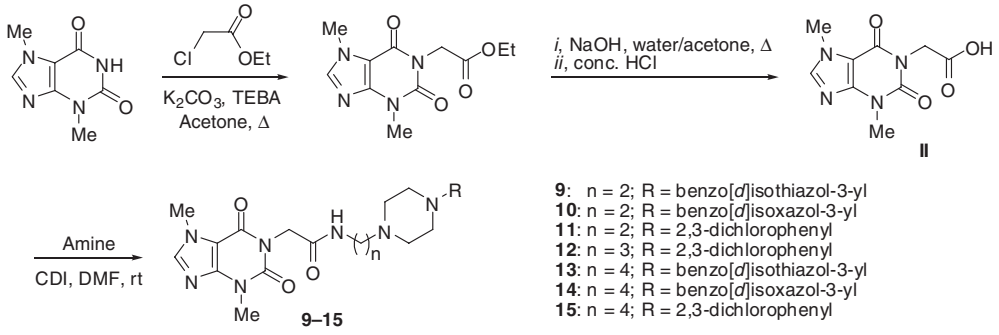
Results and discussion

The designed compounds were synthesized in reaction of appropriate xanthinylacetic acids, obtained according to the methods previously reported by Maślankiewicz et al. [9], and arylpiperazinoalkylamines, using 1,1′-carbonyldiimidazole (CDI) as activating agent (Schemes 1 and 2).

In the first step, 1,3- or 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione was alkylated by treatment with ethyl 2-chloroacetate in the presence of anhydrous K_2CO_3 and TEBA (*N*,*N*,*N*-triethylbenzylammonium chloride) in acetone, yielding ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetate [9] and 2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetate [9], respectively. The esters were subsequently hydrolyzed with 10% solution of NaOH in a water-acetone mixture (2:1), and the resulting acids were isolated after acidification of the reaction mixture. The final products were obtained by acylation of the appropriate arylpiperazino-(4-(benzo[*d*]isothiazol-3-yl)piperazino-, benzo[*d*]isoxazol-3-yl)piperazinyl-, or 4-(2,3-dichlorophenyl)piperazino-) derivative of alkylamine with 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetic acid (**I**) [9] or 2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetic acid (**II**) [9] at room temperature in DMF, using CDI as activating agent. The structures of the newly synthesized compounds **1**–**15** were confirmed by analysis of ^{1}H NMR and ^{13}C NMR spectra, LC/MS, and elemental analysis. The investigated compounds were pharmacologically tested as free bases.



Scheme 1



Scheme 2

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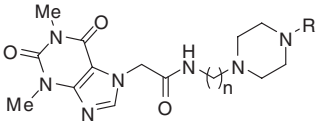
The newly synthesized *N*-(arylpiperazinylalkyl) acetamide derivatives of 1,3- and 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione were tested in competition binding experiments for 5-HT$_6$, 5-HT$_7$, and D$_2$ receptors. Compounds displayed high to low affinity for the tested receptors, ranging from 14 nM to 100 μM for 5-HT$_6$Rs, from 100 nM to 4789 nM for 5-HT$_7$Rs, and 1–2090 nM for D$_2$Rs (Tables 1 and 2).

The affinity for 5-HT$_6$ and D$_2$ receptors depended on the type of the xanthine core: 1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione derivatives displayed higher affinity for 5-HT$_6$ and D$_2$ receptors than their 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione counterparts, e.g., compound **8** vs. compound **15** ($K_{i(D_2)}$ = 85 and 1 nM, respectively). Interestingly, a type of the xanthine core did not significantly influence affinity for 5-HT$_7$Rs.

The impact of the length of the polymethylene spacer between the amide moiety and the basic nitrogen atom was evident: compounds with trimethylene spacer displayed the highest affinity for 5-HT$_6$ and D$_2$ receptors. Compounds **4** and **5** displayed over 9- and 59-fold higher affinity for 5-HT$_6$ receptors than their lower homologues, compounds **1** and **3**, respectively, and over 5- and 18-fold higher affinity than their higher homologues, compounds **6** and **8**. Although a dimethylene group spacer was the least preferential for 5-HT$_7$Rs, trimethylene, and tetramethylene analogues display comparable affinity for these sites.

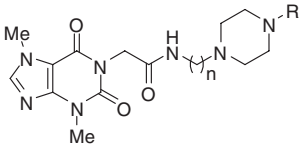
Table 1 Binding affinities of the synthesized *N*-(arylpiperazinoalkyl) acetamide derivatives of 1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione for 5-HT$_6$, 5-HT$_7$, and D$_2$ receptors.



Compound	n	R	K_i (nM)[a]		
			5-HT$_6$	5-HT$_7$	D$_2$
1	2	Benzo[*d*]isothiazol-3-yl	1873	999	273
2	2	Benzo[*d*]isoxazol-3-yl	2302	1008	1474
3	2	2,3-Dichlorophenyl	827	3056	542
4	3	Benzo[*d*]isothiazol-3-yl	208	110	2
5	3	2,3-Dichlorophenyl	14	224	7
6	4	Benzo[*d*]isothiazol-3-yl	1144	100	37
7	4	Benzo[*d*]isoxazol-3-yl	1329	121	219
8	4	2,3-Dichlorophenyl	263	268	16
Aripiprazole[b]			90	26	0.8
Ziprasidone			20	1	0.8

[a]K_i values (SEM±26) based on three independent binding experiments.
[b]From reference [10].

Table 2 Binding affinities of the synthesized *N*-(arylpiperazinoalkyl)acetamide derivatives of 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione for 5-HT$_6$, 5-HT$_7$, and D$_2$ receptors.



Compound	n	R	K_i (nM)[a]		
			5-HT$_6$	5-HT$_7$	D$_2$
9	2	Benzo[*d*]isothiazol-3-yl	4878	2176	401
10	2	Benzo[*d*]isoxazol-3-yl	>100 000	1102	2090
11	2	2,3-Dichlorophenyl	1066	4789	104
12	3	2,3-Dichlorophenyl	22	381	2
13	4	Benzo[*d*]isothiazol-3-yl	393	178	35
14	4	Benzo[*d*]isoxazol-3-yl	626	125	339
15	4	2,3-Dichlorophenyl	85	183	1
Aripiprazole[b]			90	26	0.8
Ziprasidone			20	1	0.8

[a]K_i values (SEM±26) based on three independent binding experiments.
[b]From reference [10].

Further analysis of the affinity data suggested that replacement of carbostyryl fragment in aripiprazole with xanthinylacetamide moiety increased affinity of 2,3-dichlorophenylpiperazines for 5-HT$_6$Rs (compounds **5** and **12** vs. aripiprazole). At the same time, this modification significantly decreased affinity for 5-HT$_7$Rs. As a consequence, compounds **5** and **12** were classified as potent 5-HT$_6$/D$_2$ receptor ligands. The same modification of ziprasidone structure significantly increased the affinity for 5-HT$_6$ and 5-HT$_7$ receptors, while this effect was much smaller in case of D$_2$ receptors (**4** vs. ziprasidone).

Structure-activity relationship studies in the arylpiperazine function suggested that highly lipophilic 1-(2,3-dichlorophenyl)piperazine moiety guaranteed high affinity for 5-HT$_6$ and D$_2$Rs. Compounds with 1-(benzo[*d*]isothiazol-3-yl)piperazine moiety displayed lower affinity for these receptors. Further substitution of the sulfur atom in 1-(benzo[*d*]isothiazol-3-yl)piperazine with oxygen atom, which decreased the lipophilicity of the fragment, also caused further loss of affinity. This can be easily observed with direct structural analogues **15** vs. **13** vs. **14**, containing 4-(2,3-dichlorophenyl)piperazino, 4-(benzo[*d*]isothiazol-3-yl)piperazino, and 4-(benzo[*d*]isoxazol-3-yl)piperazino moieties, respectively. Simultaneously, an influence of arylpiperazine moiety on the affinity for 5-HT$_7$ receptors suggested that generally less lipophilic substituents were preferred, but this influence was much weaker than for 5-HT$_6$ and D$_2$ receptors,

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e.g., compound **15** had comparable affinity for 5-HT$_7$Rs to those of compounds **13** and **14**.

Conclusions

We have designed and synthesized a series of 15 new *N*-(arylpiperazinylalkyl)acetamide derivatives of 1,3- and 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-diones. The study allowed for identification of potent 5-HT$_6$/D$_2$ receptor ligands (compounds **5** and **12**) and D$_2$ receptor agents (compounds **4**, **8**, and **15)**. Structure-affinity relationships studies showed that the 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione core, a polymethylene spacer containing three methylene groups, and 2,3-dichlorophenypiperazine were the optimal elements for high affinity for 5-HT$_6$ and D$_2$ receptors.

Experimental

Melting points (mp) were determined with a Büchi Melting Point B-545 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were taken with a Varian Mercury-VX (300 MHz) spectrometer in DMSO-d_6 solutions, using signals of solvent's residual ^{1}H and ^{13}C atoms as internal standards (δ = 2.49 and 39.7 ppm, respectively). LC/MS analyses were performed on Waters Acquity TQD apparatus with eλ DAD detector. For mass spectrometry, ESI+ (electrospray positive) ionization mode was used. The progress of the reactions and the purity of compounds were routinely checked by TLC using Merck Kieselgel 60 F$_{254}$ sheets and eluting with dichloromethane/methanol, 90:10. Spots were detected by UV irradiation. All final compounds had purity over 95%. Elemental analyses were taken with Elementar Vario EL III apparatus. All *in vitro* radioligand binding assays were carried out using methods published by Zajdel et al. [10].

General procedure for preparation of *N*-(arylpiperazino) acetamide derivatives of 1,3- and 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione 1–15

A mixture of 1 equiv (0.0004 mol) of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetic acid (**I**) or 2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetic acid (**II**) with 1.5 equiv of CDI in DFM was stirred in room temperature for 1 h. Afterward, 1 equiv of appropriate amine was added, and stirring was continued for 48 h. Then the mixture was concentrated under reduced pressure and crude product was purified by silica gel chromatography eluting with dichloromethane/methanol (95:5).

***N*-[2-(4-(Benzo[*d*]isothiazol-3-yl)piperazin-1-yl)ethyl]-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetamide (1):** This compound was obtained from **I** in 59% yield; mp 218–220°C; R_f = 0.31; ^{1}H NMR: δ 2.53 (t, ^3J = 6.2 Hz, 2H), 2.63–2.66 (m, 4H), 3.27 (s, 3H), 3.33 (t, ^3J = 6.2 Hz, 2H), 3.45–3.47 (m, 4H), 3.48 (s, 3H), 4.87 (s, 2H), 7.28 (ddd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, ^4J = 1.2 Hz, 1H), 7.39 (ddd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, ^4J = 1.2 Hz, 1H), 7.56–7.58 (m, 1H), 7.69 (s, 1H), 7.70–7.76 (m, 1H), 7.80 (dt, ^3J = 8.1 Hz, ^4J = 1.0 Hz, 1H); ^{13}C NMR: δ 27.8, 29.7, 36.2, 48.9, 49.6, 52.6, 56.6, 106.9, 120.5, 123.7, 124.0, 127.7, 127.8, 142.8, 148.5, 151.6, 152.4, 155.4, 163.7, 166.1. Anal. Calcd for $C_{22}H_{26}N_8SO_3$: C, 54.76; H, 5.43; N, 23.22. Found: C, 54.89; H, 5.25; N, 23.12. LC/MS: calcd *m*/*z* 483.19, found *m*/*z* 483.32.

***N*-[2-(4-(Benzo[*d*]isoxazol-3-yl)piperazino)ethyl]-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetamide (2):** This compound was obtained from **I** in 61% yield; mp 163–165°C; R_f = 0.31; ^{1}H NMR: δ 2.55 (t, ^3J = 6.0 Hz, 2H), 2.60–2.68 (m, 4H), 3.37 (s, 3H), 3.38–3.44 (m, 2H), 3.50–3.56 (m, 4H), 3.57 (s, 3H), 4.90 (s, 2H), 7.12–7.25 (m, 2H), 7.40–7.54 (m, 2H), 7.66 (d, ^3J = 8.0 Hz), 7.72 (s, 1H); ^{13}C NMR: δ 28.1, 29.9, 36.4, 48.2, 49.9, 52.1, 56.4, 106.7, 110.5, 116.0, 122.0, 122.4, 129.6, 142.3, 148.9, 151.5, 155.6, 161.1, 164.0, 165.6. Anal. Calcd for $C_{22}H_{26}N_8O_4$: C, 56.64; H, 5.62; N, 24.02. Found: C, 56.54; H, 5.29; N, 24.10. LC/MS: calcd *m*/*z* 467.21, found *m*/*z* 467.37.

***N*-[2-(4-(2,3-Dichlorophenyl)piperazino)ethyl]-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetamide (3):** This compound was obtained from **I** in 77% yield mp 222–223°C; R_f = 0.28; ^{1}H NMR: δ 2.44 (t, ^3J = 6.3 Hz, 2H), 2.49–2.59 (m, 4H), 2.82–2.96 (m, 4H), 3.21 (s, 3H), 3.24–3.28 (m, 2H), 3.41 (s, 3H), 4.81 (s, 2H), 6.72–6.87 (m, 1H), 6.96–7.07 (m, 2H), 7.60–7.70 (m, 2H); ^{13}C NMR: δ 27.7, 29.6, 36.2, 48.8, 50.7, 52.8, 56.5, 106.9, 118.4, 124.6, 127.2, 127.4, 133.8, 142.8, 148.4, 150.6, 151.6, 155.2, 166.2. Anal. Calcd for $C_{21}H_{25}N_7O_3Cl_2$: C, 51.02; H, 5.10; N, 19.83. Found: C, 51.20; H, 4.85; N, 19.91. LC/MS: calcd *m*/*z* 494.15, found *m*/*z* 494.29.

***N*-[3-(4-(Benzo[*d*]isothiazol-3-yl)piperazino)propyl]-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetamide (4):** This compound was obtained from **I** in 58% yield; mp 104–106°C; R_f = 0.40; ^{1}H NMR: δ 1.69–1.79 (m, 2H), 2.52–2.59 (m, 2H), 2.69–2.72 (m, 4H), 3.33–3.42 (m, 2H), 3.36 (s, 3H), 3.53–3.58 (m, 4H), 3.57 (s, 3H), 4.86 (s, 2H), 7.35 (ddd, ^3J = 8.4 Hz, ^3J = 6.9 Hz, ^4J = 1.0 Hz, 1H), 7.46 (ddd, ^3J = 8.5 Hz, ^3J = 6.9 Hz, ^4J = 1.0 Hz, 1H), 7.66–7.69 (m, 1H), 7.70 (s, 1H), 7.80 (dt, ^3J = 8.0 Hz, ^4J = 0.9 Hz, 1H), 7.87–7.90 (m, 1H); ^{13}C NMR: δ 25.1, 28.0, 29.8, 39.4, 49.8, 50.1, 53.0, 56.9, 106.8, 120.6, 123.8, 124.0, 127.6, 127.9, 142.4, 148.7, 151.5, 152.7, 155.5, 163.7, 165.4. Anal. Calcd for $C_{23}H_{28}N_8SO_3$: C, 55.56; H, 5.68; N, 22.56. Found: C, 55.32; H, 5.55; N, 22.51. LC/MS: calcd *m*/*z* 497.21, found *m*/*z* 497.35.

***N*-[3-(4-(2,3-Dichlorophenyl)piperazino)propyl]-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetamide (5):** This compound was obtained from **I** in 61% yield; mp 184–185°C; R_f = 0.25; ^{1}H NMR: δ 1.73 (quin, ^3J = 6.4 Hz, 2H), 2.52 (t, ^3J = 6.5 Hz, 2H), 2.28–2.77 (m, 4H), 2.99–3.21 (m, 4H), 3.34–3.40 (m, 2H), 3.38 (s, 3H), 3.58 (s, 3H), 4.87 (s, 2H), 6.98 (dd, ^3J = 6.7 Hz, ^4J = 3.1 Hz, 1H), 7.09–7.18 (m, 2H), 7.73 (s, 1H), 7.77–7.87 (m, 1H); ^{13}C NMR: δ 25.1, 28.0, 29.8, 39.4, 49.8, 51.3, 53.3, 56.7, 106.7, 118.6, 124.7, 127.4, 127.5, 134.0, 142.4, 148.9, 151.0, 151.5, 155.6, 165.3. Anal. Calcd for $C_{22}H_{27}N_7O_3Cl_2$: C, 51.97; H, 5.35; N, 19.29. Found: C, 51.81; H, 5.12; N, 19.19. LC/MS: calcd *m*/*z* 508.16, found *m*/*z* 508.32.

***N*-[4-(4-(Benzo[*d*]isothiazol-3-yl)piperazino)butyl]-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetamide (6):** This compound was obtained from **I** in 77% yield; mp 108–109°C; R_f = 0.28; ^{1}H NMR: δ 1.44–1.47 (m, 4H), 2.35 (t, ^3J = 7.2 Hz, 2H), 2.58–2.62 (m, 4H),

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3.23 (t, ^3J = 6.2 Hz, 2H), 3.24 (s, 3H), 3.43–3.46 (m, 4H), 3.45 (s, 3H), 4.82 (s, 2H), 7.25 (ddd, ^3J = 8.3 Hz, ^3J = 6.8 Hz, ^4J = 1.2 Hz, 1H), 7.37 (ddd, ^3J = 8.0 Hz, ^3J = 7.0 Hz, ^4J = 1.2 Hz, 1H), 7.50–7.52 (m, 1H), 7.67 (s, 1H), 7.68–7.69 (m, 1H), 7.78 (dd, ^3J = 6.8 Hz, ^4J = 1.2 Hz, 1H); ^{13}C NMR: δ 23.5, 26.8, 27.8, 29.6, 39.3, 48.8, 49.6, 52.7, 57.9, 106.9, 120.4, 123.7, 124.0, 127.6, 127.7, 142.9, 148.5, 151.6, 152.4, 155.3, 163.3, 166.0. Anal. Calcd for $C_{24}H_{30}N_8SO_3$: C, 56.45; H, 5.92; N, 21.94. Found: C, 56.55; H, 5.87; N, 21.81. LC/MS: calcd *m/z* 511.22, found *m/z* 511.37.

***N*-[4-(4-(Benzo[*d*]isoxazol-3-yl)piperazino)butyl]-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetamide (7):** This compound was obtained from **I** in 94% yield; mp 146–147°C; R_f = 0.38; ^{1}H NMR: δ 1.50–1.58 (m, 4H), 2.40 (t, ^3J = 6.9 Hz, 2H), 2.60–2.63 (m, 4H), 3.24–3.30 (m, 2H), 3.37 (s, 3H), 3.55–3.58 (m, 4H), 3.57 (s, 3H), 4.86 (s, 2H), 7.20 (ddd, ^3J = 8.1 Hz, ^3J = 6.4 Hz, ^4J = 1.7 Hz, 1H), 7.37 (t, ^3J = 5.4 Hz, 1H), 7.40–7.50 (m, 2H), 7.66–7.69 (m, 1H), 7.72 (s, 1H); ^{13}C NMR: δ 23.9, 27.1, 28.1, 29.9, 39.7, 48.1, 50.1, 52.4, 57.9, 106.7, 110.5, 116.1, 122.1, 122.3, 129.5, 142.5, 149.0, 151.4, 155.8, 161.2, 163.9, 165.5. Anal. Calcd for $C_{24}H_{30}N_8O_4$: C, 58.29; H, 6.11; N, 22.66. Found: C, 58.48; H, 6.05; N, 22.55. LC/MS: calcd *m/z* 495.25, found *m/z* 495.42.

***N*-[4-(4-(2,3-Dichlorophenyl)piperazino)butyl]-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6*H*)-yl)acetamide (8):** This compound was obtained from **I** in 50% yield; mp 167–169°C; R_f = 0.14; ^{1}H NMR: δ 1.54–1.58 (m, 4H), 2.44 (t, ^3J = 6.7 Hz, 2H), 2.55–2.73 (m, 4H), 3.00–3.15 (m, 4H), 3.27 (q, ^3J = 5.4 Hz, 2H), 3.39 (s, 3H), 3.59 (s, 3H), 4.86 (s, 2H), 6.96 (dd, ^3J = 6.5 Hz, ^4J = 3.2 Hz, 1H), 7.07–7.20 (m, 2H), 7.30–7.45 (m, 1H), 7.73 (s, 1H); ^{13}C NMR: δ 24.0, 27.1, 28.1, 29.9, 39.7, 50.1, 51.1, 53.2, 57.8, 106.6, 118.6, 124.7, 127.4, 127.5, 134.0, 142.4, 149.1, 151.1, 151.4, 155.8, 165.3. Anal. Calcd for $C_{23}H_{29}N_7O_3Cl_2$: C, 52.88; H, 5.60; N, 18.77. Found: C, 53.01; H, 5.38; N, 18.73. LC/MS: calcd *m/z* 522.18, found *m/z* 522.34.

***N*-[2-(4-(Benzo[*d*]isothiazol-3-yl)piperazino)ethyl]-2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetamide (9):** This compound was obtained from **II** in 69% yield; mp 235–237°C; R_f = 0.33; ^{1}H NMR: δ 2.54 (t, ^3J = 6.2 Hz, 2H), 2.64–2.67 (m, 4H), 3.34 (t, ^3J = 6.2 Hz, 2H), 3.43–3.46 (m, 4H), 3.47 (s, 3H), 3.87 (s, 3H), 4.59 (s, 2H), 7.28 (ddd, ^3J = 8.1 Hz, ^3J = 7.0 Hz, ^4J = 1.0 Hz, 1H), 7.39 (ddd, ^3J = 8.1 Hz, ^3J = 7.0 Hz, ^4J = 1.0 Hz, 1H), 7.50–7.52 (m, 2H), 7.73 (dt, ^3J = 8.1 Hz, ^4J = 1.0 Hz, 1H), 7.80 (dt, ^3J = 8.2 Hz, ^4J = 1.0 Hz, 1H); ^{13}C NMR: δ 29.7, 33.5, 35.8, 43.3, 49.6, 52.6, 56.7, 107.5, 120.5, 123.8, 124.1, 127.7, 127.8, 142.0, 148.9, 151.4, 152.4, 154.8, 163.7, 167.7. Anal. Calcd for $C_{22}H_{26}N_8SO_3$: C, 54.76; H, 5.43; N, 23.22. Found: C, 54.73; H, 5.22; N, 23.38. LC/MS: calcd *m/z* 483.19, found *m/z* 483.32.

***N*-[2-(4-(Benzo[*d*]isoxazol-3-yl)piperazino)ethyl]-2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetamide (10):** This compound was obtained from **II** in 41% yield; mp 208–210°C; R_f = 0.33; ^{1}H NMR: δ 2.60 (t, ^3J = 6.0 Hz, 2H), 2.67–2.70 (m, 4H), 3.44 (q, ^3J = 5.6 Hz, 2H), 3.53–3.56 (m, 4H), 3.57 (s, 3H), 3.96 (s, 3H), 4.70 (s, 2H), 6.35–6.45 (m, 1H), 7.22 (ddd, ^3J = 8.1 Hz, ^3J = 6.3 Hz, ^4J = 1.5 Hz, 1H), 7.41–7.54 (m, 3H), 7.66–7.69 (m, 1H); ^{13}C NMR: δ 29.8, 33.6, 35.9, 43.6, 48.2, 52.1, 56.4, 107.5, 110.5, 116.1, 122.1, 122.4, 129.6, 141.8, 149.2, 151.4, 154.8, 161.2, 164.0, 167.2. Anal. Calcd for $C_{22}H_{26}N_8O_4$: C, 56.64; H, 5.62; N, 24.02. Found: C, 56.58; H, 5.71; N, 23.92. LC/MS: calcd *m/z* 467.21, found *m/z* 467.37.

***N*-[2-(4-(2,3-Dichlorophenyl)piperazino)ethyl]-2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetamide (11):** This compound was obtained from **II** in 58% yield; mp 245–247°C; R_f = 0.28; ^{1}H NMR: δ 2.50 (t, ^3J = 6.3 Hz, 2H), 2.54–2.64 (m, 4H), 2.87–3.01 (m, 4H), 3.28–3.32 (m, 2H), 3.45 (s, 3H), 3.85 (s, 3H), 4.55 (s, 2H), 6.85 (dd, ^3J = 5.4 Hz, ^4J = 4.1 Hz, 1H), 6.97–7.10 (m, 2H), 7.51–7.53 (m, 2H); ^{13}C NMR: δ 29.6, 33.4, 36.0, 43.2, 50.8, 52.9, 56.6, 107.5, 118.5, 124.7, 127.3, 127.4, 133.9, 142.0, 148.7, 150.7, 151.4, 154.8, 167.7. Anal. Calcd for $C_{21}H_{25}N_7O_3Cl_2$: C, 51.02; H, 5.10; N, 19.83. Found: C, 51.12; H, 5.19; N, 19.69. LC/MS: calcd *m/z* 494.15, found *m/z* 494.29.

***N*-[3-(4-(2,3-Dichlorophenyl)piperazino)propyl]-2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetamide (12):** This compound was obtained from **II** in 75% yield; mp 222–224°C; R_f = 0.30; ^{1}H NMR: δ 1.68 (quin, ^3J = 6.9 Hz, 2H), 2.46 (t, ^3J = 7.0 Hz, 2H), 2.54–2.72 (m, 4H), 2.92–3.09 (m, 4H), 3.27 (t, ^3J = 6.4 Hz, 2H), 3.48 (s, 3H), 3.89 (s, 3H), 4.56 (s, 2H), 6.88 (dd, ^3J = 6.2 Hz, ^4J = 3.3 Hz, 1H), 7.05–7.10 (m, 2H), 7.51–7.53 (m, 2H); ^{13}C NMR: δ 25.3, 29.7, 33.5, 38.2, 43.3, 50.9, 53.0, 56.1, 107.5, 118.5, 124.7, 127.3, 127.5, 133.9, 141.9, 148.9, 150.7, 151.5, 154.8, 167.6. Anal. Calcd for $C_{22}H_{27}N_7O_3Cl_2$: C, 51.97; H, 5.35; N, 19.29. Found: C, 52.05; H, 5.21; N, 19.11. LC/MS: calcd *m/z* 508.16, found *m/z* 508.32.

***N*-[4-(4-(Benzo[*d*]isothiazol-3-yl)piperazino)butyl]-2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetamide (13):** This compound was obtained from **II** in 57% yield; mp 183–185°C; R_f = 0.24; ^{1}H NMR: δ 1.58–1.64 (m, 4H), 2.45–2.49 (m, 2H), 2.68–2.71 (m, 4H), 3.29–3.35 (m, 2H), 3.56 (s, 3H), 3.56–3.59 (m, 4H), 3.95 (s, 3H), 4.65 (s, 2H), 6.45–6.49 (m, 1H), 7.33–7.36 (m, 1H), 7.45 (ddd, ^3J = 8.1 Hz, ^3J = 7.0 Hz, ^4J = 1.7 Hz, 1H), 7.50 (s, 1H), 7.78–7.81 (m, 1H), 7.86–7.90 (m, 1H); ^{13}C NMR: δ 24.1, 27.2, 29.8, 33.6, 39.5, 43.6, 49.9, 52.9, 57.9, 107.5, 120.5, 123.8, 123.9, 127.5, 127.9, 141.7, 149.1, 151.4, 152.7, 154.8, 163.8, 167.1. Anal. Calcd for $C_{24}H_{30}N_8SO_3$: C, 56.45; H, 5.92; N, 21.94. Found: C, 56.63; H, 5.99; N, 21.83. LC/MS: calcd *m/z* 511.22, found *m/z* 511.37.

***N*-[4-(4-(Benzo[*d*]isoxazol-3-yl)piperazino)butyl]-2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetamide (14):** This compound was obtained from **II** in 60% yield; mp 163–165°C; R_f = 0.34; ^{1}H NMR: δ 1.57–1.51 (m, 4H), 2.44 (t, ^3J = 6.4 Hz, 2H), 2.63–2.67 (m, 4H), 3.28–3.34 (m, 2H), 3.55 (s, 3H), 3.58–3.60 (m, 4H), 3.94 (s, 3H), 4.64 (s, 2H), 6.45 (t, ^3J = 5.3 Hz, 1H), 7.20 (ddd, ^3J = 8.1 Hz, ^3J = 6.4 Hz, ^4J = 1.7 Hz, 1H), 7.40–7.48 (m, 2H), 7.50 (s, 1H), 7.67 (d, ^3J = 8.0 Hz, 1H); ^{13}C NMR: δ 24.0, 27.2, 29.8, 33.6, 39.5, 43.6, 48.1, 52.4, 57.9, 107.5, 110.4, 116.1, 122.1, 122.3, 129.5, 141.7, 149.1, 151.5, 154.8, 161.2, 163.9, 167.2. Anal. Calcd for $C_{24}H_{30}N_8O_4$: C, 58.29; H, 6.11; N, 22.66. Found: C, 58.14; H, 6.11; N, 22.71. LC/MS: calcd *m/z* 495.25, found *m/z* 495.42.

***N*-[4-(4-(2,3-Dichlorophenyl)piperazino)butyl]-2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetamide (15):** This compound was obtained from **II** in 18% yield; mp 214–216°C; R_f = 0.16; ^{1}H NMR: δ 1.48–1.55 (m, 4H), 2.42 (t, ^3J = 7.2 Hz, 2H), 2.55–2.75 (m, 4H), 2.94–3.11 (m, 4H), 3.21 (t, ^3J = 6.2 Hz, 2H), 3.49 (s, 3H), 3.90 (s, 3H), 4.58 (s, 2H), 6.91 (dd, ^3J = 6.2 Hz, ^4J = 3.3 Hz, 1H), 7.03–7.13 (m, 2H), 7.52–7.55 (m, 2H); ^{13}C NMR: δ 23.6, 27.0, 29.7, 33.5, 39.1, 43.2, 50.7, 53.0, 57.8, 107.5, 118.6, 124.7, 127.3, 127.5, 133.9, 141.9, 148.9, 150.8, 151.49, 154.9, 167.5. Anal. Calcd for $C_{23}H_{29}N_7O_3Cl_2$: C, 52.88; H, 5.60; N, 18.77. Found: C, 52.95; H, 5.44; N, 18.62. LC/MS: calcd *m/z* 522.18, found *m/z* 522.34.

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