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SYNTHESIS OF NOVEL 3,7-DIHYDRO-PURINE-2,6-DIONE DERIVATIVES

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CytRx Corporation, San Diego, California, USA

Forty-six novel 3,7-dihydro-purine-2,6-dione derivatives (substituted xanthines) with great structural diversity were synthesized for biological activity screening. Three series of substituted xanthine analogs have been prepared in moderate to excellent yields.

Keywords: Analog synthesis for biological screening; 3,7-dihydro-purine-2,6-dione derivatives; substituted xanthines; xanthine derivatives

3,7-Dihydro-purine-2,6-dione derivatives (also known as substituted xanthines) constitute an important class of pharmacologically active compounds with well-known activities as phosphodiesterase inhibitors, cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel activators, and adenosine receptor antagonists.[1] In recent years, the spectrum of clinical applications of the xanthines has continued to widen and presently includes their use as anticonvulsants,[2] nootropics,[3] oral drugs for treating asthma,[4] DPP-4 inhibitors for treatment of type 2 diabetes,[5] and therapeutics for the treatment of migraines and illnesses where underactivation of the HM74A receptor contributes to the disease.[6] In addition, they are also found in nature, such as theobromine in cocoa and caffeine in coffee and tea.[4] Therefore, novel xanthine analog synthesis continues to attract scientists' interest in the drug discovery field.

In the course of our research to develop novel small-molecule chaperone amplifiers to treat neurodegenerative diseases, we became very interested in the design and synthesis of a large number of novel analogs of 3,7-dihydro-purine-2,6-dione derivatives (**1**) (Fig. 1) for our high-throughput biological screening to identify initial hits.

There are a number of reported methods to prepare xanthine derivatives **1**.[7–9] We used modified literature methods (Schemes 1–3) to synthesize a variety of 3,7-dihydro-purine-2,6-dione derivatives (Tables 1 and 2). To the best of our knowledge, the majority of these analogs (46 out of 54) are novel compounds.

The first series of xanthine analogs we synthesized are the ones containing substituents at N-1, N-3, and N-7 positions where $R^1 = R^2$ by applying the method

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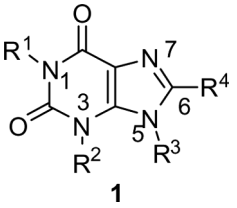
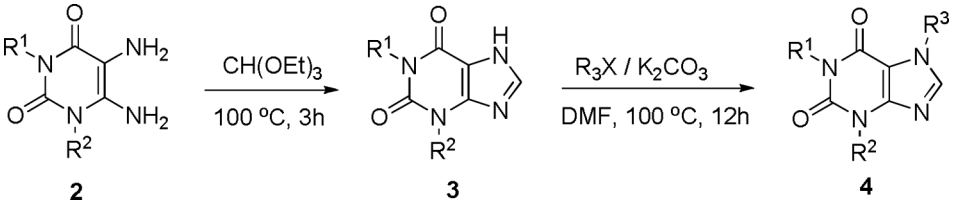


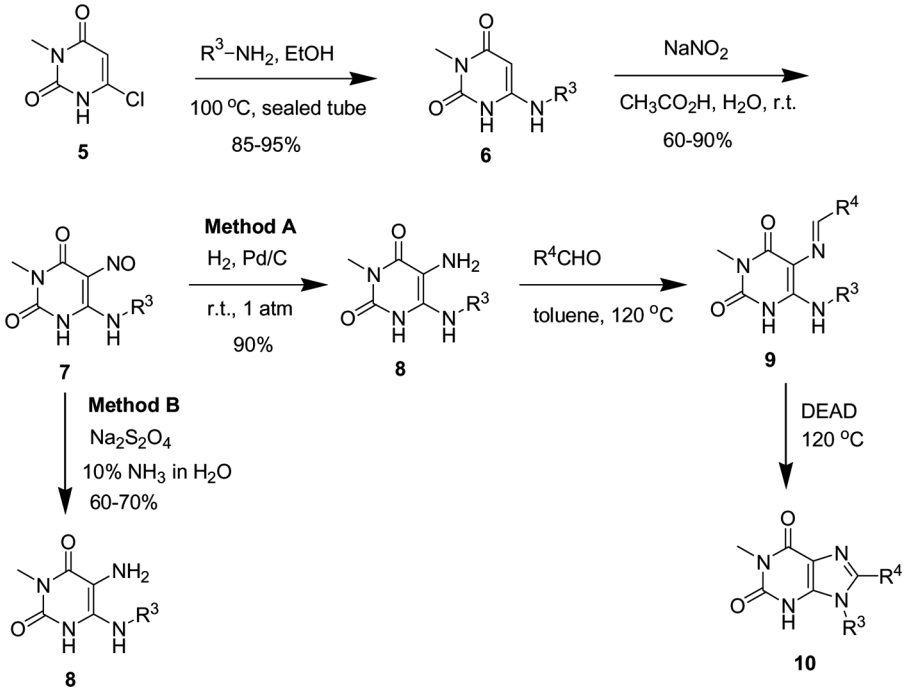
1

Figure 1. 3,7-Dihydro-purine-2,6-dione derivatives.



2 **3** **4**

Scheme 1. Synthesis of 3,7-dihydro-purine-2,6-dione derivatives **4**.



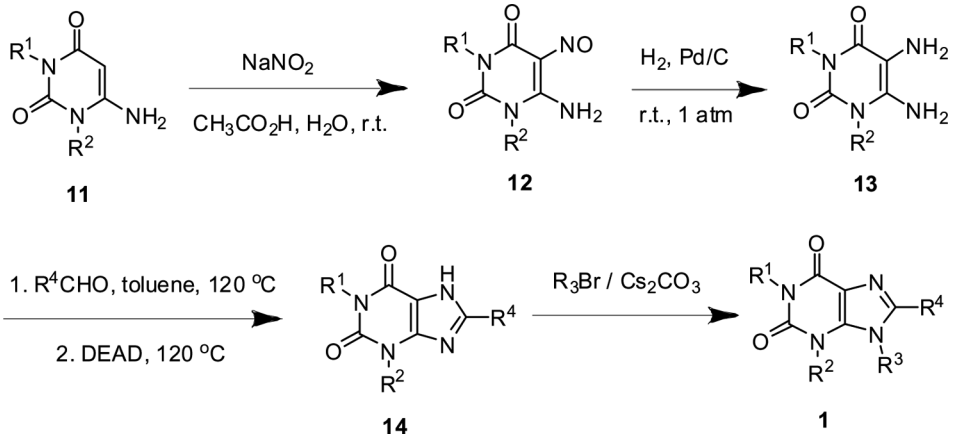
5 **6** **7** **8** **9** **8** **10**

Scheme 2. Synthesis of 3,7-dihydro-purine-2,6-dione derivatives **10**.

described in Scheme 1. The commercially available 1,3-dialkyl-5,6-diaminouracils **2** were treated with triethylorthoformate (also as solvent) under heating to provide the key intermediates **3** in good yields.[10,11] Alkylation of the key intermediates **3** at N-7 or N-5 positions by treatment with alkyl halides in the presence of a base gave the desired 3,7-dihydro-purine-2,6-dione derivatives **4** with good yields (Table 1). Overall, the synthesis was very straightforward with good yields, and the majority of the analogs in this series are novel compounds.

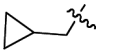
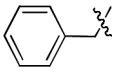
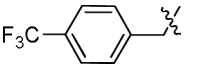
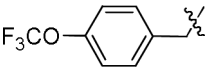
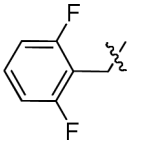
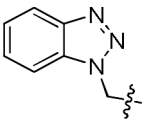
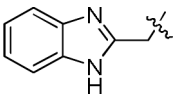
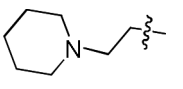
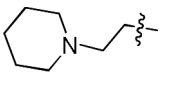
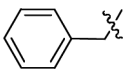
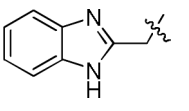
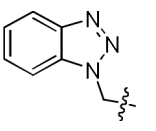
Another series of xanthine analogs substituents at N-1, N-5, and C-6 positions (compounds **10**) as shown in Scheme 2. In this case, the commercially available 6-chloro-3-methyluracil (**5**) was used as a common starting material. The analog syntheses were routinely carried out first with nucleophilic displacement of the chlorine in **5** by primary amines (excess) under heating in sealed tubes[12] to form **6**, followed by the nitroso formation with the treatment of $NaNO_2$ in acidic conditions at room temperature to afford the key intermediates **7** in good yields for both steps.[7,8,13] To reduce the nitroso moiety to an amino group, we first tried hydrogenation using Pd/C catalyst (method A), which worked for the majority of the substrates with good yields.[8,12] However, this method failed for some of the substrates of **7** where R^3 = cyclopropylmethylene, 3,3-dimethylbutyl, benzyl, or 3-dimethylaminopropyl groups. Instead, we found that $Na_2S_2O_4$ could successfully reduce the nitroso moiety present in these substrates **7** to an amino group, affording desired products **8** in fairly good yields (method B).[9] The next step, imine formation, occurred selectively at the nonsubstituted amino group, leading to **9** with the treatment of aldehydes under heating. Finally, the cyclization in the presence of diethyl azodicarboxylate (DEAD) (40% in toluene) at high temperature completed the synthesis to give the desired xanthine derivatives **10**.[9] The overall isolated yields for the last two steps were 30–50% (10a1–10g3, Table 2).

We followed a reaction sequence similar to the previous one and used **11** as the starting material to assemble the xanthine derivatives **14** substituted at N-1, N-3, and C-6 positions (Scheme 3).[9] The yields for the synthesis of **14** (**14a–c**) were similar to those of **10**, as shown in Table 2. Finally, alkylation of **14** at N-5 or N-7 by alkyl



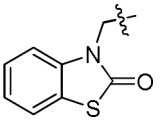
Scheme 3. Synthesis of 3,7-dihydro-purine-2,6-dione derivatives **14** and **1**.

Table 1. Synthesis of 3,7-dihydro-purine-2,6-dione derivatives (**3a, 4a–p**)

Compound	R^1	R^2	R^3	Yield (%)[a]
3a	n-Pr	n-Pr	H	86
4a	n-Pr	n-Pr	Me	90
4b	n-Pr	n-Pr	Et	89
4c	n-Pr	n-Pr		85
4d	n-Pr	n-Pr		95
4e	n-Pr	n-Pr		95
4f	n-Pr	n-Pr		90
4g	n-Pr	n-Pr		90
4h	n-Pr	n-Pr		84
4i	n-Pr	n-Pr		80
4j	n-Pr	n-Pr		82
4k	n-Pr	n-Pr		90
4l	Me	Me		85
4m	Me	Me		95
4n	Me	Me		80
4o	Me	Me		80

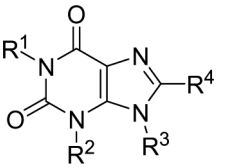
(*Continued*)

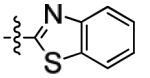
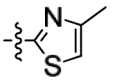
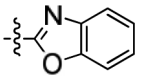
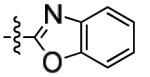
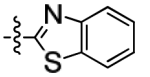
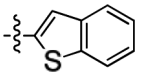
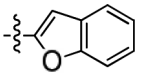
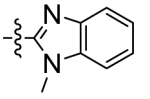
Table 1. Continued

Compound	R^1	R^2	R^3	Yield (%)[a]
4p	Me	Me		75

[a]Isolated yield for the last step.

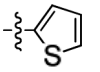
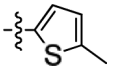
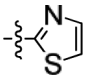
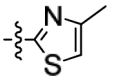
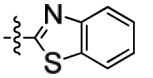
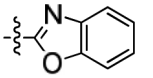
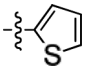
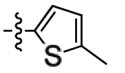
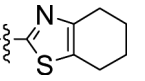
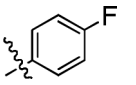
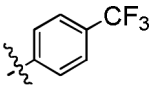
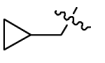
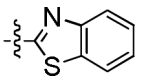
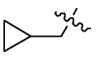
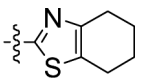
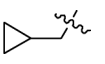
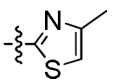
Table 2. Synthesis of 3,7-dihydro-purine-2,6-dione derivatives (**10, 14,** and **1**)



Compound	R^1	R^2	R^3	R^4	Yield (%)[a]
10a1	Me	H	Et		45
10a2	Me	H	Et		47
10a3	Me	H	Et		40
10b1	Me	H	n-Pr		40
10b2	Me	H	n-Pr		43
10b3	Me	H	n-Pr		38
10b4	Me	H	n-Pr		42
10b5	Me	H	n-Pr		35

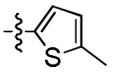
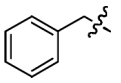
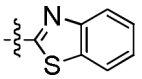
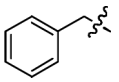
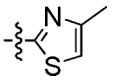
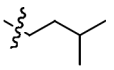
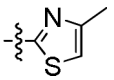
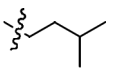
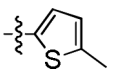
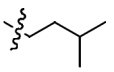
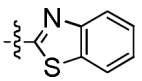
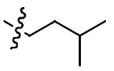
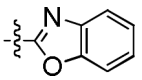
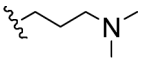
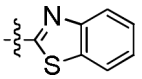
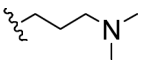
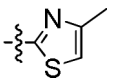
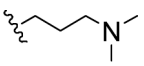
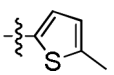
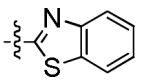
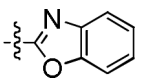
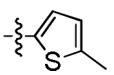
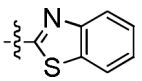
(*Continued*)

Table 2. Continued

Compound	R^1	R^2	R^3	R^4	Yield (%)[a]
10b6	Me	H	n-Pr		44
10b7	Me	H	n-Pr		46
10b8	Me	H	n-Pr		42
10b9	Me	H	n-Pr		45
10c1	Me	H	n-Bu		42
10c2	Me	H	n-Bu		40
10c3	Me	H	n-Bu		39
10c4	Me	H	n-Bu		42
10c5	Me	H	n-Bu		34
10c6	Me	H	n-Bu		30
10c7	Me	H	n-Bu		32
10c8	Me	H	n-Bu		35
10d1	Me	H			50
10d2	Me	H			34
10d3	Me	H			42

(*Continued*)

Table 2. Continued

Compound	R^1	R^2	R^3	R^4	Yield (%)[a]
10d4	Me	H			44
10e1	Me	H			46
10e2	Me	H			48
10f1	Me	H			41
10f2	Me	H			42
10f3	Me	H			45
10f4	Me	H			39
10g1	Me	H			32
10g2	Me	H			30
10g3	Me	H			35
14a	n-Pr	n-Pr	H		44
14b	n-Pr	n-Pr	H		39
14c	n-Pr	n-Pr	H		45
1a	n-Pr	n-Pr	n-Bu		79

[a]Isolated yield for the last two steps.

bromides in the presence of cesium carbonate led to the fully substituted xanthines **1** in good yields as shown in Scheme 3.

In conclusion, three series of 3,7-dihydro-purine-2,6-dione derivatives including partially or fully substituted analogs (substituted xanthines) have been made in moderate to good yields using three different methods. The majority of these substituted xanthines are novel compounds. The substituents at C-6 can vary quite bit, including alkyl, phenyl, and heterocycle moieties, yet they do not seem to affect the yields, indicating potentially broad applications of the synthetic methods. These novel compounds described here, along with their ease in synthesis, could be of interest to the scientists working in drug discovery research.

EXPERIMENTAL

Unless otherwise stated, all reactions were performed under an inert atmosphere with anhydrous reagents, solvents, and oven-dried glassware. All starting materials were purchased from Aldrich, Sigma, Fisher, or Lancaster and were used as received. Anhydrous solvents purchased from EMD were used directly without additional treatment. Preparative thin-layer chromatography (TLC) was performed using Merck (0.25, 0.5, or 1 mm) coated silica-gel Kieselgel 60 F254 plates. ^{1}H NMR spectra were recorded on Bruker AMX-500 (500-MHz) or AMX-400 (400-MHz) spectrometers, and chemical shifts are reported in parts per million (δ) using internal solvent signals as references. Coupling constants are reported in hertz (Hz).

Synthesis of 1,3-Dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (3a)[14]

1,3-Dipropyl-5,6-diaminouracil (**2a**, R^1 = n-Pr) (2 g, 8.83 mmol) was dissolved in triethylorthoformate (15 mL), and the mixture was heated to 100 °C for 3 h. The solvent was concentrated in vacuo to furnish 1,3-dipropylxanthine as key intermediate **3a** (R^1 = n-Pr) (1.8 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, J = 6.9 Hz, 6H), 1.64–1.70 (m, 2H), 1.74–1.84 (m, 2H), 4.05 (t, J = 8.0 Hz, 2H), 4.12 (t, J = 8.0 Hz, 2H), 7.79 (s, 1H), 12.60 (s, 1H,). LC-MS (ESI^+) m/z = 237.2 $[M + H]^+$.

Synthesis of 7-Methyl-1,3-dipropyl-3,7-dihydro-purine-2,6-dione (4a)[15]

K_2CO_3 (0.207 mg, 1.5 mmol) was added to a solution of 1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**3a**) (118 mg, 0.5 mmol) in dimethylformamide (DMF), followed by methyl iodide (78 mg, 0.55 mmol), and the reaction mixture was heated at 100 °C for 12 h. The solid (K_2CO_3) was filtered off, concentrated in vacuo, purified by normal phase chromatography on silica gel (with an automated system: ISCO) using a gradient (EtOAc/hexane = 1:3) to afford the methylated derivative **4a** (113 mg, 90%). Mp = 114–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, J = 7.4 Hz, 6H); 1.62–1.71 (m, 2H), 1.74–1.80 (m, 2H), 3.94–3.97 (m, 5H), 4.05 (t, J = 8.1 Hz, 2H), 7.48 (s, 1H). LC-MS (ESI^+) m/z = 251.2 $[M + H]^+$.

The following compounds were prepared according to the method described for the synthesis of compound **4a** using appropiate starting materials.

7-Ethyl-1,3-dipropyl-3,7-dihydro-purine-2,6-dione (4b)

ISCO purification gradient: 40% EtOAc in hexane; a white solid; yield: 89%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93–0.98 (m, 6H), 1.53 (t, $J = 6.4$ Hz, 3H), 1.64–1.70 (m, 2H), 1.78–1.81 (m, 2H), 3.96 (t, $J = 8.2$ Hz, 2H), 4.05 (t, $J = 8.1$ Hz, 2H), 4.34 (t, $J = 8.2$ Hz, 2H), 7.53 (s, 1H). LC-MS (ESI$^+$) $m/z = 265.2$ $[M + H]^+$.

7-Allyl-1,3-dipropyl-3,7-dihydro-purine-2,6-dione (4c)[15]

ISCO purification gradient: 35% EtOAc in hexane; a yellow solid; yield: 85%; mp = 58–61 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87–0.98 (m, 6H), 1.53 (t, $J = 7.8$ Hz, 3H), 1.64–1.69 (m, 2H), 1.75–1.81 (m, 2H), 3.96 (t, $J = 8.2$ Hz, 2H), 4.05 (t, $J = 7.9$ Hz, 2H), 4.34 (t, $J = 8.2$ Hz, 2H), 4.93 (d, $J = 6.8$ Hz, 2H), 5.24–5.30 (m, 2H), 6.01–6.08 (m, 1H), 7.54 (s, 1H). LC-MS (ESI$^+$) $m/z = 277.2$ $[M + H]^+$.

7-Cyclopropylmethyl-1,3-dipropyl-3,7-dihydro-purine-2,6-dione (4d)

ISCO purification gradient: 35% EtOAc in hexane; a yellow solid; yield: 95%; mp = 95–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.41–0.44 (m, 2H), 0.63–0.67 (m, 2H), 0.87–0.99 (m, 6H), 1.37–1.42 (m, 1H), 1.62–1.70 (m, 2H), 1.71–1.83 (m, 2H), 3.96 (t, $J = 7.8$ Hz, 2H), 4.06 (t, $J = 8.1$ Hz, 2H), 4.16 (d, $J = 6.8$ Hz, 2H), 7.62 (s, 1H). LC-MS (ESI$^+$) $m/z = 291.1$ $[M + H]^+$.

7-Benzyl-1,3-dipropyl-3,7-dihydro-purine-2,6-dione (4e)[16]

ISCO purification gradient: 35% EtOAc in hexane; a yellow solid; yield: 95%; mp = 96–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85–0.99 (m, 6H), 1.64–1.70 (m, 2H), 1.74–1.81 (m, 2H), 3.96 (t, $J = 7.8$ Hz, 2H), 4.09 (t, $J = 7.9$ Hz, 2H), 5.54 (s, 2H), 7.20–7.41 (m, 5H), 7.83 (s, 1H). LC-MS (ESI$^+$) $m/z = 327.2$ $[M + H]^+$.

7-(4-Trifluoromethylbenzyl)-1,3-dipropyl-3,7-dihydro-purine-2,6-dione (4f)

ISCO purification gradient: 25% EtOAc in hexane; a yellow solid; yield: 90%; mp = 128–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87–1.00 (m, 6H), 1.62–1.67 (m, 2H), 1.76–1.81 (m, 2H), 3.94 (t, $J = 7.8$ Hz, 2H), 4.10 (t, $J = 7.6$ Hz, 2H), 5.60 (s, 2H), 7.51 (d, $J = 6.8$ Hz, 2H), 7.62 (d, $J = 6.4$ Hz, 2H), 7.97 (s, 1H). LC-MS (ESI$^+$) $m/z = 395.2$ $[M + H]^+$.

7-(4-Trifluoromethoxybenzyl)-1,3-dipropyl-3,7-dihydro-purine-2,6-dione (4g)

ISCO purification gradient: 25% EtOAc in hexane; a yellow solid; yield: 90%; mp = 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87–0.99 (m, 6H), 1.63–1.69 (m, 2H), 1.75–1.82 (m, 2H), 3.95 (t, $J = 7.9$ Hz, 2H), 4.06 (t, $J = 7.8$ Hz, 2H), 5.51 (s, 2H), 7.25 (d, $J = 6.8$ Hz, 2H), 7.47 (d, $J = 6.8$ Hz, 2H), 7.78 (s, 1H). LC-MS (ESI$^+$) $m/z = 411.1$ $[M + H]^+$.

7-(2,6-Difluorobenzyl)-1,3-dipropyl-3,7-dihydro-purine-2,6-dione (4h)

ISCO gradient: 25% EtOAc in hexane; a white solid; yield: 84%; mp = 156–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88–0.99 (m, 6H), 1.64–1.71 (m, 2H), 1.75–1.82 (m, 2H), 3.98 (t, $J = 7.9$ Hz, 2H), 4.07 (t, $J = 7.9$ Hz, 2H), 5.68 (s, 2H), 6.95 (t, $J = 6.4$ Hz, 1H), 7.43 (d, $J = 6.8$ Hz, 2H), 7.54 (s, 1H). LC-MS (ESI^+) $m/z = 363.2$ $[M + H]^+$.

7-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (4i)

ISCO purification gradient: 50% EtOAc in hexane; a yellow solid; yield: 80%; mp = 179–181 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80–0.99 (m, 6H), 1.60–1.69 (m, 2H), 1.76–1.80 (m, 2H), 3.90 (t, $J = 7.9$ Hz, 2H), 4.10 (t, $J = 7.9$ Hz, 2H), 5.60 (s, 2H), 6.99 (t, $J = 6.4$ Hz, 2H), 7.40 (d, $J = 7.4$ Hz, 2H), 7.50 (s, 1H). LC-MS (ESI^+) $m/z = 368.2$ $[M + H]^+$.

7-((1*H*-Benz[*d*]imidazo-Yl)methyl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7h)-dione (4j)[17]

ISCO purification gradient: 50% EtOAc in hexane; a yellow solid; yield: 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (t, $J = 7.6$ Hz, 3H), 0.99 (t, $J = 7.9$ Hz, 3H), 1.70–1.78 (m, 4H), 4.03–4.10 (m, 4H), 5.66 (s, 2H), 7.02 (t, $J = 6.2$ Hz, 2H), 7.42 (d, $J = 7.2$ Hz, 2H), 7.56 (s, 1H). LC-MS (ESI^+) $m/z = 367.2$ $[M + H]^+$.

7-(2-(Piperidine-1yl)ethyl)-1,3-dipropyl-3,7-dihydro-purine-2,6-dione (4k)[16]

ISCO purification gradient: 40% EtOAc in hexane; a yellow solid; yield: 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84–0.99 (m, 6H), 1.63–2.20 (m, 10H), 2.60–2.67 (m, 4H), 2.91–2.97 (m, 2H), 3.95 (t, $J = 7.8$ Hz, 2H), 4.06 (t, $J = 7.5$ Hz, 2H), 4.60 (t, $J = 7.6$ Hz, 2H), 7.67 (s, 1H). LC-MS (ESI^+) $m/z = 348.3$ $[M + H]^+$.

7-(2-(Piperidine-1yl)ethyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (4l)

ISCO purification gradient: 45% EtOAc in hexane; a yellow solid; yield: 85%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41–1.59 (m, 10H), 2.74 (t, $J = 6.8$ Hz, 2H), 3.39 (s, 3H), 3.57 (s, 3H), 4.42 (t, $J = 7.8$ Hz, 2H), 7.69 (s, 1H). LC-MS (ESI^+) $m/z = 292.2$ $[M + H]^+$.

7-Benzyl-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (4m)[15]

ISCO purification gradient: 35% EtOAc in hexane; a white solid; yield: 95%; mp = 154–157 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.41 (s, 3H), 3.61 (s, 3H), 5.52 (s, 2H), 7.33–7.39 (m, 5H), 7.66 (s, 1H). LC-MS (ESI^+) $m/z = 271.1$ $[M + H]^+$.

7-((1*H*-Benz[d]imidazo-yl)methyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (4n)

ISCO purification gradient: 45% EtOAc in hexane; a white solid; yield: 80%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.50 (s, 3H), 3.57 (s, 3H), 6.07 (s, 2H), 7.44 (t, $J = 6.2$ Hz, 2H), 7.72 (d, $J = 7.4$ Hz, 2H), 8.26 (s, 1H). LC-MS (ESI^+) $m/z = 311.2$ $[M + H]^+$.

7-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (4o)

ISCO purification gradient: 45% EtOAc in hexane; a white solid; yield: 80%; mp = 158–162 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.21 (s, 3H), 3.39 (s, 3H), 6.00 (s, 2H), 7.46 (t, $J = 7.6$ Hz, 1H), 7.66 (t, $J = 6.4$ Hz, 1H), 8.07 (d, $J = 7.4$ Hz, 1H), 8.13 (d, $J = 7.6$ Hz, 1H), 8.53 (s, 1H), LC-MS (ESI^+) $m/z = 312.0$ $[M + H]^+$.

7-((2-Oxobenzo[*d*]thiazol-3(2*H*)-yl)methyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (4p)

ISCO purification gradient: 50% EtOAc in hexane; a yellow solid; yield: 75%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.26 (s, 3H), 3.41 (s, 3H), 6.45 (s, 2H), 7.25 (t, $J = 6.4$ Hz, 2H), 7.39 (d, $J = 7.4$ Hz, 1H), 7.70 (d, $J = 6.4$ Hz, 1H), 8.16 (s, 1H), LC-MS (ESI^+) $m/z = 344.0$ $[M + H]^+$.

General Procedure for the Synthesis of Compounds 6

An amine (R^3-NH_2, 30 mmol) [3 eq. of diisopropylethyl amine (DIPEA) needed if R^3-$NH_2 \cdot HCl$ was used] was added to a solution of 6-chloro-3-methyluracil (**5**) (10 mmol) in ethanol (15 mL) in a sealed tube. The mixture was stirred at room temperature for 10 min, and then heated to 100–110 °C with stirring overnight. The reaction mixture was cooled to room temperature, concentrated, treated with water, filtered, washed with 50% MeOH in water, and dried under high vacuum to give **6** as a solid. All the desired products were confirmed by liquid chromatography–mass spectrometry (LC-MS) analysis. Isolated yields were 85–95%.

General Procedure for the Synthesis of Compounds 7

$NaNO_2$ (11 mmol in 10 mL H_2O) was slowly added to a solution of compound **6** (10 mmol) in 50% of CH_3COOH in H_2O (40 mL for R^3 = alkyl group, 100 mL for R^3 = aryl group) over 30 min. The mixture was stirred at room temperature for 3–6 h. The reaction mixture turned to orange, then red, and a precipitation formed, which was filtered, washed with water, dried, treated with methanol, and filtered to give **7** (yield: 60–80%). All the desired products were confirmed by LC-MS analysis. Compounds **12** were made in a similar way.

General Procedure for the Synthesis of Compounds 8

Method A. Compound **7** (2 g) (for R^3 = H, Et, *n*-Pr, *i*-Pr, *n*-Bu) was dissolved in methanol (200 mL), and 10% Pd/C (0.2 g) was added under an N_2 atmosphere.

The mixture was stirred under H_2 via an H_2 balloon overnight. The reaction mixture turned to a clear solution, which was filtered quickly through celite, washed with methanol, concentrated under reduced pressure, and dried under high vacuum to give **8** (yield $>90\%$). All the products were confirmed by LC-MS analysis. Compounds **13** were made in a similar way.

Method B. $Na_2S_2O_4$ (3eq.) was added to a mixture of compound **7** (2 g) (for $R^3 = 3,3$-dimethylpropyl, 3-dimethylaminopropyl, cyclopropylmethylene, benzyl) in 10% NH_3 in H_2O (40 mL). The reaction mixture was heated to 65 °C for 3 h. After removal of the solvent, dichloromethane (DCM) and water were added, and then the separated organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and dried under high vacuum to give **8** (yield: 60–70%). All the products were confirmed by LC-MS analysis.

General Procedure for the Synthesis of Compounds 9 and 10

An aldehyde (R^4-CHO, 1.5 eq.) was added to a mixture of compound **8** (150 mg) in toluene (1 mL). The resulting mixture was heated to 110 °C with stirring in a sealed tube for 1 h to form imine intermediate **9**. The mixture containing **9** was cooled to room temperature, and 40% DEAD in toluene (3 eq.) was added. The reaction mixture was heated to 120–130 °C for 3–4 h. After cooling to room temperature, the precipitate (for $R^4 = Ar$) was filtered, washed with methanol, and dried to give **10** (crude yield: 60–70% for two steps), which was further purified by recrystalization from DMF/ethanol to give pure **10** (isolated yield for two steps: 30–50%; purity: >90%). Compounds **14** were made in a similar way.

Procedure for the Synthesis of Compound 1a

Compound **14a** (55 mg, 0.15 mmol) was dissolved in DMF (0.5 mL) in a sealed tube. Cs_2CO_3 (97.5 g, 0.3 mmol) and BuBr (62 mg, 0.45 mmol) were added. The mixture was heated at 100 °C for 3 h. TLC confirmed the completion of the reaction. Methylene chloride was added, then washed with water and brine. The separated organic layer was dried over anhydrous Na_2SO_4, concentrated, and recrystallized from EtOH to give **1a** (50 mg, 79% yield). ^{1}H NMR (DMSO-d_6): δ 0.87 (t, 3H, $J = 6.0$ Hz), 0.92 (m, 6H), 1.38 (m, 2H), 1.57 (m, 2H), 1.74 (m, 2H), 1.84 (m, 2H), 3.85 (t, 2H, $J = 6.0$ Hz), 3.98 (t, 2H, $J = 6.0$ Hz), 4.98 (t, 2H, $J = 6.0$ Hz), 7.54 (t, 1H, $J = 5.6$ Hz), 7.60 (t, 1H, $J = 5.6$ Hz), 8.10 (d, 1H, $J = 6.4$ Hz), 8.18 (d, 1H, $J = 6.4$ Hz). LC-MS (ESI^+) $m/z = 426$ $[M + H]^+$.

The following compounds were prepared according to the method described for the synthesis of compounds **10** using appropiate starting materials.

8-(Benzo[*d*]thiazol-2-yl)-9-ethyl-1-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10a1)

^{1}H NMR (DMSO-d_6): δ 1.39 (t, 3H, $J = 6.0$ Hz), 3.23 (s, 3H), 4.74 (dd, 2H, $J = 6.0$ Hz), 7.50 (t, 1H, $J = 7.0$ Hz), 7.57 (t, 1H, $J = 7.0$ Hz), 8.04 (d, 1H, $J = 6.4$ Hz), 8.16 (d, 1H, $J = 6.4$ Hz), 12.6 (s, 1H). LC-MS (ESI^+) $m/z = 328.2$ $[M + H]^+$.

9-Ethyl-1-methyl-8-(4-methylthiazol-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10a2)

^{1}H NMR (DMSO-d$_6$): δ 1.31 (t, 3H, $J = 6.0$ Hz), 2.43 (s, 3H), 3.21 (s, 3H), 4.74 (t, 2H, $J = 5.6$ Hz), 7.42 (s, 1H), 12.5 (s, 1H). LC-MS (ESI$^+$) $m/z = 292.2$ $[M + H]^+$.

8-(Benzo[*d*]oxazol-2-yl)-9-ethyl-1-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10a3)

^{1}H NMR (DMSO-d$_6$): δ 1.39 (t, 3H, $J = 6.0$ Hz), 3.22 (s, 3H), 4.74 (dd, 2H, $J = 5.6$ Hz), 7.48 (m, 2H), 7.82 (d, 1H, $J = 6.4$ Hz), 7.87 (d, 1H, $J = 6.4$ Hz), 12.62 (s, 1H). LC-MS (ESI$^+$) $m/z = 312.2$ $[M + H]^+$.

8-(Benzo[*d*]oxazol-2-yl)-1-methyl-9-propyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10b1)

^{1}H NMR (DMSO-d$_6$): δ 0.92 (t, 3H, $J = 6.0$ Hz), 1.81 (m, 2H), 3.23 (s, 3H), 4.60 (t, 2H, $J = 6.0$ Hz), 7.48 (m, 2H), 7.85 (m, 2H), 12.63 (s, 1H). LC-MS (ESI$^+$) $m/z = 326.5$ $[M + H]^+$.

8-(Benzo[*d*]thiazol-2-yl)-1-methyl-9-propyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10b2)

^{1}H NMR (DMSO-d$_6$): δ 0.92 (t, 3H, $J = 6.0$ Hz), 1.81 (m, 2H), 3.22 (s, 3H), 4.65 (t, 2H, $J = 6.0$ Hz), 7.54 (m, 2H), 8.04 (d, 1H, $J = 6.3$ Hz), 8.16 (d, 1H, $J = 6.3$ Hz), 12.60 (s, 1H). LC-MS (ESI$^+$) $m/z = 342.2$ $[M + H]^+$.

8-(Benzo[*b*]thiophen-2-yl)-1-methyl-9-propyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10b3)

^{1}H NMR (DMSO-d$_6$): δ 0.92 (t, 3H, $J = 6.0$ Hz), 1.73 (m, 2H), 3.22 (s, 3H), 4.32 (t, 2H, $J = 6.0$ Hz), 7.42 (m, 2H), 7.85 (s, 1H), 7.95 (m, 1H), 8.00 (m, 1H), 12.43 (s, 1H). LC-MS (ESI$^+$) $m/z = 341.2$ $[M + H]^+$.

8-(Benzofuran-2-yl)-1-methyl-9-propyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10b4)

^{1}H NMR (DMSO-d$_6$): δ 0.90 (t, 3H, $J = 6.0$ Hz), 1.73 (m, 2H), 3.22 (s, 3H), 4.34 (t, 2H, $J = 6.0$ Hz), 7.31 (t, 1H, $J = 5.6$ Hz), 7.41 (t, 1H, $J = 5.6$ Hz), 7.46 (s, 1H), 7.66 (d, 1H, $J = 6.0$ Hz), 7.74 (d, 1H, $J = 6.0$ Hz), 12.43 (s, 1H). LC-MS (ESI$^+$) $m/z = 325.2$ $[M + H]^+$.

1-Methyl-8-(1-methyl-1*H*-benzo[d]imidazol-2-yl)-9-propyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10b5)

^{1}H NMR (DMSO-d$_6$): δ 0.85 (t, 3H, $J = 6.0$ Hz), 1.75 (m, 2H), 3.22 (s, 3H), 4.17 (s, 3H), 4.61 (t, 2H, $J = 6.0$ Hz), 7.29 (t, 1H, $J = 6.0$ Hz), 7.37 (t, 1H, $J = 6.0$ Hz),

7.66 (t, 1H, $J = 6.0$ Hz), 7.72 (d, 1H, $J = 6.3$ Hz), 12.52 (s, 1H). LC-MS (ESI^+) $m/z = 339.2$ $[M + H]^+$.

1-Methyl-9-propyl-8-(thiophen-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10b6)

^1H NMR (DMSO-d_6): δ 0.85 (t, 3H, $J = 6.0$ Hz), 1.67 (m, 2H), 3.20 (s, 3H), 4.20 (t, 2H, $J = 6.0$ Hz), 7.20 (t, 1H, $J = 7.2$ Hz), 7.51 (d, 1H, $J = 3.0$ Hz), 7.72 (d, 1H, $J = 4.0$ Hz), 12.37 (s, 1H). LC-MS (ESI^+) $m/z = 291.1$ $[M + H]^+$.

1-Methyl-8-(5-methylthiophen-2-yl)-9-propyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10b7)

^1H NMR (DMSO-d_6): δ 0.85 (t, 3H, $J = 6.0$ Hz), 1.66 (m, 2H), 2.50 (s, 3H), 3.20 (s, 3H), 4.17 (t, 2H, $J = 6.0$ Hz), 6.89 (d, 1H, $J = 2.4$ Hz), 7.30 (d, 1H, $J = 2.0$ Hz), 12.33 (s, 1H). LC-MS (ESI^+) $m/z = 305.1$ $[M + H]^+$.

1-Methyl-9-propyl-8-(thiazol-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10b8)

^1H NMR (DMSO-d_6): δ 0.86 (t, 3H, $J = 6.0$ Hz), 1.73 (m, 2H), 3.20 (s, 3H), 4.54 (t, 2H, $J = 6.0$ Hz), 7.87 (d, 1H, $J = 2.8$ Hz), 7.98 (d, 1H, $J = 2.8$ Hz), 12.51 (s, 1H). LC-MS (ESI^+) $m/z = 292.1$ $[M + H]^+$.

1-Methyl-8-(4-methylthiazol-2-yl)-9-propyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10b9)

^1H NMR (DMSO-d_6): δ 0.87 (t, 3H, $J = 6.0$ Hz), 1.73 (m, 2H), 2.43 (s, 3H), 3.21 (s, 3H), 4.52 (t, 2H, $J = 6.0$ Hz), 7.14 (s, 1H), 12.49 (s, 1H). LC-MS (ESI^+) $m/z = 306.2$ $[M + H]^+$.

8-(Benzo[d]thiazol-2-yl)-9-butyl-1-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10c1)

^1H NMR (DMSO-d_6): δ 0.92 (t, 3H, $J = 6.0$ Hz), 1.38 (m, 2H), 1.75 (m, 2H), 3.14 (s, 3H), 4.69 (t, 2H, $J = 6.0$ Hz), 7.53 (m, 2H), 8.02 (d, 1H, $J = 6.3$ Hz), 8.16 (d, 1H, $J = 6.3$ Hz), 12.60 (s, 1H). LC-MS (ESI^+) $m/z = 356.1$ $[M + H]^+$.

8-(Benzo[*d*]oxazol-2-yl)-9-butyl-1-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10c2)

^1H NMR (DMSO-d_6): δ 0.92 (t, 3H, $J = 6.0$ Hz), 1.35 (m, 2H), 1.75 (m, 2H), 3.23 (s, 3H), 4.65 (t, 2H, $J = 6.0$ Hz), 7.49 (m, 2H), 7.85 (t, 2H, $J = 6.4$ Hz), 12.63 (s, 1H). LC-MS (ESI^+) $m/z = 340.1$ $[M + H]^+$.

9-Butyl-1-methyl-8-(thiophen-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10c3)

^{1}H NMR (DMSO-d$_6$): 0.85 (t, 3H, $J = 6.0$ Hz), 1.28 (m, 2H), 1.60 (m, 2H), 3.20 (s, 3H), 4.23 (t, 2H, $J = 6.0$ Hz), 7.20 (t, 1H, $J = 3.2$ Hz), 7.51 (d, 1H, $J = 2.1$ Hz), 7.72 (d, 1H, $J = 3.2$ Hz), 12.36 (s, 1H). LC-MS (ESI$^+$) $m/z = 305.1$ $[M + H]^+$.

9-Butyl-1-methyl-8-(5-methylthiophen-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10c4)

^{1}H NMR (DMSO-d$_6$): δ 0.85 (t, 3H, $J = 6.0$ Hz), 1.28 (m, 2H), 1.60 (m, 2H), 2.40 (s, 3H), 3.20 (s, 3H), 4.20 (t, 2H, $J = 6.0$ Hz), 6.89 (d, 1H, $J = 1.8$ Hz), 7.30 (d, 1H, $J = 1.9$ Hz), 12.33 (s, 1H). LC-MS (ESI$^+$) $m/z = 319.1$ $[M + H]^+$.

9-Butyl-1-methyl-8-(4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10c5)

^{1}H NMR (DMSO-d$_6$): δ 0.89 (t, 3H, $J = 6.0$ Hz), 1.31 (m, 2H), 1.68 (m, 2H), 1.82 (m, 4H), 2.73 (m, 2H), 2.82 (m, 2H), 3.20 (s, 3H), 4.20 (t, 2H, $J = 6.0$ Hz), 12.33 (s, 1H). LC-MS (ESI$^+$) $m/z = 360.2$ $[M + H]^+$.

9-Butyl-8-(4-fluorophenyl)-1-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10c6)

^{1}H NMR (DMSO-d$_6$): δ 0.72 (t, 3H, $J = 6.0$ Hz), 1.08 (m, 2H), 1.47 (m, 2H), 3.21 (s, 3H), 4.10 (t, 2H, $J = 6.0$ Hz), 7.37 (m, 2H), 7.72 (m, 2H), 12.33 (s, 1H). LC-MS (ESI$^+$) $m/z = 317.2$ $[M + H]^+$.

9-Butyl-8-cyclopropyl-1-methyl-1H-purine-2,6(3*H*,9*H*)-dione (10c7)

^{1}H NMR (DMSO-d$_6$): δ 0.87 (m, 5H), 0.93 (m, 2H), 1.29 (m, 2H), 1.63 (m, 2H), 2.01 (m, 1H), 3.16 (s, 3H), 4.10 (t, 2H, $J = 6.0$ Hz), 12.15 (s, 1H). LC-MS (ESI$^+$) $m/z = 263.2$ $[M + H]^+$.

9-Butyl-1-methyl-8-(4-(trifluoromethyl)phenyl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10c8)

^{1}H NMR (DMSO-d$_6$): δ 0.73 (t, 3H, $J = 6.0$ Hz), 1.10 (m, 2H), 1.49 (m, 2H), 3.22 (s, 3H), 4.16 (t, 2H, $J = 6.0$ Hz), 7.90 (m, 4H), 12.40 (s, 1H). LC-MS (ESI$^+$) $m/z = 367.2$ $[M + H]^+$.

8-(Benzo[*d*]thiazol-2-yl)-9-(cyclopropylmethyl)-1-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10d1)

^{1}H NMR (DMSO-d$_6$): δ 0.48 (d, 4H, $J = 5.2$ Hz), 1.45 (m, 1H), 3.23 (s, 3H), 4.65 (d, 2H, $J = 6.0$ Hz), 7.54 (m, 2H), 8.06 (d, 1H, $J = 6.4$ Hz), 8.17 (d, 1H, $J = 6.0$ Hz), 12.56 (s, 1H). LC-MS (ESI$^+$) $m/z = 354.1$ $[M + H]^+$.

9-(Cyclopropylmethyl)-1-methyl-8-(4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10d2)

^{1}H NMR (DMSO-d_6): δ 0.41 (m, 4H), 1.34 (m, 1H), 1.82 (m, 4H), 2.72 (m, 2H), 2.80 (m, 2H), 3.20 (s, 3H), 4.49 (d, 2H, $J = 6.0$ Hz), 12.56 (s, 1H). LC-MS (ESI^+) $m/z = 358.1$ $[M + H]^+$.

9-(Cyclopropylmethyl)-1-methyl-8-(4-methylthiazol-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10d3)

^{1}H NMR (DMSO-d_6): δ 0.42 (m, 4H), 1.37 (m, 1H), 2.43 (s, 3H), 3.21 (s, 3H), 4.52 (d, 2H, $J = 6.0$ Hz), 7.42 (s, 1H), 12.56 (s, 1H). LC-MS (ESI^+) $m/z = 318.1$ $[M + H]^+$.

9-(Cyclopropylmethyl)-1-methyl-8-(5-methylthiophen-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10d4)

^{1}H NMR (DMSO-d_6): δ 0.28 (m, 2H), 0.42 (m, 2H), 1.11 (m, 1H), 2.49 (s, 3H), 3.20 (s, 3H), 4.20 (d, 2H, $J = 6.0$ Hz), 6.90 (s, 1H), 7.40 (d, 1H, $J = 2.8$ Hz), 12.24 (s, 1H). LC-MS (ESI^+) $m/z = 317.1$ $[M + H]^+$.

8-(Benzo[*d*]thiazol-2-yl)-9-benzyl-1-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10e1)

^{1}H NMR (DMSO-d_6): δ 3.23 (s, 3H), 6.04 (s, 2H), 7.21 (m, 3H), 7.31 (m, 2H), 7.50 (m, 2H), 7.99 (d, 1H, $J = 6.4$ Hz), 8.14 (d, 1H, $J = 6.0$ Hz), 12.50 (s, 1H). LC-MS (ESI^+) $m/z = 390.1$ $[M + H]^+$.

9-Benzyl-1-methyl-8-(4-methylthiazol-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10e2)

^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H), 3.23 (s, 3H), 5.93 (s, 2H), 7.14 (d, 2H, $J = 6.0$ Hz), 7.23 (t, 1H, $J = 4.0$ Hz), 7.31 (m, 2H), 7.37 (s, 1H), 12.50 (s, 1H). LC-MS (ESI^+) $m/z = 354.1$ $[M + H]^+$.

9-Isopentyl-1-methyl-8-(4-methylthiazol-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10f1)

^{1}H NMR (DMSO-d_6): δ 0.87 (d, 6H, $J = 4.2$ Hz), 1.55 (m, 2H), 1.70 (m, 1H), 2.41 (s, 3H), 3.20 (s, 3H), 4.60 (m, 2H), 7.40 (s, 1H), 12.50 (s, 1H). LC-MS (ESI^+) $m/z = 334.2$ $[M + H]^+$.

9-Isopentyl-1-methyl-8-(5-methylthiophen-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10f2)

^{1}H NMR (DMSO-d_6): δ 0.87 (d, 6H, $J = 4.2$ Hz), 1.50 (m, 2H), 1.60 (m, 1H), 2.49 (s, 3H), 3.20 (s, 3H), 4.20 (d, 2H, $J = 6.4$ Hz), 6.80 (d, 1H, $J = 2.8$ Hz) 7.28 (d, 1H, $J = 2.8$ Hz), 12.38 (s, 1H). LC-MS (ESI^+) $m/z = 333.2$ $[M + H]^+$.

8-(Benzo[*d*]thiazol-2-yl)-9-isopentyl-1-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10f3)

^{1}H NMR (DMSO-d$_6$): δ 1.00 (d, 6H, $J = 4.2$ Hz), 1.65 (m, 2H), 1.74 (m, 1H), 3.23 (s, 3H), 4.72 (d, 2H, $J = 6.0$ Hz), 7.51 (t, 1H, $J = 5.6$ Hz), 7.59 (t, 1H, $J = 5.6$ Hz), 7.99 (d, 1H, $J = 5.6$ Hz), 8.17 (d, 1H, $J = 6.0$ Hz), 12.64 (s, 1H). LC-MS (ESI$^+$) $m/z = 370.1$ $[M + H]^+$.

8-(Benzo[*d*]oxazol-2-yl)-9-isopentyl-1-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10f4)

^{1}H NMR (DMSO-d$_6$): δ 0.97 (d, 6H, $J = 4.2$ Hz), 1.65 (m, 2H), 1.70 (m, 1H), 3.23 (s, 3H), 4.72 (d, 2H, $J = 6.0$ Hz), 7.49 (m, 2H), 7.83 (t, 2H, $J = 6.0$ Hz), 12.67 (s, 1H). LC-MS (ESI$^+$) $m/z = 354.2$ $[M + H]^+$.

8-(Benzo[*d*]thiazol-2-yl)-9-(3-(dimethylamino)propyl)-1-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (10g1)

^{1}H NMR (DMSO-d$_6$): δ 2.23 (m, 2H), 2.78 (s, 6H), 3.08 (m, 2H), 3.23 (s, 3H), 4.66 (t, 2H, $J = 5.6$ Hz), 7.50 (t, 1H, $J = 6.0$ Hz), 7.57 (t, 1H, $J = 6.0$ Hz), 8.05 (d, 1H, $J = 6.4$ Hz), 8.15 (d, 1H, $J = 6.4$ Hz). LC-MS (ESI$^+$) $m/z = 385.1$ $[M + H]^+$.

9-(3-(Dimethylamino)propyl)-1-methyl-8-(4-methylthiazol-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10g2)

^{1}H NMR (DMSO-d$_6$): δ 2.14 (m, 2H), 2.49 (s, 3H), 2.77 (s, 6H), 3.06 (m, 2H), 3.21 (s, 3H), 4.56 (t, 2H, $J = 5.6$ Hz), 7.42 (s, 1H). LC-MS (ESI$^+$) $m/z = 349.1$ $[M + H]^+$.

9-(3-(Dimethylamino)propyl)-1-methyl-8-(5-methylthiophen-2-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (10g3)

^{1}H NMR (DMSO-d$_6$): δ 1.99 (m, 2H), 2.48 (s, 3H), 2.50 (s, 6H), 2.73 (m, 2H), 3.18 (s, 3H), 4.19 (t, 2H, $J = 5.6$ Hz), 6.88 (d, 1H, $J = 2.0$ Hz), 7.28 (d, 1H, $J = 2.0$ Hz). LC-MS (ESI$^+$) $m/z = 348.1$ $[M + H]^+$.

8-(Benzo[*d*]thiazol-2-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,9*H*)-dione (14a)

^{1}H NMR (DMSO-d$_6$): δ 0.87 (t, 3H, $J = 6.0$ Hz), 0.92 (t, 3H, $J = 6.0$ Hz), 1.57 (m, 2H), 1.75 (m, 2H), 3.86 (t, 2H, $J = 6.0$ Hz), 4.01 (t, 2H, $J = 6.0$ Hz), 7.54 (t, 1H, $J = 6.0$ Hz), 7.60 (t, 1H, $J = 6.0$ Hz), 8.10 (d, 1H, $J = 6.8$ Hz), 8.19 (d, 1H, $J = 6.8$ Hz), 15.30 (s, 1H). LC-MS (ESI$^+$) $m/z = 370.2$ $[M + H]^+$.

8-(Benzo[*d*]oxazol-2-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,9*H*)-dione (14b)

^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H, $J = 6.0$ Hz), 0.93 (t, 3H, $J = 6.0$ Hz), 1.59 (m, 2H), 1.75 (m, 2H), 3.87 (t, 2H, $J = 6.0$ Hz), 4.02 (t, 2H, $J = 6.0$ Hz), 7.51 (m, 2H), 7.87 (d, 2H, $J = 6.0$ Hz), 15.20 (s, 1H). LC-MS (ESI$^+$) $m/z = 354.2$ $[M + H]^+$.

8-(5-Methylthiophen-2-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,9*H*)-dione (14c)[18]

Mp = 273–274 °C; ^{1}H NMR (DMSO-d_6): δ 0.88 (m, 6H), 1.56 (m, 2H), 1.71 (m, 2H), 2.49 (s, 3H), 3.85 (t, 2H, $J = 6.0$ Hz), 3.95 (t, 2H, $J = 6.0$ Hz), 6.89 (d, 1H, $J = 2.8$ Hz), 7.69 (d, 1H, $J = 2.8$ Hz), 13.76 (s, 1H). LC-MS (ESI$^+$) $m/z = 332.2$ $[M + H]^+$.

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