Novel 1,3-Disubstituted 8-(1-benzyl-1*H*-pyrazol-4-yl) Xanthines: High Affinity and Selective A_{2B} Adenosine Receptor Antagonists

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Adenosine has been suggested to induce bronchial hyperresponsiveness in asthmatics, which is believed to be an A_{2B} adenosine receptor (AdoR) mediated pathway. We hypothesize that a selective, high-affinity A_{2B} AdoR antagonist may provide therapeutic benefit in the treatment of asthma. In an attempt to identify a high-affinity, selective antagonist for the A_{2B} AdoR, we synthesized 8-(C-4-pyrazolyl) xanthines. Compound **22**, 8-(1*H*-pyrazol-4-yl)-1,3-dipropyl xanthine, is a N-1 unsubstituted pyrazole derivative that has favorable binding affinity ($K_i = 9$ nM) for the A_{2B} AdoR, but it is only 2-fold selective versus the A_1 AdoR. Introduction of a benzyl group at the N-1-pyrazole position of **22** resulted in **19**, which had moderate selectivity. The initial focus of the SAR study was on the preparation of substituted benzyl derivatives of **19** because the corresponding phenyl, phenethyl, and phenpropyl derivatives showed a decrease in A_{2B} AdoR affinity and selectivity relative to **19**. The preferred substitution on the phenyl ring of **19** contains an electron-withdrawing group, specifically F or CF_3 at the m-position, as in **33** and **36** respectively, increases the selectivity while retaining the affinity for the A_{2B} AdoR. Exploring disubstitutions on the phenyl ring of derivatives **33** and **36** led to the 2-chloro-5-trifluoromethylphenyl derivative **50**, which retained the A_{2B} AdoR affinity but enhanced the selectivity relative to **36**. After optimization of the substitution on the 8-pyrazole xanthine, 1,3-disubstitution of the xanthine core was explored with methyl, ethyl, butyl, and isobutyl groups. In comparison to the corresponding dipropyl analogues, the smaller 1,3-dialkyl groups (methyl and ethyl) increased the A_{2B} AdoR binding selectivity of the xanthine derivatives while retaining the affinity. However, the larger 1,3-dialkyl groups (isobutyl and butyl) resulted in a decrease in both A_{2B} AdoR affinity and selectivity. This final SAR optimization led to the discovery of 1,3-dimethyl derivative **60**, 8-(1-(3-(trifluoromethyl) benzyl)-1*H*-pyrazol-4-yl)-1,3-dimethyl xanthine, a high-affinity ($K_i = 1$ nM) A_{2B} AdoR antagonist with high selectivity (990-, 690-, and 1000-) for the human A_1, $A_{2A,}$ and A_3 AdoRs.

Introduction

Adenosine is an endogenous nonselective agonist that activates all four subtypes of adenosine receptors (AdoRs): A_1, A_{2A}, A_{2B}, and A_3.[1] Adenosine has been implicated to play a role in inflammatory airway diseases such as asthma.[2] High adenosine levels are observed in the bronchoalveolar lavage (BAL) fluid and in exhaled breath condensate of asthmatics compared to those of normal controls.[3] It is believed that the activation of the A_{2B} AdoR on human lung mast cells leads to mast cell degranulation, releasing inflammatory cytokines (IL-4, IL-8, and IL-13).[4] It has also been shown that the A_{2B} AdoR subtype is the predominant AdoR expressed in bronchial smooth muscle cells (BSMC), and its activation increases the expression and release of interleukin-6 (IL-6) and monocytic chemotactic peptide-1 (MCP-1).[5a] The presence and functional coupling of human A_{2B} AdoRs in different peripheral blood cells that play a role in immune and inflammatory process in which A_{2B} AdoRs are thought to be involved have been recently characterized.[5b] Therefore, we choose to explore the potential of selective, high-affinity A_{2B} adenosine receptor (AdoR) antagonists in the treatment of asthma.[6]

Prior to a description of our approach to obtain high-affinity A_{2B} AdoR antagonists, we described relevant background information on human AdoR antagonists that influenced our design. Theophylline **1**, 1,3-dimethyl xanthine (Figure 1), is a PDE IV inhibitor and a nonselective AdoR antagonist that has a K_i of 9 μM for the A_{2B} adenosine receptor (AdoR). Theophylline is currently approved for use in the treatment of asthma in both iv rescue therapy for acute asthma attacks and chronic oral treatment.[7−9] Theophylline has a low therapeutic index due to both CNS and cardiac side effects. We hypothesize that a more selective A_{2B} AdoR antagonist devoid of PDE IV activity may have an enhanced therapeutic index. Replacing the methyl groups of **1** with propyl groups as in **7a** (Scheme 1) increases the A_{2B} AdoR affinity ($K_i = 610$ nM) without any enhancement in selectivity.[10] Enprofylline **2**, a 3-propyl xanthine derivative, has moderate affinity for the A_{2B} AdoR ($K_i = 4.7$ μM) and also has moderate selectivity against the other AdoR subtypes (Figure 1).[10]

Suzuki and co-workers have shown that substitution at the 8-position of xanthine with cycloalkyl groups increases the A_1 AdoR affinity. For example, 8-cyclopentyl-1,3-dipropylxanthine, **3** (DPCPX), is a known A_1 antagonist that also exhibits considerable affinity for the A_{2B} AdoR ($K_i = 56$ nM, Figure 1).[11] Several research groups have synthesized 8-phenyl substituted xanthines that have high A_{2B} AdoR affinity and selectivity against the other AdoR subtypes.[12−14] Jacobson and co-workers demonstrated that the introduction of a para-substituted phenyl derivative at the 8-position of the xanthine core increases the A_{2B} AdoR affinity and selectivity against the other AdoRs as illustrated by **4**.[13,14]

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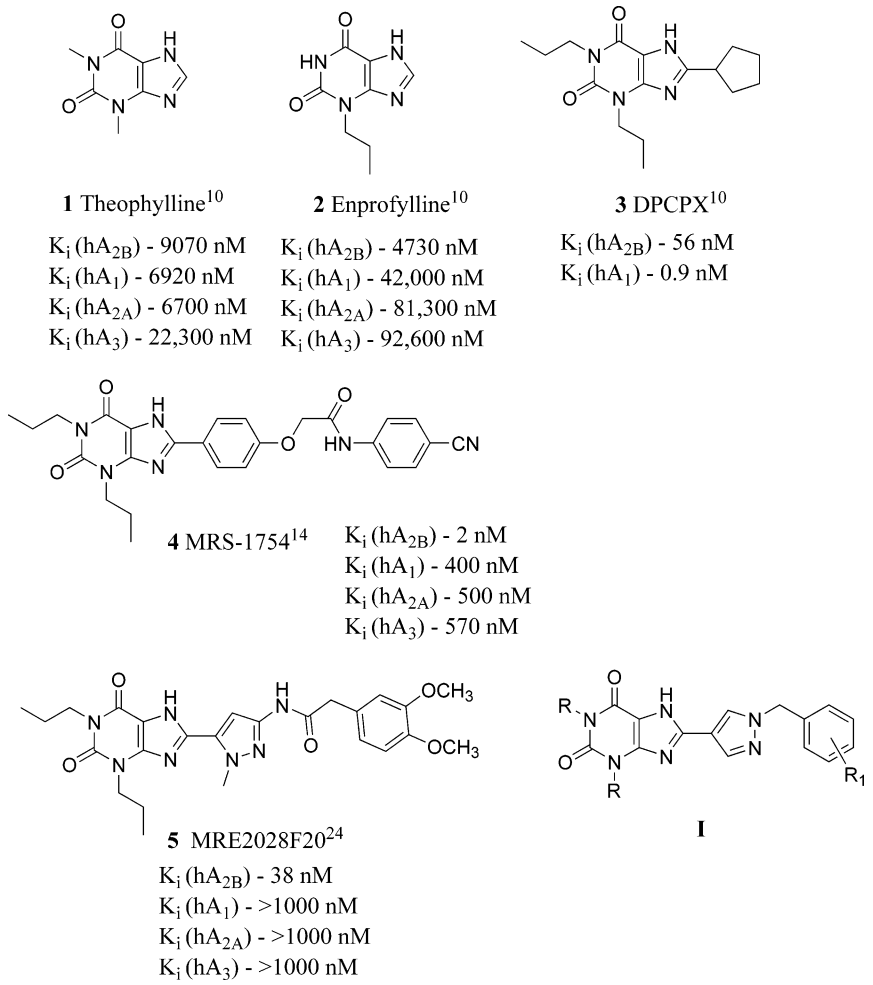
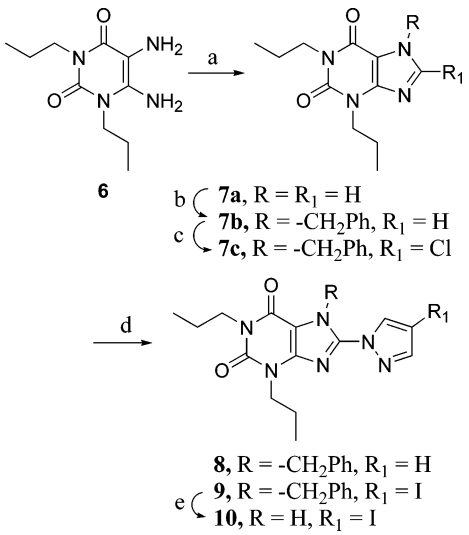


Figure 1. Representative structures of xanthine classes that have affinity for the A_{2B} AdoR.

Scheme 1[a]



[a] Reagents: (a) $CH(OC_2H_5)_3$, 70 °C; (b) $PhCH_2Br$, K_2CO_3, DMF, 80 °C, 90%; (c) NCS, THF, r.t., 75%; (d) NaH, DMF, pyrazole, 75 °C, 70% (**8**), 90% (**9**); (e) $Pd(OH)_2$, cyclohexene, ethanol, 80 °C, 18 h, 20%.

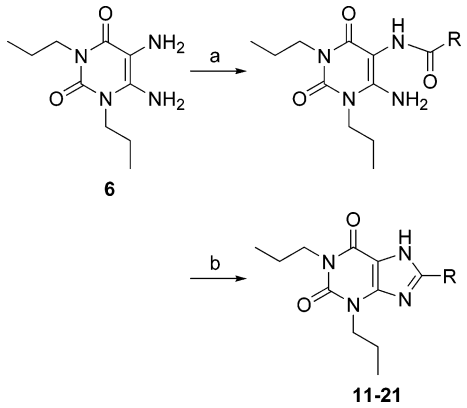
In the search for a nonxanthine class of compounds as A_{2B} AdoR antagonists, several classes of compounds have been investigated as AdoR antagonists: adenines, 9-deazaadenines, 8-azadenines, quinoxalines, and pyrazolo[1,5-a]pyridines.[15−21] Although many new heterocyclic classes are being discovered as A_{2B} AdoR antagonists, our main focus still remains on the xanthine class.

Even though several A_{2B} antagonists are known in the literature with high affinity, there are very few A_{2B} AdoR antagonists known with good affinity and selectivity.[16] Herein, we report the exploration of the 8-pyrazolyl xanthine derivatives represented by **I** (Figure 1) as a new class of adenosine receptor antagonists with the goal of achieving high affinity for the A_{2B} AdoR and selectivity over the other AdoRs. To our knowledge, there were no examples of 8-pyrazolyl xanthines evaluated as A_{2B} AdoR antagonists in the literature prior to our exploration.[22,23] Recently, Baraldi and co-workers have reported the 8-(5-pyrazolyl)-xanthines represented by structure **5**[24] that typically contain the amide functionality found in the MRS-1754 (**4**)[14] class of compounds. Our approach to the discovery of a selective, high-affinity A_{2B} AdoR antagonist through the preparation of 8-(4-pyrazolyl)-xanthines was guided by a systematic optimization of the SAR.

Chemistry

The 8-pyrazolyl xanthine derivatives were synthesized following the synthetic routes illustrated in Schemes 1−4. The 8-(N-1-pyrazolyl) derivatives **8**−**10** were prepared as shown in Scheme 1. The 1,3-dipropyl-5,6-diaminouracil (**6**) was synthesized from 1,3-dipropyl urea following previously described methods.[12] Diamine **6** was treated with triethylorthoformate to obtain 1,3-dipropyl xanthine (**7a**).[12] The N-7 position of xanthine derivative **7a** was protected by reacting with benzyl bromide

Scheme 2[a]



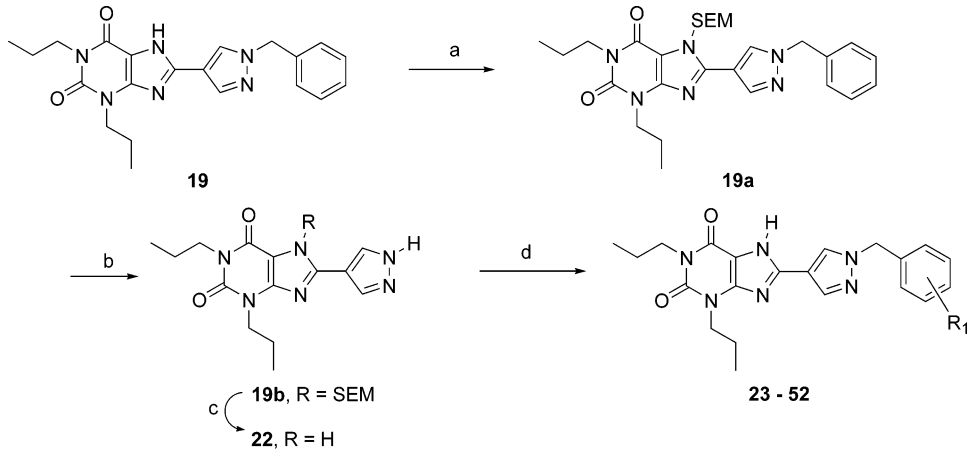
[a] Reagents: (a) R-COOH, EDCI, MeOH, r.t., 16 h, 70−85%; (b) MeOH, 10% NaOH, 80 °C; 5 h, 60−80%.

to yield **7b**, followed by treatment with *N*-chlorosuccinamide to furnish 8-chloro-7-benzyl-1,3-dipropyl xanthine (**7c**). The 8-chloro derivative **7c** was converted to the 8-(N-1-pyrazolyl) derivatives **8** and **9** by reacting with the corresponding pyrazole anions generated by treating with sodium hydride. The 8-(N-1-pyrazolyl)-1,3-dipropyl xanthine **10** was obtained by debenzylation of **9** using Pearlman's catalyst ($Pd(OH)_2$) under transfer hydrogenation conditions.

The 8-(4-pyrazolyl) xanthine derivatives **11**−**21** were synthesized as illustrated in Scheme 2. Diamine **6** was selectively acylated at the 5-position by coupling with the corresponding pyrazole acids using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) to furnish the amides followed by base induced cyclization to yield the corresponding 8-pyrazolyl xanthines **11**−**21** (Table 1).

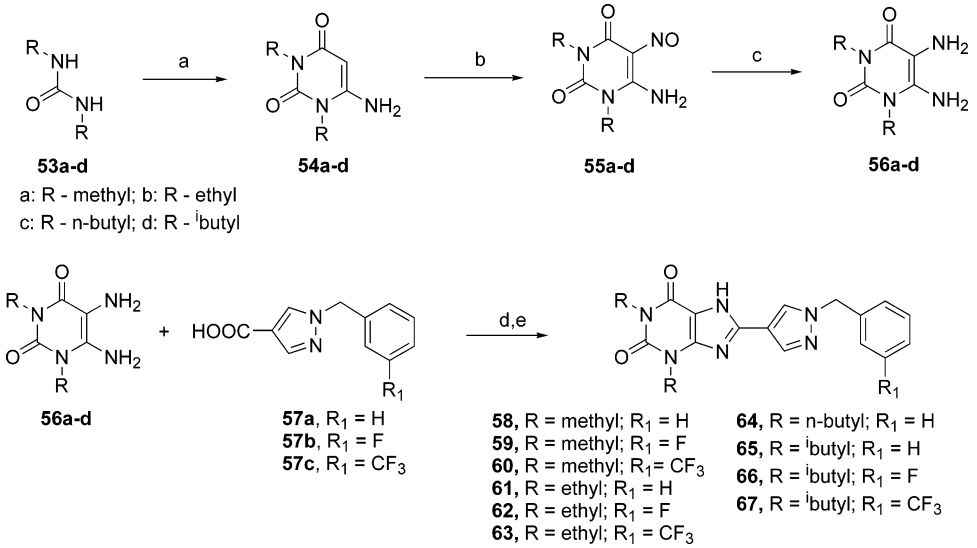
A second more convergent route was developed for the synthesis of 8-(4-pyrazolyl)xanthine derivatives that allows for N-1-pyrazolyl substitution (Scheme 3) through a common late intermediate. The N-7 position of benzyl derivative **19** was protected with SEM-Cl using K_2CO_3 in dimethylformamide to provide **19a**. Debenzylation of derivative **19a** using Pearlman's catalyst furnished the 8-(N-1*H*-pyrazol-4-yl) derivative **19b** with the N-7 position SEM protected. The treatment of **19b** with 3N HCl in ethanol furnished the unprotected derivative, 8-(1*H*-pyrazol-1-yl)-1,3-dipropyl xanthine (**22**). The unsubstituted pyrazole derivative **19b** was alkylated with various substituted benzyl halides using standard alkylation conditions to furnish

Scheme 3[a]



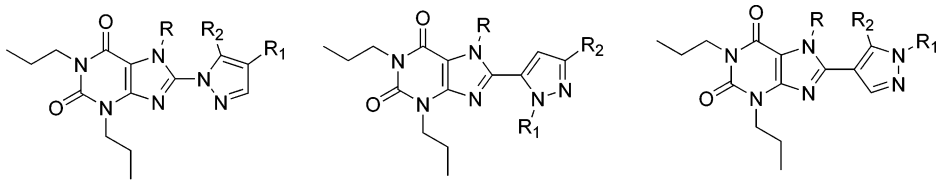
[a] Reagents: (a) SEM-Cl, K_2CO_3, DMF, 80 °C, 18 h; (b) $Pd(OH)_2$, Cyclohexene, EtOH, 80 °C, 48 h; (c) 3N HCl, EtOH, 70 °C; (d) i)R_1-Ph-CH_2Br(Cl), K_2CO_3, DMF, 80 °C; ii) 3 N HCl, EtOH, 70 °C.

Scheme 4[a]



[a] Reagents: (a) ethylcyanoacetate, NaOEt, 70 °C; (b) $NaNO_2$, CH_3COOH/H_2O (1:1), 70 °C, 1 h; (c) $Na_2S_2O_4$, 15% NH_4OH, 70 °C, 1 h; (d) EDCI, MeOH, r.t., 16 h; (e) MeOH, 10% NaOH, 80 °C, 5 h.

Table 1. Exploration of 8-Pyrazolyl Xanthines as Ligands for the A_{2B} Adenosine Receptors



8-10 **11-13** **14-22**

compd	R	R_1	R_2	K_i nM[a] (A_{2B})[b]
8	benzyl	H	H	>5800
9	benzyl	I	H	>5800
10	H	H	H	>5800
11	H	CH_3	CH_3	3700
12	H	CH_2CH_3	CH_3	2100
13	H	Ph	H	1100
14	H	Ph	H	310
15	H	Ph	CH_3	>4100
16	H	Ph	$CH_2CH_2CH_3$	>6600
17	H	Ph	CF_3	>6600
18	H	4-Cl−Ph	CF_3	>6600
22	H	H	H	9

[a] The 95% Confidence intervals are generally within 15% of the mean value. [b] The binding affinity for the A_{2B} AdoR was determined by the competition for the binding sites labeled by ^{3}H-ZM241385 (14 nM) in membranes prepared from HEK-A_{2B} cells.

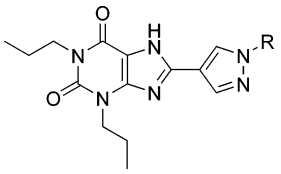
the SEM-protected derivatives followed by deprotection with 3N HCl to yield the 8-(1-substituted benzyl-pyrazol-4-yl)-1,3-dipropyl xanthines **23**−**52** in good to excellent yields (Scheme 3).

The N-1 and N-3 disubstituted 8-(4-pyrazolyl)xanthine derivatives were synthesized as illustrated in Scheme 4. The symmetrically substituted ureas, **53a**−**d** were treated with ethylcyanoacetate in the presence of sodium ethoxide to provide the corresponding substituted 6-amino uracils **54a**−**d** in good yields. Nitrosation of the 6-amino uracil derivatives **54a**−**d** was achieved by the slow addition of solid sodium nitrite to a solution of the amino uracil in 50% aqueous acetic acid. The nitroso uracils **55a**−**d** were reduced with $Na_2S_2O_4$ in 15% ammonium hydroxide to furnish diamine derivatives **56a**−**d**. The coupling of the diamine with substituted pyrazole acids **57a**−**c** followed by base-induced cyclization furnished the N-1and N-3 disubstituted 8-pyrazole xanthines **58**−**67** following the conditions described above (Scheme 2).

Results and Discussion

A series of 8-pyrazolyl xanthines were prepared from commercially available pyrazole acids with the goal of rapidly exploring the SAR with respect to A_{2B} AdoR affinity (Table 1). The 8-(N-1-pyrazolyl) xanthine derivatives **8**−**10** demonstrated low affinity for the A_{2B} AdoR. This suggests that this mode of pyrazole attachment is not conducive for binding to the A_{2B} AdoR receptor. Also, 8-(C-5-pyrazolyl) derivatives **11**−**13** demonstrated weak binding affinities (in the range of 1−3 μM) for the A_{2B} AdoR. The incorporation of a C-4-pyrazole ring at the 8-position of the xanthine as in **22** resulted in high affinity for the A_{2B} AdoR (9 nM). The effect of the addition of a N-1 phenyl ring onto **22,** as in **14**, lowered the A_{2B} AdoR affinity to 310 nM, but the 4-pyrazolyl moiety had a higher affinity than that of the corresponding 5-pyrazolyl moiety, as in **13**. The substitution at the 5-position of the pyrazole ring of **14** either with electron-donating groups (EDG), such as methyl (**15**) and propyl (**16**), or with electron-withdrawing (EWG) groups, such as trifluoromethyl (**17** and **18**), results in a decrease in the A_{2B} AdoR affinity. From our brief survey of commercially available pyrazole acids, 4-pyrazolyl analogue **22** showed the highest affinity for the A_{2B} AdoR. Therefore, we chose to further explore the 8-(pyrazol-4-yl) xanthine class in search of analogues with both high affinity and selectivity for the A_{2B} AdoR.

Table 2. Adenosine Receptor Binding Affinities of 8-(N-1-Substituted Pyrazol-4-yl) Xanthines



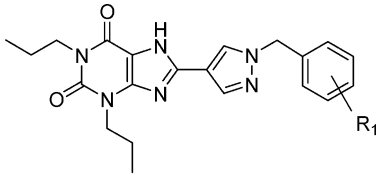
14, 19-22

		K_i nM[a]			A_{2B} selectivity	
compd	R	A_{2B}[b]	A_1[c]	A_{2A}[d]	A_1/A_{2B}	A_{2A}/A_{2B}
14	phenyl	310	770	560	2	2
22	H	9	20	230	2	23
19	benzyl	11	76	290	7	26
20	phenethyl	74	17	570	0.2	7
21	phenylpropyl	100	77	220	0.7	2

[a] The 95% Confidence intervals are generally within 15% of the mean value. [b] The binding affinity for the A_{2B} AdoR was determined by the competition for the binding sites labeled by ^{3}H-ZM241385 (14 nM) in membranes prepared from HEK-A_{2B} cells. [c] The binding affinity for the A_1 AdoR was determined by the competition for the binding sites labeled by ^{3}H-CPX (0.5 nM) in membranes prepared from CHO-A_1 cells. [d] The binding affinity for the A_{2A} AdoR was determined by the competition for the binding sites labeled by ^{3}H-ZM241385 (2 nM) in membranes prepared from HEK-A_{2A} cells.

An evaluation of the binding selectivity of 4-pyrazolyl analogue **22** versus that of other AdoR subtypes, such as A_1 and A_{2A}, is shown in Table 2. Compound **22** was found to have modest selectivity over A_{2A} (23-fold) and low selectivity over A_1. Furthermore, N-1-phenyl-substituted derivative **14** demonstrated low selectivity against both A_1 and A_{2A} AdoRs. To increase the selectivity, we had to explore various substitutions on **22**. The two options for increasing the binding selectivity are to vary the substitution either at the N-1-position of the pyrazole or at the N-1 and N-3 positions of the xanthine. Initially, we explored the substitution at the N-1-position of pyrazole **22**. The introduction of a benzyl group at the N-1 position of the pyrazole ring of **22** resulted in compound **19**, which displayed slightly enhanced selectivity over the A_1 AdoR (Table 2). Increasing the distance between the phenyl group

Table 3. Adenosine Receptor Binding Affinities of the Substituted Phenyls of 8-Pyrazol-4-yl Xanthine Derivatives



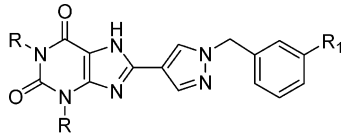
23 - 52

		K_i nM[a]			A_{2B} selectivity	
compd	R_1	A_{2B}[b]	A_1[c]	A_{2A}[d]	A_1/A_{2B}	A_{2A}/A_{2B}
23	2-CH_3	33	22	51	0.6	2
24	3-CH_3	36	48	66	1	2
25	4-CH_3	40	38	80	1	2
26	2-OCH_3	37	59	140	2	4
27	3-OCH_3	34	34	70	1	2
28	4-OCH_3	37	70	61	2	1
29	2-Cl	20	59	49	3	6
30	3-Cl	18	31	79	2	4
31	4-Cl	18	7	88	0.5	4
32	2-F	28	19	60	0.6	2
33	3-F	14	170	230	13	18
34	4-F	22	23	120	1	5
35	2-CF_3	37	44	230	1	6
36	3-CF_3	14	170	400	12	27
37	4-CF_3	20	41	150	2	7
38	2,3-di-F	240	nd[e]	nd	nd	nd
39	2,4-di-F	700	nd	nd	nd	nd
40	2,6-di-F	390	nd	nd	nd	nd
41	3,4-di-F	35	170	280	7	8
42	2-F,3-Cl	58	530	870	9	13
43	2-F-3-CH_3	44	390	460	9	10
44	3-CF_3−4-F	640	nd	nd	nd	nd
45	3-CF_3−4-Cl	200	nd	nd	nd	nd
46	3,5-di-CF_3	350	nd	nd	nd	nd
47	3-CF_3−4-OCH_3	410	nd	nd	nd	nd
48	2,5-di-Cl	29	190	70	6	2
49	2-Cl-5-F	4800	nd	nd	nd	nd
50	2-Cl-5-CF_3	22	1200	1400	54	63
51	2-F-3-Cl-5-CF_3	360	nd	nd	nd	nd
52	2,4,6-tri-F	650	nd	nd	nd	nd

[a] The 95% Confidence Intervals are generally within 15% of the mean value. [b] The binding affinity for the A_{2B} AdoR was determined by the competition for the binding sites labeled by ^{3}H-ZM241385 (14 nM) in membranes prepared from HEK-A_{2B} cells. [c] The binding affinity for the A_1 AdoR was determined by the competition for the binding sites labeled by ^{3}H-CPX (0.5 nM) in membranes prepared from CHO-A_1 cells. [d] The binding affinity for the A_{2A} AdoR was determined by the competition for the binding sites labeled by ^{3}H-ZM241385 (2 nM) in membranes prepared from HEK-A_{2A} cells. [e] Not determined.

and the N-1 position of the pyrazole ring from one carbon atom to two and three carbon atoms, as in compounds **20** and **21**, resulted in a decrease in affinity and selectivity for the A_{2B} AdoR relative to **19** (Table 2). Therefore, we chose to further investigate the effect of introducing electron-donating (EDG) and electron-withdrawing groups (EWG) on the phenyl ring of moderately selective **19** with the goal of enhancing its A_{2B} affinity and selectivity (Table 3). Derivatives with electron-donating groups, such as CH_3 (**23**−**25**) and OCH_3 (**26**−**28**), showed similar affinity at the A_1, A_{2A}, and A_{2B} adenosine receptors, regardless of the position of the substitution (ortho, meta, or para). Introducing a chloro group, a moderate EWG in compounds **29**−**31**, also resulted in good binding affinity for all of the AdoR subtypes. However, *m*-F derivative **33** retained the A_{2B} AdoR affinity (K_i = 14 nM) and had higher binding selectivity for the A_{2B} AdoR compared to that of compound **19** (Table 3). The corresponding *o*- and *p*-F analogues **32** and **34** showed similar affinity for both the A_1 and A_{2B} AdoRs. Similar to **33**, the *m*-CF_3 derivative **36** retained the A_{2B} affinity (K_i = 14 nM) and showed an increase in selectivity relative to **19**, the unsubstituted benzyl analogue (Table 3). Once again the *o*-CF_3 and *p*-CF_3 derivatives **35** and **37** did not impart any binding selectivity just as their corresponding *o*- and *p*-F derivatives **32** and **34**.

Table 4. Effect of Symmetric Substitution on the N-1 and N-3 Positions of 8-Pyrazolyl Xanthine Derivatives



19, 33, 36, 58 - 67

			K_i nM[a]			A_{2B} selectivity	
compd	R	R_1	A_{2B}[b]	A_1[c]	A_{2A}[d]	A_1/A_{2B}	A_{2A}/A_{2B}
19	propyl	H	11	76	290	7	26
33	propyl	F	14	170	230	13	17
36	propyl	CF_3	14	170	400	12	28
58	methyl	H	2300	>6000	3500	2	1
59	methyl	F	27	460	200	17	7
60	methyl	CF_3	1	990	690	990	690
61	ethyl	H	19	580	120	30	6
62	ethyl	F	5	380	290	76	58
63	ethyl	CF_3	13	570	450	44	34
64	butyl	H	980	1400	890	1	1
65	^{i}butyl	H	1250	620	1100	0.5	1
66	^{i}butyl	F	990	830	1300	1	1
67	^{i}butyl	CF_3	300	3100	4300	10	14

[a] The 95% Confidence Intervals are generally within 15% of the mean value. [b] The binding affinity for the A_{2B} AdoR was determined by the competition for the binding sites labeled by ^{3}H-ZM241385 (14 nM) in membranes prepared from HEK-A_{2B} cells. [c] The binding affinity for the A_1 AdoR was determined by the competition for the binding sites labeled by ^{3}H-CPX (0.5 nM) in membranes prepared from CHO-A_1 cells. [d] The binding affinity for the A_{2A} AdoR was determined by the competition for the binding sites labeled by ^{3}H-ZM241385 (2 nM) in membranes prepared from HEK-A_{2A} cells.

Encouraged by the enhanced binding selectivity and retained A_{2B} AdoR affinity of *m*-F and *m*-CF_3 derivatives **33** and **36**, respectively, we decided to look at the disubstituted benzyl analogues of **19** with an emphasis on EWGs. In general, various combinations of difluoro analogues **38**−**41** showed diminished affinity for the A_{2B} AdoR with the exception of 3,4-difluoro analogue **41** (K_i = 35 nM), which still had lower affinity and selectivity than the monosubstituted analogue **33**. Disubstituted analogues **42** and **43**, which contain a 2-F substituent, were found to have slightly less favorable A_{2B} AdoR affinity and selectivity than that of **33** (Table 3). In compounds **44**−**47**, the *m*-CF_3 group was retained, and the effect of an additional EWG (**44**−**46**) and EDG (**47**) substituent on the A_{2B} AdoR affinity was found to be less favorable than **36** (Table 3). We explored the effect of 2,5-disubstituted EWGs on A_{2B} AdoR affinity (**48**−**50**) with 2-chloro-5-trifluoromethyl derivative **50** resulting in high A_{2B} AdoR affinity (K_i = 22 nM) and good selectivity (A_1/A_{2B} = 50 and A_{2A}/A_{2B} = 65) (Table 3). Trisubstituted analogues **51** and **52** demonstrated reduced affinity for the A_{2B} AdoR relative to that of unsubstituted derivative **19**.

After optimization of the phenyl substitution of compound **19**, which led to **33** and **36**, the effect of varying the dialkyl substitution of the xanthine core N-1 and N-3 on A_{2B} AdoR affinity and selectivity was evaluated (Table 4). We retained the *m*-F benzyl and *m*-CF_3 benzyl N-1-pyrazolyl groups because these substitutions imparted good affinity and selectivity in the N-1,3-dipropyl derivatives **33** and **36**, respectively, compared

Table 5. A_1, A_{2A}, A_{2B}, and A_3 AdoR Affinity and A_{2B} Selectivity of Selective A_{2B} Antagonists

	K_i nM[a]				A_{2B} selectivity		
compd	A_{2B}[b]	A_1[c]	A_{2A}[d]	A_3[e]	A_1/A_{2B}	A_{2A}/A_{2B}	A_3/A_{2B}
22	9	20	230	23	2	23	2
19	11	76	290	170	7	26	15
33	14	170	230	56	13	17	4
36	14	170	400	150	12	28	10
50	22	1200	1400	2800	54	63	129
60	1	990	690	1000	990	690	1000

[a] The 95% Confidence Intervals are generally within 15% of the mean value. [b] The binding affinity for the A_{2B} AdoR was determined by the competition for the binding sites labeled by ^{3}H-ZM241385 (14 nM) in membranes prepared from HEK-A_{2B} cells. [c] The binding affinity for the A_1 AdoR was determined by the competition for the binding sites labeled by ^{3}H-CPX (0.5 nM) in membranes prepared from CHO-A_1 cells. [d] The binding affinity for the A_{2A} AdoR was determined by the competition for the binding sites labeled by ^{3}H-ZM241385 (2 nM) in membranes prepared from HEK-A_{2A} cells. [e] The binding affinity for A_3 AdoR was determined using CHO-A_3 cells with ^{125}I-AB-MECA as the radioligand.

with those of other substitution patterns. For comparison purposes, the corresponding unsubstituted benzyl derivatives were prepared as well. The 1,3-dimethyl xanthine derivative **58** with the unsubstituted benzyl derivative had low affinity for the AdoRs, whereas the corresponding *m*-F benzyl derivative **59** had good binding affinity for the A_{2B} receptor and favorable selectivity (Table 4). The 1,3-dimethyl xanthine *m*-CF_3 derivative **60** has very favorable A_{2B} AdoR binding affinity (K_i = 1 nM) and selectivity (A_1/A_{2B} = 990; A_{2A}/A_{2B} = 690) over the those of other AdoRs. 1,3-Diethyl xanthine derivatives **61**−**63** have comparable A_{2B} AdoR affinity similar to that of the dipropyl derivatives (**19**, **33**, and **36**) but displayed higher A_{2B} AdoR binding selectivity. Increasing the N-1 and N-3 alkyl chain length to *n*-butyl or *iso*-butyl groups, as in **64** and **65**−**67**, respectively, resulted in lower A_{2B} AdoR receptor affinity compared to those of the corresponding dipropyl derivative analogues (Table 4). The A_3 AdoR binding affinity of selected A_{2B} AdoR antagonists was evaluated (Table 5). Compounds **50** and **60**, which showed good A_{2B} AdoR binding affinity and selectivity versus A_1 and A_{2A} AdoR, have displayed low affinity for the A_3 AdoR, 2800 and 1000 nM, respectively. Thus, **60** has high affinity (K_i = 1 nM) and selectivity (A_1/A_{2B} = 990; A_{2A}/A_{2B} = 690 A_3/A_{2B} = 1000) for the A_{2B} AdoR over the other AdoRs.

Conclusion

A systematic optimization of 8-(pyrazol-4-yl) xanthine derivatives led to the identification of several selective, high-affinity antagonists for the A_{2B} AdoR subtype. In particular, to our knowledge, 8-(3-trifluoromethylbenzyl-1*H*-pyrazol-4-yl)-1,3-dimethylxanthine **60** has the highest affinity and selectivity described thus far. This selective A_{2B} antagonist **60** can be useful in understanding the physiological role of the A_{2B} AdoR and may serve as a lead toward the discovery of therapeutically useful agents for asthma.

Experimental Section

Commercial chemicals and solvents were of reagent-grade and were used without further purification. The following abbreviations are used for reagents and solvents: DCM, dichloromethane; DMF, dimethyl formamide; DMSO, dimethyl sulfoxide; EtOAc, ethyl acetate; Hex, hexane; EtOH, ethanol; and MeOH, methanol. Whatman silica gel (60 A^0, 230−400 mesh) was used for flash column chromatography. Analtech thin-layer chromatography plates (20 × 20 cm, 2000 microns) were used for preparative thin-layer chromatography. Proton NMR (^{1}H NMR) spectra were recorded on a Varian Gemini-400 spectrometer (400 MHz). Chemical shifts are reported in δ units (parts per million) downfield from tetramethylsilane and are assigned as singlets (s), doublets (d), doublet of doublets (dd), triplets (t), quartet (q), and multiplets (m). Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra (MS) were recorded on Micromass LCZ. Elemental analysis data for final compounds were obtained from Desert Analytics and were within ±0.4% of the theoretical values for the formulas given.

7-*N*-Benzyl-1,3-dipropyl-8-(*N*-1-pyrazolyl)xanthine (8). To a solution of **7a** in DMF, K_2CO_3 was added followed by benzyl bromide, and the reaction mixture was heated at 70 °C for 16 h. K_2CO_3 was filtered off, concentrated in vacuo, purified by column chromatography (EtOAc/Hexane 1:3) to furnish the benzylated derivative 7-*N*-benzyl-1,3-dipropylxanthine (**7b**) in 90% yield. A mixture of **7b** (7.0 g, 21.4 mmol) and *N*-chlorosuccinimide (4.28 g, 32.2 mmol) in 125 mL of THF was stirred under nitrogen at room temperature for 24 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc. The combined organics were dried over $MgSO_4$ and concentrated in vacuo to afford **7c** as an oil. Purification by silica gel column chromatography (EtOAc/Hexane 1:5) gave 5.0 g of 7-*N*-benzyl-8-chloro-1,3-dipropylxanthine (**7c**). A suspension of NaH (60% dispersion in mineral oil) (467 mg, 11.7 mmol) was washed with hexane (10 mL), and then, DMF (10 mL) was added. To this suspension, the pyrazole (797 mg, 11.7 mmol) in 10 mL of DMF was slowly added. The reaction mixture was stirred at room temperature until all bubbles subsided (10 min). Then, compound **7c** (420 mg, 1.17 mmol) was added, and the resulting reaction mixture was heated at 70 °C for 4 h. The reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC by eluting with CH_2Cl_2/MeOH (10:1) to provide 130 mg (28%) of the desired product. ^{1}H NMR ($CDCl_3$): δ 8.16 (s, 1H), 7.80 (s, 1H), 7.36−7.15 (m, 5H), 6.50 (s, 1H), 6.15 (s, 2H), 4.15−3.80 (m, 4H), 1.80−1.60 (m, 4H), 1.05−0.85 (m, 6H); MS *m*/*z* 392.9 $(M + H)^+$.

7-*N*-Benzyl-1,3-dipropyl-8-[*N*-1-(4-iodo)pyrazolyl]xanthine (9). Following the above procedure, the displacement of the 8-chloro group with 4-iodo pyrazole furnished the desired product **9** in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1 H), 7.79 (s, 1 H), 7.16−7.27 (m, 6.5 H), 6.07 (s, 2 H), 4.01 (t, *J* = 8.0 Hz, 2 H), 3.97 (t, *J* = 8.0 Hz, 2 H), 1.74−1.80 (m, 2 H), 1.64−1.72 (m, 2 H),) 0.98 (t, *J* = 8.0 Hz, 3 H), 0.96 (t, *J* = 8.0 Hz, 3 H); MS *m*/*z* 518.8 $(M + H)^+$.

1,3-Dipropyl-8-(*N*-1-pyrazolyl)xanthine (10). A mixture of **9** (100 mg, 0.255 mmol), palladium hydroxide (20 wt % Pd on carbon) (137 mg, 0.979 mmol), and cyclohexene (9 mL) in EtOH (15 mL) was heated at 80 °C for 72 h. The reaction mixture was filtered through Celite and concentrated in vacuo. The resulting solid was purified by preparative TLC (EtOAc/Hexane 1:5) to provide 13 mg of **10** as a white solid, and 55 mg of starting material **9** was recovered (55% yield based on recovered starting material). ^{1}H NMR (CD_3OD): δ 8.12 (s, 1H), 7.02 (s, 1H), 6.35 (s, 1H), 4.15−3.80 (m, 4H), 1.80−1.50 (m, 4H), 0.95−0.75 (m, 6H); MS *m*/*z* 302.9 $(M + H)^+$.

General Procedure for the Synthesis of Compounds 11−21. A mixture of diamine **6** (9.42 g, 41.7 mmol), pyrazole acid (8.0 g, 39.6 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (7.6 g, 39.6 mmol) were dissolved in methanol (100 mL) and stirred at room temperature for 16 h. The precipitate was filtered off and washed with water. The uncyclized product was dissolved in methanol (20 mL) and 10% aqueous NaOH (20 mL) and heated at 100 °C for 2 h. Methanol was evaporated, and the residue was dissolved in water and acidified with 6 N HCl to pH 3−4. The precipitate thus formed was collected and washed with water and methanol and dried to furnish xanthine derivatives **11**−**21** in 60−80% yield.

8-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-1,3-dipropyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (11). Following the general procedure described above, the coupling of diamine **6** with 1,3-dimethylpyrazole-5-carboxylic acid and cyclization furnished xanthine derivative **11** in 60% yield. ^{1}H NMR (DMSO-d_6): δ 6.75 (s, 1H), 4.13 (s, 3H),

4.01 (t, J = 8.0 Hz, 2H), 3.86 (t, J = 8.0 Hz, 2H), 2.18 (s, 3H), 1.80−1.70 (m, 2H), 1.62−1.52 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H), 0.87 (t, J = 8.0 Hz, 3H); MS *m*/*z* 331.38 $(M + H)^+$.

8-(1-Ethyl-3-methyl-1*H*-pyrazol-5-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12). The coupling of diamine **6** and 1-ethyl-3-methyl-pyrazole-5-carboxylic acid as described above furnished **12** in 70% yield. ^{1}H NMR (DMSO-d_6): δ 6.74 (s, 1H), 4.60 (q, J = 8.0 Hz, 2H), 4.00 (t, J = 8.0 Hz, 2H), 3.86 (t, J = 8.0 Hz, 2H), 2.18 (s, 3H), 1.73 (q, J = 8.0 Hz, 2H), 1.57 (q, J = 8.0 Hz, 2H), 1.32 (t, J = 8.0 Hz, 3H), 0.89 (t, J = 8.0 Hz, 3H), 0.87 (t, J = 8.0 Hz, 3H); MS *m*/*z* 345.40 $(M + H)^+$.

8-(1-Phenyl-1*H*-pyrazol-5-yl)-1,3-dipropyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (13). The coupling of diamine **6** and 1-phenyl-pyrazole-5-carboxylic acid as described above furnished xanthine derivative **13** in 70% yield. ^{1}H NMR (DMSO-d_6): δ 7.82 (s, 1H), 7.60−7.40 (m, 5H), 7.12 (s, 1H), 3.82 (t, J = 8.0 Hz, 2H), 3.64 (t, J = 8.0 Hz, 2H), 1.60−1.50 (m, 2H), 1.50−1.30 (m, 2H), 0.85 (t, J = 8.0 Hz, 3H), 0.68 (t, J = 8.0 Hz, 3H); MS *m*/*z* 379.42 $(M + H)^+$.

8-(1-Phenyl-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (14). The coupling of diamine **6** and 1-phenyl-pyrazole-4-carboxylic acid as described above furnished xanthine derivative **14** in 80% yield. ^{1}H NMR (DMSO-d_6): δ 9.04 (s, 1H), 8.36 (s, 1H), 7.95−7.35 (m, 5H), 4.03 (t, J = 8.0 Hz, 2H), 3.86 (t, J = 8.0 Hz, 2H), 1.85−1.55 (m, 4H), 0.93 (t, J = 8.0 Hz, 3H), 0.90 (t, J = 8.0 Hz, 3H); MS *m*/*z* 379.43 $(M + H)^+$.

8-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (15). Following the general procedure described above, the coupling of diamine **6** with 5-methyl-1-phenyl-pyrazole-4-carboxylic acid furnished xanthine derivative **15** in 65% yield. ^{1}H NMR (DMSO-d_6): δ 8.34 (s, 1H), 7.70−7.50 (m, 5H), 4.04 (t, J = 8.0 Hz, 2H), 3.90 (t, J = 8.0 Hz, 2H), 2.70 (s, 3H), 1.85−1.55 (m, 4H), 1.00−0.80 (m, 6H); MS *m*/*z* 393.45 $(M + H)^+$.

8-(1-Phenyl-5-propyl-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (16). Following the general procedure described above, the coupling of diamine **6** with 1-phenyl-5-propyl-pyrazole-4-carboxylic acid furnished **16** in 70% yield. ^{1}H NMR (DMSO-d_6): δ 8.36 (s, 1H), 7.75−7.45 (m, 5H), 4.03 (t, J = 8.0 Hz, 3H), 3.89 (t, J = 8.0 Hz, 3H), 3.07 (t, J = 8.0 Hz, 2H), 1.90−1.50 (m, 6H), 1.00−0.80 (m, 9H); MS *m*/*z* 421.50 $(M + H)^+$.

8-(5-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (17). Following the general procedure described above, the coupling of diamine **6** with 5-trifluoromethyl-1-phenyl-pyrazol-4-carboxylic acid furnished xanthine derivative **17** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.38 (s, 1H), 7.80−7.60 (m, 5H), 4.01 (t, J = 8.0 Hz, 2H), 3.89 (t, J = 8.0 Hz, 2H), 1.80−1.50 (m, 5H), 0.94−0.87 (m, 6H); MS *m*/*z* 447.42 $(M + H)^+$.

8-(1-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (18). Following the general procedure described above, the coupling of diamine **6** with 4-chlorophenyl-5-(trifluoromethyl)-pyrazol-4-carboxylic acid furnished xanthine derivative **18** in 65% yield. ^{1}H NMR (DMSO-d_6): δ 8.28 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.01 (t, J = 8.0 Hz, 2H), 3.88 (t, J = 8.0 Hz, 2H), 1.80−1.50 (m, 5H), 0.94−0.87 (m, 6H); MS *m*/*z* 481.85 $(M + H)^+$.

8-(1-Benzyl-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (19). The 1-benzyl-pyralzol-4-carboxylic acid required for coupling is synthesized as follows. A mixture of ethyl-4-pyrazole carboxylate (10 g, 71.4 mmol), potassium carbonate (49.3 g, 357 mmol), and benzyl bromide (12.2 g, 71.4 mmol) in acetone (400 mL) was refluxed overnight. K_2CO_3 was filtered off. The filtrate was concentrated in vacuo. The residue was taken up in MeOH (200 mL), and solid potassium hydroxide (20.5 g, 366 mmol) was added, and the resulting reaction mixture was refluxed overnight. The reaction mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was acidified to pH 3 with concd HCl. The precipitate was collected and washed with H_2O to give a 97% yield of 1-benzyl-pyrazol-4-carboxylic acid. The coupling of diamine **6** with 1-benzyl-pyrazol-4-carboxylic acid as described in the general procedure furnished xanthine derivative **19** in 80% yield. ^{1}H NMR (DMSO-d_6): δ 13.51 (s, 1 H), 8.45 (s, 1 H), 8.08 (s, 1 H), 7.38−7.27 (m, 5 H), 5.39 (s, 2 H), 3.96 (t, J = 8.0 Hz, 2 H), 3.83 (t, J = 8.0 Hz, 2 H), 1.75−1.64 (m, 2 H), 1.60−1.50 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS *m*/*z* 393.37 $(M + H)^+$; Anal. ($C_{21}H_{24}N_6O_2 \cdot 0.75H_2O$): C,H,N.

8-(1-Phenethyl-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (20). Following the general procedure described above, the coupling of diamine **6** with 1-phenethyl-pyrazole-4-carboxylic acid furnished xanthine derivative **20** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.25 (s, 1H), 8.07 (s, 1H), 7.40−7.15 (m, 5H), 4.41 (t, J = 8.0 Hz, 2H), 3.96 (t, J = 8.0 Hz, 2H), 3.84 (t, J = 8.0 Hz, 2H), 3.13 (t, J = 8.0 Hz, 2H), 1.80−1.50 (m, 4H), 0.88 (t, J = 8.0 Hz, 3H), 0.86 (t, J = 8.0 Hz, 3H); MS *m*/*z* 405.28 $(M - H)^+$; Anal. ($C_{22}H_{26}N_6O_2$): C,H,N.

8-(1-(3-Phenylpropyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (21). Following the general procedure described above, the coupling of diamine **6** with 1-(3-phenylpropyl)-pyrazole-4-carboxylic acid furnished xanthine adduct **21** in 75% yield. ^{1}H NMR (Methanol-d_4): δ 8.10 (s, 1 H), 8.04 (s, 1 H), 7.30−7.11 (m, 5 H), 4.17 (t, J = 8.0 Hz, 2 H), 4.05 (t, J = 8.0 Hz, 2 H), 3.93 (t, J = 8.0 Hz, 2H), 2.61 (t, J = 8.0 Hz, 2 H), 2.26−2.15 (m, 2 H), 1.84−1.72 (m, 2 H), 1.71−1.59 (m, 2 H), 0.96 (t, J = 8.0 Hz, 3 H), 0.92 (t, J = 8.0 Hz, 3 H); MS *m*/*z* 418.9 $(M - H)^+$; Anal. ($C_{23}H_{28}N_6O_2$): C,H,N.

General Procedure for the Synthesis of Compounds 22−54. A mixture of **19** (2.5 g, 6.38 mmol), potassium carbonate (4.40 g, 31.9 mmol) in DMF (70 mL) was stirred at room temperature under nitrogen. To this mixture was added dropwise 2-(trimethylsilyl)-ethoxymethyl chloride (5.33 g, 31.9 mmol). The resulting reaction mixture was stirred overnight at room temperature, and K_2CO_3 was filtered off. The filtrate was concentrated in vacuo, and the resulting oil was purified by silica gel column chromatography (EtOAc/Hexane 1:3) to give 3.0 g (90%) of the product, **19a**. A mixture of SEM-protected benzyl derivative **19a** (3.0 g, 5.74 mmol), palladium hydroxide (20 wt % Pd on carbon) (5.0 g), and cyclohexene (50 mL) in EtOH (100 mL) was heated at 80 °C for 2 days. The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane 1:3) to provide 1.0 g (40%) of debenzylated derivative **19b** as a white solid. A mixture of SEM-protected debenzylated **19b** (80 mg, 0.185 mmol), alkyl halide (1.85 mmol), and K_2CO_3 (255 mg, 1.85 mmol) in DMF (4 mL) was stirred overnight at room temperature, and K_2CO_3 was filtered off. The filtrate was concentrated in vacuo and was purified by preparative TLC. The product was dissolved in EtOH and treated with 2 N HCl (3 mL) at 100 °C for 2 h. The reaction mixture was concentrated in vacuo. The residue was washed with ether to provide the title compounds in 50−82% yield.

1,3-Dipropyl-8-(1*H*-pyrazol-4-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (22). A solution of **19b** (250 mg) in EtOH (5 mL) was treated with 2 N HCl (2 mL) at 100 °C for 2 h. The reaction mixture was concentrated in vacuo, and the residue was treated with ether to furnish xanthine derivative **22** in 80% yield as a white solid. ^{1}H NMR (DMSO-d_6): δ 13.39 (s, 1 H), 13.23 (s, 1 H), 8.28 (s, 1 H), 8.01 (s, 1 H), 3.90 (t, J = 8.0 Hz, 2 H), 3.77 (t, J = 8.0 Hz, 2 H), 1.68−1.59 (m, 2 H), 1.53−1.44 (m, 2 H), 0.80 (t, J = 8.0 Hz, 3 H), 0.78 (t, J = 8.0 Hz, 3 H); MS *m*/*z* 301.24 $(M - H)^+$; Anal. ($C_{14}H_{18}N_6O_2 \cdot 0.7H_2O$): C,H,N.

8-(1-(2-Methylbenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (23). Following the general procedure, the alkylation of **19b** with 2-methylbenzyl bromide followed by deprotection furnished **23** in 55% yield. ^{1}H NMR (DMSO-d_6): δ 8.40 (s, 1H), 8.0 (s, 1H), 7.36−7.05 (m, 5H), 5.38 (s, 2H), 4.14 (t, J = 8.0 Hz, 2H), 3.46 (t, J = 8.0 Hz, 2H), 2.38 (s, 3H), 1.86−1.60 (m, 4H), 0.96 (t, J = 8.0 Hz, 6H); MS *m*/*z* 407.2 $(M + H)^+$; Anal. ($C_{22}H_{26}N_6O_2 \cdot 0.5H_2O$): C,H,N.

8-(1-(3-Methylbenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (24). Following the general procedure, the alkylation of **19b** with 3-methylbenzyl bromide followed by deprotection furnished **24** in 60% yield. ^{1}H NMR (DMSO-d_6): δ 8.29 (s, 1 H), 7.94 (s, 1 H), 6.92−7.13 (m, 4 H), 5.20 (s, 2H), 3.82

(t, J = 8.0 Hz, 2 H), 3.70 (t, J = 8.0 Hz, 2 H), 2.14 (s, 3 H), 1.51−1.62 (m, 2 H), 1.36−1.48 (m, 2 H), 0.73 (t, J = 8.0 Hz, 3 H), 0.70 (t, J = 8.0 Hz, 3 H) MS m/z 407.20 $(M + H)^+$; Anal. ($C_{22}H_{26}N_6O_2$.HCl): C,H,N.

8-(1-(4-Methylbenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (25). Following the general procedure, the alkylation of **19b** with 4-methylbenzyl bromide followed by deprotection furnished **25** in 70% yield. ^{1}H NMR (DMSO-d_6): δ 8.27 (s, 1 H), 7.92 (s, 1 H), 6.99−7.08 (m, 4 H), 5.19 (s, 2 H), 3.82 (t, J = 8.0 Hz, 2 H), 3.69 (t, J = 8.0 Hz, 2 H), 2.13 (s, 3 H), 1.51−1.61 (m, 2 H), 1.36−1.47 (m, 2 H), 0.73 (t, J = 8.0 Hz, 3 H), 0.72 (t, J = 8.0 Hz, 3 H); MS m/z 407.18 $(M + H)^+$; Anal. ($C_{22}H_{26}N_6O_2 \cdot 0.5H_2O$): C,H,N.

8-(1-(2-Methoxybenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (26). Following the general procedure, the alkylation of **19b** with 2-methoxybenzyl bromide followed by deprotection furnished **26** in 70% yield. ^{1}H NMR (DMSO-d_6): δ 8.29 (s, 1 H), 8.02 (s, 1 H), 7.26−7.32 (m, 1 H), 6.95−7.05 (m, 2 H), 6.86−6.92 (m, 1 H), 5.30 (s, 2 H), 3.91−3.95 (m, 2 H), 3.78−3.83 (m, 5 H), 1.64−1.70 (m, 2 H), 1.50−1.56 (m, 2 H), 0.84 (t, J = 8.0 Hz, 3H), 0.82 (t, J = 8.0 Hz, 3 H); MS m/z 423.10 $(M + H)^+$; Anal. ($C_{22}H_{26}N_6O_3$.HCl): C,H,N.

8-(1-(3-Methoxybenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (27). Following the general procedure, the alkylation of **19b** with 3-methoxybenzyl bromide followed by deprotection furnished **27** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.45 (s, 1 H), 8.08 (s, 1 H), 7.23−7.29 (m, 1 H), 6.82−6.89 (m, 3 H), 5.35 (s, 2 H), 3.96 (t, J = 8.0 Hz, 2 H), 3.83 (t, J = 8.0 Hz, 2 H), 3.72 (s, 3 H), 1.65−1.73 (m, 2 H), 1.50−1.59 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 423.10 $(M + H)^+$; Anal. ($C_{22}H_{26}N_6O_3 \cdot 0.5H_2O$): C,H,N.

8-(1-(4-Methoxybenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (28). Following the general procedure, the alkylation of **19b** with 4-methoxybenzyl bromide followed by deprotection furnished **28** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.25 (s, 1H), 7.94 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 8.0 Hz, 2H), 5.15 (s, 2H), 3.82 (t, J = 8.0 Hz, 2H), 3.65 (t, J = 8.0 Hz, 2H), 3.60 (s, 3H), 1.62−1.36 (m, 4H), 0.74 (t, J = 8.0 Hz, 3H), 0.70 (t, J = 8.0 Hz, 3H); MS m/z 423.01 $(M + H)^+$; Anal. ($C_{22}H_{26}N_6O_3$.0.75HCl): C,H,N.

8-(1-(2-Chlorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (29). Following the general procedure, the alkylation of **19b** with 2-chlorobenzyl chloride followed by deprotection furnished **29** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.44 (s, 1 H), 8.10 (s, 1 H), 7.48−7.54 (m, 1 H), 7.32−7.39 (m, 2 H), 7.12−7.18 (m, 1 H), 5.50 (s, 2 H), 3.96 (t, J = 8.0 Hz, 2 H), 3.83 (t, J = 8.0 Hz, 2 H), 1.67−1.73 (m, 2 H), 1.52−1.59 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 427.04 $(M + H)^+$; Anal. ($C_{21}H_{23}ClN_6O_2$): C,H,N.

8-(1-(3-Chlorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (30). Following the general procedure, the alkylation of **19b** with 3-chlorobenzyl chloride followed by deprotection furnished **30** in 70% yield. ^{1}H NMR (DMSO-d_6): δ 8.40 (s, 1H), 7.96 (s, 1H), 7.30−7.05 (m, 4H), 5.26 (s, 2H), 3.82−3.72 (m, 4H), 1.62−1.36 (m, 4H), 0.78 (t, J = 8.0 Hz, 3H), 0.76 (t, J = 8.0 Hz, 3H); MS m/z 427 $(M + H)^+$; Anal. ($C_{21}H_{23}ClN_6O_2$): C,H,N.

8-(1-(4-Chlorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (31). Following the general procedure, the alkylation of **19b** with 4-chlorobenzyl chloride followed by deprotection furnished **31** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.38 (s, 1H), 7.98 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 5.24 (s, 2H), 3.82 (t, J = 8 Hz, 2H), 3.70 (t, J = 8.0 Hz, 2H), 1.62−1.36 (m, 4H), 0.78 (t, J = 8.0 Hz, 3H), 0.74 (t, J = 8.0 Hz, 3H); MS m/z 426.98 $(M + H)^+$; Anal. ($C_{21}H_{23}ClN_6O_2$.0.5CH_2Cl_2): C,H,N.

8-(1-(2-Fluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (32). Following the general procedure, the alkylation of **19b** with 2-fluorobenzyl chloride followed by deprotection furnished **32** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.44 (s, 1 H), 8.10 (s, 1 H), 7.17−7.43 (m, 4 H), 5.46 (s, 2 H), 3.96 (t, J = 8.0 Hz, 2 H), 3.83 (t, J = 8.0 Hz, 2 H), 1.67−1.73 (m, 2 H), 1.52−1.59 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 411.08 $(M + H)^+$; Anal. ($C_{21}H_{23}FN_6O_2 \cdot 0.5H_2O$): C,H,N.

8-(1-(3-Fluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (33). Following the general procedure, the alkylation of **19b** with 3-fluorobenzyl chloride followed by deprotection furnished **33** in 70% yield. ^{1}H NMR (DMSO-d_6): δ 8.49 (s, 1 H), 8.10 (s, 1 H), 7.36−7.45 (m, 1 H), 7.08−7.18 (m, 3 H), 5.42 (s, 2 H), 3.96 (t, J = 8.0 Hz, 2 H), 3.83 (t, J = 8.0 Hz, 2 H), 1.67−1.73 (m, 2 H), 1.52−1.59 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 411.07 $(M + H)^+$; Anal. ($C_{21}H_{23}FN_6O_2 \cdot 1.25H_2O$): C,H,N.

8-(1-(4-Fluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (34). Following the general procedure, the alkylation of **19b** with 4-fluorobenzyl chloride followed by deprotection furnished **34** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.38 (s, 1H), 7.96 (s, 1H), 5.24 (s, 2H), 3.82 (t, J = 8.0 Hz, 2H), 3.66 (t, J = 8.0 Hz, 3H), 1.62−1.30 (m, 4H), 0.84 (t, J = 8.0 Hz, 3H), 0.82 (t, J = 8.0 Hz, 3H); MS m/z 411 $(M + H)^+$; Anal. ($C_{21}H_{23}FN_6O_2 \cdot H_2O$): C,H,N.

8-(1-(2-(Trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (35). Following the general procedure, the alkylation of **19b** with 2-trifluoromethylbenzyl chloride followed by deprotection furnished **35** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.48 (s, 1 H), 8.13 (s, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.65 (t, J = 8.0 Hz, 1 H), 7.54 (t, J = 8.0 Hz, 1 H), 7.08 (d, J = 8.0 Hz, 1 H), 5.60 (s, 2 H), 3.96 (t, J = 8.0 Hz, 2 H), 3.84 (t, J = 8.0 Hz, 2 H), 1.67−1.73 (m, 2 H), 1.52−1.59 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 461.17 $(M + H)^+$; Anal. ($C_{22}H_{23}F_3N_6O_2 \cdot 1.25H_2O$): C,H,N.

8-(1-(3-(Trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (36). Following the general procedure, the alkylation of **19b** with 3-trifluoromethylbenzyl chloride followed by deprotection furnished **36** in 80% yield. ^{1}H NMR (DMSO-d_6): δ 8.53 (s, 1 H), 8.11 (s, 1 H), 7.68 (s, 1 H), 7.56−7.62 (m, 3 H), 5.51 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (t, J = 8.0 Hz, 3 H), 1.65−1.75 (m, 2 H), 1.52−1.59 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 461.06 $(M + H)^+$; Anal. ($C_{22}H_{23}F_3N_6O_2 \cdot H_2O$): C,H,N.

8-(1-(4-(Trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (37). Following the general procedure, the alkylation of **19b** with 4-trifluoromethylbenzyl chloride followed by deprotection furnished **37** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.52 (s, 1H), 8.10 9s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 5.50 (s, 2H), 3.96 (t, J = 8.0 Hz, 2H), 3.82 (t, J = 8.0 Hz, 2H), 1.78−1.48 (m, 4H), 0.88 (t, J = 8.0 Hz, 3H), 0.86 (t, J = 8.0 Hz, 3H); MS m/z 461 $(M + H)^+$; Anal. ($C_{22}H_{23}F_3N_6O_2$.0.75CH_2Cl_2): C,H,N.

8-(1-(2,3-Difluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (38). Following the general procedure, the alkylation of **19b** with 2,3-difluorobenzyl chloride followed by deprotection furnished **38** in 70% yield. ^{1}H NMR (DMSO-d_6): δ 8.45 (s, 1 H), 8.09 (s, 1 H), 7.07−7.47 (m, 3 H), 5.52 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (t, J = 8.0 Hz, 3 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H) MS m/z 429.33 $(M + H)^+$; Anal. ($C_{21}H_{22}F_2N_6O_2$. 0.25CH_2Cl_2): C,H,N.

8-(1-(2,4-Difluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (39). Following the general procedure, the alkylation of **19b** with 2,4-difluorobenzyl chloride followed by deprotection furnished **39** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.44 (s, 1 H), 8.07 (s, 1 H), 7.07−7.44 (m, 3 H), 5.43 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (t, J = 8.0 Hz, 3 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 429.30 $(M + H)^+$. Anal. ($C_{21}H_{22}F_2N_6O_2$. 0.5CH_2Cl_2): C,H,N.

8-(1-(2,6-Difluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (40). Following the general procedure, the alkylation of **19b** with 2,6-difluorobenzyl bromide followed by deprotection furnished **40** in 65% yield. ^{1}H NMR (DMSO-d_6): δ 8.44 (s, 1 H), 8.02 (s, 1 H), 7.43−7.52 (m, 1 H), 7.13−7.21 (m, 2 H), 5.46 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (t, J = 8.0 Hz, 3

H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 429.34 $(M + H)^+$; Anal. ($C_{21}H_{22}F_2N_6O_2$. $0.5CH_2Cl_2$): C,H,N.

8-(1-(3,4-Difluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (41). Following the general procedure, the alkylation of **19b** with 3,4-difluorobenzyl chloride followed by deprotection furnished **41** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.49 (s, 1 H), 8.10 (s, 1 H), 7.37−7.48 (m, 2 H), 7.12−7.18 (m, 1 H), 5.39 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (t, J = 8.0 Hz, 3 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 429.29 $(M + H)^+$; Anal. ($C_{21}H_{22}F_2N_6O_2$. HCl): C,H,N.

8-(1-(3-Chloro-2-fluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (42). Following the general procedure, the alkylation of **19b** with 3-chloro-2-fluorobenzyl chloride followed by deprotection furnished **42** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.49 (s, 1 H), 8.09 (s, 1 H), 7.54−7.61 (m, 1 H), 7.19−7.29 (m, 2 H), 5.51 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (t, J = 8.0 Hz, 3 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 443.18 $(M - H)^+$; Anal. ($C_{21}H_{22}ClFN_6O_2$): C,H,N.

8-(1-(2-Fluoro-3-methylbenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (43). Following the general procedure, the alkylation of **19b** with 2-fluoro-3-methylbenzyl bromide followed by deprotection furnished **43** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.43 (s, 1 H), 8.07 (s, 1 H), 7.21−7.29 (m, 1 H), 7.04−7.13 (m, 2 H), 5.43 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (t, J = 8.0 Hz, 3 H), 2.23 (s, 3 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 425.26 $(M + H)^+$; Anal. ($C_{22}H_{25}FN_6O_2 \cdot 1.25H_2O$): C,H,N.

8-(1-(4-Fluoro-3-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (44). Following the general procedure, the alkylation of **19b** with 4-fluoro-3-trifluoromethylbenzyl bromide followed by deprotection furnished **44** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 13.49 (s, 1 H), 8.52 (s, 1 H), 8.11 (s, 1 H), 7.48−7.81 (m, 3 H), 5.48 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (t, J = 8.0 Hz, 3 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 479.26 $(M + H)^+$; Anal. ($C_{22}H_{22}F_4N_6O_2$): C,H,N.

8-(1-(4-Chloro-3-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (45). Following the general procedure, the alkylation of **19b** with 4-chloro-3-trifluoromethylbenzyl bromide followed by deprotection furnished **45** in 81% yield. ^{1}H NMR (DMSO-d_6): δ 13.55 (s, 1 H), 8.53 (s, 1 H), 8.12 (s, 1 H), 7.84 (s, 1 H), 7.73 (d, J = 8.0 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 5.50 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (t, J = 8.0 Hz, 3 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 495.30 $(M + H)^+$; Anal. ($C_{22}H_{22}ClF_3N_6O_2$): C,H,N.

8-(1-(3,5-Bis(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (46). Following the general procedure, the alkylation of **19b** with 3,5-bistrifluoromethylbenzyl bromide followed by deprotection furnished **46** in 78% yield. ^{1}H NMR (DMSO-d_6): δ 8.55 (s, 1 H), 8.14 (s, 1 H), 8.10 (s, 1 H), 8.02 (s, 2 H), 5.61 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (m, 7 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 529.33 $(M + H)^+$; Anal. ($C_{23}H_{22}F_6N_6O_2 \cdot 0.5H_2O$): C,H,N.

8-(1-(3-(Trifluoromethyl)-4-methoxybenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (47). Following the general procedure, the alkylation of **19b** with 3-trifluoromethyl-4-methoxybenzyl bromide followed by deprotection furnished **47** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 8.47 (s, 1 H), 8.08 (s, 1 H), 7.63 (s, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.26 (d, J = 8.0 Hz, 1 H), 5.38 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (m, 7 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 491.35 $(M + H)^+$; Anal. ($C_{23}H_{25}F_3N_6O_3 \cdot 0.5H_2O$): C,H,N.

8-(1-(2,5-Dichlorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (48). Following the general procedure, the alkylation of **19b** with 2,5-dichlorobenzyl chloride followed by deprotection furnished **48** in 68% yield. ^{1}H NMR (DMSO-d_6): δ 8.40 (s, 1H), 8.02 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.18 (s, 1H), 5.42 (s, 2H), 3.90 (t, J = 8.0 Hz, 2H), 3.76 (t, J = 8.0 Hz, 2H), 1.73−1.40 (m, 4H), 0.82 (t, J = 8.0 Hz, 3H), 0.80 (t, J = 8.0 Hz, 3H); MS m/z 461.19 $(M + H)^+$; Anal. ($C_{21}H_{22}Cl_2N_6O_2$. $0.5CH_2Cl_2$): C,H,N.

8-(1-(2-Chloro-5-fluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (49). Following the general procedure, the alkylation of **19b** with 2-chloro-5-flouorobenzyl chloride followed by deprotection furnished **49** in 73% yield. ^{1}H NMR (DMSO-d_6): δ 13.49 (s, 1 H), 8.42 (s, 1 H), 8.02 (s, 1 H), 7.29−7.53 (m, 3 H), 5.52 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83 (t, J = 8.0 Hz, 3 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 445.26 $(M + H)^+$; Anal. ($C_{21}H_{22}ClFN_6O_2$): C,H,N.

8-(1-(2-Chloro-5-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (50). Following the general procedure, the alkylation of **19b** with 2-chloro-5-trifluoromethylbenzyl chloride followed by deprotection furnished **50** in 76% yield. ^{1}H NMR (DMSO-d_6): δ 13.55 (s, 1 H), 8.51 (s, 1 H), 8.12 (s, 1 H), 7.76 (br s, 2 H), 7.61 (s, 1 H), 5.60 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83−3.52 (m, 7 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 495.18 $(M + H)^+$; Anal. ($C_{22}H_{22}ClF_3N_6O_2$): C,H,N.

8-(1-(3-Chloro-2-fluoro-5-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (51). Following the general procedure, the alkylation of **19b** with 3-chloro-2-fluoro-5-trifluoromethylbenzyl chloride followed by deprotection furnished **51** in 66% yield. ^{1}H NMR (DMSO-d_6): δ 8.54 (s, 1 H), 8.11−8.15 (m, 1 H), 8.10 (s, 1 H), 7.76−7.80 (m, 1 H), 5.59 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83−3.50 (m, 7 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H) 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 513.36 $(M + H)^+$; Anal. ($C_{22}H_{21}ClF_4N_6O_2 \cdot H_2O$): C,H,N.

8-(1-(2,4,6-Trifluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dipropyl-1*H*-purine-2,6(3*H*,7*H*)-dione (52). Following the general procedure, the alkylation of **19b** with 2,4,6-trifluorobenzyl chloride followed by deprotection furnished **52** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 13.51 (s, 1 H), 8.44 (s, 1 H), 8.03 (s, 1 H), 7.24−7.33 (m, 2 H), 5.42 (s, 2 H), 3.96 (t, J = 8.0 Hz, 3 H), 3.83−3.50 (m, 7 H), 1.65−1.74 (m, 2 H), 1.50−1.60 (m, 2 H), 0.87 (t, J = 8.0 Hz, 3 H), 0.85 (t, J = 8.0 Hz, 3 H); MS m/z 447.40 $(M + H)^+$; Anal. ($C_{21}H_{21}F_3N_6O_2$.$0.25CH_2Cl_2$): C,H,N.

General Procedure for the Preparation of Compounds 56a−d. Diamines **56a−d** were synthesized following the methods described in the literature.[12] To a stirred solution of 1,3-dimethylurea **53a** (3.52 g, 40 mmol) in acetic anhydride (30 mL) was added cyanoacetic acid (3.74 g, 44 mmol), and the resulting mixture was stirred overnight at 70 °C. The reaction mixture was concentrated, and the resulting oily residue was diluted with H_2O (40 mL) and treated with 5 N NaOH (15 mL). The precipitate thus formed was collected by filtration, washed with cold water, and purified by recrystalization from MeOH/H_2O to give 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**54a**) as a light-yellow solid (4.0 g). Compound **54a** (4.00 g, 25.8 mmol) was stirred in 50% aquesous AcOH solution (160 mL) at 75 °C for 30 min until the reaction mixture became homogeneous. Once the reaction mixture was homogeneous, the temperature was reduced to 50 °C, and sodium nitrite (3.56 g, 51.6 mmol) was added in small portions. After the completion of the addition, the resulting mixture was cooled to r.t. and stirred for 1 h. The resulting precipitate was collected by filtration, washed with water, and dried to afford 6-amino-1,3-dimethyl-5-nitrosopyrimidine 2,4(1*H*,3*H*)-dione (**55a**) as a purple solid (4.70 g). A suspension of compound **55a** (1.10 g, 6.0 mmol) was stirred in 14.5% NH_4OH (40 mL) at 70 °C for 30 min until the reaction mixture became homogeneous. The temperature was reduced to 50 °C, and $Na_2S_2O_4$ (3.13 g, 18.0 mmol) was added in small portions. During the addition, the red solution changed to yellow-green and to light yellow, and the solution was stirred at room temperature for another 30 min. The volume of the reaction mixture was reduced to half and cooled in an ice bath for 1 h, and the precipitate was collected by filtration, followed by washing with

a small amount of water. Compound **56a**, 5,6-diamino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, was collected as a white solid (0.56 g, overall yield 60%). Following the general procedure described above and starting from 1,3-diethyl urea (**53b**) furnished diamine derivative **56b** in 65% overall yield. Following the general procedure described above and starting from 1,3-dibutyl urea (**53c**) furnished diamine derivative **56c** in 68% yield from three steps. Following the general procedure described above and starting from 1,3-diisobutyl urea (**53d**) furnished diamine derivative **56d** in 66% overall yield.

General Procedure for the Synthesis of Compounds 57a−c. To a solution of ethyl-4-pyrazole carboxylate (1 mmol) in acetone, K_2CO_3 (5 mmol) and the corresponding benzyl bromide (1.2 mmol) was added, and the mixture was heated at 50 °C for 16 h. K_2CO_3 was filtered off, and the filtrate was concentrated and used as such for the next step. The residue was dissolved in methanol, and solid KOH (2 mmol) was added, and the mixture was heated at reflux for 18 h. Mehtanol was distilled off under vacuum, and the residue was dissolved in water and washed with ethyl acetate, and the aqueous layer was acidified with 6 N HCl. The resulting precipitate was filtered, washed with water, and dried.

1-Benzyl-1*H*-pyrazole-4-carboxylic Acid (57a). The coupling of the ethyl pyrazole carboxylate with benzyl bromide followed by hydrolysis of the ester as described above furnished pyrazole carboxylic acid **57a** in 95% yield. ^{1}H NMR ($CDCl_3$): δ 12.31 (s, 1H), 8.05 (s, 1H), 8.00 (s, 1H), 7.24−7.00 (m, 5H), 5.34 (s, 2H); MS *m*/*z* 203.20 $(M + H)^+$.

1-(3-Fluorobenzyl)-1*H*-pyrazole-4-carboxylic Acid (57b). The coupling of the ethyl pyrazole carboxylate and 3-fluorobenzyl bromide followed by hydrolysis furnished pyrazole acid **57b** in 96% yield. ^{1}H NMR ($CDCl_3$): δ 8.05 (s, 1H), 7.98 (s, 1H), 7.42−7.34 (m, 1H), 7.12−7.04 (m, 2H), 7.00−6.95 (m, 1H), 5.35 (s, 2H); MS *m*/*z* 221.20 $(M + H)^+$.

1-(3-(Trifluoromethyl)benzyl)-1*H*-pyrazole-4-carboxylic Acid (57c). The coupling of the ethyl pyrazole carboxylate with 3-trifluoromethyl benzyl bromide followed by hydrolysis furnished pyrazole acid **57c** in 95% yield. ^{1}H NMR ($CDCl_3$): δ 8.04 (s, 1H), 7.98 (s, 1H), 7.40−7.33 (m, 1H), 7.12−7.04 (m, 2H), 7.00−6.94 (m, 1H), 5.36 (s, 2H); MS *m*/*z* 271.20 $(M + H)^+$.

General Procedure for the Synthesis of Compounds 58−67. To a stirred solution of substituted *1H*-pyrazol-4-carboxylic acids (**57a−c**, 0.7 mmol**)** and EDCI·HCl (0.77 mmol) in MeOH (15 mL) was added 1,3-symmetrically substituted 5,6-diamino uracils (**56a−d**, 0.7 mol), and the resulting mixture was stirred overnight at r.t. The solvent was concentrated in vacuo, and the resulting white solid was washed with water. The uncyclized product was dissolved in methanol (10 mL) and 2 N NaOH (10 mL) and stirred at 95 °C for 16 h. The reaction mixture was cooled to r.t. and then acidified with 6 N HCl to pH 3−4 in an ice bath. The white precipitate was collected by filtration, washed with water, and dried. Further washings with methanol furnished compounds **58−67** as white solids.

8-(1-Benzyl-1*H*-pyrazol-4-yl)-1,3-dimethyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (58). Following the general procedure described above, the coupling of diamine **56a** with **57a** furnished **58** in 65% yield. ^{1}H NMR (DMSO-d_6): δ 12.31 (s, 1H), 8.38 (s, 1H), 7.81 (s, 1H), 7.25−7.37 (m, 5H), 5.36 (s, 2H), 3.34 (s, 6H); MS *m*/*z* 337.35 $(M + H)^+$; Anal. ($C_{17}H_{16}N_6O_2$ $0.5CH_2Cl_2$): C,H,N.

8-(1-(3-Fluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (59). Following the general procedure described above, the coupling of diamine **56a** with **57b** furnished **59** in 60% yield. ^{1}H NMR (DMSO-d_6): δ 13.53 (s, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 7.38−7.44 (m, 1H), 7.11−7.18 (m, 3H), 5.43 (s, 2H), 3.46 (s, 3H), 3.25 (s, 3H); MS *m*/*z* 355.34 $(M + H)^+$; Anal. ($C_{17}H_{15}FN_6O_2$. $0.5CH_2Cl_2$): C,H,N.

8-(1-(3-(Trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (60). Following the general procedure described above, the coupling of diamine **56a** with **57c** furnished **60** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 13.58 (s, 1H), 8.54 (s, 1H), 8.13 (s, 1H), 7.70−7.72 (m, 2H), 7.57−7.64 (m, 2H), 5.53 (s, 2H), 3.46 (s, 3H), 3.25 (s, 3H); MS *m*/*z* 404.34 $(M + H)^+$, 425.30 $(M^+ + Na)$. Anal. ($C_{18}H_{15}F_3N_6O_2$): C,H,N.

8-(1-Benzyl-1*H*-pyrazol-4-yl)-1,3-diethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (61). Following the general procedure described above, the coupling of diamine **56b** with **57a** furnished **61** in 80% yield. ^{1}H NMR (DMSO-d_6): δ 13.55 (s, 1H), 8.47 (s, 1H), 8.10 (s, 1H), 7.29−7.38 (m, 5H), 5.40 (s, 2H), 4.05 (s, 2H), 3.94 (s, 2H), 1.24 (s, 3H), 1.13 (s, 3H); MS *m*/*z* 365.40 $(M + H)^+$; Anal. ($C_{19}H_{20}N_6O_2$ $0.5CH_2Cl_2$): C,H,N.

8-(1-(3-Fluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-diethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (62). Following the general procedure described above, the coupling of diamine **56b** with **57b** furnished **62** in 76% yield. ^{1}H NMR (DMSO-d_6): δ 13.55 (s, 1H), 8.51 (s, 1H), 8.12 (s, 1H), 7.39−7.45 (m, 1H), 7.11−7.18 (m, 3H), 5.43 (s, 1H), 4.01−4.08 (s, 2H), 3.90−3.96 (m, 2H), 1.05−1.25 (m, 6H); MS *m*/*z* 383.33 $(M + H)^+$, 405.31 $(M^+ + Na)$. Anal. ($C_{19}H_{19}FN_6O_2$ $0.5CH_2Cl_2$): C,H,N.

8-(1-(3-(Trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-diethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (63). Following the general procedure described above, the coupling of diamine **56b** with **57c** furnished **63** in 70% yield. ^{1}H NMR (DMSO-d_6): δ 13.59 (s, 1H), 8.56 (s, 1H), 8.13 (s, 1H), 7.69−7.72 (m, 2H), 7.58−7.64 (m, 2H), 5.52 (s, 2H), 4.05 (q, 2H, J = 6.64 Hz), 3.93 (q, 2H, J = 7.03 Hz), 1.24 (t, 3H, J = 7.03 Hz), 1.13 (t, 3H, J = 6.84 Hz); MS *m*/*z* 433.30 $(M + H)^+$, 455.29 $(M^+ + Na)$; Anal. ($C_{20}H_{19}F_3N_6O_2.0.5CH_2Cl_2$): C,H,N.

8-(1-Benzyl-1*H*-pyrazol-4-yl)-1,3-dibutyl-1*H*-purine-2,6(3*H*,7*H*)-dione (64). Following the general procedure described above, the coupling of diamine **56c** with **57a** furnished **64** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 13.51 (s, 1H), 8.45 (s, 1H), 8.09 (s, 1H), 7.29−7.39 (m, 5H), 5.40 (s, 2H), 4.00 (t, 2H, J = 7.03 Hz), 3.88 (t, 2H, J = 8.0 Hz), 1.63−1.70 (m, 2H), 1.49−1.56 (m, 2H), 1.26−1.33 (m, 4H), 0.88−0.93 (m, 6H); MS *m*/*z* 421.37 $(M + H)^+$, 443.37 $(M^+ + Na)$; Anal. ($C_{23}H_{28}N_6O_2$): C,H,N.

8-(1-Benzyl-1*H*-pyrazol-4-yl)-1,3-diisobutyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (65). Following the general procedure described above, the coupling of diamine **56d** with **57a** furnished **65** in 80% yield. ^{1}H NMR (DMSO-d_6): δ 13.54 (s, 1H), 8.47 (s, 1H), 8.10 (s, 1H), 7.28−7.38 (m, 5H), 5.40 (s, 2H), 3.84 (d, 2H, J = 7.03 Hz), 3.74 (d, 2H, J = 7.42 Hz), 2.20−2.28 (m, 1H), 2.02−2.09 (m, 1H), 0.87 (d, 6H, J = 6.64 Hz), 0.84 (d, 6H, J = 6.64 Hz); MS *m*/*z* 421.51 $(M + H)^+$, 443.50 $(M^+ + Na)$.

8-(1-(3-Fluorobenzyl)-1*H*-pyrazol-4-yl)-1,3-diisobutyl-1*H*-purine-2,6(3*H*,7*H*)-dione (66). Following the general procedure described above, the coupling of diamine **56d** with **57b** furnished **66** in 75% yield. ^{1}H NMR (DMSO-d_6): δ 13.55 (s, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 7.39−7.44 (m, 1H), 7.11−7.18 (m, 3H), 5.43 (s, 2H), 3.85 (d, 2H, J = 7.42 Hz), 3.74 (d, 2H, J = 7.81 Hz), 2.21−2.28 (m, 1H), 2.03−2.10 (m, 1H), 0.87 (d, 2H, J = 6.45 Hz), 0.84 (d, 6H, J = 6.45 Hz); MS *m*/*z* 439.43 $(M + H)^+$, 461.43 $(M^+ + Na)$.

8-(1-(3-(Trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)-1,3-diisobutyl-1*H*-purine-2,6(3*H*,7*H*)-dione (67). Following the general procedure described above, the coupling of diamine **56d** with **57c** furnished **67** in 80% yield. ^{1}H NMR (DMSO-d_6): δ 13.55 (s, 1H), 8.54 (s, 1H), 8.12 (s, 1H), 7.67−7.70 (m, 2H), 7.56−7.63 (m, 2H), 5.52 (s, 2H), 3.84 (d, 2H, J = 7.81 Hz), 3.73 (d, 2H, J = 7.42 Hz), 2.20−2.27 (m, 1H), 2.02−2.09 (m, 1H), 0.87 (d, 2H, J = 6.84 Hz), 0.84 (d, 6H, J = 6.84 Hz); MS *m*/*z* 489.35 $(M + H)^+$, 511.31 $(M^+ + Na)$; Anal. ($C_{24}H_{27}F_3N_6O_2$): C,H,N.

Radioligand Binding for A_{2B} Adenosine Receptor.[22] Human A_{2B} adenosine receptor cDNA was stably transfected into HEK-293 cells (referred to as HEK-A_{2B} cells). The monolayer of the HEK-A_{2B} cells was washed with PBS once and harvested in a buffer containing 10 mM HEPES (pH 7.4), 10 mM EDTA, and protease inhibitors. These cells were homogenized in polytron for 1 min at setting 4 and centrifuged at 29 000*g* for 15 min at 4 °C. The cell pellets were washed once with a buffer containing 10 mM HEPES (pH7.4), 1 mM EDTA, and protease inhibitors and resuspended in the same buffer supplemented with 10% sucrose. Frozen aliquots were kept at −80 °C. Competition assays were started by mixing 10 nM ^{3}H-ZM241385 (Tocris Cookson) with various concentrations of test compounds and 50 μg of membrane proteins in TE buffer (50 mM Tris and 1 mM EDTA) supplemented with 1 unit/mL

adenosine deaminase. The assays were incubated at 25 °C for 90 min with gentle agitation, stopped by filtration using a Packard Harvester and washed four times with ice-cold TM buffer (10 mM Tris, 1 mM $MgCl_2$, pH 7.4). Nonspecific binding was determined in the presence of 10 μM ZM241385. The affinities of compounds (i.e., K_i values) were calculated using GraphPad software.

Radioligand Binding for A_1, A_{2A}, and A_3 Adenosine Receptors.[22] Human A_1, A_{2A}, and A_3 adenosine receptor cDNAs were stably transfected into either CHO or HEK-293 cells (referred to as CHO-A_1, HEK-A_{2A}, and CHO-A_3). The membranes were prepared from these cells using the same protocol as described above. Competition assays were started by mixing 0.5 nM ^{3}H-CPX (for CHO-A_1), 2 nM ^{3}H-ZM241385 (HEK-A_{2A}), or 0.1 nM ^{125}I-AB-MECA (CHO-A_3) with various concentrations of test compounds and the perspective membranes in TE buffer (50 mM Tris and 1 mM EDTA fo CHO-A_1 and HEK-A_{2A}) or TEM buffer (50 mM Tris, 1 mM EDTA and 10 mM $MgCl_2$ for CHO-A_3) supplemented with 1 unit/mL adenosine deaminase. The assays were incubated at 25 °C for 90 min with gentle agitation, stopped by filtration using a Packard Harvester, and washed four times with ice-cold TM buffer (10 mM Tris, 1 mM MgCl2, pH 7.4). Nonspecific binding was determined in the presence of 1 μM CPX (CHO-A_1), 1 μM ZM241385 (HEK-A_{2A}), and 1 μM IB-MECA (CHO-A_3). The affinities of compounds (i.e., K_i values) were calculated using GraphPad software.

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Supporting Information Available: Elemental analysis for selected compounds is included. This material is available free of charge via the Internet at http://pubs.acs.org.

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