# Design, Synthesis, and Biological Evaluation of 1,2,3,7-Tetrahydro-6*H*-purin-6-one and 3,7-Dihydro-1*H*-purine-2,6-dione Derivatives as Corticotropin-Releasing Factor$_1$ Receptor Antagonists

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A growing body of evidence suggests that CRF$_1$ receptor antagonism offers considerable therapeutic potential in the treatment of diseases resulting from elevated levels of CRF, such as anxiety and depression. A series of novel 1,2,3,7-tetrahydro-6*H*-purin-6-one and 3,7-dihydro-1*H*-purine-2,6-dione derivatives was synthesized and evaluated as corticotropin releasing factor-1 (CRF$_1$) receptor antagonists. Compounds within this series, represented by compound **12d** ($IC_{50}$ = 5.4 nM), were found to be highly potent CRF$_1$ receptor antagonists. In addition, compounds **12d** and **12j** were determined to be selective CRF$_1$ antagonists. The synthesis, structure−activity relationships and pharmacokinetic properties of compounds within this series is presented.

## Introduction

Corticotropin releasing factor (CRF) receptors have become an important target for medicinal chemists, as CRF is believed to be the primary regulator of the hypothalamic−pituitary−adrenal (HPA) axis. Evidence for the existence of CRF was reported in 1955.[1,2] It was not until 1981, however, that CRF was isolated and characterized from ovine hypothalamus by Vale and coworkers.[3] Rat CRF was subsequently isolated in 1983[4] and was found to be identical to human CRF.[5] CRF is a 41 amino acid neuropeptide derived from the paraventricular nucleus of the hypothalamus. Upon its release from the hypothalamus, CRF travels in the bloodstream to the anterior pituitary, wherein it causes the release of adrenocorticotropic hormone (ACTH).[3] This action subsequently triggers the release of corticosteroid hormones from the adrenal glands, which cause a variety of metabolic changes that allow the body to respond to the stressor. The corticosteroid hormones also provide negative feedback at various levels in the HPA axis to turn off the stress response and maintain homeostasis.

CRF mediates its actions through two subtypes of seven-transmembrane G-protein-coupled CRF receptors, CRF$_1$ and CRF$_2$.[6−10] In addition, a soluble CRF binding protein has also been found in rats and humans.[11] Within the CRF$_2$ receptor subtype class, three splice variants, α, $\beta$ and $\gamma$ have been cloned and sequenced. It is of interest to note that CRF binds to CRF$_1$ receptors with at least 10-fold greater affinity than to CRF$_2$ receptors.[12] This observation, combined with the heterogeneous distribution patterns of CRF$_1$ and the CRF$_2$ receptor subtypes throughout the central and peripheral nervous system, suggest distinct functional roles for the receptor subtypes.[13,14]

Since its isolation and characterization, various studies have documented the important role of CRF in the regulation of the HPA axis in response to stress. Hypersecretion of CRF is associated with various endocrine and psychiatric disorders[15] including depression,[16] anxiety[6,17] and post-traumatic stress disorder. Elevated levels of CRF in cerebrospinal fluid[16,18,19] have been found in depressed patients along with increased levels of ACTH and cortisol in plasma.[6,17,20] Furthermore, intracerebroventricular administration of CRF to rats promoted behavioral effects similar to those observed in anxiety and depression.[7,21−23] On the other hand, the peptide-based CRF$_1$ receptor antagonists α-helical CRF$_{(9−41)}$ and astressin successfully blocked the effects of CRF.[6,24] Various studies have also been conducted with nonpeptide, small-molecule CRF$_1$ antagonists. Extensive investigations with pyrrolopyrimidine **1** (CP-154,526) demonstrated its effectiveness in rat models for anxiety and depression.[25−27] More recently, the results of the first human open label clinical study of the small molecule CRF$_1$ antagonist **2** (R-121,919) were reported.[19] Among the findings reported were reductions in depression and anxiety scores using both patient and clinician ratings. Thus, there is an increasing body of evidence suggesting that CRF$_1$ receptor antagonism offers considerable therapeutic potential in the treatment of diseases resulting from elevated levels of CRF.

A variety of nonpeptide CRF$_1$ receptor antagonists have been reported in the literature in recent years.[15,28,29] In general, most of the reported antagonists contain five essential structural features[15] (exemplified by compound **3** and illustrated in more detail in Figure 2). Three essential substituents are attached to a bicyclic (**4**) or monocyclic (**5**) heterocyclic aromatic scaffold containing

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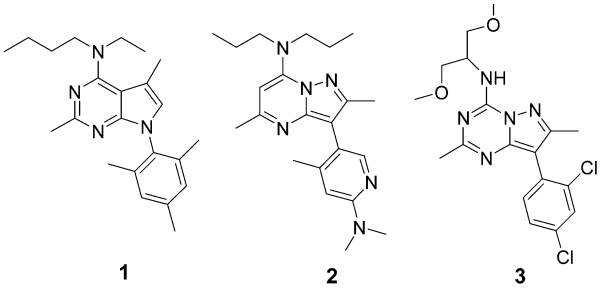
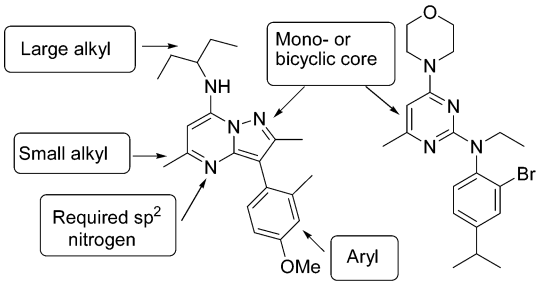


**1** CP-154,526 **2** R-121,919 **3**

**Figure 1.** Extensively studied compounds.




**4** **5**

**Figure 2.** General features of most reported small molecule $CRF_1$ receptor antagonists.

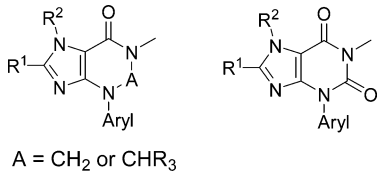



**Figure 3.** The 1,2,3,7-tetrahydro-6*H*-purin-6-one and 3,7-dihydro-1*H*-purine-2,6-dione ring systems.

an $sp^2$-hybridized basic nitrogen. This nitrogen was found to be critical for binding and is presumed to be involved in a hydrogen bonding interaction with the receptor. The small alkyl substituent is believed to fit into a small hydrophobic pocket of the receptor. The larger alkyl substituent appears to fit into a large hydrophobic pocket which can accommodate a wide variety of substituents. It was found that optimal binding occurs when the aryl group has an orthogonal relationship to the heterocyclic core as aryl groups with an ortho substituent are significantly more potent than the corresponding compounds lacking an ortho substituent.

In our search for novel $CRF_1$ antagonists, we investigated the SAR of a series of 1,2,3,7-tetrahydro-6*H*-purin-6-one and 3,7-dihydro-1*H*-purine-2,6-dione derivatives. These ring systems, depicted in Figure 3, appeared to be attractive scaffolds based on their structural relationship to known $CRF_1$ receptor antagonists. The decision to explore the SAR of compounds containing these heterocyclic ring systems was also based on our desire to investigate a series of compounds containing a bicyclic core which was not fully aromatic (i.e. non 10-$\pi$), in contrast to most previously discovered series of compounds containing a bicyclic core.[15] In addition, selective modification of the core heterocycle at "A" provided an opportunity to alter the nature of the heterocyclic ring system. The choice of substituents was based on prior SAR knowledge (vide supra). The synthesis and structure−activity relationship of these compounds is described below.

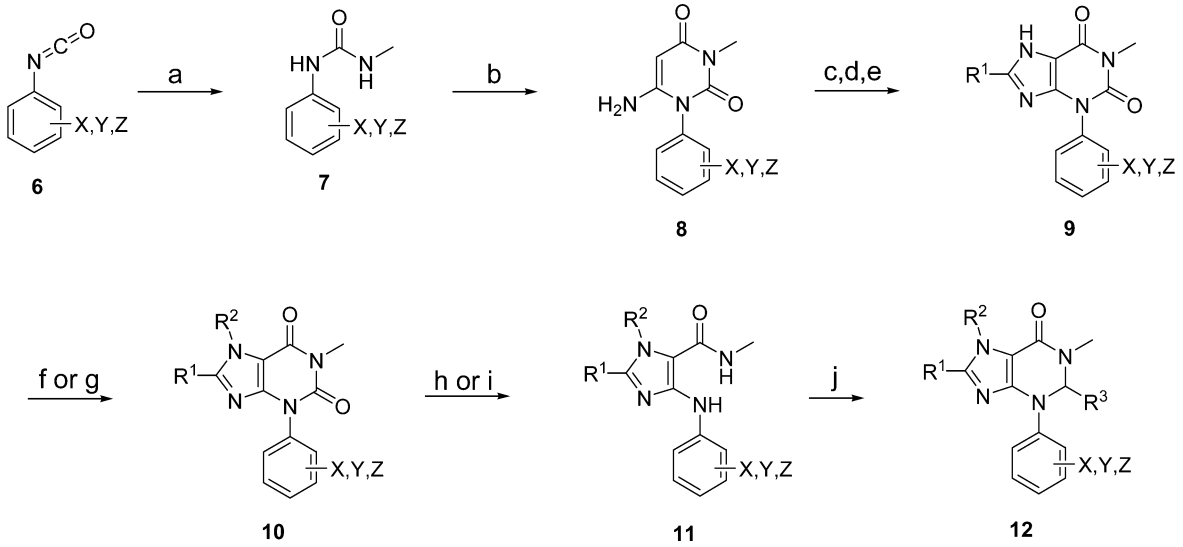
## Results and Discussion

**Chemistry.** Synthesis of the 3,7-dihydro-1*H*-purine-2,6-dione and 1,2,3,7-tetrahydro-6*H*-purin-6-one derivatives is illustrated below in Schemes 1−4. Preparation of 3,7-dihydro-1*H*-purine-2,6-dione **9** (Scheme 1) was carried out using the general procedure reported by Merlos et al.[30] with several minor modifications. The synthesis began with commercially available aryl isocyanates (**6**) which were treated with methylamine to afford the corresponding ureas in high yield. For analogues where aryl was 2-Cl-4-*i*-Pr, the resultant 4-*i*-Pr-phenyl urea was treated with *N*-chlorosuccinimide resulting in chlorination at the ortho position of the phenyl group. The ureas were heated with cyanoacetic acid followed by treatment with aqueous sodium hydroxide to afford the corresponding 6-amino uracils **8**.[31] Subsequent nitrosation and reduction[32] produced substituted 5,6-diaminouracil intermediates, which were cyclized upon heating in the presence of either triethyl orthopropionate or triethyl orthoformate to furnish **9**. Compounds **10** were prepared from **9** either by treatment with $K_2CO_3$ and an alkylating agent in DMF[33] or treatment with an aliphatic alcohol under Mitsunobu conditions.[34,35] The alkylations under basic conditions generally proceeded in higher yields.[36] For the preparation of a large number of analogues, the Mitsunobu conditions were also found to be effective because of the greater selection of commercially available alcohols. Selective hydrolysis of the urea carbonyl in **10** was achieved by treatment with either aqueous sodium hydroxide[37] or lithium aluminum hydride. The resulting imidazoles **11** were heated in toluene in the presence of an aldehyde or an aldehyde equivalent to furnish the desired target compounds **12** in good yield.

To facilitate the preparation of analogues with a variety of $R^2$ substituents, target compounds were also prepared using the modified route illustrated in Scheme 2 in which $R^2$ was introduced late in the synthetic route. Upon completion of the synthesis of the bicyclic, heterocyclic core (Scheme 1), the nitrogen at the 7-position of compound **9** was protected with a benzyloxymethyl group (Scheme 2). Chemistry described previously was then used to convert the 3,7-dihydro-1*H*-purine-2,6-dione ring system to the 1,2,3,7-tetrahydro-6*H*-purin-6-one heterocycle (**15**). The benzyloxymethyl protecting group was subsequently removed by heating in trifluoroacetic acid to afford compounds **16** in good yield. Finally, alkylation either under basic conditions or Mitsunobu conditions as described previously afforded the desired products **12**.

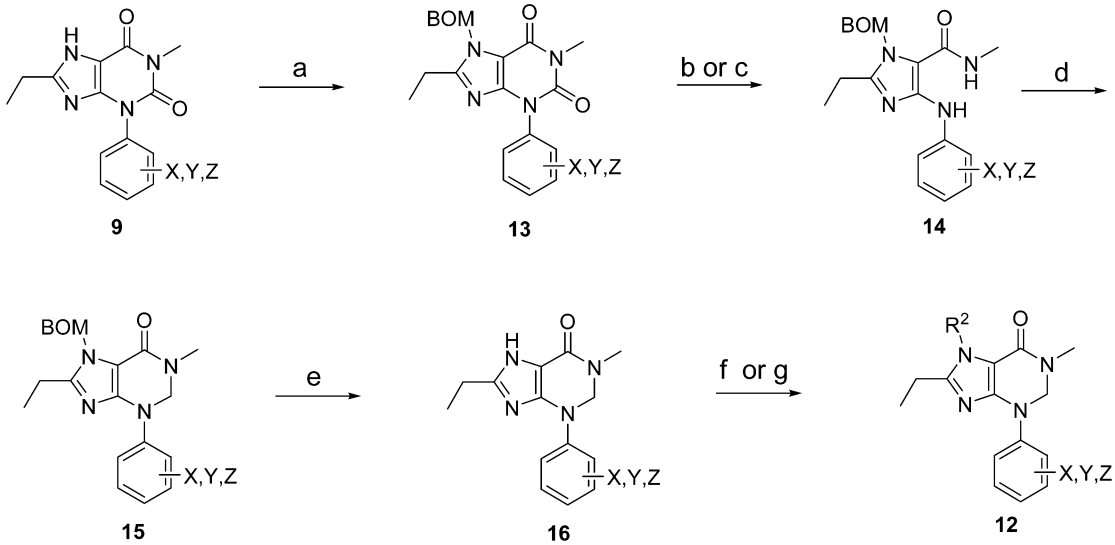
Interestingly, the nature of the substitution on the aryl group had a significant effect on the reactivity of the nitrogen at the 7-position of the 1,2,3,7-tetrahydro-6*H*-purin-6-one ring system (**16**). The presence of electron-withdrawing groups (e.g. 2,4-dichloro) facilitated reaction at the nitrogen while electron-donating substituents retarded the reactivity of this nitrogen. When the aryl group was 2,4,6-trimethylphenyl, alkylation under either basic conditions or Mitsunobu conditions proved to be ineffective. Alkylations with this substrate had to be carried out on the more electron deficient dione (**9**).

**Scheme 1**[a]




[a] Reagents and conditions: (a) (1) $NH_2Me$, THF, 74−96%; (2) (when necessary) *N*-chlorosuccinimide, MeCN, 76−90%; (b) (1) $HO_2CCH_2CN$, $Ac_2O$, 85 °C; (2) 20% NaOH, 70 °C, 54−89% (two steps); (c) $NaNO_2$, $H_2O$/HOAc, 65 °C, 81−89%; (d) $Na_2S_2O_4$, 25% aq $NH_4OH$, 50 °C, 86−97%; (e) $(MeO)_3CR^1$, EtOH, reflux, 62−92%; (f) $R^2OMs$, $K_2CO_3$, DMF, 90 °C, 60−94%; (g) $PPh_3$, $R^2OH$, DEAD, THF, 50 °C, 14−82%; (h) NaOH, $H_2O$/EtOH/dioxane, 42−61%; (i) $LiAlH_4$, THF, 26−64% **11** and 0−36% **12**; (j) $(CH_2O)_n$, or $(MeO)_2CHMe$ or EtCHO, *p*-TsOH·$H_2O$, toluene, 54−92%. Method A: a, b, c, d, e; Method B: f; Method C: g; Method D: h, j; Method E: i or i, j.

**Scheme 2**[a]



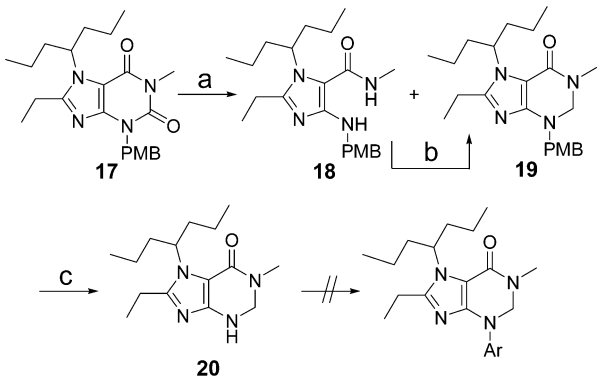

[a] Reagents and conditions: (a) BOMCl, $Bu_4NI$, $K_2CO_3$, DMF, 65−73%; (b) NaOH, $H_2O$/EtOH/dioxane, 25−53%; (c) $LiAlH_4$, THF, 50%; (d) $(CH_2O)_n$, *p*-TsOH·$H_2O$, toluene, 56−58%; (e) TFA, $CHCl_3$, 69−95%; (f) $R^2OMs$, $K_2CO_3$, DMF, 90 °C, 18−38%; (g) $PPh_3$, $R^2OH$, DEAD, THF, 12−61%. Method F: a, b, d, e; Method G: a, c, d, e; Method H: f; Method I: g.

While Scheme 2 allowed for the rapid preparation of analogues at $R^2$, preparation of analogues of the aryl group was more cumbersome since the aryl group was introduced at the start of the synthesis. Within the past few years numerous reports involving the palladium-catalyzed coupling of aryl halides[38−40] or copper-promoted coupling of aryl boronic acids[41,42] with a variety of alkylamines or anilines have appeared in the literature. It was anticipated that one of the above methods would be applicable to the preparation of aryl analogues on the 3-position of the 1,2,3,7-tetrahydro-6*H*-purin-6-one ring system.

A limited investigation was undertaken to introduce the aryl substituent near the end of the synthesis. *p*-Methoxybenzyl-protected 3,7-dihydro-1*H*-purine-2,6-dione **17** (Scheme 3) was prepared according to steps a−f in Scheme 1. Initially the urea carbonyl of compound **17** was selectively reduced with $LiAlH_4$ to give a mixture of **18** and **19**. Imidazole **18** was treated with paraformaldehyde to form additional **19**. Subsequent removal of the *p*-methoxybenzyl group afforded compound **20** in high yield. Unfortunately all attempts to couple this substrate with an aryl bromide or an aryl boronic acid resulted in no reaction.

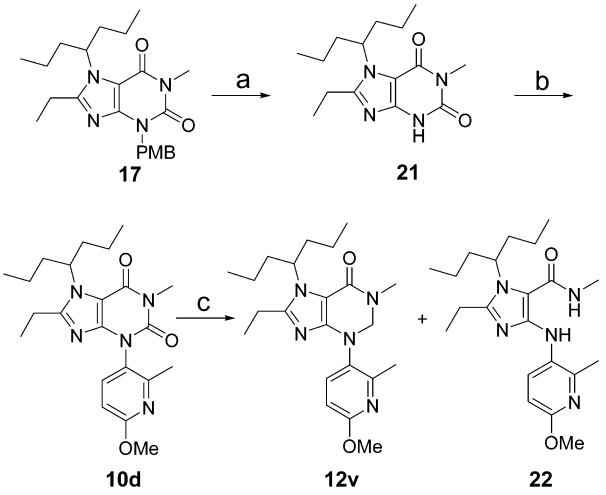
The lack of reactivity of the nitrogen on the 1,2,3,7-tetrahydro-6*H*-purin-6-one ring system was presumably due to a suboptimal p$K_a$ of this NH group. The coupling reaction was attempted on the corresponding 3,7-dihydro-1*H*-purine-2,6-dione ring system, which is more acidic. To this end, the *p*-methoxybenzyl group of **17** was removed in high yield by heating in trifluoroacetic acid to furnish **21** (Scheme 4). Attempted coupling of **21** with

**Scheme 3**[a]




[a] Reagents and conditions: (a) $LiAlH_4$, THF 53% **18** and 36% **19**; (b) $(CH_2O)_n$, *p*-TsOH·$H_2O$, toluene, 75%; (c) TFA, 95%.

**Scheme 4**[a]




[a] Reagents and conditions: (a) TFA, 91%; (b) $Cu(OAc)_2$, pyridine, 6-methoxy-2-methyl-3-pyridinylboronic acid, $CH_2Cl_2$, 41% with 52% recovered starting material; (c) $LiAlH_4$, THF, 14% **12v** and 46% **22**. Method J: a,b; Method K: a, b, c.

an aryl bromide under palladium catalysis conditions resulted in no reaction; however, coupling of **21** with 6-methoxy-2-methyl-3-pyridinylboronic acid in the presence of copper(II) acetate and pyridine afforded a 41% yield of **10d**, while the balance of the material was recovered intact (52% recovered starting material). The urea carbonyl was subsequently reduced with lithium aluminum hydride to afford the target compound **12v** along with imidazole **22**.

**Pharmacology.** Our compound progression strategy for this study was as follows. Compounds were initially screened for binding affinity at $CRF_1$. Selected compounds were screened for binding affinity at $CRF_2$ and were subsequently examined for their functional affects in Y79 and rat pituitary cells to assess antagonist properties. Subsequently, pharmacokinetic properties of selected compounds were evaluated in an in vitro assay by incubation with human and rat liver microsomes followed by in vivo rat pharmacokinetic studies.

Binding affinities were determined in a $CRF_1$ receptor binding titration assay using rat frontal cortex homogenate, in which inhibition of specific binding of [$^{125}$I]-ovine-CRF by our test compounds was measured to determine their receptor binding affinity. The $CRF_2$ receptor binding titration assay employed porcine choroid plexus homogenate and [$^{125}$I]-sauvagine binding inhibition to determine binding affinities. The binding affinities for representatives of this series of 1,2,3,7-tetrahydro-6*H*-purin-6-one and 3,7-dihydro-1*H*-purine-2,6-dione ligands are shown in Tables 1 and 2.

A comparison of the two heterocyclic cores in Table 1 shows that compounds with the 1,2,3,7-tetrahydro-6*H*-purin-6-one core were more potent than the corresponding compounds with a 3,7-dihydro-1*H*-purine-2,6-dione core (**10a** vs **12a**, **10b** vs **12d**, **10c** vs **12p**, and **10d** vs **12v**). Presumably, the urea carbonyl may have an unfavorable steric or electronic interaction with the receptor resulting in reduced binding affinity.

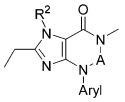
A variety of alkyl substituents at $R^2$ were prepared in order to examine the SAR at this position. Previous SAR investigations suggest that $R^2$ interacts with a large hydrophobic cavity, which can accommodate a wide variety of substituents at this position provided that they are neither strongly acidic nor basic.[43] The starting point for this investigation was a 3-pentyl group (**12a**, $IC_{50}$ = 112 nM, Table 1). Additional alkyl substituents with longer groups from the point of attachment were investigated (**12b**−**d**) and the optimal group was determined to be a 4-heptyl group (**12d**, $IC_{50}$ = 5.4 nM). Incorporation of an ether group into $R^2$ resulted in an 8-fold loss in binding affinity (compare **12d** to **12e**); however, a branched alkyl group appeared to result in a modest improvement in binding affinity (compare **12a** to **12f**).

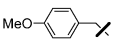
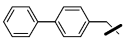
A series of cycloalkyl-substituted groups at $R^2$ was investigated (**12g**−**k**). It was found that increasing the length of the alkyl group from methyl to ethyl to propyl resulted in a continuous improvement in binding affinity, as one would expect based on the results from the straight chain alkyl substituents. Interestingly, the dicyclopropyl-methyl substituent in **12j** proved to be the most potent of the cycloalkyl substituents examined ($IC_{50}$ = 6.0 nM). The cyclobutyl methyl substituent appears to be somewhat more potent than the corresponding cyclopropyl-methyl group (compare **12k** to **12g**).

In addition to analogues with branched alkyl groups, several analogues with aryl or alkyl−aryl groups at $R^2$ were also prepared and tested (**15**, **12l**−**o**). Compounds of this type possessed only moderate binding affinity. The benzyloxymethyl (**15**), 4-methoxybenzyl (**12l**) and 2-methylbenzyl (**12m**) substituents have $IC_{50}$'s of 861, 456 and 458 nM, respectively. The compound where $R^2$ is 4-phenylbenzyl (**12n**, $IC_{50}$ = 324 nM) was somewhat more potent, indicating that both phenyl rings interact favorably with the receptor. In contrast, the analogue with a 1-naphthylmethyl substituent (**12o**) was inactive.

A limited exploration of the SAR of the aryl group was also undertaken. Among the aryl groups evaluated, the 2,4-dichlorophenyl substituent proved to be the optimal aryl group in this series. Replacement of the 4-chloro substituent on the phenyl ring with either a methoxy or isopropyl group resulted in a 5−10-fold decrease in binding affinity respectively (compare **12d**, $IC_{50}$ = 5.4 nM with **12q**, $IC_{50}$ = 27 nM and **12t**, $IC_{50}$ = 50 nM). Compounds with a 2,4,6-trimethylphenyl group were also prepared. It was found that the 2,4-dichlorophenyl-substituted aryl group was 4-fold more potent than the 2,4,6-trimethylphenyl group (compare **12d**, $IC_{50}$ = 5.4

**Table 1.** Structure Activity Relationships for the 1,2,3,7-Tetrahydro-6*H*-purin-6-one and 3,7-Dihydro-1*H*-purine-2,6-dione $CRF_1$ Receptor Antagonists

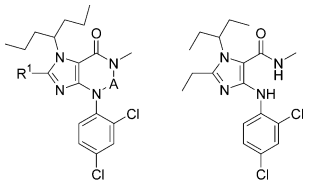



| Compound | Method | $R^{2,a}$ | A | Aryl | $IC_{50}$ (nM)[b] |
|---|---|---|---|---|---|
| **10a** | A,B or C |  | C=O | 2,4-$Cl_2$-Ph | 2990 ± 580 |
| **10b** | A,B |  | C=O | 2,4-$Cl_2$-Ph | 75 ± 21 |
| **10c** | A,B |  | C=O | 2,4,6-$Me_3$-Ph | 191 ± 26 |
| **10d** | A,B,J |  | C=O | 4-OMe-2-Me-pyridin-3-yl | 1081± 340 |
| **12a** | A,B,D |  | $CH_2$ | 2,4-$Cl_2$-Ph | 112 ± 45 |
| **12b** | A,F,I |  | $CH_2$ | 2,4-$Cl_2$-Ph | 52 ± 18 |
| **12c** | A,B,D |  | $CH_2$ | 2,4-$Cl_2$-Ph | 18 ± 1 |
| **12d** | A,B,D |  | $CH_2$ | 2,4-$Cl_2$-Ph | 5.4 ± 2.0 |
| **12e** | A,F,I |  | $CH_2$ | 2,4-$Cl_2$-Ph | 43 ± 2 |
| **12f** | A,F,H |  | $CH_2$ | 2,4-$Cl_2$-Ph | 51 ± 1 |
| **12g** | A,F,I |  | $CH_2$ | 2,4-$Cl_2$-Ph | 55 ± 12 |
| **12h** | A,F,I |  | $CH_2$ | 2,4-$Cl_2$-Ph | 14 ± 4 |
| **12i** | A,F,I |  | $CH_2$ | 2,4-$Cl_2$-Ph | 10 ± 2 |
| **12j** | A,F,I |  | $CH_2$ | 2,4-$Cl_2$-Ph | 6.0 ± 1.2 |
| **12k** | A,F,H |  | $CH_2$ | 2,4-$Cl_2$-Ph | 26 ± 3 |
| **15** | A,B[c],D |  | $CH_2$ | 2,4-$Cl_2$-Ph | 860 ± 27 |
| **12l** | A,B[c],D |  | $CH_2$ | 2,4-$Cl_2$-Ph | 456 ± 90 |
| **12m** | A,F,H[c] |  | $CH_2$ | 2,4-$Cl_2$-Ph | 458 ± 172 |
| **12n** | A,F,I |  | $CH_2$ | 2,4-$Cl_2$-Ph | 324 ± 102 |
| **12o** | A,F,I |  | $CH_2$ | 2,4-$Cl_2$-Ph | 9000 ± 1030 |
| **12p** | A,B,E |  | $CH_2$ | 2,4,6-$Me_3$-Ph | 22 ± 10 |
| **12q** | A,F,H |  | $CH_2$ | 2-Cl-4-OMe-Ph | 27 ± 6 |
| **12r** | A,F,I |  | $CH_2$ | 2-Cl-4-OMe-Ph | 113 ± 40 |
| **12s** | A,F,I |  | $CH_2$ | 2-Cl-4-OMe-Ph | 875 ± 150 |
| **12t** | A,F,H |  | $CH_2$ | 2-Cl-4-*i*-Pr-Ph | 50 ± 21 |
| **12u** | A,G,H |  | $CH_2$ | 2-Cl-4-*i*-Pr-Ph | 555 ± 140 |
| **12v** | A,B,K |  | $CH_2$ | 4-OMe-2-Me-pyridin-3-yl | 161 ± 33 |
| **12w** | A,B,K |  | $CH_2$ | 4-Cl-Ph | 173 ± 29 |

[a] All $R^2$ groups which contain a chiral center are racemic. [b] All values are the average of n = 3 ± standard deviation. [c] The alkylation was performed with the corresponding bromide or chloride.

nM to **12p**, $IC_{50}$ = 22 nM). Replacement of the phenyl group with a pyridyl group resulted in a significant loss in binding affinity (**12v**, $IC_{50}$ = 161 nM). An ortho substituent on the phenyl group is required for good

**Table 2.** Structure Activity Relationships for the 1,2,3,7-Tetrahydro-6*H*-purin-6-one and 3,7-Dihydro-1*H*-purine-2,6-dione $CRF_1$ Receptor Antagonists



10, 12



11

| compound | method | $R^1$ | A | $IC_{50}$ (nM)[a] |
|---|---|---|---|---|
| **12d** | A,B,D | Et | $CH_2$ | 5.4 ± 2.0 |
| **10b** | A,B | Et | C=O | 75 ± 21 |
| **12x** | A,B,D | Et | CHMe[b] | 383 ± 227 |
| **12y** | A,B,D | Et | CHEt[b] | 626 ± 158 |
| **12z** | A,B,D | H | $CH_2$ | 898 ± 462 |
| **11** | A,h | – | – | >10000[c] |

[a] All values are the average of n = 3 ± standard deviation unless indicated otherwise. [b] Compound is racemic. [c] Value determined by two measurements.

binding affinity as illustrated by compound **12w** with an $IC_{50}$ = 173 nM, a 35-fold decrease in binding affinity from the corresponding ortho-substituted compound **12d** ($IC_{50}$ = 5.4 nM). Presumably the ortho substituent is required to enforce an orthogonal relationship between the core ring system and the phenyl group.

A limited investigation of the SAR at "A" and $R^1$ was also conducted and the results are summarized in Table 2. The optimal group at "A" was a methylene group (**12d**). Increasing the size of this group resulted in progressively diminished binding affinity (compare **12d** to **10b, 12x**, and **12y**). The data suggests that there is limited steric tolerance in this region of the $CRF_1$ receptor binding pocket. The current pharmacophore model for $CRF_1$ receptor antagonists[15] suggests that $R^1$ fits into a small hydrophobic pocket. The data from the compounds in this series also support this model. Compounds lacking an alkyl group at $R^1$ are over 150-fold less potent than compounds with an ethyl group (compare **12z** with **12d**). The linker designated as "A" proved to be critical for obtaining potent binding affinity to the $CRF_1$ receptor in this chemotype. Removal of this group resulted in loss of binding affinity to the $CRF_1$ receptor (Compound **11**, Table 2), indicating that the constrained six-membered ring is preferred over the unconstrained structure. It is likely that the six-membered ring holds the aryl substituent in the preferred bioactive conformation.

In cell-based functional assays, the antagonist properties of compounds **12d** and **12j** were assessed by measuring the ability of these compounds to inhibit CRF-stimulated cAMP production in human Y-79 retinoblastoma cells and ACTH secretion in cultured rat pituitary cells.[44] In parallel, any potential CRF agonist properties of **12d** and **12j** were assessed by measuring the effect of these compounds on basal cAMP production (i.e. in the absence of CRF) in both Y-79 and rat pituitary cells. Both compounds **12d** and **12j** produced a concentration-dependent inhibition of CRF (1 nM)-induced cAMP production with $IC_{50}$ values of 24.2 ± 5.6 and 14.4 ± 5.7 nM, respectively, and completely suppressed CRF-stimulated cAMP production at higher concentrations, indicating that these compounds behave as antagonists. No agonist properties were detected at concentrations up to 10 $\mu$M. Similar results were obtained in an additional study. Both compounds **12d** and **12j** also produced a concentration-dependent inhibition of CRF (0.3 nM)-induced ACTH release from rat pituitary cells and completely suppressed CRF-stimulated ACTH secretion at higher concentrations, indicating that these compounds behave as antagonists at pituitary $CRF_1$ receptors (Note: the CRF $EC_{50}$ in pituitary cells was 0.25 ± 0.9 nM, $n$ = 3). To test for agonist activity, both compounds **12d** and **12j** were exposed alone to pituitary cells. Basal secretion of ACTH from cells was not altered, indicating a lack of agonist properties. Moreover, neither compound demonstrated binding affinity to the $CRF_2$ receptor in a binding assay. Taken together, these compounds are selective $CRF_1$ receptor antagonists as summarized in Table 3.

**Table 3.** cAMP Activity and $CRF_2$ Binding Profiles for Compounds **12d** and **12j**

| compound | $CRF_1$ binding $IC_{50}$ (nM) | cAMP ($IC_{50}$, nM) Y-79 cells | $CRF_2$ $IC_{50}$ (nM) |
|---|---|---|---|
| **12d** | 5.4 ± 2.0 | 24.2 ± 5.6 | >10000 |
| **12j** | 6.0 ± 1.2 | 14.4 ± 5.7 | >10000 |

An initial set of selected compounds from this series (**10b**, **12d**, **12f**, **12g**, **12h**, **12q**, and **12v**) was screened for metabolic stability by incubation with human and rat liver microsomes. The results from this study indicated that each of the above compounds was rapidly metabolized (0.297−0.300 nmol/min/kg, human; 0.298−0.300 nmol/min/kg, rat). The substitution of the methylene group at "A" with a carbonyl group appeared to have no appreciable effect on the rate of metabolism by liver microsomes.

To assess the pharmacokinetic properties of this series in more detail, a lead compound in this series, compound **12d**, was included in a rat cassette dose study. The pharmacokinetic data from this study suggests that **12d** is a high clearance compound (Cl = 4.0 L/h/kg, $V_{ss}$ = 17.0 L/kg, $t_{1/2}$ = 4.4 h, $F$ = 2%). Mass spectral data from subsequent human and rat microsomal incubations suggest that hydroxylation of the heptyl substituent was likely the major pathway of metabolism. Compound **12j** ($IC_{50}$ = 6.0 nM), containing a dicyclopropyl-methyl substituent in place of the heptyl substituent, was subsequently prepared and incubated with human and rat liver microsomes. It was found that the rate of metabolism was significantly decreased in human microsomes (0.178 nmol/min/mg) compared to **12d** (0.297 nmol/min/mg). The rate of metabolism in rat liver microsomes was similar to previously tested compounds (0.300 nmol/min/kg); thus, it appears that the improvement in metabolic stability is species dependent. The information from this study further supports the results of the mass spectroscopy study with **12d**. In addition, it provides us with a better understanding of the structural features primarily responsible for the high clearance of compound **12d** and can guide further optimization of the pharmacokinetics for this class of compounds.

## Conclusion

In conclusion, a novel series of 1,2,3,7-tetrahydro-6*H*-purin-6-one and 3,7-dihydro-1*H*-purine-2,6-dione derivatives was synthesized and evaluated as $CRF_1$ re-

ceptor antagonists. This study demonstrates that potent $CRF_1$ antagonists can be designed from a bicyclic core heterocycle which is not fully aromatic (i.e. non-10 $\pi$). SAR exploration of the "A" group of the core heterocycle indicates that the $CRF_1$ receptor is unable to accommodate $sp^3$-hybridized substituents at this site, suggesting that there is limited steric tolerance in this region of the $CRF_1$ receptor binding pocket. It was also found that the bicyclic core is critical for good binding affinity within this chemotype, a monocyclic imidazole-based analogue (**11**) was not active. Further evaluation of compounds **12d** and **12j** demonstrates that they are selective $CRF_1$ receptor antagonists. Initial assessment of the pharmacokinetic properties using compound **12d** indicates that it is a high clearance compound and further optimization is required. Replacing the heptyl substituent in **12d** with a dicyclopropyl-methyl substituent (**12j**) did, in fact, result in an improved in vitro metabolic stability profile in human liver microsomes.

## Experimental Section

**Chemistry.** All procedures were carried out under a nitrogen atmosphere unless otherwise indicated using anhydrous solvents purchased from commercial sources without further purification. Reactions requiring anhydrous conditions were performed in glassware, which was flame-dried or oven-dried and placed under a nitrogen atmosphere. Chromatography was performed on silica gel using the solvent systems indicated. Solvent systems are reported as v/v percent ratios. All reactions were monitored by TLC using EM Science, 0.25 mm, precoated silica gel plates or by low resolution APCI mass spectrometry. Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise indicted. Melting points were obtained on a Laboratory Devices, Inc. Mel Temp 3.0 melting point apparatus and are uncorrected. Proton NMR spectra were recorded on either a Varian (Palo Alto, CA) Inova 300, 400, or 500 MHz or Brucker 400 or 500 MHz NMR spectrometer. Chemical shifts are reported in $\delta$ values relative to tetramethylsilane. Atmosphere pressure chemical ionization (APCI) low-resolution mass spectra were obtained on a Finnigan Navigator LC/MS single quadrupole mass spectrometer. Electrospray ionization (ESI) high-resolution mass spectra were obtained on a Finnigan MAT95S reverse geometry sector instrument. Microanalyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. HPLC purity was measured by using an analytical C18 reversed phase column (method A) or an analytical silica gel normal phase column (method B). Method A: 0.1% TFA in water−0.1% TFA in acetonitrile gradient (15%-95% acetonitrile over 30 min); method B: hexanes−ethyl acetate with 3% methanol in the indicated ratio.

***N*-(2,4-Dichlorophenyl)-*N*′-methyl-urea (7).** A cooled (0 °C) solution of methylamine in EtOH (50 mL, 400 mmol, 8.0 M) was dissolved in anhydrous THF (300 mL) and was treated with 2,4-dichlorophenyl isocyanate (25.0 g, 133 mmol). The cooling bath was removed, and the mixture was warmed to 65 °C for 20 min. The reaction mixture was then cooled to 0 °C. The solid was collected on a Buchner funnel, washed with cold ether and dried under vacuum to afford *N*-(2,4-dichlorophenyl)-*N*′-methyl-urea (21.7 g, 74% yield) as a colorless solid: mp 213.5−214.5 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.17 (d, $J$ = 9.2 Hz, 1H), 8.11 (s, 1H), 7.55 (d, $J$ = 2.5 Hz, 1H), 7.32 (dd, $J$ = 8.8, 2.6 Hz, 1H), 6.91 (d, $J$ = 4.8 Hz, 1H), 2.65 (d, $J$ = 4.4 Hz, 3H); LRMS (APCI) *m/e* 259.9 [(M + H + $CH_3CN$)$^+$, calcd for $C_{10}H_{12}N_3OCl_2$, 260.0].

***N*-(2-Chloro-4-methoxyphenyl)-*N*′-methyl-urea (7).** A suspension of *N*-(4-methoxyphenyl)-*N*′-methyl-urea (15.00 g, 83.24 mmol) in $CH_3CN$ (120 mL) was warmed to 65 °C. *N*-Chlorosuccinimide (12.22 g, 91.56 mmol) was added, and the reaction mixture was heated at 90 °C for 40 min. The mixture was cooled to 0 °C, and the solid was collected on a Buchner funnel to afford the desired product (13.5 g, 75% yield) as a colorless solid: mp 184−185 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.85 (d, $J$ = 9.2 Hz, 1H), 7.81 (s, 1H), 7.00 (d, $J$ = 2.9 Hz, 1H), 6.86 (dd, $J$ = 9.1, 2.1 Hz, 1H), 6.58−6.57 (m, 1H), 3.72 (s, 3H), 2.63 (d, $J$ = 4.8 Hz, 3H); LRMS (APCI) *m/e* 215.0 [(M + H)$^+$, calcd for $C_9H_{12}N_2O_2Cl$ 215.1].

**6-Amino-1-(2,4-dichlorophenyl)-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (8).** A solution of *N*-(2,4-dichlorophenyl)-*N*′-methyl-urea (12.0 g, 54.8 mmol) in acetic anhydride (100 mL) was treated with cyanoacetic acid (5.6 g, 65.8 mmol). The reaction mixture was heated at 85 °C for 2.5 h. Additional cyanoacetic acid (0.90 g, 11.0 mmol) was added, and the reaction mixture was stirred for 45 min. A third portion of cyanoacetic acid (0.45 g, 5.5 mmol) was added, and the reaction mixture was stirred for 30 min. Excess acetic anhydride was distilled off under reduced pressure at a temperature less than 70 °C. The residue was treated with 20% aqueous sodium hydroxide (95 mL) in portions. During the addition a spontaneous increase in temperature (65−70 °C) occurred. The reaction mixture was heated at 60 °C for 1 h during which time the product precipitated. The reaction mixture was then cooled to 0 °C. The precipitate was collected on a Buchner funnel, washed with cold water and dried at 55 °C under vacuum. The crude product was triturated in hot toluene (stirred for 1 h at 110 °C), and the solid was immediately collected on a Buchner funnel then dried under vacuum to afford a pale yellow solid (8.46 g, 54% yield): mp 249−251 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.89 (d, $J$ = 1.8 Hz, 1H), 7.59 (d, $J$ = 1.8 Hz, 2H), 6.44 (s br, 2H), 4.79 (s, 1H), 3.09 (s, 3H); LRMS (APCI) *m/e* 286.0 [(M + H)$^+$, calcd for $C_{11}H_{10}N_3O_2Cl_2$, 286.0].

**3-(2,4-Dichlorophenyl)-8-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione (9).** To a suspension of 6-amino-1-(2,4-dichlorophenyl)-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione **8** (8.0 g, 28.0 mmol) in $H_2O$ (65 mL) and acetic acid (3.5 mL) was added $NaNO_2$ (2.12 g, 30.8 mmol) in portions. The reaction mixture was heated at 50 °C for 2 h during which time a purple color formed indicating formation of the nitroso derivative. Additional $NaNO_2$ (2.12 g, 30.8 mmol) was added, and the reaction mixture was stirred at 65 °C for an additional 2 h. Additional $NaNO_2$ (300 mg, 4.35 mmol) was added, and the reaction mixture was heated at 75 °C for another 1 h. The suspension was then cooled to 0 °C. The solid was collected on a Buchner funnel, washed with cold water and dried under vacuum at 60 °C overnight to afford the nitroso derivative as a purple solid (7.78 g, 88% yield) which was used directly in the next step without further purification: mp 230−232 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 12.62 (s, 1H), 8.70 (s, 1H), 7.98 (s, 1H), 7.68 (s, 2H), 3.32 (s, 3H); LRMS (APCI) *m/e* 314.9 [(M + H)$^+$, calcd for $C_{11}H_9N_4O_3Cl_2$, 315.0].

To a suspension of finely ground 6-amino-1-(2,4-dichlorophenyl)-3-methyl-5-nitroso-2,4(1*H*,3*H*)-pyrimidinedione (7.32 g, 23.2 mmol) in 25% $NH_4OH$ (60 mL) was added in portions $Na_2S_2O_4$ (20.0 g, 116 mmol). After the addition was complete, the reaction mixture was heated at 50 °C for 2.5 h. The purple color gradually disappeared. The reaction mixture was cooled to 0 °C. The solid was collected on a Buchner funnel, washed with cold water, then dried under vacuum overnight at 60 °C to afford a pale green solid (6.40 g, 92% yield) which was used directly in the next step without further purification: mp 170−172.5 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.88 (d, $J$ = 2.2 Hz, 1H), 7.61−7.53 (m, 2H), 5.73 (s, 2H), 3.34 (s, 2H), 3.15 (s, 3H); LRMS (APCI) *m/e* 300.9 [(M + H)$^+$, calcd for $C_{11}H_{11}H_4O_2Cl_2$, 301.0].

A suspension of 5,6-diamino-1-(2,4-dichlorophenyl)-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (4.0 g, 13.3 mmol) in EtOH (32 mL) was treated with triethylorthopropionate (12.8 mL, 63.7 mmol). The reaction mixture was heated at reflux for 6 h during which time the product precipitated from the reaction mixture. The reaction mixture was then cooled to 0 °C to achieve complete precipitation. The solid was collected on a Buchner funnel, washed with cold ether, and dried under vacuum to give a colorless solid (2.97 g). The filtrate was concentrated and the residue was purified by column chro-

matography on silica gel (5% MeOH in $CH_2Cl_2$) to afford an additional 0.87 g of desired product. The total yield of desired product **9** was 3.84 g (85% yield) as a colorless solid: mp 274.5−275.5 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 12.53 (s br, 1H), 7.61 (d, $J$ = 1.8 Hz, 1H), 7.45−7.38 (m, 2H), 3.52 (s, 3H), 2.87 (q, $J$ = 7.3 Hz, 2H), 1.38 (t, $J$ = 7.7 Hz, 3H); LRMS (APCI) *m/e* 339.0 [(M + H)$^+$, calcd for $C_{14}H_{13}N_4O_2Cl_2$, 339.0].

**3-(2,4-Dichlorophenyl)-8-ethyl-1-methyl-7-(3-pentyl)-3,7-dihydro-1*H*-purine-2,6-dione (10a).** (prepared by Method B) A solution of 3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **9** (544 mg, 1.60 mmol) in anhydrous DMF (8 mL) was treated with finely ground $K_2CO_3$ (662 mg, 4.80 mmol). After stirring 5 min at room temperature, 3-methanesulfonylpentane (682 $\mu$L, 4.48 mmol) was added via syringe and the reaction mixture was heated at 80 °C for 2 h. The mixture was cooled to room temperature and transferred to a separatory funnel containing ether (120 mL). The organic layer was washed with water (4 × 15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The solid residue was crystallized from hexane/ethyl acetate and collected on a Buchner funnel to give a colorless solid (508 mg). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (25% ethyl acetate in hexanes) to give an additional 105 mg of product. The total yield of desired product was 613 mg (94% yield) as a colorless solid: mp 186−187 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.59 (d, $J$ = 2.2 Hz, 1H), 7.44−7.36 (m, 2H), 4.00−3.90 (m, 1H), 3.45 (s, 3H), 2.74 (q, $J$ = 7.7 Hz, 2H), 2.39−2.26 (m, 2H), 2.05−1.92 (m, 2H), 1.24 (t, $J$ = 7.3 Hz, 3H), 0.83 (t, $J$ = 7.3 Hz, 6H); HRMS (ESI) *m/e* 409.1212 [(M + H)$^+$, calcd for $C_{19}H_{23}N_4O_2Cl_2$, 409.1198]. Anal. ($C_{19}H_{22}N_4O_2Cl_2$) C, H, N.

**3-(2,4-Dichlorophenyl)-8-ethyl-1-methyl-7-(3-pentyl)-3,7-dihydro-1*H*-purine-2,6-dione (10a).** (prepared by Method C) A solution of 3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **9** (100 mg, 0.295 mmol) in anhydrous THF (1.2 mL) was heated to 50 °C. $PPh_3$ (120 mg, 0.594 mmol) and 3-pentanol (96 $\mu$L, 0.889 mmol) were added. After stirring 5 min, DEAD (102 $\mu$L, 0.648 mmol) was added rapidly via syringe and the reaction mixture was stirred for 15 min at 50 °C. The mixture was cooled to room temperature and was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (two 1000 $\mu$M silica gel plates, 60% ethyl acetate/40% hexanes) to afford the desired product (88 mg, 64% yield) as a colorless solid. The spectral data is identical to the material prepared via method B.

**3-(2,4-Dichlorophenyl)-8-ethyl-7-(4-heptyl)-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione (10b).** Colorless solid; mp 185−186 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.73 (d, $J$ = 2.5 Hz, 1H), 7.38 (dd, $J$ = 8.8, 2.6 Hz, 1H), 6.94 (d, $J$ = 8.4 Hz, 1H), 4.96 (q, $J$ = 6.2 Hz, 1H), 4.20−3.95 (m br, 1H), 2.82 (s, 3H), 2.74−2.59 (m, 2H), 2.50−2.30 (m br, 1H), 2.15−2.05 (m, 1H), 1.90−1.70 (m, 2H), 1.42 (d, $J$ = 5.8 Hz, 3H), 1.15 (t, $J$ = 7.7 Hz, 3H), 0.77 (t, $J$ = 7.7 Hz, 3H), 0.72−0.68 (m, 3H); HRMS (ESI) *m/e* 437.1512 [(M + H)$^+$, calcd for $C_{21}H_{27}N_4O_2Cl_2$ 437.1511]. Anal. ($C_{21}H_{26}N_4O_2Cl_2$) C, H, N.

**4-[(2,4-Dichlorophenyl)amino]-2-ethyl-*N*-methyl-1-(3-pentyl)-1*H*-imidazole-5-carboxamide (11).** (Method D) 3-(2,4-Dichlorophenyl)-8-ethyl-1-methyl-7-(3-pentyl)-3,7-dihydro-1*H*-purine-2,6-dione **10a** (268 mg, 0.655 mmol) was dissolved in dioxane (1 mL). EtOH (1 mL) and aqueous 3 N NaOH (2 mL) were added, and the reaction mixture was heated at reflux for 3.5 h. The mixture was cooled to room temperature and transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexanes with 0.2% MeOH) to afford a colorless amorphous solid (120 mg, 48% yield): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.33 (d, $J$ = 2.2 Hz, 1H), 7.07 (dd, $J$ = 8.7, 2.5 Hz, 1H), 6.91 (s br, 1H), 6.86 (d, $J$ = 8.8 Hz, 1H), 6.20 (s, 1H), 2.82 (d, $J$ = 4.7 Hz, 3H), 2.74 (q, $J$ = 7.4 Hz, 2H), 1.98−1.86 (m, 4H), 1.33 (t, $J$ = 7.7 Hz, 3H), 0.86 (t, $J$ = 7.7 Hz, 6H); HRMS (ESI) *m/e* 383.1423 [(M + H)$^+$; calcd for $C_{18}H_{25}N_4OCl_2$ 383.1405].

**2-Ethyl-1-(4-heptyl)-*N*-methyl-4-[(2,4,6-trimethylphenyl)-amino]-1*H*-imidazole-5-carboxamide (11).** (Method E) A solution of 8-ethyl-7-(4-heptyl)-1-methyl-3-(2,4,6-trimethylphenyl)-3,7-dihydro-1*H*-purine-2,6-dione **10** (50 mg, 0.122 mmol) was cooled to −10 °C. $LiAlH_4$ (0.24 mL, 0.244 mmol, 1 M in THF) was added dropwise, and the reaction mixture was stirred at −10 °C for 1.5 h. An additional portion of $LiAlH_4$ (0.24 mL, 0.244 mmol, 1 M in THF) was added dropwise, and the cooling bath was removed and the reaction mixture was allowed to stir at room temperature for 30 min. The reaction was quenched by the dropwise addition of absolute ethanol followed by saturated aqueous $NaHCO_3$. The precipitate was removed by filtration, and the filtrate was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (1000 $\mu$M silica gel plate, 30% ethyl acetate in hexanes with 2% methanol) to afford the desired product (30 mg, 64% yield) as a tan solid: mp 135−136 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.18 (s br 1H), 6.84 (s, 2H), 5.31 (s br, 1H), 4.02 (s br, 1H), 2.78 (d, $J$ = 4.8 Hz, 3H), 2.68 (q, $J$ = 7.7 Hz, 2H), 2.24 (s, 3H), 2.11 (s, 6H), 1.92−1.62 (s br, 3H), 1.41−1.01 (m, 5H), 1.21 (t, $J$ = 7.3 Hz, 3H) 0.89 (t, 7.3 Hz, 6H); LRMS (APCI) *m/e* 385.1 [(M + H)$^+$, calcd for $C_{23}H_{37}N_4O$, 385.3].

**3-(2,4-Dichlorophenyl)-8-ethyl-1-methyl-7-(3-pentyl)-1,2,3,7-tetrahydro-6*H*-purin-6-one (12a).** 4-[(2,4-Dichlorophenyl)amino]-2-ethyl-*N*-methyl-1-(3-pentyl)-1*H*-imidazole-5-carboxamide **11** (35 mg, 0.091 mmol) was dissolved in toluene (5 mL) and was treated with paraformaldehyde (150 mg) and *p*-TsOH·$H_2O$ (10 mg, 0.053 mmol). The mixture was heated at reflux for 1.25 h in a flask equipped with a Dean−Stark trap. The mixture was cooled to room temperature and transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (1000 $\mu$M silica gel plate, 30% ethyl acetate in hexanes) to afford 3-(2,4-dichlorophenyl)-8-ethyl-7-(3-pentyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **12a** (29 mg, 81% yield) as a colorless solid: mp 132−133 °C; $^1$H NMR (500 MHz, DMSO-$d_6$, 100 °C) $\delta$ 7.61 (d, $J$ = 2.2 Hz, 1H), 7.37 (dd, $J$ = 8.4, 2.1 Hz, 1H), 7.19 (d, $J$ = 8.8 Hz, 1H), 4.81 (s, 2H), 4.35−4.25 (m, 1H), 2.86 (s, 3H), 2.67 (q, $J$ = 7.3 Hz, 2H), 2.23−2.12 (m, 2H), 1.93−1.84 (m, 2H), 1.19 (t, $J$ = 7.4 Hz, 3H), 0.80 (t, $J$ = 7.3 Hz, 6H); HRMS (ESI) *m/e* 395.1406 [(M + H)$^+$, calcd for $C_{19}H_{25}N_4OCl_2$ 395.1405]. Anal. ($C_{19}H_{24}N_4OCl_2$) C, H, N.

**7-[(Benzyloxymethyl]-3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione (13).** 3-(2,4-Dichlorophenyl)-8-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **9** (6.00 g, 17.69 mmol) was dissolved in anhydrous DMF (80 mL). $K_2CO_3$ (6.11 g, 44.23 mmol), $Bu_4NI$ (1.31 g, 3.54 mmol) and BOMCl (4.4 mL, 31.84 mmol) were added, and the reaction mixture was heated at 45 °C for 50 min. The reaction mixture was cooled to room temperature and was stirred with saturated aqueous $NaHCO_3$ (180 mL) for 30 min. The mixture was poured into a separatory funnel containing ether (600 mL). The organic layer was washed with $H_2O$ (4 × 80 mL), brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexanes) to give 7-benzyloxymethyl-3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **13** (5.28 g, 65% yield) as an amorphous solid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.59 (d, $J$ = 2.2 Hz, 1H), 7.42 (dd, $J$ = 8.4, 2.2 Hz, 1H), 7.37−7.26 (m, 6H), 5.86 (ABq, $J_{AB}$ = 11.0, $\Delta\nu$ = 39.7 Hz, 2H), 4.72 (s, 2H), 3.46 (s, 3H), 2.79 (q, $J$ = 7.7 Hz, 2H), 1.25 (t,

$J$ = 7.6 Hz, 3H); LRMS (APCI) *m/e* 459.0 [(M + H)$^+$, calcd for $C_{22}H_{21}N_4O_3Cl_2$ 459.1].

**1-Benzyloxymethyl-4-[(2,4-dichlorophenyl)amino]-2-ethyl-*N*-methyl-1*H*-imidazole-5-carboxamide (14).** 7-Benzyloxymethyl-3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **13** (5.20 g, 11.32 mmol) was dissolved in dioxane (25 mL), and the mixture was treated with EtOH (25 mL) and aqueous 3 N NaOH (50 mL). The reaction mixture was heated at 60 °C for 2 h. The mixture was then cooled to room temperature and was transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexanes → 40% ethyl acetate in hexanes with 0.2% MeOH) to afford 1-benzyloxymethyl-4-[(2,4-dichlorophenyl)amino]-2-ethyl-*N*-methyl-1*H*-imidazole-5-carboxamide **14** (2.90 g, 59% yield) as a light yellow amorphous solid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.35 (s, 1H), 8.41 (d, $J$ = 8.8 Hz, 1H), 7.44−7.29 (m, 7H), 7.16 (dd, $J$ = 9.1, 2.5 Hz, 1H), 5.45 (s, 2H), 4.63 (s, 2H), 2.89 (d, $J$ = 4.8 Hz, 3H), 2.65 (q, $J$ = 7.7 Hz, 2H), 1.35 (t, $J$ = 7.7 Hz, 3H); LRMS (APCI) *m/e* 433.1 [(M + H)$^+$, calcd for $C_{21}H_{23}N_4O_2Cl_2$ 433.1].

**7-Benzyloxymethyl-3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (15).** A solution of 1-benzyloxymethyl-4-[(2,4-dichlorophenyl)amino]-2-ethyl-*N*-methyl-1*H*-imidazole-5-carboxamide **14** (2.70 g, 6.23 mmol) dissolved in toluene (100 mL) was treated with paraformaldehyde (8.0 g) and *p*-TsOH·$H_2O$ (0.67 g, 3.52 mmol). The reaction mixture was heated at reflux for 15 min. The mixture was cooled to room temperature and transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (150 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexanes) to afford 7-benzyloxymethyl-3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **15** (1.6 g, 58% yield) as a colorless amorphous solid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.46 (d, $J$ = 2.2 Hz, 1H), 7.34−7.29 (m, 5H), 7.19 (dd, $J$ = 8.4, 2.2 Hz, 1H), 7.03 (d, $J$ = 8.8 Hz, 1H), 5.84 (s, 2H), 4.85 (s, 2H), 4.71 (s, 2H), 2.97 (s, 3H), 2.77 (q, $J$ = 7.7 Hz, 2H), 1.28 (t, $J$ = 7.7 Hz, 3H); HRMS (ESI) *m/e* 445.1212 [(M + H)$^+$, calcd for $C_{22}H_{23}N_4O_2Cl_2$ 445.1198]. Anal. ($C_{22}H_{22}N_4O_2Cl_2$) C, H, N.

**3-(2,4-Dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (16).** A solution of 7-benzyloxymethyl-3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **15** (1.3 g, 2.92 mmol) in $CHCl_3$ (2 mL) was treated with trifluoroacetic acid (15 mL). The solution was heated at 80 °C in a pressure tube for 5 h. The mixture was then cooled to room temperature and concentrated. The residue was concentrated from heptane (2×), transferred into a separatory funnel containing saturated aqueous $NaHCO_3$ (75 mL), and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (3% methanol in $CH_2Cl_2$) to furnish 3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **16** (900 mg, 95% yield) as a colorless solid: mp 200−201 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 12.05 (s, 1H), 7.47 (d, $J$ = 2.2 Hz, 1H), 7.20 (dd, $J$ = 8.8, 2.6 Hz, 1H), 7.12 (d, $J$ = 8.4 Hz, 1H), 4.90 (s, 2H), 3.02 (s, 3H), 2.79 (q, $J$ = 7.7 Hz, 2H), 1.34 (t, $J$ = 7.7 Hz, 3H); LRMS (APCI) *m/e* 325.0 [(M + H)$^+$, calcd for $C_{14}H_{15}N_4OCl_2$ 325.1].

**3-(2,4-Dichlorophenyl)-8-ethyl-7-(1-methoxymethylbutyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12e).** A solution of 3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **16** (80 mg, 0.246 mmol) in anhydrous THF (1.2 mL) was heated to 50 °C. $PPh_3$ (100 mg, 0.492 mmol) and 1-methoxy-2-pentanol (87 mg, 0.738 mmol) were added. After stirring 5 min, DEAD (85 $\mu$L, 0.541 mmol) was added rapidly via syringe and the reaction mixture was stirred 25 min at 50 °C. The mixture was cooled to room temperature and was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification of the residue by preparative TLC (two 1000 $\mu$M silica gel plates, 50% ethyl acetate/50% hexanes) followed by further purification by reverse phase HPLC furnished 3-(2,4-dichlorophenyl)-8-ethyl-7-(1-methoxymethylbutyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **12e** (59 mg, 56% yield) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.45 (d, $J$ = 2.2 Hz, 1H), 7.18 (dd, $J$ = 8.5, 2.2 Hz, 1H), 7.07 (d, $J$ = 8.4 Hz, 1H), 4.84 (ABq, $J$ = 11.4, $\Delta\upsilon$ = 46.9 Hz, 2H), 4.21 (q, $J$ = 7.4 Hz, 2H), 3.76 (dd, $J$ = 9.9, 4.4 Hz, 1H), 3.32 (s, 3H), 2.96 (s, 3H), 2.75 (q, $J$ = 7.7 Hz, 2H), 2.21−2.05 (m, 1H), 1.95−1.81 (m, 1H), 1.30−1.20 (m, 5H), 0.92 (t, $J$ = 7.0 Hz, 3H); HRMS (ESI) *m/e* 425.1519 [(M + H)$^+$, calcd for $C_{20}H_{27}N_4O_2Cl_2$ 425.1511]. HPLC: (a) 98.2%; (b) 95.8% (75% hexanes−25% ethyl acetate with 3% methanol).

**3-(2,4-Dichlorophenyl)-8-ethyl-7-(1-ethyl-2-methylpropyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12f).** A solution of 3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **16** (50 mg, 0.154 mmol) in anhydrous DMF (1.0 mL) was treated with finely ground $K_2CO_3$ (64 mg, 0.462 mmol). After stirring 5 min at room temperature, 3-methanesulfonyl-2-methylpentane (75 $\mu$L, 0.431 mmol) was added via syringe and the reaction mixture was heated at 90 °C for 4 h. The mixture was cooled to room temperature and transferred to a separatory funnel containing ethyl acetate (50 mL). The organic layer was washed with water (3 × 10 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the residue by medium-pressure liquid chromatography (10% → 20% ethyl acetate in hexanes) afforded 3-(2,4-dichlorophenyl)-8-ethyl-7-(1-ethyl-2-methylpropyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **12f** (14 mg, 22% yield) as an amber solid: mp 100−101 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44 (d, $J$ = 2.2 Hz, 1H), 7.15 (dd, $J$ = 8.5, 2.2 Hz, 1H), 6.95 (d, $J$ = 8.5 Hz, 1H), 4.83 (ABq, $J_{AB}$ = 11.5, $\Delta\upsilon$ = 25.3 Hz, 2H), 3.55−3.49 (m, 1H), 2.93 (s, 3H), 2.83−2.75 (m, 1H), 2.70 (q, $J$ = 7.5 Hz, 2H), 2.47−2.38 (m, 1H), 1.98−1.88 (m, 1H), 1.27 (t, $J$ = 7.3 Hz, 3H), 1.10−1.05 (m, 3H), 0.89−0.70 (m, 6H); HRMS (ESI) *m/e* 409.1562 [(M + H)$^+$, calcd for $C_{20}H_{27}N_4OCl_2$ 409.1562]. HPLC: (a) 100%; (b) 100% (75% hexanes−25% ethyl acetate with 3% methanol).

**3-(2,4-Dichlorophenyl)-8-ethyl-1-methyl-7-(2-pentyl)-1,2,3,7-tetrahydro-6*H*-purin-6-one (12b).** colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.45 (d, $J$ = 2.5 Hz, 1H), 7.17 (dd, $J$ = 8.4, 2.2 Hz, 1H), 7.04 (d, $J$ = 8.5 Hz, 1H), 4.84 (ABq, $J_{AB}$ = 11.4, $\Delta\upsilon$ = 26.2 Hz, 2H), 4.21−4.17 (m, 1H), 2.96 (s, 3H), 2.73 (q, $J$ = 7.7 Hz, 2H), 2.17−2.12 (m, 1H), 1.97−1.92 (m, 1H), 1.64 (d, $J$ = 6.6 Hz, 3H), 1.36−1.20 (m, 5H), 0.93 (t, $J$ = 7.3 Hz, 3H); HRMS (ESI) *m/e* 395.1368 [(M + H)$^+$, calcd for $C_{19}H_{25}N_4OCl_2$ 395.1405]. HPLC: (a) 97.3%; (b) 99.5% (65% hexanes−35% ethyl acetate with 3% methanol).

**3-(2,4-Dichlorophenyl)-8-ethyl-7-(3-heptyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12c).** colorless solid; mp 94−95 °C; $^1$H NMR (300 MHz, DMSO-$d_6$, 80 °C) $\delta$ 7.64 (d, $J$ = 2.6 Hz, 1H), 7.39 (dd, $J$ = 5.8, 2.2 Hz, 1H), 7.17 (d, $J$ = 8.8 Hz, 1H), 4.80 (s, 2H), 4.40−4.30 (m, 1H), 2.86 (s, 3H), 2.66 (q, $J$ = 7.4 Hz, 2H), 2.22−2.12 (m, 2H), 1.90−178 (m, 2H), 1.33−1.07 (m, 4H), 1.17 (t, $J$ = 7.3 Hz, 3H), 0.85 (t, $J$ = 6.6 Hz, 3H), 0.878 (t, $J$ = 7.3 Hz, 3H); HRMS (ESI) *m/e* 423.1723 [(M + H)$^+$, calcd for $C_{21}H_{29}N_4OCl_2$ 423.1718]. Anal. ($C_{21}H_{28}N_4OCl_2$) C, H, N.

**3-(2,4-Dichlorophenyl)-8-ethyl-7-(4-heptyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12d).** colorless solid: mp 117−118 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.45 (d, $J$ = 2.2 Hz, 1H), 7.17 (dd, $J$ = 8.4, 2.2 Hz, 1H), 7.00 (d, $J$ = 8.8 Hz, 1H), 4.84 (s, 2H), 4.10−4.00 (m, 1H), 2.95 (s, 3H), 2.71 (q, $J$ = 7.3 Hz, 2H), 2.30−1.80 (m, 4H), 1.40−1.15 (m, 4H), 1.27 (t, $J$ = 7.7 Hz, 3H), 0.92 (t, $J$ = 7.3 Hz, 6H); HRMS (ESI) *m/e* 423.1736 [(M + H)$^+$, calcd for $C_{21}H_{29}N_4OCl_2$ 423.1718]. Anal. ($C_{21}H_{28}N_4OCl_2$) C, H, N.

**7-(1-Cyclopropylethyl)-3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12 g).** colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.51 (d, $J$ = 2.2 Hz, 1H), 7.28 (dd, $J$ = 8.8, 2.6 Hz, 1H), 7.19 (d, $J$ = 8.4 Hz, 1H), 4.92 (ABq, $J_{AB}$ = 11.0, $\Delta\upsilon$ = 41.3 Hz, 2H), 4.05−3.95 (m, 1H), 3.02 (s, 3H), 2.96−2.88 (m, 2H), 1.85−1.75 (m, 1H), 1.78 (d, $J$ = 7.0 Hz, 3H), 1.31 (t, $J$ = 7.7 Hz, 3H), 0.83−0.79 (m, 1H), 0.78−0.59 (m, 1H), 0.57−0.40 (m, 1H), 0.39−0.21 (m, 1H); HRMS (ESI) *m/e* 393.1244 [(M + H)$^+$, calcd for $C_{19}H_{23}N_4OCl_2$ 393.1249]. Anal. ($C_{19}H_{22}N_4OCl_2$) C, H, N; calcd C, 58.02; found C, 57.35.

**7-(1-Cyclopropylpropyl)-3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12h).** Colorless oil; $^1$H NMR (500 MHz, DMSO-$d_6$, 100 °C) $\delta$ 7.62 (d, $J$ = 2.2 Hz, 1H), 7.38 (dd, $J$ = 8.6, 2.5 Hz, 1H), 7.22 (d, $J$ = 8.6 Hz, 1H), 4.82 (s, 2H), 3.80−3.70 (m, 1H), 2.87 (s, 3H), 2.68−2.64 (m, 2H), 2.55−2.40 (m, 1H), 2.20−2.05 (m, 1H), 1.85−1.77 (m, 1H), 1.18 (t, $J$ = 7.3 Hz, 3H), 0.84 (t, $J$ = 7.3 Hz, 3H), 0.72−0.65 (m, 1H), 0.45−0.37 (m, 2H), 0.20−0.15 (m, 1H); HRMS (ESI) *m/e* 407.1423 [(M + H)$^+$, calcd for $C_{20}H_{25}N_4OCl_2$ 407.1405]. HPLC: (a) 96.9%, (b) 98.5% (75% hexanes−25% ethyl acetate with 3% methanol).

**7-(1-Cyclopropylbutyl)-3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12i).** Colorless oil; $^1$H NMR (400 MHz, DMSO-$d_6$, 120 °C) $\delta$ 7.61 (d, $J$ = 2.4 Hz, 1H), 7.37 (dd, $J$ = 8.5, 2.4 Hz, 1H), 7.20 (d, $J$ = 8.5, 1H), 4.79 (s, 2H), 4.08−4.05 (m, 1H), 2.86 (s, 3H), 2.63 (q, $J$ = 7.5 Hz, 2H), 2.21−2.10 (m, 1H), 2.04−1.94 (m, 1H), 1.82−1.75 (m, 1H), 1.39−1.22 (m, 1H), 1.21−1.15 (m, 4H), 0.88 (t, $J$ = 7.3 Hz, 3H), 0.67−0.62 (m, 1H), 0.41−0.35 (m, 2H), 0.20−0.14 (m, 1H); HRMS (ESI) *m/e* 421.1567 [(M + H)$^+$, calcd for $C_{21}H_{27}N_4OCl_2$ 421.1562]. HPLC: (a) 97.2%; (b) 96.5% (60% hexanes−40% ethyl acetate with 3% methanol).

**3-(2,4-Dichlorophenyl)-7-dicyclopropylmethyl-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12j).** Colorless oil; $^1$H NMR (500 MHz, DMSO-$d_6$, 90 °C) $\delta$ 7.60 (d, $J$ = 2.2 Hz, 1H), 7.39 (dd, $J$ = 8.4, 2.2.Hz, 1H), 7.20 (d, $J$ = 8.8 Hz, 1H), 4.81 (s, 2H), 4.08−4.01 (m, 1H), 2.81 (s, 3H), 2.72−2.63 (m, 2H), 1.22−1.06 (m, 5H), 1.01−0.97 (m, 1H), 0.78−0.62 (m, 1H), 0.57−0.41 (m, 2H), 0.40−0.21 (m, 3H), 0.20−0.15 (m, 1H); HRMS (ESI) *m/e* 419.1402 [(M + H)$^+$, calcd for $C_{21}H_{25}N_4OCl_2$ 419.1405]. HPLC: (a) 98.0%; (b) 99.5% (75% hexanes−25% ethyl acetate with 3% methanol).

**7-(1-Cyclobutylethyl)-3-(2,4-dichlorophenyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12k).** Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 (d, $J$ = 2.2 Hz, 1H), 7.15 (dd, $J$ = 8.5, 2.4 Hz, 1H), 7.00 (d, $J$ = 8.5 Hz, 1H), 4.81 (ABq, $J_{AB}$ = 11.5, $\delta\upsilon$ = 36.1 Hz, 2H), 3.35−3.25 (m, 1H), 2.95 (s, 3H), 2.75 (q, $J$ = 7.5 Hz, 2H), 2.21−2.15 (m, 1H), 1.91−1.71 (m, 4H), 1.58−1.51 (m, 2H), 1.52 (d, $J$ = 6.7 Hz, 3H), 1.27 (t, $J$ = 7.6 Hz, 3H); HRMS (ESI) *m/e* 407.1406 [(M + H)$^+$, calcd for $C_{20}H_{25}N_4OCl_2$ 407.1405. HPLC: (a) 100%; (b) 100% (75% hexanes−25% ethyl acetate with 3% methanol).

**3-(2,4-Dichlorophenyl)-8-ethyl-7-(4-methoxybenzyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12l).** Colorless amorphous solid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.46 (d, $J$ = 2.2 Hz, 1H), 7.20−7.14 (m, 3H), 7.07 (d, $J$ = 8.7 Hz, 1H), 6.87 (d, $J$ = 8.8 Hz, 2H), 5.49 (s, 2H), 4.86 (s, 2H), 3.79 (s, 3H), 2.95 (s, 3H), 2.65 (q, $J$ = 7.7, 2H), 1.18 (t, $J$ = 7.7 Hz, 3H); HRMS (ESI) *m/e* 445.1200 [(M + H)$^+$, calcd for $C_{22}H_{23}N_4O_2Cl_2$ 445.1198]. Anal. ($C_{22}H_{22}N_4O_2Cl_2$) C, H, N.

**3-(2,4-Dichlorophenyl)-8-ethyl-7-(2-methylbenzyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12m).** Colorless solid; mp 142−143 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46 (d, $J$ = 2.5 Hz, 1H), 7.21−7.09 (m, 5H), 6.52 (d, $J$ = 7.6 Hz, 1H), 5.56 (s, 2H), 4.87 (s, 2H), 2.90 (s, 3H), 2.54 (q, $J$ = 7.4 Hz, 2H), 2.39 (s, 3H), 1.16 (t, $J$ = 7.6 Hz, 3H); HRMS (ESI) *m/e* 429.1257 [(M + H)$^+$, calcd for $C_{22}H_{23}N_4OCl_2$ 429.1249]. Anal. ($C_{22}H_{22}N_4OCl_2$) C, H, N.

**3-(2,4-Dichlorophenyl)-8-ethyl-1-methyl-7-(4-phenylbenzyl)-1,2,3,7-tetrahydro-6*H*-purin-6-one (12n).** Colorless solid; mp 216−217 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.1 Hz, 4H), 7.47−7.32 (m, 5H), 7.24 (s, 1H), 7.20 (dd, $J$ = 8.5, 2.2 Hz, 1H), 7.09 (d, $J$ = 8.4 Hz, 1H), 5.62 (s, 2H), 4.89 (s, 2H), 2.96 (s, 3H), 2.68 (q, $J$ = 7.3 Hz, 2H), 1.21 (t, $J$ = 7.3 Hz, 3H); HRMS (ESI) *m/e* 491.1399 [(M + H)$^+$, calcd for $C_{27}H_{25}N_4OCl_2$ 491.1405]. HPLC: (a) 98.1%; (b) 97.9% (60% hexanes−40% ethyl acetate with 3% methanol).

**3-(2,4-Dichlorophenyl)-8-ethyl-1-methyl-7-(1-naphthylmethyl)-1,2,3,7-tetrahydro-6*H*-purin-6-one (12o).** Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 8.4 Hz, 1H), 7.90 (d, $J$ = 6.9 Hz, 1H), 7.78 (d, $J$ = 8.1 Hz, 1H), 7.63−7.52 (m, 2H), 7.49 (d, $J$ = 2.6 Hz, 1H), 7.38 (t, $J$ = 7.3 Hz, 1H), 7.23 (dd, $J$ = 8.4, 2.2 Hz, 1H), 7.15 (d, $J$ = 8.4 Hz, 1H), 6.68 (d, $J$ = 6.6 Hz, 1H), 6.11 (s, 2H), 4.92 (s, 2H), 2.91 (s, 3H), 2.56 (q, $J$ = 7.3 Hz, 2H), 1.16 (t, $J$ = 7.7 Hz, 3H); HRMS (ESI) *m/e* 465.1248 [(M + H)$^+$, calcd for $C_{22}H_{23}N_4O_2Cl_2$ 465.1249]. Anal. ($C_{22}H_{22}N_4O_2Cl_2$) C, H, N.

**8-Ethyl-7-(4-heptyl)-1-methyl-3-(2,4,6-trimethylphenyl)-3,7-dihydro-1*H*-purine-2,6-dione (10c).** Colorless solid; mp 192−193 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.97 (s, 2H), 4.12−4.08 (m, 1H), 3.46 (s, 3H), 2.71 (q, $J$ = 7.6 Hz, 2H), 2.31 (s, 3H), 2.30−2.23 (m, 2H), 2.02 (s, 6H), 1.98−1.80 (m, 2H), 1.30−1.20 (m, 2H), 1.19 (t, $J$ = 7.6 Hz, 3H), 1.16−1.05 (m, 2H), 0.90 (t, $J$ = 7.3 Hz, 6H); HRMS (ESI) *m/e* 411.2756 [(M + H)$^+$, calcd for $C_{24}H_{35}N_4O_2$ 411.2760]. Anal. ($C_{24}H_{34}N_4O_2$) C, H, N; calcd C 69.58, H 9.01; found C 70.21, H 8.34.

**8-Ethyl-7-(4-heptyl)-1-methyl-3-(2,4,6-trimethylphenyl)-1,2,3,7-tetrahydro-6*H*-purin-6-one (12p).** Colorless oil; $^1$H NMR (500 MHz, DMSO-$d_6$, 30 °C) $\delta$ 6.90 (s, 2H), 4.65 (s, 2H), 4.15−4.00 m, 1H), 2.83 (s, 3H), 2.59 (q, $J$ = 7.3 Hz, 2H), 2.24 (s, 3H), 2.06 (s, 6H), 1.72−1.68 (m, 2H), 1.30−1.18 (m, 4H), 1.12−1.05 (m, 2H), 1.08 (t, $J$ = 7.3 Hz, 3H), 0.84 (t, $J$ = 7.3 Hz, 6H); HRMS (ESI) *m/e* 397.2965 [(M + H)$^+$, calcd for $C_{24}H_{37}N_4O$ 397.2967]. Anal. ($C_{24}H_{36}N_4O$) C, H, N.

**3-(2-Chloro-4-methoxyphenyl)-8-ethyl-7-(4-heptyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12q).** Colorless oil; $^1$H NMR (300 MHz, DMSO-$d_6$, 80 °C) $\delta$ 7.11 (d, $J$ = 8.8 Hz, 1H), 7.10 (d, $J$ = 2.6 Hz, 1H), 6.90 (dd, $J$ = 8.5, 2.6 Hz, 1H), 4.71 (s, 2H), 4.60−4.45 (m, 1H), 3.81 (s, 3H), 2.85 (s, 3H), 2.65 (q, $J$ = 7.3 Hz, 2H), 2.20−2.08 (m, 2H), 1.85−1.75 (m, 2H), 1.30−1.10 (m, 4H), 1.17 (t, $J$ = 7.6 Hz, 3H), 0.88 (t, $J$ = 7.3 Hz, 6H), HRMS (ESI) *m/e* 419.2215 [(M + H)$^+$, calcd for $C_{22}H_{32}N_4O_2Cl$ 419.2214]. Anal. ($C_{22}H_{31}N_4O_2Cl$) C, H, N; C, 63.07; found C, 62.66.

**3-(2-Chloro-4-methoxyphenyl)-7-(1-cyclopropylpropyl)-8-ethyl-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12r).** Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.05 (d, $J$ = 8.8 Hz, 1H), 6.99 (d, $J$ = 2.9 Hz, 1H), 6.76 (dd, $J$ = 8.8, 3.0 Hz, 1H), 4.79 (ABq, $J_{AB}$ = 11.0, $\Delta\upsilon$ = 24.7 Hz, 2H), 4.22−4.15 (m, 1H), 3.79 (s, 3H), 2.95 (s, 3H), 2.69−2.66 (m, 2H), 2.38−2.08 (m, 2H), 1.35−1.22 (m, 1 H, partially obs.), 1.25 (t, $J$ = 7.4 Hz, 3H), 0.90 (t, $J$ = 7.7 Hz, 3H), 0.79−0.66 (m, 1H), 0.52−0.35 (m, 2H), 0.30−0.17 (m, 1H); HRMS (ESI) *m/e* 403.2015 [(M + H)$^+$, calcd for $C_{21}H_{28}N_4O_2Cl$ 403.1901]. HPLC: (a) 98.3%; (b) 97.9% (75% hexanes−25% ethyl acetate with 3% methanol).

**3-(2-Chloro-4-methoxyphenyl)-8-ethyl-1-methyl-7-(2-methylbenzyl)-1,2,3,7-tetrahydro-6*H*-purin-6-one (12s).** Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.22−7.11 (m, 4H), 7.03 (d, $J$ = 2.6 Hz, 1H), 6.81 (dd, $J$ = 9.1, 2.9 Hz, 1H), 6.57 (d, $J$ = 7.0 Hz, 1H), 5.59 (s, 2H), 4.85 (s, 2H), 3.81 (s, 3H), 2.93 (s, 3H), 2.58 (q, $J$ = 7.3 Hz, 2H), 2.42 (s, 3H), 1.18 (t, $J$ = 7.7 Hz, 3H); HRMS (ESI) *m/e* 425.1738 [(M + H)$^+$, calcd for $C_{23}H_{26}N_4O_2Cl$ 425.1744]. HPLC: (a) 99.0%; (b) 100% (60% hexanes−40% ethyl acetate with 3% methanol).

**3-[2-Chloro-4-isopropylphenyl]-8-ethyl-7-(4-heptyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12t).** brown oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.29 (d, $J$ = 1.9 Hz, 1H), 7.06 (dd, $J$ = 8.4, 1.8 Hz, 1H), 7.00 (d, $J$ = 8.1 Hz, 1H), 4.84 (s, 2H), 4.15−4.00 (m, 1H), 2.98 (s, 3H), 2.87 (pent, $J$ = 6.9 Hz, 1H), 2.70 (q, $J$ = 7.3 Hz, 2H), 2.30−2.10 (m, 2H), 1.98−1.85 (m, 2H), 1.30−1.20 (m, 13H), 0.92−0.91 (t, $J$ = 7.3 Hz, 6H); HRMS (ESI) *m/e* 431.2581 [(M + H)$^+$, calcd for $C_{24}H_{36}N_4OCl$ 431.2578]. HPLC: (a) 98.0% (b) 98.5% (80% hexanes−20% ethyl acetate with 3% methanol).

**1-Benzyloxymethyl-4-[(2-chloro-4-isopropyl)amino]-2-ethyl-*N*-methyl-1*H*-imidazole-5-carboxamide (14).** 7-Benzyloxymethyl-3-(2-chloro-4-isopropyl)-8-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **13** (7.88 g, 16.0 mmol) was

dissolved in THF (84 mL). The reaction mixture was cooled to 0 °C and $LiAlH_4$ (67.6 mL, 67.6 mmol, 1 M in THF) was added dropwise. After stirring for 1.25 h at 0 °C, the reaction was quenched by the dropwise addition of ethanol followed by saturated aqueous $NaHCO_3$. The mixture was filtered through a pad of Celite and the filtrate was extracted with $CH_2Cl_2$ (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to afford 1-benzyloxymethyl-4-[(2-chloro-4-isopropyl)amino]-2-ethyl-*N*-methyl-1*H*-imidazole-5-carboxamide **14** (3.50 g, 50% yield) as an orange oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.57 (s br, 1H), 7.72 (s br, 1H), 7.44−7.30 (m, 6H), 7.18 (d, $J$ = 1.9 Hz, 1H), 7.04 (dd, $J$ = 8.5, 1.9 Hz, 1H), 5.63 (s, 2H), 4.70 (s, 2H), 2.90 (d, $J$ = 4.8 Hz, 3H), 2.83 (septet, $J$ = 7.0 Hz, 1 H, partially obs.), 2.74 (q, $J$ = 7.3 Hz, 2H), 1.33 (t, $J$ = 7.7 Hz, 3H), 1.21 (d, $J$ = 7.0 Hz, 6H).

**3-[2-Chloro-4-isopropylphenyl]-8-ethyl-7-(1-ethyl-2-methylpropyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12u).** Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.27 (m, 1H), 7.03 (dd, $J$ = 8.4, 1.8 Hz, 1H), 6.94 (d, $J$ = 8.0 Hz, 1H), 4.89 (s, 2H), 3.58−3.48 (m, 1H), 2.93 (s, 3H), 2.92−2.80 (m, 2H), 2.71 (q, $J$ = 7.3 Hz, 2H), 2.50−2.40 (m, 1H), 2.00−1.90 (m, 1H), 1.30−1.21 (m, 9H), 1.07 (d, $J$ = 6.6 Hz, 3H), 0.90−0.75 (m, 6H); HRMS (ESI) *m/e* 417.2420 [(M + H)$^+$, calcd for $C_{23}H_{34}N_4OCl$ 417.2421]. HPLC: (a) 99.9% (b) 96.9% (80% hexanes−20% ethyl acetate with 3% methanol).

**2-Ethyl-1-(4-heptyl)-4-[(4-methoxybenzyl)amino]-*N*-methyl-1*H*-imidazole-5-carboxamide (18) and 8-Ethyl-7-(4-heptyl)-3-(*p*-methoxybenzyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (19).** 8-Ethyl-7-(4-heptyl)-3-(4-methoxybenzyl)-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **17** (550 mg, 1.33 mmol) prepared according to Method A, was dissolved in THF (17 mL) and cooled to 0 °C. Lithium aluminum hydride (5.32 mL, 5.32 mmol, 1 M in THF) was added dropwise via syringe. The cooling bath was removed and the reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was cooled to 0 °C and was quenched by the dropwise addition of $H_2O$ (0.20 mL) followed by 15% aqueous NaOH (0.20 mL) then $H_2O$ (0.61 mL). The mixture was filtered through a pad of Celite and was washed with EtOAc. The filtrate was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by MPLC on silica gel (30% ethyl acetate in hexanes → 65% ethyl acetate/35% hexanes) to afford the desired products. The higher $R_f$ product, 8-ethyl-7-(4-heptyl)-3-(4-methoxybenzyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **19**, was isolated as a colorless oil (193 mg, 36% yield). The lower $R_f$ product, 2-ethyl-1-(4-heptyl)-4-[(4-methoxybenzyl)-amino]-*N*-methyl-1*H*-imidazole-5-carboxamide **18**, was isolated as a colorless oil (270 mg, 53% yield).

2-Ethyl-1-(4-heptyl)-4-(*p*-methoxybenxyl)-*N*-methyl-1*H*-imidazole-5-carboxamide **18** (220 mg, 0.570 mmol) was dissolved in toluene (18 mL) and was treated with paraformaldehyde (600 mg) and *p*-TsOH·$H_2O$ (12 mg, 0.057 mmol). The mixture was heated at 110 °C for 10 min. The mixture was cooled to room temperature and transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by MPLC (30% ethyl acetate in hexanes) to afford 8-ethyl-7-(4-heptyl)-3-(4-methoxybenzyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **19** (170 mg, 75% yield) as a colorless oil.

**Data for 2-Ethyl-1-(4-heptyl)-4-[(4-methoxybenzyl)-amino]-*N*-methyl-1*H*-imidazole-5-carboxamide 18.** Colorless oil;$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.37 (s br, 1H), 7.29 (d, $J$ = 8.5 Hz, 2H), 6.85 (d, $J$ = 8.5 Hz, 2H), 5.13 (s br, 1H), 4.25 (d, $J$ = 6.3 Hz, 2H), 3.72 (s, 3H), 2.66 (d, $J$ = 4.3 Hz, 3H), 2.59 (q, $J$ = 7.3 Hz, 2H), 2.00−1.60 (m, 4H), 1.25−0.96 (m, 4H), 1.18 (t, $J$ = 7.3 Hz, 3H), 0.81 (t, $J$ = 7.3 Hz, 6H); LRMS (APCI) *m/e* 387.6 [(M + H)$^+$, calcd for $C_{22}H_{35}N_4O_2$ 387.3].

**Data for 8-Ethyl-7-(4-heptyl)-3-(4-methoxybenzyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one 19.** Colorless oil; $^1$H NMR (300 MHz, DMSO-$d_6$, 40 °C) $\delta$ 7.12 (d, $J$ = 8.8 Hz, 2H), 6.81 (d, $J$ = 8.4 Hz, 2H), 4.61 (s, 2H), 4.34−4.20 (m, 1H), 3.71 (s, 3H), 3.25 (s, 3H), 3.22 (s, 2H), 2.66−2.58 (m, 2H), 1.88−1.77 (m, 2H), 1.71−1.59 (m, 2H), 1.24−1.12 (m, 2H), 1.18 (t, $J$ = 7.7 Hz, 3H), 1.05−0.91 (m, 2H), 0.81 (t, $J$ = 7.3 Hz, 6H); LRMS (APCI) *m/e* 399.6 [(M + H)$^+$, calcd for $C_{23}H_{35}N_4O_2$ 399.3].

**8-Ethyl-7-(4-heptyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (20).** 8-Ethyl-7-(4-heptyl)-3-(4-methoxybenzyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **19** (375 mg, 0.941 mmol) was dissolved in trifluoroacetic acid (7 mL) and was stirred at room temperature for 1 h. The mixture was concentrated. The residue was transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (30 mL), and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (5% methanol in $CH_2Cl_2$ → 10% methanol in $CH_2Cl_2$) to afford 8-ethyl-7-(4-heptyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **20** (250 mg, 95% yield) as a colorless solid: mp 129.5−130.5 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.53 (s, 1H), 4.51 (s, 2H), 4.22−4.18 (m, 1H), 2.97 (s, 3H), 2.68 (q, $J$ = 7.3 Hz, 2H), 2.25−2.10 (m, 2H), 1.85−1.75 (m, 2H), 1.32 (t, $J$ = 7.4 Hz, 3H), 1.30−1.10 (m, 4H), 0.88 (t, $J$ = 7.4 Hz, 6H); LRMS (APCI) *m/e* 279.1 [(M + H)$^+$, calcd for $C_{15}H_{27}N_4O$ 279.1].

**8-Ethyl-7-(4-heptyl)-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione (21).** 8-Ethyl-7-(4-heptyl)-3-(4-methoxybenzyl)-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **17** (4.30 g, 10.4 mmol), prepared according to Method A, was dissolved in trifluoroacetic acid (20 mL) and was heated at 105 °C in a sealed tube for 14 h. The mixture was cooled to room temperature and concentrated. The residue was transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (50 mL), and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (5% methanol in $CH_2Cl_2$) to afford 8-ethyl-7-(4-heptyl)-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **21** (2.96 g, 97% yield) as a colorless solid: mp 152.5−153 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 12.00 (s, 1H), 4.20−4.10 (m, 1H), 3.41 (s, 3H), 2.94 (q, $J$ = 7.3 Hz, 2H), 2.33−2.19 (m, 2H), 1.94−1.83 (m, 2H), 1.42 (t, $J$ = 7.4 Hz, 3H), 1.26−1.06 (m, 4H), 0.90 (t, $J$ = 7.3 Hz, 6H); LRMS (APCI) *m/e* 293.1 [(M + H)$^+$, calcd for $C_{15}H_{25}N_4O_2$ 293.2].

**8-Ethyl-7-(4-heptyl)-3-(4-methoxy-2-methylpyridin-3-yl)-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione (10d).** 8-Ethyl-7-(4-heptyl)-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **21** (3.30 g, 11.3 mmol), 6-methoxy-2-methyl-3-pyridineboronic acid (2.84 g, 17.0 mmol), copper(II) acetate (3.07 g, 17 mmol), and 4 Å powdered molecular sieves (3.0 g) were combined in a 200 mL round-bottom flask. $CH_2Cl_2$ (25 mL) and pyridine (1.81 mL, 22.6 mmol) were added, and the reaction mixture was stirred at room temperature for 2 days. Additional 6-methoxy-2-methyl-3-pyridineboronic acid (1.50 g, 8.98 mmol) and copper(II) acetate (2.0 g, 11.0 mmol) were added, and the reaction mixture was stirred at room temperature for an additional 2 days. The mixture was poured into a separatory funnel containing saturated aqueous $NH_4Cl$ (100 mL) and concd $NH_4OH$ (150 mL). The aqueous layer was extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexanes then 75% ethyl acetate/25% hexanes to recover starting material) to furnish 8-ethyl-7-(4-heptyl)-3-(4-methoxy-2-methylpyrid-3-yl)-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **10d** (1.92 g, 41% yield) and recovered starting material (1.72 g, 52% recovery). The product was isolated as a colorless solid: mp 124−126 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.45 (d, $J$ = 8.5 Hz, 1H), 6.70 (d, $J$ = 8.8 Hz, 1H), 4.18−4.05 (m, 1H), 3.97 (s, 3H), 3.46 (s, 3H), 2.72 (q, $J$ = 7.7 Hz, 2H), 2.35−2.20 (m, 1H), 2.25 (s, 3H), 1.95−1.85 (m,

3H), 1.23 (t, $J$ = 7.4 Hz, 3H), 1.20−1.05 (m, 4H), 0.94−0.87 (m, 6H); HRMS (ESI) *m/e* 414.2506 [(M + H)$^+$, calcd for $C_{22}H_{32}N_5O_3$ 414.2505]. Anal. ($C_{22}H_{31}N_5O_3$) C, H, N.

**8-Ethyl-7-(4-heptyl)-3-(4-methoxy-2-methylpyridin-3-yl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12v).** 8-Ethyl-7-(4-heptyl)-3-(4-methoxy-2-methylpyrid-3-yl)-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione **10d** (1.84 g, 4.46 mmol) was dissolved in THF (50 mL) and was cooled to 0 °C. Lithium aluminum hydride (8.92 mL, 8.92 mmol, 1 M in THF) was added dropwise via syringe. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C and was quenched by the dropwise addition of $H_2O$ (0.34 mL) followed by 15% aqueous NaOH (0.34 mL) then $H_2O$ (1.02 mL). The mixture was filtered through a pad of Celite and was washed with EtOAc. The filtrate was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Two major products were formed in the reaction. The crude material was purified by column chromatography on silica gel (30% ethyl acetate in hexanes → 50% ethyl acetate in hexanes) to afford the higher $R_f$ product (306 mg) and the lower rf product, 2-ethyl-1-(4-heptyl)-4-[(4-methoxy-2-methylpyrid-3-yl)amino]-*N*-methyl-1*H*-imidazole-5-carboxamide **22**, 800 mg, 46% yield) as a green oil. The higher $R_f$ product was purified further by column chromatography on silica gel (2% MeOH in $CH_2Cl_2$) to afford 8-ethyl-7-(4-heptyl)-3-(4-methoxy-2-methylpyrid-3-yl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **12v** (240 mg, 14% yield) as a pale green solid.

**Data for 2-Ethyl-1-(4-heptyl)-4-[(4-methoxy-2-methylpyrid-3-yl)amino]-*N*-methyl-1*H*-imidazole-5-carboxamide 22.** Green oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.14 (s br, 1H), 7.01 (d br, $J$ = 7.3 H, 1H), 6.47 (d, $J$ = 8.5 Hz, 1H), 5.42 (s br, 1H), 4.15−4.05 (m, 1H), 3.87 (s, 3H), 2.77 (d, $J$ = 5.1 Hz, 3H), 2.73 (q, $J$ = 7.3 Hz, 2H), 2.45 (s, 3H), 1.90−1.75 (m, 4H), 1.31 (t, $J$ = 7.3 Hz, 3H), 1.40−1.23 (m, 2H), 1.22−1.10 (m, 2H), 0.91 (t, $J$ = 7.4 Hz, 6H); LRMS (APCI) *m/e* 388.3 [(M + H)$^+$, calcd for $C_{21}H_{34}N_5O_2$ 388.3].

**Data for 8-Ethyl-7-(4-heptyl)-3-(4-methoxy-2-methylpyrid-3-yl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one 12v.** Pale green solid; mp 120−122 °C; $^1$H NMR (300 MHz, DMSO-$d_6$, 80 °C) $\delta$ 7.39 (d, $J$ = 8.7 Hz, 1H), 6.63 (d, $J$ = 8.8 Hz, 1H), 4.69 (s, 2H), 4.55−4.44 (m, 1H), 3.87 (s, 3H), 2.86 (s, 3H), 2.63 (q, $J$ = 7.7 Hz, 2H), 2.37 (s, 3H), 2.19−2.07 (m, 2H), 1.84−1.73 (m, 2H), 1.32−1.07 (m, 4H), 1.15 (t, $J$ = 7.3 Hz, 3H), 0.87 (t, $J$ = 7.3 Hz, 6H); HRMS (ESI) *m/e* 400.2715 [(M + H)$^+$, calcd for $C_{22}H_{34}N_5O_2$ 400.2713]. Anal. ($C_{23}H_{33}N_5O_2$) C, H, N.

**3-(4-Chlorophenyl)-8-ethyl-7-(4-heptyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12w).** Colorless solid, mp 99−100 °C; $^1$H NMR (500 MHz, DMSO-$d_6$, 100 °C) $\delta$ 7.45 (d, $J$ = 2.2 Hz, 2H), 7.32 (d, $J$ = 2.2 Hz, 2H), 4.98 (s, 2H), 4.65−4.55 (m, 1H), 2.93 (s, 3H), 2.72 (q, $J$ = 7.6 Hz, 2H), 2.14−2.08 (m, 2H), 1.85−1.78 (m, 2H), 1.31−1.27 (m, 2H), 1.27 (t, $J$ = 7.6 Hz, 3H), 1.18−1.00 (m, 2H), 0.87 (t, $J$ = 7.3 Hz, 6H); HRMS (ESI) *m/e* 389.2103 [(M + H)$^+$, calcd for $C_{21}H_{30}N_4OCl$ 389.2108]. Anal. ($C_{21}H_{29}N_4OCl$) C, H, N.

**3-(2,4-Dichlorophenyl)-1,2-dimethyl-8-ethyl-7-(4-heptyl)-1,2,3,7-tetrahydro-6*H*-purin-6-one (12x).** A solution of 4-[(2,4-dichlorophenyl)amino]-2-ethyl-*N*-methyl-1-(3-pentyl)-1*H*-imidazole-5-carboxamide **11** (58 mg, 0.151 mmol) in toluene (8 mL) was treated with acetaldehyde dimethylacetal (0.40 mL, 3.79 mmol) and *p*-TsOH·$H_2O$ (8.0 mg, 0.042 mmol). The reaction mixture was heated at reflux for 1.25 h in a flask equipped with a Dean−Stark trap. The mixture was cooled to room temperature and was transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (two 1000 $\mu$M silica plates, 60% hexanes/35% $CH_2Cl_2$/5% ethyl acetate/0.2% MeOH) to furnish 3-(2,4-dichlorophenyl)-1,2-dimethyl-8-ethyl-7-(4-heptyl)-1,2,3,7-tetrahydro-6*H*-purin-6-one **12x** (57 mg, 86% yield) as a colorless solid: mp 144−145.5 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.44 (d, $J$ = 2.2 Hz, 1H), 7.14 (dd, $J$ = 8.4, 2.2 Hz, 1H), 6.88 (d, $J$ = 8.8 Hz, 1H), 4.85 (q, $J$ = 6.3 Hz, 1H), 4.10−4.02 (m, 1H), 2.94 (s, 3H), 2.71 (q, $J$ = 7.7 Hz, 2H), 2.50−1.75 (m, 4H), 1.54 (d, $J$ = 6.2 Hz, 3H), 1.40−1.00 (m, 4H), 1.28 (t, $J$ = 7.3 Hz, 3H), 1.06−0.85 (m, 6H); HRMS (ESI) *m/e* 437.1871 [(M + H)$^+$, calcd for $C_{22}H_{31}N_4OCl_2$ 437.1875]. Anal. ($C_{22}H_{30}N_4OCl_2$) C, H, N.

**3-(2,4-Dichlorophenyl)-2,8-diethyl-7-(4-heptyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12y).** A solution of 4-[(2,4-dichlorophenyl)amino]-2-ethyl-*N*-methyl-1-(3-pentyl)-1*H*-imidazole-5-carboxamide **11** (68 mg, 0.178 mmol) in toluene (8 mL) was treated with propionaldehyde (1.0 mL, 0.81 g, 13.9 mmol) and *p*-TsOH·$H_2O$ (8.0 mg, 0.042 mmol). The reaction mixture was heated at reflux for 1 h in a flask equipped with a Dean−Stark trap. The mixture was cooled to room temperature and was transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (two 1000 $\mu$M silica plates, 60% hexanes/35% $CH_2Cl_2$/5% ethyl acetate/0.2% MeOH) to furnish 3-(2,4-dichlorophenyl)-2,8-diethyl-7-(4-heptyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one **12y** (59 mg, 74% yield) as a colorless solid: mp 116.5−117.5 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.43 (d, $J$ = 2.6 Hz, 1H), 7.15 (dd, $J$ = 8.7, 2.5 Hz, 1H), 6.95 (d, $J$ = 8.8 Hz, 1H), 4.70 (t, $J$ = 7.4 Hz, 1H), 4.10−4.00 (m, 1H), 3.02 (s, 3H), 2.70 (q, $J$ = 7.3 Hz, 2H), 2.40−1.75 (m, 6H), 1.40−1.00 (m, 4H), 1.27 (t, $J$ = 7.7 Hz, 3H), 1.01 (t, $J$ = 7.6 Hz, 3H), 0.96−0.85 (m, 6H); HRMS (ESI) *m/e* 451.2040 [(M + H)$^+$, calcd for $C_{23}H_{33}N_4OCl_2$ 451.2031]. Anal. ($C_{23}H_{32}N_4OCl_2$) C, H, N.

**3-(2,4-Dichlorophenyl)-7-(4-heptyl)-1-methyl-1,2,3,7-tetrahydro-6*H*-purin-6-one (12z).** Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.47 (d, $J$ = 2.2 Hz, 1H), 7.39 (s, 1H), 7.20 (dd, $J$ = 8.4, 2.2 Hz, 1H), 7.09 (d, $J$ = 8.4 Hz, 1H), 4.94−4.85 (m, 1H), 4.87 (s, 2H), 2.98 (s, 3H), 1.92−1.80 (m, 4H), 1.38−1.22 (m, 4H), 0.92 (t, $J$ = 7.3 Hz, 6H); HRMS (ESI) *m/e* 395.1410 [(M + H)$^+$, calcd for $C_{19}H_{25}N_4OCl_2$ 395.1405]. Anal. ($C_{19}H_{24}N_4OCl_2$) C, H, N.

**Biology. Binding Assays.** Frozen rat frontal cortex (source of $CRF_1$ receptor) or frozen porcine choroid plexus (source of $CRF_2$ receptor) were thawed rapidly in assay buffer containing 50 mM HEPES (pH 7.0 at 23 °C), 10 mM $MgCl_2$, 2 mM EGTA, 1 $\mu$g/mL aprotinin, 1 $\mu$g/mL leupeptin, 1 $\mu$g/mL pepstatin A, 0.005% Triton X-100, 10U/mL bacitracin and 0.1% ovalbumin and homogenized. The suspension was centrifuged at 32000*g* for 30 min. The resulting supernatant was discarded and the pellet resuspended by homogenization in assay buffer and centrifuged again. The supernatant was discarded and the pellet resuspended by homogenization in assay buffer and frozen at −70 °C. On the day of the experiment aliquots of the homogenate were thawed quickly and homogenate (25 $\mu$g/well rat frontal cortex or 10 $\mu$g/well porcine choroid plexus) added to ligand (150 pM $^{125}$I-ovine-CRF for $CRF_1$ binding or 100 pM $^{125}$I-sauvagine for $CRF_2$ binding) and drugs in a total volume of 100 $\mu$L of assay buffer. The assay mixture was incubated for 2 h at 21 °C. Bound and free radioligand were then separated by rapid filtration, using glass fiber filters (Whatman GF/B, pretreated with 0.3% PEI) on a Brandel Cell Harvester. Filters were then washed multiple times with ice cold wash buffer (PBS w/o $Ca^{2+}$ and $Mg^{2+}$, 0.01% Triton X-100 (pH 7.0 at 23 °C)). Nonspecific binding was defined using 1 $\mu$M DMP696 in the $CRF_1$ binding assay and 1 $\mu$M $\alpha$-helical CRF (9−41) in the $CRF_2$ binding assay. Filters were then counted in a Wallac Wizard gamma counter.

**Materials.** Rat frontal cortex and porcine choroid plexus were obtained from Analytical Biological Services, Inc. (Wilmington, DE). $^{125}$I-ovine-CRF (2200 Ci/mmol) and $^{125}$I-sauvagine (2200 Ci/mmol) were obtained from PerkinElmer Life Sciences, Inc. (Boston, MA).

**Functional Assay (Y-79 cells).** Human Y-79 retinoblastoma cells were suspended in assay buffer (Hank's Balanced Salt Solution containing 2 mM $CaCl_2$, 5 mM Mg $Cl_2$, 20 mM

HEPES, 1 mM IBMX) and plated at 20 000 cells/well in a 96-well black plate. CRF antagonists (typically 0.01 to 10 000 nM) were then added to wells as needed and allowed to equilibrate with the cells for 30 min at 37 °C. CRF (1 nM; CRF $EC_{50}$ = 1.11 ± 0.14 nM, $n = 6$), dissolved in assay buffer + 0.1% BSA, was then added to the wells (30 min at 37 °C) to stimulate the production of cAMP. The reaction was terminated by the addition of a lysis solution containing homogeneous time-resolved florescence (HTRF) cAMP XL665 conjugate followed by HTRF anti-cAMP cryptate conjugate (CIS bio International). Plates were subsequently incubated at room temperature for 1 h prior to reading the time-resolved fluorescence signal. The amount of cAMP produced was estimated from a standard curve prepared using known concentrations of cAMP. The percentage inhibition of CRF-induced cAMP production was determined for each compound (triplicate determinations). The effect of CRF antagonists on basal cAMP production (i.e. in the absence of CRF) was also determined.

**Rat Cassette Pharmakokinetic Study.** Compound **12d** was coadministered intravenously with 10 other compounds to Sprague−Dawley rats ($n = 3$) at a dose of 0.5 mg/kg for each compound. In addition, the same set of compounds was administered to rats ($n = 3$) orally at a dose of 2 mg/kg. Plasma samples were collected at 0, 0.1, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h postdose for the intravenous experiment, and at 0, 0.5, 1, 2, 4, 6, 8, and 24 h postdose for the oral experiment. Drug concentrations were determined in the plasma samples using LC/MS/MS.

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**Supporting Information Available:** Tables of elemental analysis data and high-resolution mass spectral data with HPLC purity data for compounds lacking elemental analysis data. This information is available free of charge via the Internet at http://pubs.acs.org.

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