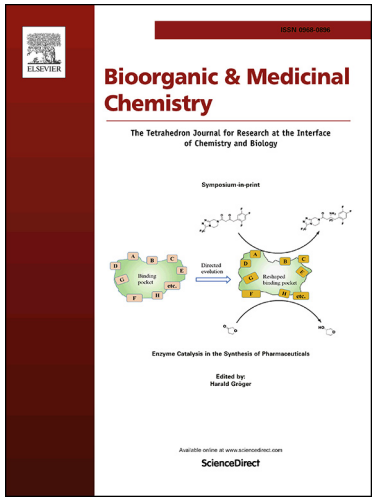
Accepted Manuscript



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Functionalized 6-(Piperidin-1-yl)-8,9-Diphenyl Purines as Inverse Agonists of the CB1 Receptor – SAR Efforts Towards Selectivity and Peripheralization

George Amato, Robert Wiethe, Amruta Manke, Vineetha Vasukuttan, Rodney Snyder, Scott Runyon and Rangan Maitra*

Discovery Science and Technology, RTI International, 3040 Cornwallis Rd., Research Triangle Park, NC 27709-2194, USA

* Corresponding author

Key Words: *CB1, cannabinoid, peripheral, antagonist, otenabant, purine, CB2, blood brain barrier, endocannabinoid, inverse agonist*

Abbreviations Used:

BBB, Blood-brain barrier, BOP, (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; CHO-K1, chinese hamster ovary cells; EtOAc, ethyl acetate; EtOH, ethanol; Ke, apparent affinity constant, MDCK-mdr1, Madin-Darby canine kidney cells transfected with the human MDR1 gene; IP_3, inositol phospahatase 3; MeOH, methanol; MRM, multiple reaction monitoring; NaHMDS, sodium bis(trimethylsilyl)amide; TEA, triethylamine.

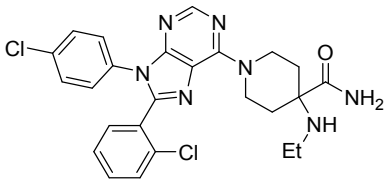
ABSTRACT

Antagonists of type 1 cannabinoid receptors (CB1) may be useful in treating diabetes, hepatic disorders, and fibrosis. Otenabant (**1**) is a potent and selective CB1 inverse agonist that was under investigation as an anti-obesity agent, but its development was halted once adverse effects associated with another marketed inverse agonist rimonabant (**2**) became known. Non-tissue selective antagonists of CB1 that have high levels of brain penetration produce adverse effects in a small subset of patients including anxiety, depression and suicidal ideation. Currently, efforts are underway to produce compounds that have limited brain penetration. In this report, novel analogs of **1** are explored to develop and test strategies for peripheralization. The piperidine of **1** is studied as a linker, which is functionalized with alkyl, heteroalkyl, aryl and heteroaryl groups using a connector in the form of an amine, amide, sulfonamide, sulfamide, carbamate, oxime, amidine, or guanidine. We also report more polar replacements for the 4-chlorophenyl group in the 9-position of the purine core, which improve calculated physical properties of the molecules. These studies resulted in compounds such as **75** that are potent inverse agonists of hCB1 with exceptional selectivity for hCB1 over hCB2. SAR studies revealed ways to adjust physical properties to limit brain exposure.

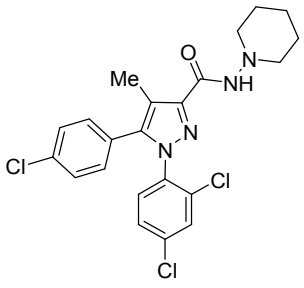
1. Introduction

Regulation of the endocannabinoid (EC) system, comprised of endocannabinoids, receptors, transporters and enzymes, has several potential medical applications.[1-6] Cannabinoid receptors CB1 and CB2 are G proteins ($G_{i/o}$)-coupled G protein-coupled receptors (GPCRs). CB1 receptors are highly expressed in the central nervous system (CNS) and in several peripheral organs. Selective attenuation of CB1 receptor signaling is a validated approach for treating obesity, diabetes, metabolic syndrome, dyslipidemias and liver diseases.[4]

The inverse agonist rimonabant (**2**, **Figure 1**), which has a high degree of CNS penetration, was clinically approved for the treatment of obesity in Europe. But this drug had to be withdrawn because of an increase in psychiatric disorders associated with antagonism of CB1 receptors in the CNS in a subset of patients.[7] The adverse side effects seen with **2** led to discontinuation of clinical development of other such compounds including **1 (Figure 1)**. Efforts are now underway to develop compounds that selectively antagonize the CB1 receptors in the periphery.[8-11] These compounds are expected to avoid CNS-related adverse effects noted with centrally acting ligands. Furthest along among these is TM38837 (**Figure 2**), which was tested in humans and demonstrated to have limited brain penetration.[12] Two additional compounds (**Figure 2**) have completed IND-enabling studies and are poised for clinical development.[13, 14] Alternative approaches for this class of therapeutics include development of neutral orthosteric antagonists, partial agonists, and negative allosteric modulators.[15, 16]



1, Otenabant
(CP-945,598)



2, Rimonabant
(SR141716A)

Figure 1. Examples of clinical CNS penetrating CB1 inverse agonists.

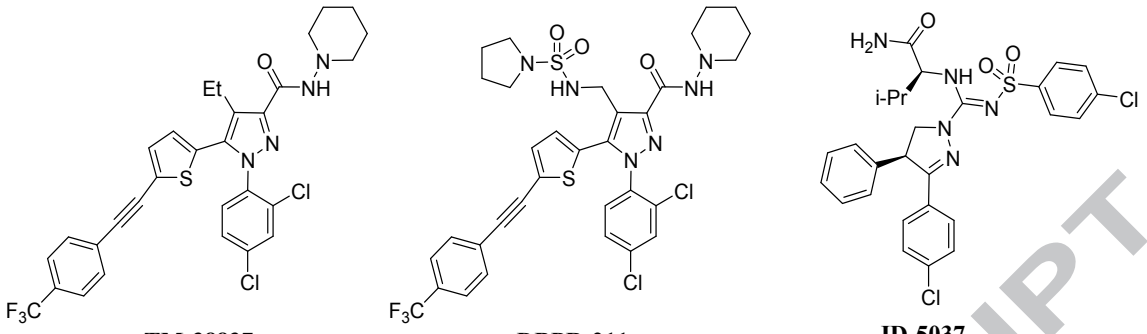
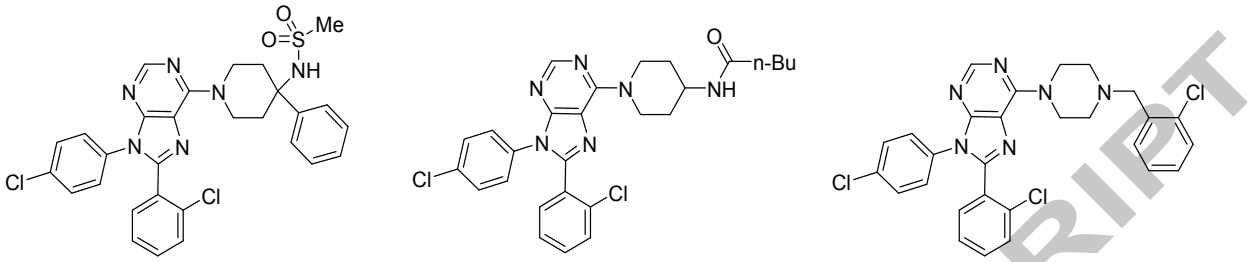


Figure 2. Examples of advanced peripherally restricted CB1 inverse agonists.

Analyses of clinically used compounds show that a topological polar surface area (TPSA) of 80-140 Å and a molecular weight of 450-600 Da can improve the likelihood of producing orally active compounds that have limited brain exposure.[17, 18] Inclusion of one or two hydrogen bond donors may also limit CNS penetration, but has the potential to negatively impact oral absorption. Incorporation of a mildly basic group into the structure can enhance oral bioavailability by improving solubility in acidic media, such as that of the stomach.[19] To improve the potential for good drug-like properties, it is also desirable to have a cLogP of less than 5. Compounds with a high cLogP may have poor aqueous solubility, which in turn can negatively impact absorption following an oral dose.[20] While analogs of **2** have been extensively explored, there are far fewer studies of compounds based on **1,** perhaps because **1** was never approved as a drug. Compound **1** has many desirable characteristics that could enable peripheralization, including a TPSA of 102 Å, 3 hydrogen bond donors and a molecular weight of >500 Da.[21] Studies indicate that intra-molecular H-bonding between the primary amide and the ethyl amine portion of **1** (observed in the X-ray structure) effectively lowers its polarity, allowing for penetration into the CNS.[21] Compounds related to **1** are particularly attractive because the mildly basic 6-piperidinyl purine core can aid in oral absorption.

A detailed analysis of the SAR associated with **1** would facilitate the development of better compounds. We began such an effort with an investigation of isomeric replacements for the 4-aminopiperidine group [22] and employment of the piperazine group as a replacement.[23, 24] Early studies

resulted in compounds **3-5**, possessing excellent hCB1 potency (Ke < 20 nM) and good selectivity (>50 fold) against hCB2 (**Figure 3**).[22, 23, 25] The goal of these studies was to further investigate related analogues.



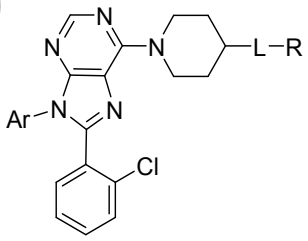
3 **4** **5**

Figure 3. Early purine based peripherally selective CB1 inverse agonists.

Recent crystal structures of hCB1 coupled with docking studies with **1** and our past research indicate that functionalization of the piperidine group at the 4-position could result in access to a binding pocket near the extracellular surface of the plasma membrane.[23, 26, 27] This pocket may accommodate polar as well as nonpolar groups and differs significantly from hCB2. By targeting this region, we hypothesized that it is possible to identify compounds with better drug-like properties that have good hCB1 potency and excellent selectivity versus hCB2.

2. Results and Discussion

2.1 Compound Design and Synthesis



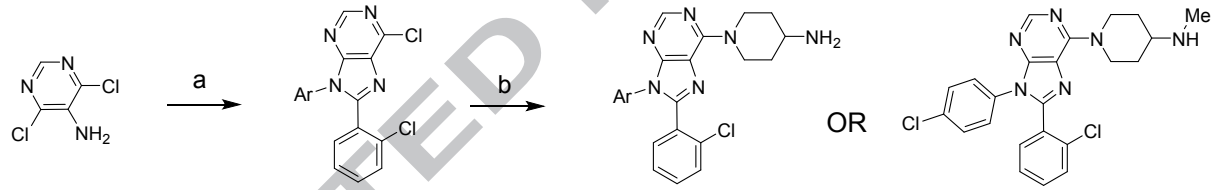
6

L = NH, NMe, NHCO, $NHSO_2$, $NHCO_2$, NHC(=NH), C(=NOH),NHC(=NH)NH
R = Alkyl, Heteroalkyl, Aryl, Heteroaryl
Ar = 4-SubstitutedPh, Heteroaryl

Figure 4. General strategy for SAR studies

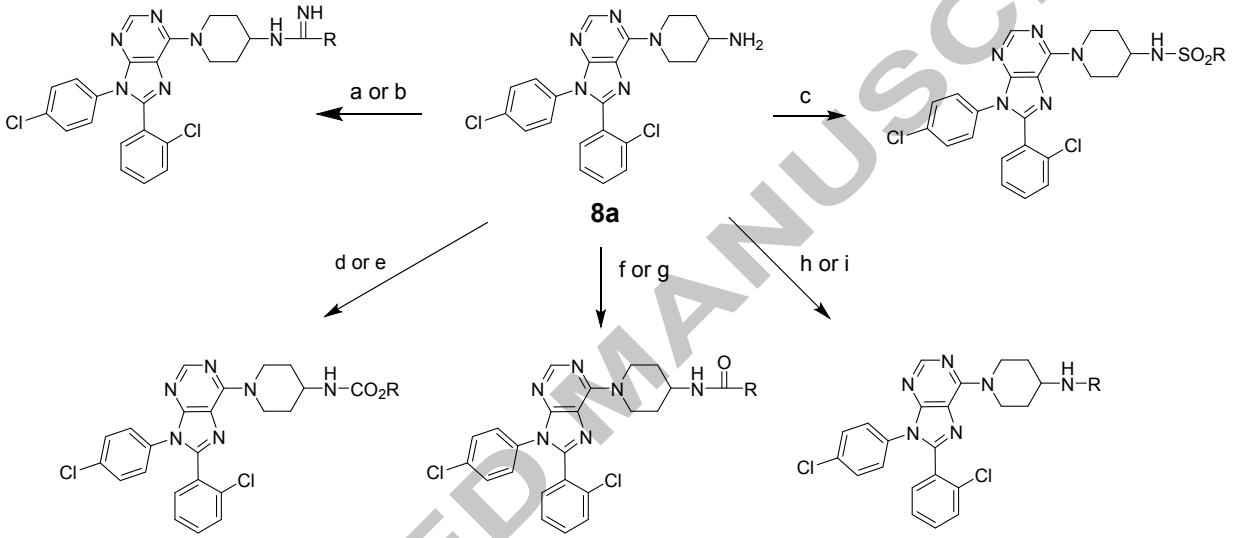
In this report, we explored functionalization of the piperidine linker at the 4-position with an amine, amide, sulfonamide, sulfamide, carbamate, oxime, amidine or guanidine connector (**6, Figure 4**). Polar and nonpolar groups were explored to establish the needed SAR to develop better compounds. We also report our attempt to increase the TPSA and reduce cLogP via replacement of the 4-chlorophenyl in the 9-position of the purine core with more polar groups, including heterocycles. Combined, these changes allowed us to design a variety of compounds with properties that were predicted to favor both peripheral selectivity and oral absorption.

To prepare most of the targeted compounds, we used the 4-aminopiperidine **8a** (**Scheme 1**) as a key intermediate, the preparation of which was previously described.[22] The 4-methylaminopiperidine analog (**9**) and analogs of **8a** with replacements for the 4-chlorophenyl group of the purine ring were prepared in a similar way as shown in **Scheme 1** and detailed in the experimental section. Of note, in the conversion of **7f** to **8f**, the acetyl group was lost during hydrolysis of the boc group.



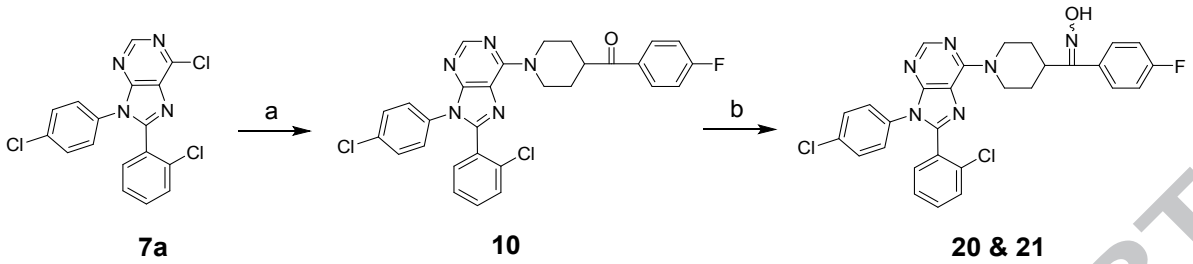
Scheme 1. Reagents and conditions: (a) (1) $ArNH_2$, 6 N HCl, n-BuOH, 80 ^oC; (2) 2-ClPhCHO, 15% $FeCl_3$/silica gel, dioxane, 95 ^oC, then DDQ, CH_2Cl_2, rt; (b) (1) 4-N-Boc-aminopiperidine or 4-N-Boc-methylaminopiperidine, K_2CO_3, NMP, 80 ^oC; (2) 6 N HCl, EtOH, 50 ^oC. **Ar** = 4-chlorophenyl (**7a, 8a**), 4-fluorophenyl (**7b, 8b**), 6-(trifluoromethyl)pyridin-3-yl (**7c, 8c**), 6-(difluoromethoxy)pyridin-3-yl (**7d, 8d**), 4-carboxamidophenyl (**7e, 8e**), 6-(acetamido)pyridin-3-yl (**7f**), 6-(amino)pyridin-3-yl (**8f**), 5-methyl-1,2-oxazol-3-yl (**7g, 8g**), 1-methyl-1H-pyrazol-4-yl (**7h, 8h**), 1-methyl-1H-pyrazol-3-yl (**7i, 8i**), 5-(trifluoromethyl)-1H-pyrazol-3-yl (**7j, 8j**).

From intermediate **8a** we prepared a variety of amines, sulfonamides, amides and carbamates using standard procedures as shown in **Scheme 2**. Intermediate **9** and analogues with a replacement for the 4-chlorophenyl group of the purine ring were functionalized in the same way. An amidine (**23**) and a guanidine (**24**) were also prepared from **8a** (**Scheme 2**). The heterocyclic analog **78** was prepared from acetylation of **77** using acetyl chloride, pyridine and tetrahydrofuran. The benzimidazole analog **22** was prepared directly from **7a** by displacement of the purine chloro with 2-(4-piperidinyl)-1H-benzimidazole.



Scheme 2. Reagents and conditions: (a) RC(=NH)OMe·HCl, NEt_3, EtOH, reflux; (b) RNH(C=NH)SMe·HI, *i*-PrOH, reflux; (c) RSO_2Cl, NEt_3, THF, rt; (d) RO_2CCl, NEt_3, DCE, rt; (e) (1) p-F-PhO_2CCl, NEt_3, DCE, rt; (2) ROH, NaHMDS, THF, rt; (f) RCOCl, NEt_3, THF, rt; (g) RCO_2H, BOP, NEt_3, THF, rt; (h) ArF, 125 ^oC; (i) RCHO, $NaCNBH_4$, AcOH, MeOH, rt.

The oximes **20** and **21** were prepared as shown in **Scheme 3**. Reaction of **7a** with commercially available 4-(4-fluorobenzoyl)piperidine provided the ketone **10**. Reaction of **10** with hydroxylamine provide a mix to the two isomeric oximes (E and Z isomers), which were separated by chromatography, but not assigned.



Scheme 3. Reagents and conditions: (a) 4-(4-Fluorobenzoyl)piperidine, NEt_3, EtOH, 80 °C; (b) $H_2NOH{\cdot}HCl$, EtOH, 80 °C.

2.2. Pharmacological Characterization

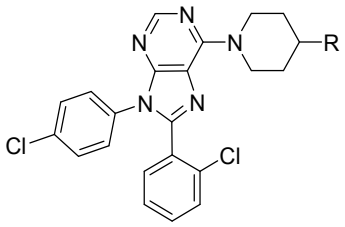
All target compounds were evaluated in a FLIPR-based calcium mobilization assay for hCB1 activity (**Tables 1-3**) as has been described in our previous publications.[22, 28] In general, those that demonstrated apparent antagonist dissociation equilibrium constant (Ke) <50 nM were further tested for affinity to hCB receptors using radioligand displacement of [^{3}H]CP55940 in purified membrane fractions overexpressing either hCB1 or hCB2. A selection of potent and selective compounds was further tested for potential peripheral selectivity by calculating % apical (A) to basal (B) permeability in a MDCK-mdr1 monolayer permeability assay, which is predictive of brain penetration.[29] A lower number predicts less transport across the blood-brain barrier (BBB). To assess metabolic stability, some compounds were advanced to a human liver microsome (HLM) stability assay, calculating half-life (HL) and clearance (Cl) values.

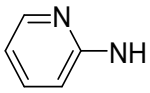
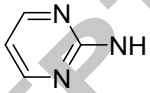
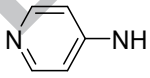
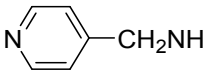
Select compounds with favorable in vitro properties were tested in mice to assess their ability to be orally absorbed and kept out of the brain. Initial studies entailed cassette dosing of mice and measuring the brain and plasma levels at multiple time points. Plasma and brain maximum concentrations (Cmax) were obtained and used to calculate and compare brain/plasma levels. The main goals were to achieve good plasma levels (>100 ng/mL after an oral dose of 2.5 mg/kg) while keeping the brain to plasma ratio as low as possible, preferably less than 0.05 (5% penetration) using the maximum concentrations in the brain and plasma.

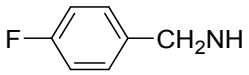
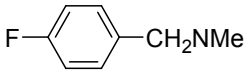
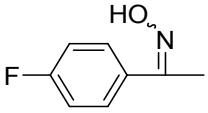
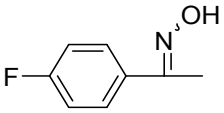
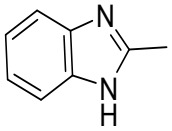
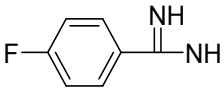
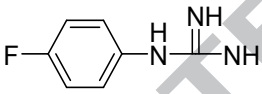
Connecting groups to the piperidine via an amine results in compounds that are basic in nature. Furthermore, the basicity can be tuned by the nature of the group that is connected. This could aid in achieving good oral bioavailability. In **Table 1**, in vitro data for a set of amines and a few related analogs are presented. Aryl amines are mildly basic, a trait that is often found in commercial drugs. The unsubstituted phenyl amine **11** was found to be highly potent and selective versus hCB1. To improve

calculated physical properties (see supplemental data) and avoid the potential metabolic liability associated with anilines, we prepared heterocyclic versions of **11**.

Table 1. In Vitro Data for CB1 Antagonists -Amines & Additional Analogs



#	R	Ke hCB1 (nM)	Ki hCB1 (nM)[a]	Ki hCB2 (nM)[a]	Selectivity Ki CB2/CB1	MDCK -mdr1 A to B (%)[b]
1	Otenabant[c]	0.2	0.7	7700	11000	ND
11	PhNH	1.4±0.4	6±1	>10000	>1600	0
12		54±7	2.4±0.7	3100±100	1300	0.1
13		43±14	ND	ND	ND	ND
14		100±30	ND	ND	ND	ND
15	BnNH	150±50	ND	ND	ND	ND
16		580±110	ND	ND	ND	ND
17	BnNMe	34±4	42±12	2700±500	64	ND

18		210±130	ND	ND	ND	ND
19		460±300	ND	ND	ND	ND
20		20±12	5±2	>10000	>2000	ND
21		21±3	7±2	>10000	>1400	ND
22		12±3	47±26	830±20	18	ND
23		170±120	780±80	>6000	>7	0.2
24		300±50	ND	ND	ND	ND

Data are reported as mean ± SD from three independent experiments.

[a]Displacement was measured using [^{3}H]CP55940 in CHO cell membrane preparations overexpressing hCB1 or hCB2 receptors.

[b]% transported from the apical side (A) to the basal side (B).

[c]See reference 21

ND: not done as compound did not meet progression criterion/criteria

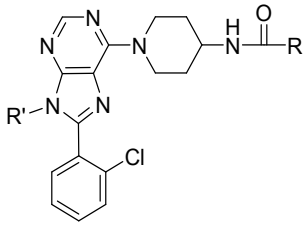
One such compound, the 2-pyridyl analog **12** retained good hCB1 potency and selectivity versus hCB2. Although the calculated physical properties were not optimal (TPSA = 72, cLogP = 6.2), they were an improvement over **11**. In the MDCK-mdr1 assay, compound **11** performed well, with 0.1% permeability across the polarized cell monolayer. To check how close we were to our pharmacokinetic goals, this

compound was progressed to an oral pk study in mice at 2.5 mg/kg. While it was orally bioavailable, the plasma Cmax was low (38 ng/mL) and the peripheral selectivity was not good enough (brain/plasma Cmax = 0.45). To enhance oral absorption, more basic compounds were of interest and so a set of benzyl amines was prepared. These compounds (**15-19**) were less active than the aryl amines and were not pursued. Interestingly, a set of compounds containing an imine were more successful. The oximes **20** and **21** (regioisomers not assigned) both presented good hCB1 potency and hCB2 selectivity. This was encouraging as oximes contain a strong hydrogen bond donor, which could favor peripheral restriction. These compounds were tested for HLM stability. One regioisomer, **21**, performed slightly better (HL = 101 minutes, Cl = 12 μL/min/mg), with values that are close to our targets (HL > 2 hours, Cl < 10 μL/min/mg). The more compact benzimidazole **22** also has good hCB1 potency, but poor selectivity versus hCB2. The more polar and basic amidine **23** and guanidine **24** were also tested. While these compounds were not highly potent, the amidine **23** (hCB1 Ke = 170 nM) is more polar (TPSA = 83), less lipophilic (cLog D = 4.1), more basic and has an added hydrogen bond donor compared to **12**. It was of interest to know if these changes would lead to an improvement in peripheral selectivity, as expected. In the MDCK-mdr1 assay, compound **23** was found to have 0.2% permeability, predicting peripheral selectivity. The HLM stability of **23** was excellent (HL = 166 minutes, Cl = 8 μL/min/mg) and the compound was progressed to a mouse oral pk study at 2.5 mg/kg. The compound was orally bioavailable with a plasma half-life of 6.0 hours and a plasma Cmax of 50 ng/mL. Compared to **12**, the peripheral selectivity of **23** was significantly better, with a brain to plasma ratio of the Cmax of 0.16, but this is still short of our goal of 0.05 or less.

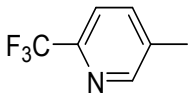
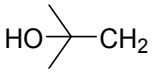
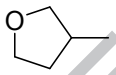
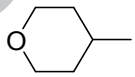
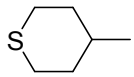
Generally, secondary amides and carbamates are good connectors for achieving peripheral selectivity, as they contain a strong hydrogen bond donor and contribute heteroatoms that increase TPSA. In **Table 2**, in vitro data for a set of alkyl and aryl amides as well as alkyl carbamates are presented. We previously reported on aliphatic amides with good hCB1 potency, but physical properties needed to be improved.[25] We tested more polar compounds by incorporating heteroatoms into the alkyl groups. The previously reported n-butyl amide **25** has good potency against hCB1, but less than desirable selectivity

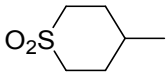
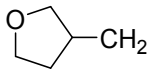
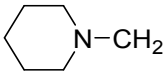
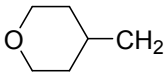
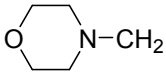
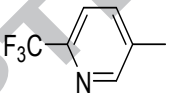
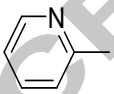
versus hCB2 and poor calculated physical properties.[25] Replacing one of the carbons of the n-butyl chain with an oxygen (**26** and **27**) or a sulfoxide (**28**) led to more desirable physical properties, but greatly diminished hCB1 potency. Similar results were obtained in our efforts to incorporate heteroatoms into cycloalkyl amides. For example, while the cyclohexylmethyl analog **41** has a hCB1 Ke of 2 nM, replacement of one of the ring atoms with oxygen or nitrogen (see compounds **42-44**) resulted in Ke values >200 nM. One exception for which an oxygen was tolerated in the alkyl group was the t-butoxyethyl amide **32**. This compound retained good hCB1 potency (Ke = 1.7 nM and Ki = 6 nM) and was highly selective versus hCB2. The maintenance of good hCB1 potency for **32** could be a result of the oxygen being shielded by the large t-butyl group. While this compound has improved calculated physical properties (cLogP of 5.0 and TPSA of 85), the MDCK-mdr1 assay predicted poor peripheral selectivity (A to B of 20%). We also investigated improving the physical properties of the n-butyl amide **25** by replacing the 4-chlorophenyl with the 6-trifluoromethypyrid-3-yl group. The resulting compound, **29**, had good hCB1 potency and selectivity versus hCB2. Calculated physical properties also improved, with a lower cLogP (5.2) and higher TPSA (89), but the MDCK-mdr1 assay predicted poor peripheral selectivity (A to B of 28%). In summary, for alkyl and cycloalkyl amides, a high TPSA combined with a high MW and a single hydrogen bond donor were not sufficient for good peripheral selectivity.

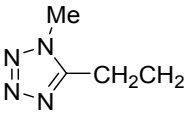
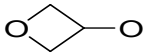
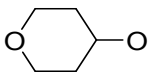
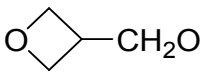
Table 2. In Vitro Data for CB1 Antagonists – Amides & Carbamates



#	R	R'	Ke hCB1 (nM)	Ki hCB1 (nM)[a]	Ki hCB2 (nM)[a]	Selectivity Ki CB2/CB1	MDCK-mdr1 A to B (%)[b]
25[c]	n-Bu	4-Cl-Ph	5	19	1000	53	ND

26	$MeOCH_2CH_2$	4-Cl-Ph	370±70	ND	ND	ND	ND
27	$MeCH_2OCH_2$	4-Cl-Ph	240±70	ND	ND	ND	ND
28	$MeSO_2CH_2CH_2$	4-Cl-Ph	6000 ±1000	ND	ND	ND	ND
29	n-Bu		4±2	3±2	420 ±180	140	28
30	t-$BuCH_2$	4-Cl-Ph	0.3±0.2	0.2±0.1	15±1	75	ND
31		4-Cl-Ph	1700±300	ND	ND	ND	ND
32	t-$BuOCH_2CH_2$	4-Cl-Ph	1.7±0.4	6±3	4900 ±1300	820	20
33[c]	c-Pen	4-Cl-Ph	0.9	1.5	60	40	ND
34		4-Cl-Ph	150±40	ND	ND	ND	ND
35[c]	c-Hex	4-Cl-Ph	3	3	840	250	ND
36		4-Cl-Ph	440±90	ND	ND	ND	ND
37		4-Cl-Ph	26±7	3±2	1900 ±700	630	ND

38		4-Cl-Ph	>10000	ND	ND	ND	ND
39[c]	c-PenCH_2	4-Cl-Ph	3	2	570	280	ND
40		4-Cl-Ph	1000±100	ND	ND	ND	ND
41[c]	c-HexCH_2	4-ClPh	2	2	2400	1200	ND
42		4-Cl-Ph	220±90	ND	ND	ND	ND
43		4-Cl-Ph	510±90	ND	ND	ND	ND
44		4-Cl-Ph	1100±300	ND	ND	ND	ND
45[d]	Ph	4-Cl-Ph	0.7	4	9600	2400	ND
46	Ph		19±13	8±3	740±60	92	3
47		4-Cl-Ph	140±30	ND	ND	ND	ND
48	2-F-Ph	4-Cl-Ph	0.6±0.2	0.98 ±0.02	6000 ±1900	6000	0.1
49	4-F-Ph	4-Cl-Ph	1.1±0.6	2±1	10000 ±4000	5000	0.2
50	2,4-DiF-Ph	4-Cl-Ph	1.2±0.6	2±1	>7000	>3500	<0.1

51	3,4-DiF-Ph	4-Cl-Ph	0.7±0.3	3±1	5900 ±1500	2000	0.2
52		4-Cl-Ph	2±1	3±2	150±70	50	<0.1
53		4-Cl-Ph	>10000	ND	ND	ND	ND
54	$MeOCH_2CH_2O$	4-Cl-Ph	6±1	17±3	>5000	>200	13
55	c-BuO	4-Cl-Ph	1.0±0.3	0.6±0.3	1050 ±70	1800	ND
56		4-Cl-Ph	92±14	ND	ND	ND	ND
57		4-Cl-Ph	320±150	ND	ND	ND	ND
58		4-Cl-Ph	77±15	ND	ND	ND	ND
59		4-Cl-Ph	1500±600	ND	ND	ND	ND
60	BnO	4-Cl-Ph	3±2	4±1	710 ±100	180	ND

Data are reported as mean ± SD from three independent experiments.

[a]Displacement was measured using [^{3}H]CP55940 in CHO cell membrane preparations overexpressing hCB1 or hCB2 receptors.

[b]% transported from the apical side (A) to the basal side (B).

[c]See reference 25

[d]See reference 22

ND: not done as compound did not meet progression criterion/criteria

Aryl amides have the potential to be more metabolically stable than alkyl amides and the previously reported unsubstituted phenyl amide **45** has excellent hCB1 potency and selectivity versus hCB2.[22] Fluorinated analogs of **45** were pursued as such compounds may have better pharmacokinetic properties, in particular oral bioavailability and plasma half-life. Furthermore, it was perceivable that the electron withdrawing nature of fluorine might enhance the acidity of the amide, thereby improving peripheral selectivity. The monofluorinated analogs **48** and **49** and the difluorinated analogs **50** and **51** were prepared and found to be highly potent hCB1 antagonists with excellent selectivity versus hCB2. The 2-fluorophenyl amide **48,** for example had a hCB1 Ke of ~0.6 nM, a Ki of ~1 nM and ~6000-fold selective for hCB1 over hCB2. These excellent results prompted us to test fluorinated phenyl amides in the MDCK-mdr1 assay for potential peripheral selectivity. Each compound tested was found to have <1% permeability in MDCK-mdr1 transport assay, indicating peripheral selectivity. The fluorinated phenyl amides, however, have values for cLogP >6 and TPSA <80 and so we sought compounds with better calculated physical properties. The 2-pyridyl amide **47** has significantly improved calculated physical properties, but a 100-fold loss in hCB1 potency. Replacement of the 4-chlorophenyl of **45** with the 6-trifluoromethylpyrid-3-yl group resulted in **46**, a compound with better calculated physical properties and acceptable hCB1 potency. In the MDCK-mdr1 assay, however, **46** did not perform well with ~3% transport.

Compared to amides, carbamates have an additional oxygen atom, which improves calculated physical properties. The c-butyl carbamate **55** had excellent hCB1 potency and selectivity versus hCB2. The calculated physical properties were near to our goals, with a TPSA of 85 and cLogP of 5.7. As with the amides, attempts to further improve the calculated properties without losing potency was difficult. One exception is the methoxyethyl carbamate **54** (TPSA = 94 and cLogP = 4.7) with a hCB1 Ke of 6 nM. In the MDCK-mdr1 assay, however, this compound performed poorly. Proton NMR indicated that the

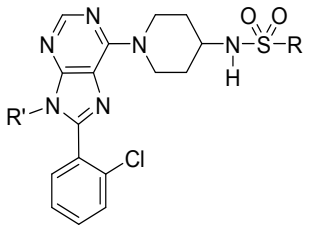
methoxyethyl group is involved in an intramolecular hydrogen bond with the amide, thereby making the compound significantly less polar and more likely to pass into the CNS.

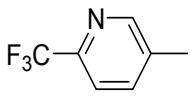
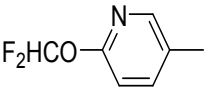
Purine sulfonamides were of interest as potential peripheral agents because of the inherent strong hydrogen bond donor and added heteroatoms that make up this connector. In **Table 3** is presented in vitro data for a set of alkyl and aryl sulfonamides. We previously reported that the methyl sulfonamide **61** has good hCB1 activity, but poor selectivity versus hCB2.[22] We proceeded to investigate larger alkyl sulfonamides to take advantage of the pocket near to the extracellular membrane surface which differs significantly between hCB1 and hCB2. Our results with analogs **62-64** support our hypothesis. These compounds were both more potent for hCB1 and more selective versus hCB2 and were subsequently tested in the MDCK-mdr1 assay for potential peripheral selectivity. Compounds **63** and **64** were both found to have A to B transport of <0.1%, predicting peripheral selectivity. The sulfamide analog of **64**, compound **65**, was of interest due to the added hydrogen bond donor, increased TPSA (105) and decreased cLogP (5.4), which favor peripheral restriction. Satisfyingly, the more polar sulfamide **65** maintained the good potency of the sulfonamide **64**. The selectivity versus hCB2, unfortunately, was not as good. Despite this set-back, it was of interest to know if such compounds would be orally bioavailable and peripherally restricted and so we proceeded to dose **65** orally to mice. Unfortunately, a low maximum plasma concentration resulted (4 ng/mL at a dose of 0.3 mg/kg).

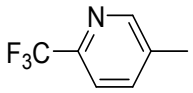
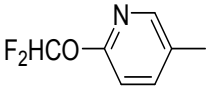
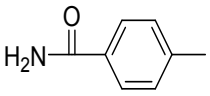
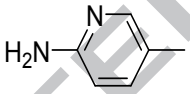
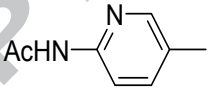
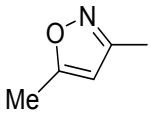
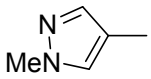
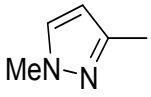
Aryl sulfonamides have the potential to be more metabolically stable than alkyl sulfonamides and the previously reported phenyl sulfonamide **66** was shown to have excellent hCB1 potency and selectivity versus hCB2.[22] Fluorinated analogs of **66** were pursued as such compounds could possess better pharmacokinetic properties, in particular oral bioavailability and plasma half-life. Furthermore, it was perceivable that the electron withdrawing nature of fluorine might enhance the acidity of the sulfonamide, thereby improving peripheral selectivity. The monofluorinated analogs **67** and **71** and the difluorinated analogs **72** and **73** were prepared and found to be highly potent hCB1 antagonists with excellent selectivity versus hCB2. The 2-fluorophenyl sulfonamide **67** was among the most potent and selective hCB1

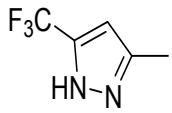
antagonists (Ke = 0.8 nM, Ki = 0.38 nM; Ki hCB2/hCB1 = 22,000). These excellent results prompted us to test fluorinated phenyl sulfonamides in the MDCK-mdr1 assay for potential peripheral selectivity. Each compound tested was found to have an A to B of 0.1% or less, favoring peripheral selectivity. With these results, the 3,4-difluorophenyl sulfonamide **73** was dosed orally to mice to assess its pharmacokinetic profile. The maximum plasma concentration of **73** was found to be low (12 ng/mL with a 2.5 mg/kg dose) and the peripheral selectivity suboptimal (brain/plasma Cmax of 0.31). While the TPSA value for this compound is 96, favorable for peripheral selectivity and oral bioavailability, the cLogP is high (6.3). To enhance the potential for desirable pharmacokinetics, it was of interest to investigate compounds with a lower cLogP. Replacements for the 4-chlorophenyl group in the 9-position of the purine core were investigated. Swapping the chloro for a fluoro (**67** vs **68**) resulted in a reduction of cLogP from 6.1 to 5.8, accompanied by a 100-fold loss in hCB1 Ke activity and a 10-fold loss in binding, highlighting the importance of the 4-chlorophenyl group for good potency. Replacement of the 4-chlorophenyl group with the 6-trifluoromethylpyrid-3-yl group, resulted in compounds with comparable potency (see **73** vs **74**). This was encouraging as the cLogP for **74** was reduced from 6.3 to 5.7 and the TPSA was increased from 96 to 106. Similarly, the 6-difluoromethoxypyrid-3-yl group was favorable for potency (see **73** vs **75**) and once again, the cLogP was reduced to 5.7 while the TPSA was increased to 116, prompting us to select this compound for additional studies. The stability of **75** to human liver microsomes (HLM) was tested and found to be excellent, with a half-life of 274 minutes and a clearance of 5 μL/min/mg. We then proceeded to dose **75** orally to mice at 2.5 mg/kg for a pharmacokinetic analysis. Encouragingly, a significant improvement over **73** was found (maximum plasma concentration of 62 ng/mL and brain/plasma Cmax of 0.18). Even more polar replacements for the 4-chlorophenyl were tried, keeping the TPSA over 110, while reducing the cLogP below 5 (see compounds 7**6-82**), but this resulted in a significant loss of hCB1 potency as we surpassed the polarity limit of this region of the binding pocket.

Table 3. In Vitro Data for CB1 Antagonists – Sulfonamides



#	R	R'	Ke hCB1 (nM)	Ki hCB1 (nM)[a]	Ki hCB2 (nM)[a]	Selectivity Ki CB2/CB1	MDCK-mdr1 A to B (%)[b]
61[c]	Me	4-Cl-Ph	71	29	1100	37	ND
62	$CF_3CH_2CH_2$	4-Cl-Ph	12±10	4±1	420±50	105	1
63	n-Pent	4-Cl-Ph	29±20	9±4	570±60	63	<0.1
64	c-HexCH_2	4-Cl-Ph	31±17	9±4	>10000	>1100	<0.1
65	c-HexNH	4-Cl-Ph	8±4	5±2	330±20	66	ND
66[c]	Ph	4-Cl-Ph	0.3	1.2	5900	5100	1
67	2-F-Ph	4-Cl-Ph	0.8±0.4	0.38 ±0.01	8500 ±2200	22000	ND
68	2-F-Ph	4-F-Ph	21±13	2.6±0.1	>10000	>3000	ND
69	2-F-Ph		0.5±0.1	4±1	400 ±120	100	ND
70	2-F-Ph		0.7±0.2	1.6±0.9	190±20	120	ND

71	4-F-Ph	4-Cl-Ph	1.1±0.5	3.3±2.8	9000 ±2000	>2000	0.1
72	2,4-DiF-Ph	4-Cl-Ph	2±1	2±1	>10000	>5000	0.1
73	3,4-DiF-Ph	4-Cl-Ph	0.5±0.4	1.7±0.7	>10000	>5000	<0.1
74	3,4-DiF-Ph		1.0±0.4	10±5	>6000	>600	ND
75	3,4-DiF-Ph		1.6±0.7	3±1	860±40	290	ND
76	3,4-DiF-Ph		330±190	ND	ND	ND	ND
77	3,4-DiF-Ph		>10000	ND	ND	ND	ND
78	3,4-DiF-Ph		2700 ±1200	ND	ND	ND	ND
79	3,4-DiF-Ph		56±28	420±90	>10000	>20	ND
80	3,4-DiF-Ph		140±130	ND	ND	ND	ND
81	3,4-DiF-Ph		120±30	ND	ND	ND	ND

82	3,4-DiF-Ph		5000 ±1000	ND	ND	ND	ND

Data are reported as mean ± SD from three independent experiments.

[a]Displacement was measured using [^{3}H]CP55940 in CHO cell membrane preparations overexpressing hCB1 or hCB2 receptors.

[b]% transported from the apical side (A) to the basal side (B).

[c]See reference 22

ND: not done as compound did not meet progression criterion/criteria

2.3 Inverse Agonism

Compounds **1** and **2** are inverse agonists. Compounds **48, 67** and **75** were further characterized using the calcium assay to establish whether these compounds are neutral antagonists or inverse agonists of the hCB1 receptor. As shown in **Figure 5**, these compounds are inverse agonists of hCB1, suppressing signaling through hCB1 with increasing concentration. The EC_{50} for **48, 67** and **75** were 94.8, 287.4 and 131.9 nM respectively.

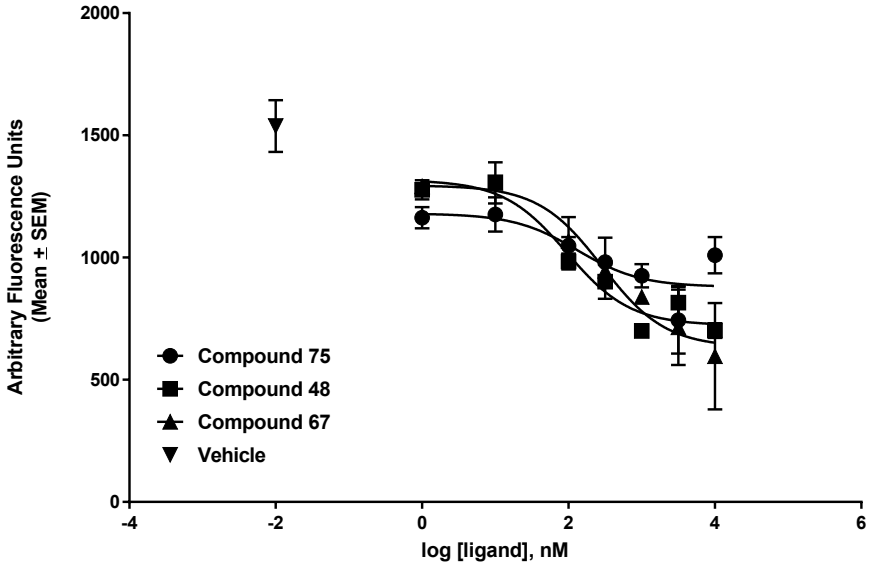


Figure 5. Compounds **48, 67** and **75** are inverse agonists of hCB1. CHO-CB1 cells were loaded with calcium indicator dye for 60 min as has been described in Methods. Cells were then stimulated by various concentrations of each compound and fluorescence change recorded using FLIPR Tetra (Molecular Devices) instrument. Data reported as Mean ± SEM from 3 independent measurements.

3. Summary and Conclusions

Peripherally restricted CB1 antagonists could become important tools in treating obesity, metabolic syndromes, dyslipidemias and liver diseases such as NASH and fibrosis. Compound **1** is a potent and selective CB1 inverse agonist developed by Pfizer, but its advancement in clinical trials was halted because of its ability to penetrate the CNS, which is associated with an increased risk of psychiatric disorders. Structure-activity relationships of **1** would be useful in developing better compounds with limited CNS penetration. Recent crystal structures of hCB1 and docking studies with otenabant indicate that the 4-postion of the piperidine group could be functionalized to access a binding pocket that may accommodate both polar and nonpolar groups. The same binding pocket differs significantly from that of hCB2 and hence could be used to obtain highly selective compounds. In this report, the piperidine group was functionalized in the 4-position with alkyl, heteroalkyl, aryl and heteroaryl groups using a connector in the form of an amine, amide, sulfonamide, sulfamide, carbamate, oxime, amidine or guanidine (**6**). We also reported in

this paper the investigation of heterocyclic replacements for the 9-phenyl group, which served to decrease the cLogP and increase the TPSA of the molecules.

Gratifyingly, our efforts have produced compounds with exceptional hCB1 potency and selectivity versus hCB2. The aryl amide **48** and the aryl sulfonamide **67** are among the most potent and selective compounds tested by our group to date. Systematic adjustment to the functionalization of the piperidine showed that polarity is tolerated close to the 4-position of the piperidine ring. Potent compounds were obtained by functionalization with polar connectors such as sulfonamides, sulfamides, amides, carbamates, amidines and oximes. On the other hand, the small alkyl or aryl groups attached to these polar connectors required a less polar nature to maintain good hCB1 potency. Attempts to further adjust molecular physical properties by replacing the 4-chlorophenyl group at the 9-position of the purine core resulted in favorable improvements with the 6-trifluoromethylpyrid-3-yl and 6-difluoromethoxypyrid-3-yl groups. We identified several compounds with good hCB1 potency, good selectivity versus hCB2 and calculated physical properties favoring peripheral restriction. Two such compounds, the aryl sulfonamide **75** and the amidine **23,** were further studied and found to have excellent HLM stability. In a mouse oral pk study, they were orally bioavailable and peripherally selective, approaching our goals. These compounds have <20% brain penetration based on Cmax values. While not meeting our stringent criterion of <5% CNS penetration, these compounds are far less brain penetrant than **1**, which has ~75% CNS penetration.[19] Most importantly, these foundational studies provide us with strategies for compound development to produce peripherally restricted CB1 receptor inverse agonists in the future. In particular, future studies will focus on polarity and hydrogen bond donors near to the piperidine linker to attain the desired level of peripheral selectivity. Deeper into piperidine linked pocket, less polar groups will be used to attain high levels of CB1 potency and selectivity versus CB2.

4. Experimental

Chemistry General. Purity and characterization of compounds were established by a combination of MS, NMR, HPLC and TLC analytical techniques, as described below. ^{1}H spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer and were determined in chloroform-*d* (7.26 ppm) or methanol-d_4 (3.31 ppm) with tetramethylsilane (0.00 ppm) or solvent peaks as the internal reference unless otherwise noted. Chemical shifts are reported in ppm relative to the solvent signal and coupling constant (*J*) values are reported in hertz (Hz). Thin-layer chromatography (TLC) was performed on EMD precoated silica gel 60 F254 plates. TLC spots were visualized with UV light or I_2 detection. Low-resolution mass spectra were obtained using a single quadrupole PE Sciex API 150EX (ESI). Unless stated otherwise, all test compounds were at least 95% pure as determined by HPLC. HPLC method: an Agilent-Varian system equipped with Prostar 210 pumps, a Prostar 335 Diode UV detector and a Phenomenex Synergi 4 μm Hydro RP 80A C18 250 x 4.6 mm column using a 20-min gradient elution of 5-95% solvent B at 1 mL/min followed by 5 min at 95% solvent B (solvent A, water with 0.1% TFA; solvent B, acetonitrile with 0.1% TFA and 5% water; absorbance monitored at 220 and 254 nm).

General Procedure A: Sulfonamides and Amides of 8 from Sulfonyl Chlorides and Acid Chlorides Respectively. To a solution of **8** (0.2 mmol, 1 equiv) in CH_2Cl_2 (2 ml) was added DMAP (0.02 mmol, 0.1 equiv), followed by TEA (0.4 mmol, 2 equiv). The sulfonyl chloride or acid chloride (0.24 mmol, 1.2 equiv) was added and the reaction stirred at rt under nitrogen for 16 h. The mixture was concentrated and then chromatographed using a silica gel column with a 0-100% gradient of EtOAc/hexanes to provide the purified sulfonamide or amide.

General Procedure B: Sulfonamides, Sulfamides and Amides of 8 from Sulfonyl Chlorides, Sulfamoyl Chlorides and Acid Chlorides Respectively. To a solution of **8** (0.2 mmol, 1 equiv) in THF (1 mL) was added the sulfonyl chloride, sulfamoyl chloride or acid chloride (0.24 mmol, 1.2 equiv), followed by TEA (0.30 mmol, 1.5 equiv). The mixture was stirred at rt for 3 h. Water (0.4 mL), EtOAc (3 mL) and then saturated $NaHCO_3$ solution (0.8 mL) were added. After 10 min, the aqueous layer was removed. Celite (600 mg) was added to the organic layer and the solvent was evaporated. Flash

chromatography using silica gel with an EtOAc/hexanes gradient provided the purified sulfonamide, sulfamide or amide.

General Procedure C: Amides of 8 from Carboxylic Acids. To a solution of **8** (0.2 mmol, 1 equiv) in CH_2Cl_2 (2 ml) were added TEA (0.6 mmol, 3 equiv), *N,N,N′,N′*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU, 0.26 mmol, 1.3 equiv) and the appropriate carboxylic acid (1.25 equiv). The reaction was stirred overnight and then concentrated. Flash chromatography, using a silica gel column with a gradient of 0−100% EtOAc/hexanes, provided the purified amide.

General Procedure D: Carbamates of 8 from Carbamoyl Chlorides. To an ice-cold solution of **8** (0.2 mmol, 1 equiv) in 1,2-dichloroethane (1 mL) was added TEA (0.24 mmol, 1.2 equiv), followed by slow addition of the chloroformate (0.24 mmol, 1.2 equiv). The ice bath was removed and stirring continued for 2 h. Ethyl acetate (3 mL) was added, followed by saturated $NaHCO_3$ solution (0.8 mL) and water (0.4 mL). After 10 minutes, the aqueous layer was removed. Celite (600 mg) was added to the organic layer and the solvent evaporated. Flash chromatography using silica gel with an EtOAc/hexanes gradient provided the purified carbamate.

General Procedure E: Carbamates of 8a from Alcohols. To an ice-cold solution of the alcohol (0.3 mmol, 1.5 equiv) in THF (1 mL) was slowly added NaHMDS (1 M/THF, 0.24 mL, 1.2 equiv). After 10 min, the 4-fluorophenyl carbamate of **8a** (0.2 mmol; prepared using general procedure C) was added. After 15 min, the ice bath was removed and the mixture stirred at rt for 15 h. Ethyl acetate (3 mL) was added, followed by brine (1 mL) and 2 N NaOH (0.4 mL). After 10 min, the aqueous layer was removed and the organic layer was washed with 0.8 M $NaHCO_3$ solution (2x1 mL). Celite (600 mg) was added to the organic layer and the solvent evaporated. Flash chromatography using silica gel with an EtOAc/hexanes gradient provided the purified carbamate.

General Procedure F: Amines of 8a or 9 from Aldehydes. To a solution of **8a** or **9** (0.2 mmol, 1 equiv) in MeOH (2.0 ml) was added the appropriate aldehyde (0.25 mmol, 1.25 equiv), then sodium

cyanoborohydride (0.4 mmol, 2 equiv), and lastly acetic acid (0.1 mL). The mixture was stirred at rt overnight, concentrated and then dissolved in EtOAc (2 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ (1 mL), washed with brine (1 mL), dried with Na_2SO_4 (20 mins), filtered and then concentrated. The resulting residue was chromatographed with a 4 g silica gel column using a 0-100% EtOAc/hexanes gradient.

General Procedure G: Heteroaryl Amines of 8a from Heteroaryl Fluorides. A 5 ml sealed tube containing **8a** (0.2 mmol, 1 equiv) and the appropriate heteroaryl fluoride (5 mmol, 25 equiv) was sparged with vacuum and nitrogen and then heated to 125 °C for 48 h in a dry heating block. The resulting residue was flash chromatographed with a 12 g silica gel column using a 0-100% EtOAc/hexanes gradient.

General Procedure H: Preparation of 7 from Aryl Amines. To a heterogeneous mixture of 5-amino-4,6-dichloropyrimidine (1.6 g, 10 mmol) and an aryl amine (10 mmol, 1 equiv) in n-BuOH (20 mL) was added 6 N HCl (0.84 mL, 0.5 equiv). The mixture was heated at 100 °C for 15 h. At rt, EtOAc (20 mL) and 2 N NaOH (8 mL) were added and the mixture stirred vigorously for 15 min. Additional EtOAc (80 mL) and saturated $NaHCO_3$ solution (40 mL) were added. The aqueous layer was removed and the organic layer washed with 0.8 M $NaHCO_3$ solution (25 mL). Celite (10 g) and toluene (10 mL) were added to the organic layer and most of the solvent evaporated. Purification by flash chromatography, using EtOAc/hexanes, provided the intermediate 5-amino-4-arylamino-6-chloropyrimidine. To a solution of the intermediate (10 mmol, 1 equiv) and 2-chlorobenzaldehyde (2.3 mL, 2 equiv) in dioxane (30 mL) was added 15% $FeCl_3$/silica gel (6.0 g, 600 mg/mmol). The mixture was stirred at rt for 10 min and then at 95 °C for 20 h. At rt, the mixture was filtered using a sintered glass funnel (sand on sodium sulfate on celite with a medium frit) and washed with chloroform (30 mL). Toluene (3 mL) was added and most of the solvent evaporated. The resulting residue was dissolved in CH_2Cl_2 (30 mL) and cooled in an ice bath. DDQ (2.2 g, 1 equiv) was added and after 10 min, the ice bath was removed. The mixture was stirred at rt for 2 h and then most of the solvent was evaporated. Ethyl acetate (100 mL) was added and the resulting organic solution washed

with water (2x50 mL). Celite (10 g) was added and the solvent evaporated. Flash chromatography using silica gel with an EtOAc/hexanes gradient provided purified **7**.

General Procedure I: Preparation of 8 or 9 from 7. To a solution of **7** (10 mmol, 1 equiv) and 4-N-boc-aminopiperidine (2.4 g, 1.2 equiv; for intermediates **8**) or 4-N-boc-methylaminopiperidine (2.5 g, 1.2 equiv; for intermediate **9**) in NMP (20 mL) was added potassium carbonate (4.1 g, 3 equiv). The mixture was stirred at rt for 15 min and then at 80 °C for 15 h. Ethyl acetate (100 mL) was added, followed by brine (40 mL) and water (20 mL). The organic layer was washed with brine/water (3/1, 2x30 mL). Celite (10 g) was added to the organic layer and the solvent evaporated. Flash chromatography using silica gel with an EtOAc/hexanes gradient provided the intermediate 9-aryl-8-(2-chlorophenyl)-6-(4-N-boc-aminopiperidin-1-yl)-9H-purine (for intermediates **8**) or 8-(2-chlorophenyl)-9-(4-chlorophenyl)-6-(4-N-boc-methylaminopiperidin-1-yl)-9H-purine (for intermediate **9**). To a mixture of the intermediate (1 mmol, 1 equiv) and ethanol (2 mL) was added 6 N HCl (1 mL). The mixture was stirred at rt for 10 min and then at 50 °C for 3 h. The mixture was cooled in an ice bath and chloroform (6 mL) was added, followed by brine (2 mL). 6 N NaOH (1.1 mL) was added slowly and after 5 min, the bath was removed. After 10 min, the layers were separated and the aqueous layer was saturated with sodium chloride. The aqueous layer was extracted with chloroform (2x2 mL). The combined organic layers was dried (sodium sulfate for 20 min), filtered and evaporated. Toluene (1 mL) was added and the solvent evaporated to provide **8** or **9**.

1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]-N-phenylpiperidin-4-amine (11). The title compound was prepared by the general procedure F to provide 129 mg (100%) of a solid, mp 103 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.46-7.55 (m, 1H), 7.30-7.44 (m, 5H), 7.12-7.23 (m, 4H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 2H), 5.40 (br s, 2H), 3.59-3.80 (m, 1H), 3.56 (br s, 1H), 3.44 (t, *J* = 11.9 Hz, 2H), 2.26 (d, *J* = 10.5 Hz, 2H), 1.43-1.69 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 153.2, 152.3, 146.8, 145.7, 134.3, 134.3, 133.1, 132.5, 131.4, 130.1, 129.7, 129.4, 128.0, 127.0, 119.8, 117.6, 113.4, 50.4, 44.4, 32.8. MS (*m/z*) 515.6 (M+1). HPLC = 99% at 17.32 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}pyridin-2-amine (12). The title compound was prepared by the general procedure G to provide 73 mg (71%) of an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.10 (dd, *J* = 1.1, 5.1 Hz, 1H), 7.47-7.56 (m, 1H), 7.29-7.46 (m, 6H), 7.14-7.25 (m, 2H), 6.57 (dd, *J* = 5.5, 6.7 Hz, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 5.41 (br s, 2H), 4.38 (d, *J* = 7.9 Hz, 1H), 3.90-4.09 (m, 1H), 3.47 (t, *J* = 12.0 Hz, 2H), 2.26 (dd, *J* = 3.1, 12.8 Hz, 2H), 1.44-1.79 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 153.9, 153.2, 152.3, 148.2, 145.6, 137.4, 134.2, 134.2, 133.1, 132.5, 131.4, 130.0, 129.7, 129.4, 128.0, 126.9, 119.8, 112.9, 107.5, 48.5, 44.4, 32.7. MS (*m/z*) 516.4 (M+1). HPLC = >99% at 17.43 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}pyrimidin-2-amine (13). The title compound was prepared by the general procedure G to provide 28 mg (21%) of a solid, mp 221-223 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.29 (d, *J* = 4.8 Hz, 2H), 7.46-7.57 (m, 1H), 7.29-7.43 (m, 5H), 7.15-7.25 (m, 2H), 6.54 (t, *J* = 4.8 Hz, 1H), 5.43 (br s, 2H), 5.18 (d, *J* = 7.9 Hz, 1H), 4.15-4.32 (m, 1H), 3.45 (t, *J* = 11.7 Hz, 2H), 2.17-2.34 (m, 2H), 1.49-1.70 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 158.1, 153.9, 153.2, 152.3, 145.6, 134.2, 133.1, 132.5, 131.4, 130.0, 129.7, 129.4, 128.0, 126.9, 119.7, 110.8, 48.3, 44.4, 32.5. MS (*m/z*) 517.5 (M+1). HPLC = >99% at 18.19 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}pyridin-4-amine (14). The title compound was prepared by the general procedure G to provide 128 mg (98%) of a solid, mp 185-186 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.20 (d, *J* = 6.2 Hz, 2H), 7.50 (d, *J* = 6.8 Hz, 1H), 7.29-7.44 (m, 5H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 6.3 Hz, 2H), 5.45 (d, *J* = 8.8 Hz, 2H), 4.25 (d, *J* = 7.7 Hz, 1H), 3.62-3.79 (m, 1H), 3.44 (t, *J* = 12.0 Hz, 2H), 2.15-2.30 (m, 3H), 1.48-1.69 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 153.2, 152.4, 152.2, 150.0, 145.8, 134.4, 134.2, 133.0, 132.5, 131.5, 130.1, 129.6, 129.4, 128.0, 127.0, 119.8, 107.9, 49.5, 44.2, 32.3. MS (*m/z*) 516.7 (M+1). HPLC = 99% at 17.90 min.

1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]-N-benzyl-piperidin-4-amine (15). The title compound was prepared by the general procedure F to provide 41 mg (39%) of an off-white solid. ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.49-7.83 (m, 3H), 7.29-7.47 (m, 10H), 7.15-7.24 (m, 2H), 5.67 (br s, 2H), 4.10 (s, 2H), 3.25 (t, *J* = 11.4 Hz, 1H), 3.01 (t, *J* = 12.4 Hz, 2H), 2.14 (d, *J* = 10.9 Hz, 2H), 1.93 (s, 1H), 1.66-1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 153.0, 152.4, 146.2, 134.4, 134.1, 132.9, 132.6, 131.5, 130.1, 130.0, 129.9, 129.5, 129.4, 128.1, 127.0, 119.8, 55.6, 48.7, 43.5, 28.5. MS (*m/z*) 529.7 (M+1). HPLC = 98% at 18.13 min.

1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]-N-(pyridin-4-ylmethyl)piperidin-4-amine (16). The title compound was prepared by the general procedure F to provide 12 mg (11%) of a pale-yellow film. ^1H NMR (300 MHz, $CDCl_3$) δ 8.48-8.60 (m, 2H), 8.38 (s, 1H), 7.46-7.55 (m, 1H), 7.28-7.44 (m, 7H), 7.14-7.25 (m, 2H), 5.37 (br s, 2H), 3.90 (s, 2H), 3.34 (t, *J* = 11.6 Hz, 2H), 2.78-2.97 (m, 1H), 1.98-2.17 (m, 2H), 1.72 (d, *J* = 12.0 Hz, 2H), 1.40-1.58 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 153.2, 152.3, 149.9, 149.9, 145.6, 134.3, 134.3, 133.1, 132.5, 131.4, 130.0, 129.7, 129.4, 128.0, 127.0, 123.3, 122.9, 119.8, 54.6, 49.6, 44.1, 32.8. MS (*m/z*) 530.5 (M+1). HPLC = 96% at 15.16 min.

N-Benzyl-1-[8-(2-chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]-N-methylpiperidin-4-amine (17). The title compound was prepared by the general procedure F to provide 15 mg (14%) of a film. ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.49-7.83 (m, 3H), 7.29-7.47 (m, 10H), 7.15-7.24 (m, 2H), 5.67 (br s, 2H), 4.10 (s, 2H), 3.25 (t, *J* = 11.4 Hz, 1H), 3.01 (t, *J* = 12.4 Hz, 2H), 2.14 (d, *J* = 10.9 Hz, 2H), 1.93 (s, 3H), 1.66-1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 153.2, 152.2, 145.3, 140.5, 134.3, 134.2, 133.2, 132.5, 131.3, 130.0, 129.8, 129.3, 128.4, 128.0, 126.9, 119.7, 55.2, 54.2, 45.6, 36.9, 30.7. MS (*m/z*) 543.5 (M+1). HPLC = 97% at 17.97 min.

1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]-N-(4-fluorobenzyl)piperidin-4-amine (18). The title compound was prepared by the general procedure F to provide 18 mg (16%) of an off-white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.51 (dd, *J* = 1.6, 6.4 Hz, 1H), 7.28-7.43 (m, 7H), 7.12-7.23 (m, 2H), 6.94-7.09 (m, 2H), 5.41 (br s, 2H), 3.88 (s, 2H), 3.28 (t, *J* = 11.1 Hz, 2H), 2.81-3.05 (m, 1H), 2.52 (br s, 2H), 1.92-2.22 (m, 2H), 1.42-1.68 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 160.6, 153.9, 153.2,

152.3, 145.6, 134.3, 134.3, 133.1, 132.5, 131.4, 130.1, 130.0, 130.0, 129.7, 129.4, 128.0, 126.9, 119.8, 115.6, 115.3, 54.6, 49.7, 44.1, 32.0. MS (*m/z*) 547.5 (M+1). HPLC = 98% at 18.25 min.

1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]-N-(4-fluorobenzyl)-N-methylpiperidin-4-amine (19). The title compound was prepared by the general procedure F to provide 12 mg (11%) of a colorless film. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.46-7.54 (m, 1H), 7.28-7.44 (m, 10H), 7.14-7.25 (m, 3H), 5.54 (br s, 2H), 3.80 (s, 2H), 3.12 (t, *J* = 12.2 Hz, 1H), 2.56 (d, *J* = 6.3 Hz, 2H), 1.76-2.00 (m, 3H), 1.62 (br s, 3H), 1.21-1.45 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 163.5, 160.7, 160.3, 153.8, 153.2, 152.2, 145.6, 136.7, 136.7, 136.0, 135.9, 134.3, 134.3, 133.1, 132.5, 131.4, 130.1, 129.8, 129.7, 129.7, 129.4, 128.8, 128.7, 128.0, 126.9, 119.7, 115.5, 115.2, 115.2, 114.9, 64.6, 56.6, 53.2, 45.4, 40.9, 28.1. MS (*m/z*) 561.4 (M+1). HPLC = 95% at 18.37 min.

{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}(4-fluorophenyl)methanone (10). To a solution of **7a** (94 mg, 0.25 mmol) in EtOH (5 ml) was added TEA (0.10 mL, 3 equiv) and 4-(4-fluorobenzoyl)piperidine (64 mg, 1.25 equiv). The mixture was stirred at 78 °C overnight, concentrated and then chromatographed on a 4 g silica gel column using a 0-100% EtOAc/hexanes gradient, thus providing 128 mg (94%) of a solid, mp 183-184 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.01 (dd, *J* = 5.4, 8.8 Hz, 2H), 7.46-7.57 (m, 1H), 7.29-7.42 (m, 5H), 7.19-7.25 (m, 2H), 7.16 (t, J = 8.6 Hz, 2H), 5.56 (br s, 2H), 3.53-3.70 (m, 1H), 3.39 (t, *J* = 11.6 Hz, 2H), 1.81-2.03 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 167.4, 164.1, 153.9, 153.2, 152.3, 145.7, 134.2, 134.2, 133.1, 132.5, 132.3, 132.3, 131.4, 131.0, 130.9, 130.0, 129.7, 129.4, 128.0, 126.9, 119.8, 116.0, 115.7, 45.0, 43.6, 28.6. MS (*m/z*) 546.3 (M+1). HPLC = 99% at 21.85 min.

1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl(4-fluorophenyl)methanone oxime (20 & 21). To a solution of ketone **10** (55 mg, 0.1 mmol) in EtOH (1.0 ml) was added hydroxylamine HCl (35 mg, 5 equiv). The solution was stirred at reflux for ~4 h. TLC showed 2 new spots, glowing blue under 254 UV light. The reaction was concentrated and chromatographed on a 12 g silica gel column using

a 0-100% EtOAc/hexanes gradient. The first peak off the column provided 12 mg (22%) of a colorless film (**20**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 8.37 (s, 1H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.28-7.43 (m, 7H), 7.14-7.24 (m, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 5.68 (br s, 2H), 3.51-3.75 (m, 1H), 3.14 (t, *J* = 11.2 Hz, 2H), 1.78-2.01 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 161.9, 161.4, 153.8, 153.2, 152.2, 145.6, 134.3, 134.2, 133.0, 132.5, 131.6, 131.6, 131.4, 130.0, 129.8, 129.7, 129.6, 129.4, 128.0, 126.9, 119.6, 115.4, 115.2, 45.7, 36.8, 28.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.56. MS (*m/z*) 561.3 (M+1). HPLC = >99% at 20.67 min. The second peak off the column provided 5 mg (9%) of a colorless film (**21**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.63 (s, 1H), 7.49 (d, *J* = 6.9 Hz, 1H), 7.27-7.42 (m, 7H), 7.06-7.22 (m, 4H), 5.55 (br s, 2H), 3.20 (t, *J* = 12.1 Hz, 2H), 2.72-2.92 (m, 1H), 1.96 (d, *J* = 12.0 Hz, 2H), 1.62-1.83 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 153.8, 153.2, 152.2, 145.6, 134.2, 133.1, 132.5, 131.4, 130.0, 129.7, 129.6, 129.5, 129.4, 129.0, 128.0, 126.9, 119.7, 115.6, 115.3, 100.0, 45.4, 42.5, 29.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.17. MS (*m/z*) 561.2 (M+1). HPLC = 99% at 20.60 min.

6-[4-(1H-Benzimidazol-2-yl)piperidin-1-yl]-8-(2-chlorophenyl)-9-(4-chlorophenyl)-9H-purine (22). To a solution of **7a** (94 mg, 0.25 mmol) in EtOH (5 ml) was added TEA (0.10 mL, 3 equiv) and 2-(4-piperidinyl)-1H-benzimidazole (63 mg, 1.25 equiv). The mixture was stirred at 78 °C overnight, concentrated and then chromatographed on a 4 g silica gel column using a 0-100% EtOAc/hexanes gradient, thus providing 64 mg (47%) of a solid, mp 156 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.99 (br s, 1H), 8.36 (s, 1H), 7.52-7.85 (m, 1H), 7.46 (d, *J* = 6.9 Hz, 2H), 7.24-7.39 (m, 6H), 7.11-7.23 (m, 4H), 5.57 (d, *J* = 9.7 Hz, 2H), 3.03-3.38 (m, 3H), 2.19 (br s, 2H), 1.89-2.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 153.9, 153.1, 152.2, 145.8, 134.3, 134.2, 133.0, 132.5, 131.5, 130.0, 129.5, 129.4, 128.0, 127.0, 122.3, 119.7, 45.4, 37.0, 30.9. MS (*m/z*) 540.3 (M+1). HPLC = >99% at 17.85 min.

***N*-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9*H*-purin-6-yl]piperidin-4-yl}-4-fluorobenzene carboximidamide (23).** A mixture of **8a** (95 mg, 0.20 mmol), 4-fluorobenzamidic acid methyl ester hydrochloride (48 mg, 1.25 equiv) and TEA (0.28 ml, 10 equiv) in isopropanol (2 ml) was heated at reflux overnight. The crude product was concentrated and chromatographed on a 12 g silica gel column using a

0-100% EtOAc/hexanes gradient, thus providing 35 mg (31%) of a solid, mp 140-150 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.64 (dd, *J* = 5.2, 8.6 Hz, 2H), 7.45-7.55 (m, 1H), 7.28-7.42 (m, 5H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.06 (t, *J* = 8.5 Hz, 2H), 5.43 (br s, 2H), 4.47-5.28 (m, 2H), 4.21 (br s, 1H), 3.29-3.56 (m, 3H), 2.20 (d, *J* = 10.4 Hz, 2H), 1.55-1.84 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 162.8, 162.0, 153.8, 153.1, 152.2, 145.7, 134.3, 134.1, 133.0, 132.5, 131.4, 130.0, 129.5, 129.4, 129.2, 129.1, 128.0, 127.0, 119.7, 116.1, 115.8, 50.6, 50.2, 44.2, 31.9. MS (*m/z*) 560.1 (M+1). HPLC = 98% at 18.00 min.

1-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9*H*-purin-6-yl]piperidin-4-yl}-3-(4-fluorophenyl) guanidine (24). A mixture of **8a** (95 mg, 0.2 mmol), 4-fluorophenyl S-methyl thiourea hydroiodide (78 mg, 1.25 equiv) and TEA (0.28 ml, 10 equiv) in isopropanol was heated at reflux overnight. The reaction was concentrated to 1 ml and flash chromatographed on a 4 g silica gel column using a 0-100% EtOAc/hexanes gradient, thus providing 25 mg (22%) of a solid, mp 96 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.94 (dd, *J* = 4.5, 8.9 Hz, 2H), 7.80 (dd, *J* = 4.6, 8.6 Hz, 1H), 7.42-7.56 (m, 3H), 7.29-7.41 (m, 7H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.93-7.09 (m, 1H), 5.44 (d, *J* = 9.9 Hz, 2H), 3.60-3.81 (m, 2H), 3.19 (t, *J* = 11.9 Hz, 2H), 2.40 (d, *J* = 10.1 Hz, 2H), 1.98 (d, *J* = 9.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ. 160.9, 153.6, 152.9, 152.2, 146.2, 134.4, 134.1, 132.9, 132.7, 132.1, 131.5, 129.9, 129.5, 129.3, 128.1, 127.2, 127.1, 119.7, 119.3, 116.4, 116.1, 64.5, 50.0, 43.6, 30.1, 25.4. MS (*m/z*) 577.4 (M+1). HPLC = 93% at 15.89 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-3-methoxypropanamide (26). The title compound was prepared by the general procedure C to provide 104 mg (99%) of a solid, mp 137-139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.47-7.56 (m, 1H), 7.30-7.43 (m, 5H), 7.14-7.25 (m, 2H), 6.42 (d, *J* = 7.9 Hz, 1H), 5.35 (br s, 2H), 4.12-4.28 (m, 1H), 3.63 (t, *J* = 5.8 Hz, 2H), 3.37-3.49 (m, 2H), 3.35 (s, 3H), 2.46 (t, *J* = 5.8 Hz, 2H), 2.10 (dd, *J* = 2.9, 12.7 Hz, 2H), 1.44-1.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 153.8, 153.1, 152.2, 145.7, 134.3, 134.2, 133.0, 132.5,

131.5, 130.0, 129.5, 129.4, 128.0, 127.0, 119.7, 68.7, 58.7, 47.5, 46.6, 37.0. MS (*m/z*) 525.4 (M+1). HPLC = 99% at 18.17 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-2-ethoxyacetamide (27). The title compound was prepared by the general procedure C to provide 37 mg (35%) of a solid, mp 119-121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.48-7.54 (m, 1H), 7.30-7.45 (m, 5H), 7.16-7.24 (m, 2H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.45 (br s, 2H), 4.14-4.37 (m, 1H), 3.93 (s, 2H), 3.56 (q, *J* = 7.1 Hz, 2H), 3.35 (t, *J* = 12.1 Hz, 2H), 3.23 (q, *J* = 7.3 Hz, 2H), 2.12 (dd, *J* = 2.8, 12.6 Hz, 2H), 1.59 (dq, *J* = 4.0, 11.9 Hz, 2H), 1.37 (t, *J* = 7.4 Hz, 2H), 1.24-1.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 153.8, 153.1, 152.2, 145.7, 134.3, 134.2, 133.0, 132.5, 131.4, 130.0, 129.6, 129.4, 128.0, 127.0, 119.7, 69.8, 67.1, 47.6, 46.2, 15.0. MS (*m/z*) 525.5 (M+1). HPLC = 95% at 19.27 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-3-(methylsulfonyl) propanamide (28). The title compound was prepared by the general procedure C to provide 102 mg (88%) of a solid, mp 94 (dec) °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.46-7.57 (m, 1H), 7.30-7.45 (m, 5H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.38 (d, *J* = 7.7 Hz, 1H), 5.39 (d, *J* = 8.1 Hz, 2H), 4.08 (dd, *J* = 3.4, 7.2 Hz, 1H), 3.25-3.46 (m, 4H), 2.95 (s, 3H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.06 (d, *J* = 10.1 Hz, 2H), 1.43-1.72 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 153.7, 153.0, 152.2, 145.8, 134.3, 134.1, 133.0, 132.5, 131.5, 130.0, 129.5, 129.4, 128.1, 127.0, 119.7, 50.4, 47.4, 47.3, 44.2, 41.2, 31.9, 28.8. MS (*m/z*) 573.3 (M+1). HPLC = 95% at 17.33 min.

N-{1-[8-(2-Chlorophenyl)-9-[6-(trifluoromethyl)pyridin-3-yl]-9H-purin-6-yl]piperidin-4-yl}pentanamide (29). The title compound was prepared by the general procedure B to provide 51 mg (76%) of an off white crystalline solid, mp 192-193. R_f = 0.28 (2% MeOH/60% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.38 (s, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 5.1 Hz, 1H), 7.32-7.52 (m, 3H), 5.47 (br s, 2H), 5.35 (d, *J* = 7.4 Hz, 1H), 4.06-4.28 (m, 1H),

3.32 (br s, 2H), 2.08-2.28 (m, 4H), 1.30-1.69 (m, 6H), 0.92 (t, *J* = 8.1 Hz, 3H). MS (*m/z*) 558.4 (M+1). HPLC = >99% at 19.73 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-3,3-dimethylbutanamide (30). The title compound was prepared by the general procedure A to provide 75 mg (70%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.46-7.56 (m, 1H), 7.29-7.45 (m, 5H), 7.15-7.24 (m, 2H), 4.18-4.61 (m, 4H), 3.61-3.89 (m, 4H), 2.62 (s, 3H), 2.33 (s, 2H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 153.9, 153.1, 152.4, 146.2, 134.4, 134.2, 132.9, 132.4, 131.5, 130.1, 129.5, 129.4, 128.0, 127.0, 119.8, 50.7, 46.8, 44.8, 32.4, 30.9, 29.8. MS (*m/z*) 537.3 (M+1). HPLC = 96% at 20.39 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-3-hydroxy-3-methylbutanamide (31). The title compound was prepared by the general procedure C to provide 43 mg (40%) of a solid, mp 77-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.50 (dd, *J* = 1.3, 6.7 Hz, 1H), 7.29-7.43 (m, 5H), 7.12-7.23 (m, 2H), 6.12 (d, *J* = 7.9 Hz, 1H), 5.44 (br s, 2H), 4.13-4.32 (m, 1H), 3.34 (t, *J* = 12.1 Hz, 2H), 2.32 (s, 2H), 2.06-2.19 (m, 2H), 1.53 (dq, *J* = 4.1, 11.9 Hz, 2H), 1.27 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 153.8, 153.1, 152.2, 145.8, 134.3, 134.2, 133.0, 132.5, 131.5, 130.0, 129.5, 129.4, 128.0, 127.0, 119.7, 69.6, 47.9, 46.7, 44.3, 32.2, 29.4. MS (*m/z*) 539.3 (M+1). HPLC = 96% at 17.88 min.

3-Tert-butoxy-N-{1-[8-(2-chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}propanamide (32). The title compound was prepared by the general procedure C to provide 54 mg (48%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.47-7.55 (m, 1H), 7.29-7.45 (m, 5H), 7.14-7.23 (m, 2H), 6.72 (d, *J* = 7.9 Hz, 1H), 5.36 (br s, 2H), 4.12-4.25 (m, 1H), 3.66 (t, *J* = 6.2 Hz, 1H), 3.60 (t, *J* = 5.6 Hz, 2H), 3.41 (t, *J* = 11.5 Hz, 2H), 2.60 (t, *J* = 6.2 Hz, 1H), 2.44 (t, *J* = 5.6 Hz, 2H), 2.13 (dd, *J* = 2.9, 12.7 Hz, 2H), 1.42-1.61 (m, 2H), 1.23-1.34 (m, 1H), 1.20 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 153.9, 153.2, 152.3, 145.6, 134.3, 134.2, 133.0, 132.5, 131.4, 130.1, 129.6, 129.4, 128.0, 127.0, 119.7, 76.6, 73.7, 58.0, 57.2, 46.4, 37.6, 35.2, 32.4, 27.5, 27.4. MS (*m/z*) 567.4 (M+1). HPLC = 99% at 20.03 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}tetrahydrofuran-3-carboxamide (34). The title compound was prepared by the general procedure C to provide 70 mg (65%) of a solid, mp 158-160 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.50 (dd, *J* = 1.5, 6.6 Hz, 1H), 7.29-7.44 (m, 5H), 7.15-7.24 (m, 2H), 5.69 (d, *J* = 7.9 Hz, 1H), 5.44 (br s, 2H), 4.04-4.25 (m, 1H), 3.85-4.00 (m, 3H), 3.73-3.85 (m, 1H), 3.31 (t, *J* = 12.0 Hz, 2H), 2.88 (quin, *J* = 6.9 Hz, 1H), 2.01-2.25 (m, 5H), 1.50 (d, *J* = 12.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 153.8, 153.1, 152.2, 145.8, 134.4, 134.2, 133.0, 132.5, 131.5, 130.1, 129.6, 129.4, 128.0, 127.0, 119.8, 71.0, 68.2, 46.9, 45.7, 44.4, 32.3, 30.6. MS (*m/z*) 537.4 (M+1). HPLC = 94% at 18.04 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}tetrahydro-2H-pyran-4-carboxamide (36). The title compound was prepared by the general procedure C to provide 56 mg (51%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.47-7.55 (m, 1H), 7.30-7.44 (m, 5H), 7.15-7.24 (m, 2H), 5.65 (d, *J* = 7.9 Hz, 1H), 5.45 (d, *J* = 7.2 Hz, 2H), 3.92-4.05 (m, 2H), 3.27-3.48 (m, 4H), 2.33 (td, *J* = 5.4, 10.6 Hz, 2H), 2.09 (dd, *J* = 2.4, 12.2 Hz, 2H), 1.66-1.88 (m, 4H), 1.50 (dq, *J* = 4.0, 11.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 153.8, 153.1, 152.2, 145.7, 134.3, 134.1, 133.0, 132.5, 131.5, 130.0, 129.5, 129.4, 128.0, 127.0, 119.7, 67.2, 47.6, 46.7, 44.4, 42.2, 29.3. MS (*m/z*) 551.3 (M+1). HPLC = 99% at 18.29 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}tetrahydro-2H-thiopyran-4-carboxamide (37). The title compound was prepared by the general procedure C to provide 54 mg (48%) of a solid, mp 107 (dec) °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.50 (dd, *J* = 1.1, 6.8 Hz, 1H), 7.29-7.43 (m, 5H), 7.13-7.23 (m, 2H), 5.61 (d, *J* = 7.9 Hz, 1H), 5.44 (br s, 2H), 3.28 (t, *J* = 12.2 Hz, 2H), 2.59-2.70 (m, 4H), 2.08-2.19 (m, 4H), 1.74-1.97 (m, 2H), 1.48 (dq, *J* = 4.0, 11.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 153.8, 153.1, 152.2, 145.8, 134.3, 134.2, 133.0, 132.5, 131.5, 130.0, 129.5, 129.4, 128.0, 127.0, 119.7, 46.7, 45.1, 44.4, 38.6, 30.5, 27.9. MS (*m/z*) 567.3 (M+1). HPLC = 96% at 19.29 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}tetrahydro-2H-thiopyran-4-carboxamide 1,1-dioxide (38). The title compound was prepared by the general procedure C to provide 55 mg (46%) of a solid, mp 111-113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.50 (dd, *J* = 1.0, 6.9 Hz, 1H), 7.30-7.45 (m, 5H), 7.15-7.23 (m, 2H), 5.49 (br s, 2H), 5.42 (d, *J* = 7.9 Hz, 1H), 4.14-4.24 (m, 1H), 3.18-3.43 (m, 4H), 2.87-3.07 (m, 2H), 2.23-2.48 (m, 5H), 2.11 (d, *J* = 10.0 Hz, 2H), 1.59 (s, 2H), 1.39-1.57 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 153.8, 153.1, 152.2, 145.9, 134.4, 134.2, 132.9, 132.5, 131.5, 130.1, 129.5, 129.4, 128.0, 127.0, 119.7, 49.8, 47.1, 44.4, 40.6, 32.2, 27.3. MS (*m/z*) 599.4 (M+1). HPLC = 99% at 17.39 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl] piperidin-4-yl}-2-(tetrahydrofuran-3-yl)acetamide (40). The title compound was prepared by the general procedure C to provide 38 mg (34%) of a solid, mp 200-203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.48-7.56 (m, 1H), 7.30-7.44 (m, 5H), 7.16-7.24 (m, 2H), 5.72 (d, *J* = 7.9 Hz, 1H), 5.43 (br s, 2H), 3.81-3.96 (m, 2H), 3.74 (q, *J* = 7.6 Hz, 1H), 3.43 (dd, *J* = 6.0, 8.6 Hz, 1H), 3.27-3.38 (m, 2H), 2.67 (td, *J* = 7.0, 14.1 Hz, 1H), 2.25 (d, *J* = 7.5 Hz, 2H), 2.06-2.17 (m, 3H), 1.42-1.65 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 153.8, 153.1, 152.2, 145.8, 134.3, 134.2, 133.0, 132.5, 131.5, 130.0, 129.5, 129.4, 128.0, 127.0, 119.7, 72.8, 67.6, 47.6, 46.9, 44.4, 40.2, 36.0, 32.0. MS (*m/z*) 551.3 (M+1). HPLC = 96% at 18.41 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-2-piperidin-1-ylacetamide (42). The title compound was prepared by the general procedure C to provide 38 mg (34%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.46-7.56 (m, 1H), 7.28-7.45 (m, 6H), 7.14-7.24 (m, 2H), 5.36 (br s, 2H), 4.15-4.30 (m, 1H), 3.44 (t, *J* = 11.7 Hz, 2H), 2.95 (s, 2H), 2.44 (t, *J* = 4.6 Hz, 4H), 2.10 (dd, *J* = 3.0, 12.4 Hz, 2H), 1.49-1.67 (m, 6H), 1.43 (d, *J* = 4.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 153.8, 153.2, 152.3, 145.7, 134.3, 134.2, 133.1, 132.5, 131.4, 130.0, 129.6, 129.4, 128.0, 127.0, 119.7, 62.3, 54.9, 45.9, 44.3, 32.4, 26.2, 23.7. MS (*m/z*) 564.3 (M+1). HPLC = 97% at 16.91 min.

N-{1-[8-(2-chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-2-(tetrahydro-2H-pyran-4-yl)acetamide (43). The title compound was prepared by the general procedure C to provide 31 mg (27%) of a solid, mp 83-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.46-7.55 (m, 1H), 7.30-7.44 (m, 5H), 7.14-7.23 (m, 2H), 5.42-5.59 (m, 2H), 5.32-5.41 (m, 1H), 4.13 (s, 1H), 3.94 (dd, *J* = 3.6, 11.1 Hz, 2H), 3.40 (dt, *J* = 1.9, 11.8 Hz, 2H), 3.24-3.32 (m, 1H), 1.82-2.19 (m, 8H), 1.64 (d, *J* = 12.3 Hz, 2H), 1.50 (dd, *J* = 3.4, 11.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 153.9, 153.2, 152.3, 145.8, 134.3, 134.2, 133.0, 132.5, 131.5, 130.1, 129.6, 129.4, 128.0, 127.0, 119.8, 67.8, 46.9, 44.3, 32.8, 32.6, 32.5. MS (*m/z*) 565.4 (M+1). HPLC = 95% at 18.68 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-2-morpholin-4-ylacetamide (44). The title compound was prepared by the general procedure C to provide 53 mg (47%) of a solid, mp 180-183 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.46-7.55 (m, 1H), 7.29-7.44 (m, 5H), 7.15-7.24 (m, 2H), 7.10 (d, *J* = 8.6 Hz, 1H), 5.42 (br s, 2H), 4.02-4.34 (m, 1H), 3.62-3.78 (m, 4H), 3.39 (t, *J* = 11.5 Hz, 2H), 3.01 (s, 2H), 2.43-2.59 (m, 4H), 2.10 (dd, *J* = 3.0, 12.6 Hz, 2H), 1.71 (s, 2H), 1.56 (dd, *J* = 3.6, 12.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 153.8, 153.2, 152.3, 145.7, 134.3, 134.2, 133.0, 132.5, 131.4, 130.1, 129.6, 129.4, 128.0, 127.0, 119.7, 67.0, 62.0, 53.8, 46.1, 44.4, 32.4. MS (*m/z*) 566.2 (M+1). HPLC = 97% at 16.21 min.

N-{1-[8-(2-Chlorophenyl)-9-[6-(trifluoromethyl)pyridin-3-yl]-9H-purin-6-yl]piperidin-4-yl}benzamide (46). The title compound was prepared by the general procedure B to provide 72 mg (100%) of an off white crystalline solid, mp 220-221 °C. R_f = 0.47 (2% MeOH/60% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.39 (s, 1H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.70-7.84 (m, 3H), 7.64 (d, *J* = 5.4 Hz, 1H), 7.32-7.56 (m, 6H), 6.06 (d, *J* = 7.7 Hz, 1H), 5.53 (br s, 2H), 4.30-4.40 (m, 1H), 3.31-3.45 (m, 2H), 2.20-2.31 (m, 2H), 1.51-1.77 (m, 2H). MS (*m/z*) 578.7 (M+1). HPLC = >99% at 19.75 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}pyridine-2-carboxamide (47). The title compound was prepared by the general procedure A to provide 52 mg (48%) of a solid, mp 88-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.7 Hz, 2H), 8.49-8.56 (m, 1H), 8.41 (s, 1H), 8.23 (t, *J* = 7.9 Hz, 3H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.97 (dt, *J* = 1.6, 7.7 Hz, 2H), 7.86 (dt, *J* = 1.6, 7.7 Hz, 1H), 7.60 (ddd, *J* = 1.0, 4.8, 7.6 Hz, 2H), 7.48 7.55 (m, 1H), 7.29-7.47 (m, 6H), 7.16-7.25 (m, 2H), 5.48 (br s, 2H), 4.22-4.49 (m, 1H), 3.45 (t, *J* = 11.9 Hz, 2H), 2.15-2.34 (m, 2H), 1.60-1.84 (m, 2H). MS (*m/z*) 544.3 (M+1). HPLC = 95% at 19.80 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-2-fluorobenzamide (48). The title compound was prepared by the general procedure B to provide 70 mg (100%) of an off white crystalline solid, mp 200-201 °C. R_f = 0.14 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.09-8.14 (m, 1H), 7.43-7.64 (m, 2H), 7.29-7.42 (m, 5H), 7.01-7.24 (m, 4H), 6.60-6.77 (m, 1H), 5.45 (br s, 2H), 4.30-4.54 (m, 1H), 3.26-3.59 (m, 2H), 2.18-2.32 (m, 2H), 1.53-1.83 (m, 2H). MS (*m/z*) 561.4 (M+1). HPLC = 99% at 20.25 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-4-fluorobenzamide (49). The title compound was prepared by the general procedure B to provide 70 mg (100%) of an off white amorphous solid, mp 233-234 °C. R_f = 0.11 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (m, 1H), 7.77 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.51 (d, *J* = 6.8 Hz, 1H), 7.29-7.44 (m, 5H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.09 (t, *J* = 8.5 Hz, 2H), 6.08 (d, *J* = 7.7 Hz, 1H), 5.52 (br s, 2H), 4.24-4.48 (m, 1H), 3.24-3.42 (m, 2H), 2.15-2.28 (m, 2H), 1.49-1.73 (m, 2H). MS (*m/z*) 561.1 (M+1). HPLC = 99% at 20.13 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-2,4-difluorobenzamide (50). The title compound was prepared by the general procedure B to provide 72 mg (100%) of an off white crystalline solid, mp 225-226 °C. R_f = 0.17 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.05-8.24 (m, 1H), 7.51 (d, *J* = 6.6 Hz, 1H), 7.30-7.45 (m, 5H), 7.20 (d, *J* = 8.5 Hz,

2H), 6.94-7.08 (m, 1H), 6.78-6.94 (m, 1H), 6.46-6.66 (m, 1H), 5.45 (br s, 2H), 4.25-4.51 (m, 1H), 3.34-3.52 (m, 2H), 2.17-2.31 (m, 2H), 1.51-1.79 (m, 2H). MS (*m/z*) 579.0 (M+1). HPLC = 99% at 20.47 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-3,4-difluorobenzamide (51). The title compound was prepared by the general procedure B to provide 72 mg (100%) of an off white amorphous solid, mp 241-242 °C. R_f = 0.15 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.57-7.74 (m, 1H), 7.45-7.56 (m, 2H), 7.29-7.43 (m, 5H), 7.10-7.24 (m, 3H), 6.15 (d, *J* = 7.7 Hz, 1H), 5.53 (br s, 2H), 4.21-4.46 (m, 1H), 3.22-3.41 (m, 2H), 2.14-2.27 (m, 2H), 1.49-1.68 (m, 2H). MS (*m/z*) 579.3 (M+1). HPLC = 99% at 20.55 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-2-phenylpropanamide (52). The title compound was prepared by the general procedure C to provide 74 mg (65%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.05-7.55 (m, 14H), 5.56 (d, *J* = 8.0 Hz, 1H), 5.32 (br s, 2H), 3.98-4.23 (m, 1H), 3.55 (q, *J* = 7.1 Hz, 1H), 3.29 (br s, 2H), 1.90-2.11 (m, 2H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.29-1.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 165.8, 153.7, 153.0, 152.0, 145.7, 141.3, 134.3, 134.1, 132.9, 132.5, 131.4, 130.0, 129.5, 129.4, 128.9, 128.3, 128.0, 127.5, 127.3, 126.9, 126.6, 124.9, 119.6, 118.5, 110.2, 47.0, 46.8, 44.3, 38.6, 32.1, 32.0, 18.5. MS (*m/z*) 571.4 (M+1). HPLC = 96% at 20.49 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-3-(1-methyl-1H-tetrazol-5-yl)propanamide (53). The title compound was prepared by the general procedure C to provide 32 mg (27%) of a solid, mp 85-88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.47-7.55 (m, 1H), 7.30-7.43 (m, 5H), 7.14-7.23 (m, 2H), 5.79 (d, *J* = 7.8 Hz, 1H), 5.40 (br s, 2H), 4.55 (t, *J* = 6.2 Hz, 2H), 3.93-4.09 (m, 1H), 3.16-3.35 (m, 3H), 2.90 (t, *J* = 6.1 Hz, 2H), 2.62 (s, 3H), 2.34-2.52 (m, 2H), 1.98 (d, *J* = 9.7 Hz, 2H), 1.33-1.54 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 153.8, 153.1, 152.3, 152.2, 145.8, 134.3, 134.2, 133.0, 132.5, 131.5, 130.0, 129.5, 129.4, 128.0, 127.0, 119.7, 47.3, 44.3, 42.8, 35.7, 32.0, 8.8. MS (*m/z*) 577.4 (M+1). HPLC = 97% at 17.60 min.

2-Methoxyethyl N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}carbamate (54). The title compound was prepared by the general procedure D to provide 72 mg (89%) of a white crystalline solid, mp 127-128 °C. R_f = 0.22 (1% MeOH/60% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.51 (d, *J* = 6.78 Hz, 1H), 7.29-7.44 (m, 5H), 7.20 (d, *J* = 8.67 Hz, 2H), 5.38 (br s, 1H), 4.77 (d, *J* = 7.35 Hz, 1H), 4.15-4.30 (m, 2H), 3.74-3.98 (m, 1H), 3.50-3.71 (m, 2H), 3.27-3.50 (m, 5H), 2.07-2.23 (m, 2H), 1.40-1.60 (m, 2H). MS (*m/z*) 341.1 (M+1). HPLC = 95% at 18.76 min.

Cyclobutyl N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}carbamate (55). The title compound was prepared by the general procedure D to provide 66 mg (88%) of a white amorphous solid, mp 114-116 °C. R_f = 0.30 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.51 (d, *J* = 5.84 Hz, 1H), 7.25-7.43 (m, 5H), 7.20 (d, *J* = 8.48 Hz, 2H), 5.41 (br s, 2H), 4.96 (br s, 1H), 4.62 (br s, 1H), 3.84 (br s, 1H), 3.34 (br s, 2H), 2.32 (br s, 2H), 1.91-2.23 (m, 2H), 1.42-1.82 (m, 6H). MS (*m/z*) 537.2 (M+1). HPLC = >99% at 21 min.

Oxetan-3-yl N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}carbamate (56). The title compound was prepared by the general procedure E to provide 49 mg (65%) of a white amorphous solid, mp 100-102 °C. R_f = 0.27 (1% MeOH/60% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.51 (d, *J* = 6.59 Hz, 1H), 7.30-7.45 (m, 5H), 7.20 (d, *J* = 8.46 Hz, 2H), 5.26-5.61 (m, 2H), 4.72-5.05 (m, 3H), 4.46-4.72 (m, 3H), 3.75-3.95 (m, 1H), 3.20-3.45 (m, 2H), 2.06-2.22 (m, 2H), 1.45-1.60 (m, 2H). MS (*m/z*) 539.0 (M+1). HPLC = >99% at 18.93 min.

Oxan-4-yl N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}carbamate (57). The title compound was prepared by the general procedure E to provide 70 mg (88%) of a white amorphous solid, mp 103-105 °C. R_f = 0.32 (1% MeOH/60% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.51 (d, *J* = 6.78 Hz, 1H), 7.28-7.43 (m, 5H), 7.20 (d, *J* = 8.48 Hz, 2H),

5.43 (br s, 2H), 4.85 (br s, 1H), 4.66 (d, *J* = 6.97 Hz, 1H), 3.76-4.06 (m, 3H), 3.26-3.63 (m, 4H), 2.07-2.22 (m, 2H), 1.81-1.99 (m, 2H), 1.42-1.79 (m, 4H). MS (*m/z*) 567.2 (M+1). HPLC = >99% at 19.19 min.

Oxetan-3-ylmethyl N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}carbamate (58). The title compound was prepared by the general procedure E to provide 64 mg (96%) of a white amorphous solid, mp 113-114 °C. R_f = 0.18 (2% MeOH/60% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.51 (d, *J* = 6.6 Hz, 1H), 7.29-7.45 (m, 5H), 7.20 (d, *J* = 7.9 Hz, 2H), 5.35-5.49 (m, 2H), 4.80 (br s, 4H), 4.48 (d, *J* = 5.8 Hz, 2H), 4.30 (br s,1 H), 3.82-3.92 (m, 1H), 3.25-3.39 (m, 2H), 3.03-3.23 (m, 1H), 2.08-2.26 (m, 2H), 1.45-1.58 (m, 2H). MS (*m/z*) 553.4 (M+1). HPLC = >99% at 18.55 min.

(1-Methylpiperidin-4-yl)methyl N-{1-[8-(2-chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}carbamate (59). The title compound was prepared by the general procedure E to provide 55 mg (77%) of an off-white amorphous solid, mp 99-100 °C. R_f = 0.26 (10% (20% NH_4OH/MeOH)/EtOAc; blue with UV; tailing). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.51 (d, *J* = 6.6 Hz, 1H), 7.30-7.44 (m, 5H), 7.20 (d, *J* = 8.7 Hz, 2H), 5.41 (br s, 2H), 4.64 (d, *J* = 7.0 Hz, 1H), 3.94 (d, *J* = 5.5 Hz, 1H), 3.86 (br s, 1H), 3.18-3.48 (m, 2H), 2.82-2.89 (m, 2H), 2.26 (s, 3H), 2.07-2.18 (m, 2H), 1.81-2.01 (m, 2H), 1.20-1.79 (m, 7H). MS (*m/z*) 594.2 (M+1). HPLC = 95% at 17.52 min.

Benzyl {1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}carbamate (60). The title compound was prepared by the general procedure D to provide 144 mg (100%) of a solid, mp 100-1021 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.45-7.57 (m, 1H), 7.28-7.43 (m, 10H), 7.14-7.24 (m, 2H), 5.39 (br s, 2H), 5.11 (s, 2H), 4.75 (d, *J* = 7.5 Hz, 1H), 3.67-4.03 (m, 1H), 3.34 (t, *J* = 12.1 Hz, 2H), 2.14 (d, *J* = 10.5 Hz, 2H), 1.42-1.61 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 153.9, 153.2, 152.3, 145.7, 136.5, 134.3, 134.2, 133.0, 132.5, 131.4, 130.1, 129.6, 129.4, 128.6, 128.2, 128.0, 127.0, 119.7, 66.8, 48.7, 44.3, 32.7. MS (*m/z*) 573.4 (M+1). HPLC = 99% at 16.48 min.

***N*-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9*H*-purin-6-yl]piperidin-4-yl}-3,3,3-trifluoropropane-1-sulfonamide (62).** The title compound was prepared by the general procedure A to provide 19 mg (32%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.47-7.54 (m, 1H), 7.30-7.42 (m, 5H), 7.15-7.23 (m, 2H), 5.41 (d, *J* = 9.7 Hz, 2H), 4.29 (d, *J* = 7.9 Hz, 1H), 3.58-3.80 (m, 1H), 3.38 (t, *J* = 12.0 Hz, 2H), 2.46 (tt, *J* = 4.8, 8.0 Hz, 1H), 2.21 (dd, *J* = 3.2, 12.8 Hz, 2H), 1.53-1.76 (m, 2H), 1.15-1.23 (m, 2H), 0.98-1.08 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 153.1, 152.3, 145.9, 134.4, 134.2, 133.0, 132.5, 131.5, 130.1, 129.6, 129.4, 128.0, 127.0, 119.8, 77.4, 77.2, 77.0, 76.6, 60.4, 51.3, 44.2, 34.0, 31.8, 21.0, 14.2, 5.8. MS (*m/z*) 543.4 (M+1). HPLC = 98% at 19.13 min.

***N*-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9*H*-purin-6-yl]piperidin-4-yl} pentylsulfonamide (63).** The title compound was prepared by the general procedure A to provide 17 mg (29%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.46 - 7.55 (m, 1H), 7.29 - 7.44 (m, 5H), 7.15 - 7.23 (m, 2H), 5.42 (d, J = 10.83 Hz, 2H), 4.25 (d, J = 7.72 Hz, 1H), 3.56 - 3.75 (m, 1H), 3.34 (t, J = 12.20 Hz, 2H), 2.93 - 3.11 (m, 2H), 2.17 (d, J = 9.89 Hz, 2H), 1.75 - 1.90 (m, 2H), 1.51 - 1.71 (m, 3H), 1.29 - 1.48 (m, 4H), 0.86 - 0.97 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 153.2, 152.3, 145.9, 134.3, 134.2, 133.0, 132.5, 131.5, 130.1, 129.6, 129.4, 128.0, 127.0, 119.7, 54.5, 51.3, 44.1, 33.9, 30.4, 23.5, 22.2, 13.7. MS (*m/z*) 573.5 (M+1). HPLC = 98% at 21.72 min.

***N*-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9*H*-purin-6-yl]piperidin-4-yl}cyclohexanesulfonamide (64).** The title compound was prepared by the general procedure A to provide 16 mg (26%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.50 (dd, *J* = 1.1, 6.8 Hz, 1H), 7.29-7.44 (m, 5H), 7.19 (d, *J* = 8.7 Hz, 2H), 5.42 (d, *J* = 9.4 Hz, 2H), 4.25 (d, *J* = 7.6 Hz, 1H), 3.54-3.78 (m, 1H), 3.34 (t, *J* = 12.0 Hz, 2H), 2.95 (d, *J* = 5.8 Hz, 2H), 2.17 (d, *J* = 10.0 Hz, 2H), 1.88-2.03 (m, 3H), 1.51-1.82 (m, 6H), 0.97-1.43 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 153.2, 145.8, 134.3, 134.2, 133.0, 132.5, 131.5, 130.1, 129.6, 129.4, 128.0, 127.0, 119.7, 77.4, 77.2, 77.0, 76.6, 61.4, 51.3, 44.2, 33.9, 33.1, 25.9, 25.8. MS (*m/z*) 599.4 (M+1). HPLC = 98% at 21.72 min.

N-Cyclohexyl({1-[8-(2-chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}amino)sulfonamide (65). The title compound was prepared by the general procedure B to provide 61 mg (85%) of a white crystalline solid, mp 199-200 °C. R_f = 0.25 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.28-7.40 (s, 5H), 7.20 (d, *J* = 7.7 Hz, 2H), 5.39 (br s, 2H), 4.01-4.26 (m, 2H), 3.58 (br s, 1H), 3.29-3.48 (m, 2H), 3.23 (br s, 1H), 2.13-2.29 (m, 2H), 1.97-2.11 (m, 2H), 1.65-1.77 (m, 2H), 1.53-1.64 (m, 4H), 1.14-1.43 (m, 4H). MS (*m/z*) 600.3 (M+1). HPLC = 99% at 15.80 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-2-fluorobenzene-1-sulfonamide (67). The title compound was prepared by the general procedure B to provide 72 mg (100%) of a white amorphous solid, mp 185-187 °C. R_f = 0.28 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.86-8.04 (m, 1H), 7.53-7.68 (m, 1H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.29-7.43 (m, 6H), 7.14-7.25 (m, 3H), 5.14-5.43 (m, 2H), 4.83 (d, *J* = 7.7 Hz, 1H), 3.51-3.72 (m, 1H), 3.20-3.38 (m, 2H), 1.86-2.02 (m, 2H), 1.42-1.65 (m, 2H). MS (*m/z*) 597.8 (M+1). HPLC = >99% at 20.43 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-fluorophenyl)-9H-purin-6-yl]piperidin-4-yl}-2-fluorobenzene-1-sulfonamide (68). The title compound was prepared by the general procedure B to provide 69 mg (100%) of a white amorphous solid, mp 145-147 °C. R_f = 0.19 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.89-8.01 (m, 1H), 7.53-7.65 (m, 1H), 7.40-7.52 (m, 1H), 7.16-7.43 (m, 7H), 7.05 (d, *J* = 7.1 Hz, 2H), 5.29 (br s, 2H), 4.91 (d, *J* = 7.4 Hz, 1H), 3.53-3.67 (m, 1H), 3.30 (br s, 2H), 1.83-2.02 (m, 2H), 1.44-1.66 (m, 2H). MS (*m/z*) 581.5 (M+1), 579.5 (M-1). HPLC = >98% at 14.77 min.

N-{1-[8-(2-Chlorophenyl)-9-[6-(trifluoromethyl)pyridin-3-yl]-9H-purin-6-yl]piperidin-4-yl}-2-fluorobenzene-1-sulfonamide (69). The title compound was prepared by the general procedure B to provide 65 mg (86%) of an off white crystalline solid, mp 223-224 °C. R_f = 0.24 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.35 (s, 1H), 7.96 (d, *J* = 7.4 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 5.6 Hz, 2H), 7.18-7.51 (m, 5H), 5.28 (br s, 2H), 4.87 (d, *J* = 7.4 Hz, 1H), 3.52-

3.67 (m, 1H), 3.25-3.39 (m, 2H), 1.89-2.10 (m, 2H), 1.45-1.73 (m, 2H). MS (*m/z*) 632.4 (M+1), 630.6 (M-1). HPLC = >99% at 15.88 min.

N-{1-[8-(2-Chlorophenyl)-9-[6-(difluoromethoxy)pyridin-3-yl]-9H-purin-6-yl]piperidin-4-yl}-2-fluorobenzene-1-sulfonamide (70). The title compound was prepared by the general procedure B to provide 75 mg (100%) of a white amorphous solid, mp 180-182 °C. R_f = 0.22 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.04 (s, 1H), 7.87-8.02 (m, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.50-7.65 (m, 2H), 7.11-7.48 (m, 6H), 6.94 (d, *J* = 8.5 Hz, 1H), 5.29 (br s, 2H), 4.89 (d, *J* = 7.2 Hz, 1H), 3.62 (br s, 2H), 3.24-3.38 (m, 2H), 1.88-2.04 (m, 2H), 1.47-1.64 (m, 2H). MS (*m/z*) 630.4 (M+1), 628.2 (M-1). HPLC = >99% at 15.35 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-4-fluorobenzene-1-sulfonamide (71). The title compound was prepared by the general procedure B to provide 72 mg (100%) of an off white amorphous solid, mp 196-197 °C. R_f = 0.28 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.93 (dd, *J* = 8.5, 5.1 Hz, 2H), 7.48 (d, *J* = 6.8 Hz, 1H), 7.28-7.42 (m, 5H), 7.10-7.24 (m, 4H), 5.11-5.41 (m, 2H), 4.95 (d, *J* = 7.5 Hz, 1H), 3.43-3.63 (m, 1H), 3.22-3.40 (m, 2H), 1.86-2.01 (m, 2H), 1.41-1.62 (m, 2H). MS (*m/z*) 597.8 (M+1). HPLC = >99% at 20.47 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-2,4-difluorobenzene-1-sulfonamide (72). The title compound was prepared by the general procedure B to provide 68 mg (92%) of an off white crystalline solid, mp 232-233 °C. R_f = 0.38 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.87-8.10 (m, 1H), 7.21-7.55 (m, 8H), 7.21 (d, *J* = 8.3 Hz, 2H), 5.32 (br s, 2H), 4.89 (d, *J* = 7.5 Hz, 1H), 3.61 (br s, 1H), 3.16-3.46 (m, 2H), 1.89-2.15 (m, 2H), 1.48-1.68 (m, 2H). MS (*m/z*) 615.3 (M+1). HPLC = >99% at 20.67 min.

N-{1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-3,4-difluorobenzene-1-sulfonamide (73). The title compound was prepared by the general procedure B to provide 73 mg (100%) of an off white amorphous solid, mp 183-184 °C. R_f = 0.33 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.62-7.85 (m, 2H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.29-7.43 (m, 6H), 7.18 (d, *J* = 8.5 Hz, 2H), 5.14-5.49 (m, 2H), 4.87 (d, *J* = 7.5 Hz, 1H), 3.43-3.67 (m, 1H), 3.22-3.39 (m, 2H), 1.89-2.04 (m, 2H), 1.42-1.62 (m, 2H). MS (*m/z*) 615.3 (M+1). HPLC = >99% at 20.91 min.

N-{1-[8-(2-Chlorophenyl)-9-[6-(trifluoromethyl)pyridin-3-yl]-9H-purin-6-yl]piperidin-4-yl}-3,4-difluorobenzene-1-sulfonamide (74). The title compound was prepared by the general procedure B to provide 68 mg (100%) of an off white crystalline solid, mp 214-215 °C. R_f = 0.28 (40% EtOAc/hexanes; blue with UV). ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.36 (s, 1H), 7.95 (d, *J* = 7.0 Hz, 1H), 7.66-7.84 (m, 3H), 7.61 (dd, *J* = 7.0, 1.7 Hz, 1H), 7.29-7.51 (m, 4H), 5.30 (br s, 2H), 4.63 (d, *J* = 7.5 Hz, 1H), 3.46-3.68 (m, 1H), 3.22-3.43 (m, 2H), 1.91-2.12 (m, 2H), 1.45-1.57 (m, 2H). MS (*m/z*) 650.4 (M+1), 648.4 (M-1). HPLC = >99% at 20.79 min.

N-{1-[8-(2-Chlorophenyl)-9-[6-(difluoromethoxy)pyridin-3-yl]-9H-purin-6-yl]piperidin-4-yl}-3,4-difluorobenzene-1-sulfonamide (75). The title compound was prepared by the general procedure B to provide 64 mg (82%) of an off white crystalline solid, mp 212-213 °C. R_f = 0.26 (40% EtOAc/hexanes; blue with UV). ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.04 (d, *J* = 2.1 Hz, 1H), 7.60-7.83 (m, 3H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.29-7.48 (m, 5H), 6.94 (d, *J* = 8.7 Hz, 1H), 5.29 (br s, 2H), 4.68 (d, *J* = 7.5 Hz, 1H), 3.45-3.67 (m, 1H), 3.22-3.40 (m, 2H), 1.91-2.05 (m, 2H), 1.43-1.60 (m, 2H). MS (*m/z*) 648.3 (M+1). HPLC = >98% at 20.25 min.

4-[8-(2-Chlorophenyl)-6-{4-[(3,4-difluorobenzene)sulfonamido]piperidin-1-yl}-9H-purin-9-yl]benzamide (76). The title compound was prepared by the general procedure B to provide 69 mg (92%) of an off white crystalline solid, mp 138-140 °C. R_f = 0.18 (2% MeOH/80% EtOAc/hexanes; blue with UV). ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.59-7.90 (m, 4H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.19-7.41 (m, 6H), 6.40 (br s, 2H), 5.79 (d, *J* = 6.2 Hz, 1H), 5.26 (br s, 2H), 3.51 (br s, 1H), 3.20-3.44 (m, 2H), 1.74-2.00 (m, 2H), 1.40-1.69 (m, 2H). MS (*m/z*) 624.4 (M+1). HPLC = >99% at 17.51 min.

N-{1-[9-(6-Aminopyridin-3-yl)-8-(2-chlorophenyl)-9H-purin-6-yl]piperidin-4-yl}-3,4-difluorobenzene-1-sulfonamide (77). The title compound was prepared by the general procedure B to provide 31 mg (52%) of a tan amorphous solid, mp 247-248 °C. R_f = 0.28 (4% MeOH/80% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.58-7.83 (m, 3H), 7.37-7.52 (m, 2H), 7.28-7.39 (m, 4H), 6.50 (d, *J* = 8.8 Hz, 1H), 6.20 (d, *J* =7.7 Hz, 1H), 5.38 (br s, 2H), 5.03 (s, 2H), 3.43-3.64 (m, 1H), 3.08-3.28 (m, 2H), 1.82-1.97 (m, 2H), 1.32-1.57 (m, 2H). MS (*m/z*) 597.7 (M+1), 595.5 (M-1). HPLC = >98% at 12.33 min.

N-{5-[8-(2-Chlorophenyl)-6-{4-[(3,4-difluorobenzene)sulfonamido]piperidin-1-yl}-9H-purin-9-yl]pyridin-2-yl}acetamide (78). To a solution of **77** (16 mg, 0.027 mmol) in THF (1 mL) was added acetyl chloride (0.003 mL, 1.2 equiv), followed by pyridine (0.004 mL, 1.5 equiv). The mixture was stirred at rt for 3 h. Water (0.4 mL) was added, followed by ethyl acetate (3 mL) and then saturated $NaHCO_3$ solution (0.8 mL). After 10 min, the aqueous layer was removed, celite (500 mg) was added to the organic layer and the solvent evaporated. Purification by flash chromatography using silica gel with an EtOAc/hexanes gradient provided 18 mg (100%) of a white crystalline solid, mp 254-255 °C. R_f = 0.23 (2% MeOH/60% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 8.15 (d, *J* = 2.1 Hz, 1H), 7.63-7.84 (m, 2H), 7.47-7.62 (m, 2H), 7.30-7.46 (m, 4H), 5.10-5.39 (m, 2H), 3.40-3.56 (m, 1H), 3.22-3.39 (m, 2H), 2.20 (s, 3H), 1.85-2.01 (m, 2H), 1.43-1.66 (m, 2H). MS (*m/z*) 639.7 (M+1), 637.5 (M-1). HPLC = >98% at 18.11 min.

N-{1-[8-(2-Chlorophenyl)-9-(5-methyl-1,2-oxazol-3-yl)-9H-purin-6-yl]piperidin-4-yl}-3,4-difluorobenzene-1-sulfonamide (79). The title compound was prepared by the general procedure B to provide 42 mg (81%) of a tan crystalline solid, mp 180-182 °C. R_f = 0.19 (40% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.65-7.85 (m, 2H), 7.60 (d, *J* = 6.2 Hz, 1H), 7.29-7.51 (m, 4H), 6.55 (s, 1H), 5.27 (br s, 2H), 4.66 (d, *J* = 7.7 Hz, 1H), 3.45-3.64 (m, 1H), 3.19-3.41 (m, 2H), 2.46 (s, 3H), 1.88-2.05 (m, 2H), 1.40-1.61 (m, 2H). MS (*m/z*) 586.4 (M+1), 584.3 (M-1). HPLC = >99% at 20.39 min.

N-{1-[8-(2-Chlorophenyl)-9-(1-methyl-1H-pyrazol-4-yl)-9H-purin-6-yl]piperidin-4-yl}-3,4-difluorobenzene-1-sulfonamide (80). The title compound was prepared by the general procedure B to provide 60 mg (85%) of a white crystalline solid, mp 162-164 °C. R_f = 0.11 (2% MeOH/60% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.62-7.85 (m, 3H), 7.33-7.55 (m, 5H), 7.17 (s, 1H), 5.13-5.31 (m, 2H), 3.89 (s, 3H), 3.20-3.58 (m, 3H), 1.85-2.01 (m, 2H), 1.42-1.66 (m, 2H). MS (*m/z*) 585.4 (M+1), 583.6 (M-1). HPLC = >99% at 18.45 min.

N-**{1-[8-(2-Chlorophenyl)-9-(1-methyl-1H-pyrazol-3-yl)-9H-purin-6-yl]piperidin-4-yl}-3,4-difluorobenzene-1-sulfonamide (81).** The title compound was prepared by the general procedure B to provide 35 mg (60%) of a tan amorphous solid, mp 206-208 °C. R_f = 0.24 (2% MeOH/80% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.65-7.82 (m, 2H), 7.50 (d, *J* = 6.4 Hz, 1H), 7.28-7.43 (m, 5H), 6.19 (s, 1H), 5.13-5.44 (m, 2H), 4.72 (d, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 3.45-3.63 (m, 1H), 3.18-3.38 (m, 2H), 1.87-2.03 (m, 2H), 1.44-1.59 (m, 2H). MS (*m/z*) 585.2 (M+1), 583.7 (M-1). HPLC = >98% at 18.45 min.

N-{1-[8-(2-Chlorophenyl)-9-[5-(trifluoromethyl)-1H-pyrazol-3-yl]-9H-purin-6-yl]piperidin-4-yl}-3,4-difluorobenzene-1-sulfonamide (82). The title compound was prepared by the general procedure B to provide 17 mg (22%) of a tan amorphous solid, mp 172-174 °C. R_f = 0.23 (60% EtOAc/hexanes; blue with UV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.62-7.83 (m, 3 H), 7.28-7.63 (m, 5H), 5.62 (br s, 1H), 5.30 (br s, 2H), 4.69 (d, *J* = 6.2 Hz, 1H), 3.51-3.67 (m, 1H), 3.22-3.43 (m, 2H), 1.90-2.06 (m, 2H), 1.45-1.63 (m, 2H). MS (*m/z*) 639.4 (M+1), 637.1 (M-1). HPLC = >95% at 19.53 min.

Testing for Pan-assay Interference (PAIN)

The compounds synthesized were considered low risk for PAIN as they are analogs of a previously well-characterized diphenyl purine scaffold specific for hCB1.[21] Additionally, compounds were manually inspected to identify structural similarities related to known PAIN compounds [30-32] and all compounds were tested using the calcium mobilization assay in parental cells without hCB1 to ensure specificity of action.

Calcium mobilization and radioligand displacement assays

Each compound was biologically characterized using a functional fluorescent hCB1 activated $G\alpha q_{16}$-coupled intracellular calcium mobilization assay in CHO-K1 cells, as has been described in our previous publications and apparent affinity (Ke) values were determined.[22, 28] Briefly, CHO-K1 cells were engineered to co-express hCB1 and $G_{\alpha q16}$. Activation of CB1 by an agonist then leads to generation of inositol phospahatase 3 (IP_3) and activation of IP_3 receptors, which leads to mobilization of intracellular calcium. Calcium flux was monitored in a 96-well format using the fluorescent dye Calcein-4 AM in an automated plate reader (Flexstation, Molecular Devices). The antagonism of a test compound was measured by its ability to shift the concentration response curve of the synthetic CB1 agonist CP55940 rightwards using the equation:

Ke = [Ligand]/[DR-1] where DR is the EC_{50} ratio of CP55940 in the presence or absence of a test agent.

For some assays, cells were loaded with Calcein-4 AM as described below and directly stimulated with various concentrations of a test agent for 90 seconds. Decrease in basal fluorescence was used in these assays to calculate EC_{50} values.

Further characterization of select compounds was performed using radioligand displacement of [^{3}H]CP55940 and equilibrium dissociation constant (Ki) values were determined as described previously.[22, 28] Selectivity of these compounds at hCB1 versus hCB2 was also determined by obtaining Ki values at either receptor in membranes of CHO cells over-expressing either receptor. Data reported are average values from 3-6 measurements typically with <30% standard error.

MDCK-mdr1 permeability assays

MDCK-mdr1 cells obtained from the Netherlands Cancer Institute were grown on Transwell type filters (Corning) for 4 days to confluence in DMEM/F12 media containing 10% fetal bovine serum and

antibiotics. Compounds were added to the apical side at a concentration of 10 μM in a transport buffer comprising of 1X Hank's balanced salt solution, 25 mM D-glucose and buffered with HEPES to pH 7.4. Samples were incubated for 1 h at 37 °C and carefully collected from both the apical and basal side of the filters. Compounds selected for MDCK-mdr1 cell assays were infused on an Applied Biosystems API-4000 mass spectrometer to optimize for analysis using multiple reaction monitoring (MRM), as previously described.[33] The chromatography was conducted with an Agilent 1100 binary pump with a flow rate of 0.5 mL/min. Mobile phase solvents were 0.1% formic acid in water (A) and 0.1% formic acid in methanol (B). The solvent conditions were 10% B for 1 min, followed by a gradient to 95% B over 5 min. Data reported are average values from 2-3 measurements.

Hepatic microsomal stability studies

Human microsomal stability assays were performed as described previously.[28] Briefly, test compounds were incubated at a 1 μM final concentration with 0.5 mg/ml pooled human liver microsomes from 200 unidentified donors (Xenotech, LLC, Lenexa, KS) in a 100 mM phosphate buffer (pH 7.4) containing 3 mM $MgCl_2$, 1 mM nicotinamide adenine dinucleotide phosphate (NADPH), 5 mM uridine diphosphate glucuronic acid (UDPGA), and 50 μg/ml alamethicin. Triplicate samples were incubated for up to 120 min. Samples were removed at regular intervals. Reactions were terminated by addition of 3 volumes of methanol and processed as described for the MDCK-mdr1 assays, but standard curves were prepared in blank matrix for each compound for quantitative assessment. Intrinsic clearance rate was calculated as described before.[34] Data reported are average values from 3 measurements.

Pharmacokinetic Testing

All animal studies were approved by institutional animal use committee of RTI International. Male or female C57BL6 mice were procured from Jackson Laboratories at 8 weeks of age and allowed to acclimate to the facility. Animals were dosed with compounds in a vehicle comprised of 1% NMP and 0.3% Tween 80 in 0.5% sodium carboxymethylcellulose (medium viscosity; deionized water). Animals were

sacrificed at multiple time-points (0.5, 1, 2, 4, 8 & 24 h) and samples were removed. Pharmacokinetic analyses were performed as has been described in our previous publications using Phoenix WinNonlin (Certara).[22]

Author Information

* To whom correspondence should be addressed. Tel: 919-485-2668. Fax: 919-541-8868. Email: rmaitra@rti.org.

Conflict of Interest Statement

The authors do not have known conflicts of interest.

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Supplementary Information

Table 1. Calculated Properties of Compounds

Table 2. Human Liver Microsome Stability

Table 3. Mouse Pharmacokinetic Data

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