Letters

Discovery of 1-[9-(4-Chlorophenyl)-8-(2-chlorophenyl)-9*H*-purin-6-yl]-4-ethylamino-piperidine-4-carboxylic Acid Amide Hydrochloride (CP-945,598), a Novel, Potent, and Selective Cannabinoid Type 1 Receptor Antagonist

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Abstract: We report the structure−activity relationships, design, and synthesis of the novel cannabinoid type 1 (CB_1) receptor antagonist **3a** (CP-945,598). Compound **3a** showed subnanomolar potency at human CB_1 receptors in binding (K_i = 0.7 nM) and functional assays (K_i = 0.12 nM). In vivo, compound **3a** reversed cannabinoid agonist-mediated responses, reduced food intake, and increased energy expenditure and fat oxidation in rodents.

The endocannabinoid system (ECS[a]), and specifically the cannabinoid type 1 (CB_1) receptor, plays a pivotal role in energy homeostasis.[1−3] As such, stimulation of the ECS promotes food intake and energy storage and may be chronically overactive in obese subjects.[4−7] In contrast, blockade of the CB_1 receptor decreases food intake and increases energy expenditure, leading to a reduction in body weight.[8−11] It was hoped that CB_1 receptor antagonists might provide effective therapy options for the management of metabolic disorders, such as obesity. Unfortunately, several CB_1 receptor inverse agonists/antagonists were recently withdrawn from clinical development including the diarylpyrazole rimonabant[12] **1** (SR141716A) and the acyclic amide taranabant[13] **2** (MK-0364).

Herein, we describe the design strategies that led to the identification of a series of purine derivatives as CB_1 receptor antagonists, and the optimization of PK properties that resulted in the discovery of the orally active **3a** (CP-945,598), a novel, potent, and selective CB_1 receptor antagonist, recently evaluated in phase 3 clinical trials for weight management.

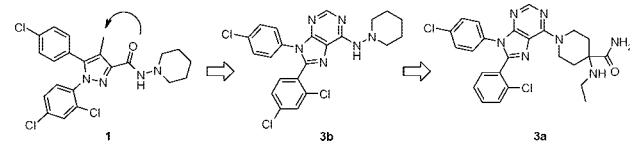

Figure 1. Medchem strategy.

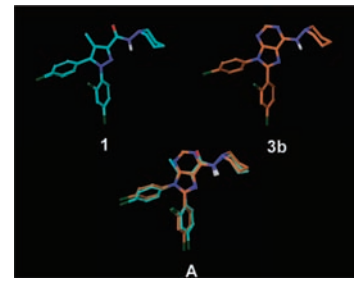

Figure 2. Lowest energy conformation of **1** where the carbonyl is adjacent to the methyl, constrained purine analogue (**3b**), and an overlay of the two structures (**A**).[22]

We hypothesized that conformationally restricted analogues of **1** that adopt its bioactive conformation would have improved potency.[14] In designing our targets, we looked to minimize lipophilicity to achieve low metabolic clearance and good solubility. To achieve good central nervous system (CNS) penetration, we sought compounds with low molecular weight (MW < 450), moderate topological polar surface area (TPSA < 90), and less than two hydrogen-bond donors (HBD).[15,16] Finally, we wanted to remove the hydrazine functionality and the corresponding potential to generate reactive metabolites.[17−20]

A reasonable low-energy conformation of **1**, depicted in Figure 1, minimizes the dipole interaction between the pyrazole and the amide carbonyl and allows for a hydrogen bond to form to the pyrazole N1 atom. We hypothesized that purine analogues would mimic this low energy conformation, locking the bioactive conformation of **1** while also providing a hydrogen bond acceptor to mimic the amide carbonyl.[21] There is excellent overlap of the minimized conformations[22] of **1** (lowest energy conformation where the carbonyl is adjacent to the methyl) and the corresponding purine analogue as depicted in Figure 2.

The synthesis of these compounds is illustrated in Scheme 1.[23] Reaction of 4-chloroaniline with 4,6-dichloro-5-aminopyrimidine (**4**) in refluxing aqueous hydrochloric acid[24] provided diaminopyrimidine **5**. Acylation with the appropriate benzoyl chlorides gave amides **6a**,**b**, which were then cyclized to purinones **7a**,**b** by heating under acidic conditions. The key chloropurines **8a**,**b**, obtained by heating **7a**,**b** in the presence of phosphorus oxychloride, were useful for preparing a variety of nitrogen, oxygen, and carbon-linked analogues.[25] In the present case, primary and secondary amines readily react with chloropurines **8a**,**b** to give the desired 6-alkylaminopurine analogues **3a**−**g**.

Compound **3b**, the corresponding conformationally constrained analogue of **1**, exhibited good in vitro binding and functional affinity, confirming the feasibility of our approach (Table 1). The intrinsic microsomal clearance of this compound was high, attributed to its lipophilicity (ElogD = 5.3).[26] The

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[a] Abbreviations: ECS, endocannabinoid system; CB_1, cannabinoid type 1; CNS, central nervous system; eLLE, ligand-lipophilicity efficiency using measured ElogD; MW, molecular weight; TPSA, topological polar surface area; HBD, hydrogen-bond donors; SAR, structure−activity relationship; FIRF; fast-induced refeeding; P-gp, P-glycoprotein; MDCK, Madin−Darby canine kidney.

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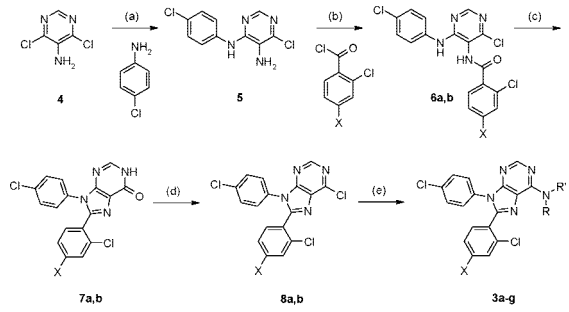
Scheme 1. Synthesis of Purines **3a**−**g**[a]



[a] (a) HCl, EtOH/H_2O, reflux; (b) pyridine or dimethylacetamide; (c) AcOH, reflux; or H_2SO_4, ^{i}PrOH, reflux; (d) $POCl_3$, reflux; or $POCl_3$, Et_3N, toluene, reflux; (e) HNRR′.

structure−activity relationships (SAR) of the amine headgroup were readily explored using small libraries, though the high MW of the purine core limited the size of amines employed. Replacement of the 1-aminopiperidinyl moiety with various small, lipophilic head groups did not lead to any loss of affinity. However, the compounds still showed rapid clearances in microsomal preparations. The lipophilicity of the series was reduced by removing one of the chloro atoms on the N1 phenyl group, leading to improved metabolic stability. For example, **3e** exhibited a 9-fold decrease in intrinsic microsomal clearance relative to **3d**.

Compound **3d** was shown to be biologically active in reversing two of the cannabinoid agonist-induced tetrad of behaviors following subcutaneous injection, but it was not orally active in an animal model of feeding behavior (Table 2) because of poor exposure of this compound. Peripheral and central unbound drug concentrations were 2 orders of magnitude below the rat K_i (rK_i). Poor oral exposure was not surprising given its high lipophilicity, which resulted in high unbound intrinsic clearance and poor solubility.[27]

Incorporation of heteroatoms (e.g., polar headgroups, heterocyclic replacements for the chlorophenyls) improved the solubility of compounds (e.g., **3f** and **3g**; Table 2). Compound **3f** was the first orally active analogue in the series as demonstrated by its efficacy in inhibiting fast-induced refeeding (FIRF, Table 2). Central exposure was ∼17% rK_i 2 h postdosing.

Compound **3f** exhibited potent activity in the hERG potassium ion channel assay, suggesting possible issues with QTc prolongation. We therefore sought to introduce an electron-withdrawing substituent adjacent to the amine to increase the polarity of the molecule and decrease the basicity of the adjacent amine, with the aim of attenuating the microsomal clearance and hERG affinity.[28] Library and singleton chemistries were used to prepare analogues containing polar basic amines, taking care not to increase PSA too high and impair CNS permeability. The 4-alkylamino-4-aminocarbonylpiperidine headgroup proved ideal and balanced the properties of **3a**, resulting in a potent cannabinoid CB_1 receptor antagonist (Table 1) with moderate unbound microsomal clearance, low hERG affinity, and adequate CNS penetration. While the rat binding affinity of **3a** is similar to that of **3f**, **3a** was more potent in the human binding and functional assays (Table 1). Furthermore, **3a** also displayed anorectic properties in the FIRF assay (Table 2) with unbound exposure similar to **3f** at 2 h. Compound **3a** has similar in vitro potency but ∼6-fold lower intrinsic microsomal clearance than **1**.

Compound **3a** showed subnanomolar potency at human CB_1 receptors in binding (hK_i = 0.7 nM) and functional (K_i = 0.12 nM) assays. In vivo, **3a** reversed four cannabinoid agonist-mediated behaviors (locomotor activity, hypothermia, analgesia, and catalepsy) following administration of the synthetic CB_1 receptor agonist 5-(1,1-dimethylheptyl)-2-[(1*S*,2*S*,5*S*)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]phenol, **9** (CP-55,940).[29] Compound **3a** exhibited dose-dependent anorectic activity in a model of acute food intake in rodents and increased energy expenditure and fat oxidation.[30]

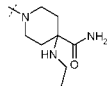
Comparison of brain to plasma concentration ratios in P-glycoprotein (P-gp) knockout (mdr1a/1b−/−) vs wild-type mice[31] with **3a** indicated P-gp-mediated efflux (data not shown). Furthermore, the brain to plasma unbound concentration ratio of **3a** in rats measured in the FIRF assay was ∼0.1 (Table 2). Despite these data indicating active efflux from the CNS in rodents, preclinical efficacy of **3a** was demonstrated in a number of animal models.[30] Human dose predictions assumed impaired CNS penetration as observed in rats. Good plasma/brain concentration−effect relationships have been observed wherein reductions in food intake correlate with compound potency and free CNS drug levels.[32] Studies in Caco-2 cells and Madin−Darby canine kidney (MDCK) cells expressing human MDR1[33] indicated moderate permeability of **3a** but suggested no active efflux from the CNS in humans. This was confirmed in an in vitro ATPase assay[34] in human cells where no or low ATP turnover was observed at 1.25−25 mM **3a** (data not shown). By use of a calcein-AM assay[35] in human cell lines, **3a** was shown to be a weak P-gp inhibitor, with IC_{50} ranging from 15 to 30 mM, indicating it is unlikely that **3a** will inhibit P-gp in the CNS. Further details of the pharmacology of **3a** will be reported in future publications.

Despite our best intentions, **3a** exceeded several physiochemical criteria we had set at the outset of the project (MW, 510; TPSA, 102; HBD, 3). The moderately impaired CNS penetration observed in rodents was unsurprising given the physiochemical properties of **3a** that lie outside the typical CNS property space.[36,37] The geminal arrangement of the aminoamide functionality was critical to achieving reasonable CNS penetration. It is apparent from the crystal structure (data not shown) that a hydrogen bond between the amide NH and the amine lone pair may reduce the effective polarity and allow for reasonable CNS penetration. Further details of this SAR will be reported in future publications.

Ligand efficiency[38] (Table 1) remained fairly constant, ranging from 0.36 to 0.41, for the compounds described above. During our designs we were careful to use lipophilicity as efficiently as possible. Significant gains were made in the binding energy achieved by nonlipophilic interactions, as reflected in the ligand-lipophilicity[39] (eLLE, ligand-lipophilicity efficiency using measured ElogD) increases observed during the course of our work. Compound **3d**, which lacked oral efficacy, had an eLLE of 2.3. Judicious introduction of polarity provided orally efficacious **3f** with an eLLE of 3.3. Further optimization gave candidate **3a** with an eLLE of 5.2.

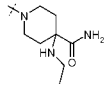
In summary, a novel purine derivative **3a** was discovered with good CB_1 receptor binding and functional activity and good in vivo activity in rodent models of feeding. Judicious introduction of polar functionality to reduce lipophilicity led to reductions in intrinsic clearance and hERG activity. Compound **3a** falls outside the normal property space for a CNS agent, yet still exhibits good efficacy. Clinical development of **3a** was recently discontinued on the basis of changing regulatory perspectives on the risk/benefit profile of the CB_1 class and likely new regulatory requirements for approval.

Table 1. Biochemical Properties of Purine CB_1 Antagonists **1** and **3a**−**g**[a]

compd	X	NRR′	MW	ElogD	rK$_i$ (nM)	hK$_i$ (nM)	LE	eLLE	hGTPγ[^{35}S] K$_i$ (nM)	r μsome CL$_{int}$ mL/min/kg	h μsome CL$_{int}$ mL/min/kg	hERG IC$_{50}$ (μM)
1	NA	NA	463.80	5.8	0.65	0.9 ± 0.5	0.41	3.2	0.19 ± 0.06	9000	1700	
3a	H		510.42	4.0	2.8 ± 1	0.7 ± 0.1	0.36	5.2	0.12 ± 0.04	1200	740	> 3
3b	Cl		473.80	5.3	3.6	7.4 ± 2.0	0.36	2.7	1.7 ± 1.0	4100	1700	2.7
3c	Cl		472.81	6.3	12	7.1 ± 2.7	0.36	1.8	1.5 ± 0.9	24000	28000	> 3
3d	Cl		458.78	5.9	4.2	6.1 ± 5.3	0.37	2.3	1.7 ± 1.1	77000	28000	> 3
3e	H		424.34	5.4	2.1	2.3 ± 0.4	0.41	3.3	1.1 ± 0.7	8600	3100	> 3
3f	Cl		473.80	4.8	5.9	5.2 ± 3.1	0.36	3.3	1.5 ± 0.9	5900	740	0.35
3g	H		439.35	4.1	24	2.8 ± 0.9	0.39	4.5	1.6 ± 1.0	1500	300	0.63

[a] MW, molecular weight; h, human; r, rat; LE, ligand efficiency; eLLE, ligand-lipophilicity efficiency using measured ElogD; μsome, liver microsome.

Table 2. Biological Characteristics of Purine CB_1 Antagonists **3a**−**g**[a]

compd	X	NRR′	thermodynamic solubility (μgA/mL)		tetrad (%reversal; 10 mg/kg; sc)		FIRF (2 h post-dose; 10 mg/kg; po)		
			0.1 M phosphate buffered saline (pH 6.5)	USP simulated gastric fluid (no pepsin, pH 1.2)	analgesia	hypothermia	% reduction in food intake vs controls	plasma (nM, free)	brain (nmol/g, free)
3a	H		1.3 ± 0.3	291 ± 1	85%ǂ	73%ǂ	54%*	4.6	0.51
3b	Cl		1.4 ± 0.1	161 ± 1					
3c	Cl		< 0.1	4.1 ± 0.2					
3d	Cl		< 0.1	3.5 ± 0.5	72%ǂ	29%ǂ	6%	0.043	0.0028
3e	H		< 0.1	8.8 ± 1.1					
3f	Cl		0.7 ± 0.1	4930 ± 1	74%ǂ	4%	25%*[a]	2.2	0.94
3g	H		0.33 ± 0.03	1290 ± 1					

[a] FIRF, fast-induced refeeding; po, oral administration; sc, subcutaneous; ∗, $P < 0.05$ vs vehicle; †, $P < 0.05$ vs the cannabinoid CB_1 receptor agonist **9**; a, 20 mg/kg.

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Supporting Information Available: Experimental details and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

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