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Design of a Potent CB_1 Receptor Antagonist Series: Potential Scaffold for Peripherally-Targeted Agents

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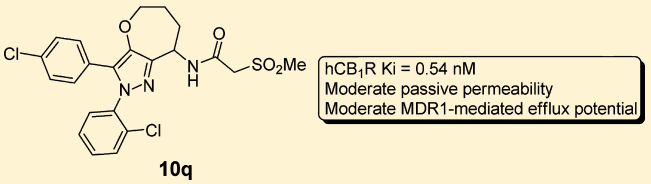
Supporting Information

ABSTRACT: Antagonism of cannabinoid-1 (CB_1) receptor signaling has been demonstrated to inhibit feeding behaviors in humans, but CB_1-mediated central nervous system (CNS) side effects have halted the marketing and further development of the lead drugs against this target. However, peripherally restricted CB_1 receptor antagonists may hold potential for providing the desired efficacy with reduced CNS side effect profiles. In this report we detail the discovery and structure−activity-relationship analysis of a novel bicyclic scaffold (**3**) that exhibits potent CB_1 receptor antagonism and oral activity in preclinical feeding models. Optimization of physical properties has led to the identification of analogues which are predicted to have reduced CNS exposure and could serve as a starting point for the design of peripherally targeted CB_1 receptor antagonists.



10q

KEYWORDS: *Obesity, cannabinoid receptor, antagonist, clearance, polar surface area, multidrug resistance protein 1, ligand efficiency, ligand-lipophilicity efficiency*

Epidemiological studies have underscored the high incidence of obesity in developed countries, exemplified by a prevalence of one in three U.S. adults.[1] Obesity is a contributing factor to a number of chronic disease states, including diabetes, heart disease, hypertension, stroke, and arthritis.[2] Because of its impact on this broad array of diseases, obesity has recently displaced smoking as the leading cause of preventable death.[3] In general, the failure of obese patients to adhere to the preferred treatment strategy of diet and exercise has led to intensive research efforts to identify pharmacological agents that reverse this disease state. Weight gain/loss involves a balance of both satiety and the metabolic state of the individual. Therefore, modulation of the mechanisms involved in controlling either or both of these end points has been targeted for pharmacotherapy. The only chronic weight loss treatment currently approved for human use is orlistat, which disrupts fat absorption through intestinal lipase inhibition. Since the side effect profile of orlistat limits its widespread use, additional treatment options for obesity are warranted.

Disruption of endocannabinoid signaling via blockade of cannabinoid (CB) receptors has been shown to significantly inhibit food intake and increase energy expenditure in both preclinical models and humans.[4,5] The CB_1 receptor subtype, which is distributed both centrally and peripherally, is responsible for controlling satiety and energy expenditure.[6] While the selective CB_1 receptor antagonist rimonabant (**1**) was approved for the treatment of obesity in European markets, it was later withdrawn due to CNS derived side effects including depression, anxiety, and suicide-ideation.[7] In addition, a number of structurally distinct antagonists (otenabant, taranabant, and ibipinabant) were also advanced to late stage clinical testing and were found to have similar CNS side effect profiles.[5,8] Though these findings were a significant setback, there may still be a path forward for this mechanism in the treatment of obesity. Recent genomic data suggests that certain polymorphisms of the CB_1 receptor gene alone or in combination with variants in the serotonin transporter gene are linked to the development of anxiety and depression.[9] On the basis of these findings, genetic screening could pave the way for the selection of a patient population in which CB_1 antagonist treatment would have a much improved safety profile. Alternatively, since these side effects are centrally mediated, it has been proposed that peripherally targeted CB_1 receptor antagonists would possess an improved therapeutic index.[10,11] This strategy has been pursued through increasing the polar surface area[12−14] of lead CB_1 receptor antagonist chemotypes and through the recognition by CNS efflux transporters (i.e., multidrug resistant protein 1 (MDR1)),[15] as a means of reducing central exposure.

Our group recently disclosed the potent, orally active CB_1 receptor antagonist **2** (PF-0514273), which was advanced to human clinical trials for the treatment of obesity.[16] The bicyclic lactam core of **2** arose through conformational-restriction of the C-3/C-4 positions of the pyrrole core of **1**. Besides locking in a favorable vector for the N-substituent, this antagonist maintains

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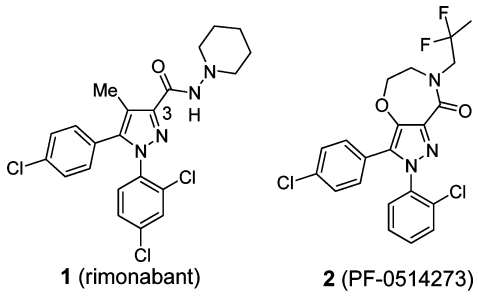
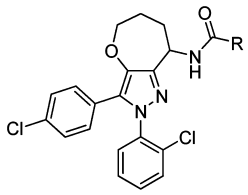


1 (rimonabant) **2** (PF-0514273)



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a molecular weight and lipophilicity profile which is similar to that of **1** (log $D_{7.4}$ of **1** = 4.7; **2** = 4.1).[17] This latter point is particularly important, since **1**, as well as a majority of CB_1 antagonists, are on the edge of acceptable property space[18] and previous efforts directed toward peripheral-restriction have typically resulted in significantly increased molecular weight.[12−14] Thus, improving the physiochemical profile of the core structure arising from our follow-on efforts related to **2** became a design goal. This driver, along with pharmacophore overlap analyses, led to the prioritization of the design represented by **3**. Conformational analysis of representative analogues of **3** predicts the acylamino substituent to be nearly coplanar with the pyrazole ring, similar to that observed for the hydrazide group of **1** (Figure 1; *R* enantiomer shown).[19]

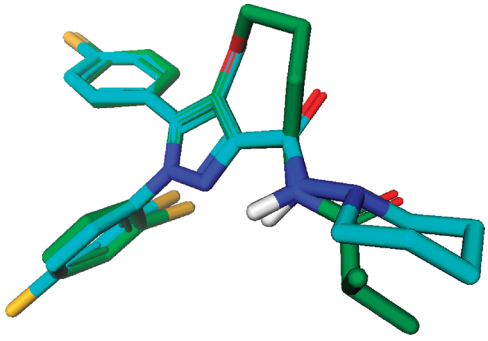

Figure 1. Overlay of minimized conformations of **1** (cyan) and **10d** (green).

Modeling also reveals a high degree of overlap between the amide substituents of **1** and **3**, which represents a considerable improvement relative to that observed for the amide substituent in **2**.[16] While **2** demonstrates that direct overlap of this portion of the pharmacophore is not critical for potent CB_1 antagonism, it may still be of value to have an enhanced overlap with the hydrazide substituent of **1**. One potential advantage may lie in the finding that polar functionality is well tolerated in the terminus of the piperidine ring of **1**, which has led to agents with high peripheral/CNS partitioning ratios.[12−15] In addition, **3** possesses a slightly increased polar surface area (PSA) relative to those of both **1** and **2** (PSA = 50.4, 47.4, and 56.2 for **1**, **2**, and **3** (e.g., R = alkyl), respectively, which could be an advantage as a starting point for reduced brain penetration. Herein, we describe our efforts in developing series **3** into highly potent, orally active CB_1 antagonists with the potential to serve as a structural platform for the discovery of peripherally targeted agents.

Target compounds based on **3** were synthesized as described in Scheme 1 or 2. Alkylation of the potassium salt of hydroxypyrazole **4**[16] with *tert*-butyl 4-bromobutanoate afforded ether **5** in 82% yield following recrystallization from cyclohexane. Dieckmann cyclization of diester **5** afforded bicyclic *β*-ketoester **6** in 90% yield. Removal of the ester functionality with trifluoroacetic acid, followed by thermal decarboxylation of the resulting acid provided ketone **7** in 84% overall yield. Conversion to amines **8** and **9** was achieved in 55−60% overall yield by reductive amination utilizing the requisite amine and sodium cyanoborohydride. The enantiomers of **8** were separated by utilizing chiral phase high-pressure liquid chromatography, and the absolute stereochemistry of each was assigned via single crystal X-ray analysis of the corresponding *p*-bromobenzamide derivative. These crystal structures were consistent with the predicted conformation (Figure 1), in which the acylamino substituent is planar with the bicyclic core. Conversion of amines **8** and **9** to the targeted amide, carbamate, and urea derivatives was accomplished in high yields by employing standard protocols. Cyclic amide **12** was prepared through acylation of **8** with 4-chlorobutyryl chloride and intramolecular alkylation by employing potassium *tert*-butoxide in 38% overall yield (Scheme 2).

While primary amine **8** is a modestly potent inhibitor of the human CB_1 receptor, acetylation led to a substantial increase in affinity (**10a**, Table 1). Binding activity translated well into functional inhibition of the human CB_1 receptor, with a K_i for **10a** that is comparable to those observed for **1** and **2**. Analysis of CB_2 receptor binding affinity revealed **10a** to be a highly selective inhibitor (CB_2/CB_1 > 20,000). In line with the goal of identifying chemical space which is more compatible with designing in CNS exclusion, **10a** possesses improved ligand-lipophilicity efficiency (LLE)[20] relative to those of **1** and **2** (5.6 vs 4.1 and 5.0 for **1** and **2**, respectively). On the basis of human liver microsomal (HLM)[21] analysis ($CLint_{app}$ < 8 mL/min/kg), this acetamide is predicted to have low oxidative clearance in vivo. Extending the methyl group of **10a** to an ethyl or isopropyl substituent led to improvements in CB_1 receptor inhibitory activity, with **10c** being a 40 pM functional antagonist. This highly potent isobutyramide possesses a LLE of 6.7, which is well within the targeted space of marketed oral drugs.[20] Incorporation of additional hydrophobic bulk (e.g., **10f**) does not provide significant improvements in CB_1 receptor binding affinity, while negatively impacting microsomal clearance.

With modeling and X-ray analysis supporting a low energy conformation of **3** in which the amide functionality is nearly planar with the pyrazole ring, we evaluated the importance of this conformation via preparation of tertiary amide derivatives. N-Methylation (**11**) of **10c** or incorporation of a cyclic amide (**12**) resulted in a >150-fold reduction in CB_1 receptor functional activity, while increasing HLM clearance. Increased steric interaction of the tertiary amide substituent with the bicyclic core in these cases would be expected to rotate the amide out of plane and is supported by the observation of amide rotamers in NMR experiments with **11**. These results are consistent with an in-plane amide requirement and support conformation models proposing the predicted binding of **1** to the CB_1 receptor involving an in-plane relationship between the central pyrazole core and the amide side chain.[19]

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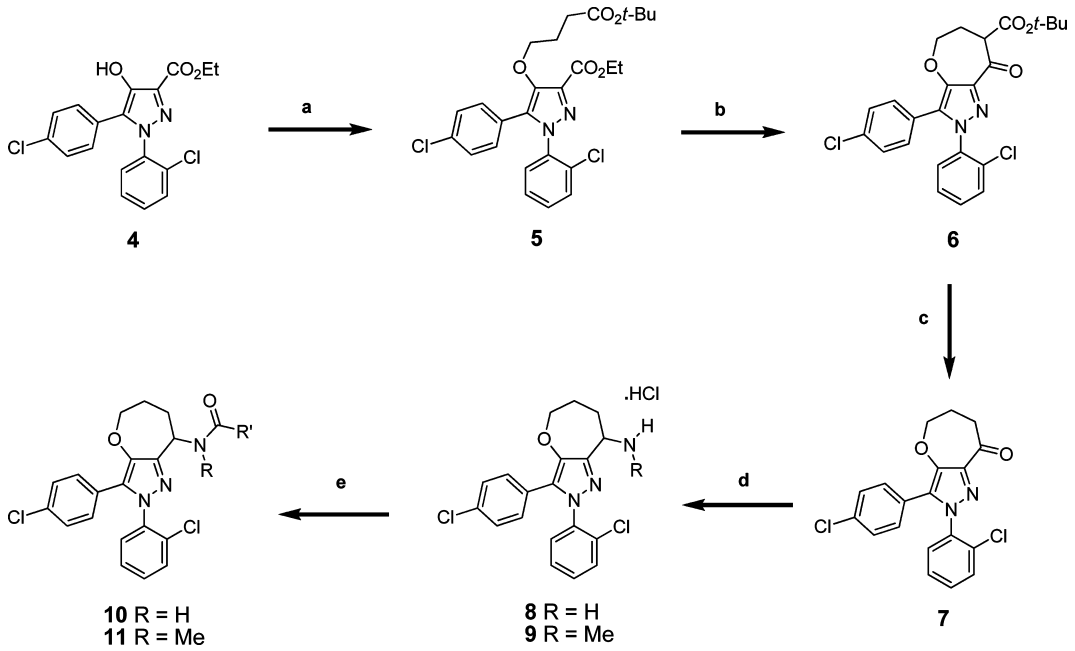
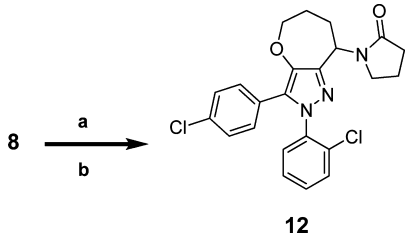
Scheme 1. Syntheses of Acylaminobicyclics 10a−q and 11[a]



[a]Reagents and conditions: (a) *tert*-butyl 4-bromobutanoate, potassium *tert*-butoxide, DMF, 0−25 °C; (b) potassium bis(trimethylsilyl)amide, THF, −78−25 °C; (c) 2:1 CH_2Cl_2/TFA, RT, then 1:1 toluene/*p*-dioxane, reflux; (d) ammonium acetate or methylamine hydrochloride, sodium cyanoborohydride, MeOH/CH_2Cl_2, RT, then 4 N HCl in *p*-dioxane; (e) acid chloride, chloroformate or isocyanate, triethylamine, CH_2Cl_2, RT.

Scheme 2. Syntheses of 12[a]



[a]Reagents and conditions: (a) 4-chlorobutyryl chloride, triethylamine, CH_2Cl_2, RT; (b) KO*t*-Bu, THF, RT.

At the outset of this work, it was unclear what impact the chiral center in this series would have on CB_1 receptor antagonism. Single crystal X-ray structures of the *p*-bromobenzamide derivatives of the enantiomers of **8** confirmed our initial modeling analysis showing the amide substituent would occupy nearly identical space for both isomers. Analysis of the individual enantiomers of **10c** revealed that essentially all the CB_1 receptor inhibitory activity resides in the *R*-enantiomer (**10d**), with it being 250-fold more potent than the *S*-enantiomer (**10e**). The three carbon atoms bridging the oxygen atom and the chiral center of the fused 7-membered ring occupy significant steric space on opposite faces of the bicyclic core for the enantiomers of **10** (Figure 1). It is therefore likely that these bridging atoms are responsible for driving the differential CB_1 receptor affinity observed for the enantiomers of **10**.

To confirm that this series possessed functional CB_1 receptor antagonism *in vivo*, **10d** was screened in two legs of the tetrad assay.[22] A 3 mg/kg, subcutaneous dose of **10d** in mice produced a 72% reversal of the analgesia induced by the cannabinoid agonist CP-55940 in the hot plate model (Figure 2). This dose also fully reversed the hypothermic response induced by CP-55940 in these mice. These effects were comparable to that observed for rimonabant (**1**) at 3 mg/kg. On the basis of these results, **10d** was advanced to a rodent model of food intake inhibition. Following an overnight fast, Sprague−Dawley rats were dosed orally with **10d**, **1**, or vehicle, and food intake was continuously monitored for 2 h post food reintroduction (Figure 3). All three doses (0.3, 1, and 3 mg/kg) of **10d** produced a statistically significant reduction in cumulative food intake relative to the vehicle control at both 0.5 and 2 h. At both time points, a dose of 0.3 mg/kg of **10d** produced an effect comparable to that observed for rimonabant at 3 mg/kg.

Having demonstrated that this bicyclic scaffold displays potent *in vitro* and *in vivo* CB_1 antagonism, our attention turned to evaluating the impact of the introduction of polar functionality into the acylamino substituent of **3**. These modifications, through either direct impact on PSA[12−14] or potential recognition by MDR1,[15,23] could serve to reduce CNS exposure. While single heteroatom incorporations into larger acylamino substituents (e.g., **10f** to **10g**) had a modestly favorable impact on PSA and microsomal clearance, while retaining potent primary pharmacology, these changes did not improve recognition by the MDR1 efflux system. This modification applied to smaller acylamino substituents also did not appear to be a viable approach. For example, **10h** has greatly diminished CB_1 receptor functional activity, and in the case of the ethoxyacetamido derivative **10i**, high microsomal clearance was observed. An alternative approach pursued to minimizing molecular weight and maximizing polarity was replacement of the acylamino functionality of **10d** with a carbamate or urea (**10j−l**). All three of these analogues retained potent CB_1 receptor pharmacology and have potential to serve as starting points for further optimization. As part of a broader profiling of acylamino substituents, cyanocyclopropyl derivative **10m** was found to be a subnanomolar antagonist of the CB_1

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Table 1. In Vitro Pharmacology and Microsomal Stability Data for 1, 2, 8, 9, 10a−q, 11, and 12

	R′	hCB$_1$ K_i (nM)[a]	hCB$_2$ K_i (nM)[a]	hCB1 GTPγ[^{35}S] K_i (nM)[a]	HLM CLint$_{app}$ (mL/min/kg)	MDR1 P_{app} A:B ($\times 10^{-6}$ cm/s)	MDR1 B:A/A:B	MW	PSA
1		1.8	522	1.6	46	N.D.	N.D.	464	50.4
2		1.0	>10,000	0.82	<8	7.1	1.0	452	47.4
8		57	N.D.[b]		21	N.D.	N.D.	374	53.1
9		46	N.D.		54	N.D.	N.D.	388	39.1
10a	methyl	0.75	20,600	0.87	<8	14.1	1.7	416	56.1
10b	ethyl	0.41	16,600	0.11	28	12.1	1.5	430	56.1
10c	*iso*-propyl	0.16	5,400	0.04	50	6.9	2.2	444	56.1
10d	*iso*-propyl (*R-ent*)	0.14	3,290	0.03	25	8.4	1.3	444	56.1
10e	*iso*-propyl (*S-ent*)	5.1	11,000	7.5	42	N.D.	N.D.	444	56.1
10f	cyclohexyl	0.59	953	0.05	>250	N.D.	N.D.	484	56.1
10g	4-tetrahydropyranyl	0.09	15,200	0.07	41	6.8	1.1	486	65.4
10h	methoxymethyl	1.4	15,400	5.6	42	9.1	1.9	446	65.4
10i	ethoxymethyl	0.56	6,540	1.2	206	6.5	2.0	460	65.4
10j	methoxy	0.25	>30,000	0.72	<8	9.1	1.9	432	65.4
10k	*iso*-propoxy	0.26	N.D.	0.12	15	N.D.	N.D.	460	65.4
10l	*N*-ethylamino	0.12	14,700	0.11	34	6.3	2.7	445	68.2
10m	1-cyanocyclopropyl	0.13	21,200	0.08	<8	1.0	1.5	467	79.9
10n	isoxazol-3-yl	1.6	16,900	0.26	<8	6.6	1.5	469	82.2
10o	isoxazol-5-yl	0.55	12,100	0.23	36	3.2	2.1	469	82.2
10p	1,2,5-oxadiazol-3-yl	1.7	>30,000	0.08	<8	3.0	3.5	470	95.1
10q	$MeSO_2CH_2$-	0.54	59,000	0.82	16	2.7	2.9	494	98.7
11	*iso*-propyl	4.5	8,700	4.3	134	N.D.	N.D.	458	47.4
12		1.0	75,600	6.5	149	11.2	1.7	442	47.4

[a]These data were obtained from one to three determinations run in triplicate. [b]Value not determined.

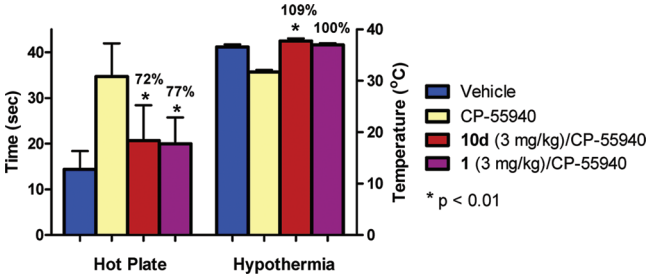

Figure 2. Reversal of CP-55940-induced analgesia and hypothermia in mice by **1** or **10d**.

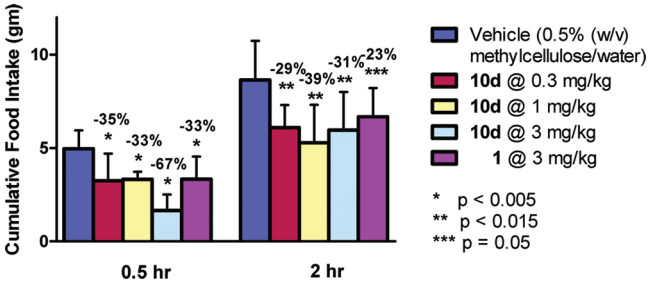

Figure 3. Inhibition of cumulative food intake in rats following an oral dose of **1** or **10d**.

receptor and to exhibit low microsomal clearance and enhanced PSA. Evaluation of the above compounds in the Madin−Darby canine kidney cell line transfected with the MDR1 gene (MDR1-MDCK)[24] suggests that they are unlikely to be substrates for the MDR1 transporter.

Incorporation of small polar heteroaromatics (**10n−p**) resulted in a more promising profile, with PSA values up to 40 units higher than that of **10d**. Regioisomeric isoxazoles **10n** and **10o** retain subnanomolar potency against the CB$_1$ receptor and low predicted microsomal clearances. Oxadiazole **10p**, with a PSA of 95, which is near the upper limit of that observed for CNS drugs,[25] retains excellent CB$_1$ receptor functional antagonism (80 pM) and is predicted to be a low clearance compound on the basis of HLM analysis. Assessment in MDR1-MDCK revealed **10p** to possess a B/A:A/B ratio of 3.5, which is consistent with it being an efflux substrate. This data, along with a low to moderate passive permeability (3×10^{-6} cm/s), is suggestive that the CNS exposure of **10p** would be significantly restricted in humans.[22] CB$_1$ receptor pharmacology was found to tolerate the *β*-ketone sulfone functionality of **10q**, which is in similar PSA space to **10p**. MDR1 mediated efflux (B/A:A/B = 2.9) and moderate permeability (2.7×10^{-6} cm/s) were also observed for **10q**, suggesting the potential for reduced brain exposure.

In summary, the acylamino substituted bicyclic design **3** has been shown to possess potent and selective CB$_1$ antagonism. Resolution of the enantiomeric acylamino derivatives revealed that CB$_1$ receptor binding and antagonism resides mostly in the *R*-isomer. A prototypical member (**10d**) of this series has demonstrated *in vivo* functional antagonism of CB$_1$-mediated behaviors and oral activity in a rodent model of feeding. Toward a goal of peripheral-restriction, structure−activity studies revealed that introduction of polar functionality into the acylamino substituent is tolerated. The profiles observed for both **10p** and **10q** suggest that they may hold potential as peripherally targeted agents or serve as starting points for further optimization toward this goal.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details for the syntheses and the spectroscopic and pharmacological characterizations of the compounds in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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