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Synthesis and activity of 4,5-diarylimidazoles as human CB1 receptor inverse agonists

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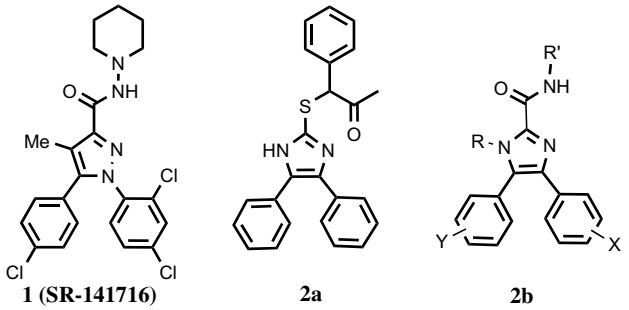
Abstract—Structure–activity relationship studies directed toward the optimization of 4,5-diarylimidazole-2-carboxamide analogs as human CB1 receptor inverse agonists resulted in the discovery of the two amide derivatives **24a** and **b** (hCB1 IC_{50} = 6.1 and 4.0 nM) which also demonstrated efficacy in overnight feeding studies in the rat for reduction in both food intake and overall body weight.

1. Introduction

Excess energy intake leading to obesity has emerged as a major health threat in industrialized nations, increasing the chances for obese individuals of developing type 2 diabetes, hypertension, heart disease, stroke, cancer, and arthritis.[1] With the percentage of the population considered to be obese increasing annually, scientific advancements in the understanding of obesity have provided opportunities to seek therapeutic solutions for addressing this issue. The cannabinoid receptor type 1 (CB1) and its endogenous ligands, the endocannabinoids,[2] have been found to be involved in the control of weight and energy balance via a dual mechanism of food intake modification and the regulation of energy expenditure.[3] SR-141716 (Fig. 1, Rimonabant, **1**) was reported to have potent human CB1 receptor affinity[4] and was later demonstrated with feeding studies in the rat to afford a dose-dependent reduction in both food intake and body weight.[5,6] CB1 receptors are coupled to the $G_{i/o}$ class of G-proteins, which inhibit adenylate cyclase activity.[7] CB1 agonists, such as CP-55940,[8] decrease forskolin-induced cAMP accumulation in tissue from rodent and mammalian brain in a concentration-dependent manner. However, **1** produced a dose-dependent increase in forskolin-induced cAMP,[9] thus suggesting that inverse agonism of the CB1 receptor was responsible for the observed effects.[10]



1 (SR-141716) hCB1 IC_{50} = 6 nM
2a hCB1 IC_{50} = 7000 nM
2b

Figure 1. Structure and binding affinity of SR-141176 and the Merck lead structure. For the imidazole structure **2b**, see Tables 1 and 2.

Our search for novel anti-obesity agents based on the endocannabinoid hypothesis was initiated with a high throughput screening of the Merck sample collection

Keywords: Imidazole; Obesity; CB1 inverse agonist; Cannabinoid.
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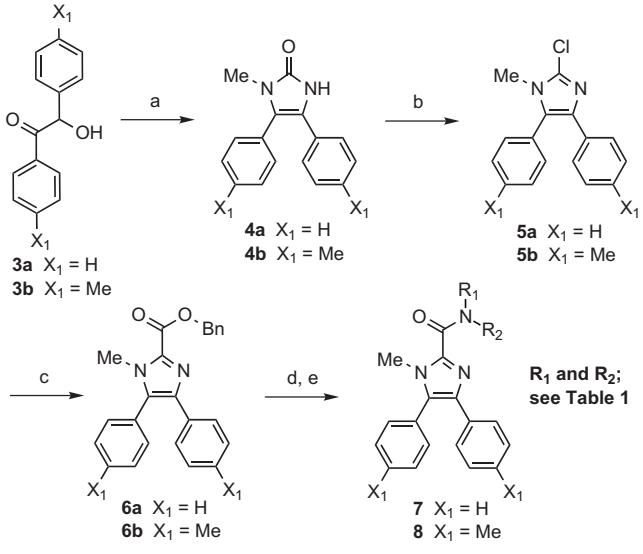
to identify possible human CB1 (hCB1) receptor antagonist leads. The 4,5-diarylimidazole **2a** (Fig. 1), having an analogous, but novel, scaffold from **1**, was found to have moderate affinity for the hCB1 receptor (hCB1 IC_{50} = 7000 nM) and inspired the investigation of the corresponding imidazole structure **2b**. Since modeling studies reported for **1** implied a critical role for the N-2 pyrazole nitrogen,[11] it was hoped that the more basic imidazole nitrogen might enhance this interaction. The benzyl moiety was thought to take the place of the *N*-piperidine amide. The moderate affinity of **2a** was attributed to the lack of an amide interaction and no substitution on the phenyls. As reported herein, our initial efforts investigated various phenyl substitutions in conjunction with the introduction of the requisite C-2 amide moiety. The utilization of alternative core heterocycles, such as a 4,5-diphenylthiazole, 1,5-diphenyltriazole, and an isomeric 1,2-diphenylimidazole, was very recently reported.[12] In addition, the incorporation of a 5,6-diphenylpyridine with a six-membered core heterocyclic ring has also been reported from these laboratories[13] and by researchers at Sanofi-Synthelabo.[14]

2. Chemistry[15]

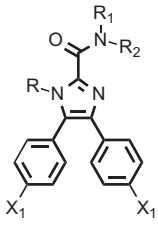
Preparation of the 4,5-bis-(phenyl) and (4-methylphenyl)imidazole derivatives **7** and **8** (Scheme 1) started with the thermal cyclization of benzoin (**3a**) or 4,4′-dimethylbenzoin (**3b**) with *N*-methylurea in ethylene glycol at 180 °C to give the *N*-methyl imidazolones **4a** and **b**.[16,17] Treatment with phosphorous oxychloride provided the 2-chloroimidazoles **5a**,**b**, which were converted to the benzyl esters **6a**,**b** via *n*-butyllithium exchange and quenching of the C-2 anions with benzyl chloroformate. Catalytic hydrogenation afforded the crude acids which were directly converted to the desired amide products **7a**–**c** and **8a**–**c** (see Table 1) with Py-BOP and the requisite amines. Variable amounts of the C-2 unsubstituted imidazoles were observed during purification of the amides due to competing decarboxylation of the acids under the reaction conditions.



Scheme 1. Reactants and conditions: (a) *N*-Methylurea, ethylene glycol, 180 °C, 1.5 h (40–60%, from EtOH); (b) $POCl_3$, 100 °C, 16 h (70–85%); (c) *n*-BuLi, THF, −70 to −20 °C, 1.5 h, then added to BnOCOCl, THF, −20 °C to rt (25–42%); (d) H_2 (50 p.s.i), 10% Pd/C, MeOH (quant.); (e) HNR_1R_2, Py-BOP, DCM, rt (35–80%).

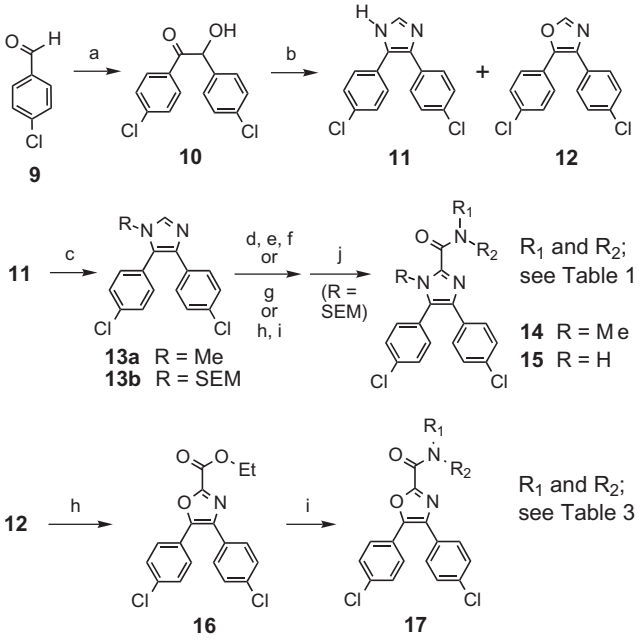
An alternative synthesis (Scheme 2) of the corresponding 4,5-bis-(4-chlorophenyl)imidazole derivatives **14a**–**f** was developed to avoid anticipated complications with the lithium exchange reaction and allowed for the preparation of the N-1 unsubstituted derivatives **15a**,**b** (see Table 1). Benzoin condensation of 4-chlorobenzaldehyde (**9**) afforded 4,4′-dichlorobenzoin (**10**). Cyclization in formamide and paraformaldehyde afforded the N-1 and C-2 unsubstituted imidazole **11** as well as the minor oxazole by-product **12**.[18] Alkylation of **11** with methyl iodide or SEM chloride in DMF using sodium hydride as base gave the *N*-Me or *N*-SEM-protected intermediates **13a**,**b**. Selective deprotonation with *n*-butyllithium at −70 °C again afforded the C-2 anions which could be quenched with benzyl chloroformate as in Scheme 1 or, when available, with the appropriate isocyanates to afford the desired amide products **14b**,**e**,**f** directly. Hydrolysis of the intermediate benzyl ester and conversion to amides as above and/or final removal of the SEM protecting group with TBAF generated the *N*-methyl or *N*–H imidazole derivatives **14a**,**c**,**d** and **15a**,**b**. Alternatively, again due to variable amounts of decarboxylation of the intermediate C-2 acids, reaction with ethyl chloroformate and direct amide formation was used for the

Table 1. Structures and hCB1 affinities for imidazole derivatives **7**,**8**,**14**,**15**



Compd #	R	X_1	$-NR_1R_2$	hCB1 IC_{50} (nM)[a]	(SD)[b]
1				6.2	
7a	Me	H	−NH(*N*-piperidinyl)	1900	(400)
7b	Me	H	−NH(cyclohexyl)	1800	(60)
7c	Me	H	−(piperidinyl)	19,000	(800)
8a	Me	Me	−NH(*N*-piperidinyl)	460	(340)[c]
8b	Me	Me	−NH(cyclohexyl)	900	(180)
8c	Me	Me	−(piperidinyl)	3400	(1700)
14a	Me	Cl	−NH(*N*-piperidinyl)	260	(60)
14b	Me	Cl	−NH(cyclohexyl)	450	(100)
14c	Me	Cl	−(piperidinyl)	1100	(400)
14d	Me	Cl	−NH(*N*-morpholinyl)	3100	(700)
14e	Me	Cl	−NH(*n*-hexyl)	540	(140)
14f	Me	Cl	−NH(*t*-butyl)	900	(140)
15a	H	Cl	−NH(*N*-piperidinyl)	6000	(400)
15b	H	Cl	−NH(cyclohexyl)	1500	(40)

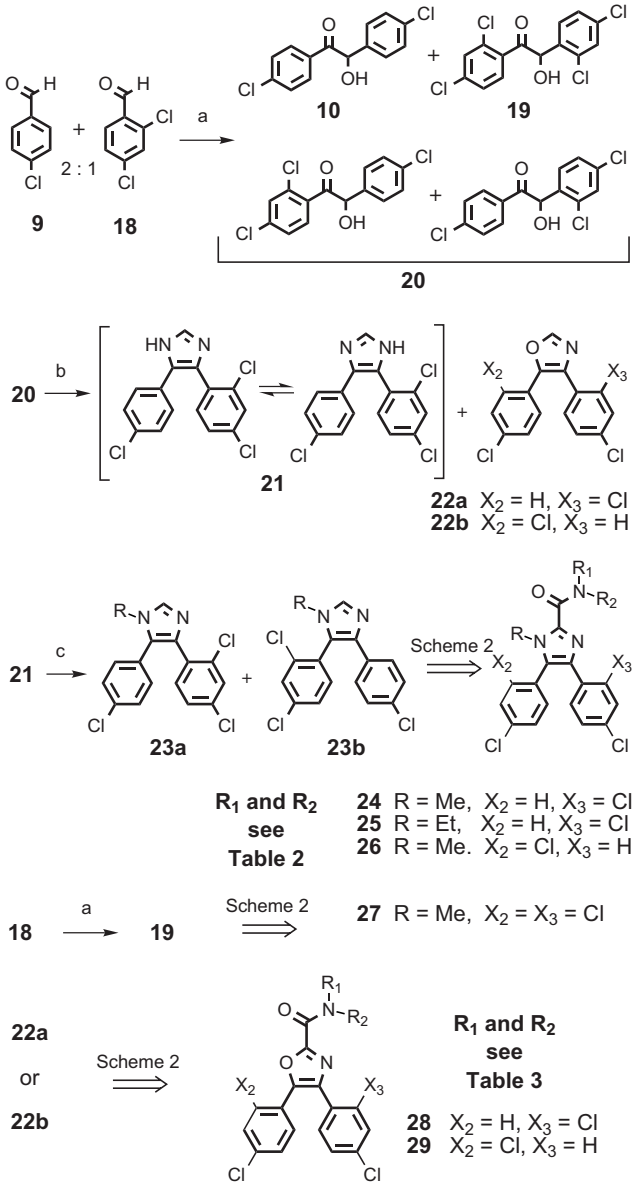
[a] See Ref. 21 for assay details.
[b] $n = 2$, except as noted.
[c] $n = 3$.



Scheme 2. Reactants and conditions: (a) NaCN, H_2O:EtOH/3:1, 100 °C, 4 h; (b) paraformaldehyde, formamide, 200–220 °C (65%); (c) MeI or SEM-Cl, NaH, DMF, rt (80–96%); (d) *n*-BuLi, THF, −70 °C; then added to BnOCOCl, THF, −70 °C to rt (32–56%); (e) 5 N NaOH, MeOH, rt, 16 h (quant.); (f) HNR_1R_2, Py-BOP, DCM, rt (14–50%); (g) *n*-BuLi, THF, −70 °C; then added to R_1–NCO, −70 °C to rt (24–77%); (h) *n*-BuLi, THF, −70 °C; then added to EtOCOCl, THF, −70 °C to rt (65–85%); (i) HNR_1R_2, dioxane, 100 °C (30–80%); (j) 1 N TBAF, THF, rt (15–60%).

conversion of the oxazole **12** to the amides **17a**,**b** (see Table 3) via the ethyl ester **16**.

While the structure–activity relationships (SAR) conducted thus far in the above symmetrical series indicated a 2- to 10-fold improvement in hCB1 binding potency with the 4-methyl or 4-chloro substitution on each phenyl ring, the binding was still weak compared to **1**. Optimization of the 4-phenyl with 2,4-dichloro substitution as in **1** proved to be critical in establishing good receptor affinity.[12,13b] The preparation of the required unsymmetrical trichlorobenzoins and conversion to the two possible trichloro final products is shown in Scheme 3. In addition, the oxazole and tetrachloro derivatives were also prepared. Reaction of a 2:1 mixture of 4-chlorobenzaldehyde (**9**) and 2,4-dichlorobenzaldehyde (**18**) in the benzoin condensation afforded a separable (flash silica gel chromatography, 10% DCM in 10–25% ethyl acetate/hexanes) mixture of dichloro **10** (lowest R_f), the two trichloro isomers **20** (middle R_f), and tetrachloro **19** (trace, highest R_f) products. The mixture of trichlorobenzoin isomers was then cyclized as above to the imidazole **21** (two indistinguishable tautomers) and the two separable oxazole by-products **22a,b**. Alkylation of **21** as above with either methyl or ethyl iodide gave the separable N-1 alkyl intermediates **23a**,**b**. The final product amides **24**–**26** were then obtained by direct reaction of the C-2 anions with the requisite isocyanate or via transamidation of the ethyl ester intermediates. The two trichloro isomers were assigned based on NOE effects



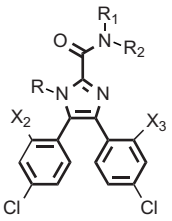
Scheme 3. Reactants and conditions: (a) NaCN, H_2O:EtOH/3:1, 100 °C, 4 h; (b) paraformaldehyde, formamide, 200–220 °C; (c) MeI or EtI, NaH, DMF, rt (80–90%).

observed between the *N*-Me and the 4-phenyl *ortho* hydrogens.[19] The tetrachlorobenzoin **19**, prepared in an independent benzoin condensation of **18** alone, was carried forward to the amide products **27a**,**b** (Table 2). Similarly, the oxazoles **22a** (higher R_f isomer) and **22b** (lower R_f isomer) were converted to amide products **28** and **29** (Table 3), respectively. The structural assignments for **28** and **29** were determined by HMBC NMR experiments.[19]

3. Results and discussion

Binding affinities on recombinant human CB1 receptors expressed in Chinese Hamster Ovary (CHO) cells for compounds in Tables 1–3 were determined with a standard binding assay using [^{3}H]CP-55940 as the

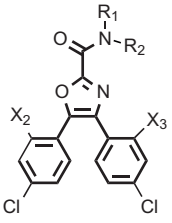
Table 2. Structures and hCB1 affinities for imidazole derivatives **24–27**



Compd #	R	X_2	X_3	$-NR_1R_2$	hCB1 IC_{50} (nM)[a]	(SD)[b]
24a	Me	H	Cl	−NH(*N*-piperidinyl)	6.1	(2.8)[c]
24b	Me	H	Cl	−NH(cyclohexyl)	4.0	(2.0)[c]
24d	Me	H	Cl	−NH(*N*-morpholinyl)	170	(55)
24g	Me	H	Cl	−NH(cyclopentyl)	17	(3)
24h	Me	H	Cl	−NH(cycloheptyl)	8.0	(1.7)
24i	Me	H	Cl	−NMe(cyclohexyl)	70	(40)
24j	Me	H	Cl	$-NH(C_6H_5)$	60	(3)
25b	Et	H	Cl	−NH(cyclohexyl)	4.1	(2.6)[d]
26a	Me	Cl	H	−NH(*N*-piperidinyl)	190	(80)
26b	Me	Cl	H	−NH(cyclohexyl)	46	(14)
27a	Me	Cl	Cl	−NH(*N*-piperidinyl)	16	(8)
27b	Me	Cl	Cl	−NH(cyclohexyl)	5.2	(0.4)[d]

[a] See Ref. 21 for assay details.
[b] $n = 2$, except as noted.
[c] $n = 8$.
[d] $n = 4$.

Table 3. Structures and hCB1 affinities for oxazole derivatives



Compd #	X_2	X_3	$-NR_1R_2$	hCB1 IC_{50} (nM)[a]	(SD)[b]
17a	H	H	−NH(*N*-piperidinyl)	2200	(700)
17b	H	H	−NH(cyclohexyl)	500	(300)
28a	H	Cl	−NH(*N*-piperidinyl)	260	(50)
28b	H	Cl	−NH(cyclohexyl)	80	(3)
29a	Cl	H	−NH(*N*-piperidinyl)	470	(50)
29b	Cl	H	−NH(cyclohexyl)	1000	(500)
30a	Cl	Cl	−NH(*N*-piperidinyl)	200	(30)
30b	Cl	Cl	−NH(cyclohexyl)	70	(50)

[a] See Ref. 21 for assay details.
[b] $n = 2$.

radio-ligand.[20,21] Interesting compounds were further evaluated in a functional assay also using recombinant human CB1 receptor expressed in CHO cells in the presence of forskolin.[21] Binding affinities were also routinely measured for the CB2 receptor expressed in CHO cells and using [^{3}H]WIN-55,212-2 as radioligand.[21,22] While the initial results with the unsubstituted 4,5-phenyl derivatives **7a**,**b** were disappointing (IC_{50} = 1900 and 1800 nM), the 2- to 10-fold improvement in the binding activity for the 4,5-bis-(4-methylphenyl and 4-chlorophenyl) compounds **8a-b** (IC_{50} = 460 and 900 nM) and **14a**,**b** (IC_{50} = 260 and 400 nM) seemed to validate the hypothesis that the imidazole could replace the pyrazole of **1** and that the trichloro derivative analogous to **1** should be made. In addition, the cyclohexylamine amide derivatives **8b** and **14b** were within a factor of 2 in potency to the *N*-piperidines, indicating that there might be some SAR potential for other amides with the imidazole scaffold (see **14d–f** and below). Also encouraging was the finding that the hCB1 functional assay indicated that both **14a** (up to −150% response relative to the agonist CP-55940 with an $EC_{50} = 100 \pm 40$ nM, $n = 2$) and **14b** (average −75% relative response with an $EC_{50} = 500 \pm 200$ nM, $n = 2$) were interacting with the hCB1 receptor as inverse agonists as desired. Importantly, **14a** was found to be $\geqslant$10-fold selective for hCB1 over hCB2 (IC_{50} > 2000 nM (40%)).[22] The diminished hCB1 affinity for the N-1 unsubstituted compounds **15a** and **15b** (IC_{50} = 6000 and 1500 nM) was surprising and indicated the importance of the methyl, possibly in order to optimally direct the neighboring amide moiety for binding to the hCB1 receptor or to remove an unfavorable polar moiety from a hydrophilic receptor area. The secondary amides **7c**, **8c** and **14c** (IC_{50} = 19,000, 4500 and 1100 nM) were also comparatively inactive, while the benzyl ester **6b** (see Scheme 1; IC_{50} = 850 nM) was within 2-fold of the amide **8a**, thus indicating that the amide *N*–H was not critical for binding affinity.

The tetrachloro *N*-piperidine derivative **27a** displayed a significant 15-fold improvement in binding affinity compared to the dichloro **14a** (IC_{50} = 16 vs 250 nM) while the cyclohexyl analog **27b** was even better with a 90-fold enhancement from **14b** (IC_{50} = 5.2 vs 450 nM). However, it was the unsymmetrical trichloro derivatives **24a** and **24b**, with substitution analogous to **1**, which appeared to be optimal (IC_{50} = 6.1 and 4.0 nM). The binding affinities for the isomeric trichloro compounds **26a**,**b** were intermediate between the dichloro and tetrachloro results. The hCB1 functional assay again indicated that both **24a** (average −120% relative response with an $EC_{50} = 5 \pm 2$ nM ($n = 5$)) and **24b** (average −110% relative response with an $EC_{50} = 18 \pm 4$ nM ($n = 4$)) were interacting with the hCB1 receptor as inverse agonists. These compounds were also found to be 60-fold selective for hCB1 over hCB2 (hCB2 IC_{50} = 350 and 250 nM, respectively), in the binding assays.[22] Based on the results of **24a**,**b**, the cyclopentyl (**24g**, IC_{50} = 17 nM) and cycloheptyl (**24h**, IC_{50} = 8 nM), *N*-methyl-*N*-cyclohexyl (**24i**, IC_{50} = 75 nM), and aniline (**24j**, IC_{50} = 60 nM) analogs were prepared, but none appeared more potent and the hope of an expanded SAR with the imidazole scaffold was not realized. The surprisingly poor results for the *N*-morpholines **14d** and **24d** (IC_{50} = 3100 and 175 nM) indicated that polarity in the amide alkyl region was not well tolerated. Finally, the N-1 ethyl analog **25b** was found to be comparable to **24b** (IC_{50} = 4.1 vs 4.0 nM), thus hinting at the possible use of this site for further modification. These results were in good agreement with the amide SARs reported in the literature for the pyrazoles and other core heterocycles.[12]

The binding affinity for the dichloro oxazole analogs **17a**,**b** (Table 3, IC_{50} = 2200 and 500 nM) appeared to mimic the poorer affinity of the imidazole *N*–H compounds. The same decrease in affinity was seen for the two trichloro isomers **28a**,**b** (IC_{50} = 260 and 80 nM) compared to **24a**,**b**. While the tetrachloro compounds **30a**,**b** (IC_{50} = 200 and 70 nM) were about equivalent to **28a**,**b**, the overall affinity for these oxazoles was still only moderate compared to the imidazoles. Thus, the oxazoles were not investigated further.

As noted above, the hCB2 binding affinities were also routinely assessed.[22] Fortunately, in general the hCB2 SAR was not as sensitive to the substitution pattern of the phenyls and, thus, greater selectivity was realized as the hCB1 affinity was enhanced. Initially, all the compounds of Table 1 were $\geqslant$2000 nM. While the hCB2 affinity was also seen to be enhanced with the additional 2-chlorophenyl substitution, the actual hCB1 to hCB2 ratios were improved. Interestingly, the hCB2 SAR appeared to be more sensitive to the N-3 substitution (hCB2 IC_{50} = 22% at 2000, 300, and 165 for **15b**, **24b** and **25b**, respectively).

4. In vivo studies

Based on their favorable hCB1 binding and functional characteristics, **24a** and **24b** were selected for further in vivo evaluation (Table 4). Preliminary pharmacokinetic (PK) studies[23] (1 mg/kg, iv, 2 mg/kg po) for **24a** indicated good iv properties (AUC_{nom} = 1.32 μM h kg/mg; Cl_p = 27.5 mL/min/kg; Vd_{ss} = 3.7 L/kg; $t_{1/2}$ = 2.4 h) and oral absorption (F = 50%), as well as rapid brain penetration and a high brain-to-plasma ratio (B/P ratio = 2.99–3.40 between 0.25 and 4 h).[24] In a food intake and body weight loss study using diet-induced obese rats fed ad libitum over 18 h (Fig. 2), **24a** showed a dose-dependent, immediate and prolonged reduction in food intake as reported for **1**[6] (**24a** @ 1, 3, and 10 mg/kg po = −13.4%, −30.6%, −67.5% relative to vehicle treated animals). Also, at 18 h post-dosing, the 10 mg/kg dose afforded a cumulative, statistically-significant ($p < 0.0001$), dose-dependent weight loss of 13 g compared to a 6 g gain for vehicle treated animals. These results were in agreement with good systemic exposure, which produced the weight loss component of CB1 inverse agonism, and favorable CNS exposure, as evident from the B/P ratio experiment and the observed immediate food intake reduction.[6] A feeding study with the slightly more potent cyclohexyl amide **24b** afforded a similar, dose-dependent reduction in food intake (**24b** @ 1, 3, and 10 mg/kg po = −25%, −39%, −53%), and a significant (p = 0.013) net weight loss of 2 g versus a 10 g gain for vehicle treated animals. The results with **24b** were consistent with a slightly poorer PK profile (AUC_{nom} = 1.82 μM h kg/mg; Cl_p = 19.8 mL/min/kg; Vd_{ss} = 1.9 L/kg; $t_{1/2}$ = 1.9 h), lower oral absorption (F = 30%), and slower brain penetration (B/P ratio = 0.84–2.61 between 0.25 and 4 h).

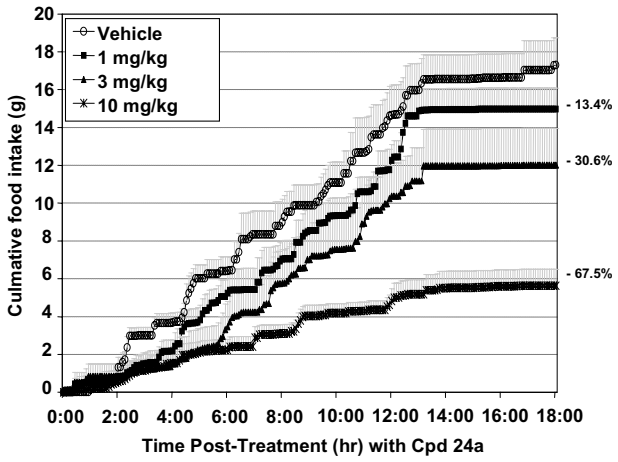


Figure 2. Acute treatment of male diet-induced obese rats (n = 4 at each dose) with CB1 inverse agonist **24a** reduced cumulative dark cycle food intake. Vehicle (10% Tween 80 in water) or **24a** was administered to rats 1 h prior to the onset of the dark cycle. Percent reduction in cumulative food intake relative to vehicle control is shown.

Table 4. Pharmacokinetic parameters, B/P ratios, and rat feeding study results for **24a** and **24b**

Compd #		**24a**	**24b**
Rat PK[a]			
	AUC_{nom} (μM h kg/mg)	1.3 ± 0.2	1.8
	Cl_p (mL/min/kg)	28 ± 3	20
	Vd_{ss} (L/kg)	3.7 ± 0.1	1.9
	$t_{1/2}$ (h)	2.4 ± 0.6	1.9
	%F	50 ± 7	30 ± 11
B/P ratio[b]			
	@ 0.25 h	3.0 ± 0.6	0.8 ± 0.4
	@ 1.0 h	3.6 ± 1.0	2.1 ± 0.6
	@ 2.0 h	2.9 ± 0.2	1.3 ± 0.1
	@ 4.0 h	3.4 ± 1.0	2.6 ± 0.4
Feeding study[c]			
Food intake	Vehicle	17 g/—	20 g/—
	@ 1 mg/kg	15 g/−13.4%	15 g/−25%
	@ 3 mg/kg	12 g/−30.6%	12 g/−39%
	@ 10 mg/kg	5.4 g/−67.5%	9.4 g/−53%
Weight Δ	Vehicle	6 g	10 g
	@ 1 mg/kg	2 g	4 g
	@ 3 mg/kg	−1 g	0
	@ 10 mg/kg	−13 g	−2 g

[a] See Ref. 23 for details.
[b] See Ref. 24 for details.
[c] See Ref. 6 and Figure 2 for details.

5. Conclusions

Herein, we have described the synthesis and hCB1 activities for a series of 4,5-diphenyl-1-methylimidazole-2-carboxamides related to the pyrazole SR-141716 **(1)**. The phenyl substitution SAR was found to be the same as **1**, namely, the 4-(2,4-dichlorophenyl)-5-(4-chlorophenyl) analogs **24a** and **24b** appeared to be optimal, although the tetrachloro derivatives **27a** and **27b** were only slightly less potent. However, the amide SAR was more interesting in that both the *N*-piperidinyl and cyclohexyl carboxamides were found to be potent hCB1 inverse agonists. Both of these compounds were

orally bioavailable with good pharmacokinetics. These compounds were also shown to be efficacious in obese rat feeding studies, showing reductions in both food intake and overall body weight. In addition, the *N*-ethyl derivative **25b** was shown to be equally potent. These findings might allow some flexibility in the selection of derivatives in the future with enhanced PK and CNS exposure profiles with improved physical and/or off-target properties. Further SAR studies of both the C-2 amide and N-1 alkyl group will be published elsewhere in the near future.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2004.12.078.

References and notes

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24. Male Sprague-Dawley rats were dosed at 1.0 mg/kg iv ($n = 3$ at each time point) via the tail vein. Compounds were formulated at 1 mg/mL in TWEEN 80:EtOH:water (10:23:67). Plasma and brain concentrations were determined by LC–MS/MS.