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Diaryl piperidines as CB_1 receptor antagonists

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ABSTRACT

The syntheses and SAR investigations of novel CB_1 receptor antagonists based on a 1,2-diaryl piperidine core have been described. Optimization of this core afforded a compound with robust in vivo potency by reducing food intake in a mouse DIO model.

To date, two receptors in the cannabinoid system have been cloned, CB_1[1] and CB_2.[2] Both of these receptors belong to the GPCR superfamily. The CB_1 receptor is expressed in the CNS and several peripheral tissues while the CB_2 receptor is expressed in the immune system, gastrointestinal system and to a lesser extent in the brain. Antagonists or inverse agonists of the CB_1 receptor have been shown to reduce food intake in both animals[3] and in humans[4] leading to a possible treatment for obesity. Rimonabant (**1**, Fig. 1),[5] a potent and selective CB_1 inverse agonist, has been shown in clinical studies to reduce body weight and improve cardiovascular biomarkers such as plasma lipid levels.[4] Rimonabant was approved as a treatment for obesity in the European Union in 2006; however, it was removed from the market in 2008 due to psychiatric side-effects. Taranabant (**2**),[6] which has an acyclic amide core, and otenabant (**3**)[7] were both in phase III clinical trials when their respective developments were discontinued. In spite of these results, there remains a significant motivation to identify novel CB_1 receptor antagonists as it is unclear whether the observed side-effects are solely mechanism of action based.

Most of the CB_1 antagonists or inverse agonists reported in the literature are based on a heteroaromatic core substituted with two aromatic groups.[8] Examples of CB_1 modulators based on non-aromatic cores include taranabant, a series of diarylpyrazolines[9] and recent reports of inverse antagonists based on a piperazine core[10] and antagonists with a bicyclic lactam core.[11]

Molecular modeling of rimonabant within the CB_1 receptor has provided significant information towards the understanding of the inverse agonist-receptor interactions. The two aromatic substituents of rimonabant have been proposed to play an important role with the interaction of an aromatic microdomain in the CB_1 receptor.[12] It has also been reported that the carbonyl of rimonabant acts as a hydrogen bond acceptor to the inactive state of the CB_1 receptor leading to the observed inverse agonism.[13] An in-house pharmacophore model derived from eight reported CB_1 antagonists or inverse agonists used these key domains and an additional hydrophobic pocket to screen for CB_1 antagonists.[14]

In-house screening of our compound inventory towards the identification of CB_1 antagonists indicated that compounds with a fully saturated core could be viable leads for this program.[15] Initial efforts focused on the preparation of a saturated cyclic core substituted with two aryl groups. Based on literature precedent for the preparation of 1,6-diarylpiperidin-2-ones[16] that were amenable to further elaboration at the 3-position, a piperidin-2-one core structure was investigated (Fig. 2).

Initial SAR investigations were focused on optimal relative stereochemistry of the core along with the chlorination pattern on the two aromatic substituents. Friedel–Crafts acylation of 4-chlorobenzene or 2,4-dichlorobenzene afforded the necessary ketone (Scheme 1). A two step reductive amination using 4-chloroaniline

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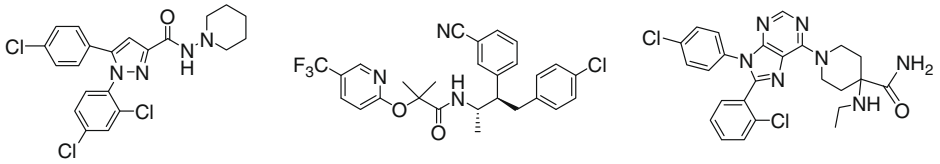


Figure 1.

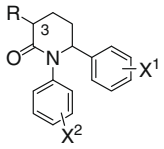


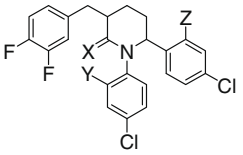
Figure 2.

was followed by hydrolysis of the ester and subsequent lactam formation to afford piperidinones **6a** and **6b**. Benzylation at the 3-position of the piperidin-2-ones provided both *cis* and *trans* diastereomers. Reduction of the piperidinones afforded piperidines **8a–c**. Compound **9** with a 2,4-dichlorophenyl substituent on the piperidine nitrogen (pictured in Table 1) was prepared via aromatic chlorination of piperidine **8a** using sulfuryl chloride.

As summarized in Table 1, targets with the piperidine core had improved affinity for the CB_1 receptor[17] compared to their corresponding piperidinones. For example piperidine **8a** had a sixfold higher affinity for the CB_1 receptor compared to the piperidinone **7a**. This increased affinity may be due to an improved orientation of the piperidine core substituents versus those substituents on the piperidinone core. With respect to the relative stereochemistry of these analogs, the *trans* piperidine **8a** exhibited at least a 22-fold higher affinity compared to the *cis* stereoisomer **8b**.

To gain further understanding of the importance of stereochemistry in this series, stereoisomers **8a** and **8b** were mapped to the previously mentioned pharmacophore model.[14] Figure 3 shows the overlay of the (*R*,*R*)-enantiomer of **8a** and rimonabant to the CB_1 model. The two chlorophenyl rings matched the two aromatic features, while the chlorine atom of the *N*-phenyl substituent and the difluorophenyl group each matched one hydrophobic feature. The hydrogen bond acceptor feature was absent in compounds **8a** and **8b**. Both enantiomers of **8a** (*trans* configuration) matched the pharmacophore quite well with the best mapped conformation having a conformational energy of 0.7 kcal/mol above that of the minimum energy conformation. The three phenyl rings were nearly co-planar in this mapped conformation. Overall, the piperidine core provided a nice scaffold for the crucial functional groups to reach their desired 3D locations. Unlike the *trans* configuration,

Table 1
Binding affinities of piperidine and piperidinone analogs



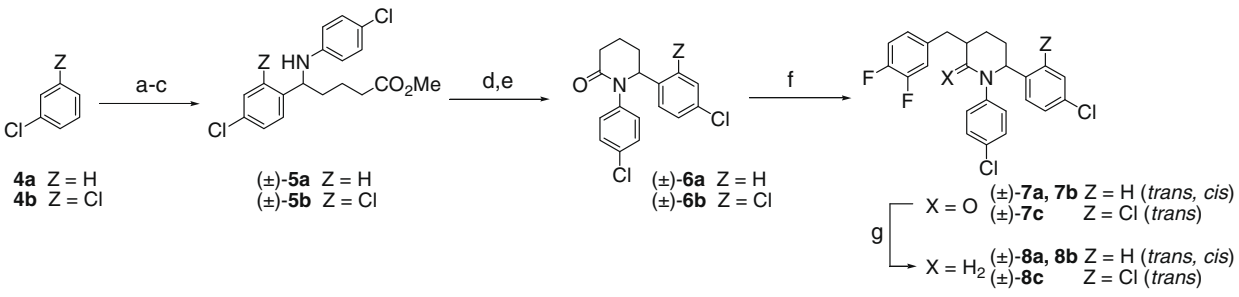
7a-7c, 8a-8c, 9

Compound	X	Y	Z	Relative stereochemistry	hCB_1 K_i (nM)	hCB_2 K_i (nM)
1	—	—	—	—	2.4	560
7a	O	H	H	*trans*	444	574
7b	O	H	H	*cis*	714	>1778
8a	H_2	H	H	*trans*	72	>1765
8b	H_2	H	H	*cis*	>1636	>1846
7c	O	H	Cl	*trans*	109	>1678
8c	H_2	H	Cl	*trans*	15	>1846
9	H_2	Cl	H	*trans*	467	>1846

in order to match the pharmacophore model both enantiomers of the *cis* configuration (**8b**) needed to adopt high energy conformations with the piperidine ring in a twist form. The best mapped conformation of the *cis* substituted piperidine had a conformational energy of 3.3 kcal/mol above the energy minimum. The extra conformational energy penalty in **8b** may account for the reduction in affinity for the CB_1 receptor.

Previously it has been reported[18] that 2,4-dichloro substitution of one of the phenyl substituents provided up to a 10-fold improved affinity compared to the corresponding 4-chloro phenyl analog. Compound **8c** with the carbon linked 2,4-dichlorophenyl substituent possessed sixfold improved binding affinity compared to analog **8a**. Dichloro substitution of the nitrogen linked phenyl ring was detrimental to the binding affinity of compound **9** as the affinity decreased fivefold compared to **8a**. Further SAR investigations focused on the substitution at the 5-position of the optimized *trans* piperidine core corresponding to analog **8c**.

Hydroxymethylation of piperidinone **6b** was accomplished via a two step protocol (Scheme 2). Alkylation alpha to the carbonyl



Scheme 1. Reagents and conditions: (a) Methyl 5-chloro-5-oxovalerate, $AlCl_3$, 100 °C, 32% (Z = Cl) or glutaric anhydride, $AlCl_3$, 47%; MeOH, H_2SO_4, reflux, 85% (Z = H); (b) 4-chloroaniline, $TsOH{\cdot}H_2O$, Dean–Stark, reflux; (c) $NaBH_4$, MeOH, −30 °C; (d) 2 M LiOH (aq), MeOH; (e) $SOCl_2$, pyridine, toluene, 52% Z = H (four steps), 43% Z = Cl (four steps); (f) LDA or LHMDS; 3,4-difluorobenzyl bromide, 11–39%; (g) $BH_3{\cdot}$THF complex, THF reflux, 61%.

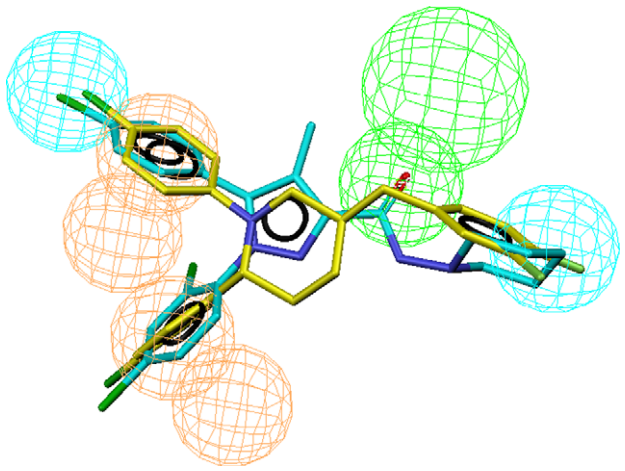


Figure 3. Overlay of the (*R*,*R*)-enantiomer of **8a** and rimonabant to the CB_1 pharmacophore model. The pharmacophore features are represented by meshed spheres. Aromatic ring features are represented by pairs of solid brown spheres; hydrophobic features by cyan spheres; hydrogen bond acceptor by a pair of green spheres. Nitrogen atoms are colored as dark blue, oxygen atoms are red, and the halogen atoms are green. Carbon atoms of rimonabant are colored light blue, and those of **8a** are colored yellow.

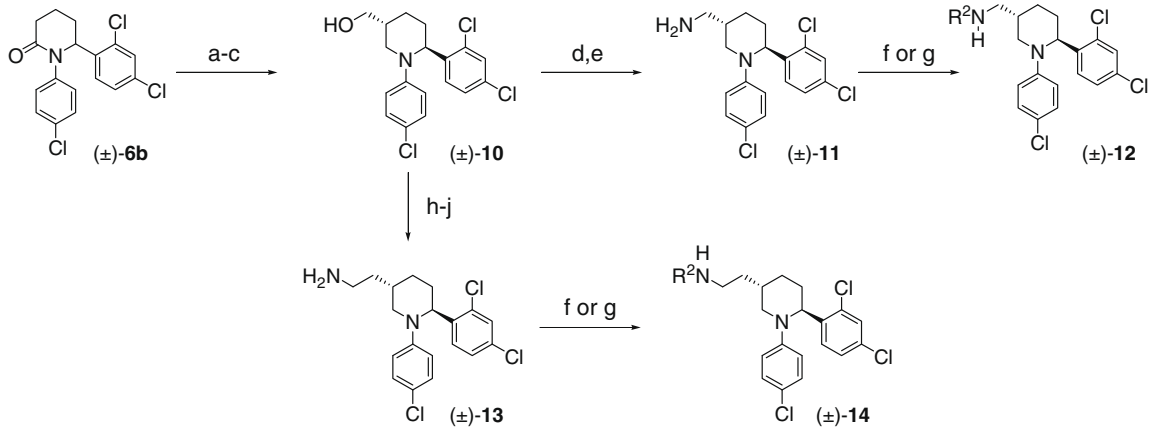
with benzyloxymethyl chloride afforded a separable 10:1 mixture of *trans*:*cis* isomers. Cleavage of the benzyl group with boron tribromide followed by reduction of the carbonyl provided alcohol **10**. This alcohol provided a core with synthetic versatility that was used to prepare several classes of analogs. Conversion to the amine **11** was accomplished via azide introduction under Mitsunobu conditions followed by a Staudinger reduction of the resultant azide. The amine was then substituted to afford a series of sulfonamides and amides. Homologation of the linker proceeded through the conversion of alcohol **10** to the nitrile. Reduction of the nitrile afforded the ethylene linked amine **13** which was further elaborated to provide analogs to investigate the importance of this linker.

In general, for the methylene linked analogs **12a**–**12f**, the larger substituents on the amine in both the amide and sulfonamide series conferred higher affinities for the CB_1 receptor (Table 2). For example, the naphthyl sulfonamide **12d** had a 69-fold improved affinity compared to the cyclopropyl sulfonamide **12b**. This trend was not observed to as great an extent with the ethylene linked series as most of the analogs had high affinity for the receptor. For example, the cyclopropyl sulfonamide **14a** and the 4-cyanobenzene sulfonamide **14b** both possessed similar single digit nanomolar K_i's (3.8 nM and 4.2 nM, respectively) towards the CB_1 receptor. The acetamide analog **14d** with a K_i of 42 nM was an exception to this trend. This may indicate that the smaller alkyl groups on the methylene linked analogs may not reach deep enough into the hydrophobic pocket of the receptor. Molecular modeling indicated, in both the methylene and ethylene linked series, that one of the sulfonamide oxygens can match the hydrogen bond acceptor feature of the CB1 pharmacophore model.

To determine the importance of the absolute stereochemistry of these CB_1 antagonists, the enantiomers of **14a** were separated via chiral HPLC.[19] The faster eluting enantiomer **14f** had a 16-fold increased affinity compared to the slower eluting enantiomer **14g**. The difference in affinities between enantiomers in this piperidine series was not as profound as that observed with in the previously reported pyrazoline series in which the enantiomers possessed ~100-fold difference in affinities.[9] The lack of significant disparity between the affinities of enantiomers **14f** and **14g** was not surprising as it had been previously noted that both enantiomers of **8a** oriented well in our pharmacophore model. Also noteworthy is that all of the compounds listed in Table 2 had moderate to high selectivity for the CB_1 receptor compared to the CB_2 receptor.

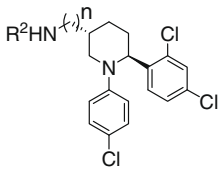
As mentioned previously, alcohol **10** was a common intermediate in the preparation of several other types of analogs (Scheme 3). Conversion to and displacement of the mesylate by *N*-Boc piperazine was followed by deprotection and nitrogen substitution to afford analogs **15a**–**15g**. A two step oxidation of the alcohol to a carboxylic acid was followed by amide bond formation to afford the amide analogs **16a**–**16d**. Finally, conversion of alcohol **10** to sulfonamides **17a**–**17d** was accomplished via a five step sequence featuring the displacement of a mesylate with sodium sulfite and chlorination to afford the sulfonyl chloride, followed by derivatization with various amines.

The binding affinities of these three classes of analogs is summarized in Tables 3–5. In the piperazine series (Table 3), the smaller capping groups, acetyl and methane sulfonyl (**15e** and **15c**, respectively) had significantly less affinity for the CB_1 receptor compared to the *tert*-butyl carbamate analog **15a**. The more lipophillic branched alkyl analogs **15d**, **15f** and **15g** had 10- to 50-fold improved affinities compared to **15c** and **15e**. The affinity of compound **15g** with the basic moiety in the lipophillic region of the receptor was 4- to 7-fold less compared to the non-basic counterparts **15a** and **15f**. The loss of affinity due to a basic piperazine substituent was also reported in a series of CB_1 receptor inverse agonists based on a pyridine core.[20]

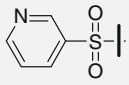
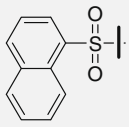
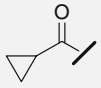
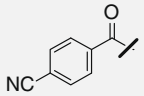
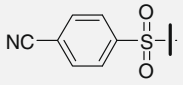
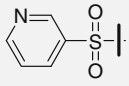
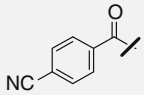


Scheme 2. Reagents and conditions: (a) LDA; BOMCl, THF −78 to −50 °C, 52%; (b) BBr_3, CH_2Cl_2, 0 °C, 88%; (c) BH_3·THF complex, THF, reflux 87%; (d) DIAD, PPh_3, $(PhO)_2P(O)N_3$, THF, 83%; (e) PPh_3, THF, 60 °C; H_2O, THF, 45 °C, 90%; (f) RSO_2Cl, Et_3N, CH_2Cl_2, 71–79%; (g) RC(O)OH, EDCI, HOBt, MeCN 36–87%; (h) MsCl, Et_3N, CH_2Cl_2, rt, 99%; (i) KCN, 18-crown-6, MeCN, reflux 16 h, 95%; (j) BH_3·THF complex, THF, reflux, 69%.

Table 2
Binding affinities of alkylene amino piperidines



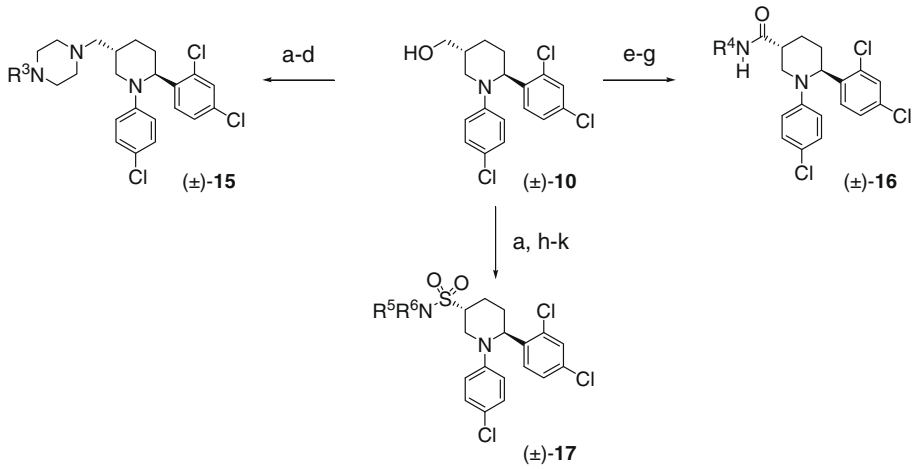
11, 12a-12f
13, 14a-14f

Compound	*n*	R^2	hCB_1 K_i (nM)	hCB_2 K_i (nM)
11	1	H	133	>1846
12a	1		48	25%[a]
12b	1		158	>1847
12c	1		6	>1847
12d	1		2.3	5%[a]
12e	1		112	25%[a]
12f	1		5	1407
13	2	H	61	>2220
14a	2		3.8	>2220
14b	2		4.2	>2220
14c	2		5.8	>2220
14d	2		42	>2400
14e	2		5.1	>2450
14f[b]	2		3.4	>2400
14g[b]	2		57	>2400

[a] Percent inhibition measured at 1 μM.
[b] Separated enantiomers of **14a**. The absolute stereochemistry of these enantiomers was not determined. See Ref.[19] for HPLC conditions.

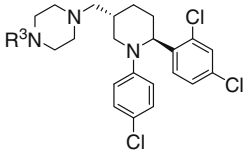
The amidopiperidine series **16a**–**16d** represented analogs similar to rimonabant with the hydrogen bond accepting amide carbonyl directly attached to the core ring. All four amidopiperidine analogs showed similar double digit nanomolar affinities for the CB_1 receptor (Table 4) with no apparent benefit for larger more lipophillic groups in this particular series.

In the sulfonamide linked series, the isobutyl and isopentyl analogs, **17a** and **17d**, respectively, both had single digit nano-

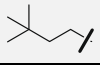


Scheme 3. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, rt; (b) *N*-Boc-piperazine, *i*Pr_2NEt, MeCN, reflux (59%, two steps); (c) 4 N HCl (dioxane), MeOH, rt, 83%; (d) RSO_2Cl, or RC(O)Cl, Et_3N, CH_2Cl_2 or RCHO, $NaBH(OAc)_3$, DCE; (e) $(COCl)_2$, DMSO, −78 °C; Et_3N −78 °C to rt, 90%; (f) $AgNO_3$, NaOH, H_2O, EtOH, 0 °C, 70%; (g) R^4NH_2, EDCI, HOBt, Et_3N, DMF, rt, 60–80%; (h) NaI, acetone, reflux, 40%; (i) Na_2SO_3, EtOH, H_2O, 100 °C, 49%; (j) phosgene, DMF, toluene; (k) R^5R^6NH, CH_2Cl_2, 21–33% (two steps).

Table 3
Binding affinities of piperazine analogs

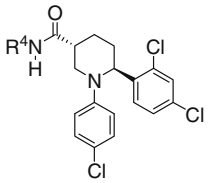


15a-15g

Compound	R^3	hCB_1 K_i (nM)	hCB_2 K_i (nM)
15a		8	>1846
15b	H	554	>2000
15c		690	>1846
15d		44	>2222
15e		451	>1846
15f		13	>2400
15g		57	>1500

molar affinities while the cyclohexyl analog **17b** exhibited slightly less affinity for the CB_1 receptor (Table 5). The isobutyl analog in the sulfonamide series, **17a**, showed a fivefold improved affinity compared to the isobutyl amide analog **16a** with K_i's of 6.3 and 33 nM, respectively. In contrast, the cyclohexyl substituted sulfonamide **17b** had an affinity similar to that of the corresponding cyclohexyl amide **16b**. Generally, having a short linker between the core and hydrogen bond acceptor provided piperidine analogs that were more potent than those with the hydrogen bond acceptor linked directly to the core. As had been observed with previous analogs, all of these antagonists exhibited moderate to high selectivity for the CB_1 receptor over the CB_2 receptor.

Table 4
Binding affinities of amido piperidines



16a-16d

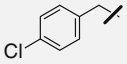
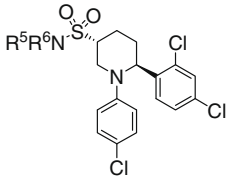
Compound	R^4	hCB_1 K_i (nM)	hCB_2 K_i (nM)
16a		33	1578
16b		18	368
16c		63	>1846
16d		33	1384

Table 5
Binding affinities of sulfonamide piperidines



17a-17d

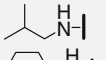
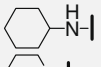
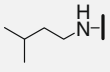
Compound	$-NR^5R^6$	hCB_1 K_i (nM)	hCB_2 K_i (nM)
17a		6.3	1915
17b		35	1246
17c		16	1189
17d		9.1	1275

Table 6
Percentage of food intake reduction in DIO mice

Compound	Dose (mg/kg)	Food intake reduction[a]				Plasma conc.[b] (ng/mL)	Brain conc.[b] (ng/g)
		2 h	4 h	6 h	24 h		
12f	3	**22 ± 5**	**22 ± 5**	**24 ± 4**	10 ± 6	28	12
14f	3	**39 ± 4**	**37 ± 11**	**38 ± 11**	**37 ± 7**	15	66
15f	3	0	0	3 ± 6	9 ± 5	1	0
17a	3	5 ± 7	0	0	0	4	0

[a] Bolded values were statistically significant (ρ <0.05) compared to vehicle-treated mice.
[b] Total concentrations measured at the 24-h time point.

To investigate the in vivo efficacy of these CB_1 antagonists, four of the previously described analogs were evaluated in a mouse DIO model[21] to determine the effectiveness in reducing food intake over a 24-h period. These compounds were dosed orally at 3 mg/kg and food intake was compared to vehicle-treated mice. As listed in Table 6, the ethylene linked sulfonamide **14f** was the most potent of the piperidines tested, reducing food intake 38% at the 24-h time point when dosed at 3 mg/kg. The amide **12f** exhibited statistically significant food intake reduction (ρ <0.05) up to 6 h; however, it was not effective at the 24-h time point. The reduced efficacy of **12f** compared to that of **14f** can be accounted for by the observed lower brain exposure and brain to plasma ratio at 24 h for **12f**. The other two analogs, **15f** and **17a**, demonstrated no significant reduction of food intake in this model. Poor pharmacokinetic profiles and/or the inability of the compounds to partition into the brain could be factors for the lack of observed in vivo potency for these two compounds. Both of these compounds showed very low plasma exposure and no brain exposure at the 24-h time point.

In conclusion, a new class of CB_1 receptor antagonists has been described based on a 5-substituted 1,2-diaryl piperidine core. Several of the compounds exhibited single digit nanomolar affinities for the CB_1 receptor with greater than 100-fold selectivity compared to the CB_2 receptor. The sulfonamide **14f** also produced a robust reduction of food intake in a DIO mouse assay over a 24-h period. Future reports will describe the evolution of a structurally similar series with further improvements in binding affinity and in vivo activity.

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