Letters

Discovery of *N*-[(1*S*,2*S*)-3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (MK-0364), a Novel, Acyclic Cannabinoid-1 Receptor Inverse Agonist for the Treatment of Obesity

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Abstract: The discovery of novel acyclic amide cannabinoid-1 receptor inverse agonists is described. They are potent, selective, orally bioavailable, and active in rodent models of food intake and body weight reduction. A major focus of the optimization process was to increase in vivo efficacy and to reduce the potential for formation of reactive metabolites. These efforts led to the identification of compound **48** for development as a clinical candidate for the treatment of obesity.

Obesity is a serious and chronic medical condition that is rapidly growing throughout the world. In many cases, the excessive body weight is the root cause of subsequent comorbidities, including diabetes, hypertension, cardiovascular disease, cancer, and arthritis.[1] Although lifestyle modifications may be the preferred approach for the management of obesity, it is often insufficient or unsustainable. Therefore, new anti-obesity therapeutics are actively pursued. The involvement of the cannabinoid receptor system in regulating feeding behavior has been demonstrated in animal and clinical studies.[2,3] Several cannabinoid-1 receptor (CB1R) inverse agonists including SR141716 (rimonabant)[4] and SLV319[5] (Figure 1) have been reported to be efficacious in various models of feeding behavior, and rimonabant has been approved in the EU for the treatment of obesity. Herein, the discovery of novel, acyclic CB1R inverse agonists is described.

Our efforts started with a screening lead (**1**) that was determined to be a racemic mixture of the *anti*-diastereomers[6] (Figure 2). Preparative chiral HPLC separation afforded the (*S*,*S*)-isomer **2** and the (*R*,*R*)-isomer **3**. The stereochemical assignments were established by X-ray analysis. The racemate of the *syn*-diastereomers of **1** was synthesized and was less

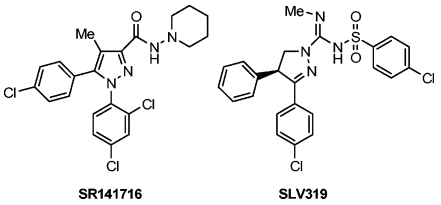

Figure 1. Structures of SR141716 and SLV319.

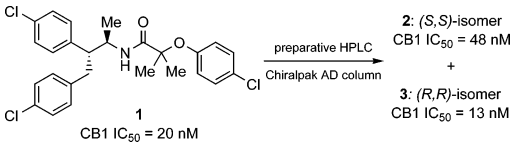

Figure 2. Racemic **1** was separated into slower eluting (*S*,*S*)-enantiomer **2** and faster eluting (*R*,*R*)-enantiomer **3**.

active (CB1R $IC_{50} = 95 \pm 23$ nM). The more potent enantiomer **3** demonstrated good pharmacokinetic properties in the rat (1 mg/kg iv, 2 mg/kg po, $F = 68\%$, $t_{1/2} = 2$ h). However, when evaluated in the diet-induced obese (DIO) rat model, **3** (up to 10 mg/kg po) showed no significant effects on overnight food intake or body weight reduction, thereby setting the stage for lead optimization.

After a thorough investigation of the backbone scaffold of **1** that did not yield any significant improvements in potency, further efforts focused on varying the substituents of the two aromatic rings of the amine fragment. The synthetic route began with substituted phenyl acetates **4** (Scheme 1). Base-catalyzed alkylation with benzyl halides was followed by conversion to the Weinreb amide **6**. Reaction of **6** with methyl Grignard reagent afforded ketone **7**. Reduction of **7** was accomplished with sodium borohydride or lithium tri(*sec*-butyl)borohydride to afford **8** as the major diastereomer.[7] The reduction with sodium borohydride was generally less diastereoselective (4:1) than with tri(*sec*-butyl)borohydride (>10:1). The resulting secondary alcohol **8** was converted to the amine **9**, which was subsequently coupled to a fibric acid to give the *anti*-diastereomer **10** as the major product in racemic form. The less selective borohydride reduction provided a useful amount of the minor *syn*-diastereomers of **10** for structure-activity-relationship (SAR) comparisons.

The individual enantiomers of **10d** were prepared by an enantiospecific route (Scheme 2), starting from (1*R*,2*R*)- or (1*S*,2*S*)-1-phenylpropylene oxide (**11** or **12**).[7] Epoxide opening with 4-chlorobenzylmagnesium chloride afforded the secondary alcohols (*S*,*R*)-**13** and (*R*,*S*)-**14**, respectively, which were separately converted to the amines (*S*,*S*)-**15** and (*R*,*R*)-**16** and subsequently to the amides **17** and **18**.

With the enantiomerically pure amines **15** and **16** in hand, the SAR of the aromatic ring of the acid moiety was then addressed. The synthesis of the acid fragments followed several different routes (Scheme 3). The first route was a one-step reaction between 1,1,1-trichloro-*tert*-butanol **19** and a substituted phenol **20** to afford fibrate **21**.[8] Since hydroxypyridines were generally poor substrates for this reaction, an alternative route was developed. Reaction of 2- or 3-hydroxypyridine **(23**, **24)** with benzyl lactate **22** under Mitsunobu conditions afforded

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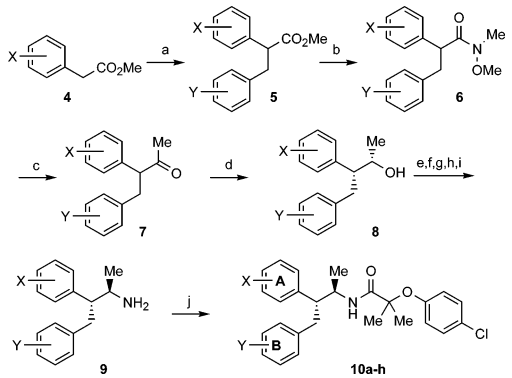
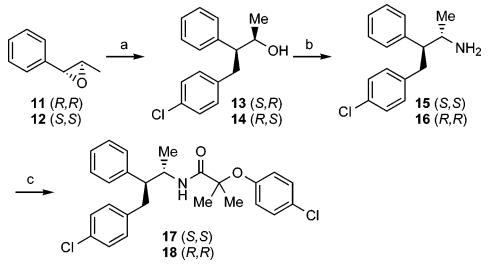
Scheme 1[a]



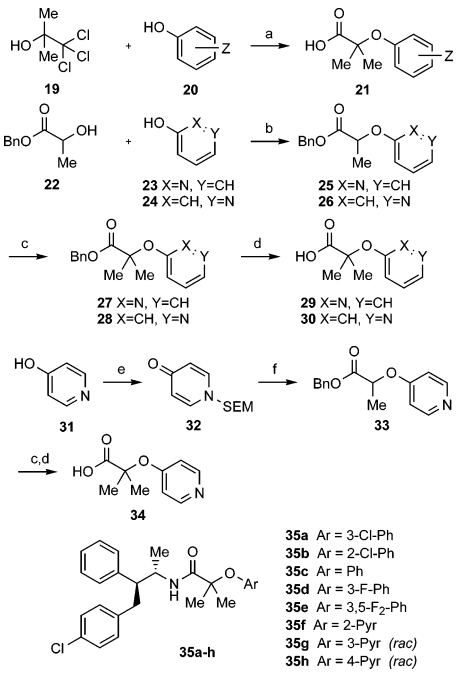
[a] (a) Y-PhCH$_2$Br, KHMDS, −78 °C → room temp; (b) MeONH(Me)·HCl, Me$_2$AlCl, room temp; (c) MeMgCl, ether, 0 °C; (d) NaBH$_4$, MeOH or LiBH(*sec*-Bu)$_3$, THF, −78 °C; (e) MsCl, Et$_3$N; (f) NaN$_3$, DMF, 100 °C; (g) H$_2$, Boc$_2$O, PtO$_2$ (cat.), EtOAc; (i) HC/dioxane, EtOAc; (j) fibric acid, (COCl)$_2$, then *N*-methylmorpholine, CH$_2$Cl$_2$.

Scheme 2[a]



[a] (a) 4-ClPhCH$_2$MgCl, 0 °C; (b) Scheme 1, steps e−i; (c) fibric acid, (COCl)$_2$, then *N*-methylmorpholine, CH$_2$Cl$_2$.

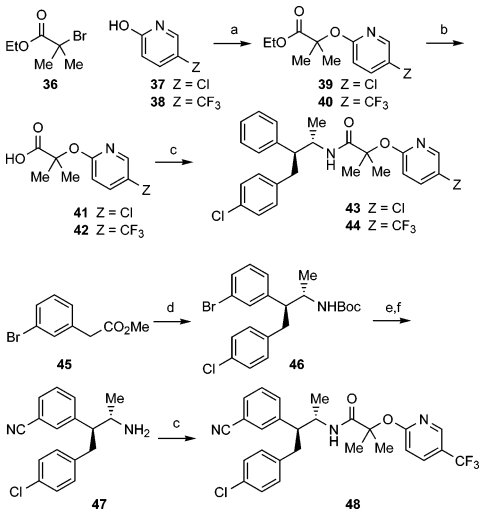
Scheme 3[a]



[a] (a) NaOH, acetone; (b) DEAD, Ph$_3$P, CH$_2$Cl$_2$; (c) KHMDS, MeI, THF, −78 °C; (d) H$_2$, Pd/C (cat.), MeOH; (e) SEMCl; (f) BnO$_2$CCH(Me)OTf, 60 °C.

esters **25** and **26** along with some *N*-alkylated side products. Methylation of **25** and **26** followed by hydrogenolysis afforded acids **29** and **30**. Because 4-hydroxypyridine (**31**) afforded the *N*-alkylated product exclusively under Mitsunobu conditions,

Scheme 4[a]



[a] (a) Cs$_2$CO$_3$, CH$_3$CN, 50 °C; (b) NaOH, H$_2$O/MeOH; (c) PyBop, *N*-methylmorpholine, CH$_2$Cl$_2$, room temp; (d) Scheme 1, steps e−g; (e) Zn(CN)$_2$, Pd$_2$(dba)$_3$, dppf, DMF/H$_2$O (98:2), 100 °C; (f) HCl/dioxane, EtOAc.

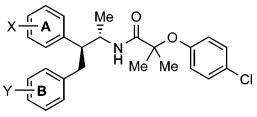
another procedure was investigated. Protection of the pyridine nitrogen with a SEM group provided **32**, which was reacted with benzyl lactate *O*-triflate to yield the desired *O*-alkylation product. The SEM group was cleaved upon workup to give **33**, which was converted to acid **34** under standard conditions. These new acids were then coupled to amine **15** to give the desired amides (**35a**−**h**).

Further optimization resulted in a two-step synthesis of pyridine acids **41** and **42** (Scheme 4). Reaction of appropriately substituted 2-hydroxypyridines with α-bromoisobutyrate in the presence of cesium carbonate afforded the esters **39** and **40**, which were hydrolyzed to acids **41** and **42**. Coupling of these acids with the (*S*,*S*)-amine **15** provided amides **43** and **44**. The bromo-substituted amine **46** was converted to the cyano amine **47** under palladium-catalyzed cyanation conditions.[9] Amide coupling with acid **42** followed by HPLC on a chiral column afforded the more potent (*S*,*S*)-isomer **48**.[10]

Inhibition data of [^{3}H]CP-55940 binding to recombinant human CB1R and CB2R expressed in CHO cells are summarized in Table 1. The *anti*-diastereomers were generally 2- to 10-fold more potent than the *syn*-diastereomers, so only the data for the *anti*-diastereomers are listed. Deletion of the 4-chloro substituent from phenyl ring A in **10d** resulted in an increase in binding affinity, whereas replacement with fluorine resulted in a loss of potency (**10a**). Fluorine substitution at the 2-position had little effect (**10c**), but substitution at the 3-position enhanced potency (**10b**). For phenyl ring B, the 4-substituent was required for optimal potency (**10d**,**f**,**g** vs **10h**). Substitution at the 2-position resulted in significant loss of binding activity (**10e**). It is interesting that whereas the more potent enantiomer of **1** is **3** with the (*2R*,*3R*)-configuration, the more potent enantiomer of **10d** is **17** with the (*2S*,*3S*)-configuration.

Employing the potency enhancing substitution pattern on the amine fragment found in **10d** (**17**), the SAR of the aryloxy group was then explored (Table 2). Both 4- and 3-substitutions on the phenyl ring of the acid moiety were tolerated and were preferred over 2-substitution. The 3,5-difluoro analogue **35e** is among the more potent compounds. In addition, replacement of the phenyl ring with a 2-pyridyl group was well tolerated (**35f**), although the regioisomeric 3- or 4-pyridyl groups were less favorable (**35g** and **35h**). Compound **35e** was also found

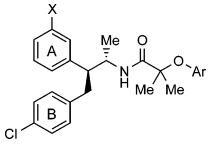
Table 1. Inhibition of CB1R and CB2R (IC_{50}, nM)[a] by Substituted Amides[b]



compd	X	Y	CB1R IC_{50}, nM	CB2R IC_{50}, nM
1	4-Cl	4-Cl	20 ± 12	1100 ± 1100
(*S*,*S*)-**2**	4-Cl	4-Cl	48 ± 17	>2000
(*R*,*R*)-**3**	4-Cl	4-Cl	13 ± 6	600 ± 200
10a	4-F	4-Cl	90 ± 4	
10b	3-F	4-Cl	2.8 ± 0.8	530 ± 6
10c	2-F	4-Cl	12 ± 3	410 ± 130
10d	H	4-Cl	2.5 ± 1.1	610 ± 370
10e	H	2-Cl	140 ± 25	
10f	H	4-CF_3	3.4 ± 1.4	
10g	H	4-F	14 ± 0.6	
10h	H	H	33 ± 0.3	
(*S*,*S*)-**17**	H	4-Cl	3.0 ± 1.2	770 ± 620
(*R*,*R*)-**18**	H	4-Cl	170 ± 110	1700 ± 700
SR141716			6.1 ± 2.5	600 ± 650
SLV319			17 ± 8	1100 ± 200

[a] Inhibition of binding (mean ± SD) ($n \geq 2$ independent experiments).[11] [b] Racemic mixture of the *anti*-diastereomers except as noted.

Table 2. Inhibition of CB1R and CB2R (IC_{50}, nM)[a] by Substituted Amides[b]



compd	X	Ar	CB1R IC_{50}, nM	CB2R IC_{50}, nM
17a	H	4-Cl-Ph	3.0 ± 1.2	770 ± 620
35a	H	3-Cl-Ph	1.5 ± 0.5	190 ± 80
35b	H	2-Cl-Ph[c]	18 ± 4	
35c	H	Ph	2.0 ± 1.4	450 ± 180
35d	H	3-F-Ph	1.6 ± 0.8	290 ± 60
35e	H	3,5-F_2-Ph	1.1 ± 1.0	200 ± 110
35f	H	2-pyr	1.8 ± 1.4	88 ± 28
35g	H	3-pyr[c]	19 ± 3	
35h	H	4-pyr[c]	17 ± 1	1200 ± 300
43	H	5-Cl−2-pyr	1.3 ± 0.3	100 ± 20
44	H	5-CF_3-2-pyr	0.5 ± 0.2	140 ± 20
48	CN	5-CF_3-2-pyr	0.3 ± 0.1	290 ± 60

[a] Inhibition of binding (mean ± SD) ($n \geq 2$ independent experiments).[11] [b] (*S*,*S*)-Enantiomer. [c] Racemic mixture of *anti*-diastereomers.

to have good pharmacokinetic properties (1 mg/kg iv, 2 mg/kg po, $F = 19\%$, $t_{1/2} = 2.4$ h) and brain exposure (1 mg/kg iv, brain and plasma concentrations of 0.27 and 0.35 μM at 1 h, respectively) in the rat. In contrast to **3**, **35e** was highly efficacious in the DIO rat model, resulting in dose-dependent reduction in overnight food intake (−55 ± 2% and −81 ± 6% at 3 and 10 mg/kg po, respectively; $P < 0.05$ vs vehicle at both doses).

Formation of reactive metabolites and subsequent covalent modifications of proteins are implicated in cases of allergic and/or idiosyncratic immune-mediated toxicities.[12] Because such toxicities may not manifest themselves until the later stages of development or after marketing, bioactivation should be minimized in drug candidates. Compound **35e** was evaluated for the potential of reactive metabolite formation. Tritiated **35e** was incubated with human and rat liver microsomes and afforded very high levels of irreversible binding of radioactivity (1700 pmol equiv./mg protein).[13] When the incubation was performed with glutathione as an additive, covalent adducts of **35e** with glutathione were detected by LC−MS. Careful analysis of the

Table 3. Covalent Binding to Human Liver Microsomal Proteins Obtained by Incubation of Tritiated Compounds[13]

compd	binding[a]
35c	3900 ± 300
35e	1700 ± 320
35f	910 ± 110
43	300 ± 81
44	88 ± 4
48 (MK-0364)	27 ± 2

[a] pmol equiv/mg protein at 1 h of incubation.

MS pattern suggested that the covalent linkage was formed between the 3,5-difluorophenoxy fragment of **35e** and the sulfhydryl group of glutathione. Presumably, the electron-rich phenyl ring was oxidized to a putative arene oxide intermediate that then reacted with glutathione or nucleophilic species on microsomal proteins, resulting in formation of covalent adducts.

The mechanism of bioactivation for **35e** was believed to be oxidation of the electron rich aryloxy group, so a more electron-deficient aryl group would be expected to be less prone to such metabolic activation. Indeed, **35f** was found to have reduced levels of covalent binding (910 pmol equiv/mg protein) when the 3,5-difluorophenyl ring was replaced with the more electron-deficient 2-pyridyl ring (Table 3).[13] Further reduction of bioactivation was accomplished by introduction of an electron-withdrawing substituent such as a 5-chlorine (3-fold) or 5-trifluoromethyl group (10-fold). The addition of the 5-trifluoromethyl group (**44**) also improved potency and selectivity relative to the unsubstituted pyridine derivative **35f**. The residual covalent binding in **44** (88 pmol equiv/mg protein) was thought to result from the bioactivation of the unsubstituted phenyl ring A. Substitution of ring A with an electron-withdrawing group was sought to further reduce the potential for bioactivation. This effort was highlighted by the incorporation of a cyano substituent, which afforded a CB1R inverse agonist (**48**, MK-0364) with minimal potential for covalent protein binding.

Compound **48** was an exceptionally potent and selective (900-fold over CB2) CB1R inverse agonist with >500-fold improvement in affinity over the original lead (**1**). In a functional assay of cyclic-AMP production, **48** was determined to be an inverse agonist ($EC_{50} = 2.4 \pm 1.4$ nM, −123% maximal activation; relative to CP-55940). Compound **48** also had a good pharmacokinetic profile in three species (rat, 1 mg/kg iv, 2 mg/kg po, $F = 74\%$, $t_{1/2} = 2.7$ h; dog, 0.2 mg/kg iv, 0.4 mg/kg po, $F = 31\%$; $t_{1/2} = 14$ h; rhesus monkey, 0.2 mg/kg iv, 0.4 mg/kg po, $F = 31\%$, $t_{1/2} = 3.6$ h) and good brain exposure (1 mg/kg iv, brain and plasma concentrations of 0.11 and 0.18 μM at 1 h, respectively).

The in vivo activity of **48** was first assessed with a rat hypothermia model. In this model, a rapid 4−5 °C decrease in body temperature was first induced by CB1R agonist CP-55940. Administration of **48** (3 mg/kg iv) completely blocked the temperature decrease ($P < 0.00001$ vs vehicle), consistent with total in vivo inhibition of the CB1 receptors.[14] The effects of **48** on feeding behavior were evaluated in the DIO rat model. After 14 days of treatment at 0.3, 1, and 3 mg/kg (po, qd), a sustained and dose-dependent reduction relative to the vehicle-treated animals in body weight (4 ± 1%, 5 ± 1%, and 7 ± 1%, respectively; $P < 0.05$) was observed.[14] The effects on food intake and body weight were shown to be mediated by CB1R by the lack of such effects in *Cnr1* knockout mice.[14] More details of the in vivo pharmacology of **48** will be reported in future publications.[14]

In summary, we have discovered a series of novel, acyclic CB1R inverse agonists that are potent, selective, and orally

bioavailable. A major focus of the optimization effort was to increase in vivo efficacy and to attenuate the potential for bioactivation of the initial lead. These compounds are active in models of feeding behavior and hypothermia, and **48** (MK-0364) is currently undergoing clinical evaluation for the treatment of obesity.

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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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