

Letters

Discovery of 2-(2-Chlorophenyl)-3-(4-chlorophenyl)-7-(2,2-difluoropropyl)-6,7-dihydro-2H-pyrazolo[3,4-f][1,4]oxazepin-8-(5H)-one (PF-514273), a Novel, Bicyclic Lactam-Based Cannabinoid-1 Receptor Antagonist for the Treatment of Obesity

Robert L. Dow,* Philip A. Carpino, John R. Hadcock, Shawn C. Black,[†] Philip A. Iredale, Paul DaSilva-Jardine, Steven R. Schneider, Ernest S. Paight, David A. Griffith, Dennis O. Scott, Rebecca E. O'Connor, and Chudy I. Nduka

Departments of Cardiovascular, Metabolic and Endocrine Diseases, Neuroscience, and Drug Safety, Pfizer Global Research and Development, Groton, Connecticut 06340

Received February 28, 2009

Abstract: We report the design, synthesis, and structure–activity relationships of novel bicyclic lactam-based cannabinoid type 1 (CB₁) receptor antagonists. Members of these series are potent, selective antagonists in in vitro/in vivo efficacy models of CB₁ antagonism and exhibit robust oral activity in rodent models of food intake. These efforts led to the identification of **19d**, which has been advanced to human clinical trials for weight management.

The endocannabinoid system, and specifically the cannabinoid type 1 (CB₁)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 CB₁ receptor decreases food intake and increases energy expenditure, leading to a reduction in body weight.^{8–11}

CB₁ receptor antagonists may provide effective therapy options for the management of metabolic disorders, such as obesity. It was hoped that CB₁ receptor antagonists might provide effective therapy options for the management of metabolic disorders, such as obesity. Unfortunately, several CB₁ receptor inverse agonists/antagonists were recently withdrawn from clinical development including the diarylpyrazole rimnabant¹² **1** (SR141716A) and the acyclic amide taranabant¹³ **2** (MK-0364) (Figure 1).

Our group recently reported the discovery of a series of potent pyrazolopyrimidinone-based (e.g., **3**) CB₁ receptor antagonists.¹⁴ While members of this series possess potent CB₁ antagonism in vitro and in vivo, there are issues that have impeded their further development. These consist of impaired absorption (solubility-limited) for certain members of the series and more importantly a very narrow therapeutic index (TI) in preclinical safety models (vide infra). On the basis of a number of

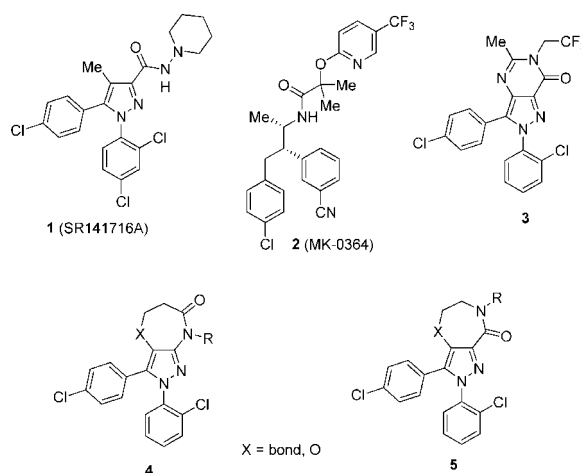


Figure 1. Structures of **1**, **2**, and bicyclic pyrazoles.

preclinical safety studies, this side effect profile and narrow TI appear to be a class effect associated with the pyrazolopyrimidinone core structure. Herein we describe efforts to overcome these issues, resulting in the identification of **19d** (PF-514273) which has been advanced to human clinical trials for weight management.

On the basis of the promising in vitro profile of members of bicyclic series such as **3**, follow-on efforts focused on approaches toward improving the solubility properties within this class. One of several tacks pursued toward improving solubility was disruption of the planar nature of the bicyclic core of these systems. We reasoned that fused six-/seven-membered lactam systems such as **4** and **5** would have the potential to provide improved oral bioavailability, relative to the pyrazolopyrimidinone core, via disruption of crystal packing forces.¹⁵ In addition, it was hoped that this significant alteration of the core chemotype of **3** would afford a greater preclinical safety window while retaining a desirable CB₁ antagonist profile.

When the overlays of low energy conformations are compared, a better overlap of the lactam nitrogen substituent (R) with the piperidyl side chain of **1** is predicted for **4** relative to regioisomeric lactam **5**. However, previous results from our laboratory (unpublished) with a series of N-acylated 3-aminopyrazoles had revealed positive in vitro micronucleus activity associated with this chemotype. Not surprisingly, initial analogues from series **4** were also found to possess this genotoxic liability. This finding led us to direct our efforts on regioisomeric lactams **5**.

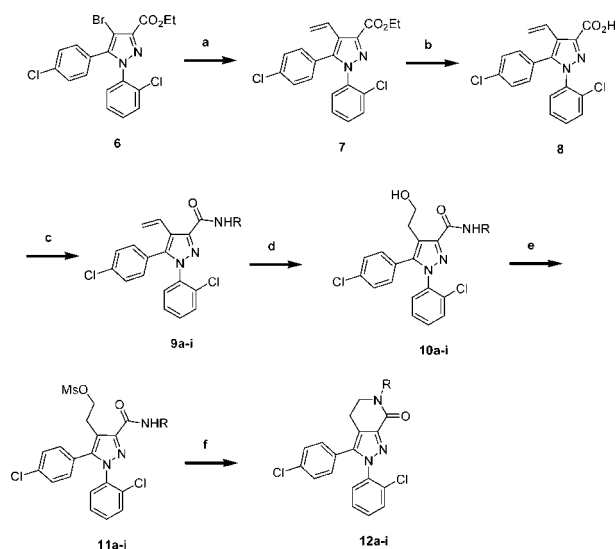
Synthesis of the six-membered lactam series **5** (X = bond) is detailed in Scheme 1. Bromopyrazole **6**¹⁶ is homologated via Stille vinylation to afford **7**. Hydrolysis and amidation afford amides **9a–i**. Hydroboration of the olefin and conversion of the hydroxyl group to mesylates **11a–i** set the stage for cyclization via intramolecular alkylation employing lithium bis(trimethylsilyl)amide to afford lactams **12a–i**. The corresponding amine-based bicyclic **13** is prepared from **12i** by reduction with lithium aluminum hydride (Figure 2).

Scheme 2 details the preparation of the ether-based lactams **19a–e**, starting from the known ketoester **14**.¹⁷ Insertion of the diazo species generated from 2-chloroaniline followed by

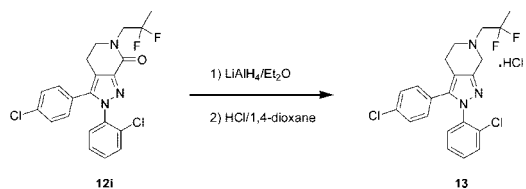
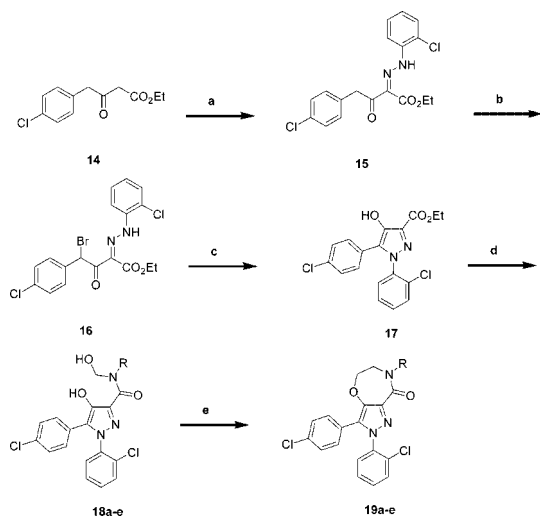
* To whom correspondence should be addressed. Phone: 860-441-4423. Fax: 860-441-1128. E-mail: robert.l.dow@pfizer.com.

[†] Present address: Johnson & Johnson Pharmaceutical Research and Development, Welsh & McKean Roads, Spring House, PA 19477-0776.

Abbreviations: AUC, area under curve; CB, cannabinoid; GTP, guanosine triphosphate; PK, pharmacokinetic; CNS, central nervous system; TI, therapeutic index.

Scheme 1. Synthesis of Bicyclic Lactams **12a–i**^a

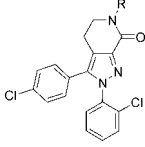
^a (a) Tributylvinyltin, Pd(PPh₃)₄, DMF, 110 °C; (b) KOH, H₂O, EtOH, 50 °C; (c) (iPr)₂NEt, RNH₂, 1-propanephosphonic anhydride; (d) 9-BBN, THF, 70 °C; (e) MeSO₂Cl, TEA, CH₂Cl₂; (f) LiN(TMS)₂, THF.

Figure 2. Preparation of amino analogue **13**.Scheme 2. Synthesis of Bicyclic Lactams **19a–e**^a

^a (a) 2-Chloroaniline, NaNO₂, AcOH, H₂O, 0 °C; (b) CuBr₂, EtOAc, CHCl₃, 60 °C; (c) NaOAc, MeOH, reflux; (d) RNHCH₂CH₂OH, 125 °C; (e) triphenylphosphine, 1,1'-(azodicarbonyl)dipiperidine, toluene.

bromination and cyclization under mild conditions affords hydroxypyrazole **17**.¹⁸ Amide formation with the requisite *N*-hydroxyethylamine followed by Mitsunobu cyclization affords the ether-based lactams **19a–e**.

Incorporation of small *N*-alkyl substituents into the six-membered bicyclic lactam core (**12b–e**) provides single-digit nanomolar CB₁ antagonists (Table 1). Comparable levels of functional CB₁ receptor antagonism (GTPγ[³²S], CP-55,940 utilized as agonist) are observed, as well as high levels of

Table 1. Biochemical Properties of Lactams **12a–i** and **13**


compd	R	CB-1 K _i (nM) ^a	CB-2 K _i (nM) ^a	GTPγ[³² S] (nM) ^b
1		1.8 ± 1.4	1569 ± 845	1.6 ± 0.7
3		0.6 ± 0.1	>10000	1.0
12a	H	61		
12b	CH ₂ CH ₃	4.7	23440	25
12c	CH(CH ₃) ₂	2.5 ± 0.8	>10000	5.5 ± 0.8
12d	CH ₂ CH(CH ₃) ₂	2.5	1780	9.8
12e	C(CH ₃) ₃	4.7	6810	11
12f	<i>n</i> -pentyl	24		
12g	CH ₂ C(CH ₃) ₂ (OCH ₃)	11	162	13
12h	CH ₂ CF ₃	1.7 ± 1	>10000	3.1 ± 1.4
12i	CH ₂ CF ₂ CH ₃	0.7 ± 0.2	>10000	0.8 ± 0.2
13		30		

^a K_i determinations (mean ± SD of ≥3 runs in triplicate or single determination run in triplicate). ^b CP-55,940 (10 μM) utilized as agonist.

selectivity versus CB₂ receptor binding. Incorporation of cycloalkyl (**12f**) or heteroatoms (**12g**) into the lactam substituent had negative effects on CB₁ binding and in the latter example greatly reduced selectivity versus the CB₂ receptor.

These early results confirmed that the bicyclic lactam motif could serve as a replacement for the pyrazolopyrimidinone core. While structure–activity trends for lactams **12** generally follow those observed for the pyrazolopyrimidinone series, the one exception was a lack of translation upon incorporation of small fluorine containing substituents (**12h–i**). In the case of the pyrazolopyrimidinone series incorporation of the trifluoroethyl or 2,2-difluoropropyl groups provide a >10-fold improvement in CB₁ binding affinity relative to the parent alkyl substituents.¹⁴ However, for the lactam series **12** this modification does not produce a dramatic improvement in affinity or functional response. While the difference in projected trajectories for the *N*-substituents of these two series is subtle, there is clearly a significant impact on binding affinity for certain pairs of compounds. These results are consistent with the rather tight constraints¹⁴ on CB₁ receptor space in the vicinity of the *N*-substituent for these series (e.g., **12f** = 24 nM), which contrasts with the fairly broad tolerance for substituents in the vector occupied by the amide functionality of **1**.¹⁹ This idea is further supported by the finding that eliminating the in-plane projection of the difluoropropyl substituent through reduction to the amine (**13**) dramatically lowers binding affinity, though the concomitant production of a basic center could also be contributing to this resultant loss in potency.

Compound **12i** was selected for profiling in efficacy and preclinical safety models based on its in vitro profile. Pharmacokinetic analysis in the rat revealed a good profile for **12i** (1 mg/kg iv, 5 mg/kg po, *F* = 99%, *T*_{1/2} = 3.6 h, *V*_{ss} = 2.6 L/kg). As expected from its structure, this compound penetrates the brain via passive diffusion and is not excluded by active transport processes, achieving a steady-state total brain to plasma ratio of 3.2 (unbound ratio = 1). Functional antagonism of central-mediated CB₁ pharmacology was confirmed by complete reversal of four cannabinoid agonist-mediated (CP-55,940) behaviors (locomotor activity, hypothermia, analgesia, and catalepsy) at doses of 1 mg/kg, sc, of **12i**. Compound **12i** exhibited dose-dependent anorectic activity in a model of acute

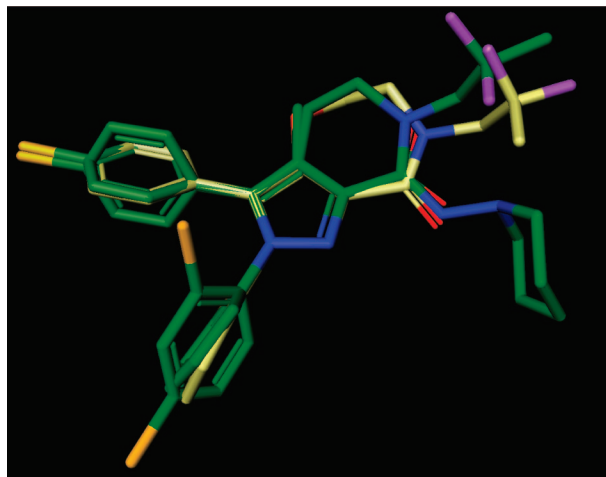


Figure 3. Overlay of crystal structures of **12i** (green)/**19d** (yellow) and the minimized structure²¹ of **1**.

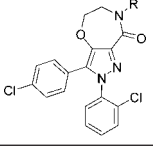
food intake in rodents and increased energy expenditure and fat oxidation.

Pyrazolopyrimidinone **3** and close-in analogues exhibited substantial adverse behavioral effects in preclinical efficacy and early safety studies in rats. From these studies with **3**, a TI of at most 10-fold (based on plasma concentrations) is projected for this class of compounds.²⁰ Broad receptor profiling failed to identify any specific pharmacological end points that might be associated with these behavioral side effects. In contrast, efficacy studies with **12i** and related analogues appeared to be devoid of the frank toxicities observed in similar studies with **3**. Evaluation of **12i** in a 4-day, rat in vivo toleration assay reveals this compound to possess a relatively clean safety profile. On the basis of plasma exposures, it is estimated that **12i** possesses a TI in the 40- to 200-fold range, a significant improvement relative to the pyrazolopyrimidinone class of agents.

Regarding the expectation that the bicyclic lactam motif would aid in disruption of the planar nature of the pyrazolopyrimidinone ring present in **3** (mp = 225 °C), crystalline **12i** has a relatively low melting point (103 °C). While the aqueous solubility of **12i** is very low (0.2 µg A/mL), crystalline material exhibits high oral bioavailability at doses up to 50 mg/kg in rat (50% at 500 mg/kg). The greater than expected fraction absorbed, based on experimentally determined aqueous solubility, suggests enhanced solubilization of **12i** in the intestinal tract. This is supported by solubility measurements in media intended to replicate the mixed micelles (sodium taurocholate/phosphatidyl choline salts) found in intestines that provide a nearly 100-fold increase in solubility (18.5 µg A/mL) for **12i**.

The hypothesis that disruption of the planar nature of **3** was responsible for the improved safety profile and improved physical properties associated with series **12** led to the design of seven-membered lactams **5** (X = O). These ether-based lactam structures were hypothesized to possess improved physical properties due to increased polar surface area and greater disruption of crystal packing forces relative to the six-membered lactam series. Also, from overlays of the modeled structures (confirmed by crystal structures, see Figure 3), the amide substituent vector of the seven-membered lactams is predicted to be directed closer to that of the amide functionality of **1**, allowing for interactions of the lactam substituent with CB₁ binding domains not accessible from **12**. Previous work has hypothesized that a hydrogen bond between the carbonyl oxygen of **1** and Lys192 of the CB₁ receptor is a significant

Table 2. Biochemical Properties of Lactams **19a–e**



compd	R	CB-1 <i>K_i</i> (nM) ^a	CB-2 <i>K_i</i> (nM) ^a	GTPγ[³⁵ S] (nM) ^b
1		1.8 ± 1.4	1569 ± 845	1.6 ± 0.7
19a	H	83		
19b	CH(CH ₃) ₂	1.3	> 10000	4.8
19c	CH ₂ CF ₃	1.9	> 10000	1.5
19d	CH ₂ CF ₂ CH ₃	1.0 ± 0.7	> 10000	0.82 ± 0.2
19e	CH ₂ CF ₂ CH ₂ CH ₃	1.4	> 10000	0.7

^a *K_i* determinations (mean ± SD of ≥ 3 runs in triplicate or single determination run in triplicate). ^b CP-55,940 (10 µM) utilized as agonist.

component of the binding affinity of **1**.²¹ Given the orientation of the carbonyl oxygen of lactams **12** and **19** are directed ~120° relative to that of **1**, it is unlikely that the carbonyl functionality in the former is interacting with Lys192 of the CB₁ receptor.

Table 2 details the CB pharmacology profile of a core set of ether-based lactams. The ring expanded analogues **19a–e** have CB₁ binding affinities that are comparable to the six-membered lactams and **3**. The parallel structure–activity trends between **12** and **19** suggest that the respective lactam substituents are occupying similar CB₁ receptor space.

On the basis of its in vitro biochemical profile, **19d** was selected for further evaluation. Pharmacokinetic analysis in the rat revealed a good profile (1 mg/kg iv, 5 mg/kg po, *F* = 42%, *T*_{1/2} 3.5 h, *V*_{ss} = 2.6 L/kg). In analogy to **12i**, this ether-based homologue penetrates the brain via passive diffusion and is not excluded by active transport processes, achieving a total steady-state brain to plasma ratio of 3.1 (unbound ratio = 1). Compound **19d** was able to completely reverse the four CB₁ agonist-mediated (CP-55,940) effects induced in the rat at doses of ≥ 1 mg/kg, sc. On the basis of confirmation of in vivo antagonism of the CB₁ pathway, **19d** was evaluated in two models of feeding behavior. Acute analysis in a fast-induced refeeding rat model produced a dose-responsive reduction (2 h measurement after food introduction) in food intake over a 2 h test period. An oral dose (methyl cellulose vehicle) of 1 mg/kg **19d** produced a 40 ± 11% reduction in food intake, while the positive control **1** was 43 ± 9% at 3 mg/kg. In a chronic setting, 7 days of oral dosing in diet-induced obese mice, **19d** produced a cumulative 23% reduction in food intake at 1 mg/kg relative to a control group (21% for 3 mg/kg **1**). A statistically significant reduction in weight gain of 5.9 ± 0.8% was observed at the 1 mg/kg dose over the 7 days, which was comparable to 5.2 ± 0.8% produced by **1** at 3 mg/kg.

No clinical signs or histological changes were observed for **19d** in a 4 day in vivo safety assessment of **19d** in rats ((3/sex)/dose) at oral doses of 5, 50, and 500 mg/kg. Pharmacokinetic analysis of this study revealed good dose proportional plasma exposures up to 50 mg/kg and with oral bioavailability of crystalline material (methylcellulose vehicle) ranging from 51 to 74%. At the top dose of 500 mg/kg, the average plasma AUC was >170 mg·h/mL for both sexes. These results combined with the plasma concentrations required for efficacy in the feed intake studies provide a minimum safety TI of 200-fold in the rat. Further details on the efficacy, pharmacokinetic, and safety profiles of **19d** will be the subject of future publications.

In summary, we have discovered a novel series of bicyclic lactams that are potent, selective CB₁ receptor antagonists.

Improved solubility through disruption of crystal packing forces has led to improved oral efficacy in models of feeding behavior relative to lead **3**. In addition, these agents show substantially improved safety profiles relative to the initial lead **3**. On the basis of its pharmacological, pharmacokinetic, and early safety profile, compound **19d** was advanced to human clinical studies for weight management.

Acknowledgment. We thank Robert Day, Darrin Dutcher, Denise Gautreau, Jeffrey Lizano, Mark Niosi, Dawn Kelly-Sullivan, Andrew Swick, and Karen Ward for their contributions to this study.

Supporting Information Available: Experimental details, X-ray crystallographic data, and elemental analysis results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Kershaw, E. E.; Flier, J. S. Adipose tissue as an endocrine organ. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 2548–2556.
- (2) Kirkham, T. C. Endocannabinoids in the regulation of appetite and body weight. *Behav. Pharmacol.* **2005**, *16*, 297–313.
- (3) Pagotto, U.; Marsicano, G.; Cota, D.; Lutz, B.; Pasquali, R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocr. Rev.* **2006**, *27*, 73–100.
- (4) Matias, I.; Gonthier, M. P.; Orlando, P.; Martiadis, V.; De Petrocellis, L.; Cervino, C.; Petrosino, S.; Hoareau, L.; Festy, F.; Pasquali, R.; Roche, R.; Maj, M.; Pagotto, U.; Monteleone, P.; Di Marzo, V. Regulation, function, and dysregulation of endocannabinoids in models of adipose and beta-pancreatic cells and in obesity and hyperglycemia. *J. Clin. Endocrinol. Metab.* **2006**, *91*, 3171–3180.
- (5) Hao, S.; Avraham, Y.; Mechoulam, R.; Berry, E. M. Low dose anandamide affects food intake, cognitive function, neurotransmitter and corticosterone levels in diet-restricted mice. *Eur. J. Pharmacol.* **2000**, *392*, 147–156.
- (6) Engeli, S.; Böhnke, J.; Feldpausch, M.; Gorzelniak, K.; Janke, J.; Bätke, S.; Pacher, P.; Harvey-White, J.; Luft, F. C.; Sharma, A. M.; Jordan, J. Activation of the peripheral endocannabinoid system in human obesity. *Diabetes* **2005**, *54*, 2838–2843.
- (7) Kirkham, T. C.; Williams, C. M.; Fezza, F.; Di Marzo, V. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. *Br. J. Pharmacol.* **2002**, *136*, 550–557.
- (8) Jbilo, O.; Ravinet-Trillou, C.; Arnone, M.; Buisson, I.; Bribes, E.; Péleraux, A.; Pénarier, G.; Soubrié, P.; Le Fur, G.; Galiègue, S.; Casellas, P. The CB1 receptor antagonist rimonabant reverses the diet-induced obesity phenotype through the regulation of lipolysis and energy balance. *FASEB J.* **2005**, *19*, 1567–1569.
- (9) Thornton-Jones, Z. D.; Kennett, G. A.; Benwell, K. R.; Revell, D. F.; Misra, A.; Sellwood, D. M.; Vickers, S. P.; Clifton, P. G. The cannabinoid CB1 receptor inverse agonist, rimonabant, modifies body weight and adiponectin function in diet-induced obese rats as a consequence of reduced food intake. *Pharmacol., Biochem. Behav.* **2006**, *84*, 353–359.
- (10) Vickers, S. P.; Webster, L. J.; Wyatt, A.; Dourish, C. T.; Kennett, G. A. Preferential effects of the cannabinoid CB1 receptor antagonist, SR 141716, on food intake and body weight gain of obese (fa/fa) compared to lean Zucker rats. *Psychopharmacology (Berlin, Ger.)* **2003**, *167*, 103–111.
- (11) Hildebrandt, A. L.; Kelly-Sullivan, D. M.; Black, S. C. Antiobesity effects of chronic cannabinoid CB1 receptor antagonist treatment in diet-induced obese mice. *Eur. J. Pharmacol.* **2003**, *462*, 125–132.
- (12) Rinaldi-Carmona, M.; Barth, F.; Héaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Néliat, G.; Caput, D.; et al. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett.* **1994**, *350*, 240–244.
- (13) Lin, L. S.; Lanza, T. J., Jr.; Jewell, J. P.; Liu, P.; Shah, S. K.; Qi, H.; Tong, X.; Wang, J.; Xu, S. S.; Fong, T. M.; Shen, C. P.; Lao, J.; Xiao, J. C.; Shearman, L. P.; Stribling, D. S.; Rosko, K.; Strack, A.; Marsh, D. J.; Feng, Y.; Kumar, S.; Samuel, K.; Yin, W.; Van der Ploeg, L. H.; Goulet, M. T.; Hagmann, W. K. 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. *J. Med. Chem.* **2006**, *49*, 7584–7587.
- (14) Carpino, P. A.; Griffith, D. A.; Sakya, S.; Dow, R. L.; Black, S. C.; Hadcock, J. R.; Iredale, P. A.; Scott, D. O.; Fichtner, M. W.; Rose, C. R.; Day, R.; Dibirio, J.; Butler, M.; Debartolo, D. B.; Dutcher, D.; Gautreau, D.; Lizano, J. S.; O'Connor, R. E.; Sands, M. A.; Kelly-Sullivan, D.; Ward, K. M. New bicyclic cannabinoid receptor-1 (CB1-R) antagonists. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 731–736.
- (15) Lipinski, C. A. In *Pharmaceutical Profiling in Drug Discovery for Lead Selection*; Borchardt, R. T., Kerns, E. H., Lipinski, C. A., Thakker, D. R., Wang, B., Eds.; AAPS Press: Arlington, VA, 2004; Part II, Chapter 1, pp 93–126.
- (16) Katoch-Rouse, R.; Pavlova, O. A.; Caulder, T.; Hoffman, A. F.; Mukhin, A. G.; Horti, A. G. Synthesis, structure–activity relationship, and evaluation of SR141716 analogues: development of central cannabinoid receptor ligands with lower lipophilicity. *J. Med. Chem.* **2003**, *46*, 642–645.
- (17) Svenstrup, N.; Simonsen, K. B.; Thorup, N.; Brodersen, J.; Dehaen, W.; Becher, J. A pyrazole to furan rearrangement. Thermolysis of 5-azido-4-formylpyrazoles. *J. Org. Chem.* **1999**, *64*, 2814–2820.
- (18) Soliman, F. S. G.; Shafik, R. M. Polysubstituted pyrazoles. *Pharmazie* **1975**, *30*, 436–439.
- (19) (a) Muccioli, G. G.; Lambert, D. M. Current knowledge on the antagonists and inverse agonists of cannabinoid receptors. *Curr. Med. Chem.* **2005**, *12*, 1361–1394. (b) Antel, J.; Gregory, P. C.; Nordheim, U. CB1 cannabinoid receptor antagonists for treatment of obesity and prevention of comorbid metabolic disorders. *J. Med. Chem.* **2006**, *49*, 4008–4016.
- (20) At exposures of $\geq 10\times$ the efficacious plasma concentrations in Sprague–Dawley rats, **3** exhibited substantial clinical signs (decreased activity and rapid respiration). Similar narrow therapeutic indexes were observed for other members of this chemical class. These side effects and their associated TI were chemical class dependent, suggesting it is not mechanism related.
- (21) (a) Shim, J.-Y.; Welsh, W. J.; Cartier, E.; Edwards, J. L.; Howlett, A. C. Molecular interaction of the antagonist *N*-(piperidin-1-yl)-5-(4-(chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide with the CB1 cannabinoid receptor. *J. Med. Chem.* **2002**, *45*, 1447–1459. (b) Hurst, D.; Umejiego, U.; Lynch, D.; Seltzman, H.; Hyatt, S.; Roche, M.; McAllister, S.; Fleischer, D.; Kapur, A.; Aboud, M.; Shi, S.; Jones, J.; Lewis, D.; Reggio, P. Biarylpyrazole inverse agonists at the cannabinoid CB1 receptor: importance of the C-3 carboxamide oxygen/lysine3.28(192) interaction. *J. Med. Chem.* **2006**, *49*, 5969–5987.

JM900255T