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Furo[2,3-*b*]pyridine-based cannabinoid-1 receptor inverse agonists: Synthesis and biological evaluation. Part 1

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ABSTRACT

The synthesis, SAR and binding affinities of cannabinoid-1 receptor (CB1R) inverse agonists based on furo[2,3-*b*]pyridine scaffolds are described. Food intake, mechanism specific efficacy, pharmacokinetic, and metabolic evaluation of several of these compounds indicate that they are effective orally active modulators of CB1R.

Treatment options for morbidly obese patients are limited. Surgical interventions while effective[1] are often irreversible and are associated with many risks[2] that would not generally be associated with a pharmaceutical agent. In fact, a study examining the six month complication rate of bariatric surgeries from 2001–2002 found about 40% of patients had complications that required re-hospitalization.[3] With advances in laparoscopic techniques, among other things, this rate has improved to 33% in the period of 2001–2006.[4] The unmet medical needs of this patient population still require reversible, risk appropriate treatment options.

CNS permeable inverse agonists/antagonists of the cannabinoid-1 receptor (CB1R)[5] have been shown to be effective in reducing food intake with concomitant weight loss in both human[6] and other animal[7] studies. In our previous reports,[8] we disclosed the SAR and lead optimization of a screening hit containing a pyridine core arrayed by three hydrophobic domains. This was further optimized by ring annulation leading to naphthyridinone **1** (Fig. 1) which exhibited good acute efficacy (similar to that of taranabant)[9] and had low clearance in rats and dogs.[10] Further elaboration of the core structure to pyrido[2,3-*d*]pyrimidine **2** and ultimately triazolone **3** allowed for adequate in vivo efficacy in rats, but with greatly improved clearance.[11] Unfortunately, **3** suffered from low bioavailability in both dog and monkey; precluding its further development.

Since the N-linked heterobicyclic systems (e.g., **1** and **3**) exhibited improved efficacy for suppressing food intake relative to the monocyclic pyridine core previously disclosed,[11] we continued to pursue modifications to the heterobicyclic scaffold. The goal in this lead optimization was to improve the scaffold sufficiently to have a compound with a pharmacokinetic (PK) and safety profile suitable for human clinical evaluation with efficacy in a rat food intake model comparable to the clinical candidate, taranabant. We were particularly interested in avoiding the low clearance/long $T_{1/2}$ that **1** displayed. Herein we describe our initial evaluation of the general furo[2,3-*b*]pyridine structures **6** and **7**.

Entry into the 6,5 ring system of the furopyridines was readily accomplished using the previously described 2-pyridone **5** (Scheme 1).[10] Deprotonation of **5** with Cs_2CO_3 afforded an ambident anion, which was alkylated with an α-haloketone. This provided a mixture of O- and N-alkylated products typically

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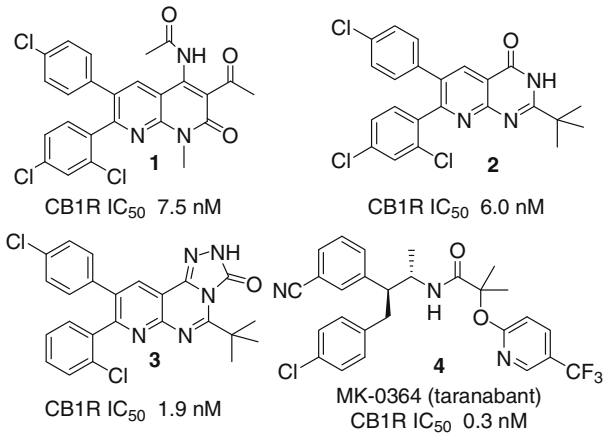
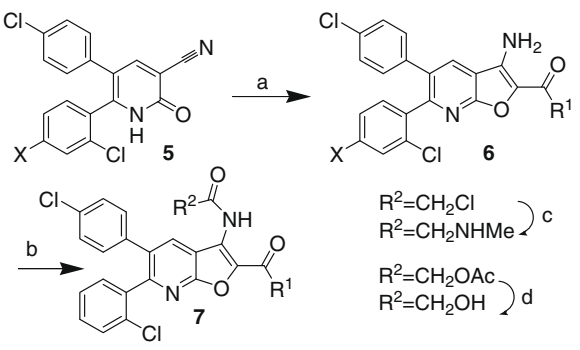


Figure 1. Heterobicyclic and tricyclic Merck leads and MK-0364.

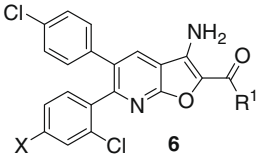
produced in a 1:1 to 4:1 ratio respectively. The desired O-alkylated isomer could be purified from the reaction mixture or further deprotonated causing intramolecular nucleophilic attack upon the adjacent nitrile which provided the furopyridine of general formula **6**. The amino group of **6** was further elaborated into amides and ureas by treatment with the appropriate acylating agent. Not surprisingly, the amino group, in the form of a vinylogous amide, was a poor nucleophile. For example, acylation with acetic anhydride in acetic acid required heating to 80 °C for 2–3 h to get the reaction to go to completion. This was the preferred route to compound **7f** since exposure of **6** (where X = H) to acetic anhydride with base resulted in over acylation while treatment with acetyl chloride led to less pure reaction mixtures, including over acylation.

Human binding affinities (Tables 1 and 2) were determined using a standard protocol and all compounds tested were found to be functional inverse agonists of CB1R.[12] One of the first compounds prepared in this series was **6g**. It shared the same trichloro halogenation pattern as **1** and **2** and had similar potency (5.5 nM) at CB1R (Table 1). With structural similarities to both **1**, **2** and **3** we were eager to evaluate **6g** in vivo to determine its anorectic effects in DIO (diet induced obese) rats (Table 3). Compound **6g** was dosed orally (PO) at 1 mg/kg and rats were monitored for 18 h to determine changes in body weight (BW) and ability to suppress food intake (FI) relative to vehicle control.[9] Compound **6g** suppressed FI 50% relative to vehicle control in addition to causing a 5 g loss in BW relative to vehicle treated rats that gained 13 g. This was the same FI response we saw with **3**, but with only 1/3 the dose. Compound **1** had previously shown a very strong FI response (−68% relative to vehicle at 3 mg/kg), but with a very long $T_{1/2}$ in rats (>8 h).



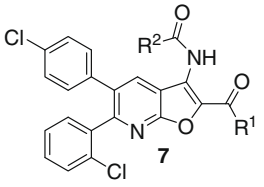
Scheme 1. Reagents and conditions: (a), α-haloketone, Cs_2CO_3 or K_2CO_3, DMF, rt to 65 °C, 45–80%; (b) RC(O)Cl or Ac_2O/AcOH when R^2 is Ac, MeCN, rt to 80 °C, 46–95%; (c) CH_3NH_2, DMF, rt, 80%; (d) LiOH·H_2O, MeOH, THF, rt, 87%.

Table 1
Binding affinity of compounds at the human CB1R and CB2R expressed as IC_{50} (nM)[12]



Compound	R^1	X	CB1R	CB2R
6a	Me	Cl	56	1000
6b	Et	Cl	17	360
6c	Et	H	13	1000
6d	*i*-Pr	Cl	1.9	640
6e	*i*-Pr	H	1.7	1300
6f	Ph	Cl	3.5	440
6g	*t*-Bu	Cl	5.5	440
6h	*t*-Bu	H	4.3	1900
6i	$C(CH_3)_2OH$	H	20	2100

Table 2
Binding affinity of compounds at the human CB1R and CB2R expressed as IC_{50} (nM)[12]



Compound	R^1	R^2	CB1R	CB2R
7a	*t*-Bu	Me	0.58	>2000
7b	*t*-Bu	NMe_2	0.39	1970
7c	*t*-Bu	CH_2NHMe	1.2	3300
7d	*t*-Bu	CH_2OH	1.2	3400
7e	*i*-Pr	CH_2OH	0.40	5100
7f	$C(CH_3)_2OH$	Me	5.4	5400
7g	$C(CH_3)_2OH$	CH_2OH	4.3	5400

Compound **3** had improved $T_{1/2}$ in rats (5.6 h) relative to **1**, but had very little bioavailability (F%) in both dog (2.1%) and monkey (9.7%). The pharmacokinetic properties of **6g** are shown in Table 4. The $T_{1/2}$ of **6g** decreased in both rats (4.6 h) and dogs (7.9 h) relative to **1**. However, monkey showed fast clearance and a short $T_{1/2}$ of 2.4 h with a low bioavailability of 11%. The high clearance of **6g** in monkey was not initially a concern as this compound showed low metabolic stability when incubated in monkey liver microsomes (only about 25% remaining after 60 min) while its response in human microsomes was much more like that of rat and dog showing little turnover (near 100% remaining after a 60 min incubation). These results were consistent with the poor PK seen in monkey (Table 4).

The metabolism of tritiated **6g** was also explored. In rat plasma parent compound was the major circulating species at 2, 6 and 24 h. However, in rat brain at all time points a hydroxylated metabolite (presumably one of the methyls of the *t*-butyl group) was observed in a 1:1 ratio with parent. This undesired level of metabolite in the brain was further complicated by potentially poor dose recovery. Excretion of tritiated **6g** from bile-duct cannulated rats was monitored for 120 h in IV (2 mg/kg) treated animals. Bile and urine were examined and essentially the entire dose was recovered in the bile. Total recovery was only 41% after 5 days.[13] This was presumably due to the compounds lipophilicity manifested by a high log *D* of 6.7.[14]

Table 3
DIO rat overnight (18 h) body weight change (g) and food intake[a]

Compound	Δ BW (vehicle)	Δ BW (compound)	% Food intake suppression
6g	+13	−5	53
6h	+8	−4	33
7d	+5	−6	24
7e	+5	−7	37
7g	+6	−7	47
7f (0.1 mpk)	+10	−1	28
7f (0.3 mpk)	+10	−1	41
7f	+10	−13	72

[a] BW = body weight. All rats were dosed at 1 mg/kg unless otherwise indicated. All p values were $\leqslant 0.05$. mpk = mg/kg.

Table 4
Pharmacokinetic profiles (monkey = Rhesus macaque)

Compound (animal)	F (%)	$T_{1/2}$ (h)	Clp (mL/min/kg)	Rat B/P (μM)
6g (rat)	59	4.2	5.6	0.22/0.22 = 1.0
6g (dog)	63	7.9	7.3	—
6g (monkey)	11	2.4	29	—
6h (rat)	100	2.8	22	0.29/0.13 = 2.3
7d (rat)	32	3.5	10	0.086/0.049 = 1.8
7d (dog)	42	11	3.0	—
7e (rat)	38	3.3	20	0.15/0.16 = 0.94
7e (dog)	31	52	4.9	—
7f (rat)	61	4.8	16	0.056/0.072 = 0.77
7f (dog)	87	26	5.0	—
7f (monkey)	100	45	2.8	—
7g (rat)	64	7.5	8.6	0.094/0.147 = 0.64
7g (dog)	9	1.8	33	—
7g (monkey)	50	17	2.1	—

Brain/plasma (B/P) concentrations were determined at 4 h following 1 mg/kg IV dosing.

Table 5
DIO rat 2 week efficacy following daily administration: body weight change (g) and food intake[a]

Compound	Δ BW (vehicle)	Δ BW (compound)	% Food intake suppression
6g	+29	−3	19
7d	+21	−19	19
7g	+24	−2	24
Taranabant[*]	+23	−3	21

[a] BW = body weight. All rats were dosed at 1 mg/kg. All p values were $\leqslant 0.05$. 14 day study: the study ended 18 h post dose day 14.
[*] This study ended on day 13.

Further examination of the physical properties of **6g** indicated photo-oxidative instability in solution. After 40 h in an aqueous pH 7.4 phosphate buffer solution exposed to air, 40 percent of the material was observed to degrade to multiple products. This was somewhat suppressed by a blanket of argon over the solution resulting in a 15% loss of material to degradation while in solution. The exact mechanism of the degradation was not investigated, but it was clear there were several key deficiencies in this compound that would need to be overcome to bring a compound forward for further advancement. The most important of which would be to improve the stability and dose recovery.

Continued optimization of this series was driven by the need to increase stability and reduce the lipophilicity of **6g**. Table 1 shows the initial efforts. As the steric bulk of the *t*-butyl group at the 2-position was decreased, it was found that the isopropyl group improved potency to about 2 nM in both **6d** and **6e**. Further reductions to either an ethyl (13 or 17 nM CB1R for **6c** and **6b**) or a methyl group (56 nM CB1R for **6a**) resulted in lower activity. The hydroxy isopropyl **6i** showed a 4-fold loss of activity relative to **6g** but had improved solubility and log D (4.7 compared to 6.7 for **6g**). Of interest was the fact that the 4-chloro of the dihalogenated phenyl ring was not necessary for good binding, as the bis-chloro analog **6h** had essentially the same CB1R activity at 4.3 nM as **6g**. None of the modifications at the 2-position of a 3-amino furopyridine were sufficient to improve the profile of a compound like **6g** sufficiently to advance further. However, modifications to the 3-position of the furan ring (Table 2) led to more significant changes.

Optimization of the 3-position began with acetylation of **6h**. This led to **7a** with a 7-fold increase in CB1R potency (0.58 nM), bringing the specificity of CB1R to CB2R to over 3400:1. Unfortunately with the increase in potency came a decrease in solubility. In fact the compound defied all attempts at formulation and in vivo analysis was not possible. Installation of hetero atoms became a necessity to improve the physicochemical properties (vehicle solubility). Dimethyl urea **7b** (0.39 nM CB1R) and sarcosine amide **7c** (1.2 nM) were more soluble than **7a**, but showed only 7% and 11% bioavailability respectively in rat. Glycolamide **7d** showed improved log D (6.0) relative to **6g**. The hydroxyl group greatly improved solubility relative to **7a** allowing for formulation and a determination of in vivo properties. Examination of the glycolamide with the isopropyl ketone **6e** provided **7e** and a further reduction in log D (5.7) with improvement in potency to 0.4 nM at CB1R. Moving the hydroxyl group to the ketone position for acetamide **7f** resulted in a ninefold loss of potency to 5.4 nM at CB1R relative to 0.58 nM for **7a**. Bishydroxylated **7g** showed about the same potency at 4.3 nM as **7f** however the log D dropped to 4.9. It was observed that acylation of the 3-amino group resolved the oxidative/photoinstability seen with amino compound **6g**. The four hydroxyl containing compounds were selected for further evaluation.

Table 3 showed the acute food intake effects elicited after a 1 mg/kg oral dose. All compounds effectively suppressed FI and decreased BW gain relative to vehicle treated controls. Of the four, **7f** and **7g** stood out, exhibiting the most robust effects. Even at a dose as low as 0.1 mg/kg, **7f** significantly suppressed 18-h FI and reduced BW in similar fashion to **7d**, but at only one tenth the dose.

In vivo profiles of **7d**–**g** (Table 4) were required to further differentiate these compounds. Both **7d** and **7e** had good exposure in rats with about the same 3.5 h $T_{1/2}$. They also both exhibited considerable deacylation with the corresponding 3-aminofuropyridine metabolite circulating following PO administration in rats. In contrast, compounds **7g** and **7f** did not exhibit this behavior. While **7f** had a 4.8 h $T_{1/2}$ in rats, it was long-lived in higher species showing a one and two day $T_{1/2}$ in dog and monkey, respectively. At this point we focused our efforts on the evaluation of **7g** as we viewed the multi day $T_{1/2}$ for **7f** as too long.

While **7g** had good bioavailability in both rats (64%) and monkey (50%) it exhibited fast clearance in dog with only 9% oral bioavailability. To see if this would be problematic for human PK, the metabolic stability of **7g** was evaluated in liver microsome incubations (Fig. 2). In the initial evaluation of oxidative metabolism, **7g** was incubated with liver microsomes for 60 min in the presence of NADPH (data not shown). This experiment provided no guidance as the compound showed little turnover in rat, dog, monkey or human microsomes. However when the experiment was repeated to also allow for glucuronidation [NADPH+ uridine diphosphate glucuronic acid (UDPGA)] **7g** was rapidly turned over in only dog microsomes. This was consistent with the rapid clearance seen solely in dog PK. Since this fast glucuronidation appeared to be only associated with dog it did not appear to be a liability for human testing.

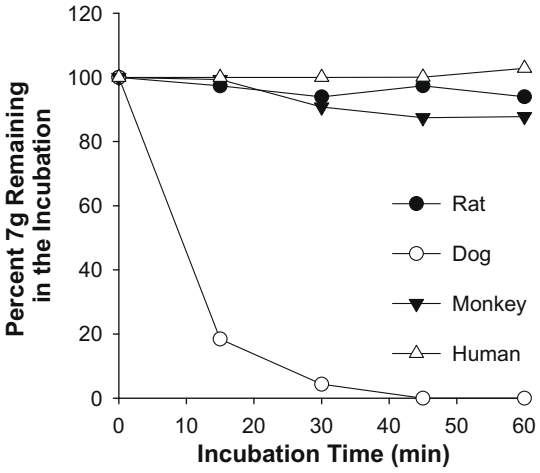


Figure 2. Metabolic stability of **7g** in liver microsomes.

In order to confirm that the anorectic effects displayed by **7g** were mediated through actions at CB1R, an overnight food intake study[15] using CB1R-deficient (*Cnr1*−/−) mice was conducted. After appropriate dose selection in C57BL/6 wild-type mice,[16] *ad libitum* fed 14–16 week-old male mice (*Cnr1*+/+, $n = 10$; *Cnr1*−/−, n = 7) were dosed orally with **7g** at 1 mg/kg. Compound **7g** significantly inhibited overnight (18 h) FI (53% suppression, $p < 0.0001$) (Fig. 3) and inhibited BW gain (−0.79 g loss relative to 1.39 gain for vehicle, $p < 0.0001$) in wild-type (*Cnr1*+/+) mice (Fig. 4). **7g** had no significant effect on any of these parameters in *Cnr1*−/− mice. These data demonstrate that the anorectic actions of **7g** are mediated by CB1R.

Chronic evaluation of **7g** was carried out with oral dosing for 2 weeks in DIO rats. As Figure 5 indicates **7g** showed a dose dependent response in its ability to affect changes in BW. Dosing at 0.1 mg/kg proved ineffective, while 0.3 or 1 mg/kg significantly reduced BW gain relative to vehicle. At 1 mg/kg, **7g** suppressed cumulative FI 24% ($p < 0.005$) resulting in a 4.3% BW loss relative to vehicle treated rats. This was on par with our clinical candidate

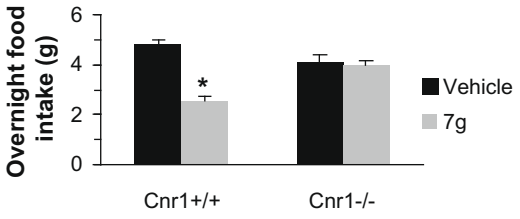


Figure 3. Overnight food intake with wild-type and CB1-deficient mice (* = $p < 0.0001$).

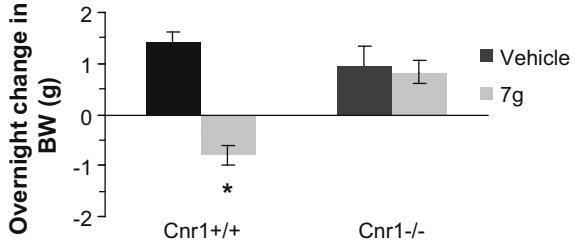


Figure 4. Overnight body weight change with wild-type and CB1-deficient mice (* = $p < 0.0001$).

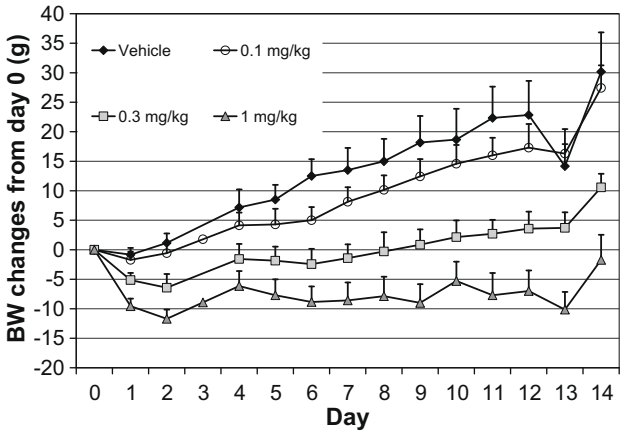


Figure 5. DIO Rat 2 week efficacy following daily administration of **7g** at 0.1, 0.3, and 1 mg/kg: body weight change (g).

(**4**) at 1 mg/kg which showed a 21% suppression in FI resulting in a 6.0% BW loss relative to vehicle treated rats in a similar 13 day study. Compounds **6g** (5.3% BW loss relative to vehicle) and **7d** (6% BW loss relative to vehicle) are also included in Table 5 for comparison.

Compound **7g** had a reduced log *D* value of 4.9 relative to 6.7 for **6g**. To determine if this would result in improved dose recovery, tritiated **7g** was prepared and dosed IV to bile-duct cannulated rats at 1 mg/kg. Radioactivity excretion[17] measured as a percent of dose was determined to be 87% in bile and 5% in urine, indicating acceptable dose recovery for continued evaluation of the compound.

Off target activity of **7g** was evaluated as well. It was shown not to be a significant inhibitor of the cytochrome p450 enzymes (IC_{50} in μM): CYP3A4 98, CYP2C9 17, CYP2D6 73, CYP2C19 43, CYP1A2 >100. The activity of **7g** in the hERG potassium channel assay was determined to be 6.6 μM IC_{50}. This was followed up with an in vivo readout of cardiac parameters carried out in anesthetized dogs at a 1–3–10 mg/kg cumulative dose IV infusion (each dose infused over 30 min). Plasma levels of **7g** reached 50 μM by the end of the infusion. No meaningful changes in mean arterial pressure, heart rate, or ECG intervals (including QTc) were observed as compared to vehicle treated animals. Finally, **7g** was screened broadly against a customized panel of 175 assorted radioligand binding and enzymatic assays.[18]

Of concern was a hit in a rat ligand-gated ion-channel receptor $GABA_A$, showing an estimated IC_{50} of 1.8 μM. In house patch clamp electrophysiological evaluation of the effects of **7g** on Ltk cells expressing human $\alpha_1\beta_3\gamma_2$ $GABA_A$ receptors indicated that it behaved as a partial agonist with an EC_{50} of about 700 nM with a maximum efficacy of 18% at 3 μM relative to maximum GABA activity. Additionally the responses showed very slow kinetics relative to GABA. Currents induced by **7g** were inhibited by GABA receptor antagonists picrotoxin and bicuculline, suggesting activity via the GABA binding site. Since γ-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system, it was of utmost importance to ascertain what if any effects in vivo might occur by the modulation of $GABA_A$ by **7g**. Initial evaluation in a rotarod[19] assay at 100 times the MED in male Sprague Dawley rats (orally dosed at 30 mg/kg) showed no visible effects with plasma and brain drug levels of about 0.5 μM. In CD1 mouse mild symptoms occurred at 30 mg/kg (plasma 7 μM, brain 2.3 μM) while at 100 mg/kg more pronounced hyperactivity, hyperreactivity and ataxia were observed (plasma 24 μM, brain 6.5 μM). With these findings, further development of **7g** was halted. Evaluation of other furopyridines indicated that there was still reason for optimism about this series as other compounds in this series such as **6g**

showed greatly reduced $GABA_A$ activity (about 22% inhibition at 10 μM) and were devoid of adverse neurological effects after dosing CD1 mice at 500 mg/kg.

In summary, we have shown that the heterobicyclic furo[2,3-*b*]pyridines exemplified by **7g** and **7f** are potent CB1R inverse agonists that are effective in modulating feeding behavior to suppress both FI and BW gain. These effects were determined to be mechanism based. While the efficacy, physical properties, pharmacokinetics, drug metabolism and disposition were acceptable, off-target $GABA_A$ activity in lead compound **7g** prevented clinical advancement. Further SAR studies to avoid $GABA_A$ activity, pharmacological evaluation and safety profiling of alternative furopyridine analogs will be reported in due course.

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12. The reported binding results were an average of 2–8 independent determinations (each done in replicate) which were normally within 50% of the average value. For both the binding and functional assay conditions, see: Felder, C. C.; Joyce, K. E.; Briley, E. M.; Mansouri, J.; Mackie, K.; Blond, O.; Lai, Y.; Ma, A. L.; Mitchell, R. L. *Mol. Pharmacol.* **1995**, *48*, 443.
13. Feces were not collected.
14. HPLC Log *D* values were determined at pH 7.3.
15. C57BL/6 mice were purchased from Taconic Farms. *Cnr1* knockout mice were generated by the laboratory of Dr. Andreas Zimmer, National Institute of Mental Health, NIH (Zimmer, A.; Zimmer, A. M.; Hohmann, A. G.; Herkenham, M.; Bonner, T. I. *Proc. Natl. Acad. Sci.* **1999**, *96*, 5780) and generously provided by him.
16. Experimental methods were similar to that described in Ref. 10 except **7g** was only dosed at 1 and 3 mg/kg based on its improved efficacy.
17. Rats were monitored for 120 h.
18. Discovery Pharmacology services provided by MDS Pharma Services, Taipei, Taiwan.
19. A rotarod test is used to assess the rodent's sensomotor coordination by evaluating how long it can remain on a rotating rod with a steady or increasing rate of rotation.