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Letter

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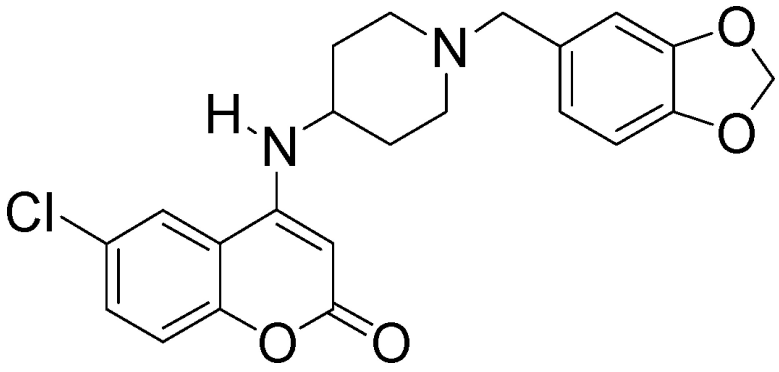

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Discovery and Characterization of Aminopiperidinecoumarin Melanin Concentrating Hormone Receptor 1 Antagonists

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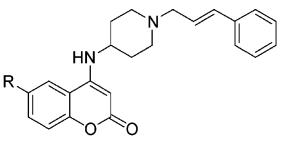
Received June 23, 2005

Abstract: 4-(1-Benzo[1,3]dioxol-5-ylmethylpiperidine-4-ylmethyl)-6-chlorochromen-2-one (**7**) is a potent, orally bioavailable melanin concentrating hormone receptor 1 (MCHr1) antagonist that causes dose-dependent weight loss in diet-induced obese mice. Further evaluation of **7** in an anesthetized dog model of cardiovascular safety revealed adverse hemodynamic effects at a plasma concentration comparable to the minimally effective therapeutic concentration. These results highlight the need for scrutiny of the cardiovascular safety profile of MCHr1 antagonists.

Melanin-concentrating hormone[1] (MCH) is a cyclic, 19 amino acid peptide expressed by neurons in the lateral hypothalamus and zona incerta and shown to play a major role in body weight regulation in rodents.[1,2] A single injection of MCH into the central nervous system stimulates food intake in rodents,[3] and chronic administration leads to increased body weight.[4] Similarly, transgenic mice overexpressing the MCH gene are susceptible to insulin resistance and obesity.[5] Mice lacking the gene encoding MCH are hypophagic, lean, and maintain elevated metabolic rates.[6] Consistent with this phenotype, animals that lack the gene encoding the MCH receptor maintain elevated metabolic rates and thus remain lean despite hyperphagia on a normal diet.[7,8] Finally, the observation that chronic administration of small-molecule MCHr1 antagonists leads to the reduction of body weight provides further validation of MCHr1 blockade as a novel target for antiobesity pharmacotherapy.[9]

Aminopiperidinecoumarin **1** was identified by high-throughput screening as a moderate affinity ($IC_{50} = 191 \pm 40$ nM) MCHr1 antagonist. Exploration of substitution effects on the coumarin ring system (Figure 1) rapidly identified C6 substitution as being critical for improvement in MCHr1 affinity and functional antagonism. Specifically, C6-chloro and C6-methoxy substitution delivered potent MCHr1 antagonists that were evaluated further in pharmacokinetic assays in lean mice. The C6-chloro analogue **2** demonstrated efficient penetration into the brain upon oral dosing at 10 mg/kg. On the basis of favorable brain exposure of the 6-chloro analogue (1.35 and 0.44 AUC_{brain}:AUC_{plasma} for **2** and **3**, respectively), we focused our investigation of the SAR of cinnamyl replacements on the 6-chlorocoumarin series.



	1: R = H	**2**: R = Cl	**3**: R = OMe
MCHr1 binding IC_{50} (nM)[a]	191 ± 40	9 ± 4	4 ± 1
Ca^{2+} release IC_{50} (nM)[a]	1036 ± 12	211 ± 48	44 ± 6
Plasma AUC (μg·hr/mL)[b]	NT[c]	1.92	0.98
Brain AUC (μg·hr/g)[b]	NT[c]	2.60	0.43

Figure 1. Aminopiperidinecoumarin MCHr1 antagonists: (footnote a) values represent an average of at least three determinations (in duplicate); (footnote b) 10 mg/kg, po in lean mice, where interanimal variability was less than 25% for all values; (footnote c) NT, where **1** was not evaluated in animals.

The synthesis of the aminopiperidinecoumarin analogues is shown in Scheme 1. Treatment of hydroxycoumarin **4** with trifluoromethanesulfonic anhydride in the presence of base provided the triflate, which was subsequently displaced by 4-amino-1-*N*-Boc-piperidine and deprotected under acidic conditions to provide aminopiperidinecoumarin **5**. Derivatization of the piperidine nitrogen was accomplished by reductive amination of arylaldedydes or nucleophilic displacement of cinnamyl chloride or benzyl halides to provide the MCHr1 antagonists.

Table 1 summarizes the structure−activity relationships for the MCHr1 binding affinity and functional inhibition observed with the aminopiperidinecoumarin analogues. The naphthyl analogue **6** maintained potency comparable to that of the cinnamyl lead **2**, indicating steric tolerance of the receptor for bicyclic substituents. Efforts to incorporate heteroatoms into the proximal ring of the bicyclic system resulted in loss of MCHr1 potency (data not shown), but the receptor did tolerate heteroatom substitution into the distal ring. In particular, [6,5]-bicyclic heterocycles were well tolerated by the receptor, and we rapidly identified the piperonyl analogue **7** as a potent inhibitor of MCH-mediated Ca^{2+} release. Several other [6,5]-bicyclic heterocycles were also active; in particular, potent functional MCHr1 antagonism was observed with dihydrobenzo[*b*]furan **8** and the indole analogues **12** and **14**.

Representative potent MCH antagonists were subsequently evaluated in diet-induced obese (DIO) mice to determine the impact of the bicyclic heterocyle on brain and plasma exposure after oral dosing (Table 2). The piperonyl analogue **7** provided the best combination of

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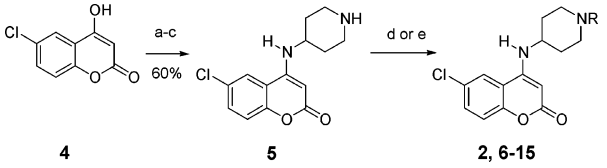
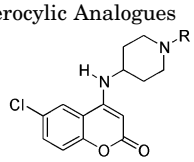
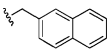
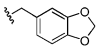
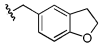
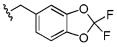
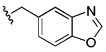
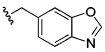
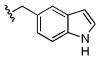
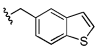
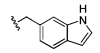
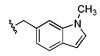
Scheme 1. Synthesis of Aminopiperidinecoumarin MCHr1 Antagonists[a]



[a] Reagents and conditions: (a) Tf_2O, Et_3N, CH_2Cl_2, 0 °C; (b) 4-amino-1-*N*-Boc-piperidine, *i*Pr_2NEt, CH_3CN; (c) 4 N HCl, dioxane (yield for steps a−c = 92%); (d) aldehyde, $NaCNBH_3$, MeOH (yield = 65−90%); (e) alkyl halide, K_2CO_3, DMF (yield = 28−40%).

Table 1. SAR of Heterocylic Analogues



Compd	R	MCHr1 binding IC_{50} (nM)[a,c]	Ca^{2+} release IC_{50} (nM)[b,c]
6		21 ± 11	92 ± 25
7		2 ± 1	28 ± 5
8		27 ± 3	41 ± 3
9		19 ± 2	581 ± 49
10		3 ± 1	163 ± 40
11		75 ± 16	461 ± 55
12		7 ± 3	63 ± 4
13		6 ± 2	189 ± 25
14		24 ± 4	28 ± 1
15		60 ± 47	162 ± 46

[a] Displacement of [^{125}I]MCH from IMR-32 (I3.4.2) cell membranes (MCH binding K_d = 0.66 ± 0.25 nM, B_{max} = 0.40 ± 0.08 pmol/mg). [b] Inhibition of MCH-mediated Ca^{2+} release in whole IMR-32 cells (MCH EC_{50} = 62.0 ± 3.6 nM). [c] All values are the mean ± SEM and are derived from at least three independent experiments (all duplicates).

Table 2. Selected Pharmacokinetic Parameters of Aminopiperidinecoumarin Analogues Dosed at 10 mg/kg in DIO Mice[a]

compd	plasma AUC_{0-24h} (μg·h/mL)	brain AUC_{0-24h} (μg·h/g)	brain C_{max} (ng/g)	brain C_{12h} (ng/g)
7	6.35	4.17	454 ± 36	175 ± 15
8	0.621	0.449	294 ± 60	0
10	0[b]	0[b]	0[b]	0[b]
12	2.87	1.18	182 ± 40	18 ± 6.3

[a] All values are the mean ± SEM (n = 3). [b] No drug levels detected in any animal (n = 3) because of instability of compound in plasma.

potent functional antagonism, metabolic stability,[10] and exposure in the brain (AUC = 4.17 μg·h/g) and plasma (AUC = 6.35 μg·h/mL) with oral dosing in DIO mice (10 mg/kg) and therefore was selected for further evaluation. Of particular importance, a 10 mg/kg dose of **7** delivered significant drug levels in the brain throughout a 12 h period (brain C_{12h} = 175 ng/g), suggesting that twice a day (b.i.d.) dosing may provide sufficient drug concentration in the brain to deliver in vivo efficacy.

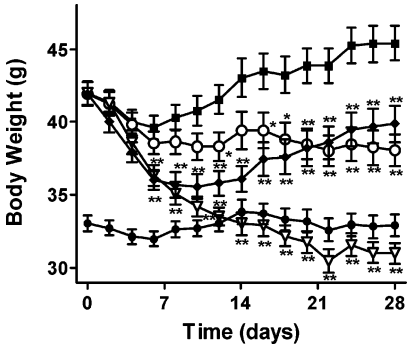


Figure 2. Effect of **7** (dosed at 10 (○) and 30 (▽) mg/kg, po, b.i.d. in 1% Tween-80 in water) and sibutramine (10 mg/kg, po, b.i.d., ◆) on the body weight of DIO mice, and the effect of **7** (30 mg/kg, po, b.i.d., ●) on the body weight of lean mice. Control DIO (■) mice were treated b.i.d. with 4 mL/kg vehicle. All values are the mean ± SEM for n = 12: (**) $p < 0.01$ and (*) $p < 0.05$ for comparisons against vehicle group by Dunnett's test.

Evaluation of coumarin **7** against 61 enzymes and receptors at Novascreen[11] revealed moderate cross-reactivity against three G-protein coupled receptors that also bind biogenic amine ligands (nonselective adrenergic-α1, 75% at 10 μM; nonselective opiate, 69% at 10 μM; nonselective dopamine, 60% inhibition at 10 μM) (see Supporting Information). Compound **7** did not show appreciable affinity to MCHr2[12] or other receptors that have been implicated in weight loss (galanin, CCK1, or serotonin transporter). Compound **7** did bind to the hERG potassium channel with moderate affinity (IC_{50} = 2.25 ± 0.61 μM).

Compound **7** was evaluated for its effects on body weight in DIO mice that were fed a high-fat diet (60% lard) ad libitum in a 28-day study. Animals were dosed orally with **7** (10 or 30 mg/kg, b.i.d.), sibutramine (10 mg/kg, b.i.d.), or vehicle, and body weight was measured daily (22 animals per group). Vehicle-treated DIO mice continued to gain weight throughout the study (8% body weight increase, Figure 2). The sibutramine-treated animals rapidly lost weight through day 7. The weight loss plateaued during days 7−14, and the animals started to regain weight after 14 days of treatment. Similar to previously described MCHr1 antagonists,[9] **7** caused a dose-dependent decrease in the body weight of treated DIO mice throughout the study. After 28 days, DIO mice treated with sibutramine (10 mg/kg, qd) weighed 12% less than vehicle-treated mice (Table 3), while mice dosed with coumarin **7** weighed 16% and 32% less in the 10 and 30 mg/kg b.i.d. groups, respectively. DIO mice treated with **7** at 30 mg/kg reached a body weight comparable to those of lean mice within 13 days of dosing, after which further body weight reduction was minimal. No evidence of overt toxicity or behavioral abnormalities was noted in drug-treated animals (Irwin analysis) on day 28 during a 5 h observation period immediately following administration of the final dose. A group of lean mice was also dosed with coumarin **7** (30 mg/kg, b.i.d.) in the 28 day study, and body weight in these mice remained stable throughout the duration of treatment. In separate studies, rats treated with a single 30 mg/kg dose of **7**

Table 3. Body Weight (BW) of All Animal Groups at Days 0 and 28 and % Change of the Drug-Treatment Groups Relative to Vehicle[a]

group[b]	BW_{day0} (g)	BW_{day28} (g)	% change from vehicle
lean, 30 mg/kg **7**	33.1 ± 2.5	32.9 ± 2.4	
DIO, vehicle	41.9 ± 3.9	45.4 ± 3.8	
10 mg/kg sibutramine	41.9 ± 3.8	39.9 ± 4.0	−12
10 mg/kg **7**	41.9 ± 3.8	38.1 ± 3.5	−16
30 mg/kg **7**	42.0 ± 3.8	31.0 ± 2.2	−31

[a] All values are the mean ± SEM ($n = 12$). [b] All doses were given in 4 mL/kg body weight volume of vehicle (1% Tween-80 in water). Compound **7** was administered po by gavage at doses of 10 and 30 mg/kg, b.i.d., and sibutramine was administered at a dose of 10 mg/kg, po, qd. Body weights were determined daily for 28 days.

Table 4. Change in Body Weight (% Change from Vehicle) and Drug Exposure Data after Final Dose on Day 13

dose (mg/kg, po, b.i.d.)	% change BW from vehicle	plasma (μg/mL)[a]	brain (μg/g)[a]
10	−6.9 ± 1.4	2.00 ± 0.39	2.21 ± 0.15
30	−18.2 ± 1.9	6.01 ± 1.16	6.46 ± 0.42

[a] Drug concentrations in plasma and in brain determined 1 h after the final dose. All values are the mean ± SEM ($n = 3$).

demonstrated normal behavioral satiety sequence and normal behavior in a conditioned taste-aversion test.[13]

Encouraged by the dose-dependent weight loss in DIO mice and weight-neutral effects of dosing coumarin **7** in lean mice, we performed a follow-up study to investigate the drug exposure required to achieve weight loss in DIO mice and the food intake profile associated with administration of **7**. Dosing DIO mice for 13 days with coumarin **7** (10 or 30 mg/kg b.i.d.) again resulted in dose-dependent reduction in body weight in compound-treated animals (Table 4). Interestingly, the 10 mg/kg b.i.d. dose of **7** led to significant reduction in body weight after 13 days of dosing but did not reduce cumulative food intake (FI) compared to vehicle-treated controls (38.7 ± 4.1 and 40.2 ± 3.6 g, respectively). The weight loss observed upon treatment with **7** at 10 mg/kg could be the result of an alteration in energy expenditure. Similar findings have been reported in MCHr1 −/− mice, which consumed the same amount of food on a normal diet as the wild-type mice, yet were resistant to weight gain as a result of increased energy expenditure.[7,8] The additional weight loss observed in DIO mice treated with the higher dose of **7** (30 mg/kg, b.i.d., Table 4) is accounted for by the reduction in food intake in the animals in this dose group (cumulative FI = 24.2 ± 1.7 g). Given the high end-of-study drug levels achieved in the brain (6.46 μg/g), it is possible that some of the weight loss observed in the animals dosed at 30 mg/kg could be due to off-target activities of the compound.

The end-of-study drug levels (1 h after last dose) indicated high levels of drug present in plasma (2 μg/mL at 10 mg/kg; 6 μg/mL at 30 mg/kg) and brain (2.2 μg/g at 10 mg/kg; 6.5 μg/g at 30 mg/kg). The minimally effective therapeutic plasma concentration was taken from the plasma drug concentration 1 h (C_{max}) after the administration of the final 10 mg/kg dose (2 μg/mL).

Supported by the compelling efficacy profile in DIO mice, coumarin **7** was selected for analysis of pharmacokinetic parameters in male beagle dogs and for safety assessment in an anesthetized dog cardiovascular model. Following a single iv bolus of 2.5 mg/kg, the apparent

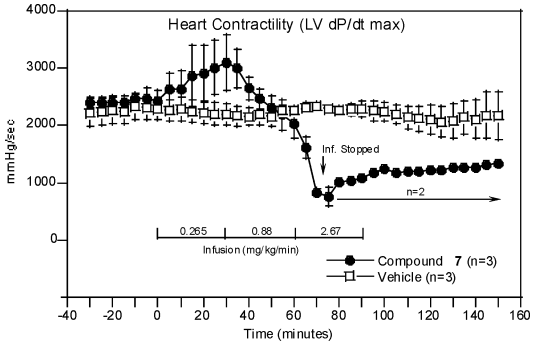
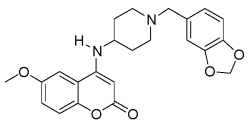


Figure 3. Functional effects of intravenous administration of **7** were assessed in male beagle dogs anesthetized with sodium pentobarbital (35 mg/kg, 6 (mg/kg)/h maintenance infusion). Animals were intubated, mechanically ventilated, and instrumented for acute measurement of mean arterial pressure, cardiac contractile function, and pulmonary arterial pressure. After a 30-min baseline period, **7** was infused as a series of three 30-min infusions followed by a 60-min post-treatment period

half-life was 3.9 ± 0.5 h, the mean maximum plasma concentration (C_{max}) was 1.60 ± 0.12 μg/mL, the plasma clearance (CL_p) was 0.95 ± 0.15 L/(h·kg), and the average total exposure ($AUC_{0\to\infty}$) achieved was 2.66 ± 0.38 μg·h/mL. After oral administration of **7** in dogs, the C_{max} was 0.20 ± 0.06 μg/mL, the half-life was 4.4 ± 0.5 h, and the oral bioavailability was 48 ± 12%.

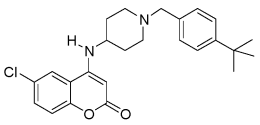
Compound **7** was evaluated further in a pentobarbital anesthetized dog model of cardiovascular function using an escalating dosing paradigm.[14] Compound **7** was administered intravenously as a series of three 30-min infusions at doses of 8, 26, and 80 (mg/kg)/30 min. At the end of the first two infusion periods, respective plasma concentrations achieved were 3.33 ± 0.16 and 11.80 ± 0.49 μg/mL. The third infusion was terminated after approximately 12 min because of pronounced functional effects leading to risk of cardiovascular collapse (Figure 3). Subsequently, the maximum drug concentration measured was 19.89 ± 6.34 μg/mL. Principal hemodynamic effects of the compound included an initial significant increase in indices of cardiac contractility (dP/dt_{max}) early in the dosing cycle followed by a steep, dose-dependent decrease as plasma drug concentrations approached maximum values. In addition, pulmonary arterial pressure trended upward during the first dose, in parallel with dP/dt. However, as dP/dt decreased and plasma concentrations continued to increase, pulmonary arterial pressure increased steeply to values nearly 2-fold above baseline, and escalating doses of **7** resulted in a dose-dependent decrease in mean arterial pressure. Given that the minimally effective therapeutic drug concentration derived from the efficacy study in DIO mice was 2.0 ± 0.4 μg/mL, further development of this compound was halted because of an insufficient therapeutic index.

Coumarin **7** is a structurally novel MCHr1 antagonist characterized by potent functional antagonism, prolonged exposure in the brain with oral dosing, and dose-dependent weight loss leading to normalization of body weight within 13 days of dosing (30 mg/kg, b.i.d.) in DIO mice. However, the compound fails to deliver an acceptable therapeutic index with respect to multiple adverse hemodynamic cardiovascular parameters after intravenous dosing in male beagle dogs. The factors that



16

MCHr1 Ca^{2+} release IC_{50} = 11 +/- 3 nM



17

MCHr1 Ca^{2+} release IC_{50} > 10,000 nM

Figure 4. Structures and functional activities of additional aminopiperidinecoumarins evaluated in dog cardiovascular assay.

contribute to the insufficient therapeutic index for this compound are twofold: (1) high plasma concentration is required to deliver sufficient drug levels to the brain to achieve chronic weight loss; (2) deleterious effects on the cardiovascular system occur at low micromolar plasma drug concentration. The conundrum of high plasma concentration required to achieve efficacy (2.0 $\pm$ 0.4 μg/mL) despite potent functional antagonism (Ca^{2+} release $IC_{50} = 28 \pm 5$ nM) is the result of multiple factors, including high nonspecific plasma protein binding (96.01 $\pm$ 0.03% bound in DIO mouse plasma) limiting the availability of free drug to interact with the receptor. In addition, the observed cardiovascular toxicity at low micromolar concentration of **7** in the anesthetized dog assay raises significant concern. To determine whether the deleterious cardiovascular activity was attributable to off-target effects associated with the aminopiperidinecoumarin chemotype or linked to MCHr1 antagonism, we evaluated two additional analogues in the dog cardiovascular safety assay. The 6-methoxycoumarin **16** was selected as a closely related active MCHr1 antagonist, and the 4-*tert*-butylphenyl substituted **17** was selected as a representative aminopiperidinecoumarin with no MCHr1 functional antagonism observable at 10 μM (Figure 4). Evaluation of **16** and **17** revealed significant compound-induced changes in multiple cardiovascular parameters, including heart contractility (see Supporting Information), within the first 30 min of infusion in the dog assay. The plasma concentrations achieved at the end of the first infusion were 2.84 (2.75−2.93) μg/mL for the active analogue **16** and 1.39 (1.36−1.43) μg/mL for the inactive analogue **17**. These results and other data (unpublished) led to the conclusion that the adverse cardiovascular profile observed for this class of MCHr1 antagonist was likely due to an unknown off-target effect of these compounds and not to MCHr1 antagonism. Since coumarin **7** was >500-fold selective against a broad panel of receptors and enzymes,[11] the link to a specific off-target cross-reactivity responsible for the adverse cardiovascular effects remains undiscovered.

The comprehensive profiling of **7** was instructive in highlighting the exciting potential of MCHr1 antagonists to deliver sustained weight loss with chronic dosing in DIO mice and the significant cardiovascular safety hurdles that must be overcome to ultimately lead to identification of a safe and effective pharmaceutical agent. This led us to adopt a novel screening paradigm focused on rapid assessment of hemodynamic liabilities associated with multiple MCHr1 antagonist chemotypes in our lead optimization strategy. The full details of this strategy will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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