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Constrained 7-fluorocarboxychromone-4-aminopiperidine based Melanin-concentrating hormone receptor 1 antagonists: The effects of chirality on substituted indan-1-ylamines

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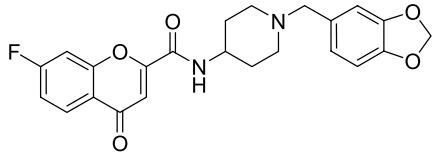
Abstract—The incorporation of constrained tertiary amines into an existing class of *N*-benzyl-4-aminopiperidinyl chromone-based MCHr1 antagonists led to the identification of a series of chiral racemic compounds that displayed good to excellent functional potency, binding affinity, and selectivity over the hERG channel. Further separation of two distinct chiral racemic compounds into their corresponding pairs of enantiomers revealed a considerable selectivity for MCHr1 for one configuration, in addition to a striking difference in oral exposure between one pair of enantiomers in diet-induced obese mice. Oral administration of the most potent compound in this class in the same animal model led to significant reduction of fat mass in a semi-chronic model for weight loss.

Melanin-concentrating hormone[1] (MCH) is a neuropeptide that plays a role in multiple physiologic processes, including the regulation of feeding behavior and energy balance. Multiple lines of evidence support the role of MCH in the regulation of body weight in rodents,[2] as a single injection of MCH into the CNS stimulates food intake,[3] and chronic administration leads to increased body weight.[4] Additionally, transgenic mice overexpressing the MCH gene are susceptible to insulin resistance and obesity,[5] while mice lacking the gene encoding MCH are hypophagic, lean, and maintain elevated metabolic rates.[6] Genetically altered mice that lack the gene encoding the MCH receptor similarly maintain elevated metabolic rates and thus remain lean despite hyperphagia on a normal diet.[7] Finally, multiple reports of small molecule antagonists that confer a reduction of body weight and/or food intake[8] in rodents have been reported recently, providing validation of MCHr1 blockade as a possible pharmacotherapy for obesity.



1

MCHr1 IC_{50} (μM)	0.003
Ca^{2+} release IC_{50} (μM)	0.029
hERG (Dof) IC_{50} (μM)	15.0
Brain AUC (μg·hr/g)	12.66

Figure 1. *N*-benzyl-4-aminopiperidine-based orally active MCHr1 antagonist **1**.

Keywords: MCHr1; Obesity.
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A previous report from these laboratories described the 7-fluorinated chromone analog **1**, which showed a promising combination of MCHr1 affinity, functional potency, and hERG selectivity (Fig. 1) while demonstrating oral efficacy in a chronic model for weight loss in diet-induced obese mice (DIO).[9] In an effort to further capitalize on the encouraging properties of antagonist **1**, we explored the *N*-benzyl piperidine region of this molecule with the hopes of further improving the functional potency and hERG selectivity.

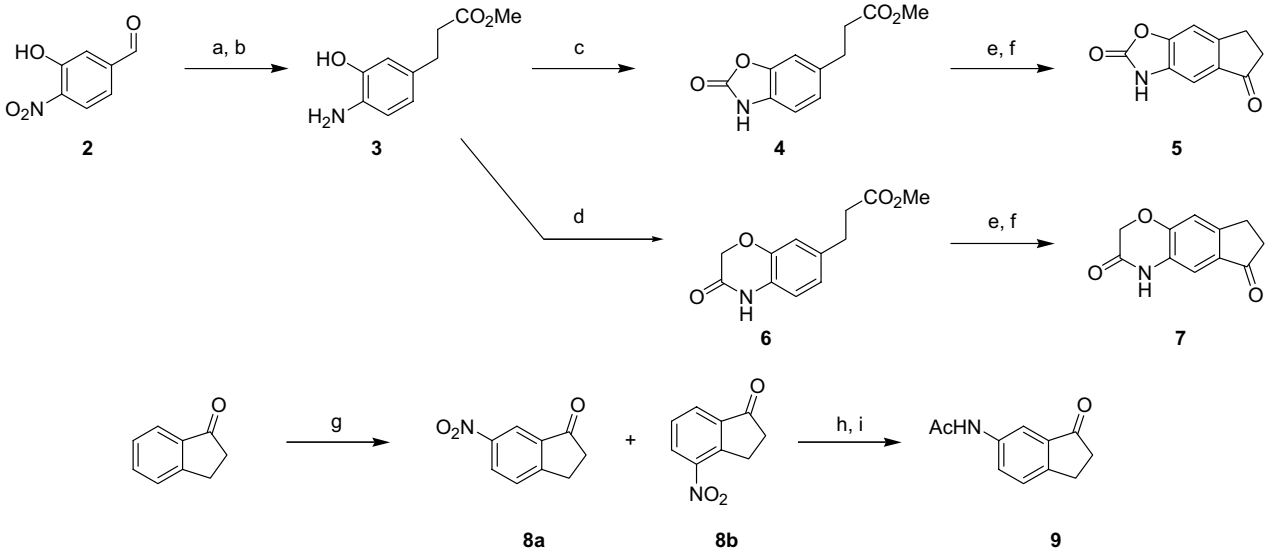
In the course of our search for more potent analogs, we focused on the piperonyl region of the molecule, and reasoned that incorporation of an appropriately placed constraint could enhance functional antagonism by locking the molecule into a highly active conformation, an effect that could also improve the selectivity profile against other receptors and ion channels. We were additionally interested in the incorporation of more polar benzylic amine moieties in order to probe for greater hERG selectivity. To this end, several novel constrained compounds were designed, synthesized, and evaluated in both in vitro and in vivo assays.

The indanone building blocks were generally prepared from the corresponding propionic acid derivatives (Scheme 1). These intermediates, in turn, were elaborated from the appropriately functionalized benzaldehyde derivatives via a Horner–Wadsworth–Emmons (HWE) homologation followed by a reduction/cyclization sequence. Both methylenedioxyphenyl indanone regioisomers were prepared according to Nichols et al.[10] A similar sequence was utilized for the preparation of the benzoxazine derivatives **5** and **7**. HWE homologation of 3-hydroxy-4-nitro-benzaldehyde followed by exhaustive reduction afforded the intermediate **3**, which was then reacted with carbonyl diimidazole or bromoacetylbromide to afford the 5,6 and 6,6 substituted esters **4** and **6**, respectively. Saponification furnished the corresponding propionic acid derivatives and set the stage for cyclization. Unfortunately, these acids proved to be highly resistant to Lewis acid-mediated cyclization, and multiple attempts under several reaction conditions resulted in little or no conversion. Harsh treatment with phosphoric acid-based reagents was also attempted, yet led to decomposition with little conversion to the desired compounds in all cases. Faced with this challenge, we then attempted a melt procedure, employing solid aluminum chloride in the absence of solvent at 140 °C for 2 h. Fortuitously, this protocol furnished the desired ketones **5** and **7** in 70% and 78%, respectively, as single regioisomers.

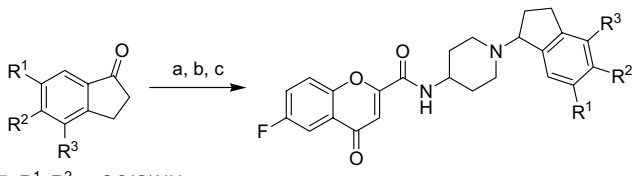
Finally, the acetamide **9** was prepared according to Scheme 1. Nitration of 1-indanone afforded a regioisomeric mixture of **8a** and **8b**, which could be separated via column chromatography. Intermediates **8a** and **8b** were then individually subjected to iron-mediated nitro reduction followed by acylation to afford the desired ketones.

The final compounds were prepared according to Scheme 2. Briefly, Ti(^{i}OPr)$_4$-mediated enamine formation using 4-*N*-boc-aminopiperidine and the desired ketone was followed by treatment with $NaBH(OAc)_3$ to afford the corresponding intermediate amines. Acid-mediated deprotection and amide coupling with 7-fluoro-4-oxo-4H-chromene-2-carboxylic acid[9] furnished the final products.

As demonstrated in Table 1, the chiral racemic analog **12** was a high-affinity ligand to MCHr1, and showed functional antagonism that was nearly equal to that of



Scheme 1. Reagents and conditions: (a) Triethyl phosphonoacetate, NaO^{t}Bu, DMF; (b) H_2, Pd/C, EtOH/EtOAc; (c) CDI, THF, 50 °C; (d) Bromoacetylbromide, K_2CO_3, rt then 50 °C; (e) LiOH, THF/H_2O (3:1); (f) $AlCl_3$, LiCl, 140 °C, 2 h; (g) HNO_3; (h) Fe, NH_4Cl, 80% EtOH, 60 °C; (i) AcOH, EDCI.



5: R^1, R^2 = -OC(O)NH-
7: R^1, R^2 = $-OCH_2C(O)NH-$
9: R^1 = $-NHC(O)CH_3$
10: R^1, R^2 = $-OCH_2O-$
11: R^1, R^2 = $-OCH_2O-$

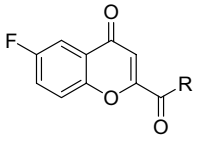
Scheme 2. Reagents and conditions: (a) Amine, $Ti(^iOPr)_4$, THF, 50 °C, 5 h, then $NaBH(OAc)_3$; (c) CH_2Cl_2, 2 N HCl/ether; (d) EDCI, HOBt, NMM, RCO_2H, DMF.

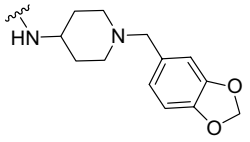
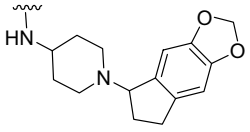
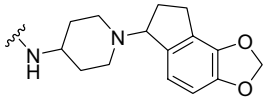
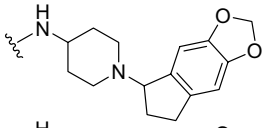
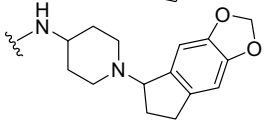
1. The presence of the indane ring had the effect of slightly increasing the hERG affinity, although the selectivity for MCHr1 was still promising. In contrast, the regioisomeric analog **13** showed a 20-fold decrease in MCHr1 binding affinity relative to **1**, and over 100-fold decrease in functional antagonism. Interestingly, this constitutional isomerism had a significant effect on the hERG binding, as **13** showed a three- and fivefold increase in hERG affinity relative to **12** and **1**, respectively.

Following separation[11] of the enantiomers of **12**, in vitro analysis revealed striking receptor selectivity for one configuration, as the binding affinity of (−)-**12** was nearly 700-fold higher than that of enantiomer (+)-**12**. Additionally, the functional potency of the parent racemate resided solely in the former compound, as the oppositely configured (+)-**12** showed no activity up to the assayed concentration. A moderate selectivity over the hERG channel was revealed as well. Fortunately, the more potent enantiomer showed decreased hERG activity, and showed an improved relative selectivity as compared to the parent analog **1**.

These promising data encouraged the further exploration of the constrained amine derivatives in the hopes that analogs with further gains in potency and hERG selectivity could be identified. Since the linearly fused 5,6,5-indan-1-ylamine system proved to be critical as demonstrated by the remarkable differences in MCHr1 and hERG activity between **12** and **13**, we designed compounds that retained the conformation of the former analog. Additionally, prior efforts had demonstrated that enhanced polarity within the *N*-benzyl region of

Table 1. SAR of indanone-based compounds[a]



Compound	R	MCHr1 IC_{50}[b] (μM)	Ca^{2+} IC_{50}[c] (μM)	hERG IC_{50}[d] (μM)
1		0.004	0.025	15
12		0.005	0.036	11.2
13		0.076	2.75	5.86
(−)-**12**[e]		0.001	0.015	9.31
(+)-**12**[e]		0.760	>10	7.87

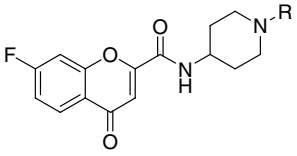
[a] All compounds were >95% pure by HPLC and characterized by ^1H NMR and HRMS. All values are mean values ± SEM (n = 3 unless specified otherwise).
[b] Displacement of [^{125}I]MCH from MCHr1 expressed in IMR-32 (I3.4.2) cells (MCH binding K_d = 0.66 ± 0.25 nM, B_{max} = 0.40 ± 0.08 pmol/mg).
[c] Inhibition of MCH-mediated Ca^{2+} release in whole IMR-32 cells (MCH EC_{50} = 62.0 ± 3.6 nM).
[d] Displacement of [^{3}H]dofetilide from hERG/HEK membrane homogenates at 6 concentrations, 1/2 log apart, in duplicate using a 96-well plate design. IC_{50} values calculated using Graphpad Prizm software.
[e] See Ref. 11 for details regarding the chiral separation.

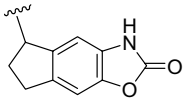
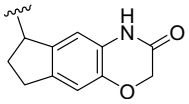
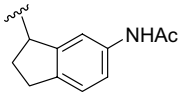
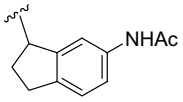
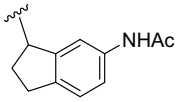
the molecule was effective in decreasing the hERG affinity.[9] We consequently designed and synthesized the 5,6,5-constrained cyclic carbamate **14** (Scheme 1), in addition to the homologated 5,6,6 analog **15** in order to probe the chemical space in this region.

As demonstrated in Table 2, analogs **14** and **15** exhibited a decrease in both MCHr1 affinity and functional potency relative to (−)-**12**, yet the hERG binding was decreased considerably. The presence of the carbamate and amide functionalities in these analogs appeared to be beneficial with respect to decreasing the affinity for the hERG channel. Additionally, the presence of the methylene unit in **15** conferred enhanced MCHr1 activity relative to **14**, and we reasoned that excision of the aryl ether oxygen could combine the desired properties of both compounds. To this end, the indanone **8** was prepared (Scheme 1) and functionalized accordingly to afford the amide **16**. Gratifyingly, in vitro analysis of this compound revealed an excellent binding affinity toward MCHr1, good functional potency, and decreased hERG activity relative to **1**. Encouraged by these properties, we separated the components of **16**[12] to furnish the pure enantiomers (−)-**16** and (+)-**16**. Similar to the enantiomeric pair (−)-**12** and (+)-**12**, chirality had a remarkable effect, as the binding and functional activity of **16** resided predominantly in one isomer {(−)-**16**}.

The enantiomeric sets of compounds were then evaluated for single dose plasma and brain penetration in DIO mice (Table 3). Both (+)-**12** and (−)-**12** showed similar in vivo properties, characterized by high plasma exposure, although (+)-**12** showed a twofold increase in brain exposure. Both enantiomers had prolonged plasma and brain half-lives relative to parent **1**, despite the observation that brain exposure was decreased. Surprisingly, (−)-**16** showed a ten-fold higher plasma AUC and C_{max} relative to the less active enantiomer (+)-**16**. However, the presence of the amide functionality had a detrimental effect on the brain penetration for both enantiomers. The more active (−)-**16** had no measurable drug levels in the brain, while the brain concentration of (+)-**16** was very low. That no brain penetration was observed in the face of considerable plasma exposure for both analogs is likely the result of the increased polarity and hydrogen-bond capacity of the amide functionality. Additionally, the modest CNS penetration of the less active enantiomer while the more extensively plasma-absorbed analog (−)-**16** had none indicates that active transport mechanisms could play a role. Interestingly, the presence of the indan-1-ylamine constraint had the effect of substantially increasing the plasma exposure for all of the analogs relative to the parent **1**, with the exception of (+)-**16**.

Table 2. In vitro parameters of analogs[a]



Compound	R	MCHr1 IC_{50}[b] (μM)	Ca^{2+} IC_{50}[c] (μM)	hERG IC_{50}[d] (μM)
14		0.011	0.173	25.0
15		0.021	0.095	14.6
16		0.003	0.056	34.8
(−)-**16**[e]		0.004	0.026	27.2
(+)-**16**[e]		2.57	>10	15.6

[a] See Table 1, footnote a.
[b] See Table 1, footnote b.
[c] See Table 1, footnote c.
[d] See Table 1, footnote d.
[e] See Ref. 12 for details regarding the chiral separation.

Table 3. Selected PK properties of indanone analogs (DIO mice, 10 mg/kg po)[a]

Compound	**1**	(−)-**12**	(+)-**12**	(−)-**16**	(+)-**16**
Plasma AUC(μg h/mL)[b]	9.29	140	113	41.6	3.76
Plasma C_{max} (μg/mL)[b]	1.78	15	15.5	14.6	1.41
Plasma $T_{1/2}$ (h)	2.5	4.5	3.6	2.3	1.3
Brain AUC (μg h/g)[b]	12.7	4.85	8.26	0.00	0.043
Brain C_{max} (μg/g)[b]	4.37	0.686	1.43	0.00	0.017
Brain $T_{1/2}$ (h)	2.4	5.7	4.1	NF	NF

[a] Compounds are dosed in DIO mice at 10 mg/kg, po in a vehicle containing 1% Tween 80 and water.

[b] The three mice with highest plasma and brain concentrations were averaged to provide the peak plasma and brain concentrations (C_{max}) ± SEM, respectively. The mean plasma or brain concentration data were submitted to multi-exponential curve fitting using WinNonlin. The area under the mean concentration-time curve from 0 to t hours (time of the last measurable concentration) after dosing (AUC_{0-t}) was calculated using the linear trapezoidal rule for the concentration-time profile. The residual area was extrapolated to infinity, determined as the final measured mean concentration (C_t) divided by the terminal elimination rate constant (β), and was added to AUC_{0-t} to produce the total area under the curve ($AUC_{0-\infty}$). NF, not found.

The introduction of polar functional groups into the indan-1-ylamine portion of the molecule provided compounds with similar MCHr1 activity and superior hERG selectivity relative to **1**, although the lack of acute CNS penetration in the animal efficacy model obviated the further assessment of these compounds. Consequently, we focused on chiral non-racemic analog (−)-**12**, which demonstrated the best combination of binding and functional potency relative to any previously synthesized compound within the *N*-benzyl-4-aminopiperidine class of MCHr1 antagonists.[13] Furthermore, in receptor selectivity panels, (−)-**12** showed weak affinity ($IC_{50} > 10$ μM) for other peptide receptors that are structurally related to MCHr1, including MCHr2, somatostatin, and the opioid receptors, and over 100-fold selectivity for all other GPCrs and ion channels tested.[14] While the brain/plasma ratio was decreased compared to the non-cyclized **1**, the enhanced cellular potency of (−)-**12** and its favorable CNS exposure and half-life upon single dosing were deemed sufficient criteria to predict efficacy in a semi-chronic model for weight loss.

To this end, a single oral dose of 3 mg/kg bid was selected for (−)-**12**. For a two-week period, DIO mice fed a high-fat diet ad libitum were administered this compound, D-fenfluramine (10 mg/kg, qd) as a drug-treated control, or vehicle. Food intake and body weight were measured at days 1, 5, 7, 11, and 14 for each group. In reproducible fashion, the D-fenfluramine treatment group was characterized by a rapid decrease in body weight (Fig. 2), secondary to a decrease in food intake, followed by a characteristic rebound that started on day 8 and continued throughout the remainder of the study (final weight reduction and % weight loss from day 0 were 4 g and 9%, respectively).[8c] In contrast, treatment with compound (−)-**12** induced a gradual decrease in body weight that culminated in a 7% weight reduction compared to vehicle controls by the end of the study (3 g, $p < 0.01$). No significant effect on food intake was observed at any point within the study. Subsequent DEXA analysis revealed that the loss of body mass was directly attributed to a selective loss of fat mass, and that chronic treatment had no effect on lean mass (data not shown). Finally, Irwin analysis revealed no overt behavioral abnormalities or compound-induced effects on movement, coordination, and muscle strength, indicating that no gross toxicity was conferred by the administration of compound (−)-**12**.

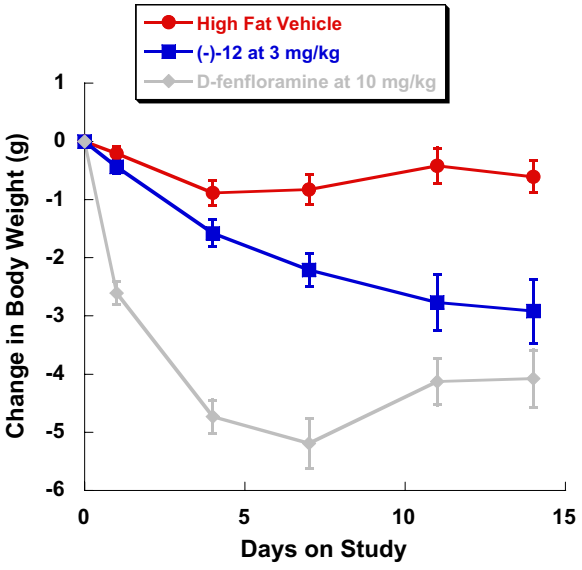


Figure 2. Effect of compound (−)-**12** (3 mg/kg, po, bid in 1% Tween 80 in water) and D-fenfluramine (D-fen, 10 mg/kg, po, qd) on the body weight of DIO mice. Change is registered as the number of grams of body weight difference for each measurement time point relative to day zero. All values are mean values ± SEM for $n = 12$. $^{**}p < 0.05$ for comparisons against vehicle group.

Blood samples collected at 1 and 17 h post-final-dose determined the therapeutic (C_{max}) plasma and brain concentrations of (−)-**12** to be 3680 and 530 ng/mL, respectively (Table 4). The former value is less than

Table 4. Exposure levels of (−)-12 (3 mg/kg, bid, po) at 1 and 17 h post-final dose[a]

Time (h)	Plasma (ng/mL)[a]	Brain (ng/g)[a]
1	3680	530
17	203	0.00

[a] Drug concentrations in plasma and in brain were determined either 1 or 17 h after the final dose. All values are mean values ± SEM ($n = 3$).

expected based upon the C_{max} observed with the acute dose of 10 mg/kg, and could reflect a gradual metabolic induction. Interestingly, the brain C_{max} was equivalent to the measured concentration in the single dose experiment, and because of the decreased plasma concentration, the brain/plasma ratio was enhanced 10-fold to 0.15 at the maximum concentration. After 17 h, the compound was effectively cleared from the plasma and brain, with the latter tissue containing negligible amounts at this time point.

In summary, incorporation of indan-1-ylamine-based constraints into the *N*-benzyl portion of our previously disclosed series of chromone-based MCHr1 antagonists afforded novel chiral compounds with enhanced in vitro and pharmacological profiles. Specifically, compound (−)-**12** demonstrated the most potent functional activity of any compound within this class, good hERG selectivity, and efficacy when dosed at 3 mg/kg bid in a semi-chronic model for weight loss in DIO mice. Additionally, a remarkable effect of chirality on the in vitro and pharmacokinetic properties of enantiomers (−)-**16** and (+)-**16** was manifested in significant differences in receptor activity and oral exposure of the purified enantiomers. It is quite possible that incorporation of this type of constraint could have similar effects on other classes of small molecules, and thus represents an additional strategy to modulate this in vivo parameter.

Acknowledgments

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References and notes

1. Saito, Y.; Nothacker, H.-P.; Civelli, O. *Trends Endocrinol. Metab.* **2000**, *11*, 299.
2. Schwartz, M. W.; Woods, S. C.; Porte, D., Jr.; Selley, R. J.; Baskin, D. G. *Nature* **2000**, *404*, 661.
3. Della-Zuana, O.; Presse, F.; Ortola, C.; Duhault, J.; Nahon, J. L.; Levens, N. *Int. J. Obes.* **2002**, *26*, 1289.
4. Gomori, A.; Ishihara, A.; Ito, M.; Mashiko, S.; Matsushita, H.; Yumoto, M.; Ito, M.; Tanaka, T.; Tokita, S.; Moriya, M.; Iwaasa, H.; Kanatani, A. *Am. J. Physiol. Endocrinol. Metab.* **2003**, *284*, E583.
5. Ludwig, D. S.; Tritos, N. A.; Mastaitis, J. W.; Kulkarni, R.; Kokkotou, E.; Elmquist, J.; Lowell, B.; Flier, J. S.; Maratos-Flier, E. *J. Clin. Invest.* **2001**, *107*, 379.
6. Shimada, M.; Tritos, N. A.; Lowell, B. B.; Flier, J. S.; Maratos-Flier, E. *Nature* **1998**, *396*, 670.
7. Marsh, D. J.; Weingarth, D. T.; Novi, D. E.; Chen, H. Y.; Trumbauer, M. E.; Chen, A. S.; Guan, X.-M.; Jiang, M. M.; Feng, Y.; Camacho, R. E.; Shen, Z.; Frazier, E. G.; Yu, H.; Metzger, J. M.; Kuca, S. J.; Shearman, L. P.; Gopal-Truter, S.; MacNeil, D. J.; Strack, A. M.; MacIntyre, D. E.; Van der Ploeg, L. H. T.; Qian, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3240; Chen, Y.; Hu, C.; Hsu, C.-K.; Zhang, Q.; Bi, C.; Asnicar, M.; Hsiung, H. M.; Fox, N.; Slieker, L. J.; Yang, D. D.; Heiman, M. L.; Sh, Y. *Endocrinology* **2002**, *143*, 2469.
8. (a) Borowsky, B.; Durkin, M. M.; Ogozalek, K.; Marzabadi, M. R.; DeLeon, J.; Lagu, B.; Heurich, R.; Lichtblau, H.; Shaposhnik, Z.; Daniewska, I.; Blackburn, T. P.; Branchek, T. A.; Gerald, C.; Vaysse, P. J.; Forray, C. *Nat. Med.* **2002**, *8*, 779; (b) Takekawa, S.; Asami, A.; Ishihara, Y.; Terauchi, J.; Kato, K.; Shimomura, Y.; Mori, M.; Murakoshi, H.; Kato, K.; Suzuki, N.; Nishimura, O.; Fujino, M. *Eur. J. Pharmacol.* **2002**, *438*, 129; (c) Souers, A. J.; Gao, J.; Brune, M.; Bush, E.; Wodka, D.; Vasudevan, A.; Judd, A.; Mulhern, M.; Brodjian, S.; Dayton, B.; Shapiro, R.; Hernandez, L. E.; Marsh, K. C.; Sham, H. L.; Collins, C. A.; Kym, P. R. *J. Med. Chem.* **2006**, *49*, 2339; (d) Souers, A. J.; Gao, J.; Wodka, D.; Judd, A. S.; Mulhern, M. M.; Napier, J. J.; Brune, M. E.; Bush, E. N.; Brodjian, S. J.; Dayton, B. D.; Shapiro, R.; Hernandez, L. E.; Marsh, K. C.; Sham, H. L.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*(11), 2752; (e) McBriar, M. D.; Guzik, H.; Shapiro, S.; Paruchova, J.; Xu, R.; Palani, A.; Clader, J. W.; Cox, K.; Greenlee, W. J.; Hawes, B. E.; Kowalski, T. J.; O'neill, K.; Spar, B. D.; Weig, B.; Weston, D. J.; Farley, C.; Cook, J. *J. Med. Chem.* **2006**, *49*, 2294.
9. Lynch, J. K.; Freeman, J. C.; Judd, A. S.; Iyengar, R. R.; Mulhern, M.; Zhao, G.; Napier, J. J.; Wodka, D.; Brodjian, S.; Dayton, B. D.; Falls, H. D.; Ogiela, C.; Reilly, R. M.; Campbell, T. J.; Polakowski, J. S.; Hernandez, L.; Marsh, K. C.; Shapiro, R.; Knourek-Segal, V.; Droz, B.; Bush, E.; Brune, M.; Preusser, L. C.; Fryer, R. M.; Reinhart, G. A.; Houseman, K.; Diaz, G.; Mikhail, A.; Limberis, J. T.; Sham, H. L.; Collins, C. A.; Kym, P. R. *J. Med. Chem.* **2006**, DOI: 10.1021/jm060683e.
10. Nichols, D. E.; Brewster, W. K.; Johnson, M. P.; Oberlender, R.; Riggs, R. M. *J. Med. Chem.* **1990**, *33*, 703.
11. Chiralcell O. J., Hex/EtOH/MeOH (50/25/25), 0.8 mL/min, UV 220 nM. Both (−)-**12** and (+)-**12** were purified to enantiomeric purity within the limits of detection. The elution times for (−)-**12** and (+)-**12**, respectively, are 6.1 and 9.2 min.
12. Chiralcell O. J., Hex/EtOH/MeOH (70/15/15), 0.8 mL/min, UV 240 nM. Both (−)-**16** and (+)-**16** were purified to enantiomeric purity within the limits of detection. The elution times for (−)-**16** and (+)-**16**, respectively, are 7.57 min and 5.43 min.
13. See the following reference to 4-aminopiperidin- based MCHR1 antagonists Kym, Philip R.; Iyengar, Rajesh; Souers, Andrew J.; Lynch, John K.; Judd, Andrew S.; Gao, Ju; Freeman, Jennifer; Mulhern, Mathew; Zhao, Gang; Vasudevan, Anil; Wodka, Dariusz; Blackburn, Christopher; Brown, Jim; Che, Jennifer Lee; Cullis, Courtney; Lai, Su Jen; LaMarche, Matthew; Marsilje, Tom; Roses, Jon; Sells, Todd; Geddes, Brad; Govek, Elizabeth; Patane, Michael; Fry, Dennis; Dayton, Brian D.; Brodjian, Sevan; Falls, Doug; Brune, Michael; Bush, Eugene; Shapiro, Robin; Knourek-Segel, Victoria; Fey, Thomas; McDowell, Cathleen; Reinhart, Glenn A.; Preusser, Lee C.; Marsh, Kennan; Hernandez, Lisa; Sham, Hing L.; Collins, Christine A. *J. Med. Chem.* **2005**, *48*, 5888.
14. Cross-reactivity assays were performed by CEREP. www.cerep.com.