Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 874–878

An evaluation of 3,4-methylenedioxy phenyl replacements in the aminopiperidine chromone class of MCHr1 antagonists

Rajesh R. Iyengar,[a,*] John K. Lynch,[a] Mathew M. Mulhern,[a] Andrew S. Judd,[a] Jennifer C. Freeman,[a] Ju Gao,[a] Andrew J. Souers,[a] Gang Zhao,[a] Dariusz Wodka,[a] H. Doug Falls,[a] Sevan Brodjian,[a] Brian D. Dayton,[a] Regina M. Reilly,[a] Sue Swanson,[c] Zhi Su,[b] Ruth L. Martin,[b] Sandra T. Leitza,[b] Kathryn A. Houseman,[b] Gilbert Diaz,[b] Christine A. Collins,[a] Hing L. Sham[a] and Philip R. Kym[a]

[a]*Metabolic Disease Research, Metabolic Disease Research, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA*
[b]*Integrative Pharmacology, Metabolic Disease Research, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA*
[c]*Exploratory Pharmacokinetics, Metabolic Disease Research, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA*

Received 26 October 2006; revised 16 November 2006; accepted 20 November 2006
Available online 1 December 2006

Abstract—The optimization of potent MCHr1 antagonist **1** with respect to improving its in vitro profile by replacement of the 3,4-methylenedioxy phenyl (piperonyl) moiety led to the discovery of **19**, a compound that showed excellent MCHr1 binding and functional potencies in addition to possessing superior hERG separation, CYP3A4 profile, and receptor cross-reactivity profiles.

Melanin-concentrating hormone (MCH) is a cyclic 19-amino acid peptide that is produced predominantly in neurons in the lateral hypothalamus and zona incerta.[1] Several lines of evidence involving experiments with the MCH peptide support the role of MCH in the regulation of body weight in rodents[2] and suggest that inhibition of the interaction of MCH with its receptor in the brain would be a potential anti-obesity pharmacotherapy. A single injection of the MCH peptide into the lateral hypothalamus of rodents stimulates food intake and chronic administration leads to increased body weight.[3,4] Additionally, transgenic mice overexpressing the MCH gene are susceptible to obesity and insulin resistance.[5] In contrast, mice lacking the gene encoding MCH are lean, hypophagic, and maintain elevated metabolic rates.[6] Genetically altered animals that lack the single gene encoding the MCH receptor (MCHr1) in rodents maintain elevated metabolic rates and remain lean despite hyperphagia on a normal diet.[7] Finally, a number of small molecule MCHr1 antagonists have been reported to be causative in the reduction of body weight and/or food intake in rodents, which provides further validation of the potential of MCHr1 antagonism as an effective anti-obesity target.[8]

A recent report from these laboratories disclosed a potent MCHr1 antagonist **1** that demonstrated significant, dose-dependent weight loss in a DIO mouse model upon oral administration.[9] Unfortunately, this compound was later discovered to have dose-dependent QT interval prolongation in an pentobarbital-anesthetized dog model, related to functional blockade at the hERG (Human *Ether-a-go-go* Related Gene) channel demonstrated by this compound. This gene encodes the potassium channel (I_{Kr}) that is essential for ventricular repolarization and normal cardiac function.[10] A blockade of hERG is associated with QT interval prolongation, *torsades de pointes* and sudden cardiac death. Thus, the prospect of association of drug agents with hERG channel blockade is an important safety consideration in drug discovery and development. In order to ameliorate the association of our chemical series with hERG channel binding, eliminating or significantly decreasing this affinity without

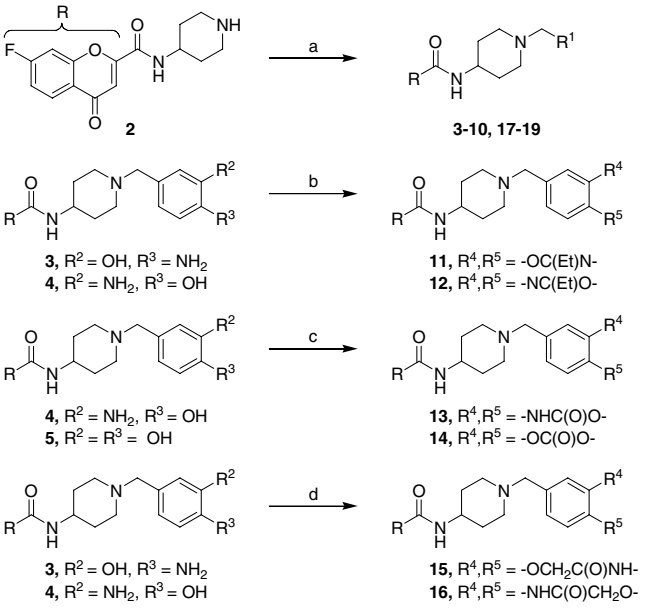
Keywords: MCHR1; Obesity; hERG; Piperonyl replacements.
* Corresponding author. Tel.: + 1 847 937 9151; fax: + 1 847 938 1674; e-mail: rajesh.iyengar@abbott.com

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.11.065

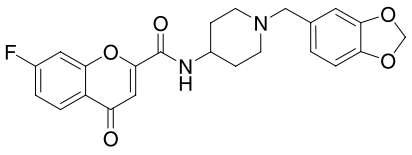
sacrificing MCHr1 potency became a priority. Ideally, any reduction in hERG channel affinity (IC_{50} 15.1 μM for **1**, [^{3}H]-dofetilide assay) would be of even greater significance when accompanied with a concomitant increase in MCHr1 functional potency to enable a better selectivity window for our compounds (ratio of hERG IC_{50}/MCH Ca^{2+} release IC_{50}: 520 for **1**). Additionally, to avoid potential complications due to competitive CYP3A4 inhibition and other receptor cross-reactivity, we also sought to improve the general cross-reactivity profile of future compounds as compared to **1**. The CYP3A4 subfamily of isozymes is responsible for the metabolism of about 60% of known therapeutic drugs.[11] Inhibition of CYP3A4 is frequently associated with drug–drug interactions and sometimes associated with adverse cardiovascular events as well. The need for a 'clean' candidate is especially relevant in the drug development for anti-obesity and other metabolic disorders, which would likely entail protracted therapy in an often cardiovascular-compromised patient population.[12]

Early SAR evaluation on the 7-fluorochromone-4-aminopiperidines had led to the discovery that the attachment of the 3,4-methylenedioxy phenyl moiety with respect to the piperidine nitrogen connectivity be an optimal component for maintaining binding affinity with good functional potency.[9] This structure–activity evaluation had also revealed that differential functionalization on the terminal phenyl ring, including changes to the methylenedioxy group itself, seemed to have an impact limited to either MCHr1 potency or hERG affinity and with **1** possessing the best overall in vitro profile (Fig. 1).[9] We decided to expand this exploration to alternative bicyclic termini replacements to the piperonyl moiety while retaining the optimized 7-fluorochromone-4-minopiperidine core of **1**. To this end, several compounds in different benzofused bicyclic families were designed, synthesized, and evaluated in MCHr1 and hERG in vitro assays.

Compounds **3**–**10** and **17**–**19** (Scheme 1 and Table 1) were generally prepared by an alkylation reaction on the piperidine nitrogen of the previously described[9] 7-fluorochromone-4-aminopiperidine core **2** using commercially available benzaldehydes or alkyl halides. In some cases, the aldehydes or alkyl halides were synthesized from the respective benzylic methyl precursors using standard protocols[13] and then condensed with the amine under alkylation conditions. In other instances, initial condensates were further modified to construct heterocyclic rings on the phenyl terminus. Thus, ring forming reactions were carried out on the corresponding 3,4-dihydroxy phenyl or *o*-amino phenol precursors to synthesize analogs **11**–**16**.



Scheme 1. Reagents and conditions: (a) R_1CHO, $NaBH_3CN$, MeOH, DCM or $NaBH(OAc)_3$, THF, rt to 50 °C or R_1CH_2Br, DMF, rt or heating, 5–90%; (b) 3-hexyn-2-one, MeOH, reflux, 15 h, 1%; (c) *N*,*N*′-carbonyldiimidazole, THF, 50 °C, 15 h, 8–15%; (d) chloroacetyl chloride, DCM, rt, 30–50%.



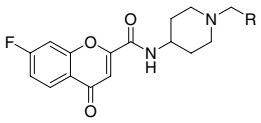
1

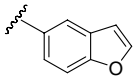
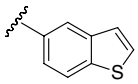
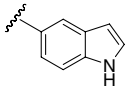
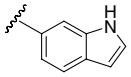
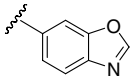
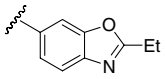
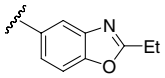
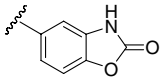
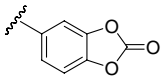
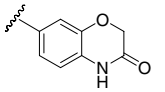
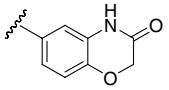
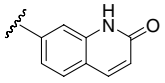
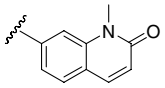
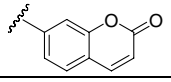
MCHr1 binding IC_{50} (μM)	0.003
MCH Ca^{2+} release IC_{50} (μM)	0.029
hERG IC_{50} (μM)	15.1
hERG IC_{50}/MCH Ca^{2+} release IC_{50} ratio	520
CYP3A4 inhibition (μM)	23.5

Figure 1. 7-Fluorochromone-4-aminopiperidine-based orally active MCHr1 antagonist **1**.

Although several of the initially assayed heterocyclic benzofused bicyclic compounds possessed good binding affinity and functional potency against MCHr1, most of them also displayed an increased affinity for hERG channel binding as compared to **1** (compounds **6**–**9**, Table 1). The benzoxazole analog **10** was the only compound in the initial subset that displayed the in vitro selectivity profile that was desired although it was still not better than **1** (hERG IC_{50}/MCH Ca^{2+} release IC_{50} ratio: 426 for **10**). However, it was of interest to us to note that the affinity for hERG channel seemed to reasonably track the polarity of the bicyclic termini.[14] Hence, in subsequent examples, we sought to incorporate polarity at this site as a strategy to perhaps decrease the affinity of the compounds to bind to the hERG channel while retaining or improving MCHr1 activity.[9,14,15] To investigate the possibility of further improving the in vitro profile of benzoxazole-bearing analogs, **11** and **12** were synthesized and evaluated to see if this moiety tolerated further substitution. This derivatization of **10**, however, resulted in the loss of MCHr1 potency. Only the corresponding benzoxazolone analog **13** regained some of the MCHr1 potency displayed by **10**. The analogous benzodioxalone-bearing compound **14** showed a dramatic decrease in its hERG channel affinity albeit losing most of its MCHr1 affinity as well. It was interesting to note that between compounds **11**

Table 1. SAR of piperonyl replacements of **1**[a]



Compound	R	MCHr1 IC_{50}[b] (μM)	Ca^{2+} IC_{50}[c] (μM)	hERG IC_{50}[d] (μM)	hERG/Ca^{2+} ratio
6		0.007	0.035	5.28	151
7		0.004	0.057	1.37	24
8		0.038	0.110	6.08	55
9		0.005	0.066	2.53	38
10		0.010	0.106	34.6[e]	326
11		1.267[e]	>10[e]	26.7	>2
12		0.095	1.38	20	14
13		0.043	0.569	25	44
14		2.01[f]	5.59[f]	85.2[f]	15
15		0.166[f]	2.41[e]	nt	—
16		0.019[e]	0.233[e]	5.79[e]	25
17		0.007	0.162	85.8[e]	530
18		0.003	0.044	47.4	1030
19		0.001	0.046	51.1	1110

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

and **12**, the MCHr1 potency resided with one regioisomer, which bore the nitrogen at the *meta*-position with respect to the aminopiperidine connectivity. This regioisomeric theme was similarly reflected in the analog sets **8**–**9** and **15**–**16**.[16]

The application of this observation to the corresponding quinolone-bearing analog resulted in **17**, which showed a dramatic improvement in MCHr1 potency with similar hERG separation as **1** (hERG IC_{50}/MCH Ca^{2+} release IC_{50} ratio: 530 for **17**). Subsequent exploration

of this finding was directed towards the evaluation of an *N*-alkyl quinolone analog to clarify the need of an intact quinolone –NH group. We were quite pleased to find that the corresponding *N*-methyl quinolone analog **18** was even better than the parent in terms of its MCHr-1 potency and its selectivity profile was further improved (hERG IC_{50}/MCH Ca^{2+} release IC_{50} ratio: 1030 for **18**). Finally, **19**, the corresponding coumarin-bearing analog, designed as a structural analog of the quinolones, not only had a very potent MCHr1 activity profile, but also possessed much decreased hERG channel affinity (hERG IC_{50}/Ca^{2+} release IC_{50} ratio: 1110 for **19**).

The CEREP profiling of this compound revealed a clean cross-reactivity profile, similar to **1**, across a panel of GPCR receptors and ion channels.[17] Furthermore, analogs **18** and **19** possessed an improved CYP3A4 profile as compared to **1** (**18**, IC_{50} = 60 μM; **19**, IC_{50} = 62.1 μM versus **1**, IC_{50} = 23.5 μM).[18] Finally, analog **19** was evaluated in a patch-clamp assay of functional hERG blockade.[19] In this definitive in vitro hERG assay, **19** demonstrated < 20% current block at 30 μM, a robust improvement over **1** (90% current block at 7 μM).

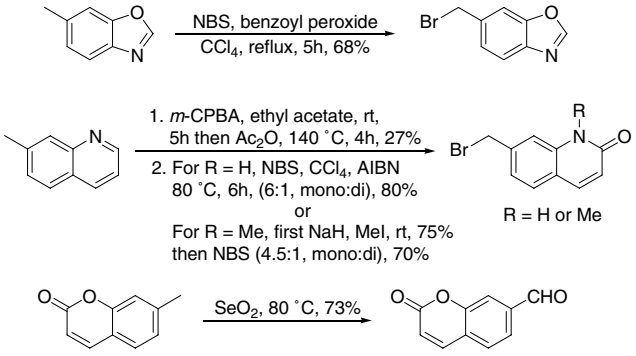
In summary, several bicyclic replacements of the 3,4-methylenedioxy phenyl moiety in **1** have been evaluated. Compound **19**, in particular, possessed one of the best overall in vitro profiles in terms of MCHr1 potency, receptor cross-reactivity, reduction of CYP liability and lack of hERG channel affinity of the compounds evaluated in our program. While some of bicyclic replacements came at the cost of MCHr1 functional potency and/or increased hERG channel affinity, we discovered a set of piperonyl replacements that were comparable to or significantly better than **1** in terms of its potency and several other parameters.

Acknowledgments

The authors thank Christopher Ogiela and Dennis Fry for preparing the IMR-32 cells and aiding with the execution of the binding and functional assays, Paul Richardson and J.J. Jiang for MCH production, and James Napier for the scale-up and supply of **2**.

References and notes

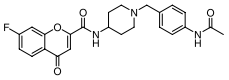
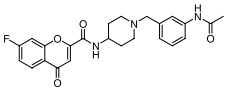
1. Saito, Y.; Nothacker, H-P.; Civelli, O. *Trends Endocrinol. Metab.* **2000**, *11*, 299.
2. Schwartz, M. W.; Woods, S. C.; Porte, D. Jr.; Selley, R. J.; Baskin, D. G. *Nature* **2000**, *404*, 661.
3. Gomori, A.; Ishihara, A.; Ito, M.; Mashiko, S.; Matsushita, H.; Yumoto, M.; Ito, M.; Tanaka, T.; Tokita, S.; Moriya, M.; Iwaasa, H.; Kanatani, A. *Am. J. Physiol. Endocrinol. Metab.* **2003**, *284*, E583.
4. Della-Zuana, O.; Presse, F.; Ortola, C.; Duhault, J.; Nahon, J. L.; Levens, N. *Int. J. Obesity* **2002**, *26*, 1289.
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. (a) 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; (b) 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. S.; Mulhern, M. 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.* **2005**, *48*, 1318; (d) Kym, P. R.; Iyengar, R. R.; Souers, A. J.; Lynch, J. K.; Judd, A. S.; Gao, J.; Freeman, J. C.; Mulhern, M. M.; Zhao, G.; Vasudevan, A.; Wodka, D.; Blackburn, C.; Brown, J.; Che, J. L.; Cullis, C.; Lai, S. J.; LaMarche, M.; Marsilje, T.; Roses, J.; Sells, T.; Geddes, B.; Govek, E.; Patane, M.; Fry, D.; Dayton, B. D.; Brodjian, S.; Falls, D.; Brune, M.; Bush, E.; Shapiro, R.; Knourek-Segel, V.; Fey, T.; McDowell, C.; Reinhart, G. A.; Preusser, L. C.; Marsh, K.; Hernandez, L.; Sham, H. L.; Collins, C. A. *J. Med. Chem.* **2005**, *48*, 5888; (e) Kym, P. R.; Souers, A. J.; Campbell, T. J.; Lynch, J. K.; Judd, A. S.; Iyengar, R.; Vasudevan, A.; Gao, J.; Freeman, J. C.; Wodka, D.; Mulhern, M.; Zhao, G.; Wagaw, S.; Napier, J. J.; Brodjian, S.; Dayton, B. D.; Reilly, R. M.; Segreti, J.; Fryer, R. M.; Preusser, L. C.; Reinhart, G. A.; Hernandez, L.; Marsh, K. C.; Sham, H. L.; Collins, C. A.; Polakowski, J. S. *J. Med. Chem.* **2006**, *49*, 2339; (f) 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; For excellent reviews on the subject, see (g) Kowalski, T. J.; McBriar, M. D. *Expert Opin. Invest. Drugs* **2004**, *13*, 1113; (h) Browning, A. *Expert Opin. Ther. Pat.* **2004**, *14*, 313; (i) Collins, C. A.; Kym, P. R. *Curr. Opin. Invest. Drugs* **2003**, *4*, 386.
9. Lynch, J. K.; Freeman, J. C.; Judd, A. S.; Iyengar, R.; Mulhern, M.; Zhao, G.; Napier, J. J.; Wodka, D.; Brodjian, S.; Dayton, B. D.; Falls, D.; Ogiela, C.; Reilly, R. M.; Campbell, T. J.; Polakowski, J. S.; Hernandez, L.; Marsh, K. C.; Shapiro, R.; Knourek-Segel, 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**, *49*, 6569.
10. For reviews of hERG blockade and QT prolongation, see (a) Finalyson, K.; Witchel, H. J.; McCulloch, J.; Sharkey, J. *Eur. J. Pharmacol.* **2004**, *500*, 129; (b) Fermini, B.; Fossa, A. A. *Nat. Rev., Drug Disc.* **2003**, *2*, 439.
11. For a review of inhibition of cytochrome P450 3A4 by therapeutic drugs, see Zhou, S.; Chan, S. Y.; Goh, B. C.; Chan, E.; Duan, W.; Huang, M.; McLeod, H. L. *Clin. Pharmacokin.* **2004**, *44*, 279.

12. For a review of relationships of metabolic syndrome, obesity, heart disease with related therapies, see: Rana, J. S.; Nieuwdorp, M.; Jukema, J. W.; Kastelein, J. J. P. *Diabetes, Obesity and Metabolism*, online early, *DOI: 10.1111/j.1463-1326.2006.00594.x*.
13. 

14. The modulation of compound polarity/lipophilicity to attenuate hERG channel binding is precedented. For a recent review of hERG optimization in medicinal chemistry, see: Jamieson, C., Moir, E. M., Rankovic, Z., Wishart, G. *J. Med. Chem.* **2006**, *49*, 5029.
Most of our analogs also showed good correlation between compound lipophilicity and affinity for hERG channel binding, as depicted in the table below. Compound **16** was the only gross outlier in this subset.

Compound	*C*log *P* (Calcd)	hERG IC_{50} (μM)
1	2.47	15.1
6	3.06	5.28
7	3.53	1.37
8	2.49	6.08
10	1.77	34.6
12	2.57	20
13	1.52	25
14	1.35	85.2
16	1.23	5.79
17	1.17	85.8
18	1.65	47.4
19	1.77	51.1

15. For recent publications on modulating hERG channel binding via aryl group modifications in the context of MCHr1 antagonists, see: (a) McBriar, M. D.; Guzik, H.; Shapiro, S.; Xu, R.; Paruchova, J.; Clader, J. W.; O'Neill, K.; Hawes, B.; Sorota, S.; Margulis, M.; Tucker, K.; Weston, D. J.; Cox, K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4262; (b) Meyers, K. M.; Kim, N.; Méndez-Andino, J. L.; Hu, X. E.; Mumin, R. N.; Klopfenstein, S. R.; Wos, J. A.; Mitchell, M. C.; Paris, J. L.; Ackley, D. C.; Holbert, J. K.; Mittelstadt, S. W.; Reizes, O. *Bioorg. Med. Chem. Lett.* **2006**, ASAP, DOI:10.1016/j.bmcl.2006.10.053; (c) Souers, A. J.; Iyengar, R.; Judd, A. S.; Beno, D. W. A.; Gao, J.; Zhao, G.; Brune, M. E.; Napier, J. J.; Mulhern, M. M.; Lynch, J. K.; Freeman, J. C.; Wodka, D.; Chen, C. J.; Falls, H. D.; Brodjian, S.; Dayton, B. D.; Diaz, G.; Bush, E.; Shapiro, R.; Droz, B.; Knourek-Segel, V.; Hernandez, L. E.; Marsh, K. C.; Sham, H. L.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2006**, submitted; (d) Judd, A. S.; Souers, A. J.; Wodka, D.; Zhao, G.; Mulhern, M. M.; Iyengar, R. R.; Gao, J.; Lynch, J. K.; Freeman, J. C.; Falls, H. D.; Brodjian, S.; Dayton, B. D.; Reilly, R. M.; Gintant, G. A.; Limberis, J. T.; Mikhail, A.; Leitza, S. T.; Houseman, K. A.; Diaz, G.; Bush, E. N.; Shapiro, R.; Knourek-Segel, V.; Hernandez, L. E.; Marsh, K. C.; Sham, H. L.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2006**, submitted.
16. Instances of regioisomerism resulting in improved MCHr1 potency were seen in other compound sets as well. For example,

Compound	MCHr1 IC_{50} (μM)	Ca^{2+} IC_{50} (μM)	hERG IC_{50} (μM)
	1.7	>10	47.7
	0.047	0.551	60.7

17. Compounds were evaluated for cross-reactivity in 75 GPCR receptors and ion channels panel at 10 μM run by CEREP (www.cerep.com). A sample subset of the 75 panel assay is shown below.

CEREP panel % inhibition at 10 μM	**1**	**19**
Adenosine, A1(h)	8	11
Adrenergic, α1	32	13
Adrenergic, α2	18	28
Adrenergic, β2	21	16
Dopamine, D1(h)	43	7
DA transporter (h)	26	**67**
Histamine, H1 (central)	**65**	36
Histamine, H2	16	21
Muscarinic, M1 (h)	**55**	16
Muscarinic, M2 (h)	42	15
NE transporter (h)	48	45
Opiate, κ (h)	**66**	43
Seratonin, 5HT1A (h)	48	25
5HT1B	−6	5
5HT2A (h)	17	−10
Sigma (nonselective)	**104**	37
Ca^{2+} Channel (L, verapamil site)	31	10
Na^{+} Channel (site 2)	**91**	**72**
K^{+} Channel (SK + Ca Channel)	−20	17

18. CYP3A4 subfamily enzyme's inhibition was determined as the concentration of compound needed for competitive inhibition of [^{3}H]-terfenadine oxidation in human hepatic microsomes.
19. Effects of compound were evaluated based on tail currents measured during a 3-s depolarizing pulse to 0 mV followed by a 4-s repolarization test pulses to −50 mV using HEK293 cells stably expressing hERG.