Bioorganic & Medicinal Chemistry Letters 19 (2009) 5339–5345

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of novel diarylketoxime derivatives as selective and orally active melanin-concentrating hormone 1 receptor antagonists

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ARTICLE INFO

Article history:
Received 20 May 2009
Revised 28 July 2009
Accepted 29 July 2009
Available online 6 August 2009

Keywords:
Melanin-concentrating hormone 1 receptor
Antagonist
Oxime
Obesity

ABSTRACT

Optimization of the lead **2a** led to the identification of a novel diarylketoxime class of melanin-concentrating hormone 1 receptor (MCH-1R) antagonists. Our focus was directed toward improvement of hERG activity and metabolic stability. The representative derivative **4b** showed potent and dose-dependent body weight reduction in diet-induced obese (DIO) C57BL/6J mice after oral administration. The synthesis and structure–activity relationships of the novel diarylketoxime MCH-1R antagonists are described.

Melanin-concentrating hormone (MCH) is a cyclic 19-amino acid polypeptide that is expressed predominantly in the lateral hypothalamus (LH). The LH is a region of the brain involved in the regulation of feeding, the neuroendocrine axis, and thermogenesis. Several lines of investigation suggest that MCH is an important mediator of energy homeostasis. Mice lacking prepro-MCH are lean, hypophagic, and have an elevated metabolic rate.[1] Conversely, prepro-MCH overexpression in mice results in a greater susceptibility to obesity.[2] Furthermore, overexpression of MCH mRNA has been found in obese rodents, such as ob/ob, db/db, and Ay/a mice.[3–5] Exogenous administration of MCH stimulates food intake,[3,6] and chronic ICV infusion of the MCH[7,8] or a related MCH-1R agonist[9] produces obesity with hyperphagia. Even when pair-feeding is employed to prevent hyperphagia, ICV infusion of MCH still produces anabolic changes.[10] The effects of MCH are mediated through G protein-coupled receptors located in the CNS, and thus far two receptor subtypes, MCH-1R and MCH-2R, have been identified.[11–14] Since rodents possess only MCH-1R, all pharmacological effects of MCH in rodents are likely mediated via MCH-1R.[15] Recently, peptide and non-peptidic MCH-1R antagonists have been developed; both antagonists produced anti-obese effects in diet-induced obese (DIO) rats.[9,16,17] Collectively, these data indicate that MCH-1R is an important regulator of energy homeostasis, and suggest that it may play an important role in the development of obesity. Hence, MCH antagonists could be effective therapeutic agents for the treatment of obesity. Currently, GW856464,[18] AMG-076[19] and NGD-4715[20] have entered clinical trials for the treatment of obesity. Our group recently disclosed highly potent and selective MCH-1R antagonists **1a** and **1b**, which feature a unique spiro-piperidine structure with a propyl amide linkage. In these reports, compound **1a** was shown to display extremely potent binding affinity (IC_{50} = 0.09 nM at the human MCH-1R (hMCH-1R)), and [^{35}S]-**1b** was shown to be a useful radioligand for ex vivo receptor occupancy studies (Fig. 1).[21,22] Issues associated with developing clinical candidates from these leads were metabolic stability[23,24] and P-gp susceptibility.[25] In order to address these issues, smaller and conformationally rigid leads were desired. Compound **2a**, which has an IC_{50} value of 3.5 nM at hMCH-1R, was designed based on our spiro-structure in **1a** and the difluorophenoxyphenyl structure in the Synaptic's compound **1c** (Fig. 1).[26,27] The molecular weight of **2a** is substantially reduced (MW = 425) relative to **1a** (MW = 531). Issues associated with **2a** are its human ether-a-go-go related gene (hERG) K^+ channel activity (IC_{50} = 24 nM) and poor microsomal stability. In this report, we

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doi:10.1016/j.bmcl.2009.07.132

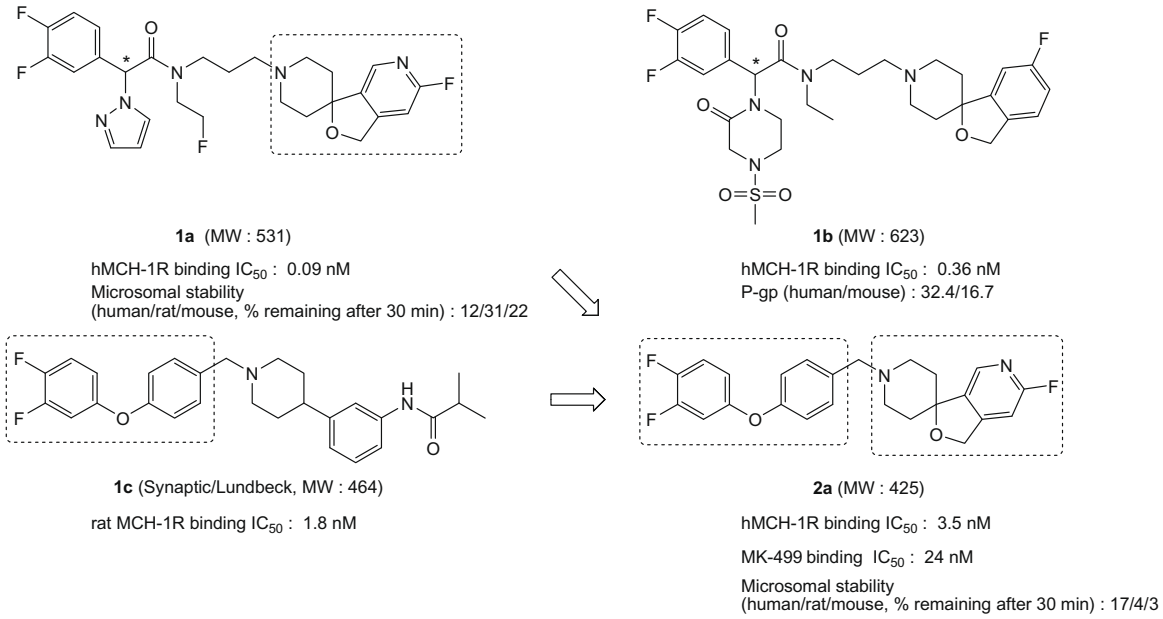
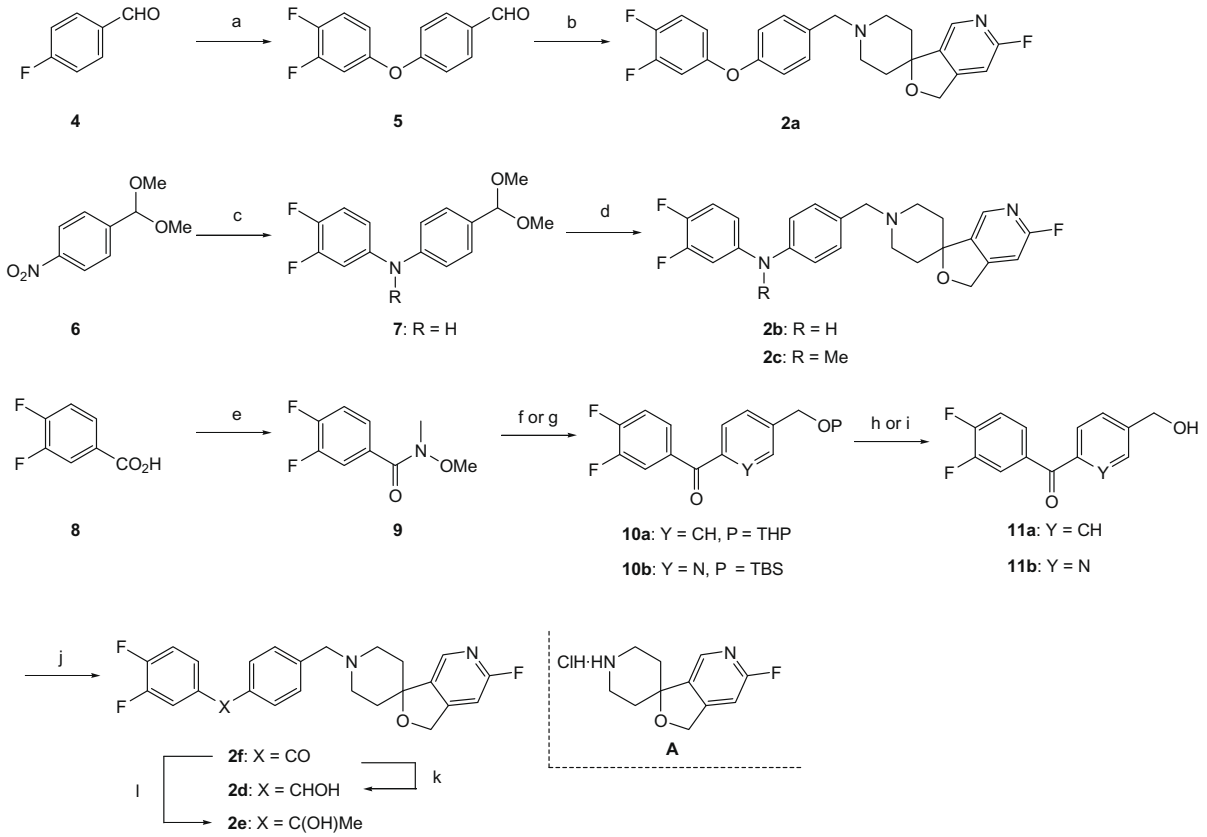


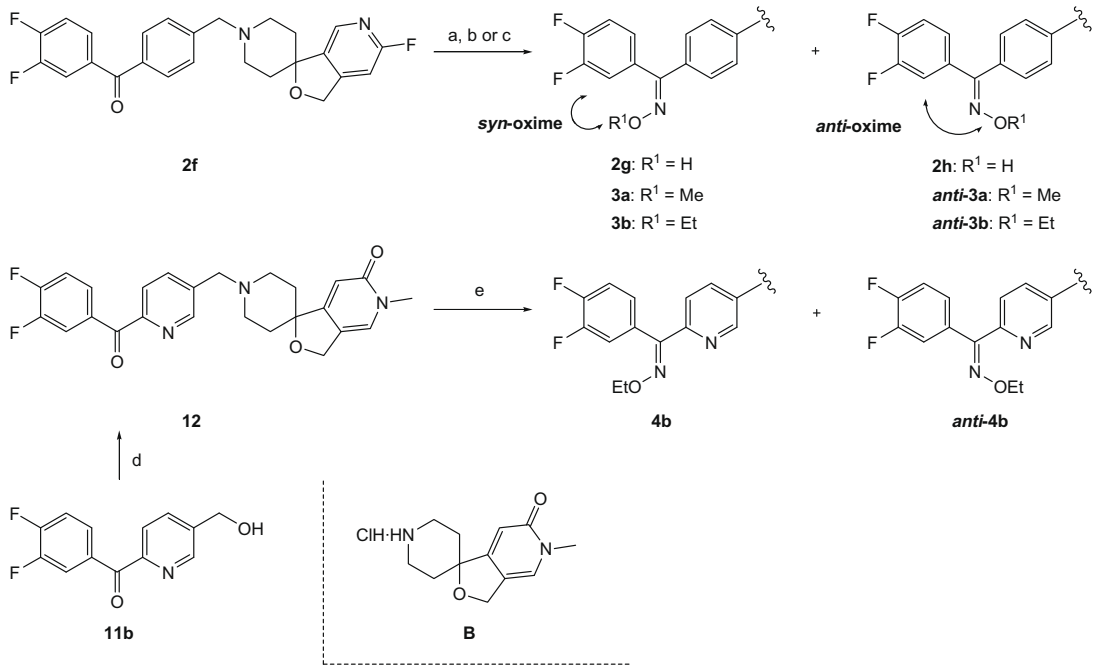
Figure 1. Design of lead **2a** from compounds **1a–c**.

describe further optimization of lead **2a** and the discovery of the orally active derivative **4b** that exhibits reduced hERG activity.

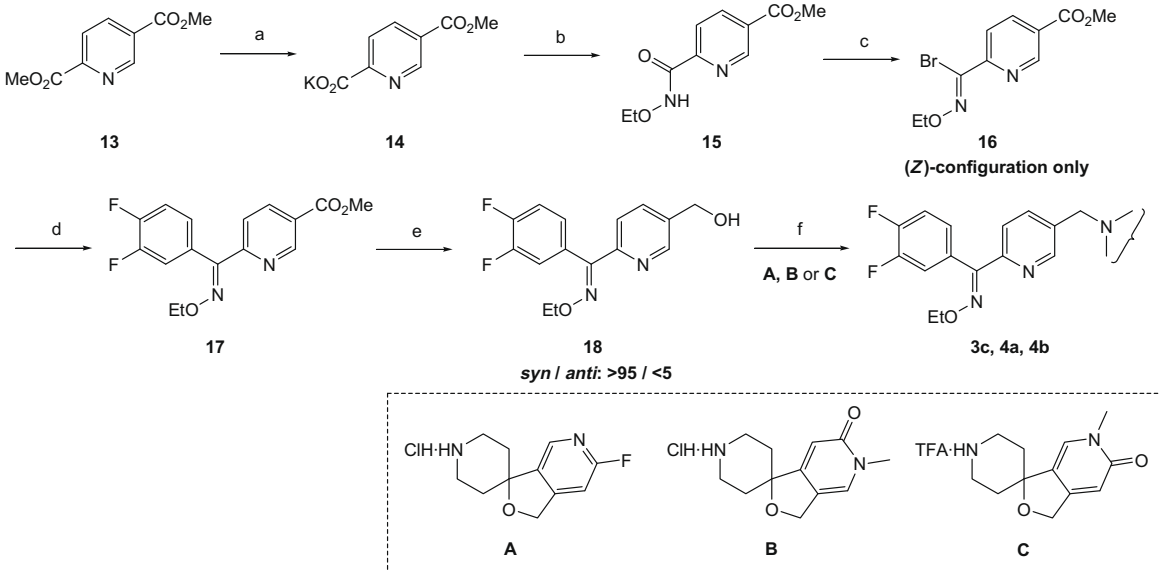
The synthesis of compounds described herein is outlined in Schemes 1–3. Compounds **2a–f** were prepared as shown in Scheme



Scheme 1. Preparation of diaryl derivatives **2a–f**. Reagents and conditions: (a) 3,4-difluorophenol, K_2CO_3, DMA, 155 °C, 17 h, 70%; (b) amine **A**, Et_3N, $Zn(BH_3CN)_2$, THF–MeOH, rt, 17 h, 86%; (c) 0.5 M 3,4-difluorophenylmagnesium bromide in THF, $FeCl_2$, THF, −10 °C, 1 h, then $NaBH_4$, EtOH, rt, 17 h, 63%; (d) (i) NaH, MeI, THF, 0 °C→rt, 17 h; (ii) 1 N HCl aq, rt, 20 min; (iii) amine **A**, Et_3N, $Zn(BH_3CN)_2$, THF–MeOH, rt, 17 h, **2c** (49% over three steps), **2b** (4% over three steps); (e) Me(MeO)NH·HCl, EDCI·HCl, HOBt·H_2O, Et_3N, $CHCl_3$, rt, 17 h, 99%; (f) 2-[(4-bromobenzyl)oxy]tetrahydro-2*H*-pyran, *n*-BuLi, THF–hexane, −78 °C, 1 h, then **9**, −78 °C, 1 h, 0 °C, 1 h, **10a** (49%); (g) 2-bromo-5-(1-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)pyridine, *n*-BuLi, toluene–hexane, −78 °C, 2 h, then **9**, −78 °C, 1 h, 0 °C, 18 h, **10b** (65%); (h) *p*-TsOH·H_2O, MeOH, rt, 5.5 h, **11a** (92%); (i) TBAF, THF, 0 °C, 30 min, **11b** (68%); (j) (i) MsCl, Et_3N, EtOAc, 0 °C, 20 min; (ii) amine **A**, Et_3N, $CHCl_3$, rt, 3 h, 66% over two steps; (k) $NaBH_4$, MeOH, 0 °C, 10 min, 78%; (l) 1.0 M MeMgBr in THF, 0 °C, 1 h, rt, 1 h, 79%.



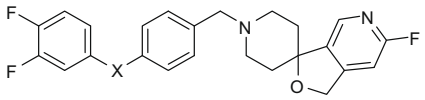
Scheme 2. Synthesis of the oxime derivatives **2g**, **2h**, **3a**, **3b** and **4b**. Reagents and conditions: (a) $HONH_2$·HCl, pyridine, rt, 17 h, **2g** (51%), **2h** (33%); (b) $MeONH_2$·HCl, pyridine, rt, 17 h, **3a** (40%), ***anti*-3a** (29%); (c) (i) $EtONH_2$·HCl, pyridine, rt, 11 h; (ii) separation by HPLC (CHIRALPAK AD-H, hexanes/EtOH/Et_2NH = 80/20/0.05), **3b** (38%, the second-eluted isomer), ***anti*-3b** (29%, the first-eluted isomer); (d) (i) MsCl, Et_3N, EtOAc, 0 °C, 20 min; (ii) amine **B**, Et_3N, $CHCl_3$, rt, 17 h, 83% over two steps; (e) (i) $EtONH_2$·HCl, pyridine, rt, 6 h; (ii) separation by HPLC (CHIRALPAK AD-H, hexanes/EtOH/Et_2NH = 60/40/0.04), **4b** (50%, the first-eluted isomer), ***anti*-4b** (22%, the second-eluted isomer).



Scheme 3. Stereo-selective synthesis of the oxime derivatives **3c**, **4a** and **4b**. Reagents and conditions: (a) KOH (1.0 equiv), MeOH, rt, 7 h, 82%; (b) (i) $SOCl_2$, 90 °C, 3 h; (ii) $EtONH_2$·HCl, Et_3N, $CHCl_3$, rt, 14 h, 85% over two steps; (c) Ph_3P, CBr_4, CH_3CN, 90 °C, 72 h, 59% ((*Z*)-configuration only); (d) 3,4-difluorophenylboronic acid, $Pd(OAc)_2$ (12 mol %), Ph_3P (24 mol %), $NaHCO_3$ aq, toluene, 80 °C, 48 h, 93%; (e) $LiAlH_4$, THF, −78 °C, 1 h, 96% (*syn*/*anti*: >95/<5); (f) (i) MsCl, *N*,*N*-diisopropylethylamine, EtOAc, 0 °C, 30 min; (ii) amines **A**, **B** or **C**, *N*,*N*-diisopropylethylamine, $CHCl_3$, rt, 5–17 h, 45–68% over two steps.

1. 4-Fluorobenzaldehyde **4** was substituted with 3,4-difluorophenol to give phenoxybenzaldehyde **5** following the known procedure.[28] The derivative **2a** was obtained by reductive amination of the aldehyde **5** with the spiro-amine **A**.[29] 3,4-Difluorophenylmagnesium bromide was reacted with the nitro group of **6**[30] followed by reduction using iron dichloride and sodium borohydride to afford aniline **7**.[31] *N*-Methylation of aniline **7** failed to go to completion and gave a mixture of unreacted starting **7** and the desired methylated product. This mixture was subjected to the subsequent reactions to give a mixture of **2b** and **2c** which were isolated by PTLC. Commercially available carboxylic acid **8** was converted to the corresponding Weinreb amide **9**, which was reacted with the anions generated from 2-[(4-bromobenzyl)oxy]tetrahydro-2*H*-pyran or 2-bromo-5-(1-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)pyridine[32] with *n*-BuLi to give benzophenones **10a**,**b**. Deprotection of the protecting group of **10a,b** gave alcohols **11a,b**. The hydroxyl

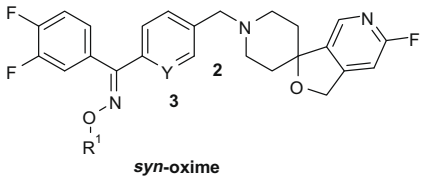
Table 1
Human MCH-1R and hERG binding activity of the diaryl derivatives **2a**–**h**[a]



Compound	X	hMCH-1R[b] (IC_{50}, nM)	hERG[c] (IC_{50}, nM)
2a	O	3.5	24
2b	NH	4.6	23
2c	NMe	1.3	25
2d (racemate)	CHOH	6.3	520
2e (racemate)	C(OH)Me	2.6	530
2f	C=O	1.4	17
2g (*syn*-oxime)	C=N–OH	0.26	310
2h (*anti*-oxime)	C=N–OH	1.2	280

[a] The values are the means of two experiments.
[b] Inhibition of [^{125}I]MCH binding to hMCH-1R in CHO cells.
[c] Inhibition of [^{35}S]MK-499 binding to hERG K^+ channel in HEK293 cells.

Table 2
Human MCH-1R and hERG binding activity of compounds **2g**, **3a**–**c**[a]



***syn*-oxime**

Compound	R^1	Y	hMCH-1R[b] (IC_{50}, nM)	hERG[c] (IC_{50}, nM)
2g (*syn*-oxime)	H	CH	0.26	310
3a (*syn*-oxime)	Me	CH	0.22	250
3b (*syn*-oxime)	Et	CH	0.12	140
3c (*syn*-oxime)	Et	N	0.35	1790

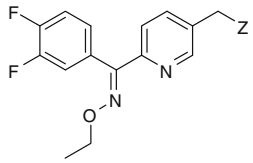
[a] The values are the means of two experiments.
[b] Inhibition of [^{125}I]MCH binding to hMCH-1R in CHO cells.
[c] Inhibition of [^{35}S]MK-499 binding to hERG K^+ channel in HEK293 cells.

group of **11a** was mesylated and displaced by the spiro-piperidine **A** to afford **2f**. Ketone **2f** was reduced with sodium borohydride to give **2d**. Treatment of **2f** with methylmagnesium bromide furnished **2e**. The oxime derivatives **2g**, **2h**, **3a**, **3b** and **4b** were synthesized as depicted in Scheme 2. Oxime formation of benzophenone **2f** with alkoxy amines ($RONH_2$·HCl, R = H, Me, Et) proceeded smoothly, and the resultant geometric isomers were separated by PTLC or chiral HPLC. Herein, *syn*- and *anti*-oximes are defined by the orientation of the N–O bond of the oxime and the difluorophenyl ring. When these two groups are on the same side, the isomer is named a *syn*-oxime (Scheme 2). In all cases, *syn*-oximes **2g**, **3a** and **3b** were preferentially formed and the geometry of the oxime group was determined by NOE.[33] The ethyl oxime derivatives (**4b** and *anti*-**4b**) containing the spiro-pyridone structure were prepared in the same manner.[33,34] Next, we developed a stereo-selective synthesis of the *syn*-oxime derivatives by stereo-controlled palladium coupling between an imidoyl bromide and an arylboronic acid as outlined in Scheme 3. Using this synthetic route, *syn*-oximes **3c**, **4a** and **4b** were prepared with high stereo-selectivity (*syn*-/*anti*-oxime: >95/<5). Potassium carboxylate **14**[35] derived from pyridine dimethylcarboxylate **13** was activated with thionyl chloride followed by the treatment with ethoxy amine to give ethoxy amide **15** in 85% yield. The amide **15** was treated with triphenylphosphine and carbon tetrabromide to afford (*Z*)-imidoyl bromide **16** exclusively.[36–39] (*Z*)-Imidoyl bromide **16** was effectively coupled with 3,4-difluorophenylboronic acid in the presence of palladium acetate (II) to afford ethyl oxime **17**, which was reduced to primary alcohol **18** (*syn*-/*anti*-oxime: >95/<5). Finally, the hydroxyl group of **18** was mesylated and displaced by the spiro-piperidines **A**, **B** and **C**[34] to give **3c**, **4a** and **4b** respectively.[40]

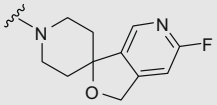
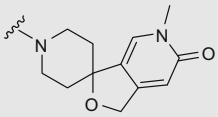
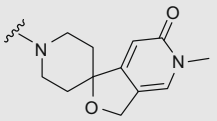
The linkage (X) between the two phenyl rings was screened (Table 1). The aniline derivative **2b** was equipotent to **2a**, and the *N*-methyl aniline derivative **2c** showed increased hMCH-1R activity (IC_{50} = 1.3 nM). However, these aniline derivatives showed potent hERG activity. With the aim of reducing hERG activity by introducing hydrophilic substituents, the *sec*- and *tert*-alcohol derivatives **2d** and **2e** were examined. Both compounds displayed improved hERG profiles while retaining good hMCH-1R activity. The benzophenone derivative **2f**, on the other hand, exhibited improved hMCH-1R activity (IC_{50} = 1.4 nM) and potent hERG activity (IC_{50} = 17 nM). Introduction of an oxime structure resulted in the identification of the potent derivatives **2g** and **2h**. The *syn*-oxime **2g** was found to be the active isomer, which has an IC_{50} value of 0.26 nM at hMCH-1R. In addition to its high intrinsic hMCH-1R potency, **2g** showed attenuated hERG activity. Next, alkyl substituents (R^1) were introduced to the hydroxyl group of the oxime **2g** (Table 2). The *syn*-methyloxime derivative **3a** was equipotent to the *syn*-oxime derivative **2g**, and the *syn*-ethyloxime derivative **3b** showed an increase in activity (IC_{50} = 0.12 nM). The hERG activities of **3a** and **3b** were equivalent to that of **2g**. Regarding the oxime geometry, the *syn*-alkyloximes **3a** and **3b** (R^1 = Me, Et) were the hMCH-1R active isomers.[41] Incorporation of a nitrogen atom into the inner phenyl ring as in **3c** resulted in a substantial improvement in hERG activity while maintaining potent hMCH-1R activity.

Having identified **3c** with potent hMCH-1R activity and reduced hERG activity, our focus was directed toward improving the metabolic stability of **3c**. As shown in Table 3, compound **3c** was metabolized by microsomes extensively.[23,24] Replacement of the fluoropyridine portion of the right-hand spiro-structure by *N*-methylpyridone as in **4a** was found to be an effective strategy to increase metabolic stability; however, **4a** showed a substantial loss of potency (IC_{50} = 45 nM). It was soon realized that the corresponding pyridone regio-isomer **4b** has increased hMCH-1R activity (IC_{50} = 6.8 nM) while maintaining good metabolic stability. After oral administration, compound **4b** displayed an attractive pharmacokinetic profile in Sprague-Dawley (SD) rats (Table 4). Given these balanced profiles, compound **4b** was further characterized. The binding affinities of **4b** for the rat and mouse MCH-1R receptors are IC_{50} values of 8.8 and 12 nM, respectively, indicating no significant species difference in binding affinity. In the cellular functional assay (FLIPR),[42] compound **4b** inhibited MCH-induced Ca^{2+} release with an IC_{50} value of 25 nM. Compound **4b** displayed good selectivity over MCH-2R (IC_{50} >10 μM) and a panel of 171 diverse unrelated binding sites (IC_{50} >1 μM for all the binding sites tested). Brain permeability of **4b** was examined in SD rats (Table 5). Following oral administration at 10 mg/kg, **4b** showed a brain-to-plasma ratio of 0.49, which was thought to be relatively low for a basic molecule. As shown in Table 5, **4b** was found to be a rodent P-gp substrate, which would be a major factor for the observed modest brain penetrability of **4b**.[25] Brain penetrability of **4b** in humans is unlikely to be limited by P-gp since it is not a human P-gp substrate. In addition, the appreciable free brain concentration of **4b** was assessed by its CSF concentration. Compound **4b** displayed appreciable exposure in DIO C57BL/6J mice after oral administration at 10 and 30 mg/kg (Table 6) where the plasma and brain levels 24 h after 30 mg/kg oral administration were 0.119 μM and 0.052 nmol/g, respectively. The brain-to-plasma ratio of 0.43 in DIO C57BL/6J mice is consistent with that observed in SD rats. Given these favorable data, chronic effects of the MCH-1R antagonist

Table 3
Human MCH-1R and hERG binding activity and microsomal stability of *syn*-oximes **3c**, **4a** and **4b**



***syn*-oxime**

Compound	*Z*	hMCH-1R[a,b] (IC_{50}, nM)	hERG[a,c] (IC_{50}, nM)	Microsomal stability[a,d] (% remaining after 30 min)		
				Human	Rat	Mouse
3c (*syn*-oxime)		0.35	1790	0	2	11
4a (*syn*-oxime)		45	>10,000	77	84	74
4b (*syn*-oxime)		6.8	3670	68	71	57

[a] The values are the means of two experiments.
[b] Inhibition of [^{125}I]MCH binding to hMCH-1R in CHO.
[c] Inhibition of [^{35}S]MK-499 binding to hERG K^+ channel in HEK293 cells.
[d] Incubation mixture consists of 0.25 mg protein/mL, 3 mM magnesium chloride, glucose-6-phosphate dehydrogenase (1 unit/mL), 10 mM sodium D-glucose-6-phosphate, and 1 μM substrate in 0.1 M potassium phosphate buffer (pH 7.4). Incubations were conducted at 37 °C for 30 min. To calculate percent of parent compound remaining, the peak area at 30 min was divided by the peak area at time zero.

Table 4
Pharmacokinetic parameters for **4b** in SD rats[a]

Compound	iv (1 mg/kg)			po (3 mg/kg)		
	CL_p (mL/min/kg)	Vdss (L/kg)	$T_{1/2}$ (h)	C_{max} (μM)	$AUC_{0-\infty\ h}$ (μM h)	F[b] (%)
4b	13	1.6	1.4	1.85	6.57	87

[a] The values are the means for $n = 3$ animals.
[b] Based on $AUC_{0-\infty\ h}$ values after iv and po dosings.

Table 5
Brain penetration and P-gp susceptibility of **4b**

Compound	Brain penetration in SD rats[a]					P-gp susceptibility[b]	
	Plasma (μM)	Brain (nmol/g)	CSF (μM)	Ratio brain/plasma	CSF/brain	Transcellular transport ratio (B-to-A)/(A-to-B)	
						MDR1	*mdr1a*
4b	4.50	2.20	0.130	0.49	0.06	1.9	5.1

[a] The concentrations were determined at 2 h after 10 mg/kg oral administration. The values are the mean for $n = 3$ animals.
[b] Transcellular transport ratio ((B-to-A)/(A-to-B)) in human *MDR1*- and mouse *mdr1a*-transfected LLC-PK1 cell line. The values are the means of three experiments.

Table 6
Exposure of **4b** after oral administration in DIO C57BL/6J mice[a]

Compound	po (10 mg/kg)			po (30 mg/kg)		
	C_{max} (μM)	T_{max} (h)	$AUC_{0-\infty\ h}$ (μM h)	C_{max} (μM)	T_{max} (h)	$AUC_{0-\infty\ h}$ (μM h)
4b	4.27	2.0	15.4	15.6	2.0	90.7

[a] The values are the means for $n = 3$ animals.

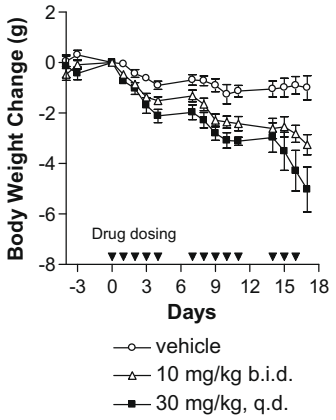


Figure 2. Effect of **4b** on the body weight of DIO C57BL/6J mice. Mice were orally administered either vehicle or the MCH-1R antagonist at doses of 10 mg/kg, b.i.d. or 30 mg/kg, q.d. for 13 days (n = 7–9).

4b in DIO C57BL/6J mice was examined (Fig. 2).[43] As a result, 13-day oral treatment with **4b** at 10 mg/kg (twice daily) and 30 mg/kg (once daily) potently and dose-dependently reduced body weight of DIO C57BL/6J mice by 4% and 8%, respectively.

In summary, the selective and orally active MCH-1R antagonist **4b** was identified by optimization of the lead **2a**. Compound **4b** has reduced hERG inhibitory activity and exhibited a useful pharmacokinetic profile in rats. Subsequent to oral dosing, **4b** showed potent and dose-proportional body weight reduction in DIO C57BL/6J mice. Further evaluation of **4b** to assess its potential for clinical development is ongoing.

Acknowledgments

We would like to thank Dr. Shigeru Nakajima for performing NOE studies and Atsushi Hirano for selecting HPLC conditions for the separation of the oxime geometric isomers. We also thank Dr. Peter T. Meinke (Merck Research Laboratories, Rahway, NJ) for the editing of this manuscript.

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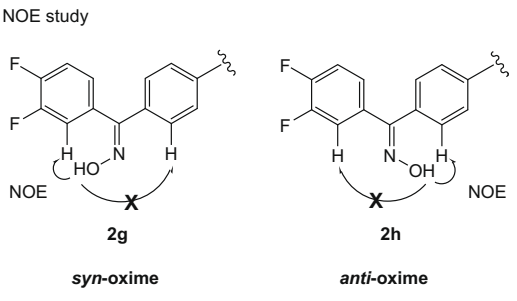

34. The spiro-amines **B** and **C** were prepared from the corresponding Boc-protected intermediates disclosed in the following patent. Suzuki, T.; Ando, M.; Miyazoe, H.; Kameda, M.; Sekino, E.; Moriya, M. WO 2008047544, 2008. Removal of Boc groups by 4 N HCl–EtOAc at room temperature for 2 h or TFA at room temperature for 10 min afforded the spiro-amines **B** and **C** quantitatively.
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40. *Data for* **4b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, J = 7.1 Hz), 1.70–1.73 (2H, m), 1.80–1.85 (2H, m), 2.35–2.41 (2H, m), 2.72–2.76 (2H, m), 3.49 (3H, s), 3.55 (2H, s), 4.27 (2H, q, J = 7.1 Hz), 4.78 (2H, s), 6.31 (1H, s), 7.10–7.20 (3H, m), 7.25–7.30 (1H, m), 7.71–7.77 (2H, m), 8.46 (1H, s). ESI-MS Found: m/z 495[M+H]$^+$; HPLC purity (99.6%).
41. The hMCH-1R IC_{50} values for the corresponding *anti*-oximes of **3a**, **3b** and **4b** are 0.71, 0.62 and 83 nM, respectively.
42. For the MCH-1R functional assay, MCH (5 nM)-induced intracellular Ca^{2+} changes were measured in CHO cells expressing human MCH-1R in the presence of several concentrations of test compounds using FLIPR (Molecular Devices, Sunnyvale, CA).
43. Male C57BL/6J mice (CLEA Japan, Tokyo, Japan) were used. Mice were housed individually in plastic cages under controlled temperature and humidity (23 ± 2 °C, 55 ± 15%), and a 12-h light-dark cycle (lights on 7:00–19:00). The mice were fed a moderately high-fat (MHF) diet (Oriental BioService Kanto, Ibaraki, Japan; 52.4% energy as carbohydrate, 15.0% as protein and 32.6% as fat, 4.4 kcal/g) for about 6 months before the experiment. Mice had *ad libitum* access to tap water. The mice were divided into 3 groups to match averaged body weight, and each group was orally administered either vehicle or the MCH-1R antagonist at doses of 10 mg/kg, b.i.d. or 30 mg/kg, q.d. for 13 days (n = 7–9). Drugs were administered only on weekdays. Drug administration was done about 1 h after lights-on (morning) and about 1 h before lights-off (evening), and measurement of body weight was done just before the evening drug administration. In the vehicle- and 30 mg/kg, q.d.-treated groups, mice were treated with vehicle at the morning administration. All experimental procedures were approved by the Institutional Animal Care and Use Committee.