Bioorganic & Medicinal Chemistry Letters 19 (2009) 3072–3077

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Discovery of novel spiro-piperidine derivatives as highly potent and selective melanin-concentrating hormone 1 receptor antagonists

Takao Suzuki [a,*], Minoru Moriya [a], Toshihiro Sakamoto [a], Takuya Suga [a], Hiroyuki Kishino [a], Hidekazu Takahashi [a], Makoto Ishikawa [a], Keita Nagai [a], Yumiko Imai [a], Etsuko Sekino [a], Masahiko Ito [b], Hisashi Iwaasa [b], Akane Ishihara [c], Shigeru Tokita [b], Akio Kanatani [b], Nagaaki Sato [a,*], Takehiro Fukami [a]

[a] Department of Medicinal Chemistry, Tsukuba Research Institute, Merck Research Laboratories, Banyu Pharmaceutical Co., Ltd, Okubo 3, Tsukuba, Ibaraki 300-2611, Japan
[b] Department of Metabolic Disorder, Tsukuba Research Institute, Merck Research Laboratories, Banyu Pharmaceutical Co., Ltd, Okubo 3, Tsukuba, Ibaraki 300-2611, Japan
[c] Department of Pharmacology, Tsukuba Research Institute, Merck Research Laboratories, Banyu Pharmaceutical Co., Ltd, Okubo 3, Tsukuba, Ibaraki 300-2611, Japan

ARTICLE INFO

Article history:
Received 16 January 2009
Revised 1 April 2009
Accepted 3 April 2009
Available online 9 April 2009

Keywords:
Melanin-concentrating hormone
MCH
MCH-1R antagonists
Obesity

ABSTRACT

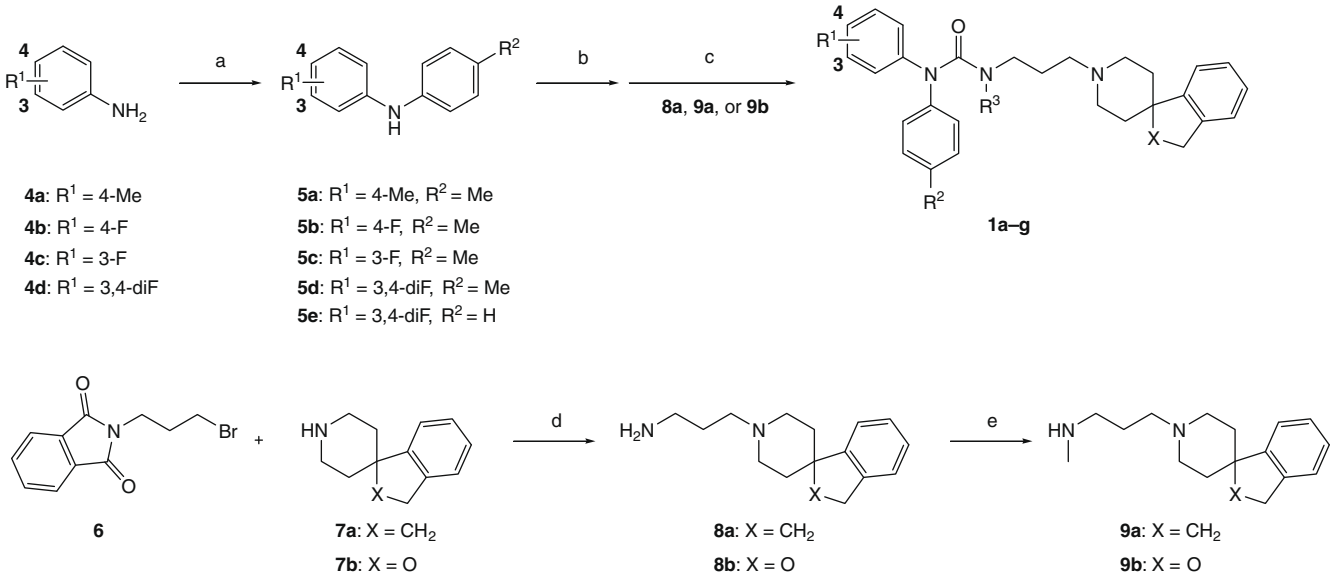
Optimization of high-throughput screening hit **1a** led to the identification of a novel spiro-piperidine class of melanin-concentrating hormone 1 receptor (MCH-1R) antagonists. Compound **3c** was identified as a highly potent and selective MCH-1R antagonist, which has an IC_{50} value of 0.09 nM at hMCH-1R. The synthesis and structure–activity relationships of the novel spiro-piperidine 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 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. Screening of Merck sample collections against human MCH-1R (hMCH-1R) resulted in the identification of a spiro-piperidine class of lead **1a**, which has an IC_{50} value of 42 nM. Subsequent optimization efforts were centered on improvement of the MCH-1R activity and reduction of human α_{1A}-adrenoceptor (hα1A) activity to identify the potent and selective derivative **3c**. The synthesis and structure–activity relationships (SAR) of this novel spiro-piperidine class of MCH-1R antagonists are described.

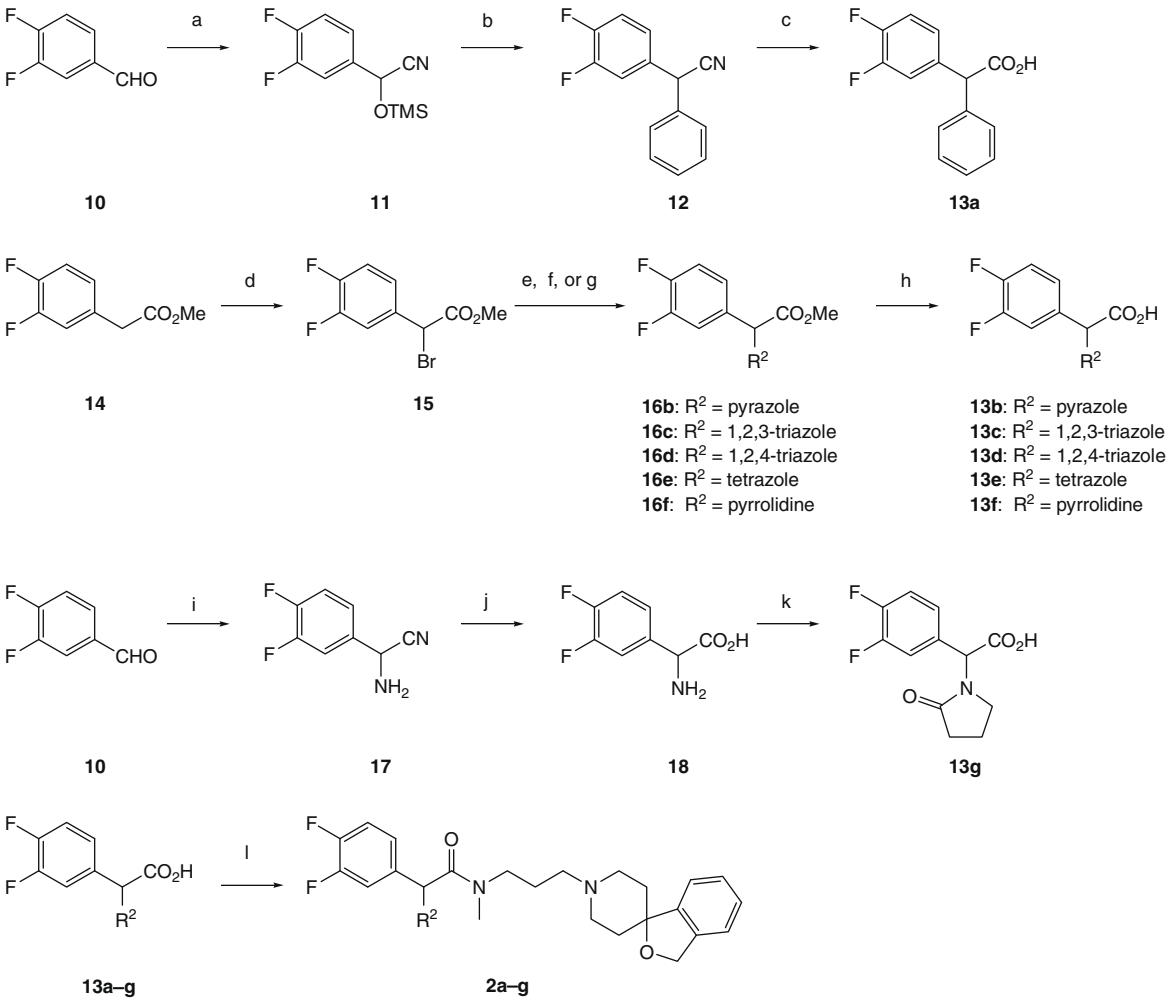
The synthesis of compounds described herein is outlined in Schemes 1–3. Compounds **1a–g** were prepared as shown in Scheme 1. Substituted anilines **4** were coupled with 4-methylphenylboronic acid or phenylboronic acid in the presence of copper acetate (II) and triethylamine to give diaryl amines **5a–e**, which were reacted with triphosgene followed by amines **8a**, **9a**, or **9b** to give compounds **1a–g**. Amines **8a**, **9a**, and **9b** were derived from *N*-(3-bromopropyl)-phthalimide **6** using standard procedures as depicted in Scheme 1.[18,19] Compounds **2a–g** were synthesized as outlined in Scheme 2. 3,4-Difluorobenzaldehyde (**10**) was converted to the corresponding cyanohydrin trimethylsilyl ether **11**. The trimethylsilyloxy group of **11** was displaced by a phenyl group followed by hydrolysis of the cyano group to give **13a**. Ester **14** was brominated to give **15**. The bromo group of **15** was displaced by the desired azoles and pyrrolidine followed by hydrolysis of the ester

* Corresponding authors. Tel.: +81 29 877 2218; fax: + 81 29 877 2029 (T.S.).
E-mail address: takao_suzuki@merck.com (T. Suzuki).

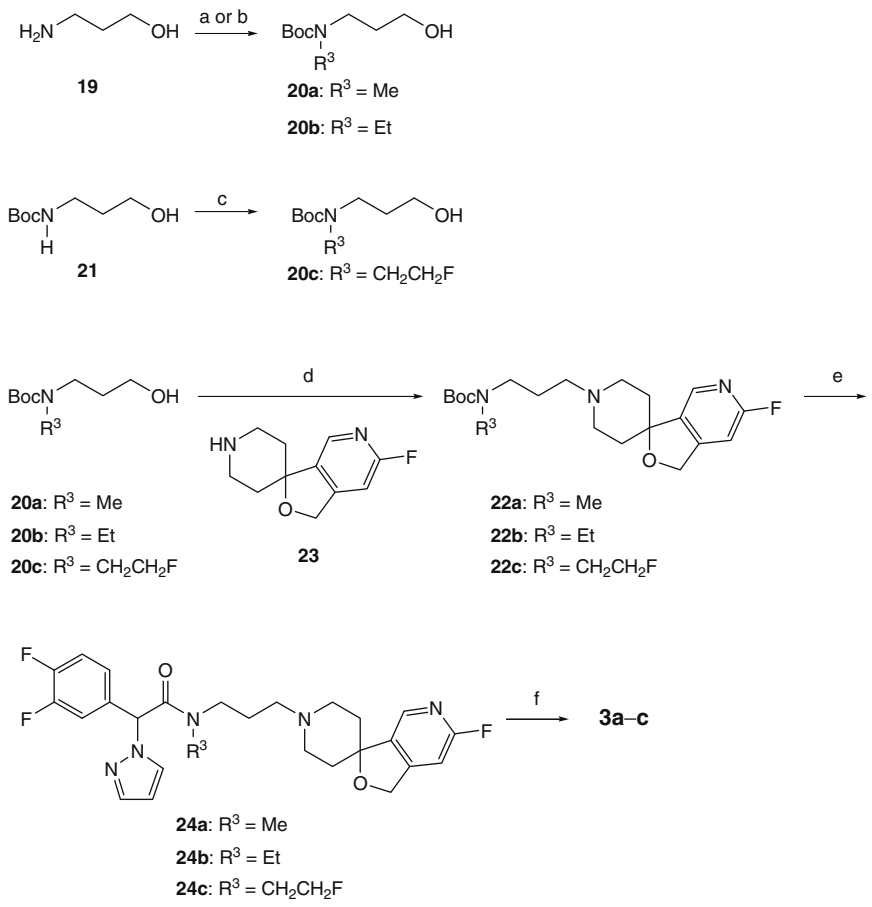
0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.04.016



Scheme 1. Preparation of urea derivatives **1a–g**. Reagents and conditions: (a) $Cu(OAc)_2$, Et_3N, 4-methylphenylboronic acid or phenylboronic acid, CH_2Cl_2, rt, 17 h, 48–90%; (b) triphosgene, Et_3N, $CHCl_3$, 0 °C→ rt, 2–17 h, 62–99%; (c) Et_3N, $ClCH_2CH_2Cl$, 60–100 °C, 2–3 h, 50–85%; (d) (i) K_2CO_3, KI, DMF, 80 °C, 17 h, 46–95%, (ii) $H_2NNH_2{\cdot}H_2O$, EtOH, reflux, 3 h, 99%; (e) (i) $ClCO_2Et$, Et_3N, $CHCl_3$, rt, 17 h, 99%, (ii) $LiAlH_4$, 1,4-dioxane, reflux, 17 h, 98–99%.

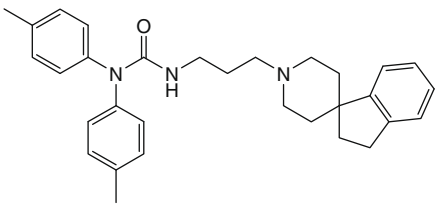


Scheme 2. Synthesis of compounds **2a–g**. Reagents and conditions: (a) TMSCN, $ZnCl_2$, CH_2Cl_2, rt, 4 h, 93%; (b) benzene, conc. H_2SO_4, 0 °C, 1.5 h, 15%; (c) conc. H_2SO_4, H_2O, 100 °C, 17 h, 66%; (d) NBS, HBr, CCl_4, reflux, 17 h, 98%; (e) pyrazole, *n*-BuLi, cat. 2,2′-bipyridyl, THF, −30 °C→ rt, 20 h, 60%; (f) 1,2,3-triazole or 1,2,4-triazole, NaH, THF, 0 °C→ rt, 17 h, 34–46%; (g) tetrazole or pyrrolidine, K_2CO_3, DMF–THF, rt, 3 h, 40–78%; (h) 4 N NaOH aq, MeOH, rt→ 50 °C, 2–17 h, 60–97%; (i) NH_3 aq, MeOH, 0 °C, 3 h, and then TMSCN, rt, 17 h, 94% over two steps; (j) 40% H_2SO_4 aq, 90 °C, 17 h, 99%; (k) (i) 4-chlorobutanoyl chloride, Et_3N, 1,4-dioxane-H_2O, 0 °C, 30 min, 60%, (ii) *tert*-BuOK, THF, 0 °C, 2 h, 85%; (l) amine **9b**, EDCI·HCl, HOBt·H_2O, $NaHCO_3$, DMF, rt, 17 h, 17–98%.



Scheme 3. Preparation of spiro-fluorofuropyridine derivatives **3a–c**. Reagents and conditions: (a) (i) HCO_2Et, THF, rt, 17 h, (ii) $LiAlH_4$, 0 → 60 °C, 3 h, (iii) Boc_2O, 1 N NaOH aq, THF, rt, 2 h, 67% over three steps; (b) (i) Ac_2O, THF, rt, 17 h, (ii) $LiAlH_4$, 0→70 °C, 2 h, (iii) Boc_2O, 1 N NaOH aq, THF, rt, 2 h, 85% over three steps; (c) (i) TBDMSCl, imidazole, DMF, rt, 2.5 h, 99%, (ii) 2-fluoroethyltosylate, NaH, DMF, rt, 60 h, 67%, (iii) TBAF, THF, 0 °C→rt, 1 h, 92%; (d) (i) MsCl, *N*,*N*-diisopropylethylamine, EtOAc, 0 °C, 30 min, 99%, (ii) **23**, K_2CO_3, KI, DMF, 80 °C, 17 h, 43–81%; (e) (i) 4 N HCl–EtOAc, 0 °C, 30 min, 99%, (ii) **13b**, EDCI·HCl, HOBt·H_2O, $NaHCO_3$, DMF, rt, 17 h, 28–76%; (f) chiral resolution by HPLC (CHIRALCEL OD, hexanes/EtOH = 8/2).

group to afford carboxylic acids **13b–f**. Treatment of aldehyde **10** with aqueous ammonia followed by trimethylsilanecarbonitrile furnished **17**, which was subjected to acidic conditions for hydrolysis of the nitrile group to give carboxylic acid **18**. The amino group of **18** was coupled with 4-chlorobutanoyl chloride followed by treatment with potassium *tert*-butoxide to effect intramolecular cyclization to afford **13g**. The α-substituted phenyl acetic acids **13a–g** were coupled with amine **9b** to give the target compounds **2a–g**. The preparation of compounds **3a–c** is outlined in Scheme 3. The 3-alkylaminopropanols **20a–c** protected by a *tert*-butoxylcarbonyl (Boc) group were prepared by standard procedures as shown in Scheme 3.[20] The hydroxyl group of **20a–c** were mesylated and displaced by the piperidine analogue **23**[21] to give **22a–c**. Compounds **24a–c** were obtained by deprotection of the Boc group of **22a–c** followed by coupling of the resulting amino group with the carboxylic acid **13b**. The racemates **24a**, **24b**, and **24c** were resolved by HPLC to give the corresponding active enantiomers **3a**, **3b**, and **3c**, respectively.[22]



1a

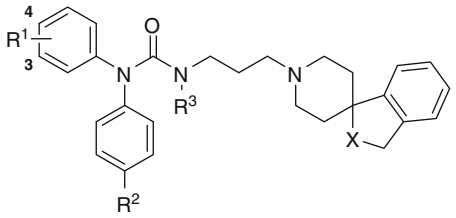
hMCH-1R binding IC_{50} : 42 nM

hα_{1A} binding IC_{50} : 540 nM

Figure 1. Structure of the lead compound **1a**.

High-throughput screening of Merck sample collections against hMCH-1R led to the identification of **1a**, which has an IC_{50} value of 42 nM. Compound **1a** was found to have moderate activity for hα1A (IC_{50} = 540 nM) (Fig. 1). Modification of **1a** was initiated to increase MCH-1R activity and reduce hα1A activity (Table 1). The 4- and 3-fluorophenyl derivatives **1b** and **1c** were equipotent to **1a**. The 3,4-difluorophenyl derivative **1d** was found to be more potent than **1a**. The potency was further improved by *N*-methylation as in **1e** (IC_{50} = 2.1 nM), a 20-fold improvement over **1a**. The introduction of an oxygen atom to the spiro-indane portion, as in **1f**, resulted in reduced hα1A activity while retaining MCH-1R activity. Removal of a 4-methyl group on the distal *N*-phenyl group (**1g**) was found to be detrimental for MCH-1R activity (IC_{50} = 19 nM). Conversion of the urea linkage of **1g** to the amide led to the identification of the potent amide derivative **2a**, which shows an IC_{50} value of 1.0 nM at hMCH-1R (Table 2). The R^2 substituent of **2a** was further explored. The pyrazole and triazole derivatives **2b–d** displayed good activities for hMCH-1R and decreased hα1A activities. The tetrazole derivative **2e** exhibited decreased activity. The pyrrolidine derivative **2f** showed a significant loss of potency; however, the corresponding oxo-derivative **2g** was surprisingly potent, with an IC_{50} value of 2.7 nM at hMCH-1R. Permeability-glyco-

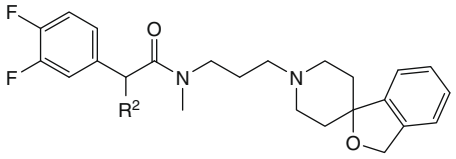
Table 1
Human MCH-1R and α_{1A} binding activity of urea derivatives **1a**–**g**[a]

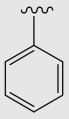
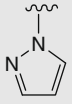
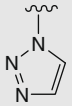
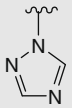
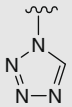
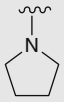
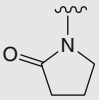


Compound	R^1	R^2	R^3	X	hMCH-1R[b] (IC_{50}, nM)	hα1A[c] (IC_{50}, nM)
1a	4-Methyl	Me	H	CH_2	42	540
1b	4-Fluoro	Me	H	CH_2	54	340
1c	3-Fluoro	Me	H	CH_2	42	490
1d	3,4-Difluoro	Me	H	CH_2	9.6	350
1e	3,4-Difluoro	Me	Me	CH_2	2.1	230
1f	3,4-Difluoro	Me	Me	O	2.1	470
1g	3,4-Difluoro	H	Me	O	19	920

[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 [^{3}H]prazosin binding to human α_{1A}-adrenoceptor in LMtk$^-$ cells.

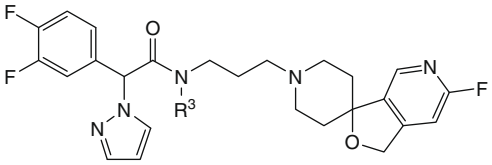
Table 2
Human MCH-1R and α_{1A} binding activity and P-gp susceptibility of compounds **2a**–**g**[a]

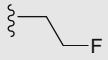


Compound	R^2	hMCH-1R[b,c] (IC_{50}, nM)	hα1A[b,d] (IC_{50}, nM)	P-gp Susceptibility[e,f] transcellular transport ratio (B-to-A)/(A-to-B)	
				MDR1	*mdr1a*
2a		1.0	600	1.4	3.7
2b		1.7	3600	1.8	4.9
2c		1.9	1920	4.1	4.9
2d		2.9	1910	9.2	3.4
2e		9.9	1910	NT	NT
2f		125	1160	NT	NT
2g		2.7	1000	24.8	32.9

[a] Compounds **2a**–**g** were tested as racemates.
[b] The values are the means of two experiments.
[c] Inhibition of [^{125}I]MCH binding to hMCH-1R in CHO cells.
[d] Inhibition of [^{3}H]prazosin binding to human α_{1A}-adrenoceptor in LMtk$^-$ cells.
[e] Transcellular transport ratio ((B-to-A)/(A-to-B)) in human *MDR1*- and mouse *mdr1a*-transfected LLC-PK1 cell line.
[f] NT, not tested.

Table 3
Human MCH-1R and α_{1A} binding activity and P-gp susceptibility of compounds **24a** and **3a–c**



Compound	R^3	hMCH-1R[a,b] (IC_{50}, nM)	hα1A[a,c] (IC_{50}, nM)	P-gp Susceptibility[d] transcellular transport ratio (B-to-A)/(A-to-B)	
				MDR1	*mdr1a*
24a (racemate)		1.3	>10,000	3.3	6.8
3a (active isomer of **24a**)[e]		0.46	>10,000	5.5	16.9
3b (active isomer of **24b**)[e]		0.15	>10,000	2.2	1.5
3c (active isomer of **24c**)[e]		0.09	>10,000	2.7	3.7

[a] The values are the means of two experiments.
[b] Inhibition of [^{125}I]MCH binding to hMCH-1R in CHO.
[c] Inhibition of [^{3}H]prazosin binding to human α_{1A}-adrenoceptor in LMtk$^-$ cells.
[d] Transcellular transport ratio ((B-to-A)/(A-to-B)) in human *MDR1*- and mouse *mdr1a*-transfected LLC-PK1 cell line.
[e] Single isomer. The absolute configuration was not determined.

protein (P-gp) susceptibility of potent derivatives was evaluated by transcellular transport ratios obtained from human *MDR1*- and mouse *mdr1a*-transfected porcine renal epithelial (LLC-PK1) cell monolayers.[23] P-gp is expressed in the blood-brain barrier and excludes its substrates from the brain. In this P-gp transport assay, a compound with a B-to-A/A-to-B ratio above 3 is considered to be a P-gp substrate. All test compounds were human and mouse P-gp substrates except for **2a** and **2b** in human P-gp; compounds **2a** and **2b** were found not to be a human P-gp substrate (Table 2). In addition, **2b** showed the best selectivity against hα1A among the derivatives **2a**–**g**.

We subsequently realized that the replacement of the spiro-isobenzofurane structure of **2b** with the spiro-fluorofuropyridine structure as in **24a** is very effective to reduce the hα1A activity (Table 3) while retaining MCH-1R activity. The racemate **24a** was resolved, and the active isomer **3a**[24] was found to have a remarkably potent MCH-1R activity (IC_{50} = 0.46 nM). Further potency enhancement was achieved by modification of the *N*-alkyl group (R^3). The ethyl derivative **3b** (active isomer)[24] displayed an IC_{50} value of 0.15 nM. Compound **3b** was further substituted with fluorine as in **3c**,[24,25] which has an IC_{50} value of 0.09 nM at the MCH-1R. This highly potent compound **3c** showed good selectivity over MCH-2R (IC_{50} > 1 μM) and a panel of 171 diverse unrelated binding sites (IC_{50} > 1 μM for all the binding sites tested) and not a human P-gp substrate.

In summary, the highly potent and selective MCH-1R antagonist **3c** was identified by structural optimization of high-throughput screening hit **1a**. Evaluation of **3c** to assess its potential for clinical development is ongoing. Compound **3c** is also an attractive compound as a PET tracer due to its excellent potency, hydrophilicity ($\log D_{7.4}$ = 2.3), and possible labeling with ^{18}F.

Acknowledgments

We would like to thank Dr. Norihiro Takenaga for performing the P-gp assays and Atsushi Hirano for measuring the log *D* values.

References and notes

1. Shimada, M.; Tritos, N. A.; Lowell, B. B.; Flier, L. S.; Maratos-Flier, E. *Nature* **1998**, *396*, 670.
2. 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.
3. Qu, D. Q.; Ludwig, D. S.; Gammeltoft, S.; Piper, M.; Pelleymounter, M. A.; Cullen, M. J.; Mathes, W. F.; Przypek, J.; Kanarek, R.; Maratos-Flier, E. *Nature* **1996**, *380*, 243.
4. Mizuno, T. M.; Kleopoulos, S. P.; Bergen, H. T.; Roberts, J. L.; Priest, C. A.; Mobbs, C. V. *Diabetes* **1998**, *47*, 294.
5. Hanada, R.; Nakazato, M.; Matsukura, S.; Murakami, N.; Yoshimatsu, H.; Sakata, T. *Biochem. Biophys. Res. Commun.* **2000**, *268*, 88.
6. Rossi, M.; Choi, S. J.; Oshea, D.; Miyoshi, T.; Ghatei, M. A.; Bloom, S. R. *Endocrinology* **1997**, *138*, 351.
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.
8. 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.
9. Shearman, L. P.; Camacho, R. E.; Stribling, D. S.; Zhou, D.; Bednarek, M. A.; Hreniuk, D. L.; Feighner, S. D.; Tan, C. P.; Howard, A. D.; Van der Ploeg, L. H. T.; MacIntyre, D. E.; Hickey, G. J.; Strack, A. M. *Eur. J. Pharmacol.* **2003**, *475*, 37.
10. Ito, M.; Gomori, A.; Ishihara, A.; Oda, Z.; Mashiko, S.; Matsushita, H.; Yumoto, M.; Ito, M.; Sano, H.; Tokita, S.; Moriya, M.; Iwaasa, H.; Kanatani, A. *Am. J. Physiol. Endocrinol. Metab.* **2003**, *284*, E940.
11. Saito, Y.; Nothacker, H. P.; Wang, Z. W.; Lin, S. H. S.; Leslie, F.; Civelli, O. *Nature* **1999**, *400*, 265.
12. Chambers, J.; Ames, R. S.; Bergsma, D.; Muir, A.; Fitzgerald, L. R.; Hervieu, G.; Dytko, G. M.; Foley, J. J.; Martin, J.; Liu, W. S.; Park, J.; Ellis, C.; Ganguly, S.; Konchar, S.; Cluderay, J.; Leslie, R.; Wilson, S.; Sarau, H. M. *Nature* **1999**, *400*, 261.
13. Hill, J.; Duckworth, M.; Murdock, P.; Rennie, G.; Sabido-David, C.; Ames, R. S.; Szekeres, P.; Wilson, S.; Bergsma, D. J.; Gloger, I. S.; Levy, D. S.; Chambers, J. K.; Muir, A. I. *J. Biol. Chem.* **2001**, *276*, 20125.
14. Sailer, A. W.; Sano, H.; Zeng, Z. Z.; McDonald, T. P.; Pan, J.; Pong, S. S.; Feighner, S. D.; Tan, C. P.; Fukami, T.; Iwaasa, H.; Hreniuk, D. L.; Morin, N. R.; Sadowski, S. J.; Ito, M.; Ito, M.; Bansal, A.; Ky, B.; Figueroa, D. J.; Jiang, Q. P.; Austin, C. P.; MacNeil, D. J.; Ishihara, A.; Ihara, M.; Kanatani, A.; Van der Ploeg, L. H. T.; Howard, A. D.; Liu, Q. Y. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7564.
15. Tan, C. P.; Sano, H.; Iwaasa, H.; Pan, J.; Sailer, A. W.; Hreniuk, D. L.; Feighner, S. D.; Palyha, O. C.; Pong, S. S.; Figueroa, D. J.; Austin, C. P.; Jiang, M. M.; Yu, H.; Ito, J.; Ito, M.; Ito, M.; Guan, X. M.; MacNeil, D. J.; Kanatani, A.; Van der Ploeg, L. H. T.; Howard, A. D. *Genomics* **2002**, *79*, 785.

16. 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*, 825.
17. Borowsky, B.; Durkin, M. M.; Ogozalek, K.; Marzabadi, M. R.; DeLeon, J.; Heurich, R.; Lichtblau, H.; Shaposhnik, Z.; Daniewska, I.; Blackburn, T. P.; Branchek, T. A.; Gerald, C.; Vaysse, P. J.; Forray, C. *Nat. Med.* **2002**, *9*, 1039.
18. For the preparation of compound **6**, see: Cesari, N.; Biancalani, C.; Vergelli, C.; Piaz, D. V.; Graziano, A.; Biagini, P.; Ghelardini, C.; Galeotti, N.; Giovannoni, P. M. *J. Med. Chem.* **2006**, *49*, 7826.
19. For the preparation of compound **7a**, see: (a) Chambers, M. S.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Wong, E. H. F. *J. Med. Chem.* **1992**, *35*, 2033; For the preparation of compound **7b**, see: (b) Marxer, A.; Rodriguez, H. R.; McKenna, J. M.; Tsai, H. M. *J. Org. Chem.* **1975**, *40*, 1427.
20. Yokoyama, H.; Ejiri, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 852.
21. Moriya, M.; Sakamoto, T.; Ishikawa, M.; Kanatani, A.; Fukami, T. WO 069798, 2004.
22. Compounds **24a–c** were resolved by CHIRALCEL OD, eluting with hexanes/EtOH = 8/2. Compound **3a** was obtained as the second-eluted enantiomer by the HPLC resolution of **24a**. Compounds **3b** and **3c** were obtained as the first-eluted enantiomers by the HPLC resolution of **24b** and **24c**, respectively.
23. (a) Yamazaki, M.; Neway, W. E.; Ohe, T.; Chen, I.-W.; Rowe, J. F.; Hochman, J. H.; Chiba, M.; Lin, J. H. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 723; (b) Ohe, T.; Sato, M.; Tanaka, S.; Fujino, N.; Hata, M.; Shibata, Y.; Kanatani, A.; Fukami, T.; Yamazaki, M.; Chiba, M.; Ishii, Y. *Drug Metab. Dispos.* **2003**, *31*, 1251.
24. The IC_{50} values for the corresponding enantiomers of **3a**, **3b** and **3c** are 9.1, 1.1, and 22 nM, respectively.
25. Data of **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65–2.12 (m, 6H), 2.34–2.52 (m, 4H), 2.72–2.97 (m, 2H), 3.32–3.42 (m, 1H), 3.45–3.67 (m, 2H), 3.70–3.93 (m, 1H), 4.46–4.78 (m, 2H), 5.04 (s, 2H), 6.30 (t, 3/4H, *J* = 2.0 Hz), 6.32 (t, 1/4H, *J* = 2.0 Hz), 6.56 (s, 1/4H), 6.77 (s, 1H), 6.90 (s, 3/4H), 7.02–7.12 (m, 1H), 7.13–7.24 (m, 2H), 7.45 (d, 3/4H, *J* = 2.4 Hz), 7.50 (d, 1/4H, *J* = 2.4 Hz), 7.54 (d, 3/4H, *J* = 2.0 Hz), 7.56 (d, 1/4H, *J* = 2.0 Hz), 7.96 (s, 1/4H), 7.98 (s, 3/4H); MS (ESI) *m/z* 532.3 $[M+H]^+$; HPLC purity (99.6%).