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Discovery of novel phenethylpyridone derivatives as potent melanin-concentrating hormone 1 receptor antagonists

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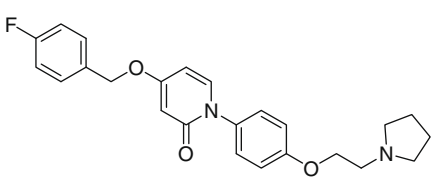
ABSTRACT

Novel phenethylpyridone derivatives were identified as potent human melanin-concentrating hormone 1 receptor (MCH-1R) antagonists. A search for surrogates for the 4-(2-aminoethoxy)phenyl moiety of **1** resulted in discovery of 2-[4-(aminomethyl)phenyl]ethyl substructure as in **6a**. Successive optimization of the right-hand moiety led to the identification of a number of potent derivatives.

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. Biology and pharmacology results 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, and both antagonists produced anti-obese effects in diet-induced obese rats.[9,16,17] Collectively, these data indicate that MCH-1R plays an important role in the development of obesity, suggesting that MCH antagonists could be effective therapeutic agents for the treatment of obesity in humans.

Our group has previously reported on a novel series of phenylpyridones exemplified by **1** (Fig. 1), which exhibit potent binding activity (IC_{50} = 5.6 nM).[18] We subsequently searched for surrogates for the 4-(2-aminoethoxy)phenyl moiety on the right-hand part of **1** to identify structurally distinct substructures tolerated for MCH-1R binding activity. As a consequence, 2-[4-(aminomethyl)phenyl]ethyl analogs, such as **6a**, were found to have MCH-1R activity equal to the related phenylpyridone compound **1**. This letter will describe the synthesis and structure–activity relationships (SAR) of the novel phenethylpyridone class of MCH-1R antagonists.

The synthesis of compounds described herein is outlined in Schemes 1–3. Synthesis of phenethylpyridone derivatives **6a**, **6b**, **6h**, **6i**, and **6l**–**n** are illustrated in Scheme 1. Pyridone **8** was coupled with **10**, **11**, or **12** in the presence of potassium carbonate or cesium carbonate to give intermediates **14a–c**. Deprotection of compounds **14a–c** by treatment with 1 N hydrochloric acid or tetrabutylammonium fluoride, followed by chlorination with $SOCl_2$ and subsequent coupling with corresponding amines, furnished



1
hMCH-1R IC_{50}: 5.6 nM

Figure 1. Structure and hMCH-1R binding activity of compound **1**.

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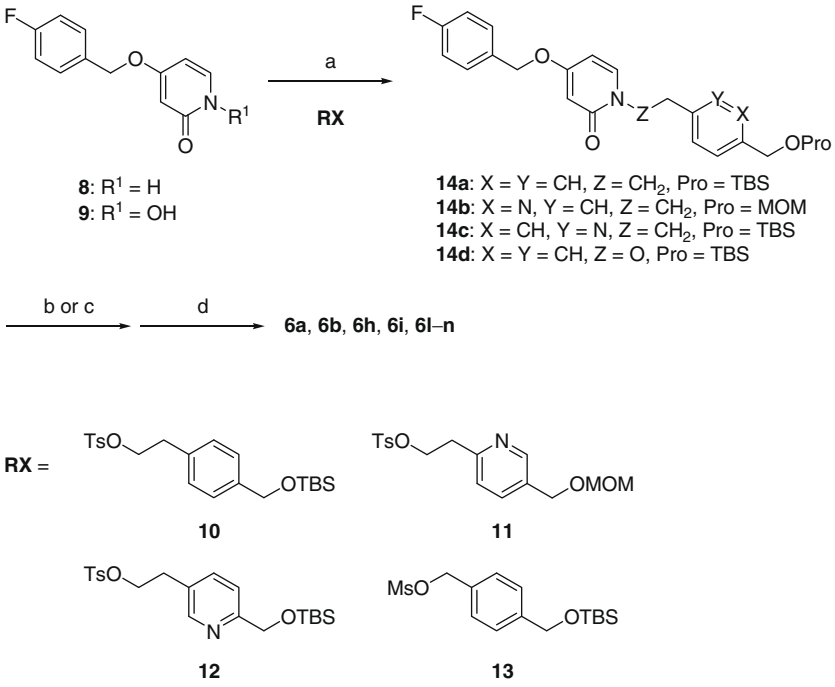
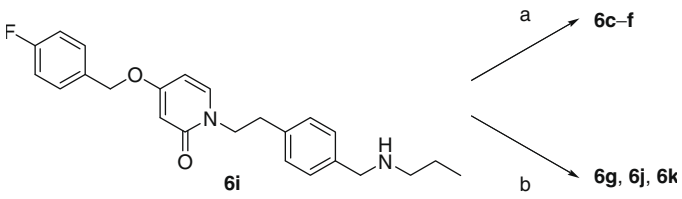
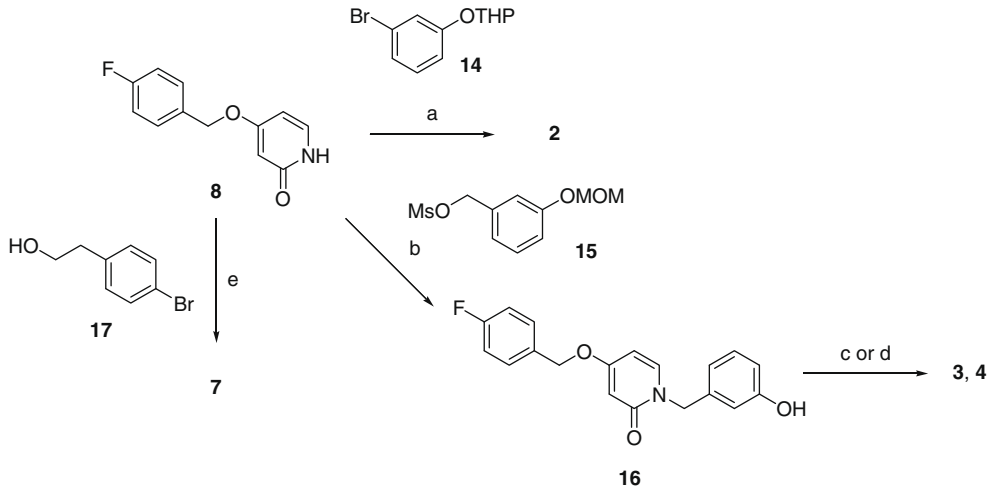


Scheme 1. Preparation of phenethylpyridone derivatives **6a**, **6b**, **6h**, **6i**, and **6l–n**. Reagents and conditions: (a) RX, Cs_2CO_3 or K_2CO_3, DMF, 80 °C, 2–17 h, 37–64%; (b) 1 N HCl, THF or MeOH, rt or reflux, 2–18 h, 27–100%; (c) TBAF, THF, rt, 1 h, 89%; (d) (i) $SOCl_2$, $CHCl_3$, 0 °C to rt, 1 h, (ii) amine, K_2CO_3, NMP, 80 °C, ON, 37–63% over two steps.

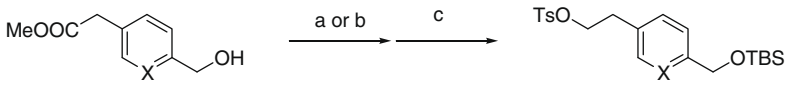


Scheme 2. Synthesis of phenethyl pyridone derivatives **6c–g**, **6j**, and **6k**. Reagents and conditions: (a) aldehyde or ketone, $ZnCl_2$, $NaBH_3CN$, rt, ON, 23–53%; (b) RX, K_2CO_3, CH_3CN, 80 °C, ON, 38–51%.

desired phenethylpyridones **6a**, **6b**, **6h**, **6i**, **6l**, and **6m**. Compound **6n** was prepared from *N*-hydroxypyridone **9**[19] and **13**[19] in the same manner. Compounds **6c–g**, **6j**, and **6k** were synthesized as outlined in Scheme 2. Reductive alkylation of **6i** with the corresponding carbonyl compound gave phenethylpyridones **6c–f**. Alkylation of **6i** with corresponding alkyl halides afforded desired compounds **6g**, **6j**, and **6k**. Preparation of **2–4** and **7** are described in Scheme 3. Pyridone **8** was coupled with bromobenzene **14** in the presence of copper iodide, followed by removal of the THP group and a subsequent coupling reaction with 2-(pyrrolidin-1-yl)ethanol to give compound **2**. Treatment of **8** with compound **15**[19] followed by deprotection of the methoxymethyl (MOM) group afforded **16**, which was converted to compound **3** by coupling with 1,2-bromoethane and successive amination with pyrrolidine. The intermediate **16** was also converted to **4** by alkylation with (3-bromopropyl)pyrrolidine hydrobromide. Pyridone **8** and phenetylalcohol **17** were coupled under Mitsunobu conditions[20] followed



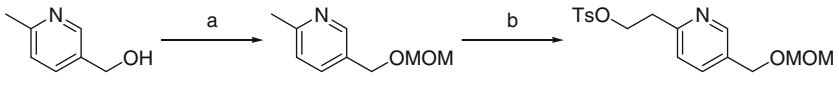
Scheme 3. Preparation of derivatives **2–4** and **7**. Reagents and conditions: (a) (i) **14**, CuI, K_2CO_3, pyridine, DMF, reflux, 18 h, 73%, (ii) cat. PPTS, EtOH, reflux, 2 h, (iii) 2-(pyrrolidin-1-yl)ethanol, ADDP, *t*-Bu_3P, THF, 0 °C to rt, 19 h, 31% over two steps; (b) (i) **15**, Cs_2CO_3, DMF, 80 °C, 4 h, 13%, (ii) 1 N HCl, MeOH, rt, 0 °C to rt, 17 h, 94%; (c) (i) 1,2-dibromoethane, Cs_2CO_3, CH_3CN, 80 °C, 48 h, 55%, (ii) pyrrolidine, NMP, 150 °C, MW, 5 min, 57%; (d) 1-(3-bromopropyl)pyrrolidine hydrobromide, K_2CO_3, DMF, 80 °C, 11 h, 43%; (e) (i) **17**, ADDP, *t*-Bu_3P, CH_2Cl_2, rt, 17 h, 29%, (ii) pyrrolidine, cat. $Pd_2(dba)_3$, cat. BINAP, NaO*t*-Bu, toluene, 80 °C, 20 h, 70%.



18: X = CH
19: X = N

10: X = CH
12: X = N

Scheme 4. Preparation of intermediates **10** and **12**. Reagents and conditions: (a) **18**, TBSCl, imidazole, THF, 0 °C to rt, 17 h, 65%; (b) **19**, TBSCl, Et_3N, DMF, rt, 13 h, 90%; (c) (i) LAH, THF, −78 °C to rt, 1–17 h, 54–100%, (ii) TsCl, Et_3N, cat. DMAP, $CHCl_3$, 0 °C to rt, ON, 76–89%.



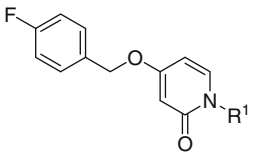
20 **21** **11**

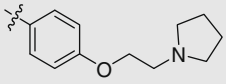
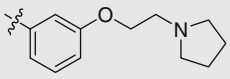
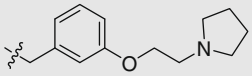
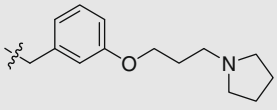
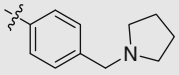
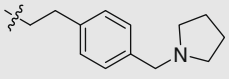
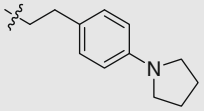
Scheme 5. Preparation of intermediate **11**. Reagents and conditions: (a) MOMCl, NaH, DMF, −20 °C, 30 min, 30%; (b) (i) 37% aq formaldehyde, 150 °C, 17 h, 28%, (ii) TsCl, Et_3N, cat. DMAP, 0 °C to rt, 14 h, 87%.

by reaction with pyrrolidine in the presence of a palladium catalyst to furnish compound **7**.

Key intermediates **10** and **12** were prepared according to Scheme 4. The hydroxyl group of phenylacetates **18**[19] and **19** was protected using *tert*-butyldimethylsilyl chloride followed by reduction of the ester and subsequent tosylation of the resulting hydroxyl group to give intermediates **10** and **12**. Synthesis of tosylate **11** is outlined in Scheme 5. Compound **20** was converted to MOM-protected 2-picoline, which was then thermally treated with formaldehyde followed by treatment with tosyl chloride to afford tosylate **11**.[21]

Table 1
Human MCH-1R binding activity of compounds **1–7**[a]



Compound	R^1	hMCH-1R IC_{50} (nM)
1		5.6
2		>1000
3		29
4		30
5		>1000
6a		5.0
7		>1000

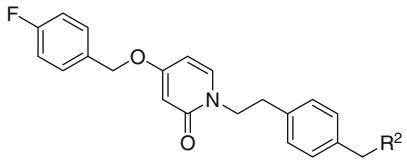
[a] The values represent the means for $n = 2$. Inhibition of [^{125}I]MCH binding to hMCH-1R in CHO cells.

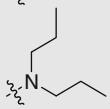
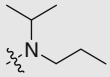
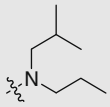
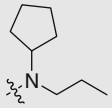
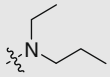
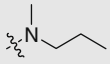
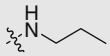
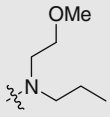
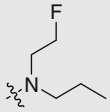
A series of phenethylpyridone derivatives were tested in a [^{125}I]MCH binding assay using Chinese hamster ovary (CHO-K1) cell membranes expressing human recombinant MCH-1R receptors.[22] Selected compounds were evaluated for metabolic stability using human and mouse hepatic microsomes.[23] Modification of the linkage and substituent position of the aminoalkyl group in the right part of **1** was initiated to identify structurally diverse substructures (Table 1). 3-Aminoethoxy substitution as in **2** was detrimental to potency. Introduction of a methylene linkage between a pyridone and a phenyl ring as in **3** dramatically improved hMCH-1R activity compared to **2**. Aminopropoxy analogue **4** was equipotent to the aminoethoxy compound **3**. Removal of the methylene oxy linker between the phenyl group and the pyrrolidine as in **5**[19] provided significant reduction in hMCH-1R potency. Importantly, installation of an ethylene chain into **5** resulted in derivative **6a** with a comparable potency to **1**. When a methylene linkage of **6a** was removed as in **7**, a complete loss of potency was observed. On the basis of these preliminary results, the phenethyl derivative **6a** was selected as a template for further SAR studies.

Variation of substituents of the amine moiety of **6a** was examined (Table 2). The binding and metabolic stability profiles of diethylamine **6b** were similar to those of the parent **6a**. Di(*n*-propyl)amine **6c** displayed a slightly improved hMCH-1R potency, although the metabolic turnover was much higher than **6a** in both humans and mice. Next, one of the *n*-propyl groups of **6c** was replaced by a variety of functional groups. Replacement with sterically more demanding substituents such as isopropyl, 2-methylpropyl, and cyclopentyl as in **6d–f** resulted in a comparable activity to **6a**, but these derivatives showed low metabolic stability in hepatic microsomes. Shortening the *n*-propyl group of **6c** as in **6g–i** conferred significant improvement in microsomal stability, and the *n*-propylamine **6i** was found to be the most potent analogue, displaying a twofold increase of potency relative to **6a**. Introduction of a fluorine or methoxy group on the ethyl group of **6g** did not provide a benefit of intrinsic potency and metabolic stability as in **6j** and **6k**. In this SAR study, various amine functions were tolerated in terms of hMCH-1R activity, and the *n*-propyl derivative **6i** was identified as the most potent compound.

Having established the optimum substituents on the amine part, insertion of a hetero atom into a phenyl ring and ethylene linkage of **6i** was finally investigated as shown in Table 3. The 3-aminopyridine analog **6l** showed improved microsomal stability in mice and a slight decrease of potency. The 2-aminopyridine

Table 2
SAR of derivatives **6a–k**[a]

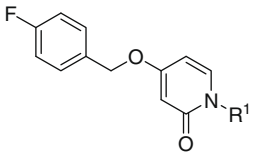


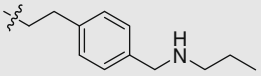
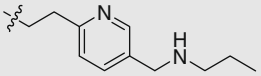
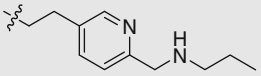
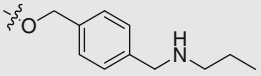
Compound	R^2	hMCH-1R[b] (IC_{50}, nM)	Metabolic stability[c] (% remaining)	
			Human	Mouse
6a		5.0	60	39
6b		5.9	54	26
6c		3.3	1	1
6d		5.2	4	1
6e		4.9	0	0
6f		3.5	1	1
6g		4.4	26	6
6h		3.5	58	22
6i		2.6	85	62
6j		5.4	0	0
6k		11	0	0

[a] The values represent the means for $n = 2$.
[b] Inhibition of [^{125}I]MCH binding to hMCH-1R in CHO cells.
[c] % Remaining after 30 min incubation in hepatic microsomes.

analog **6m** was fourfold less potent than **6i**. Introduction of an oxygen atom into the ethylene linker as in **6n** resulted in significant loss of potency. Among the derivatives possessing potent MCH-1R potency and good microsomal stability, compounds **6i** and **6l** were evaluated for their in vitro functional activity.[22] Both derivatives exhibited potent antagonistic activity (**6i**: IC_{50} = 20 nM, **6l**: IC_{50} = 27 nM). It should be noted that compounds **6i** and **6l** had low human ether-a-go-go related gene (hERG) binding activity (**6i**: hERG IC_{50} = 4200 nM, **6l**: hERG IC_{50} = 5100 nM).[24]

Table 3
SAR of derivatives **6i** and **6l–n**[a]



Compound	R^1	hMCH-1R[b] (IC_{50}, nM)	Metabolic stability[c] (% remaining)	
			Human	Mouse
6i		2.6	85	62
6l		7.0	91	93
6m		11	87	76
6n		34	72	74

[a] The values represent the means for $n = 2$.
[b] Inhibition of [^{125}I]MCH binding to hMCH-1R in CHO cells.
[c] % Remaining after 30 min incubation in hepatic microsomes.

In summary, we have modified the right part of our previously identified series of phenylpyridones to provide a new series of MCH-1R antagonists. Representative compounds **6i** and **6l** have been shown to be potent with good hepatic microsomal stability. In addition, both compounds displayed excellent selectivity over 10 diverse and unrelated binding sites (IC_{50} > 5 μM for adrenergic α1, opiate (μ, κ, δ), histamine H1-4, adenosine A2a, and muscarinic M1). Further evaluation of this series is ongoing, including pharmacokinetics and in vivo efficacy in rodents.

Acknowledgments

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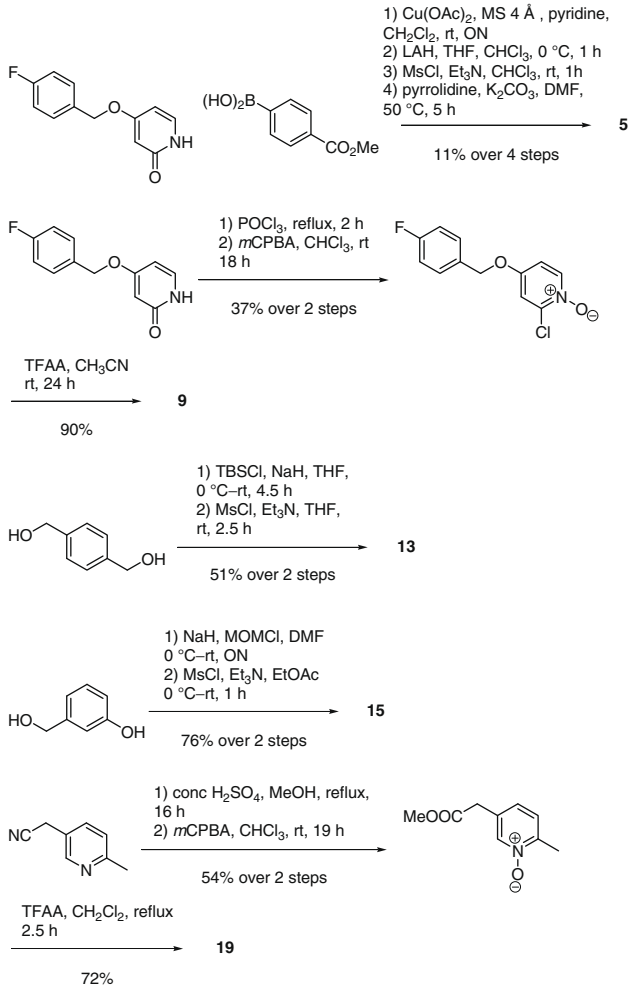
References and notes

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.; MaratosFlier, 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**, *8*, 1039.
18. (a) Ito, M.; Ishihara, A.; Gomori, A.; Egashira, S.; Matsushita, H.; Mashiko, S.; Ito, J.; Ito, M.; Nakase, K.; Haga, Y.; Iwaasa, H.; Suzuki, T.; Ohtake, N.; Moriya, M.; Sato, N.; MacNeil, D. J.; Takenaga, N.; Tokita, S.; Kanatani, A. *Eur. J. Pharmacol.*, submitted for publication.; (b) Otake, N.; Haga, Y.; Naya, A.; Mizutani, S; Kanatani, A. PCT Int. Appl. WO2005085200.
19. The preparation of compounds **5**, **9**, **13**, **15**, and **19** is as follows.



20. Coupling of **8** with **17** was conducted according to a literature procedure. See the following reference: Comins, D. L.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 2819.
21. Tullock, C. W.; McElvain, S. M. *J. Am. Chem. Soc.* **1939**, *61*, 961.
22. For [125I]MCH binding and FLIPR assay protocols, see Moriya, M.; Kishino, H.; Sakuraba, S.; Sakamoto, T.; Suga, T.; Takahashi, H.; Suzuki, T.; Ito, M.; Ito, J.; Moriya, R.; Takenaga, N.; Iwaasa, H.; Ishihara, A.; Kanatani, A.; Fukami, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3568.
23. For microsomal stability assay protocol, see: Mitsuya, M.; Ogino, Y.; Kawakami, K.; Uchiyama, M.; Kimura, T.; Numazawa, T.; Hasegawa, T.; Ohtake, N.; Noguchi, K.; Mase, T. *Bioorg. Med. Chem. Lett.* **2000**, *8*, 825. Human and mouse hepatic microsomes were purchased from Xenotech and BD Gentest, respectively.
24. Butcher, J. W.; Claremon, D. A.; Connolly, T. M.; Dean, D. C.; Karczewski, J.; Koblan, K. S.; Kostura, M. J.; Liverton, N. J.; Melillo, D. G. Radioligand and Binding Assay. World Patent Application WO 02/05860, 2002.