http://dx.doi.org/10.5012/bkcs.2013.34.8.2305

2-Heteroaryl Benzimidazole Derivatives as Melanin Concentrating Hormone Receptor 1 (MCH-R1) Antagonists

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Received April 4, 2013, Accepted May 7, 2013

A novel series of 2-heteroaryl substituted benzimidazole derivatives, containing the piperidinylphenyl acetamide group at the 1-position, were synthesized and evaluated as MCH-R1 antagonists. Extensive SAR investigation probing the effects of C-2 heteroaryl group led to the identification of 2-[2-(pyridin-3-yl)ethyl] analog **3o**, which exhibits highly potent MCH-R1 binding activity with an IC_{50} value of 1 nM. This substance **3o** also has low hERG binding activity, good metabolic stability, and favorable pharmacokinetic properties.

Key Words : Melanin concentrating hormone (MCH), MCH-R1 antagonist, 2-Heteroaryl benzimidazole, Obesity

Introduction

Since the melanin concentrating hormone (MCH) system is known to be involved in both regulation of feeding and energy homeostasis, this peptide has received a great recent attention as a target for obesity treatment among many centrally-acting neuropeptides.[1] MCH is a cyclic 19-amino acid polypeptide which is expressed predominantly in the lateral hypothalamus of the brain.[2] The effects of MCH are mediated by two types of G protein-coupled receptors, MCH receptor 1 and 2 (MCH-R1 and MCH-R2).[3] While the exact biological functions of MCH-R2 are still unknown, previous genetic and pharmacological studies have demonstrated that MCH-R1 plays an important role in the control of food intake and body-weight.[4] Therefore, these findings suggest that this receptor is one of the most promising targets for the obesity treatment. Indeed, a number of MCH-R1 antagonists have been found to display anti-obesity efficacy in diet-induced obesity (DIO) animal models.[5] Although extensive efforts of numerous pharmaceutical companies have been made to develop a variety of pharmacophore derivatives of MCH-R1 antagonists as potential anti-obesity agents, few candidates have advanced to the phase 1 clinical stage owing to their unsuitable pharmacokinetic (PK) profiles and safety concerns.[6]

In a previous study, we found that the 2-aryl benzimi-

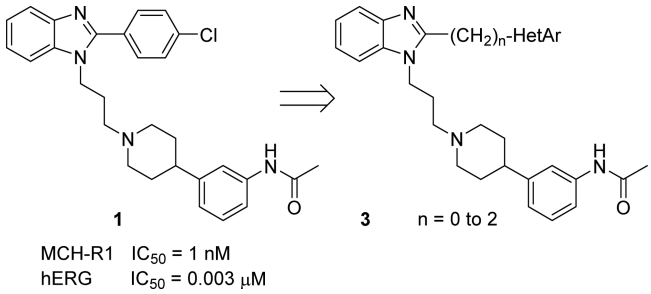
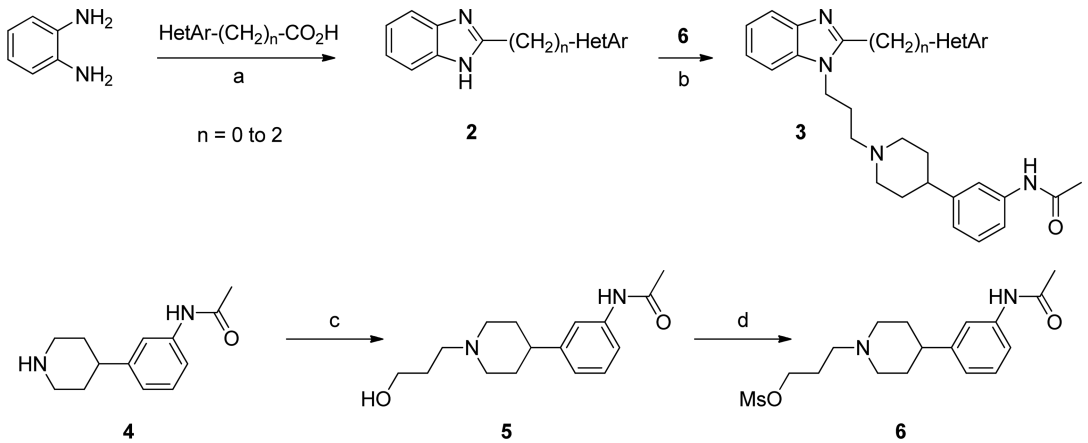


Figure 1. Structural modification of benzimidazole based MCH-R1 antagonists.



Scheme 1. (a) PPA, reflux, 3 h; (b) K_2CO_3, DMF, 80 °C, 5 h; (c) 3-bromo-1-propanol, K_2CO_3, DMF, 60 °C, 5 h; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt , 3 h.

dazole derivatives linked to piperidinylphenyl acetamide moiety at the 1-position are potent MCH-R1 antagonists.[7] Among these compounds, the 2-(*p*-chlorophenyl) derivative **1** was found to exhibit a high binding affinity to MCH-R1 (IC_{50} = 1 nM) (Figure 1). However, this substance has a strong inhibition activity of human ether-a-go-go related gene (hERG) potassium channel (IC_{50} = 0.003 μM), which is involved in causing side effects of cardiovascular risks.[8] As a part of our drug discovery program directed toward development of potent and safe MCH-R1 antagonists as anti-obesity agents,[9] we have explored replacement of the C-2 aryl group of the benzimidazole with heteroaryl groups. We envisioned that this approach might not only lead to an improved physiochemical profile but also to minimize toxicity properties while maintaining MCH-R1 binding activity. Below, we now wish to report the synthesis, biological evaluation, and structure-activity relationships (SAR) of a variety of 2-heteroaryl benzimidazole derivatives as MCH-R1 antagonists.

Chemistry

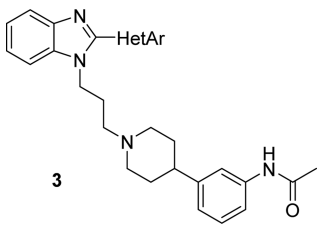
The general synthetic routes employed for the preparation of 2-heteroaryl benzimidazole derivatives **3** are outlined in Scheme 1. The condensation of 1,2-phenylenediamine with several carboxylic acids containing a heteroaryl residue using polyphosphoric acid (PPA) afforded 2-heteroaryl substituted benzimidazoles **2** as a key intermediate. In a parallel sequence, compound *N*-[3-(4-piperidinyl)phenyl]acetamide **4**[10] was treated with 3-bromo-1-propanol using potassium carbonate as a base to provide 3-hydroxypropyl product **5**. Treatment of **5** with methanesulfonyl chloride in the presence of triethylamine generated methanesulfonate **6**, which was directly used in the next step without further purification. The target compounds **3** were obtained by simple coupling reaction of **2** with **6** in the presence of potassium carbonate in DMF.

Results and Discussion

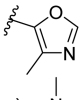
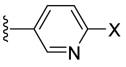
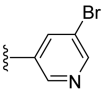
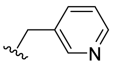
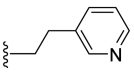
The binding affinities of 2-heteroaryl benzimidazole derivatives **3** to the membranes of CHO cells expressing human MCH-R1 were evaluated by using a competitive binding assay with Eu-labeled MCH and a time-resolved fluorometric (TRF) assay.[11]

The initial SAR investigation was focused on the exploration of 5-membered heteroaryl group at C-2 position of the benzimidazole moiety and the results are summarized in Table 1. The 3-furyl (**3a**) and 2-thiophenyl (**3b**) derivatives were observed to exhibit good binding affinities for MCH-R1. In addition, the substance having 1-methyl-2-pyrrolyl group (**3c**) has high binding affinity with IC_{50} value of 9 nM. Furthermore, incorporation of 4-methyl-5-oxazolyl derivative (**3d**) at C-2 position of the benzimidazole led to additional 3-fold enhancement in binding affinity compared to **3c**. However, other benzimidazoles possessing 1-methyl-2-imidazoyl (**3e**) and 4-thiazolyl (**3f**) groups all displayed low binding activities.

Table 1. MCH-R1 binding affinities of 2-heteroaryl benzimidazole derivatives



3

Compound	HetAr	MCH-R1 IC_{50}[a,b] (nM)
3a		25
3b		15
3c		9
3d		3
3e		44
3f		306
3g		33
		
3h	X=H	60
3i	X=Me	42
3j	X=Cl	1
3k		5
3l		30
3m		150
3n		47
3o		1

[a]MCH-R1 binding affinities of compounds were determined by using a competitive binding with Eu-MCH and a TRF assay. [b]Values are means of at least two measurements.

Next, the effects of replacement of 5-membered heteroaryl group with pyridyl moiety at the C-2 of the benzimidazole to MCH-R1 binding affinity were examined. Among unsubstituted pyridyl derivatives, binding affinities of 2-pyridyl (**3g**) and 3-pyridyl (**3h**) derivatives were higher than that of 4-pyridyl derivative **3m**. Incorporation of methyl group at 6-position of 3-pyridyl ring (**3i**) led to a slight increase in binding affinity compared to unsubstituted analog **3h**. Moreover, the presence of chloro substituent (**3j**) at the same

Table 2. Selected *in vitro* data and pharmacokinetic properties of **3o**

Parameter	Value
Solubility (μg/mL)	37
PAMPA permeability (10^{-6} cm/sec)	5.4
hERG IC_{50} (μM)	70.3
$t_{1/2}$ (h)[a]	1.7
oral AUC (μg h/mL)[a]	0.5
iv CL (mL/kg min)[a]	10.1
%F[a]	53

[a]Determined in rats by administration of 10 mg/kg, iv and po (n = 3).

position led to a substance which has the most potent MCH-R1 binding affinity (IC_{50} = 1 nM) among those tested. The 5-bromo-3-pyridyl derivative (**3k**) also retained high binding affinity. However, the introduction of methoxy group at 2-position of 3-pyridyl ring (**3l**) resulted in a decrease in binding affinity. Additionally, the effects of chain length between the benzimidazole and 3-pyridyl ring were investigated. When the length of linker is increased from C-0 (**3h**) to C-1 (**3n**) and C-2 (**3o**), a large increase in MCH-R1 binding affinity was observed. The ethyl linked derivative **3o** exhibited the most potent binding (IC_{50} = 1 nM) to MCH-R1.

The 2-(6-chloropyridin-3-yl) (**3j**) and 2-[2-(pyridin-3-yl)ethyl] (**3o**) benzimidazole derivatives, which have the most potent MCH-R1 binding activities, were subjected to further studies. The compound **3j** showed potent hERG binding activity (IC_{50} = 0.7 μM), while compound **3o** have significantly reduced hERG inhibition (IC_{50} = 70.3 μM). In addition, the pharmacokinetic profiles of **3o** in an iv/po pharmacokinetic study (10 mg/kg) in rats are shown in Table 2. **3o** displayed moderate oral bioavailability (F = 53%) with an acceptable clearance (Cl = 10.1 mL/kg min), plasma level (AUC = 0.5 μg h/mL) and half-life ($t_{1/2}$ = 1.7 h). Furthermore, **3o** appeared to be metabolically stable when tested in vitro in human and rat liver microsomes (43% and 86% for 30 min, respectively) and exhibited moderate permeability (5.4×10^{-6} cm/sec, PAMPA) and acceptable aqueous solubility (37 μg/mL).

Conclusion

In summary, a series of novel 2-heteroaryl benzimidazole derivatives linked to piperidinylphenyl acetamide moiety at the 1-position were prepared and found to be potent MCH-R1 antagonists. Extensive optimization probing the effects of C-2 heteroaryl group on the benzimidazole resulted in the identification of 2-[2-(pyridin-3-yl)ethyl] analog **3o**, which has the most potent MCH-R1 binding activity. Interestingly, this compound displayed much lower hERG binding activity than previously derived 2-(*p*-chlorophenyl) analog. Compound **3o** also exhibited good metabolic stability, and favorable pharmacokinetic properties.

Experimental

General. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 or a Bruker DRX-300 spectrometer. Mass spectra were obtained with a JEOL JMS-DM 303 instrument by using electron impact or chemical ionization techniques. Column chromatography was carried out using silica gel (230-400 mesh). All solvents and reagents were commercially available and used without further purification.

Synthesis of 2-[2-(Pyridin-3-yl)ethyl]-1*H*-benzimidazole (2o). 2.0 g (18.5 mmol) of 1,2-phenylenediamine and 3.4 g (22.2 mmol) of 3-pyridinepropionic acid were added to 20 g polyphosphoric acid (PPA) and mixed homogeneously. The reaction mixture was heated at 140 °C for 4 h. Then the reaction mixture was cooled to room temperature and neutralized with 5 N NaOH. The resulting solid was filtered, washed with water and dried *in vacuo*. The title compound was obtained by recrystallization using ethanol (3.6 g, 88%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.14-3.19 (m, 4H), 7.10-7.13 (m, 2H), 7.26-7.31 (m, 1H), 7.40-7.42 (m, 1H), 7.52-7.53 (m, 1H), 7.66 (dd, *J* = 7.8, 2.2 Hz, 1H), 8.39 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.47 (d, *J* = 1.9 Hz, 1H), 12.3 (s, 1H).

Synthesis of 2-[2-(Pyridin-3-yl)ethyl]-1-{3-[4-(3-acetamidophenyl)piperidin-1-yl]propyl}-1*H*-benzimidazole (3o). To a stirred solution of 40 mg (0.18 mmol) of 2-[2-(pyridin-3-yl)ethyl]-1*H*-benzimidazole (**2o**) in *N*,*N*-dimethylformamide (5 mL) were added 71 mg (0.22 mmol) of 3-[4-(3-acetamidophenyl)piperidin-1-yl]propyl methanesulfonate (**6**) and 75 mg (0.54 mmol) of K_2CO_3. The reaction mixture was stirred at 80 °C for 5 h. After cooling, water (50 mL) was added, and the mixture was extracted with ethylacetate (50 mL × 2). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (5% MeOH/CH_2Cl_2) to obtain the title compound (75 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55-1.65 (m, 2H), 1.74-2.05 (m, 6H), 2.20 (t, *J* = 6.1 Hz, 2H), 2.26 (s, 3H), 2.40-2.48 (m, 1H), 2.87 (d, *J* = 11.4 Hz, 2H), 3.26-3.42 (m, 4H), 4.28 (t, *J* = 6.1 Hz, 2H), 6.87 (d, *J* = 7.7 Hz, 1H), 7.05 (s, 1H), 7.35-7.40 (m, 4H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.75-7.78 (m, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 8.50 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.74 (d, *J* = 1.4 Hz, 1H), 9.30 (s, 1H); MS *m/z* 481 (M^+).

2-(Furan-3-yl)-1-{3-[4-(3-acetamidophenyl)piperidin-1-yl]propyl}-1*H*-benzimidazole (3a). 38 mg (61%) of the title compound was obtained by the same procedure for the compound **3o**, using 26 mg (0.14 mmol) of 2-(furan-3-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (m, 4H), 2.03 (m, 4H), 2.17 (s, 3H), 2.39 (t, *J* = 6.3 Hz, 2H), 2.48 (m, 1H), 2.94 (m, 2H), 4.41 (t, *J* = 7.3 Hz, 2H), 6.99 (m, 1H), 7.06 (m, 1H), 7.25-7.36 (m, 4H), 7.45 (m, 2H), 7.59 (m, 1H), 7.63 (br s, 1H), 7.74 (m, 1H), 8.21 (br s, 1H); MS *m/z* 442 (M^+).

2-(Thiophen-2-yl)-1-{3-[4-(3-acetamidophenyl)piperidin-1-yl]propyl}-1*H*-benzimidazole (3b). 54 mg (84%) of the title compound was obtained by the same procedure for the compound **3o**, using 28 mg (0.14 mmol) of 2-(thiophen-2-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70-1.83 (m, 4H), 1.97-2.09 (m, 4H), 2.16 (s, 3H), 2.40 (t, *J* = 6.6 Hz, 2H), 2.47 (m, 1H), 2.93 (m, 2H), 4.51 (t, *J* = 7.3 Hz,

2H,), 6.97 (d, J = 7.4 Hz, 1H), 7.19 (dd, J = 5.0, 3.8 Hz, 1H), 7.22-7.35 (m, 4H), 7.45 (m, 2H), 7.51 (dd, J = 5.0, 0.9 Hz, 1H), 7.64 (br s, 1H), 7.67 (m, 1H), 7.77-7.80 (m, 1H); MS *m/z* 458 (M^+).

2-(1-Methylpyrrol-2-yl)-1-{3-[4-(3-acetamidophenyl) piperidin-1-yl]propyl}-1*H*-benzimidazole (3c). 70 mg (67%) of the title compound was obtained by the same procedure for the compound **3o**, using 45 mg (0.23 mmol) of 2-(1-methylpyrrol-2-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71-1.83 (m, 4H), 1.97-2.11 (m, 4H), 2.16 (s, 3H), 2.41 (t, J = 6.5 Hz, 2H), 2.47 (m, 1H), 2.55 (s, 3H), 2.95 (m, 2H), 4.48 (t, J = 7.2 Hz, 2H), 6.84 (m, 1H), 6.97 (m, 1H), 7.22-7.36 (m, 5H), 7.41-7.47 (m, 3H), 7.68 (br s, 1H), 7.75 (m, 1H); MS *m/z* 455 (M^+).

2-(4-Methyloxazol-5-yl)-1-{3-[4-(3-acetamidophenyl) piperidin-1-yl]propyl}-1*H*-benzimidazole (3d). 45 mg (70%) of the title compound was obtained by the same procedure for the compound **3o**, using 28 mg (0.14 mmol) of 2-(4-methyloxazol-5-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68-1.83 (m, 4H), 1.94-2.10 (m, 4H), 2.17 (s, 3H), 2.36 (br t, J = 6.8 Hz, 2H), 2.47 (m, 1H), 2.64 (s, 3H), 2.93 (m, 2H), 4.50 (t, J = 7.1 Hz, 2H), 6.97 (m, 1H), 7.21-7.34 (m, 4H), 7.42 (m, 2H), 7.49 (m, 1H), 7.82 (m, 1H), 7.99 (s, 1H); MS *m/z* 457 (M^+).

2-(1-Methyl-1*H*-imidazol-2-yl)-1-{3-[4-(3-acetamido-phenyl)piperidin-1-yl]propyl}-1*H*-benzimidazole (3e). 66 mg (85%) of the title compound was obtained by the same procedure for the compound **3o**, using 34 mg (0.17 mmol) of 2-(1-methyl-1*H*-imidazol-2-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-1.84 (m, 4H), 2.04 (m, 4H), 2.18 (s, 3H), 2.40 (t, J = 6.7 Hz, 2H,), 2.48 (m, 1H), 2.96 (m, 2H), 3.98 (s, 3H), 4.42 (t, J = 7.4 Hz, 2H), 6.97 (d, J = 7.6 Hz, 1H), 7.24 (m, 1H), 7.32 (m, 2H), 7.37 (m, 1H), 7.43 (m, 1H), 7.50 (m, 1H), 7.54 (br s, 1H), 7.67 (br s, 1H), 7.70 (br s, 1H), 7.80 (m, 1H); MS *m/z* 456 (M^+).

2-(Thiazol-4-yl)-1-{3-[4-(3-acetamidophenyl)piperidin-1-yl]propyl}-1*H*-benzimidazole (3f). 34 mg (80%) of the title compound was obtained by the same procedure for the compound **3o**, using 19 mg (0.09 mmol) of 2-(4-thiazolyl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, CD_3OD) δ 1.74-1.90 (m, 4H), 2.10 (s, 3H), 2.24 (m, 2H), 2.44 (m, 2H), 2.61 (m, 1H), 2.76 (t, J = 7.5 Hz, 2H), 3.22 (m, 2H), 4.86 (m, 2H), 6.94 (m, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.30-7.40 (m, 3H), 7.48 (br s, 1H), 7.69 (d, J = 7.4 Hz, 2H), 8.38 (d, J = 1.8 Hz, 1H), 9.21 (d, J = 1.9 Hz, 1H); MS *m/z* 459 (M^+).

2-(Pyridin-2-yl)-1-{3-[4-(3-acetamidophenyl)piperidin-1-yl]propyl}-1*H*-benzimidazole (3g). 83 mg (53%) of the title compound was obtained by the same procedure for the compound **3o**, using 70 mg (0.36 mmol) of 2-(pyridin-2-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65-1.80 (m, 4H), 2.15 (s, 3H), 1.93-2.24 (m, 4H), 2.43 (t, J = 6.8 Hz, 2H), 2.48 (m, 1H), 2.98 (m, 2H), 4.90 (t, J = 7.3 Hz, 2H), 6.95 (m, 1H), 7.21-7.39 (m, 6H), 7.52 (m, 1H), 7.67 (br s, 1H), 7.84 (m, 2H), 8.40 (d, J = 7.9 Hz, 1H), 8.86(d, J = 4.1 Hz, 1H); MS *m/z* 453 (M^+).

2-(Pyridin-3-yl)-1-{3-[4-(3-acetamidophenyl)piperidin-1-yl]propyl}-1*H*-benzimidazole (3h). 83 mg (51%) of the title compound was obtained by the same procedure for the compound **3o**, using 70 mg (0.36 mmol) of 2-(pyridin-3-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58-1.77 (m, 4H), 1.89-2.04 (m, 4H), 2.17 (s, 3H), 2.27 (t, J = 6.6 Hz, 2H), 2.42 (m, 1H), 2.80 (m, 2H), 4.41 (t, J = 7.2 Hz, 2H), 6.95 (m, 1H), 7.21-7.40 (m, 5H), 7.48-7.53 (m, 2H), 7.65 (br s, 1H), 7.84 (m, 1H), 8.14 (dt, J = 7.9, 1.8 Hz, 1H), 8.76 (dd, J = 4.9, 1.5 Hz, 1H), 9.03 (m, 1H); MS *m/z* 453 (M^+).

2-(6-Methylpyridin-3-yl)-1-{3-[4-(3-acetamidophenyl) piperidin-1-yl]propyl}-1*H*-benzimidazole (3i). 46 mg (yield 89%) of the title compound was obtained by the same procedure for the compound **3o**, using 23 mg (0.11 mmol) of 2-(6-methylpyridin-3-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56-1.68 (m, 2H), 1.76 (m, 2H), 1.90-2.03 (m, 4H), 2.17 (s, 3H), 2.27 (t, J = 6.6 Hz, 2H), 2.43 (m, 1H), 2.65 (s, 3H), 2.82 (m, 2H), 4.39 (t, J = 7.3 Hz, 2H), 6.96 (m, 1H), 7.23 (m, 1H), 7.31-7.36 (m, 4H), 7.40 (br s, 1H), 7.50 (m, 2H), 7.83 (m, 1H), 8.02 (dd, J = 8.0, 2.3 Hz, 1H), 8.90 (d, J = 2.1 Hz, 1H); MS *m/z* 467 (M^+).

2-(6-Chloropyridin-3-yl)-1-{3-[4-(3-acetamidophenyl) piperidin-1-yl]propyl}-1*H*-benzimidazole (3j). 40 mg (75%) of the title compound was obtained by the same procedure for the compound **3o**, using 25 mg (0.11 mmol) of 2-(6-chloropyridin-3-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (m, 2H), 1.77 (m, 2H), 1.92-2.06 (m, 4H), 2.18 (s, 3H), 2.27 (t, J = 6.3 Hz, 2H), 2.44 (m, 1H), 2.82 (m, 2H), 4.41 (t, J = 7.4 Hz, 2H), 6.99 (m, 1H), 7.23-7.40 (m, 6H), 7.51 (m, 2H), 7.83 (m, 1H), 8.16 (dd, J = 8.3, 2.5 Hz, 1H), 8.90 (m, 1H); MS *m/z* 488 (M^+).

2-(5-Bromopyridin-3-yl)-1-{3-[4-(3-acetamidophenyl) piperidin-1-yl]propyl}-1*H*-benzimidazole (3k). 47 mg (80%) of the title compound was obtained by the same procedure for the compound **3o**, using 30 mg (0.11 mmol) of 2-(5-bromopyridin-3-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (m, 2H), 1.77 (m, 2H), 1.91-2.05 (m, 4H), 2.18 (s, 3H), 2.28 (t, J = 6.5 Hz, 2H), 2.43 (m, 1H), 2.82 (m, 2H), 4.42 (t, J = 7.2 Hz, 2H), 6.97 (m, 1H), 7.22-7.40 (m, 6H), 7.52 (m, 1H), 7.84 (m, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.82 (d, J = 2.2 Hz, 1H), 8.96 (d, J = 1.8 Hz, 1H); MS *m/z* 532 (M^+).

2-(2-Methoxypyridin-3-yl)-1-{3-[4-(3-acetamidophenyl)-piperidin-1-yl]propyl}-1*H*-benzimidazole (3l). 53 mg (78%) of the title compound was obtained by the same procedure for the compound **3o**, using 32 mg (0.14 mmol) of 2-(2-methoxypyridin-3-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 2H), 1.73 (m, 2H), 1.90 (m, 4H), 2.16 (s, 3H), 2.23 (t, J = 6.8 Hz, 2H), 2.47 (m, 1H), 2.80 (m, 2H), 3.98 (s, 3H), 4.19 (t, , J = 7.2 Hz, 2H), 6.94 (m, 1H), 7.06 (dd, J = 7.2, 5.1 Hz, 1H), 7.21-7.39 (m, 6H), 7.50 (m, 1H), 7.82 (m, 1H), 7.88 (dd, J = 7.3, 1.8 Hz, 1H), 8.34 (dd, J = 5.0, 1.8 Hz, 1H); MS *m/z* 483 (M^+).

2-(Pyridin-4-yl)-1-{3-[4-(3-acetamidophenyl)piperidin-1-yl]propyl}-1*H*-benzimidazole (3m). 92 mg (56%) of the title compound was obtained by the same procedure for the compound **3o**, using 70 mg (0.36 mmol) of 2-(pyridin-4-yl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (m, 2H), 1.74 (m, 2H), 1.90-2.02 (m, 4H), 2.20 (s, 3H), 2.25 (t,

2H), 2.42 (m, 1H), 2.79 (d, 2H), 4.47 (t, 2H), 6.91 (d, 1H), 7.21-7.50 (m, 6H), 7.76 (d, 2H), 7.85 (m, 1H), 7.82 (d, 2H); MS *m/z* 453 (M^+).

2-(Pyridin-3-ylmethyl)-1-{3-[4-(3-acetamidophenyl)piperidin-1-yl]propyl}-1*H*-benzimidazole (3n). 60 mg (71%) of the title compound was obtained by the same procedure for the compound **3o**, using 38 mg (0.18 mmol) of 2-(pyridin-3-ylmethyl)-1*H*-benzimidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-2.04 (m, 8H), 2.19 (s, 3H), 2.28 (t, J = 6.3 Hz, 2H), 2.50 (m, 1H), 2.95 (m, 2H), 4.16 (t, J = 6.8 Hz, 2H), 4.47 (s, 2H), 6.96 (m, 1H), 7.22-7.30 (m, 4H), 7.37 (m, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.57 (m, 1H), 7.77 (m, 1H), 8.03 (br s, 1H), 8.51 (dd, J = 4.7, 1.4 Hz, 1H), 8.68 (m, 1H); MS *m/z* 467 (M^+).

3-[4-(3-Acetamidophenyl)piperidin-1-yl]propan-1-ol (5). To a solution of 5.3 g (20.8 mmol) of 4-(3-acetylaminophenyl)piperidine hydrochloride (**4**) in *N,N*-dimethylformamide (50 mL) were added 3.8 g (27.0 mmol) of 3-bromo-1-propanol and 8.6 g (62 mmol) of K_2CO_3. The mixture was stirred at 60 ºC for 5 h, diluted with water (150 mL), and extracted with ethylacetate (100 mL × 5). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (10% methanol/CH_2Cl_2) to give 4.8 g (85%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76-1.86 (m, 6H), 2.13 (m, 2H), 2.17 (s, 3H), 2.55 (m, 1H), 2.71 (t, 2H), 3.25 (d, 2H), 3.84 (t, 2H), 6.95 (d, 1H), 7.19-7.31 (m, 3H), 7.43 (s, 1H, NH).

3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl Methanesulfonate (6). To a solution of 3-[4-(3-acetylamino phenyl)piperidin-1-yl]propan-1-ol (**5**) (4.5 g, 16.3 mmol) and triethylamine (6.7 mL, 48.0 mmol) in dichloromethane (70 mL) was added a solution of methanesulfonyl chloride (1.15 mL, 19.5 mmol) in dichloromethane (10 mL) slowly at 0 ºC. The mixture was stirred at 0 ºC for 3 h, diluted with water (100 mL), and extracted with CH_2Cl_2 (100 mL × 2). The combined organic layer was washed with saturated aqueous solution of $NaHCO_3$ (30 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford 5.2 g (90%) of the title compound. The resulting compound was used in a next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90-2.03 (m, 4H), 2.21 (s, 3H), 2.39 (m, 1H), 2.43 (m, 2H), 2.80 (s, 3H), 2.82 (m, 2H), 3.07 (m, 2H), 3.58 (m, 2H), 4.40 (t, 2H), 6.93 (d, 1H), 7.20 (dd, 1H), 7.42 (br s, 1H), 7.58 (d, 1H), 8.48 (s, 1H).

MCH Receptor Binding Assay. Receptor binding assays with europium-labeled MCH (Eu-MCH) were performed in 96-well AcroWell™ plates. The MCH labeled with europium at N1 position was supported from Wallac labeling service (PerkinElmer Oy). The human recombinant MCH-1 receptor membrane preparation (MCH-1/SLC1 membrane) was from Euroscreen S.A. (PerkinElmer Oy). The assay buffer contained 25 mM HEPES, 5 mM $MgCl_2$, 1 mM $CaCl_2$, 0.5% bovine serum albumin pH 7.4. Non-specific Eu-MCH binding was determined experimentally by the presence of 0.5 μM unlabeled MCH (human). After incubation at room temperature for 90 min, the incubation mixtures were filtered in the automatic vacuum filtration system for filter plates and rapidly washed three times with 300 μL of ice-cold 25 mM HEPES buffer (pH 7.4). The europium was dissociated from the bound ligand by the addition of 150 μL of DELFIA enhancement solution (PerkinElmer Oy) and incubated for 10 min with shaking. Dissociated europium created highly fluorescent complexes, which were measured in a multilabel counter with a time-resolved fluorescence (TRF) option (Victor II, PerkinElmer Oy). The counter setting was 340 nm excitation, 400 μs delay, and emission collection for 400 μs at 615 nm. The extent of antagonism was expressed as % displacement. The IC_{50} value was characterized in an 8-dose response study to generate the compound concentration required to yield 50% displacement.

Acknowledgments. This research was supported by a grant from the Ministry of Science, ICT & Future Planning (2011-0019397) and the R&D program of MOTIE/KEIT (10038744), Korea.

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