Synthesis and Structure–Activity Relationship of Naphtho[1,2-*b*]furan-2-carboxamide Derivatives as Melanin Concentrating Hormone Receptor 1 Antagonists

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The discovery that novel naphtho[1,2-*b*]furan-2-carboxamides containing linked piperidinylphenylacetamide groups serve as melanin concentrating hormone receptor 1 (MCH-R1) antagonists is described. An extensive structure–activity relationship (SAR) study, probing members of this family that contain a variety of aryl and heteroaryl groups at C-5 of the naphtho[1,2-*b*]furan-2-carboxamide skeleton and having different chain linker lengths, led to the identification of the 5-(4-pyridinyl) substituted analog 10b as a highly potent MCH-R1 antagonist with an IC_{50} value of 3 nM. This substance also displays good metabolic stability and it does not significantly inhibit cytochrome P450 (CYP450) enzymes. However, 10b has unacceptable oral bioavailability.

Key words melanin concentrating hormone (MCH); MCH-receptor 1 antagonist; obesity; naphtho[1,2-*b*]-furan-2-carboxamide

Obesity, occurring because of an imbalance between energy intake and expenditure, is rapidly increasing worldwide and has become nearly a global epidemic.[1] Moreover, obesity is a major risk factor associated with a number of severe diseases, including type 2 diabetes, dyslipidemia, coronary heart disease, stroke and certain cancers.[2] Many biological targets for treating obesity have been evaluated, including prevention of fat absorption, modulation of fat metabolism or storage, increase of thermogenesis, and modulation of central satiety and hunger regulating systems.[3,4] Among several centrally acting targets, the melanin concentrating hormone (MCH) has received great attention as a target for obesity treatment. MCH, an orexigenic cyclic 19-amino acid polypeptide, is expressed predominantly in the lateral hypothalamus of the brain and is known to play a physiological role in both the regulation of feeding and energy homeostasis.[5,6] The effects of this peptide are mediated through its interaction with two types of G protein-coupled receptors called MCH-receptor 1 and 2 (MCH-R1 and -R2).[7,8] While the exact biological functions of MCH-R2 are still unknown, those of MCH-R1 have been demonstrated in previous genetic and pharmacological studies. Genetically altered mice that lack the gene encoding MCH-R1 maintain elevated metabolic rates and remain lean despite hyperphagia on a normal diet.[9] Specifically, the results of these efforts have shown that MCH-R1 plays an essential role in the control of food intake and body weight.[9–12] As a consequence of these properties, MCH-R1 is considered to be one of the most promising targets for treating obesity, though it still remains to be seen whether this translates to safe clinical efficacy in humans.

Numerous MCH-R1 antagonists have been found to have anti-obesity efficacy in diet-induced obesity (DIO) animal models.[13–16] In the last decade, extensive research by numerous pharmaceutical companies and academic groups have led to the identification of a variety of pharmacophore derivatives of MCH-R1 antagonists as potential anti-obesity agents. To date, few candidates including GW856464,[17,18] AMG-076,[19] NGD-4715,[20,21] ALB-127158,[22–24] and BMS-830216,[25] a prodrug of BMS-819881 (structure undisclosed) have advanced to the phase 1 clinical stage owing to their unsuitable pharmacokinetic (PK) profiles and safety concerns[26–28] (Fig. 1). In particular, diverse piperidinylphenylacylamide derivatives, based on the structure of SNAP-7941, have been reported to serve as MCH-R1 antagonists.[29–32]

Recently, we uncovered novel benzimidazole and phthalazin-1(2*H*)-one derivatives that are linked to piperidinylphenylacetamide groups, which serve as potent MCH-R1 antagonists.[33–36] In a continuation of these initial efforts aimed at the development of potent MCH-R1 antagonists as anti-obesity agents,[37] we newly prepared 5-aryl benzofuran derivative **13** possessing the piperidinylphenylacetamide moiety, which has an IC_{50} value of 380 nM. An initial effort focused on substances containing a modified benzofuran core and explored the effects of fusing rings. The effects of naphthofuran ring system were investigated using substrates having a 4-chlorophenyl substituent. Among naphthofuran derivatives, the naphtho[1,2-*b*]furan derivative **9f** was found to have a fivefold higher binding affinity (IC_{50}=70 nM) compared to the benzofuran derivative, while the [2,1-*b*]- and [2,3-*b*]naphthofuran ring systems also displayed slightly increased binding affinities (Fig. 2). Based on the results described above, the naphtho[1,2-*b*]furan heterocyclic system was proposed as a potentially interesting scaffold for the development of new MCH-R1 antagonists.[38] Herein, the synthesis, evaluation as MCH-R1 antagonists, and structure–activity relationships (SAR) of a variety of 5-substituted naphtho[1,2-*b*]furan-2-carboxamide derivatives are described.

Chemistry The general, convergent synthetic routes employed for the preparation of 5-substituted-naphtho[1,2-*b*]-furan-2-carboxamide derivatives **9**–**12** are outlined in Charts 1–3. The 5-substituted naphtho[1,2-*b*]furan-2-carboxylic acids, serving as key coupling partners in the routes, were prepared

The authors declare no conflict of interest.

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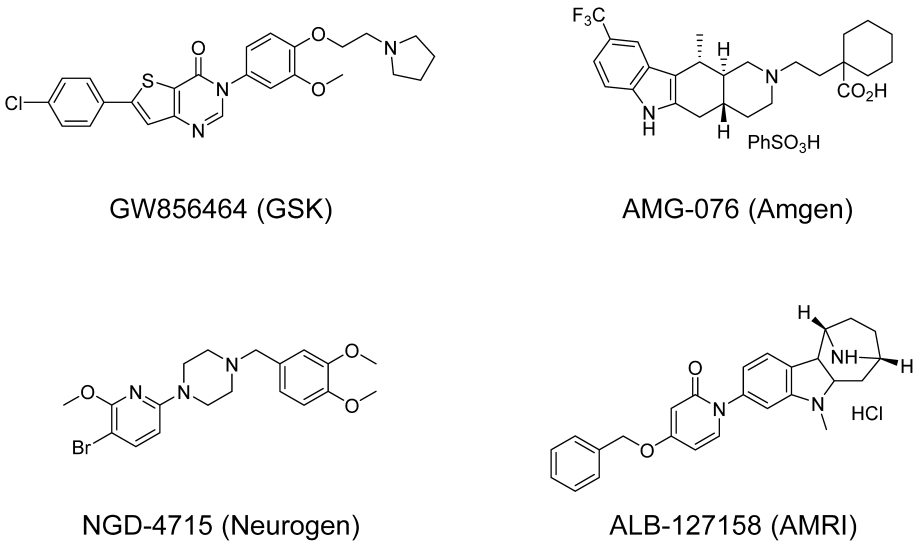


Fig. 1. Representative Structures of MCH-R1 Antagonists

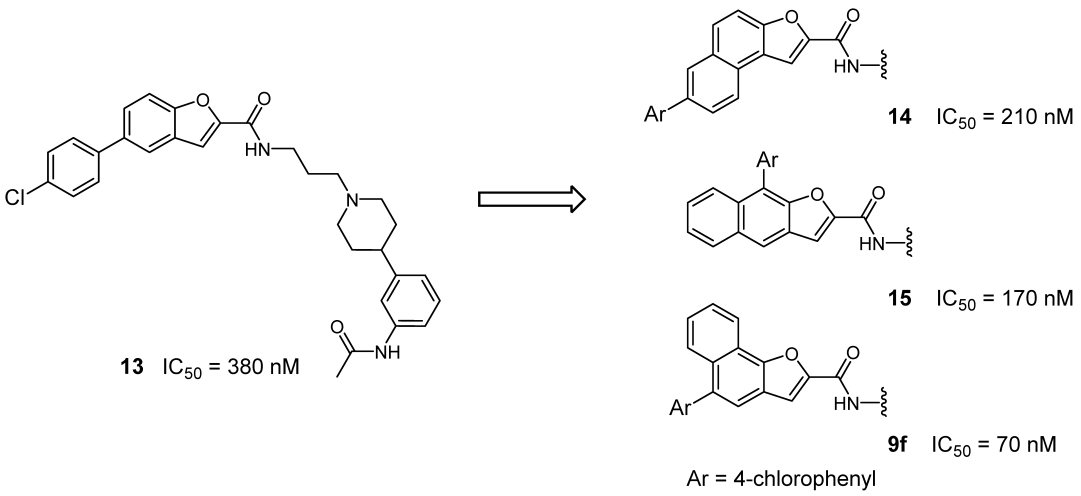
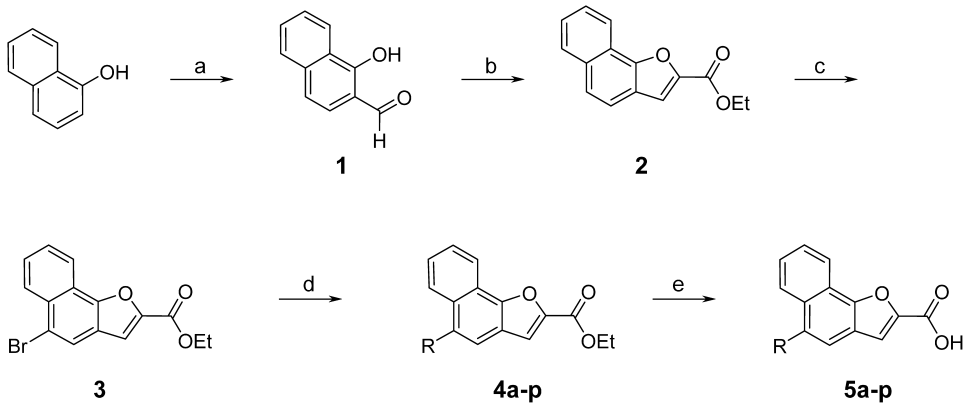


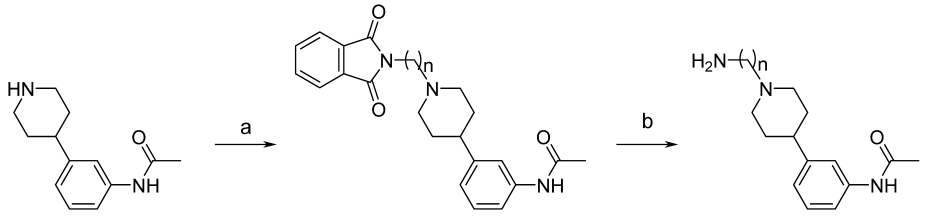
Fig. 2. Lead Generation of Naphtho[1,2-*b*]furan-2-carboxamides



Reagents and conditions: (a) $MgCl_2$, paraformaldehyde, Et_3N, CH_3CN, reflux, 15 h; (b) ethyl bromo acetate, K_2CO_3, CH_3CN, reflux, 1.5 h; (c) Br_2, CH_2Cl_2, r.t., 1 h; (d) aryl or heteroaryl boronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene–MeOH (1 : 1), reflux, 2 h; (e) 6 N KOH, MeOH, 60°C, 2 h.

Chart 1. Synthesis of 5-Substituted Naphtho[1,2-*b*]furan-2-carboxylic Acids **5a**–**p**

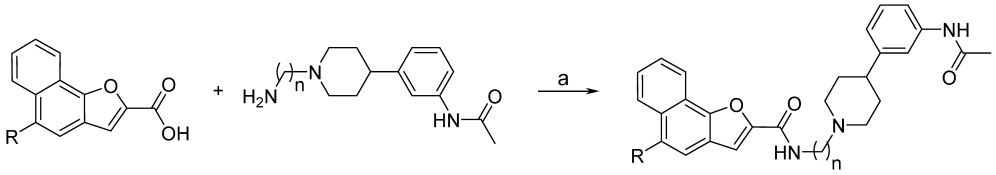
from 1-naphthol using the five-step sequence displayed in Chart 1. The sequence begins with reaction of 1-naphthol with paraformaldehyde in the presence of magnesium chloride ($MgCl_2$) and triethylamine as the base to give 1-hydroxy-2-naphthaldehyde **1**.[39] Subsequent treatment of **1** with ethyl bromoacetate in the presence of potassium carbonate yields ethyl naphtho[1,2-*b*]furan-2-carboxylate **2**, which upon treatment with bromine produces regioselectively the 5-bromo



6 **7a n=2** **7b n=3** **7c n=4** **7d n=5** **8a n=2** **8b n=3** **8c n=4** **8d n=5**

Reagents and conditions: (a) *N*-Bromoalkyl phthalimide, K_2CO_3, DMF, 70°C, 18 h; (b) NH_2NH_2, EtOH, r.t., 18 h.

Chart 2. Preparation of Aminoalkyl-Piperidinylphenylacetamides **8a**–**d**



5a-p **8a-d n=2-5** **9-12 n=2-5**

Reagents and conditions: (a) (i) $SOCl_2$, $ClCH_2CH_2Cl$, 80°C, 3 h; (ii) Et_3N, CH_3CN, r.t., 12 h.

Chart 3. Synthesis of **9**–**12**

product **3**. The 5-aryl and heteroaryl substituted naphtho[1,2-*b*]furan-2-carboxylic acid ethyl esters **4a**–**p** are then generated by reaction of **3** with selected aryl- and heteroaryl-boronic acids under standard Suzuki coupling conditions. Hydrolysis of the derived esters **4a**–**p** using potassium hydroxide in refluxing methanol affords the target acids **5a**–**p**.

The sequence for preparation of *ω*-aminoalkyl-piperidinylphenylacetamides **8a**–**d**, the other coupling partners, utilizes the known *N*-[3-(4-piperidinyl)phenyl]acetamide **6**[40] and begins by alkylation reactions of this substance with *N*-*ω*-bromoalkylphthalimides in the presence of potassium carbonate in acetonitrile at 60°C. The formed *N*-alkylated piperidines **7a**–**d** are then treated with hydrazine in ethanol at room temperature to give the corresponding free amines **8a**–**d** (Chart 2).

Finally, amide bond forming coupling reactions of acids **5a**–**p** with amines **8a**–**d** were performed utilizing the conventional acid chloride mediated method (Chart 3). Specifically, reactions of acids **5a**–**p** in refluxing thionyl chloride gave the acid chlorides, which were then treated with the corresponding amines **8a**–**d** using triethylamine in acetonitrile to produce the target amide products **9**–**12**.

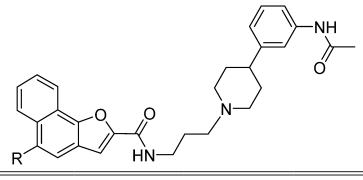
Results and Discussion

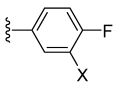
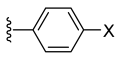
Binding affinities of the 5-substituted naphtho[1,2-*b*]-furan-2-carboxamide derivatives **9**–**12** to membranes of Chinese hamster's ovary (CHO) cells expressing human MCH-R1 were determined. Measurements were performed by using a competitive binding based assay with Eu-labeled MCH and time-resolved fluorescence (TRF) measurements.[41] Based on results coming from our earlier studies,[33–35] the effects of substituents at the 5-position of the naphtho[1,2-*b*]furan-2-carboxamide moiety were initially investigated using substrates having a fixed (n=3) length of the linker connecting the naphtho[1,2-*b*]furan and piperidinylphenyl moieties. As shown by inspection of the SAR results displayed in Table 1, the unsubstituted (**9a**, R=H) and 5-bromo-substituted (**9b**) naphtho[1,2-*b*]furan-2-carboxamides have moderate binding affinities to MCH-R1, whereas in comparison to these substances the simple phenyl derivative **9c** has a 2.5-fold increased binding affinity (IC_{50}=150 nM).

The effects of substituents at the C-5 position of the phenyl ring of the naphtho[1,2-*b*]furan-2-carboxamide framework were explored further. While the substance having a methyl group at the *para*-phenyl position (**9d**) displays a slightly reduced binding activity compared to **9c**, the introduction of *p*-fluoro (**9e**) and *p*-chloro group (**9f**) results in a large increase in MCH-R1 binding affinity with respective IC_{50} values of 57 nM and 70 nM. In addition, the *p*-cyano analog **9g** has 15-fold increased binding affinity (IC_{50}=10 nM) compared to **9c**. Repositioning the chloro and cyano substituents from the *para* (**9f**, **g**) to the *meta* position (**9h**, **i**) leads to a large decrease in binding to MCH-R1. Furthermore, derivatives containing di-substitution, such as 3,4-difluoro (**9j**) and 3-chloro-4-fluoro (**9k**), display reduced binding affinities. The effects of replacement of the C-5 aryl group on the naphtho[1,2-*b*]-furan-2-carboxamide framework with heteroaromatic moieties on the MCH-R1 binding affinity were also explored. Among pyridine-substituted derivatives, the 4-pyridinyl analog **9n** was found to have a binding activity that is near equal to that of the *p*-cyanophenyl analog **9g** and much higher than substances possessing 2-pyridinyl (**9l**) and 3-pyridinyl (**9m**) groups. Finally, C-5 substitution with other types of heteroaryl groups, such as 3-furyl (**9o**) and 3-thiophenyl (**9p**), leads to lower binding affinities than the phenyl counterpart.

We next attempted to optimize the binding affinities of the 5-(*p*-chlorophenyl) derivative by varying the length of the chain between its naphtho[1,2-*b*]furan and piperidinylphenyl moieties (Table 2). Unlike trends observed earlier for the related benzimidazole and phthalazin-1(2*H*)-one analogs,[33–35] an

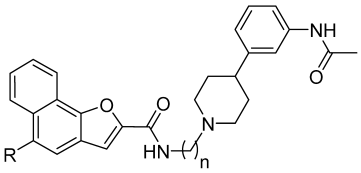
Table 1. Effects on MCH-R1 Binding Affinity of Substituents at C-5 of Naphtho[1,2-*b*]furan-2-carboxamide Derivatives

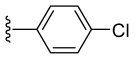
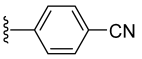
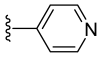


Compound	R	MCH-R1 $IC_{50}^{a,b)}$ (nM)	Compound	R	MCH-R1 $IC_{50}^{a,b)}$ (nM)
9a	H	377			
9b	Br	370			
			**9j**	X=F	120
			9k	X=Cl	200
9c	X=H	150			
9d	X=Me	211	**9l**		570
9e	X=F	57			
9f	X=Cl	70	**9m**		60
9g	X=CN	10			
			**9n**		10
9h	X=Cl	160	**9o**		140
9i	X=CN	70			
			9p		270

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

Table 2. Effects on MCH-R1 Binding Affinity of the Chain Length between the Naphtho[1,2-*b*]furan and Piperidinylphenyl Moieties



Compound	*n*	R	MCH-R1 $IC_{50}^{a,b)}$ (nM)
10	2		5
9f	3		70
11	4		7
12	5		450
10a	2		7
9g	3		10
10b	2		3
9n	3		10

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

ethylene (2 carbon) linker was found to be preferable to propylene (**9f**), butylene (**11**) and pentylene (**12**) linkers. Also, the *p*-cyanophenyl (**10a**) and 4-pyridinyl (**10b**) analogs possessing two-carbon linkers display higher binding affinities than the corresponding analogs **9g** and **9n** containing three-carbon linkers. The 4-pyridinyl derivative **10b** was observed to exhibit the most potent binding affinity to MCH-R1 (IC_{50}=3 nM) among all of the substances tested.

5-(4-Pyridinyl) substituted naphtho[1,2-*b*]furan-2-carboxamide **10b** was subjected to further biological studies. This substance was observed to display good metabolic stability in human and rat liver microsomes (100% and 99% for 30 min, respectively) and very low inhibition of the cytochrome P450 enzymes 2D6 and 3A4 (<10% at 10 μM). However, the results of an intravenous and oral pharmacokinetic study (10 mg/kg) demonstrate that **10b** exhibits low oral bioavailability (F=4.1%) with a high clearance (CL=82 mL/min/kg) and low plasma level (AUC=0.08 g h/mL), probably due to poor aqueous solubility.

Conclusion

The studies described above have led to the discovery of substances containing linked naphtho[1,2-*b*]furan-2-carboxamides and piperidinylphenylacetamide moieties that serve as novel MCH-R1 antagonists. An extensive optimization effort, probing the effects of substituents on aryl and heteroaryl ring located at C-5 of the naphtho[1,2-*b*]furan-2-carboxamide framework and the chain length between the naphtho[1,2-*b*]furan and piperidinylphenyl groups, have led to the identification of 5-(4-pyridinyl) substituted naphtho[1,2-*b*]furan-2-carboxamide **10b** as the most potent MCH-R1 antagonist. This substance displays good metabolic stability and low inhibition of CYP450 enzymes. Further studies focusing on the improvement of the pharmacokinetic properties of the linked naphtho[1,2-*b*]furan-2-carboxamides–piperidinylphenylacetamides are now in progress.

Experimental

General ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 or Bruker DRX-300 spectrometer. High resolution mass spectra (HR-MS) were recorded on a JEOL JMS-700 mas spectrometer. Column chromatography was carried out using silica gel (230–400 mesh). All solvents and reagents were commercially available and used without purification.

1-Hydroxy-2-naphthaldehyde (1) To a solution of naphthalene-1-ol (2.0 g, 13.89 mmol) and paraformaldehyde (2.4 g, 83.34 mmol) in acetonitrile (50 mL) were added magnesium chloride (1.98 g, 20.8 mmol) and triethylamine (7.2 mL, 51.4 mmol). After being stirred at reflux for 15 h, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water and 5% aqueous hydrogen chloride solution, dried over anhydrous sodium sulfate, and concentrated *in vacuo*, giving a residue that was subjected to column chromatography on silica gel (ethyl acetate–*n*-hexane 1 : 10) to obtain 800 mg (33%) of the title compound. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 12.67 (s, 1H), 9.97 (s, 1H), 8.44 (d, J=8.4 Hz, 1H), 7.79 (d, J=8.4 Hz, 1H), 7.66 (dd, J=8.4, 8.1 Hz, 1H) 7.55 (dd, J=8.4, 8.1 Hz, 1H), 7.49 (d, J=8.6 Hz, 1H), 7.37 (d, J=8.6 Hz, 1H).

Ethyl Naphtho[1,2-*b*]furan-2-carboxylate (2) To a solution of 1-hydroxy-2-naphthaldehyde (**1**, 100 mg, 0.58 mmol) and ethyl bromoacetate (98 mg, 0.69 mmol) in acetonitrile (3 mL) was added potassium carbonate (161 mg, 1.16 mmol). After being stirred at reflux for 1.5 h, the mixture was diluted with water (20 mL), and extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous sodium sulfate

and concentrated *in vacuo*, giving a residue that was subjected to column chromatography on silica gel (ethyl acetate–*n*-hexane 1 : 10) to obtain 100 mg (76%) of the title compound. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.47 (d, J=8.4 Hz, 1H), 7.93 (d, J=8.4 Hz, 1H), 7.53–7.73 (m, 5H), 4.46 (q, J=7.1 Hz, 2H), 1.46 (t, J=7.1 Hz, 3H).

Ethyl 5-Bromonaphtho[1,2-*b*]furan-2-carboxylate (3) To a solution of ethyl naphtho[1,2-*b*]furan-2-carboxylate (**2**, 1.0 g, 4.42 mmol) in dichloromethane (30 mL) was added bromine (918 mg, 5.75 mmol) at room temperature. After stirring for 1 h at room temperature, the mixture was concentrated *in vacuo*, giving a residue that was subjected to column chromatography on silica gel (ethyl acetate–*n*-hexane 1 : 3) to give 1.3 g (96%) of the title compound. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44–8.52 (m, 1H), 8.31–8.38 (m, 1H), 8.01 (s, 1H), 7.65–7.74 (m, 2H), 7.59 (s, 1H), 4.46 (q, J=7.1 Hz, 2H), 1.46 (t, J=7.1 Hz, 3H); HR-MS (EI): Calcd for $C_{15}H_{11}BrO_3$ $[M]^+$ 317.9892, Found 317.9881.

General Procedure for the Synthesis of Ethyl 5-Aryl-naphtho[1,2-*b*]furan-2-carboxylate (4a–p) Ethyl 5-bromonaphtho[1,2-*b*]furan-2-carboxylate (**3**, 0.5 mmol), appropriate arylboronic acid or heteroarylboronic acid (0.6 mmol), 2 M sodium carbonate (1.5 mmol), and catalytic amount of $Pd(PPh_3)_4$ were dissolved in 5 mL of toluene and methanol (1 : 1). The mixture was stirred at reflux for 2 h, diluted with water (20 mL), and extracted with ethyl acetate (40 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, giving a residue that was subjected to column chromatography on silica gel (ethyl acetate–*n*-hexane 1 : 10) to give target compound.

Ethyl 5-(Pyridin-4-yl)naphtho[1,2-*b*]furan-2-carboxylate (**4n**): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.75 (d, J=5.3 Hz, 2H), 8.56 (d, J=8.2 Hz, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.63–7.73 (m, 1H), 7.66 (s, 1H), 7.59 (s, 1H), 7.51–7.62 (m, 1H), 7.44 (d, J=5.3 Hz, 2H), 4.78 (q, J=7.0 Hz, 2H), 1.47 (t, J=7.0 Hz, 3H); HR-MS (EI): Calcd for $C_{20}H_{15}NO_3$ $[M]^+$ 317.1052, Found 317.1037.

General Procedure for the Synthesis of 5-Aryl-naphtho[1,2-*b*]furan-2-carboxylic Acid (5a–p) To a solution of 5-aryl-naphtho[1,2-*b*]furan-2-carboxylic acid (**4a**–**p**, 0.5 mmol) in methanol (3 mL) was added 2 M sodium hydroxide (0.5 mL, 1 mmol) at room temperature. After stirring at reflux for 2 h, the mixture was acidified by addition of 2 N HCl solution and extracted with ethyl acetate (30 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give target compound.

5-(Pyridin-4-yl)naphtho[1,2-*b*]furan-2-carboxylic Acid (**5n**): ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.93 (m, 2H), 8.45 (d, J=7.7 Hz, 1H), 7.97 (m, 2H), 7.90 (m, 2H), 7.83 (m, 1H), 7.69 (m, 1H), 7.60 (m, 1H); HR-MS (EI): Calcd for $C_{18}H_{11}NO_3$ $[M]^+$ 289.0739, Found 289.0742.

***N*-(3-{1-[2-(1,3-Dioxoisoindolin-2-yl)ethyl]piperidin-4-yl}phenyl)acetamide (7a)** *N*-[3-(Piperidin-4-yl)phenyl]-acetamide (**6**, 600 mg, 2.36 mmol), *N*-(2-bromoethyl)-phthalimide (720 mg, 2.83 mmol), and sodium carbonate (979 mg, 7.08 mmol) were dissolved in DMF (10 mL). After being stirred at 70°C for 18 h, the mixture was diluted with water (50 mL), and extracted with ethyl acetate (50 mL×2). The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*, giving a residue that was subjected to column chromatography on silica gel (10% MeOH–CH_2Cl_2) to afford 924 mg (99%) of the title compound. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.81–7.88 (m, 2H), 7.69–7.74 (m, 2H), 7.58 (s, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.32 (s, 1H), 7.21 (dd, J=8.0, 7.6 Hz, 1H), 6.93 (d, J=7.6 Hz, 1H), 3.85 (t, J=6.9 Hz, 2H), 3.05–3.16 (m, 2H), 2.66 (t, J=6.9 Hz, 2H), 2.37–3.52 (m, 1H), 2.15 (s, 3H), 2.05–2.18 (m, 2H), 1.58–1.84 (m, 4H).

***N*-(3-{1-[2-(1,3-Dioxoisoindolin-2-yl)propyl]piperidin-4-yl}phenyl)acetamide (7b)** The title compound (4.13 g, 99%) was prepared in the same manner as described for **7a** using *N*-[3-(piperidin-4-yl)phenyl]acetamide (2.6 g, 10.21 mmol). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 9.81 (s, 1H), 7.86–7.92 (m, 2H), 7.79–7.91 (m, 2H), 7.35 (d, J=7.9 Hz, 1H), 7.32 (s, 1H), 7.14 (dd, J=7.9, 7.5 Hz, 1H), 6.63 (d, J=7.5 Hz, 1H), 3.68 (t, J=6.4 Hz, 2H), 2.80–2.86 (m, 2H), 2.33–2.38 (m, 2H), 2.25–2.33 (m, 1H), 2.03 (s, 3H), 1.74–1.89 (m, 4H), 1.53–1.60 (m, 2H), 1.17–1.27 (m, 2H).

***N*-(3-{1-[2-(1,3-Dioxoisoindolin-2-yl)butyl]piperidin-4-yl}phenyl)acetamide (7c)** The title compound (609 mg, 61%) was prepared in the same manner as described for **7a** using *N*-[3-(piperidin-4-yl)phenyl]acetamide (600 mg, 2.36 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.80–7.88 (m, 2H), 7.68–7.75 (m, 2H), 7.53 (s, 1H), 7.38 (d, J=8.2 Hz, 1H), 7.34 (s, 1H), 7.22 (dd, J=8.2, 7.7 Hz, 1H), 6.96 (d, J=7.7 Hz, 1H), 3.72 (t, J=7.2 Hz, 2H), 2.99–3.09 (m, 2H), 2.42–2.53 (m, 1H), 2.38–2.47 (m, 2H), 2.17 (s, 3H), 1.99–2.10 (m, 2H), 1.75–1.85 (m, 4H), 1.66–1.76 (m, 2H), 1.53–1.65 (m, 2H).

***N*-(3-{1-[2-(1,3-Dioxoisoindolin-2-yl)pentyl]piperidin-4-yl}phenyl)acetamide (7d)** The title compound (621 mg, 61%) was prepared in the same manner as described for **7a** using *N*-[3-(piperidin-4-yl)phenyl]acetamide (600 mg, 2.36 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.81–7.88 (m, 2H), 7.67–7.76 (m, 2H), 7.56 (s, 1H), 7.40 (d, J=8.2 Hz, 1H), 7.34 (s, 1H), 7.23 (dd, J=8.2, 7.7 Hz, 1H), 6.96 (d, J=7.7 Hz, 1H), 3.70 (t, J=7.2 Hz, 2H), 3.02–3.12 (m, 2H), 2.42–2.55 (m, 1H), 2.35–2.45 (m, 2H), 2.18 (s, 3H), 1.99–2.13 (m, 2H), 1.76–1.88 (m, 4H), 1.66–1.77 (m, 2H), 1.54–1.66 (m, 2H), 1.31–1.44 (m, 2H).

***N*-{3-[1-(2-Aminoethyl)piperidin-4-yl]phenyl}acetamide (8a)** To a solution of *N*-(3-{1-[2-(1,3-dioxoisoindolin-2-yl)-ethyl]piperidin-4-yl}phenyl)acetamide (**7a**, 924 mg, 2.36 mmol) in ethanol (10 mL) was added hydrazine hydrate (0.31 mL, 7.08 mmol) at room temperature. After being stirred for 18 h at room temperature, the mixture was concentrated *in vacuo*, giving a residue that was subjected to column chromatography on silica gel (ethyl acetate–*n*-hexane 1 : 3) to give 270 mg (44%) of the title compound. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.70 (s, 1H), 7.39 (d, J=8.1 Hz, 1H), 7.39 (s, 1H), 7.20 (dd, J=8.1, 7.6 Hz, 1H), 6.92 (d, J=7.6 Hz, 1H), 2.90–3.01 (m, 2H), 2.89 (br s, 2H), 2.82 (t, J=6.2 Hz, 2H), 2.44 (t, J=6.2 Hz, 2H), 2.34–2.43 (m, 1H), 2.15 (s, 3H), 1.96–2.08 (m, 2H), 1.65–1.78 (m, 4H).

***N*-{3-[1-(3-Aminopropyl)piperidin-4-yl]phenyl}acetamide (8b)** The title compound (1.02 g, 99%) was prepared in the same manner as described for **8a** using *N*-(3-{1-[3-(1,3-dioxoisoindolin-2-yl)propyl]piperidin-4-yl}phenyl)acetamide (**7b**, 1.5 g, 3.70 mmol). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.45 (s, 1H), 7.37 (d, J=8.6 Hz, 1H), 7.36 (s, 1H), 7.17 (dd, J=8.6, 7.4 Hz, 1H), 6.89 (d, J=7.4 Hz, 1H), 3.11–3.14 (m, 2H), 3.09 (br s, 2H), 2.92–3.04 (m, 2H), 2.74–2.79 (m, 1H), 2.39 (t, J=7.2 Hz, 2H), 2.11 (s, 3H), 1.92–1.98 (m, 2H), 1.62–1.76 (m,

2H), 1.52–1.62 (m, 4H).

***N*-{3-[1-(4-Aminobutyl)piperidin-4-yl]phenyl}acetamide (8c)** The title compound (270 mg, 53%) was prepared in the same manner as described for **8a** using *N*-(3-{1-[4-(1,3-dioxoisoindolin-2-yl)butyl]piperidin-4-yl}phenyl)acetamide (**7c**, 924 mg, 2.36 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.03 (s, 1H), 7.43 (d, J=8.1 Hz, 1H), 7.30 (s, 1H), 7.19 (dd, J=8.1, 7.7 Hz, 1H), 6.92 (d, J=7.7 Hz, 1H), 3.80 (brs, 2H), 2.96–3.07 (m, 2H), 2.76 (t, J=6.6 Hz, 2H), 2.37–2.50 (m, 1H), 2.31–2.39 (m, 2H), 2.16 (s, 3H), 1.92–2.07 (m, 2H), 1.64–1.82 (m, 4H), 1.47–1.64 (m, 4H); HR-MS (EI): Calcd for $C_{17}H_{27}N_3O$ $[M]^+$ 289.2154, Found 289.2156.

***N*-{3-[1-(5-Aminopentyl)piperidin-4-yl]phenyl}acetamide (8d)** The title compound (422 mg, 99%) was prepared in the same manner as described for **8a** using *N*-(3-{1-[5-(1,3-dioxoisoindolin-2-yl)pentyl]piperidin-4-yl}phenyl)acetamide (**7d**, 621 mg, 1.39 mmol). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 9.89 (s, 1H), 7.45 (s, 1H), 7.36 (d, J=7.9 Hz, 1H), 7.16 (dd, J=7.9, 7.6 Hz, 1H), 6.87 (d, J=7.6 Hz, 1H), 4.74 (brs, 2H), 2.84–2.97 (m, 2H), 2.62 (t, J=6.8 Hz, 2H), 2.30–2.44 (m, 1H), 2.18–2.28 (m, 2H), 2.00 (s, 3H), 1.83–1.96 (m, 2H), 1.50–1.74 (m, 4H), 1.36–1.48 (m, 4H), 1.18–1.37 (m, 2H); HR-MS (EI): Calcd for $C_{18}H_{29}N_3O$ $[M]^+$ 303.2311, Found 303.2311.

***N*-{2-[4-(3-Acetamidophenyl)piperidin-1-yl]ethyl}-5-(pyridin-4-yl)naphtho[1,2-*b*]furan-2-carboxamide (10b)** To a solution of 5-(pyridin-4-yl)naphtho[1,2-*b*]furan-2-carboxylic acid (75 mg, 0.26 mmol) in 1,2-dichloroethane (5 mL) was added $SOCl_2$ (0.50 mL). The mixture was stirred at reflux for 3 h, and concentrated *in vacuo*. After the resulting residue was dissolved in dichloromethane (10 mL), *N*-{3-[1-(2-aminoethyl)piperidin-4-yl]phenyl}acetamide (**8a**, 135 mg, 0.36 mmol) and excess triethylamine were added. the resulting mixture was stirred for 15 h at room temperature, diluted with water (20 mL), and extracted with dichloromethane (30 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*, giving a residue that was subjected to column chromatography on silica gel (10% MeOH–CH_2Cl_2) to give the title compound (55 mg, 77%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.76 (d, J=4.4 Hz, 2H), 8.45 (d, J=8.0 Hz, 1H), 7.89 (d, J=8.4 Hz, 1H), 7.65 (m, 3H), 7.55 (m, 2H), 7.46 (m, 3H), 7.39–7.19 (m, 3H), 7.05 (d, J=6.5 Hz, 1H), 3.67 (m, 2H), 3.15 (d, J=11.6 Hz, 2H), 2.74 (t, J=5.2 Hz, 2H), 2.60 (m, 1H), 2.25 (m, 2H), 2.16 (s, 3H), 1.93 (m, 4H); HR-MS (EI): Calcd for $C_{33}H_{32}N_4O_3$ $[M]^+$ 532.2474, Found 532.2448.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(4-chlorophenyl)benzofuran-2-carboxamide (13)** The title compound (100 mg, 51%) was prepared in the same manner as described for **10b** using 5-(4-chlorophenyl)benzofuran-2-carboxylic acid (100 mg, 0.37 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.74 (s, 1H), 7.78 (s, 1H), 7.45–7.55 (m, 4H), 7.33–7.45 (m, 5H), 7.18–7.31 (m, 2H), 7.02 (d, J=7.3 Hz, 1H), 3.54–3.67 (m, 2H), 3.13–3.26 (m, 2H), 2.55–2.70 (m, 3H), 2.08–2.22 (m, 2H), 2.09 (s, 3H), 1.92–2.04 (m, 4H), 1.76–1.89 (m, 2H).

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-7-(4-chlorophenyl)naphtho[2,1-*b*]furan-2-carboxamide (14)** The title compound (22 mg, 12%) was prepared in the same manner as described for **10b** using 7-(4-chlorophenyl)-naphtho[2,1-*b*]furan-2-carboxylic acid (100 mg, 0.31 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.74 (s, 1H), 8.20 (d, J=8.6 Hz, 1H), 8.09 (s, 1H), 7.97 (s, 1H), 7.82 (d, J=8.6 Hz, 1H), 7.58–7.75 (m, 4H), 7.43–7.54 (m, 3H), 7.28–7.39 (m, 3H), 7.02 (d, J=7.4 Hz, 1H), 3.55–3.66 (m, 2H), 3.15–3.28 (m, 2H), 2.57–2.74 (m, 3H), 2.13–2.27 (m, 2H), 2.12 (s, 3H), 1.96–2.10 (m, 4H), 1.75–1.90 (m, 2H).

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-9-(4-chlorophenyl)naphtho[2,3-*b*]furan-2-carboxamide (15)** The title compound (56 mg, 44%) was prepared in the same manner as described for **10b** using 9-(4-chlorophenyl)-naphtho[2,3-*b*]furan-2-carboxylic acid (70 mg, 0.22 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.09 (s, 1H), 7.88 (d, J=8.3 Hz, 1H), 7.64 (d, J=8.0 Hz, 2H), 7.47–7.56 (m, 3H), 7.39–7.47 (m, 3H), 7.27–7.39 (m, 4H), 7.18 (s, NH), 7.08 (d, J=7.2 Hz, 1H), 3.56–3.66 (m, 2H), 3.17–3.27 (m, 2H), 2.58–2.68 (m, 3H), 1.98–2.24 (m, 6H), 1.94 (s, 3H), 1.74–1.86 (m, 2H).

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-naphtho[1,2-*b*]furan-2-carboxamide (9a)** The title compound (133 mg, 43%) was prepared in the same manner as described for **10b** using naphtho[1,2-*b*]furan-2-carboxylic acid (140 mg, 0.66 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.32 (d, J=7.7 Hz,1H), 7.93 (d, J=8.2 Hz, 1H), 7.99 (m, 1H), 7.68 (m, 2H), 7.60 (s, 1H), 7.51 (m, 1H), 7.43 (m, 3H), 7.16 (s, 1H), 7.12 (t, J=7.9 Hz, 1H), 6.86 (d, J=7.6 Hz, 1H), 3.64 (m, 2H), 3.22 (d, J=11.5 Hz, 2H), 2.68 (t, J=6.4 Hz, 2H), 2.50 (m, 1H), 2.20 (m, 2H), 2.12 (s, 3H), 1.98–1.86 (m, 6H); HR-MS (EI): Calcd for $C_{29}H_{31}N_3O_3$ $[M]^+$ 469.2365, Found 469.2361.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-bromonaphtho[1,2-*b*]furan-2-carboxamide (9b)** The title compound (58 mg, 77%) was prepared in the same manner as described for **10b** using 5-bromonaphtho[1,2-*b*]furan-2-carboxylic acid (40 mg, 0.14 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.43 (d, J=8.1 Hz, 1H), 8.32 (d, J=8.1 Hz, 1H), 8.26–8.28 (m, 1H), 8.00 (s, 1H), 7.52–7.66 (m, 4H), 7.46 (d, J=9.0 Hz, 1H), 7.25 (m, 1H), 7.15 (d, J=7.8 Hz, 1H), 6.87 (d, J=7.5 Hz, 1H), 3.65–3.72 (m, 2H), 3.38 (t, J=11.7 Hz, 2H), 2.86 (t, J=6.6 Hz, 2H), 2.53–2.59 (m, 1H), 2.39 (t, J=11.7 Hz, 2H), 2.17 (s, 3H), 2.06–2.12 (m, 4H), 1.89–1.93 (m, 2H); HR-MS (EI): Calcd for $C_{29}H_{30}BrN_3O_3$ $[M]^+$ 547.1471, Found 547.1486.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-phenylnaphtho[1,2-*b*]furan-2-carboxamide (9c)** The title compound (98 mg, 43%) was prepared in the same manner as described for **10b** using 5-phenylnaphtho[1,2-*b*]furan-2-carboxylic acid (120 mg, 0.42 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44 (m, 1H), 8.03 (m, 1H), 7.91 (m, 1H), 7.61 (d, J=2.3 Hz, 2H), 7.56–7.39 (m, 7H), 7.23 (s, 1H), 7.12 (t, J=7.8 Hz, 1H), 6.87 (d, J=7.7 Hz, 1H), 3.68 (m, 2H), 3.26 (d, J=11.7 Hz, 2H), 3.23 (m, 2H), 2.56 (m, 1H), 2.23 (m, 2H), 2.12 (s, 3H), 2.07–1.84 (m, 6H); HR-MS (EI): Calcd for $C_{35}H_{35}N_3O_3$ $[M]^+$ 545.2678, Found 545.2682.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(4-methylphenyl)naphtho[1,2-*b*]furan-2-carboxamide (9d)** The title compound (88 mg, 39%) was prepared in the same manner as described for **10b** using 5-(4-methylphenyl)-naphtho[1,2-*b*]furan-2-carboxylic acid (120 mg, 0.40 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.43 (m, 1H), 8.08 (s, 1H), 7.91 (m, 1H), 7.61 (s, 2H), 7.57 (s, 1H), 7.51–7.41 (m, 3H), 7.36 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 7.21 (s, 1H), 7.11 (t, J=7.8 Hz, 1H), 6.85 (d, J=7.6 Hz, 1H,), 3.66 (m, 2H), 3.22 (d, J=11.7 Hz, 2H), 2.71 (t, J=6.1 Hz, 2H), 2.56–2.48 (m, 1H), 2.46 (s, 3H), 2.20 (m, 2H), 2.12 (s, 3H), 2.04–1.83 (m, 6H); HR-MS (EI): Calcd for $C_{36}H_{37}N_3O_3$ $[M]^+$ 559.2835, Found 559.2835.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(4-fluorophenyl)naphtho[1,2-*b*]furan-2-carboxamide (9e)** The title compound (96 mg, 55%) was prepared in the same manner as described for **10b** using 5-(4-fluorophenyl)naphtho[1,2-*b*]furan-2-carboxylic acid (95 mg, 0.31 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44 (m, 1H), 8.04 (m, 1H), 7.83 (m, 1H), 7.66 (m, 2H), 7.57 (s, 1H), 7.52–7.40 (m, 5H), 7.27 (m, 1H), 7.19 (t, J=8.7 Hz, 2H), 7.11 (t, J=7.8 Hz, 1H), 6.86 (d, J=7.6 Hz, 1H), 3.68 (m, 2H), 3.27(d, J=11.7 Hz, 2H), 3.24 (t, J=6.3 Hz, 2H), 2.53 (m, 1H), 2.25 (m, 2H), 2.13 (s, 3H), 2.10–1.89 (m, 6H); HR-MS (EI): Calcd for $C_{35}H_{34}FN_3O_3$ $[M]^+$ 563.2584, Found 563.2563.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(4-chlorophenyl)naphtho[1,2-*b*]furan-2-carboxamide (9f)** The title compound (15 mg, 21%) was prepared in the same manner as described for **10b** using 5-(4-chlorophenyl)-naphtho[1,2-*b*]furan-2-carboxylic acid (40 mg, 0.12 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.40–8.42 (m, 1H), 7.84–7.91 (m, 2H), 7.60 (d, J=6.8 Hz, 2H), 7.40–7.50 (m, 4H), 7.36–7.43 (m, 3H), 7.09–7.26 (m, 3H), 6.88 (d, J=7.6 Hz, 1H), 3.65–3.71 (m, 2H), 3.25 (d, J=11.0 Hz, 2H), 2.69 (t, J=6.4 Hz, 2H), 2.51–2.59 (m, 1H), 2.16–2.24 (m, 2H), 2.11 (s, 3H), 1.88–2.04 (m, 6H); HR-MS (EI): Calcd for $C_{35}H_{34}ClN_3O_3$ $[M]^+$ 579.2289, Found 579.2286.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(4-cyanophenyl)naphtho[1,2-*b*]furan-2-carboxamide (9g)** The title compound (134 mg, 57%) was prepared in the same manner as described for **10b** using 5-(4-cyanophenyl)naphtho[1,2-*b*]furan-2-carboxylic acid (40 mg, 0.14 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.46 (m, 1H), 8.00 (m, 1H), 7.85–7.78 (m, 3H), 7.65–7.56 (m, 4H), 7.51 (m, 2H), 7.33 (m, 2H), 7.18 (brs, 1H), 7.10 (t, J=7.5 Hz, 1H), 6.87 (d, J=7.3 Hz, 1H), 3.70 (m, 2H), 3.27 (d, J=11.0 Hz, 2H), 2.71 (m, 2H), 2.57 (m, 1H), 2.23 (m, 2H), 2.13 (s, 3H), 2.04–1.88 (m, 6H); HR-MS (EI): Calcd for $C_{36}H_{34}N_4O_3$ $[M]^+$ 570.2631, Found 570.2611.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(3-chlorophenyl)naphtho[1,2-*b*]furan-2-carboxamide (9h)** The title compound (72 mg, 27%) was prepared in the same manner as described for **10b** using 5-(3-chlorophenyl)-naphtho[1,2-*b*]furan-2-carboxylic acid (123 mg, 0.38 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.45 (m, 1H), 8.06 (m, 1H), 7.84 (m, 1H), 7.61 (s, 1H), 7.58 (s, 1H), 7.53–7.26 (m, 9H), 7.11 (t, J=7.3 Hz, 1H), 6.87 (d, J=7.7 Hz, 1H), 3.68 (m, 2H), 3.27 (d, J=10.9 Hz, 2H), 2.74 (t, J=5.8 Hz, 2H), 2.55 (m, 1H), 2.25 (m, 2H), 2.13 (s, 3H), 2.05–1.84 (m, 6H); HR-MS (EI): Calcd for $C_{35}H_{34}ClN_3O_3$ $[M]^+$ 579.2289, Found 579.2281.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(3-cyanophenyl)naphtho[1,2-*b*]furan-2-carboxamide (9i)** The title compound (109 mg, 53%) was prepared in the same manner as described for **10b** using 5-(3-cyanophenyl)naphtho[1,2-*b*]furan-2-carboxylic acid (113 mg, 0.36 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.51 (d, J=7.4 Hz, 1H), 8.21 (m, 1H), 7.80–7.36 (m, 12H), 7.14 (t, J=8.3 Hz, 1H), 6.90 (d, J=7.6 Hz, 1H), 3.72 (m, 2H), 3.43 (m, 2H), 2.90 (m, 2H), 2.64 (m, 1H), 2.45 (m, 2H), 2.14 (s, 3H), 2.23–1.93 (m, 6H); HR-MS (EI): Calcd for $C_{36}H_{34}N_4O_3$ $[M]^+$ 570.2631, Found 570.2621.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(3,4-difluorophenyl)naphtho[1,2-*b*]furan-2-carboxamide (9j)** The title compound (68 mg, 34%) was prepared in the same manner as described for **10b** using 5-(3,4-difluorophenyl)naphtho[1,2-*b*]furan-2-carboxylic acid (104 mg, 0.32 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.49 (d, J=8.3 Hz, 1H), 8.09 (s, 1H), 7.83 (d, J=8.3 Hz, 1H), 7.62 (s, 1H), 7.58 (s, 1H), 7.48–7.50 (m, 2H), 7.38–7.45 (m, 2H), 7.25–7.34 (m, 3H), 7.21 (s, 1H), 7.13 (dd, J=7.9, 7.9 Hz, 1H), 6.89 (d, J=7.9 Hz, 1H), 3.64–3.78 (m, 2H), 3.30–3.43 (m, 2H), 2.77–2.86 (m, 2H), 2.52–2.67 (m, 1H), 2.27–2.43 (m, 2H), 2.14 (s, 3H), 1.99–2.17 (m, 4H), 1.87–1.99 (m, 2H); HR-MS (EI): Calcd for $C_{35}H_{33}F_2N_3O_3$ $[M]^+$ 581.2490, Found 581.2476.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(3-chloro-4-fluorophenyl)naphtho[1,2-*b*]furan-2-carboxamide (9k)** The title compound (109 mg, 26%) was prepared in the same manner as described for **10b** using 5-(3-chloro-4-fluorophenyl)naphtho[1,2-*b*]furan-2-carboxylic acid (130 mg, 0.38 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.43–8.50 (m, 1H), 8.19 (s, 1H), 7.72–7.83 (m, 1H), 7.65 (s, 1H), 7.56 (s, 1H), 7.42–7.54 (m, 5H), 7.28–7.40 (m, 3H), 7.15 (dd, J=7.8, 7.3 Hz, 1H), 6.92 (d, J=7.3 Hz, 1H), 3.66–3.77 (m, 2H), 3.43–3.53 (m, 2H), 2.89–3.00 (m, 2H), 2.56–2.71 (m, 1H), 2.35–2.54 (m, 2H), 2.13 (s, 3H), 2.05–2.23 (m, 4H), 1.91–2.02 (m, 2H); HR-MS (EI): Calcd for $C_{35}H_{33}ClFN_3O_3$ $[M]^+$ 597.2194, Found 597.2194.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(pyridin-2-yl)naphtho[1,2-*b*]furan-2-carboxamide (9l)** The title compound (78 mg, 77%) was prepared in the same manner as described for **10b** using 5-(pyridin-2-yl)naphtho[1,2-*b*]furan-2-carboxylic acid (78 mg, 0.28 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.78 (d, J=4.0 Hz, 1H), 8.60 (d, J=8.1 Hz, 1H), 8.50 (m, 1H), 8.07 (d, J=8.1 Hz, 2H), 7.85 (m, 1H), 7.77 (s, 1H), 7.67 (s, 1H), 7.62–7.56 (m, 2H), 7.50 (m, 2H), 7.36 (m, 1H), 7.22 (s, 1H), 7.15 (t, J=8.0 Hz, 1H), 6.85 (d, J=7.7 Hz, 1H), 3.70 (m, 2H), 3.47 (m, 2H), 3.03 (m, 2H), 2.49 (m, 3H), 2.21 (m, 4H), 2.17 (s, 3H), 1.80 (m, 2H); HR-MS (EI): Calcd for $C_{34}H_{34}N_4O_3$ $[M]^+$ 546.2631, Found 546.2629.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(pyridin-3-yl)naphtho[1,2-*b*]furan-2-carboxamide (9m)** The title compound (153 mg, 74%) was prepared in the same manner as described for **10b** using 5-(pyridin-3-yl)-naphtho[1,2-*b*]furan-2-carboxylic acid (110 mg, 0.38 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.75 (m, 1H), 8.71 (d, J=3.6 Hz, 1H), 8.46 (m, 1H), 8.03 (s, 1H), 7.85–7.78 (m, 2H), 7.63 (d, J=2.6 Hz, 2H), 7.53–7.42 (m, 3H), 7.36–7.29 (m, 2H), 7.18 (m, 1H), 7.11 (t, J=7.8 Hz, 1H), 6.89 (d, J=7.7 Hz, 1H), 3.70 (m, 2H), 3.29 (d, J=11.2 Hz, 2H), 2.73 (m, 2H), 2.59 (m, 1H), 2.24 (m, 2H), 2.12 (s, 3H), 2.05–1.88 (m, 6H); HR-MS (EI): Calcd for $C_{34}H_{34}N_4O_3$ $[M]^+$ 546.2631, Found 546.2609.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(pyridin-4-yl)naphtho[1,2-*b*]furan-2-carboxamide (9n)** The title compound (100 mg, 45%) was prepared in the same manner as described for **10b** using 5-(pyridine-4-yl)-naphtho[1,2-*b*]furan-2-carboxylic acid (120 mg, 0.41 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.75 (d, J=3.9 Hz, 2H), 8.47 (d, J=7.1 Hz, 1H), 7.98 (s, 1H), 7.86 (d, J=7.1 Hz, 1H), 7.63 (d, J=4.7 Hz, 2H), 7.49–7.57 (m, 2H), 7.45 (d, J=3.9 Hz, 2H), 7.37 (d, J=7.9 Hz, 1H), 7.33 (s, 1H), 7.24–7.30 (m, 1H), 7.13 (dd, J=7.9, 7.9 Hz, 1H), 6.89 (d, J=7.9 Hz, 1H), 3.65–3.73 (m, 2H), 3.26–3.35 (m, 2H), 2.72–2.80 (m, 2H), 2.55–2.62 (m, 1H), 2.28–2.48 (m, 2H), 2.16 (s, 3H), 2.00–2.20 (m, 4H), 1.86–2.00 (m, 2H); HR-MS (EI): calcd for $C_{34}H_{34}N_4O_3$ $[M]^+$ 546.2631, Found 546.2632.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(furan-3-yl)naphtho[1,2-*b*]furan-2-carboxamide (9o)** The

title compound (128 mg, 63%) was prepared in the same manner as described for **10b** using 5-(furan-3-yl)naphtho[1,2-*b*]furan-2-carboxylic acid (106 mg, 0.38 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.42 (d, J=8.0 Hz, 1H), 8.15 (d, J=7.2 Hz, 1H), 8.08 (m, 1H), 7.70–7.56 (m, 5H), 7.54–7.40 (m, 4H), 7.12 (t, J=7.8 Hz, 1H), 6.85 (d, J=7.4 Hz, 1H), 6.68 (d, J=7.4 Hz, 1H), 3.66 (m, 2H), 3.27 (d, J=10.4 Hz, 2H), 2.74 (m, 2H), 2.54 (m, 1H), 2.25 (m, 2H), 2.14 (s, 3H), 2.08–1.82 (m, 6H); HR-MS (EI): Calcd for $C_{33}H_{33}N_3O_4$ $[M]^+$ 535.2471, Found 535.2474.

***N*-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-5-(thiophen-3-yl)naphtho[1,2-*b*]furan-2-carboxamide (9p)** The title compound (148 mg, 79%) was prepared in the same manner as described for **10b** using 5-(thiophen-3-yl)-naphtho[1,2-*b*]furan-2-carboxylic acid (100 mg, 0.34 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.35 (d, J=8.1 Hz, 1H), 8.04 (d, J=8.1 Hz, 1H), 7.96 (s, 1H), 7.62–7.68 (m, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 7.34–7.52 (m, 5H), 7.22–7.29 (m, 2H), 7.09 (dd, J=8.0, 7.6 Hz, 1H), 6.84 (d, J=7.6 Hz, 1H), 3.57–3.69 (m, 2H), 3.06–3.18 (m, 2H), 2.53–2.64 (m, 2H), 2.42–2.55 (m, 1H), 2.11 (s, 3H), 2.00–2.12 (m, 2H), 1.76–1.93 (m, 6H); HR-MS (EI): Calcd for $C_{33}H_{33}N_3O_3S$ $[M]^+$ 551.2243, Found 551.2243.

***N*-{2-[4-(3-Acetamidophenyl)piperidin-1-yl]ethyl}-5-(4-chlorophenyl)naphtho[1,2-*b*]furan-2-carboxamide (10)** The title compound (138 mg, 79%) was prepared in the same manner as described for **10b** using 5-(4-chlorophenyl)-naphtho[1,2-*b*]furan-2-carboxylic acid (100 mg, 0.31 mmol). ^{1}H-NMR(300 MHz, $CDCl_3$) δ: 8.46 (d, J=8.0 Hz, 1H), 7.81 (m, 3H), 7.70–7.49 (m, 6H), 7.47 (br s, 1H), 7.34 (m, 1H), 7.26 (m, 3H), 7.04 (d, J=6.9 Hz, 1H), 3.67 (m, 2H), 3.14 (d, J=11.6 Hz, 2H), 2.74 (t, J=5.2 Hz, 2H), 2.60 (m, 1H), 2.25 (m, 2H), 2.16 (s, 3H), 1.97 (m, 4H); HR-MS (EI): Calcd for $C_{34}H_{32}ClN_3O_3$ $[M]^+$ 565.2132, Found 565.2137.

***N*-{4-[4-(3-Acetamidophenyl)piperidin-1-yl]butyl}-5-(4-chlorophenyl)naphtho[1,2-*b*]furan-2-carboxamide (11)** The title compound (136 mg, 79%) was prepared in the same manner as described for **10b** using 5-(4-chlorophenyl)-naphtho[1,2-*b*]furan-2-carboxylic acid (100 mg, 0.31 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.57 (d, J=8.0 Hz, 1H), 8.31 (s, 1H), 7.82 (m, 2H), 7.66 (s, 1H), 7.64–7.56 (m, 2H), 7.53 (s, 1H), 7.49–7.41 (m, 3H), 7.41–7.33 (m, 2H), 7.31 (br s, 1H), 7.02 (t, J=7.9 Hz, 1H), 6.89 (d, J=7.9 Hz, 1H), 3.61 (m, 2H), 3.55 (m, 2H), 3.02 (m, 2H), 2.75–2.56 (m, 3H), 2.31 (m, 2H), 2.22 (s, 3H), 2.02 (m, 2H), 1.95–1.76 (m, 4H); HR-MS (EI): Calcd for $C_{36}H_{36}ClN_3O_3$ $[M]^+$ 593.2445, Found 593.2435.

***N*-{5-[4-(3-Acetamidophenyl)piperidin-1-yl]pentyl}-5-(4-chlorophenyl)naphtho[1,2-*b*]furan-2-carboxamide (12)** The title compound (38 mg, 25%) was prepared in the same manner as described for **10b** using 5-(4-chlorophenyl)-naphtho[1,2-*b*]furan-2-carboxylic acid (80 mg, 0.25 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44 (d, J=8.2 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 7.59–7.70 (m, 3H), 7.61 (s, 1H), 7.58 (s, 1H), 7.33–7.54 (m, 5H), 7.22 (d, J=8.0, 7.6 Hz, 1H), 6.91–7.00 (m, 2H), 6.95 (d, J=7.6 Hz, 1H), 3.51–3.64 (m, 2H), 3.08–3.23 (m, 2H), 2.86–2.99 (m, 2H), 2.42–2.60 (m, 3H), 2.18 (s, 3H), 2.12–2.22 (m, 2H), 1.61–1.91 (m, 6H), 1.40–1.54 (m, 2H); HR-MS (EI): Calcd for $C_{37}H_{38}ClN_3O_3$ $[M]^+$ 607.2602, Found 607.2603.

***N*-{2-[4-(3-Acetamidophenyl)piperidin-1-yl]ethyl}-5-(4-cyanophenyl)naphtho[1,2-*b*]furan-2-carboxamide (10a)** The title compound (90 mg, 50%) was prepared in the same manner as described for **10b** using 5-(4-cyanophenyl)-naphtho[1,2-*b*]furan-2-carboxylic acid (100 mg, 0.32 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.46 (d, J=8.0 Hz, 1H), 7.81 (m, 3H), 7.70–7.49 (m, 6H), 7.47 (br s, 1H), 7.34 (m, 1H), 7.26 (m, 3H), 7.04 (d, J=6.9 Hz, 1H), 3.67 (m, 2H), 3.14 (d, J=11.6 Hz, 2H), 2.74 (t, J=5.2 Hz, 2H), 2.60 (m, 1H), 2.25 (m, 2H), 2.16 (s, 3H), 1.97 (m, 4H); HR-MS (EI): Calcd for $C_{35}H_{32}N_4O_3$ $[M]^+$ 556.2474, Found 556.2459.

MCH Receptor Binding Assay Receptor binding assays with europium-labeled MCH (Eu-MCH) were performed in 96-well AcroWell™ plates. MCH labeled with europium at the N-1 position was supplied by 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 *N*-(2-hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid (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 measuring the presence of 0.5 μM unlabeled MCH (human). After incubation at room temperature for 90 min, the mixtures were filtered in a 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). 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 subjected in a multilabel counter to 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 determined in an 8-dose response study to generate the compound concentration required to yield 50% displacement.

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