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Discovery, synthesis, and structure–activity relationship of 6-aminomethyl-7,8-dihydronaphthalenes as human melanin-concentrating hormone receptor 1 antagonists

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ABSTRACT

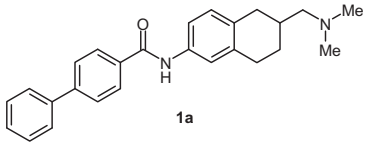
Human melanin-concentrating hormone receptor 1 (hMCHR1) antagonists are promising targets for obesity treatment. We identified the tetrahydronaphthalene derivative **1a** with modest binding affinity for hMCHR1 by screening an in-house G protein-coupled receptor (GPCR) ligand library. We synthesized a series of 6-aminomethyl-5,6,7,8-tetrahydronaphthalenes and evaluated their activity as hMCHR1 antagonists. Modification of the biphenylcarbonylamino group revealed that the biphenyl moiety played a crucial role in the interaction of the antagonist with the receptor. The stereoselective effect of the chiral center on binding affinity generated the novel 6-aminomethyl-7,8-dihydronaphthalene scaffold without a chiral center. Optimization of the amino group led to the identification of a potent antagonist **2s** (4′-fluoro-*N*-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide), which significantly inhibited the nocturnal food intake in rats after oral administration. Pharmacokinetic analysis confirmed that **2s** had good oral bioavailability and brain penetrance. This antagonist appears to be a viable lead compound that can be used to develop a promising therapy for obesity.

1. Introduction

Melanin-concentrating hormone (MCH) is a cyclic hypothalamic neuropeptide which was originally isolated by Kawauchi et al. from salmon pituitary as a hormone responsible for color changes in response to environmental background.[1] Human MCH is a cyclic 19-amino-acid peptide and is identical to rat MCH.[2] MCH is present in neurons of both central[3] and peripheral nervous systems[4,5] and is predominantly expressed in lateral hypothalamus and zona incerta.[3] Both these regions have been implicated in various physiological functions including feeding and energy balance.[6] Among its potential functions, regulatory roles of MCH in feeding have been studied in the past decade. Intracerebroventricular administration of MCH promotes feeding behavior in rats. The mRNA levels of MCH in lateral hypothalamus are upregulated during fasting and in obese (*ob*/*ob*) mice.[7] Mice lacking the MCH peptide gene are lean because of hypophagia and show an increase in the metabolic rate.[8] In contrast, transgenic mice overexpressing MCH in lateral hypothalamus are obese and exhibit insulin resistance.[9]

Shimomura et al.[10] and 4 other groups[11–14] used "orphan receptor strategy" and identified the orphan G protein-coupled receptor (GPCR) SLC-1 as a human MCH receptor 1 (hMCHR1).[15] MCH binds the receptor expressed as 7-transmembrane (7TM) domain receptor at nanomolar affinity and its mRNA was expressed in specific brain regions implicated in feeding behavior, such as the hypothalamus and hippocampus.[11] Further, MCH receptor expressed in the central nervous system[15] is up-regulated in *ob*/*ob* mice and by fasting condition.[16] Accordingly, hMCHR1 antagonists should be effective in inhibiting food intake, thereby providing a novel therapy for treating obesity.

Through a screening of our in-house GPCR ligand library, we identified the tetrahydronaphthalene derivative **1a** (Fig. 1) with



1a

Figure 1. Chemical structure of hit compound **1a**.

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modest binding affinity for hMCHR1 as one of the potential leads. Our pharmacokinetic study showed that **1a** exhibits good oral bioavailability; hence, we started investigation of potential hMCHR1 antagonists as anti-obesity agents. We reported, for the first time, the discovery of the small molecule hMCHR1 antagonist, T-226296 ((−)-enantiomer of **1h**), which has been identified in our medicinal chemistry program.[17] In the present report, we describe the details of our initial medicinal chemistry efforts starting from **1a**, focusing especially on a distal phenyl ring, a core scaffold and an amino group. Moreover, we discuss the validity of a unique docking model for hMCHR1 and antagonists on the basis of the results of a structure–activity relationship (SAR) study.

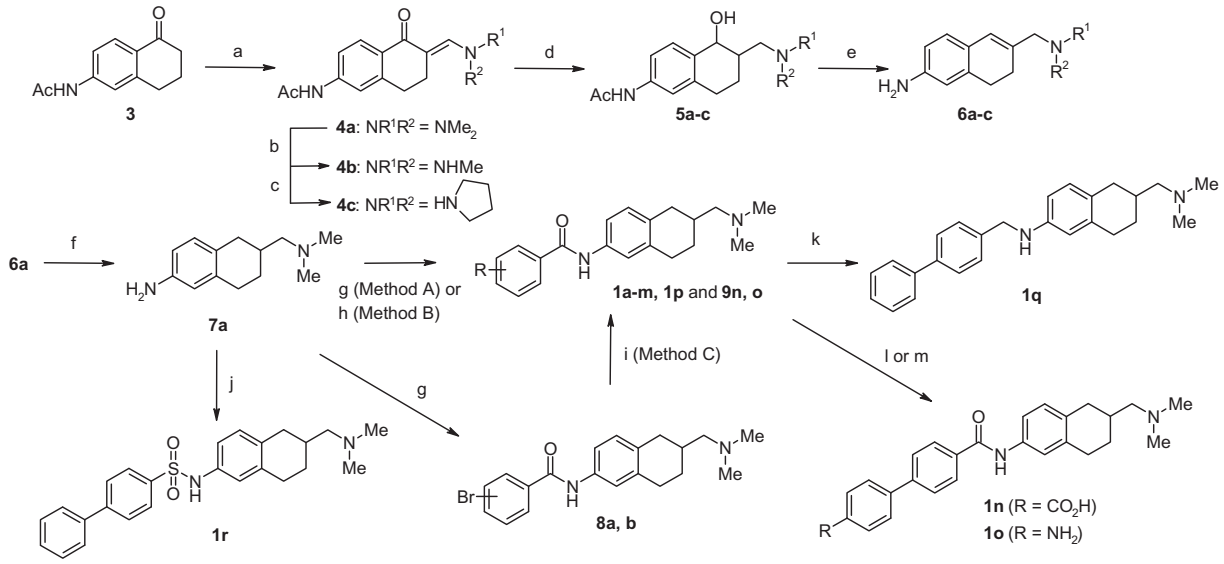
2. Chemistry

Tetrahydronaphthalene derivatives **1** were synthesized starting from tetralone **3** as outlined in Scheme 1. Compound **3**, prepared as described in Section 6, was reacted with dimethylformamide dimethylacetal to give enaminone **4a**. The dimethylamino group in **4a** was replaced by heating the compound with methylamine or pyrrolidine to afford **4b** and **4c**, respectively. Stepwise reduction of **4a–c** using $NaBH(OAc)_3$ and subsequently with $NaBH_4$ followed by heating with concentrated hydrochloric acid gave 7,8-dihydro-2-naphthalenamine **6a–c**. Compound **6a** was hydrogenated over 10% Pd/C to afford 5,6,7,8-tetrahydro-2-naphthalenamine **7a** as a racemic mixture.

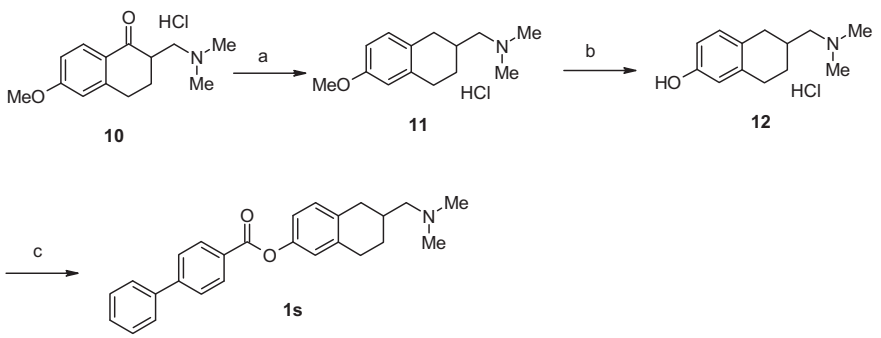
The intermediate **7a** was converted to **1** and **9** by treatment with an acid chloride (Method A) or carboxylic acid in the presence of peptide coupling reagents (Method B). In another Method C, **1** and **9** were obtained by Suzuki coupling of boronic acid and bromides **8a** and **8b**, which were prepared by the reaction of **7a** and bromobenzoyl chloride. Compounds **1n** and **1o**, containing a carboxylate or amino residue, were synthesized by hydrolysis of the corresponding ester **9n** or amide **9o**, respectively. The sulfonamide **1r** was also derived from **7a**. Reduction of the oxo group in **1a** with borane afforded **1q**. The enantiomers of **1g** were separated by standard preparative chiral high-performance liquid chromatography (HPLC).

The synthetic route to ester **1s** is shown in Scheme 2. Stepwise reductive deoxygenation of the Mannich base **10**[18] and demethylation of the resultant amine **11** gave phenol **12**, which was acylated using 4-biphenylcarboxylic acid to give **1s**.

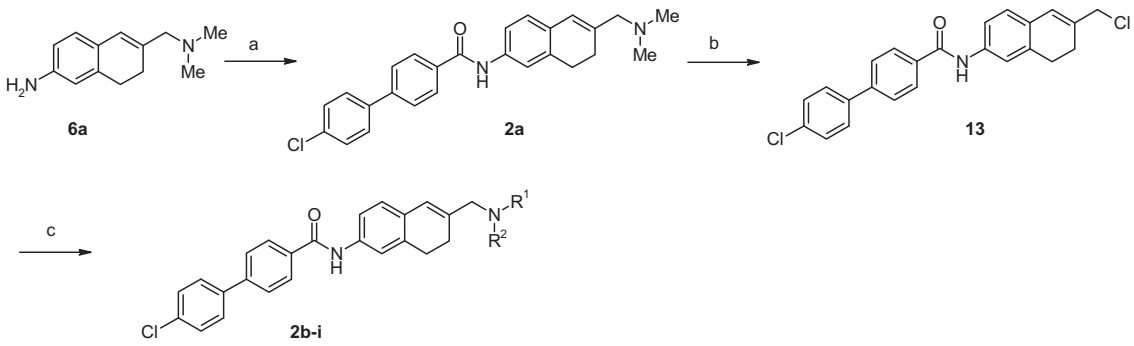
Compounds **2b–i** with various amines were prepared as depicted in Scheme 3. Dihydronaphthalene derivative **2a** was synthesized by condensation of **6a** with 4′-chlorobiphenylcarboxylic acid using peptide coupling reagents (EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide). Acylation of the amino group of **6a** by the acid chloride method was unsuccessful owing to the very rapid



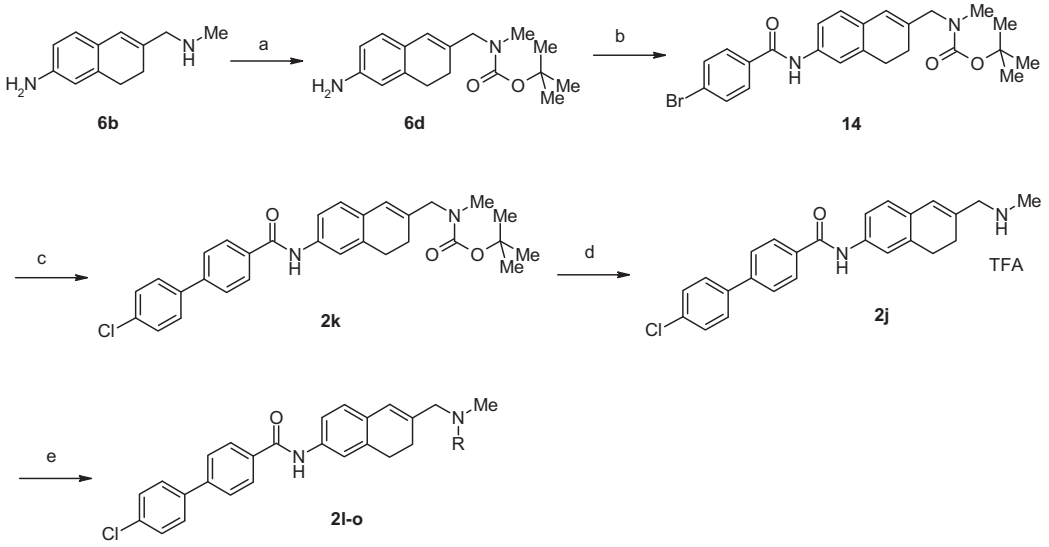
Scheme 1. Reagents and conditions: (a) $Me_2NCH(OMe)_2$, 84%; (b) 40% $MeNH_2$ in MeOH, 82%; (c) pyrrolidine, 88%; (d) $NaBH(OAc)_3$, AcOH, THF then $NaBH_4$, *i*PrOH; (e) concentrated HCl, 64–79%; (f) H_2/Pd–C, 1 M HCl, MeOH, 54%; (g) substituted benzoyl chloride, TEA, THF, 19–89%; (h) bromobenzoic acid, EDC·HCl, DMAP, HOBt, DMF, 36–86%; (i) $Pd(PPh_3)_4$, substituted phenylboronic acid, 2 M Na_2CO_3, DME–THF, 7–92%; (j) biphenyl-4-sulfonyl chloride, TEA, MeCN, 59%; (k) 1 M BH_3 in THF, 36%; (l) 1 M NaOH, EtOH, 95% for **1n**; (m) 1 M NaOH, MeOH–THF, 100% for **1o**.



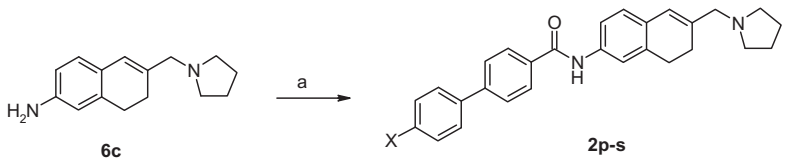
Scheme 2. Reagents and conditions: (a) (i) $NaBH_4$, MeOH, (ii) Pd/C, MeOH, 69%; (b) HBr, 72%; (c) 4-biphenylcarboxylic acid, EDC·HCl, pyridine, 53%.



Scheme 3. Reagents and conditions: (a) 4′-chlorobiphenylcarboxylic acid, EDC·HCl, HOBt, DMF, 54%; (b) ClCOOEt, THF, 82%; (c) R^1R^2NH, *i*-Pr_2NEt, DMF, 8–63%.



Scheme 4. Reagents and conditions: (a) Boc_2O, TEA, MeCN, 87%; (b) 4-bromobenzoyl chloride, TEA, THF, 85%; (c) 4-chlorophenylboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF, 69%; (d) TFA, 97%; (e) various acylating reagents, pyridine, 78–85%.



Scheme 5. Reagents and conditions: (a) substituted biphenylcarboxylic acid, EDC·HCl, HOBt, DMF, 56–67%.

C–N bond cleavage at the C-6 position; we used this feature of the compound for converting the dimethylamino group in **2a**. Reaction of **2a** with ethyl chlorocarbonate[19] afforded chloride **13**, which was treated with various amines to afford a variety of dihydronaphthalene derivatives **2b–i**.

Secondary amine **2j** and various acylated compounds **2l–o** were prepared as shown in Scheme 4. Selective protection of aliphatic amine **6b** with Boc group was successful under ice cooling condition to give **6d**. Acylation of **6d** with 4-bromobenzoyl chloride and the subsequent Suzuki coupling reaction with **14** and 4-chlorophenylboronic acid afforded biphenyl derivative **2k**. Removal of Boc group in **2k** using TFA afforded **2j** as a salt, which was acylated with various acid chlorides or isocyanate to give **2l–o**.

Scheme 5 shows the preparation of **2p–s**, which were synthesized by condensation of **6c** with the corresponding biphenylcarboxylic acids.

3. Homology modeling and automated docking

A homology model of hMCHR1 was constructed on the basis of the crystal structure of bovine rhodopsin (PDB code 1F88) as a structural template by using the Molecular Operating Environment (MOE) 2005.06[20] after truncating a part of the extracellular region (residues 179–200). Primary sequence alignment between hMCHR1 and bovine rhodopsin was performed using MOE. Several different models were prepared by probing the possible rotamer states of the residues Asp123, Tyr272, Tyr273, and Asn294 in the TM ligand binding region. Antagonists of hMCHR1 were docked into hMCHR1 models by using the automated docking program GOLD.[21] Reasonable binding modes were selected on the basis of Gold Score and the SAR results. Further, to take into account the flexibility of side chains, the resulting binding modes were refined through energy minimization using MOE.

4. Results and discussion

We evaluated the binding affinities of the compounds prepared in this study to hMCHR1[10,17] and rat MCHR1 (rMCHR1),[10,17] and expressed the compounds in Chinese hamster ovary (CHO) cells using [^{125}I]-MCH (4–19) as the ligand. Secondary in vitro functional assay (GTPγS) was performed to establish that compounds exhibit hMCHR1 antagonistic activity.[17] At first, the importance of [1,1′-biphenyl]-4-carbonyl moiety of lead compound **1a** was indicated by the following results (Table 1). Removal of the terminal phenyl ring diminished the activity (cf. **1a** vs **1b**). In addition, the position of the terminal phenyl ring was found to be crucial for binding affinity (cf. **1a** vs. **1c** and **1d**).

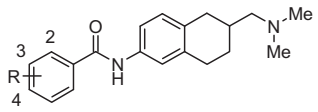
Then, we examined the effects of the substituent (X) on the terminal phenyl ring (Table 2). The *para*-position was the most effective in hMCHR1 substitution (cf. **1g** vs **1e** and **1f**). Among compounds with various substituents X, the compounds **1g** (X = 4′-Cl), **1h** (X = 4′-F), and **1i** (X = 4′-Me) showed potent binding affinities. Introduction of any bulky or polar group like X decreased the activity of these compounds (cf. **1i** vs **1j–m**; **1a** vs **1n–p**). These results suggest that small lipophilic substituent groups such as halogen and methyl at the *para*-position are favorable for the potent activity. SARs of rMCHR1 indicated the same tendency as those of hMCHR1. The docking views of **1g** in hMCHR1 and details of the biphenyl binding pocket are shown in Figure 2. This binding pocket is a hydrophobic field formed by Phe213, Ala216, and Phe217 on TM5 and Tyr273 on TM6. As indicated by the tight SAR of the biphenyl moiety (Tables 1 and 2) and the docking model study, there is a linear biphenyl pocket and a small hydrophobic binding site of the 4′-substituent in hMCHR1.

We examined the effect of replacement of the amide spacer (Z) between the biphenyl group and the tetrahydronaphthalene core (Table 3). Methylenamine derivative **1q** and sulfonamide derivative **1r** attenuated the activity. On the other hand, ester **1s** showed moderate binding affinity with IC_{50} value of the order of 10^{-7} M. These findings are in agreement with the docking model shown in Figure 2, which shows that the carbonyl group forms key interaction with the side chain of Gln127 on TM3 by hydrogen bonding and the interaction with NH group on amide and hMCHR1 is obscure.

We next investigated the contribution of the configuration at C-6 position of the tetrahydronaphthalene ring in receptor binding. Interestingly, the IC_{50} values of (−)- and (+)-**1g** were the same (Table 4). Additionally, the previously reported T-226296[17] ((−)-**1h**) also exhibited equal binding affinity to (+)-**1h**. The details of the binding pocket of the amino-terminal region and one of the 2 enantiomers **1g** and **2a** are shown in Figure 3. This model suggested that the aminomethyl group of (*S*)-**1g** forms equatorial bond at the C-6 position to interact with carboxamide of Asn294 on TM7. The hydrogen bond length between side-chain of Asn294 and the cationic amine may signify the binding affinity. We then designed and synthesized dihydronaphthalene derivative **2a** without a chiral center. The activity of compound **2a** was found to be the same or more potent than that of the corresponding **1g**, as we had expected.

Replacement of the amino group in dihydronaphthalene derivative **2** having 4′-chlorobiphenylamide moiety was then examined (Table 5). Compound **2b** containing an amine of low basicity (pK_a 3.2),[22] such as methoxylmethylamine, was poorly active. Since the basicity of an aniline (**2e**: pK_a 4.8)[22] or a morpholine group (**2f**: pK_a 7.5)[22] was weaker than that of dimethylamine moiety (**2a**: pK_a 9.3),[22] the activity of both compounds decreased

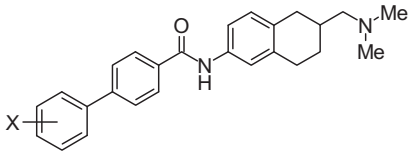
Table 1
In vitro binding affinity and antagonist activity (GTPγS) of tetrahydronaphthlene derivatives **1a–d**



Compd	R	hMCHR1		rMCHR1
		Binding IC_{50}[a] (nM)	GTPγS IC_{50}[a] (nM)	Binding IC_{50}[a] (nM)
1a	4-Ph	76	91	95
1b	H	>10,000	—	—
1c	2-Ph	>10,000	—	—
1d	3-Ph	10,000	—	—

[a] IC_{50} values are calculated with one experiment performed in duplicate.

Table 2
In vitro binding affinity and antagonist activity (GTPγS) of tetrahydronaphthalene derivatives **1e–p**



Compd	X	hMCHR1		rMCHR1
		Binding IC_{50}[a] (nM)	GTPγS IC_{50}[a] (nM)	Binding IC_{50}[a] (nM)
1e	2′-Cl	17	65	23
1f	3′-Cl	140	340	220
1g	4′-Cl	5.3	11	8.0
1h	4′-F	14	43	24
1i	4′-Me	8.4	18	12
1j	4′-Et	19	43	21
1k	4′-Pr	84	220	210
1l	4′-Ph	1300	—	—
1m	4′-OMe	17	37	22
1n	4′-CO_2H	230	—	—
1o	4′-NH_2	350	—	—
1p	4′-CN	380	—	—

[a] IC_{50} values are calculated with one experiment performed in duplicate.

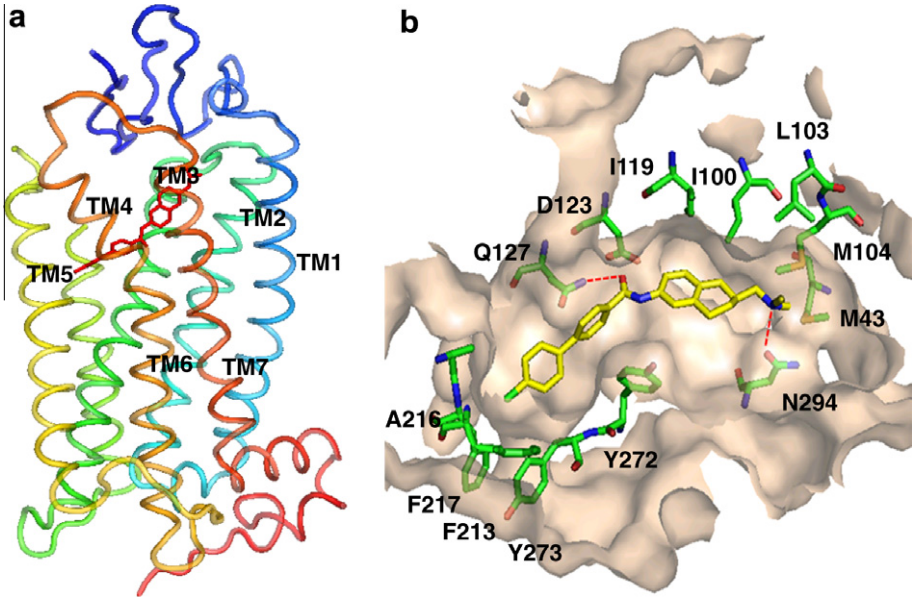
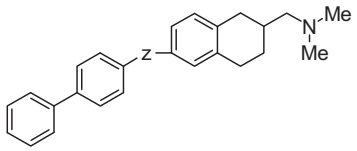


Figure 2. Docking model of *S*-form of **1g** with hMCHR1. (a) Overall structure (colored for helices) and (b) binding pocket of **1g** (carbon atoms in yellow for ligand and in green for receptor, nitrogen atoms in blue, oxygen atoms in red, and chlorine atom in light green).

Table 3
In vitro binding affinity of tetrahydronaphthalene derivatives **1q–s**

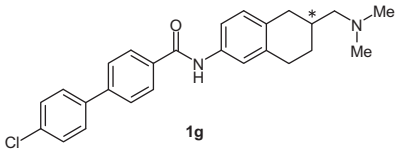


Compd	Z	hMCHR1 Binding IC_{50}[a] (nM)	rMCHR1 Binding IC_{50}[a] (nM)
1q	$-CH_2NH-$	>1000	>1000
1r	$-SO_2NH-$	>1000	>1000
1s	$-CO_2-$	190	280

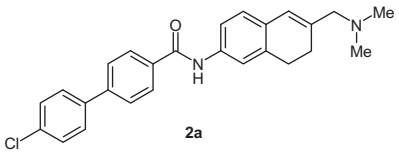
[a] IC_{50} values are calculated with one experiment performed in duplicate.

accordingly. Replacement of dimethylamino (**2a**) with monomethylamino (**2j**) or diethylamino (**2c**) group slightly decreased the binding affinity. On the other hand, cyclization of distal amino groups **2g–i** increased the potent affinities as compared to those of diethyl amine derivative **2c**. The alkylene group in pyrrolidine (**2g**) or piperidine (**2h**) moiety should be fitted in a wide space leading to favorable lipophilic interaction with Leu103 and Met104 on TM2 (Fig. 3). Methylphenethylamino analog **2d** also retained binding affinity with an IC_{50} value of 10^{-9} M order. Replacement of the amino group revealed that amino basicity is a key factor for tight interaction with the carboxamide of Asn 294 and the size of the phenethylmethylamino group is presumably tolerable for hMCHR1 binding pocket. Interestingly, intermediate **2k** with Boc group showed moderate binding affinity, indicating that neutral compounds can be acceptable as hMCHR1 antagonists. We introduced various acylated groups for methylamine of **2j**. Acyl derivatives **2l** and **2m** exhibited IC_{50} value of 10^{-9} M order and showed equal affinity to **2j**. On the other hand, formation of urethane (**2n**) or urea (**2o**) resulted in approximately eightfold drop in activity. The docking model of **2l** and the receptor (Fig. 4) suggests that the interaction between carbonyl moiety in acetyl group and carboxamide of Asn294 should be by means of a hydrogen bond. Moreover, alkyl group in acetyl or propionyl may result in lipophilic interactions in the wide hydrophobic pocket composed by Leu103, Met104, and Pro31, and a hydrophilic group such as a urethane or a urea may be unfavorable for the binding affinity.

Table 4
In vitro binding affinity and antagonist activity (GTPγS) of both enantiomers of **1g** and dihydronaphthalene derivative **2a**



1g



2a

Compd	hMCHR1		rMCHR1
	Binding IC_{50}[a] (nM)	GTPγS IC_{50}[a] (nM)	Binding IC_{50}[a] (nM)
(−)-**1g**	3.5	9.4	5.3
(+)-**1g**	3.4	9.1	6.2
2a	1.8	6.6	2.7

[a] IC_{50} values are calculated with one experiment performed in duplicate.

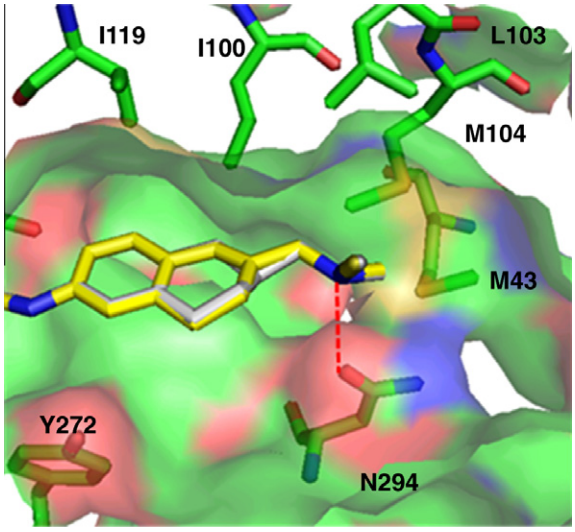


Figure 3. Details of the binding pocket at the amino-terminal region with *S*-form of **1g** (carbon atoms in yellow) and **2a** (carbon atoms in white). The aminomethyl group of each of the enantiomers takes an equatorial form at the C-6 position to interact with the carbonyl group of Asn294 on TM7.

Some researchers[23] reported hMCHR1 antagonists with their docking models and described ionic interaction between carboxylate of Asp123 with protonated amine moiety. We could not obtain reasonable binding modes in our automatic docking study with distance constraints between any atom of ligands and an oxygen atom of carboxylate of Asp123. In addition, carboxylate of a protein, in general, does not directly interact with carbonyl group of a compound by hydrogen bonding. In fact, our proposed docking model is in excellent agreement with hydrogen bond formation with the side chain of Asn294 and other compounds, and no crucial contradictory SAR is observed. Unfortunately, **2l** and **2m** showed poor pharmacokinetic profiles in rat owing to insufficient rat hepatic metabolic stability; however, this finding may open a new insight into drug design. Compound **2g** with the pyrrolidine moiety

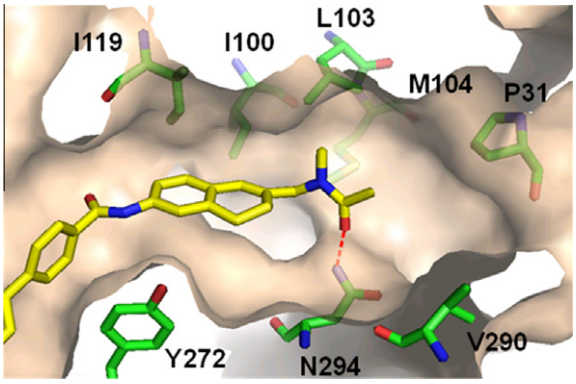


Figure 4. Detail of binding pocket of amino-terminal region with **2l**. Acetyl group forms a hydrogen bond with the side chain of Asn294 and binds in the hydrophobic field composed of Leu103, Met104, and Pro31.

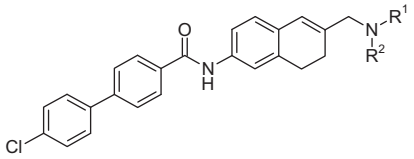
showed potent binding affinity and antagonist activity and was thus selected for further modification.

The optimization results of substituent (X) are summarized in Table 6. The substituents (X) selected on the basis of the results obtained for tetrahydronaphthalenes (Table 2) were introduced to the *para*-position of the terminal phenyl ring of **2g**. Incorporation of methyl (**2q**), methoxy (**2r**), and fluoro (**2s**) groups exhibited potent affinity for hMCHR1 as well as that of a chloro group.

Selected compounds with potent in vitro binding affinity were further tested for their inhibitory effects on spontaneous food intake using KKA^{y} mice. As shown in Table 7, all selected tetrahydro- and dihydronaphthalene derivatives inhibited food intake after oral administration (30 mg/kg). In particular, the compound **2s** exhibited statistically significant inhibitory effect on food intake during 2 h. Moreover, **2s** was effective until 25 h (31% inhibition after 25 h at 30 mg/kg). Compound **2s** was selected for further evaluation.

In vitro GTPγS assay has shown that compounds **2s** act as an antagonist of hMCHR1 (Tables 6) and rMCHR1 (rat GTPγS IC_{50} = 11 nM). Compound **2s** showed a significant suppressing ef-

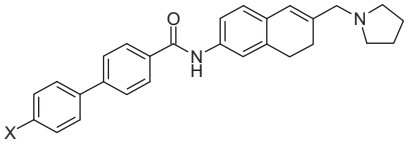
Table 5
In vitro binding affinity and antagonist activity (GTPγS) of dihydronaphthalene derivatives **2b–o**



Compd	NR^1R^2	hMCHR1		rMCHR1
		Binding IC_{50}[a] (nM)	GTPγS IC_{50}[a] (nM)	Binding IC_{50}[a] (nM)
2b	NMe(OMe)	380	–	–
2c	NEt_2	9.9	–	14
2d	$NMe(CH_2)_2Ph$	7.4	33	12
2e	NMePh	11	47	20
2f	4-Morpholinyl	8.4	29	12
2g	1-Pyrrolidinyl	1.4	4.8	2.2
2h	1-Piperidinyl	1.9	5.9	2.5
2i	4-Me-1-piperazinyl	2.8	–	5.3
2j	NHMe	5.5	–	8.5
2k	NMeBoc	140	–	250
2l	NMeCOMe	6.8	–	13
2m	NMeCOEt	4.6	–	6.2
2n	$NMeCO_2Et$	50	–	64
2o	NMeCONHEt	33	–	70

[a] IC_{50} values are calculated with one experiment performed in duplicate.

Table 6
In vitro binding affinity and antagonist activity (GTPγS) of dihydronaphthalene derivatives **2p–s**



Compd	X	hMCHR1		rMCHR1
		Binding IC_{50}[a] (nM)	GTPγS IC_{50}[a] (nM)	Binding IC_{50}[a] (nM)
2p	H	6.4	17	12
2q	Me	1.6	—	2.4
2r	OMe	2.2	—	3.7
2s	F	1.9	7.9	4.1

[a] IC_{50} values are calculated with one experiment performed in duplicate.

Table 7
Effects of selected compounds on food intake in KKA^{y} mice

Compd	Mean food intake inhibition[a] (%) 30 mg/kg
1h	63**
2g	46**
2p	52**
2s	62**

** P <0.01 Dunnett's test.
[a] Food intake during 2 h was measured.

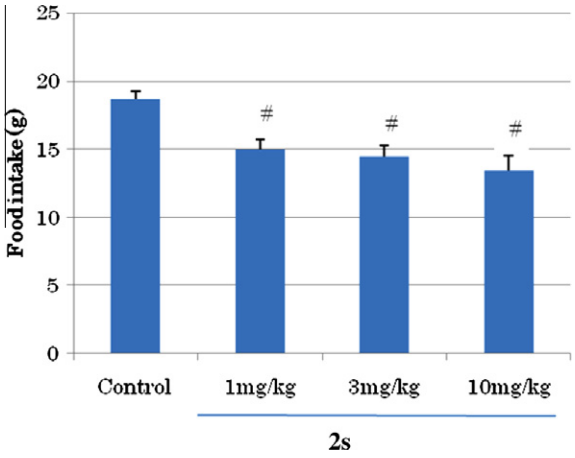


Figure 5. Effect of **2s** on nocturnal food intake in SD rats. The graph shows food intake measured for 12 h. # P <0.025 by Williams test. Each value represents means ± SEM. n = 5.

fect on spontaneous food intake in Sprague–Dawley (SD) rats at night (Fig. 5). The minimum effective dose was 1 mg/kg or less at oral administration. Pharmacokinetic study confirmed that **2s** had good oral bioavailability and excellent brain permeability in SD rats [10 mg/kg, po: BA = 34.1%; C_{max} = 0.15 μg/mL, T_{max} = 8 h, AUC = 2.89 μg h/mL (plasma); C_{max} = 17.3 μg/g, T_{max} = 8 h, AUC = 218 μg h/g (forebrain)], indicating that durable and high brain concentration of **2s** could achieve clear in vivo anorectic effect. Since rMCHR1 antagonists suppressed food intake in rats by blocking physiological function of MCH, hMCHR1 antagonists could be useful for treatment of feeding disorders and obesity in humans.

5. Conclusion

Lead optimization of the tetrahydronaphthalene derivative **1a** led to the discovery of a number of tetrahydro- and dihydronaphthalenes as potent hMCHR1 antagonists. The present investigation revealed that the stereochemistry at C-6 position of the tetrahydronaphthalene ring does not affect hMCHR1 binding affinity. Further, the achiral dihydronaphthalene core was found to be an excellent scaffold compared with the tetrahydronaphthalene nucleus in terms of the binding affinity and difficulty in asymmetric synthesis. A SAR study of the amino group at the C-6 position showed that basicity was important for the potency within this class of antagonists, and cyclic amino groups were found to be more effective for the receptor. Among compounds with potent in vitro affinity, **2s** significantly suppressed nocturnal food intake of SD rats at 1–10 mg/kg after oral administration. Pharmacokinetic study confirmed that **2s** was orally bioavailable and could penetrate the brain of SD rats. In addition to our previous finding,[17] these results indicate that hMCHR1 antagonists could be useful for treatment of feeding disorder and obesity in humans. Further evaluation of this series is ongoing, which includes evaluation of their safety profiles. During the course of this study, we unexpectedly found that compounds **2l** and **2m**, having acylamino group instead of amino group, showed potent binding affinity. Docking study suggested a possibility that their carbonyl group may interact with side chain of Asn294 by hydrogen bonding. This finding may open a new insight into the drug design of hMCHR1 antagonists.

6. Experimental section

Melting points (mp) were determined on a Yanagimoto micro melting point apparatus or Buchi melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) and JEOL JNM-LA300 (300 MHz) NMR spectrometer. Chemical shifts were reported in δ value (ppm) with tetramethylsilane as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; dd, double doublet; br s, broad singlet; m, multiplet. Coupling constants (J) are reported in hertz (Hz). Elemental analyses (C, H, N) were carried out by Takeda Analytical Research Laboratories, Ltd, and the results were within 0.4% of theoretical values. Thin-layer chromatography (TLC) analyses were performed with silica gel 60 F_{254} plate (Merck Art. 5715), alumina 60 F_{254} plate (Type E) and NH TLC plates (Fuji Silysia Chemical Ltd). Chromatographic separations were performed with Merck Aluminium oxide 90 (basic, activity III) and NH silica gel (Fuji Silysia Chemical Ltd). Yields are unoptimized. The purities of all compounds tested in biological systems were assessed as being >95% using elemental analysis.

6.1. *N*-(5-Oxo-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide (3)

To fuming nitric acid (1000 mL) was added portionwise 4-oxo-4-phenylbutanoic acid (200 g, 1.12 mol) at ice-bath cooling and the reaction mixture was stirred for 2 h. The solution was poured into ice. The resulting precipitates were collected and washed with water, ethanol and isopropyl ether. The solid was recrystallized from hot EtOAc to afford 4-(3-nitrophenyl)-4-oxobutanoic acid (157 g, 63%) as a white solid.

A mixture of 4-(3-nitrophenyl)-4-oxobutanoic acid (20.0 g, 87.3 mmol) and 10% Pd/C (4.0 g) in acetic acid (500 mL) was maintained under 0.4 Mpa of hydrogen for 3 h at room temperature. Concentrated HCl (9.0 mL) was added to the solution and the mixture was maintained under 0.4 Mpa of hydrogen for 4 h continuously. The catalyst was filtered off and the filtrate was concen-

trated in vacuo. The residue was washed with EtOAc to afford 4-(3-aminophenyl)butanoic acid hydrochloride (18.4 g, 98%) as a white solid.

Acetic anhydride (12.3 mL, 131 mmol) was added dropwise to a solution of 4-(3-aminophenyl)butanoic acid hydrochloride (23.5 g, 109 mmol) in pyridine (250 mL) and the reaction mixture was stirred for 1 h at room temperature. The solution was concentrated in vacuo and the residue was dissolved with EtOAc. The solution was washed with 4 M HCl and brine. The extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was recrystallized from EtOAc and hexane to give 4-[3-(acetylamino)phenyl]butanoic acid (22.6 g, 94%) as a white solid.

To a suspension of 4-[3-(acetylamino)phenyl]butanoic acid (1.00 g, 4.52 mmol) in nitromethane (20 mL) was added thionyl chloride (361 μL, 4.97 mmol) at ice-bath cooling and the reaction mixture was stirred for 1 h. Aluminum chloride (1.51 g, 11.3 mmol) was added portionwise to this solution at room temperature. The reaction mixture was stirred for 30 min, poured into ice, and extracted with EtOAc. The extracts were washed with brine, 4 M NaOH and brine again. The extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was recrystallized from EtOAc and hexane to give **3** (800 mg, 87%) as a white solid. ^{1}H NMR ($CDCl_3$) δ: 2.07–2.16 (2H, m), 2.21 (3H, s), 2.62 (2H, t, J = 6.0 Hz), 2.94 (2H, t, J = 6.0 Hz), 7.19–7.22 (1H, m), 7.57 (1H, br s), 7.69 (1H, s), 7.97 (1H, d, J = 8.4 Hz).

6.2. 6-Amino-2-[(dimethylamino)methylidene]-3,4-dihydro-1(2*H*)-naphthalenone (4a)

A mixture of dimethylformamide dimethylacetal (100 mL) and **3** (16.5 g, 81.3 mmol) was heated at 100 °C for 18 h under N_2. The mixture was cooled to room temperature and diluted with EtOAc. The resulting precipitates were collected and washed with EtOAc to afford **4a** (17.9 g, 84%) as a yellow solid, mp 207–210 °C (EtOAc). ^{1}H NMR ($CDCl_3$) δ: 2.19 (3H, s), 2.79–2.83 (2H, m), 2.88–2.92 (2H, m), 3.11 (6H, s), 7.14–7.17 (1H, m), 7.68 (1H, s), 7.69 (1H, s), 7.95 (1H, d, J = 8.1 Hz), 7.96 (1H, s).

6.3. 6-Amino-2-[(methylamino)methylidene]-3,4-dihydro-1(2*H*)-naphthalenone (4b)

A mixture of 40% methylamine in MeOH (178 mL) and **4a** (9.00 g, 34.8 mmol) was heated at 60 °C for 2 h under N_2. The mixture was cooled to room temperature, and the resulting precipitates were collected and washed with EtOAc to afford **4b** (7.00 g, 82%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ: 2.05 (3H, s), 2.42–2.47 (2H, m), 2.70–2.74 (2H, m), 2.97 (3H, m), 7.01 (1H, d, J = 12.6 Hz), 7.39–7.44 (1H, m), 7.50–7.53 (1H, m), 7.69–7.74 (1H, m), 7.91–9.77 (1H, m), 10.06 (1H, s).

6.4. 6-Amino-2-[1-pyrrolidinylmethylidene]-3,4-dihydro-1(2*H*)-naphthalenone (4c)

A mixture of pyrrolidine (135 mL) and **4a** (20.0 g, 77.4 mmol) was heated at 110 °C for 2 h under N_2. The mixture was cooled to room temperature and diluted with *i*-Pr_2O. The resulting precipitates were collected and washed with *i*-Pr_2O to afford **4c** (19.3 g, 88%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ: 1.90 (4H, m), 2.18 (3H, s), 2.82 (2H, m), 2.91 (2H, m), 3.58 (4H, m), 7.15 (1H, d, J = 8.4 Hz), 7.66 (1H, s), 7.77 (1H, br s), 7.89 (1H, s), 7.98 (1H, d, J = 8.4 Hz).

6.5. 6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine (6a)

To an ice-cooled solution of **4a** (500 mg, 1.94 mmol) in THF (10 mL) and acetic acid (40 mL) was added $NaBH(OAc)_3$ (615 mg, 2.90 mmol) and the reaction mixture was stirred for 30 min. The mixture was concentrated in vacuo with water-bath cooling and the residue was suspended with isopropanol (40 mL). To this suspension was added $NaBH_4$ (147 mg, 3.88 mmol) at ice-bath cooling and the reaction mixture was stirred for 1 h. The mixture was concentrated in vacuo and the residue was quenched with water. Aqueous 1 M HCl was added to the residue and the solution was washed with EtOAc. Potassium carbonate was added to the aqueous solution and the basic solution was extracted with EtOAc. The extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated in vacuo to give **5a** (350 mg, 69%) as an oil. A solution of **5a** (5.40 g, 20.6 mmol) in concentrated HCl (150 mL) was heated at 100 °C for 6 h and the mixture was cooled to room temperature. The solution was poured into 4 M NaOH and the solution was extracted with EtOAc. The extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was chromatographed on Alumina (basic) eluting with EtOAc to give **6a** (3.80 g, 93%) as a solid. ^{1}H NMR ($CDCl_3$) δ: 2.22 (6H, s), 2.28 (2H, t, J = 8.1 Hz), 2.74 (2H, t, J = 8.1 Hz), 2.94 (2H, s), 3.60 (2H, br s), 6.24 (1H, s), 6.45–6.47 (2H, m), 6.82 (1H, d, J = 8.4 Hz).

The following compounds (**6b** and **6c**) were prepared in the same manner as described for **6a**.

6.6. 6-[(Methylamino)methyl]-7,8-dihydro-2-naphthalenamine (6b)

Yield 90%. ^{1}H NMR ($CDCl_3$) δ: 2.24 (2H, t, J = 7.8 Hz), 2.43 (3H, s), 2.74 (2H, t, J = 7.8 Hz), 3.28 (2H, s), 3.59 (2H, br s), 6.26 (1H, s), 6.44–6.47 (2H, m), 6.82 (1H, d, J = 8.7 Hz).

6.7. 6-(1-Pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine (6c)

Yield 79%. ^{1}H NMR ($CDCl_3$) δ: 1.76–1.80 (4H, m), 2.30 (2H, t, J = 7.8 Hz), 2.47–2.49 (4H, m), 2.74 (2H, t, J = 7.8 Hz), 3.13 (2H, s), 3.59 (2H, br s), 6.26 (1H, s), 6.45–6.47 (2H, m), 6.82 (1H, d, J = 8.7 Hz).

6.8. 6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenamine (7a)

A mixture of **6a** (3.80 g, 18.8 mmol), concentrated HCl (1.60 mL) and dry 10% Pd/C (380 mg) in MeOH (200 mL) was maintained under an atmosphere of hydrogen (balloon) for 4 h. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. Water was added to the residue and the solution was washed with EtOAc. Potassium carbonate was added to the aqueous solution and the basic solution was extracted with EtOAc. The extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated in vacuo to give **7a** (2.06 g, 54%) as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.36 (1H, m), 1.93 (2H, m), 2.20–2.35 (3H, m), 2.22 (6H, s), 2.75 (3H, m), 3.49 (2H, m), 6.47 (2H, m), 6.88 (1H, d, J = 7.8 Hz).

6.9. Method A

6.9.1. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide hydrochloride (1a)

To a solution of **7a** (1.59 g, 7.77 mmol) and triethylamine (1.08 mL, 7.77 mmol) in THF (25 mL) was added portionwise [1,1′-biphenyl]-4-carbonyl chloride (1.68 g, 7.77 mmol) at ice-bath cooling, and the mixture was stirred at room temperature for 16 h. The suspension was diluted with EtOAc and the solution was washed with aqueous K_2CO_3 and brine. The extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was chromatographed on Alumina (basic) eluting with hexane–

EtOAc (1:1) to give a free base of **1a** (2.10 g, 70%) as a white solid, mp 164–166 °C (EtOAc–Hexane). ^{1}H NMR ($CDCl_3$, free base) δ: 1.40 (1H, m), 1.94 (2H, m), 2.25–2.44 (3H, m), 2.83–2.93 (3H, m), 7.08 (1H, d, J = 8.4 Hz), 7.31 (1H, m), 7.39 (4H, m), 7.60–7.69 (4H, m), 7.84 (1H, br s), 7.93 (2H, d, J = 8.4 Hz).

Treatment of the free base with 1 equiv. of 4 M HCl–EtOAc gave **1a** (97%) as a solid, mp >250 °C (MeOH–Et_2O). Anal. Calcd for $C_{26}H_{28}N_2O$·HCl: C, 74.18; H, 6.94; N, 6.65. Found: C, 73.90; H, 6.86; N, 6.63.

The following compounds (**1c**, **1k** and **1p** and **8a**, **b**) were prepared in the same manner as described for **1a**.

6.9.2. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1′-biphenyl]-2-carboxamide hydrochloride (1c)

Yield 58%, mp 196–197 °C (MeOH–EtOAc). ^{1}H NMR (DMSO-d_6) δ: 1.39 (1H, m), 1.99 (1H, m), 2.17 (1H, m), 2.42 (1H, m), 2.78 (6H, s), 2.88 (1H, m), 3.06 (2H, t, J = 5.7 Hz), 3.38 (2H, s), 6.94–7.62 (11H, m), 7.64 (1H, d, J = 1.7 Hz), 10.11 (1H, br s), 10.18 (1H, s). Anal. Calcd for $C_{26}H_{28}N_2O$·HCl·1.1H_2O: C, 70.85; H, 7.13; N, 6.36. Found: C, 70.49; H, 6.77; N, 6.57.

6.9.3. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4′-propyl[1,1′-biphenyl]-4-carboxamide (1k)

Yield 74%, mp 186–188 °C (EtOAc–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 0.98 (3H, t, J = 7.5 Hz), 1.40 (1H, m), 1.69 (2H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25–2.45 (3H, m), 2.64 (2H, t, J = 7.5 Hz), 2.85 (3H, m), 7.08 (1H, d, J = 7.8 Hz), 7.26 (3H, m), 7.46 (1H, s), 7.54 (2H, d, J = 8.1 Hz), 7.67 (2H, d, J = 8.1 Hz), 7.81 (1H, s), 7.91 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{29}H_{34}N_2O$: C, 81.65; H, 8.03; N, 6.57. Found: C, 81.30; H, 7.94; N, 6.40.

6.9.4. 4′-Cyano-*N*-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (1p)

Yield 19%, mp 183–185 °C (EtOAc–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.42 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 2.24–2.46 (3H, m), 2.84–2.95 (3H, m), 7.10 (1H, d, J = 8.4 Hz), 7.30 (2H, m), 7.46 (1H, s), 7.74 (7H, m), 7.98 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{27}H_{27}N_3O$·0.5H_2O: C, 77.48; H, 6.74; N, 10.04. Found: C, 77.82; H, 6.69; N, 10.03.

6.9.5. 3-Bromo-*N*-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (8a)

Yield 43%. ^{1}H NMR (DMSO-d_6) δ: 1.31 (1H, m), 1.89 (2H, m), 2.17 (6H, s), 2.17–2.35 (3H, m), 2.77 (3H, m), 7.04 (1H, d, J = 8.4 Hz), 7.49 (3H, m), 7.79 (1H, d, J = 8.1 Hz), 7.94 (1H, d, J = 7.8 Hz), 8.13 (1H, s), 10.20 (1H, s).

6.9.6. 4-Bromo-*N*-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (8b)

Yield 89%, mp 141–143 °C (EtOAc–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.40 (1H, m), 1.96 (2H, m), 2.26 (6H, s), 2.26–2.48 (3H, m), 2.82–2.96 (3H, m), 7.08 (1H, d, J = 8.1 Hz), 7.28 (1H, m), 7.41 (1H, s), 7.61 (2H, d, J = 8.4 Hz), 7.73 (3H, m).

6.10. Method B

6.10.1. 4′-Chloro-*N*-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (1g)

To a solution of **7a** (831 mg, 4.07 mmol), 4′-chloro[1,1′-biphenyl]-4-carboxylic acid (950 mg, 4.07 mmol), 1-hydroxybenzotriazole (690 mg, 4.47 mmol), 4-dimethylaminopyridine (500 mg, 4.13 mmol) and triethylamine (1.15 mL, 8.26 mmol) in dimethylformamide (40 mL) was added EDC·HCl (1.17 g, 6.10 mmol) at ice-bath cooling, and the mixture was stirred at room temperature for 20 h. The suspension was diluted with EtOAc and THF (1:1) and the solution was washed with aqueous $NaHCO_3$ and brine. The extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was recrystallized from THF and EtOAc to give **1g** (1.30 g, 77%) as a white solid, mp 187–189 °C (THF–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.33–1.50 (1H, m), 1.90–2.10 (2H, m), 2.16–2.47 (9H, m), 2.81–2.99 (3H, m), 7.09 (1H, d, J = 8.0 Hz), 7.31 (1H, d, J = 7.6 Hz), 7.44 (3H, m), 7.56 (2H, d, J = 8.6 Hz), 7.66 (2H, d, J = 8.0 Hz), 7.78 (1H, s), 7.94 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_{26}H_{27}ClN_2O$: C, 74.54; H, 6.50; N, 6.69. Found: C, 74.46; H, 6.34; N, 6.75.

Enantiomeric pure compounds, (−)-**1g** and (+)-**1g** were obtained by chromatographic separation by CHIRALCEL OD (50 mm ID x 500 mm L) eluting with hexane/ethanol = 85:15.

(−)-**1g**: $[\alpha]_D$ = −47.3° (DMSO, c 0.493); >99.9% ee (87% purity containing 13% of **2a**).

(+)-**1g**: $[\alpha]_D$ = +48.4° (DMSO, c 0.499); >99.9% ee (94% purity containing 6% of **2a**).

The following compounds (**1b**, **1h–j** and **1m**) were prepared in the same manner as described for **1g**.

6.10.2. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (1b)

Yield 62%, mp 149–151 °C (EtOAc–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.28–1.60 (1H, m), 1.82–2.10 (2H, m), 2.12–2.50 (9H, m), 2.77–3.00 (3H, m), 7.08 (1H, d, J = 8.1 Hz), 7.20–7.33 (1H, m), 7.40–7.60 (4H, m), 7.70 (1H, s), 7.80–7.92 (2H, m). Anal. Calcd for $C_{20}H_{24}N_2O$·0.7H_2O: C, 74.83; H, 7.98; N, 8.73. Found: C, 74.83; H, 7.83; N, 8.76.

6.10.3. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4′-fluoro[1,1′-biphenyl]-4-carboxamide (1h)

Yield 70%, mp 179–180 °C (THF–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.36–1.52 (1H, m), 1.90–2.08 (2H, m), 2.19–2.48 (9H, m), 2.80–3.05 (3H, m), 7.10 (1H, d, J = 9.4 Hz), 7.19 (2H, d, J = 8.6 Hz), 7.31 (1H, d, J = 8.2 Hz), 7.46 (1H, s), 7.59 (2H, dd, J = 5.2, 8.6 Hz), 7.65 (2H, d, J = 8.6 Hz), 7.67 (1H, s), 7.93 (2H, d, J = 8.6 Hz). Anal. Calcd for $C_{26}H_{27}FN_2O$: C, 77.58; H, 6.76; N, 6.96. Found: C, 77.42; H, 6.30; N, 7.02.

6.10.4. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4′-methyl[1,1′-biphenyl]-4-carboxamide (1i)

Yield 36%, mp 181–182 °C (EtOAc–Hexane). ^{1}H NMR ($CDCl_3$) δ: 1.30–1.51 (1H, m), 1.85–2.06 (2H, m), 2.23–2.47 (12H, m), 2.86–3.00 (3H, m), 7.08 (1H, d, J = 8.4 Hz), 7.26–7.32 (3H, m), 7.46 (1H, s), 7.53 (2H, d, J = 8.4 Hz), 7.68 (2H, d, J = 8.4 Hz), 7.78 (1H, s), 7.92 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.59; N, 7.03. Found: C, 81.26; H, 7.34; N, 7.13.

6.10.5. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4′-ethyl[1,1′-biphenyl]-4-carboxamide (1j)

Yield 76%, mp 137–138 °C (EtOAc–Hexane). ^{1}H NMR ($CDCl_3$) δ: 1.29 (3H, t, J = 7.5 Hz), 1.41–1.51 (1H, m), 1.90–2.06 (2H, m), 2.23–2.47 (6H, m), 2.26 (6H, s), 2.71 (2H, q, J = 7.5 Hz), 2.73–3.01 (3H, m), 7.09 (1H, d, J = 8.4 Hz), 7.31 (3H, m), 7.46 (1H, s), 7.56 (2H, d, J = 8.4 Hz), 7.69 (2H, d, J = 8.4 Hz), 7.77 (1H, s), 7.92 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{28}H_{32}N_2O$·0.1H_2O: C, 81.16; H, 7.83; N, 6.76. Found: C, 80.98; H, 7.88; N, 6.80.

6.10.6. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4′-methoxy[1,1′-biphenyl]-4-carboxamide (1m)

Yield 44%, mp 170–175 °C (EtOAc–Hexane). ^{1}H NMR ($CDCl_3$) δ: 1.40 (1H, m), 1.90 (2H, m), 2.23–2.48 (9H, m), 2.90 (3H, m), 3.87 (3H, s), 7.00 (2H, d, J = 8.8 Hz), 7.09 (1H, d, J = 8.4 Hz), 7.30 (1H, m), 7.47–7.75 (6H, m), 7.91 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{27}H_{30}N_2O_2$·0.1H_2O: C, 77.89; H, 7.31; N, 6.63. Found: C, 77.65; H, 7.40; N, 6.72.

6.11. Method C

6.11.1. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1′-biphenyl]-3-carboxamide hydrochloride (1d)

Tetrakis(triphenylphosphine)palladium(0) (9.0 mg, 7.7 μmol) was added to a solution of **8a** (100 mg, 0.258 mmol), phenylboronic acid (37.8 mg, 0.310 mmol) and 2 M Na_2CO_3 in dimethoxyethane (3 mL) and THF (0.3 mL), and the mixture was heated for 5 h at 90 °C under N_2. The suspension was diluted with EtOAc and the solution was washed with aqueous K_2CO_3 and brine. The extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was chromatographed on Alumina (basic) eluting EtOAc to give a free base of **1d**. Treatment of the free base with 1 equiv. of 4 M HCl–EtOAc gave **1d** (100 mg, 92%) as a solid, mp 145–148 °C (EtOAc–Et_2O). ^{1}H NMR (DMSO-d_6) δ: 1.43 (1H, m), 2.02 (1H, m), 2.21 (1H, m), 2.42 (1H, m), 2.81 (6H, s), 2.88 (3H, m), 3.09 (2H, m), 7.06 (1H, m), 7.42–7.65 (6H, m), 7.78–7.95 (4H, m), 8.22 (1H, s), 10.27 (1H, s). Anal. Calcd for $C_{26}H_{28}N_2O{\cdot}HCl{\cdot}1.7H_2O$: C, 69.16; H, 7.23; N, 6.24. Found: C, 68.93; H, 6.91; N, 6.29.

The following compounds (**1e**, **1f**, **1l**, **9n** and **9o**) were prepared in the same manner as described for **1d**.

6.11.2. 2′-Chloro-*N*-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (1e)

Yield 74%, mp 176–177 °C (THF–Hexane). ^{1}H NMR ($CDCl_3$) δ: 1.30–1.52 (1H, m), 1.90–2.10 (2H, m), 2.23–2.47 (9H, m), 2.80–3.00 (3H, m), 7.09 (1H, d, J = 8.4 Hz), 7.28–7.38 (4H, m), 7.43–7.52 (2H, m), 7.56 (2H, d, J = 8.4 Hz), 7.79 (1H, s), 7.93 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{26}H_{27}ClN_2O$: C, 74.54; H, 6.50; N, 6.69. Found: C, 74.59; H, 6.61; N, 6.65.

6.11.3. 3′-Chloro-*N*-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (1f)

Yield 78%, mp 138–139 °C (THF–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.38–1.52 (1H, m), 1.90–2.10 (2H, m), 2.23–2.47 (9H, m), 2.80–3.00 (3H, m), 7.10 (2H, d, J = 8.0 Hz), 7.29–7.55 (4H, m), 7.61 (1H, s), 7.68 (2H, d, J = 8.4 Hz), 7.75 (1H, s), 7.95 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{26}H_{27}ClN_2O$: C, 74.54; H, 6.50; N, 6.69. Found: C, 74.31; H, 6.46; N, 6.66.

6.11.4. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4′-phenyl[1,1′-biphenyl]-4-carboxamide hydrochloride (1l)

Yield 7%, mp 220 °C (decomp.) (MeOH–Et_2O). ^{1}H NMR (DMSO-d_6, free base) δ: 1.32 (1H, m), 1.93 (2H, m), 2.15 (6H, s), 2.15–2.36 (3H, m), 2.74–2.94 (3H, m), 7.05 (1H, d, J = 8.4 Hz), 7.40–7.55 (5H, m), 7.73–7.91 (8H, m), 8.07 (2H, d, J = 8.4 Hz), 10.14 (1H, s). Anal. Calcd for $C_{32}H_{32}N_2O{\cdot}HCl{\cdot}2H_2O$: C, 72.10; H, 7.00; N, 5.25. Found: C, 71.81; H, 6.57; N, 5.08.

6.11.5. Ethyl 4′-[[[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]amino]-carbonyl] [1,1′-biphenyl]-4-carboxylate (9n)

Yield 68%, mp 156–158 °C (EtOAc–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.42 (4H, m), 1.95 (2H, m), 2.26 (6H, s), 2.26–2.42 (3H, m), 2.89 (3H, m), 4.41 (2H, q, J = 7.2 Hz), 7.09 (1H, d, J = 8.4 Hz), 7.31 (1H, d, J = 8.4 Hz), 7.47 (1H, s), 7.70 (4H, m), 7.80 (1H, s), 7.96 (2H, d, J = 8.4 Hz), 8.14 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{29}H_{32}N_2O_3$: C, 76.29; H, 7.06; N, 6.14. Found: C, 76.25; H, 7.07; N, 6.09.

6.11.6. 4′-[[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]amino]carbonyl][1,1′-biphenyl]-4-carboxylic acid (1n)

To a solution of ethyl 4′-[[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]amino]carbonyl][1,1′-biphenyl]-4-carboxylate (100 mg, 0.219 mmol) in ethanol (3 mL) was added 1 M NaOH (329 μL) at room temperature. The mixture was stirred at 90 °C for 5 h, and then the solution was allowed to cool to room temperature. Aqueous 1 M HCl (329 μL, 0.329 mmol) was added to the solution, and the resulting precipitates were collected and washed with water to give **1n** (88.9 mg, 95%) as a white solid, mp 143 °C (decomp.) (EtOH–H_2O). ^{1}H NMR (DMSO-d_6) δ: 1.34 (1H, m), 1.91 (2H, m), 2.24 (6H, s), 2.24–2.30 (3H, m), 2.81 (3H, m), 7.05 (1H, d, J = 8.4 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.55 (1H, s), 7.89 (4H, m), 8.07 (4H, m), 10.18 (1H, s). Anal. Calcd for $C_{27}H_{28}N_2O_3{\cdot}2H_2O$: C, 69.81; H, 6.94; N, 6.03. Found: C, 69.57; H, 7.01; N, 5.93.

6.11.7. *N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4′-[(trifluoroacetyl)amino] [1,1′-biphenyl]-4-carboxamide (9o)

Yield 80%, mp 235–237 °C (EtOAc–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.41 (1H, m), 2.05 (2H, m), 2.26 (6H, s), 2.26–2.42 (3H, m), 2.89 (3H, m), 7.09 (1H, d, J = 8.4 Hz), 7.29 (2H, m), 7.46 (1H, s), 7.69 (7H, m), 7.94 (2H, d, J = 8.1 Hz). Anal. Calcd for $C_{28}H_{28}F_3N_3O_2$: C, 67.87; H, 5.70; N, 8.48. Found: C, 67.70; H, 5.53; N, 8.42.

6.11.8. 4′-Amino-*N*-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]][1,1′-biphenyl]-4-carboxamide (1o)

To a solution of *N*-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4′-[(trifluoroacetyl)amino][1,1′-biphenyl]-4-carboxamide (850 mg, 1.72 mmol) in MeOH (8 mL) and THF (4 mL) was added 1 M NaOH (1.72 mL) at 50 °C. The mixture was stirred for 16 h, and then concentrated in vacuo. The residue was collected and washed with water to give **1o** (698 mg, 100%) as a solid, mp 148–150 °C (MeOH–H_2O). ^{1}H NMR ($CDCl_3$) δ: 1.31 (1H, m), 1.89 (2H, m), 2.15 (6H, s), 2.15–2.34 (3H, m), 2.83 (3H, m), 5.36 (2H, s), 6.67 (2H, d, J = 8.4 Hz), 7.03 (1H, d, J = 8.1 Hz), 7.48 (4H, m), 7.68 (2H, d, J = 8.1 Hz), 7.96 (2H, d, J = 8.4 Hz), 10.02 (1H, s). Anal. Calcd for $C_{26}H_{29}N_3O{\cdot}1.1H_2O$: C, 74.47; H, 7.50; N, 10.02. Found: C, 74.39; H, 7.41; N, 9.82.

6.11.9. 6-[*N*-(4-Biphenylyl)methyl]amino-2-(*N*,*N*-dimethylamino)methyltetralin (1q)

To a solution of **1a** (0.172 g, free base) in THF (3 mL) was added 1 M borane in THF (2 mL) and the reaction mixture was heated under reflux for 1 h. Water was added to the solution and then 6 M hydrochloric acid was added thereto. After the mixture was stirred at room temperature for 1 h, the reaction mixture was made basic with an aqueous solution of 1 M NaOH and extracted with EtOAc. The organic layer was washed with water, brine, dried and concentrated in vacuo. The residue was purified by alumina column chromatography (EtOAc–Hexane, 1:4) and recrystallized from EtOAc–Hexane to afford **1q** (0.060 g). Mp 106–108 °C (EtOAc–Hexane). ^{1}H NMR ($CDCl_3$) δ: 1.35–1.41 (1H, m), 1.90–2.04 (2H, m), 2.19–2.37 (9H, m), 2.72–2.85 (3H, m), 4.34 (2H, s), 6.41–6.48 (2H, m), 6.91 (1H, d, J = 8.4 Hz), 7.30–7.36 (1H, m), 7.40–7.45 (4H, m), 7.54–7.59 (4H, m). Anal. Calcd for $C_{26}H_{30}N_2{\cdot}0.3H_2O$: C, 83.07; H, 8.20; N, 7.45. Found: C, 83.01; H, 8.18; N, 7.41.

6.11.10. *N*-{6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydronaphthalen-2-yl}biphenyl-4-sulfonamide hydrochloride (1r)

4-Biphenylsulfonyl chloride (200 mg, 0.79 mmol) was added to a mixture of **7a** (200 mg, 0.72 mmol) and TEA (0.401 mL, 2.88 mmol) in CH_3CN (30 mL) at ice cooling bath and the mixture was stirred for 3 h at same temperature. Water was added to the reaction mixture and the solution was extracted with EtOAc. The organic layer was washed with water, brine, dried, and then concentrated in vacuo. The residue was purified using alumina column chromatography (hexane–EtOAc, 2:3). To the residue was added

4 M HCl–EtOAc and the salt was solidified by MeOH–*i*-Pr_2O to give **1r** (194 mg, 59%) as an amorphous solid. ^{1}H NMR (DMSO-d_6) δ: 1.32–1.36 (1H, m), 1.91–1.96 (1H, m), 2.11 (1H, m), 2.30–2.39 (1H, m), 2.68–2.79 (4H, m), 2.74 (3H, s), 2.76 (3H, s), 2.90–3.10 (2H, m), 6.86–6.94 (3H, m), 7.40–7.52 (3H, m), 7.70 (1H, d, J = 6.7 Hz), 7.85 (5H, s), 9.92 (1H, br s), 10.23 (1H, s). Anal. Calcd for $C_{25}H_{28}N_2O_2S{\cdot}HCl{\cdot}1.8H_2O$: C, 61.35; H, 6.51; N, 5.73. Found: C, 61.19; H, 6.82; N, 6.13.

6.11.11. 2-(*N*,*N*-Dimethylamino)methyl-6-methoxytetralin hydrochloride (11)

Aqueous solution of 1 M NaOH was added to 2-(*N*,*N*-dimethylamino)methyl-6-methoxy-1-tetralone hydrochloride[18] (3.08 g, 11.4 mmol) to convert a free form, which was extracted with EtOAc. The extract was dried, and then concentrated. Sodium borohydride (0.97 g, 25.6 mmol) was added to a MeOH solution (30 mL) of the resulting residue under ice cooling bath, and the mixture was then stirred at room temperature for 2 h. Water was added to the reaction mixture. The solution was concentrated in vacuo to remove MeOH, and then extracted with EtOAc. The organic layer was washed with brine, dried and concentrated in vacuo. Concentrated hydrochloric acid (2.4 g) and 10% palladium–carbon (0.3 g) were added to an ethanol solution (30 mL) of the resulting residue and the mixture was stirred under atmospheric hydrogen pressure at room temperature for 8 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue was recrystallized from MeOH–EtOAc to afford **11** (2.02 g, 69%): ^{1}H NMR ($CDCl_3$) δ: 1.22–1.49 (1H, m), 1.80–2.04 (2H, m), 2.12–2.44 (3H, m), 2.24 (6H, s), 2.79–2.98 (3H, m), 3.77 (3H, s), 6.60–6.72 (2H, m), 7.01 (1H, d, J = 8 Hz).

6.11.12. 2-(*N*,*N*-Dimethylamino)methyl-6-hydroxytetralin hydrochloride (12)

The mixture of **11** (0.365 g) and 48% hydrobromic acid (10 mL) was heated under reflux for 3 h. After cooling to room temperature, the mixture was neutralized with an aqueous solution of 1 M NaOH and made basic with a solution of 10% potassium carbonate. The solution was extracted with EtOAc and the organic layer was washed with brine, dried and concentrated in vacuo. The residue was purified by alumina column chromatography (hexane–EtOAc, 2:1) and converted to a hydrochloride salt to afford **12** (0.211 g, 72%). ^{1}H NMR ($CDCl_3$) δ: 1.21–1.50 (2H, m), 1.86–2.03 (2H, m), 2.25–2.44 (2H, m), 2.30 (6H, s), 2.68–2.91 (3H, m), 4.18 (1H, br s), 6.52–6.62 (2H, m), 6.90 (1H, d, J = 8 Hz).

6.11.13. [(*N*,*N*-Dimethylamino)methyl]-6-tetralinyl 4-biphenylylcarboxylate (1s)

4-Biphenylylcarboxylic acid (580 mg, 2.93 mmol) and EDC·HCl (560 mg, 2.92 mmol) were added to pyridine solution (6 mL) of **12** (300 mg, 1.24 mmol) and the mixture was stirred at room temperature for 3 days. Saturated sodium bicarbonate solution and water were added to the reaction mixture and the solution was extracted with EtOAc. The organic layer was washed with water, brine, dried, and then concentrated in vacuo. The residue was purified using alumina column chromatography (hexane–EtOAc, 10:1) and recrystallized from hexane to give **1s** (300 mg, 53%). Mp 85–86 °C. ^{1}H NMR ($CDCl_3$) δ: 1.39–1.49 (1H, m), 1.95–2.04 (2H, m), 2.20–2.48 (9H, m), 2.85–2.99 (3H, m), 6.93 (2H, m), 7.12–7.15 (1H, m), 7.38–7.50 (3H, m), 7.64–7.73 (4H, m), 8.25 (2H, d, J = 8.7 Hz). Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.93; H, 7.10; N, 3.67.

6.11.14. 4′-Chloro-*N*-[6-[-[(*N*,*N*-dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl] [1,1′-bi- phenyl]-4-carboxamide (2a)

A mixture of **6a** (1.00 g, 5.00 mmol), 4-chlorobiphenylcarboxylic acid (2.31 g, 10.0 mmol), EDC·HCl (1.92 g, 10.0 mmol), HOBt (1.35 g, 10.0 mmol) and DMAP (1.22 g, 10.0 mmol) in DMF (25 mL) was stirred at room temperature for 15 h. The mixture was poured into H_2O, and extracted with EtOAc. The extract was washed with 2 M NaOH and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane–THF, 1:10) to give crude crystals, which were recrystallized from EtOAc–Hexane to give **2a** (1.12 g, 54%) as white crystals, mp 204–207 °C. ^{1}H NMR ($CDCl_3$) δ: 2.25 (6H, s), 2.34 (2H, t, J = 7.8 Hz), 2.86 (2H, t, J = 7.8 Hz), 2.99 (2H, s), 6.34 (1H, s), 7.03 (1H, d, J = 8.7 Hz), 7.39 (1H, d, J = 8.1 Hz), 7.45 (2H, d, J = 8.7), 7.48 (1H, s), 7.56 (2H, d, J = 8.4 Hz), 7.67 (2H, d, J = 8.4 Hz), 7.78 (1H, s), 7.94 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{26}H_{25}ClN_2O$: C, 74.90; H, 6.04; N, 6.72. Found: C, 74.64; H, 6.14; N, 6.56.

6.11.15. 4′-Chloro-*N*-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (13)

To a solution of **2a** (0.75 g, 1.80 mmol) in THF (30 mL) was added ethyl chloroformate (0.23 mL) at −78 °C. The mixture was stirred for 30 min at room temperature, and concentrated in vacuo. The residue was recrystallized from THF–hexane to give **13** (0.60 g, 82%) as yellow crystals, mp 179–181 °C. ^{1}H NMR (DMSO-d_6) δ: 2.34 (2H, t, J = 8.1 Hz), 2.82 (2H, t, J = 8.1 Hz), 4.40 (2H, s), 6.61 (1H, s), 7.09 (1H, d, J = 8.1 Hz), 7.54–7.64 (4H, m), 7.79 (2H, d, J = 8.4 Hz), 7.84 (2H, d, J = 8.4 Hz), 8.04 (2H, d, J = 8.4 Hz), 10.28 (1H, s).

6.11.16. 4′-Chloro-*N*-[6-[[*N*-methoxy(*N*-methyl)amino]methyl]-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (2b)

A mixture of **13** (65.0 mg, 0.150 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (60.0 mg, 0.600 mmol) and *N*,*N*-diisopropylethylamine (0.26 mL, 1.5 mmol) in DMF (5 mL) was heated at 120 °C for 2 days. The reaction mixture was concentrated in vacuo, the residue was poured into aqueous $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane–THF, 1:10) to give crude crystals, which were recrystallized from EtOAc–Hexane to give **2b** (41 mg, 63%) as yellow crystals, mp 190–192 °C. ^{1}H NMR ($CDCl_3$) δ: 2.41 (2H, t, J = 8.1 Hz), 2.61 (3H, s), 2.86 (2H, t, J = 8.1 Hz), 3.37 (2H, s), 3.52 (3H, s), 6.39 (1H, s), 7.03 (1H, d J = 8.1 Hz), 7.36 (1H, d, J = 8.1 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.53 (1H, s), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.83 (1H, s), 7.93 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{26}H_{25}ClN_2O_2{\cdot}0.3H_2O$: C, 71.24; H, 5.89; N, 6.39. Found: C, 71.02; H, 5.66; N, 6.39.

The compounds (**2c–2i**) were prepared by the similar procedure for the preparation of **2b**.

6.11.17. 4′-Chloro-*N*-[6-[-[(*N*,*N*-diethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (2c)

Yield 8%, yellow crystals, mp 142–144 °C (EtOAc–Hexane). ^{1}H NMR ($CDCl_3$) δ: 1.07 (6H, t, J = 7.2 Hz), 2.36 (2H, t, J = 5.1 Hz), 2.59 (4H, q, J = 7.2 Hz), 2.85 (2H, t, J = 5.1 Hz), 3.16 (2H, s), 6.38 (1H, s), 7.02 (1H, d, J = 8.4 Hz), 7.43–7.58 (6H, m), 7.67 (2H, d, J = 8.1 Hz), 7.79 (1H, s), 7.94 (2H, d, J = 8.1 Hz). Anal. Calcd for $C_{28}H_{29}ClN_2O$: C, 75.57; H, 6.57; N, 6.30. Found: C, 75.44; H, 6.66; N, 6.26.

6.11.18. 4′-Chloro-*N*-(6-[[methyl(2-phenylethyl)amino]methyl]-7,8-dihydro-2-naphthalenyl)[1,1′-biphenyl]-4-carboxamide (2d)

Yield 30%, yellow crystals, 173–175 °C (THF–hexane). ^{1}H NMR ($CDCl_3$) δ: 2.25–2.32 (2H, m), 2.32 (3H, s), 2.60–2.66 (2H, m), 2.77–2.83 (4H, m), 3.10 (2H, s), 6.32 (1H, s), 6.98 (1H, d, J = 8.1 Hz), 7.18–7.29 (5H, m), 7.35–7.45 (4H, m), 7.54 (2H, d, J = 8.7 Hz), 7.65 (2H, d, J = 8.4 Hz), 7.80 (1H, s), 7.92 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{33}H_{31}ClN_2O$: C, 78.17; H, 6.16; N, 5.52. Found: C, 78.09; H, 6.20; N, 5.62.

6.11.19. 4′-Chloro-*N*-[6-[(methylanilino)methyl]-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (2e)

Yield 20%, yellow crystals, mp 177–179 °C (THF–hexane). ^{1}H NMR ($CDCl_3$) δ: 2.23–2.28 (2H, m), 2.84–2.90 (2H, m), 3.00 (3H, s), 4.00 (2H, s), 6.29 (1H, s), 6.68–6.76 (3H, m), 6.97 (1H, d, J = 8.4 Hz), 7.20–7.25 (2H, m), 7.30–7.33 (1H, m), 7.43 (2H, m), 7.53–7.57 (3H, m), 7.66 (2H, d, J = 8.4 Hz), 7.76 (1H, s), 7.93 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{31}H_{27}ClN_2O$: C, 77.73; H, 5.68; N, 5.85. Found: C, 77.45; H, 5.57; N, 6.04.

6.11.20. 4′-Chloro-*N*-[6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (2f)

Yield 30%, yellow crystals, mp 194–196 °C (THF–hexane). ^{1}H NMR ($CDCl_3$) δ: 2.34 (2H, t, J = 7.8 Hz), 2.45 (4H, m), 2.84 (2H, t, J = 7.8 Hz), 3.06 (2H, s), 3.73 (4H, m), 6.36 (1H, s), 7.02 (1H, d, J = 8.1 Hz), 7.36–7.57 (6H, m), 7.67 (2H, d, J = 8.4 Hz), 7.80 (1H, s), 7.94 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{28}H_{27}ClN_2O_2$: C, 73.27; H, 5.93; N, 6.10. Found: C, 73.30; H, 5.93; N, 5.98.

6.11.21. 4′-Chloro-*N*-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (2g)

Yield 40%, white crystals, mp 185–187 °C (THF–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.83 (4H, m), 2.35 (2H, t, J = 8.1 Hz), 2.52 (4H, m), 2.84 (2H, t, J = 8.1 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.02 (1H, d, J = 8.4 Hz), 7.39–7.56 (6H, m), 7.66 (2H, d, J = 7.5 Hz), 7.82 (1H, s), 7.93 (2H, d, J = 7.5 Hz). Anal. Calcd for $C_{28}H_{27}ClN_2O{\cdot}0.2H_2O$: C, 75.31; H, 6.18; N, 6.27. Found: C, 75.14; H, 5.99; N, 6.35.

6.11.22. 4′-Chloro-*N*-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (2h)

Yield 43%, white crystals, mp 209–211 °C (THF–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.26–1.61 (6H, m), 2.30–2.36 (6H, m), 2.83 (2H, t, J = 8.4 Hz), 3.02 (2H, s), 6.33 (1H, s), 7.01 (1H, d, J = 8.1 Hz), 7.36–7.49 (4H, m), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.81 (1H, s), 7.93 (2H, d, J = 8.1 Hz). Anal. Calcd for $C_{29}H_{29}ClN_2O{\cdot}1.5H_2O$: C, 71.96; H, 6.66; N, 5.79. Found: C, 71.42; H, 6.14; N, 5.64.

6.11.23. 4′-Chloro-*N*-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (2i)

Yield 21%, yellow crystals, mp 220–222 °C (THF–hexane). ^{1}H NMR ($CDCl_3$) δ: 2.30 (3H, s), 2.25–2.50 (10H, m), 2.83 (2H, t, J = 8.1 Hz), 3.07 (2H, s), 6.35 (1H, s), 7.01 (1H, d, J = 8.1 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.51 (1H, s), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.84 (1H, s), 7.93 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{29}H_{30}ClN_3O$: C, 73.79; H, 6.41; N, 8.90. Found: C, 73.73; H, 6.45; N, 8.72.

6.11.24. *tert*-Butyl (6-amino-3,4-dihydronaphthalen-2-yl)methyl(methyl)carbamate (6d)

Di-*tert*-butyl dicarbonate (4.22 mL, 18.4 mmol) in CH_3CN (100 mL) was added dropwise to a solution of **6b** (3.46 g, 18.4 mmol) and triethylamine (2.56 mL, 18.4 mmol) in CH_3CN (50 mL) at 0 °C for 1 h. The reaction mixture was stirred for 3 h at same temperature and concentrated in vacuo and the oil was purified by silica gel column chromatography eluting 25% - 50% EtOAc in hexane to give **6d** (4.62 g, 87%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.15 (2H, t, J = 8.1 Hz), 2.73 (2H, t, J = 8.1 Hz), 2.82 (3H, br s), 3.61 (2H, s), 4.08 (2H, br s), 6.17 (1H, s), 6.46–6.48 (2H, m), 6.82 (1H, d, J = 8.7 Hz).

6.11.25. *tert*-Butyl (6-(4-bromobenzamido)-3,4-dihydronaphthalen-2-yl)methyl(methyl)carbamate (14)

4-Bromobenzoyl chloride (3.51 g, 16.0 mmol) was added dropwise to a solution of **6d** (4.61 g, 16.0 mmol) and TEA (4.45 mL, 32.0 mmol) in THF (70 mL) at 0 °C for 1 h and the reaction mixture was stirred for 2 h at same temperature. The reaction mixture was diluted with EtOAc and the solution was washed with 10% K_2CO_3 and brine, dried over Na_2SO_4. The solution was passed through NH silica gel (eluted with EtOAc) and concentrated in vacuo. The oil was purified by silica gel column chromatography eluting 25% - 50% EtOAc in hexane to give **14** (6.44 g, 85%) as a solid, which was collected and washed with i-Pr_2O. ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.20 (2H, t, J = 8.1 Hz), 2.80–2.85 (5H, m), 3.96 (2H, s), 6.24 (1H, s), 6.99 (1H, d, J = 7.8 Hz), 7.33 (1H, d, J = 9.0 Hz), 7.46 (1H, s), 7.61 (2H, d, J= 8.7 Hz), 7.72 (2H, d, J = 8.7 Hz), 7.80 (1H, s).

The following compound (**2k**) was prepared in the same manner as described for **1d**.

6.11.26. *tert*-Butyl (6-(4′-chlorobiphenyl-4-ylcarboxamido)-3,4-dihydronaphthalen-2-yl)methyl(methyl) carbamate (2k)

Yield 69%, white crystals, mp 191–193 °C (i-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.22 (2H, m), 2.82–2.88 (5H, m), 3.96 (2H, m), 6.25 (1H, s), 7.01 (1H, d, J = 8.1 Hz), 7.38 (1H, d, J = 8.4 Hz), 7.42–7.46 (2H, m), 7.51–7.57 (3H, m), 7.66 (2H, d, J = 8.4 Hz), 7.80 (1H, s), 7.93 (2H, d, J = 8.7 Hz). Anal. Calcd for $C_{30}H_{31}ClN_2O_3$: C, 71.63; H, 6.21; N, 5.57. Found: C, 71.65; H, 6.25; N, 5.52.

6.11.27. 4′-Chloro-*N*-[6-(methylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide 2,2,2-trifluoroacetate (2j)

A solution of **2k** (4.72 g, 9.38 mmol) in TFA (50 mL, 9.38 mmol) was stirred for 30 min and concentrated in vacuo. The residue was solidified with EtOAc and washed with same solvent to afford **2j** (4.70 g, 97%) as a light gray solid. Mp >210 °C (EtOAc, decomposition). ^{1}H NMR (DMSO-d_6) δ: 2.29–2.34 (2H, t, J = 8.1 Hz), 2.59 (3H, s), 2.79–2.93 (2H, t, J = 8.1 Hz), 3.70 (2H, s), 6.58 (1H, s), 7.10 (1H, d, J = 8.4 Hz), 7.54–7.66 (4H, m), 7.78–7.85 (4H, m), 8.05 (2H, d, J = 8.4 Hz), 8.69 (2H, br s), 10.30 (1H, s). Anal. Calcd for $C_{27}H_{24}ClF_3N_2O_3$: C, 62.73; H, 4.68; N, 5.42; Cl, 6.86; F, 11.03. Found: C, 62.51; H, 4.75; N, 5.27.

6.11.28. 4′-Chloro-*N*-(6-((*N*-methylacetamido)methyl)-7,8-dihydronaphthalen-2-yl)biphenyl-4-carboxamide (2l)

To a solution of **2j** (200 mg, 0.39 mmol) in pyridine (2 mL) was added acetic anhydride (0.073 mL, 0.77 mmol) at room temperature. The reaction mixture was stirred for 2 h and product was crystallized. H_2O was added to the mixture and the precipitates were washed with CH_3CN and i-Pr_2O to afford **2l** (135 mg, 78%) as a white powder. Mp 233–235 °C (pyridine–H_2O). ^{1}H NMR (DMSO-d_6) δ: 2.02–2.19 (5H, m), 2.73–2.93 (5H, m), 4.05 (2H, s), 6.20, 6.27 (1H, sx2), 7.02–7.07 (1H, m), 7.54–7.62 (4H, m), 7.78–7.85 (4H, m), 8.05 (2H, d, J = 8.4 Hz), 10.22, 10.23 (1H, sx2). Anal. Calcd for $C_{27}H_{25}ClN_2O_2$: C, 72.88; H, 5.66; N, 6.30; Cl, 7.97. Found: C, 72.84; H, 5.71; N, 6.35.

The following compounds (**2m–o**) was prepared in the same manner as described for **2l**.

6.11.29. 4′-Chloro-*N*-(6-((*N*-methylpropionamido)methyl)-7,8-dihydronaphthalen-2-yl)biphenyl-4-carboxamide (2m)

Yield 80%, white crystals, mp 220–222 °C (EtOAc). ^{1}H NMR (DMSO-d_6) δ: 0.97–1.05 (3H, m), 2.07–2.18 (2H, m), 2.29–2.43 (2H, m), 2.73–2.82 (2H, m), 2.84, 2.92 (3H, sx2), 4.06 (2H, s), 6.18, 6.26 (1H, sx2), 7.01–7.06 (1H, m), 7.54–7.62 (4H, m), 7.78–7.85 (4H, m), 8.05 (2H, d, J = 8.4 Hz), 10.22 (1H, s). Anal. Calcd for $C_{28}H_{27}ClN_2O_2{\cdot}0.1H_2O$: C, 72.98; H, 5.95; N, 6.08; Cl, 7.72. Found: C, 72.83; H, 5.96; N, 6.13.

6.11.30. Ethyl (6-(4′-chlorobiphenyl-4-ylcarboxamido)-3,4-dihydronaphthalen-2-yl)methyl(methyl) carbamate (2n)

Yield 79%, white crystals, mp 181–182 °C (EtOAc–i-Pr_2O). ^{1}H NMR (DMSO-d_6) δ: 1.20 (3H, m), 2.11–2.16 (2H, m), 2.75–2.82 (5H, m), 3.98 (2H, s), 4.07 (2H, q, J = 6.9 Hz), 6.27 (1H, s), 7.04

(1H, d, J = 7.8 Hz), 7.54–7.61 (4H, m), 7.78–7.85 (4H, m), 8.05 (2H, d, J = 8.4 Hz), 10.23 (1H, s). Anal. Calcd for $C_{28}H_{27}ClN_2O_3$: C, 70.80; H, 5.73; N, 5.90. Found: C, 70.84; H, 5.79; N, 5.90.

6.11.31. 4′-Chloro-*N*-(6-((3-ethyl-1-methylureido)methyl)-7,8-dihydronaphthalen-2-yl)biphenyl-4-carboxamide (2o)

Yield 85%, white crystals, mp 247–249 °C (pyridine–H_2O, decomp.). ^{1}H NMR (DMSO-d_6) δ: 1.01 (3H, t, J = 6.9 Hz), 2.07–2.12 (2H, m), 2.72–2.77 (5H, m), 3.02–3.10 (2H, m), 3.94 (2H, s), 6.20 (1H, s), 6.29 (1H, t, J = 5.4 Hz), 7.00 (1H, d, J = 8.1 Hz), 7.53–7.58 (4H, m), 7.77–7.84 (4H, m), 8.04 (2H, d, J = 8.1 Hz), 10.21 (1H, s). Anal. Calcd for $C_{28}H_{28}ClN_3O_2$: C, 70.95; H, 5.95; N, 8.87; Cl, 7.48. Found: C, 70.93; H, 6.00; N, 8.74.

The compounds (**2p–2s**) were prepared from **6c** by the similar procedure for the preparation of **2a**.

6.11.32. *N*-[6-(1-Pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (2p)

Yield 67%, white crystals, mp 176–177 °C (*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.75–1.90 (4H, m), 2.34 (2H, t, J = 8.1 Hz), 2.45–2.60 (4H, m), 2.85 (2H, t, J = 8.1 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.02 (1H, d, J = 8.1 Hz), 7.27–7.55 (5H, m), 7.63 (2H, d, J = 7.3 Hz), 7.70 (2H, d, J = 8.4 Hz), 7.82 (1H, s), 7.94 (2H, d, J = 8.1 Hz). Anal. Calcd for $C_{28}H_{28}N_2O$: C, 82.32; H, 6.91; N, 6.86. Found: C, 81.99; H, 6.69; N, 6.91.

6.11.33. 4′-Methyl-*N*-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide compound (2q)

Yield 56%, yellow crystals, mp 176–177 °C (EtOAc–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.81 (4H, m), 2.36 (2H, t, J = 8.1 Hz), 2.41 (3H, s), 2.52 (4H, m), 2.85 (2H, t, J = 8.1 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.01 (2H, d, J = 8.1 Hz), 7.27–7.39 (3H, m), 7.49 (1H,s), 7.53 (2H, d, J = 8.1 Hz), 7.69 (1H, d, J = 8.4 Hz), 7.81 (1H, s), 7.91 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{29}H_{30}N_2O{\cdot}0.2H_2O$: C, 81.73; H, 7.19; N, 6.57. Found: C, 81.78; H, 7.09; N, 6.65.

6.11.34. 4′-Methoxy-*N*-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (2r)

Yield 57%, pale yellow crystals, mp 187–188 °C (EtOAc–*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.80 (4H, m), 2.36 (2H, t, J = 7.8 Hz), 2.52 (4H, m), 2.86 (2H, t, J = 7.8 Hz), 3.18 (2H, s), 3.87 (3H, s), 6.36 (1H, s), 7.00–7.03 (3H, m), 7.26 (1H, m), 7.38 (1H, d, J = 8.3 Hz), 7.49 (1H, s), 7.58 (2H, d, J = 8.6 Hz), 7.67 (1H, d, J = 8.2 Hz), 7.78 (1H, s), 7.90 (2H, d, J = 8.2 Hz). Anal. Calcd for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.21; H, 6.88; N, 6.35.

6.11.35. 4′-Fluoro-*N*-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1′-biphenyl]-4-carboxamide (2s)

Yield 56%, white crystals, mp 189–192 °C (*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ: 1.75–1.90 (4H, m), 2.35 (2H, t, J = 8.2 Hz), 2.45–2.60 (4H, m), 2.84 (2H, t, J = 8.2 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.01(1H, d, J = 8.1 Hz), 7.16 (2H, t, J = 8.1 Hz), 7.38 (2H, d, J = 8.1 Hz), 7.48 (1H, br s), 7.56–7.61 (1H, m), 7.64 (2H, d, J = 8.4 Hz), 7.83 (1H, s), 7.93 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{28}H_{27}FN_2O$: C, 78.85; H, 6.38; N, 6.57. Found: C, 78.75; H, 6.39; N, 6.45. MS (FAB) m/z = 427 $[M+H]^+$.

6.12. Homology modeling and ligand docking

The homology model of hMCHR1 was constructed using the crystal structure of bovine rhodopsin (PDB code 1F88), which obtained from the RCSB Protein Data Bank, as a structural template.[24] The primary alignment of the amino acid sequences between hMCHR1 and rhodopsin using MOE 2005.06. Construction of hMCHR1 homology models and side chain rotamer search were performed with MOE. Antagonists were docked into the obtained receptor models using the program GOLD. Resulting docking modes with receptor models were subjected energy minimization with MOE. In the energy minimization process, the MMFF94s forcefield was used.

6.13. Human MCHR1 and rat MCHR1 binding assays

CHO cell lines expressing human or rat MCHR1 were established as described before (Shimomura, Y et al. B.B.R.C. **1999**, *261*, 622). Briefly, a cDNA encoding human or rat MCHR1 was cloned from a cDNA library derived from embryonic brain (Gibco BRL) and ligated to an expression vector plasmid, pAKKO-111H. The constructed vector was introduced into the CHO dhfr$^-$ cell lines and the transformed cells were selected in a selection medium (ribonucleic acid and deoxyribonucleic acid free α-MEM containing 10% dialysed FCS).

The cells were dispersed using phosphate-buffered saline (PBS), pH 7.4 containing 0.2 mM EDTA and suspended in a 10 mM sodium carbonate buffer containing 1 mM EDTA, 0.25 mM PMSF, 20 μg/mL of leupeptin, 10 μg/mL of phosphoramidon, and 1 μg/mL pepstatin. Then, the cells were homogenized with a polytron homogenizer and centrifuged at 1000*g* for 10 min. The supernatants were ultracentrifuged twice at 100,000*g* for 60 min. The pellets were then suspended in an assay buffer (25 mM Tris–HCl, pH 7.4 containing 0.1% BSA, 1 mM EDTA, 0.25 mM PMSF, 20 μg/mL of leupeptin, 10 μg/mL of phosphoramidon, and 1 μg/mL pepstatin) and used as membrane fractions.

Binding assays were performed in 96-well plates. The membrane fraction (0.2 μg protein was used for each assay) dissolved in the assay buffer containing 0.0625% CHAPS was incubated with 25 pM [^{125}I]-MCH (4–19) and various concentrations of test compounds at room temperature for 60 min. Nonspecific binding was defined as [^{125}I]-MCH (4–19) binding in the presence of 1 μM MCH (Peptide Research Inc, Japan). The binding reaction was terminated by rapid filtration through GF/C glass filter plates pre-soaked in 0.2% polyethylenimine and 0.02% BSA, followed by washing three times with 300 μL of 50 mM Tris–HCl, pH 7.5. Then the plates were dried for 1 h at 37 °C and Microscint-O scintillation fluid (Packard, USA) was added. The radioactivity retained in the filters was determined with Topcount scintillation counter (Packard, USA). The concentrations of test compounds causing 50% inhibition of the specific binding (IC_{50} value) were derived by fitting the data into a pseudo-Hill equation: $\log[\%SB/(100 - \%SB)] = n[\log(C) - \log(IC_{50})]$, where %SB is a specific binding, n is a pseudo-Hill constant, and C is the concentration of the test compound.

6.14. Human MCHR1 GTPγS binding assay

Membrane fraction (4 μg protein was used for each assay) of hMCHR1 was suspended in the GTPγS assay buffer (50 mM Tris–HCl, pH 7.5 containing 0.1% BSA, 1 mM EDTA, 10 mM $MgCl_2$, 100 mM NaCl, 1 μM GDP, 0.25 mM PMSF, 20 μg/mL of leupeptin, 10 μg/mL of phosphoramidon, and 1 μg/mL pepstatin) and incubated with 0.33 nM [^{35}S]GTPγS (NEN) and 0.3 nM MCH in the presence of the test compound at various concentrations. The mixture was incubated for 60 min at room temperature and then filtered onto GF/C plates. After washing three times with 300 μL of 50 mM Tris–HCl buffer, pH 7.4, the plates were dried for 1 h at 37 °C. The radioactivity retained in the plates was determined using with Topcount scintillation counter (Packard, USA). IC_{50} values were calculated as described above.

6.15. In vivo pharmacological study

All animal experiments were performed in compliance with the Guidelines for the Care and Use of Laboratory Animals of Takeda Pharmaceutical Company.

6.16. KKA^{y} mice study

Female KKA^{y} mice (13-week old: CLEA Japan) were housed individually and given powdery chow diet (CE-2: CLEA Japan). Four days later, body weight and food intake for 1 day were measured. Mice were grouped based on the food intake and the body weight. At 1 h before dark phase, 0.5% methylcellulose solution was administered orally to the control group, and 0.5% methylcellulose suspension of test compounds (30 mg/kg) and vehicle was administered orally to the compound administration groups at 2 mL/kg (5–6 mice per group). The food intake from the initial administration to 2 h and 25 h later was measured. The food intake inhibition rate of each compound administration group to the control group was calculated.

6.17. SD rats study

Male SD rats (10-week-old: Charles River Japan) were housed individually and given chow diet (CE-2: CLEA Japan). Two weeks later, the rats were weighed and food bins were removed from their cages. Simultaneously, 0.5% methylcellulose solution was administered orally to the control group, and 0.5% methylcellulose suspension (1, 3, and 10 mg/kg) of the compound was administered orally to the compound administration group at 2 mL/kg (5 rats per group). Food bin for each rat was inserted at the beginning of the dark phase (1 h after administration). At the end of the dark phase (12 h after presentation of food bin), food intake of each rat was measured.

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