Synthesis and SAR Investigations for Novel Melanin-Concentrating Hormone 1 Receptor (MCH_1) Antagonists Part 2: A Hybrid Strategy Combining Key Fragments of HTS Hits

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A novel series of melanin-concentrating hormone (MCH_1) receptor antagonists based on combining key fragments from the high-throughput screening (HTS) hits compound **2** (**SNAP 7941**) and compound **5** (chlorohaloperidol) are described. The resultant analogs, exemplified by compounds **11a**−**11h**, **15a**−**15h**, and **16a**−**16g**, were evaluated in in vitro and in vivo assays for their potential in treatment of mood disorders. From further SAR investigations, *N*-(3-{1-[4-(3,4-difluorophenoxy)benzyl]-4-piperidinyl}-4-methylphenyl)-2-methylpropanamide (**16g**, SNAP 94847) was identified to be a high affinity and selective ligand for the MCH_1 receptor. Compound **16g** also shows good oral bioavailability (59%) and exhibits a brain/plasma ratio of 2.3 in rats. Compound **16g** showed in vivo inhibition of a centrally induced MCH-induced drinking effect and exhibited a dose-dependent anxiolytic effect in the rat social interaction model.

Introduction

The melanin-concentrating hormone (MCH), a cyclic 19-amino-acid polypeptide,[1,2] has been reported to participate in a variety of processes, including feeding and psychiatric disorders.[3−6] The effects of deletion or overexpression of MCH were summarized in the preceding paper.[7−9,10e] The effects of MCH are mediated through two distinct receptors in the rhodopsin superfamily of 7-transmembrane G-protein-coupled receptors, MCH_1 and MCH_2 receptors. MCH_1 receptor has been isolated in humans and rodents, whereas functional MCH_2 receptor have not been found in rats and mice.[3,4] The effects of small molecule MCH_1 receptor antagonists in rodent feeding models have been described by several groups,[10,11] and the results support the hypothesis that MCH_1 receptor antagonists are potentially useful agents in the treatment of obesity. Compound **1** (T-226296) exhibited >90% suppression of MCH-stimulated food intake at 30 mg/kg in lean rats.[10a] Compound **2** was used as an in vivo tool to demonstrate that an MCH_1 receptor antagonist may be useful for the treatment of depression and anxiety as well as for the management of obesity.[10b] In addition to the confirmation of the anxiolytic results of compound **2** by Millan's group,[12a] Taisho/Arena have recently reported on MCH_1 receptor antagonist **4** (ATC0175, Figure 1), which possess antidepressant and anxiolytic properties.[10d] More recent MCH_1 receptor publications have described additional pharmacological evaluations and use of MCH_1 antagonists in control of food intake and mood disorders.[12b−d]

In the preceding paper,[10e] modifications of the dihydropyrimidinone moiety of a high-throughput screening (HTS) lead compound **2** resulted in compound **6** (SNAP 102739) with improved pharmacokinetic and pharmacodynamic properties. Herein, a hybrid approach to the design and synthesis of a novel series of MCH_1 receptor antagonists is described based on combining key fragments of initial HTS hits, compounds **2** and **5** (chlorohaloperidol[17]) shown in Figure 1.

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Synthetic Chemistry

The synthesis of *N*-(3-piperidin-4-yl-phenyl)-acetamide (**8**) and 3-piperidin-4-yl-phenylamine (**9**) have been described previously.[10e] The *N*-alkylation of compound **8** with various commercially available substituted 4-chloro-1-aryl-butan-1-ones **7a**−**7e** in DMF using potassium carbonate at 80−100 °C afforded the desired compounds **11a**−**11e** (Scheme 1).

The *N*-alkylation of 3-piperidin-4-yl-phenylamine (**9**) with commercially available 4-chloro-1-(4-chloro-phenyl)-butan-1-one (**7b**) in toluene in the presence of K_2CO_3 and 18-crown-6 at 110 °C gave the intermediate, 4-[4-(3-amino-phenyl)-piperidin-1-yl]-1-(4-chloro-phenyl)-butan-1-one (**10**). Compound **10** reacted with a variety of acid chlorides to afford compounds **11f**−**11h**.

The synthesis of compounds **15a**−**15h** and **16a**−**16g** is depicted in Scheme 2. The starting materials, 3-aryloxybenzaldehydes (**12a**−**12h**), are commercially available from Sigma-Aldrich, while the 4-aryloxybenzaldehydes (**13a**−**13e**) are either commercially available from Sigma-Aldrich (**13a**) or prepared via an Ullmann-type reaction (**13b**−**e**).[12] The syntheses of piperidines **14a**−**14c** have been described previously.[10e] The reductive amination of piperidines **14a**−**14c** with appropriately substituted 3-aryloxybenzaldehydes **12a**−**12h** and 4-aryloxybenzaldehydes **13a**−**13e** using sodium triacetoxyborohydride in 1,2-dichloroethane gave the desired products **15a**−**15h** and **16a**−**16g**.[13]

Results and Discussion

Initial high-throughput screening of a GPCR-biased compound collection against human MCH_1 receptor in a functional assay measuring intracellular Ca^{2+} mobilization resulted in the identification of several hits with a common 4-arylpiperidine scaffold. Among them, compound **2** has previously been reported to have high affinity to and selectivity for the melanin-concentrating hormone 1 receptor (MCH_1 receptor).[10b] However, the metabolic stability, in particular, of compound **2** is not ideal.[10j] Compound **5** (chlorohaloperidol)[17] has appropriate CNS druglike properties, displays moderate affinity for the rat MCH_1

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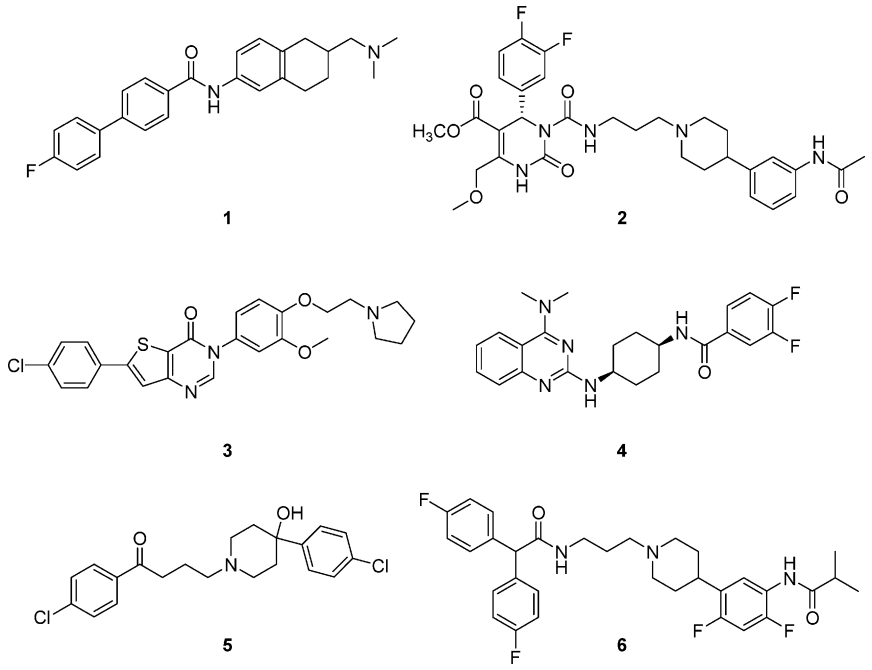
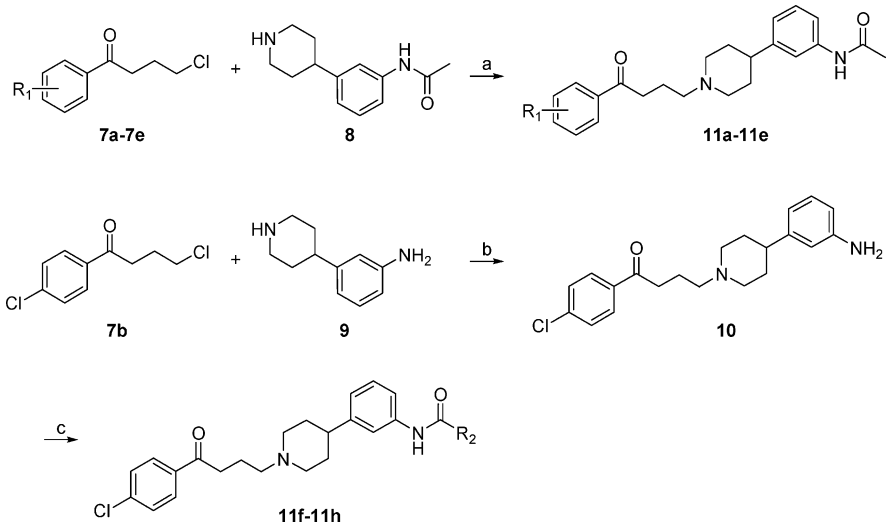


Figure 1. Representative nonpeptide MCH_1 receptor antagonists.

Scheme 1[a]



[a] Reagents and conditions: (a) NaI, K_2CO_3, DMF, 80-100 °C overnight; (b) 18-crown-6, K_2CO_3, toluene, 110 °C, 48 h; (c) R_2COCl, DIPEA, CH_2Cl_2, rt, overnight.

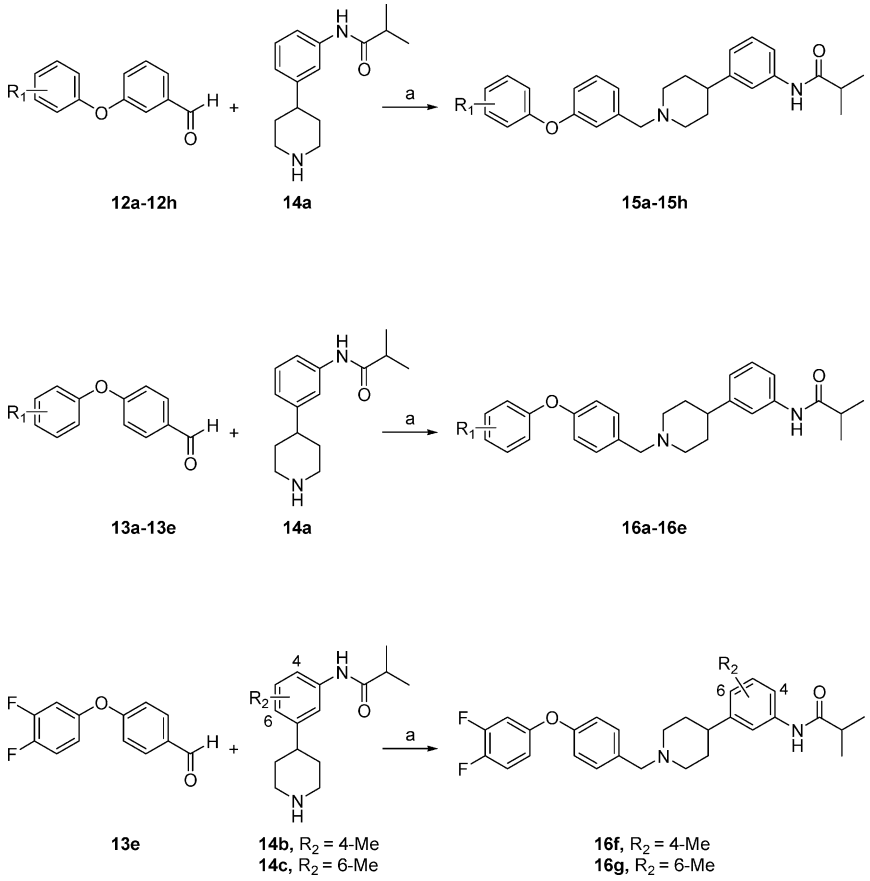
receptor (K_i = 346 nM), but displays cross-reactivities against the hα_{1A} and the hD_2 receptors. This led us to prepare a hybrid series of compounds, **11a**−**11h**, by incorporating the key fragments from compound **2** and compound **5**.

Table 1 summarizes the rat MCH_1 receptor binding affinities and the human α_{1A} and the human D_2 receptor cross-reactivities of the *N*-{3-[1-(4-oxo-4-aryl-butyl)-piperidin-4-yl]-phenyl}-alkylamides **11a**−**11h**. Compounds **11a**, **11c**, and **11d**, containing an electron-neutral or electron-donating group at the para position (R_1 = H, 4-Me, and 4-OPh) of the butyrophenone group, showed MCH_1 receptor affinities similar to chlorohaloperidol (**5**) in the range of 350−490 nM. Compound **11b**, with an electron-withdrawing group at the para position (R_1 = 4-Cl), exhibited a K_i of 70 nM at the MCH_1 receptor with greater than 20-fold selectivity over the human D_2 receptor. The MCH_1 receptor affinity and the hD_2 selectivity of the disubstituted analog **11e** (R_1 = 3,4-dimethyl) is also improved when compared with that shown by compound **5**.

Modifications at the terminal aryl group R_1 and the anilide moiety is shown in Table 1. Compounds with R_2 = cyclohexyl (**11g**) and benzyl (**11h**) substitution at the anilide position showed MCH_1 receptor affinities comparable to compound **11b**. Within compounds **11a**−**11h**, described in Table 1, a dramatic increase in MCH_1 receptor affinity was observed by the introduction of an isopropyl group at the anilide position (**11f**). Compound **11f** showed 5.0 nM affinity at the MCH_1 receptor and 120-fold selectivity over the human D_2 receptor. The initial improvements in MCH_1 receptor binding affinity and the human D_2 selectivity of compounds **11a**−**11f** prompted exploration of the SAR of the *N*-alkyl linker moiety. The 3- and 4-aryloxybenzyl substitutions, shown in compounds **15a**−**15h** and **16a**−**16g**, are particularly effective replacements (Tables 2−5).

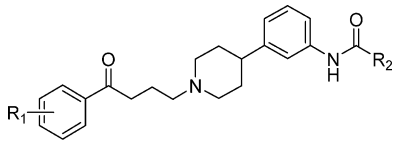
Table 2 displays the MCH_1 receptor and D_2 receptor affinities for 3-aryloxybenzyl-substituted analogs **15a**−**15h**. Within compounds **15a**−**15h**, described in Table 2, compound **15c**, substituted with a bulky 4-*t*-Bu group showed poor MCH_1

Scheme 2[a]



[a] Reagents: (a) $NaBH(OAc)_3$, HOAc,DCM or 1,2-dichloroethane.

Table 1. Rat MCH_1 Receptor, Human α_{1A}, and Human D_2 Binding Affinities for **11a**−**11h**



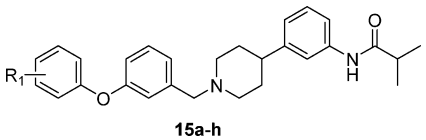
			affinity		
cmpd	R_1	R_2	rMCH_1[a] K_i ± SEM (nM)	hα_{1A}[b] K_i ± SEM (nM)	hD_2[c] K_i ± SEM (nM)
2 (SNAP 7941)	NA	NA	0.25 ± 0.01	40 ± 10	2800 ± 300
5 (chlorohaloperidol)	NA	NA	350 ± 30	150 ± 10	190 ± 10
11a	H	Me	350 ± 30	ND[d]	ND
11b	4-Cl	Me	70 ± 10	ND	1400 ± 100
11c	4-Me	Me	360 ± 30	ND	ND
11d	4-OPh	Me	490 ± 80	ND	ND
11e	3,4-diMe	Me	100 ± 30	ND	6100 ± 200
11f	4-Cl	*i*-Pr	5.0 ± 1.2	ND	610 ± 150
11g	4-Cl	cyclohexyl	200 ± 30	ND	ND
11h	4-Cl	CH_2Ph	84 ± 2	ND	780 ± 50

[a] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant rat MCH_1. Binding assays were performed by incubating membranes isolated from transfected cells with varying concentrations of [^{3}H]-**1** in binding buffer (50 mM Tris, 10 mM $MgCl_2$, 0.16 mM PMSF, 1 mM 1,10-phenanthroline, and 0.2% BSA, pH 7.4) at 25 °C for 90 min, as described previously.[10b] See the Experimental Section for details on functional antagonism data of the compounds assessed using FLIPR calcium mobility assay in cells stably expressing rat MCH_1. [b] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant human α_{1A} adrenoceptor using [^{125}I]HEAT. [c] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant human D_2 dopamine receptor using [^{3}H]spiperone. [d] ND = not determined.

receptor binding affinity, while compounds with small electron-neutral (R_1 = H, **15a**; R_1 = 4-Me, **15b**), electron-donating groups (R_1 = 4-OMe, **15d**), or electron-withdrawing groups (R_1 = 4-Cl, **15e**) showed favorable MCH_1 receptor affinities. The disubstituted analog **15g** (R_1 = 3,4-diCl) exhibited a K_i of 18 nM at the MCH_1 receptor.

Table 3 shows the MCH_1 receptor affinities and α_{1A} receptor selectivities for the 4-aryloxybenzyl analogs **16a**−**16e**. A comparison of compounds **15** and **16**, described in Tables 2 and 3, showed that the 4-substituted compounds **16a**−**16e** showed better MCH_1 receptor affinity profiles than the corresponding 3-aryloxybenzyl analogs **15a**−**15h**. The 3,4-dichloro

Table 2. The SAR for 3-Aryloxybenzyl Analogs **15a**−**15h**

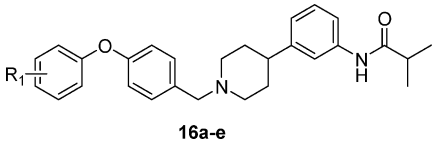


15a-h

		affinity	
cmpd	R_1	$rMCH_1$[a] $K_i \pm$ SEM (nM)	hD_2[b] $K_i \pm$ SEM (nM)
15a	H	28 ± 4	ND[c]
15b	4-Me	31 ± 3	1300 ± 400
15c	4-*t*-Bu	540 ± 140	ND
15d	4-OCH_3	43 ± 1	1000 ± 400
15e	4-Cl	23 ± 1	ND
15f	3-CF_3	65 ± 3	ND
15g	3,4-di-Cl	18 ± 1	ND
15h	3,5-di-Cl	140 ± 20	ND

[a] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant rat MCH_1. Binding assays were performed by incubating membranes isolated from transfected cells with varying concentrations of [^{3}H]-**1** in binding buffer (50 mM Tris, 10 mM $MgCl_2$, 0.16 mM PMSF, 1 mM 1,10-phenanthroline, and 0.2% BSA, pH 7.4) at 25 °C for 90 min, as described previously.[10b] See the Experimental Section for details on functional antagonism data of the compounds assessed using FLIPR calcium mobility assay in cells stably expressing rat MCH_1. [b] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant human D_2 dopamine receptor using [^{3}H]spiperone. [c] ND = not determined.

Table 3. The SAR for 4-Aryloxybenzyl Analogs **16a**−**e**



16a-e

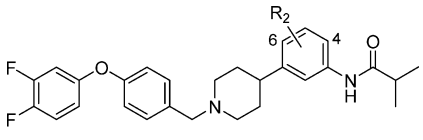
		affinity		
cmpd	R_1	$rMCH_1$[a] $K_i \pm$ SEM (nM)	$h\alpha_{1A}$[b] $K_i \pm$ SEM (nM)	hD_2[c] $K_i \pm$ SEM (nM)
16a	H	10 ± 3	ND[d]	120 ± 20
16b	4-Cl	5.3 ± 0.6	ND	110 ± 30
16c	4-OCH_3	35 ± 3	ND	1400 ± 400
16d	3,4-di-Cl	8.2 ± 1.2	34 000 ± 2100	2900 ± 1700
16e	3,4-di-F	1.8 ± 0.2	200 ± 20	470 ± 70

[a] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant rat MCH_1. Binding assays were performed by incubating membranes isolated from transfected cells with varying concentrations of [^{3}H]-**1** in binding buffer (50 mM Tris, 10 mM $MgCl_2$, 0.16 mM PMSF, 1 mM 1,10-phenanthroline, and 0.2% BSA, pH 7.4) at 25 °C for 90 min, as described previously.[10b] See the Experimental Section for details on functional antagonism data of the compounds assessed using FLIPR calcium mobility assay in cells stably expressing rat MCH_1. [b] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant human α_{1A} adrenoceptor using [^{125}I]HEAT ± 0.1 nM. [c] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant human D_2 dopamine receptor using [^{3}H]spiperone. [d] ND = not determined.

and 3,4-difluoro analogs, **16d** and **16e**, in particular, showed high MCH_1 receptor affinity and human α_{1A} and D_2 receptor selectivity profiles.

The SAR of the 4-arylpiperidine modification, in compounds **16e**−**16g**, is depicted in Table 4. Within this series of compounds, the introduction of a methyl group in the 4-position of the aromatic ring (**16f**) resulted in 13-fold loss of MCH_1 receptor potency. Compound **16g**, with a methyl group in the 6-position, showed a favorable combination of MCH_1 receptor affinity ($K_i = 2.2$ nM) and human α_{1A} receptor (>80-fold) and D_2 (>500-fold) selectivity and was chosen for further in vivo evaluation. Furthermore, compound **16g** did not show any

Table 4. The SAR of the 4-Arylpiperidine Moiety



16e-g

		affinity		
cmpd	R_2	$rMCH_1$[a] $K_i \pm$ SEM (nM)	$h\alpha_{1A}$[b] $K_i \pm$ SEM (nM)	hD_2[c] $K_i \pm$ SEM (nM)
16e	H	1.8 ± 0.2	200 ± 20	470 ± 70
16f	4-Me	27 ± 1	1010 ± 10	400 ± 100
16g (SNAP 94847)	6-Me	2.2 ± 0.4	180 ± 20	7400 ± 2400

[a] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant rat MCH_1. Binding assays were performed by incubating membranes isolated from transfected cells with varying concentrations of [^{3}H]-**1** in binding buffer (50 mM Tris, 10 mM $MgCl_2$, 0.16 mM PMSF, 1 mM 1,10-phenanthroline, and 0.2% BSA, pH 7.4) at 25 °C for 90 min, as described previously.[10b] See the Experimental Section for details on functional antagonism data of the compounds assessed using FLIPR calcium mobility assay in cells stably expressing rat MCH_1. [b] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant human α_{1A} adrenoceptor using [^{125}I]HEAT. [c] Mean values ± standard error of the mean (SEM) determined in binding assays ($n = 3$) to the recombinant human D_2 dopamine receptor using [^{3}H]spiperone.

significant cross-reactivity for anxiety related targets in an in-house panel of 18 receptors as well as a broad CRO cross-reactivity panel.

Pharmacokinetic (PK) properties of compound **16g** in rats are shown in Table 5. Compound **16g** exhibited good bioavailability (59%), low plasma and blood clearances of 4.2 L/hr/kg and 3.3 L/hr/kg, respectively, and the half-life was shown to be 5.2 h in rats. Furthermore, the brain levels in rats at 4 h were determined to be 2.3 times higher than the plasma levels at 10 mg/kg oral dosing.

MCH was recently reported to stimulate water intake independent of food intake.[16] As a measure of centrally mediated MCH_1 receptor antagonism, we examined the effects of compound **16g** on basal and MCH-stimulated water intake in rats. Compound **16g** (10 mg/kg, p.o.) had no effect on basal water consumption measured over 2 h: vehicle-treated (2.0 ± 0.0 mL, $N = 4$); **16g**-treated (2.3 ± 0.25 mL; $N = 4$). A dramatic increase in 2 h water consumption was produced in response to centrally administered MCH peptide (10 μg, icv; Figure 2). MCH-evoked water intake was inhibited significantly by compound **16g** at doses of 1.0, 2.5, and 10 mg/kg. To examine whether this effect was likely to result from selective MCH-1 receptor antagonism or a nonspecific effect on water intake in general, we examined the effect of **16g** on a dose of angiotensin-II (100ng, icv) that evoked a similar degree of water consumption.[18] Water intake in response to angiotensin-II was not affected significantly by **16g**. We conclude, therefore, that significant occupancy of **16g** at central MCH_1 receptors occurs at oral doses of 1 mg/kg and above.

The rat social interaction animal model is used as a predictive tool for anxiolytic activity.[14] The design and procedure for the social interaction test was modified from that previously described by Kennett et al.[15] Animals were treated with either vehicle (20% cyclodextrin), chlordiazepoxide (CDP; 5 mg/kg p.o.), or various concentrations of compound **16g**. In this test, compound **16g**, administered orally 1 h prior to test, produced a significant increase in social interaction time relative to vehicle-treated rats, with a minimally effective dose = 0.3 mg/kg (basal, 58.6 ± 3.4 s; chlordiazepoxide, 99.3 ± 1.4 s; **16g**,

Table 5. The PK Properties of Compound **16g** in Rats

%$F^{a,b}$	$CL_b{}^{a,c}$ (L/hr/kg)	$CL_p{}^{a,d}$ (L/hr/kg)	$T_{1/2}{}^{a,e}$ (hrs)	brain levels^f (ng/g)	$V_{ss}{}^g$ (L/kg)	[brain]/[plasma]^f
59	3.3	4.2	5.2	184 ± 2^h	29	2.3

[a] The rats were dosed at 2 mg/kg po ($n = 2$) and 1 mg/kg iv ($n = 2$). [b] $F\%$ = rat bioavailability. [c] CL_b = blood clearance. [d] CL_p = plasma clearance. [e] $T_{1/2}$ = half-life. [f] In a separate experiment, the rats were dosed at 10 mg/kg po, and the brain and the plasma exposures were determined 4 h after dosing ($n = 2$). [g] V_{ss} = volume of distribution at steady state. [h] The analytical limit of quantitation for compounds **16g** was determined to be ±2 ng/mL for plasma measurements and ±2 ng/g for brain measurements.

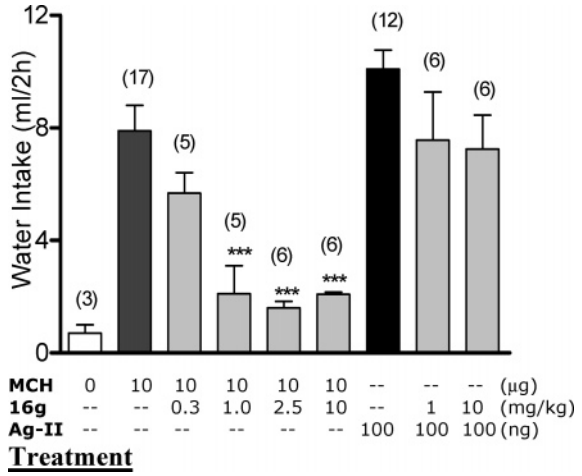


Figure 2. Compound **16g** antagonism of MCH-evoked drinking. MCH (10 ug, icv) produced a robust increase in water consumption in rats over a 2 h period. Compound **16g**, given orally 1 h before MCH, produced a significant reduction in the response to MCH. In contrast, compound **16g** failed to significantly modify drinking in response to angiotensin-II (100ng, icv). ***$p < 0.001$ vs MCH alone (Newman−Keuls post hoc test; *N* values in parentheses).

81.0 ± 4.4 s; $p < 0.05$; Newman−Keuls post hoc test). In the social interaction study, no effect on the locomotor activity was observed upon administration of compound **16g**.

Conclusions

In summary, lead optimization of the initial high-throughput screening based on a strategy of combining key fragments from compounds **2** and **5** led to the identification of *N*-(3-{1-[4-(3,4-difluorophenoxy)benzyl]-4-piperidinyl}-4-methylphenyl)-2-methylpropanamide (**16g**). Compound **16g** is a novel high affinity and highly selective MCH_1 receptor antagonist with good physicochemical properties in rats. Compound **16g** shows high brain-to-plasma exposure levels (2.3-fold) 4 h after oral dosing in rats. Compound **16g** showed inhibition of a centrally induced MCH effect and is orally efficacious in the rat social interaction assay, an acute model of anxiety. Additional studies of compound **16g** and related compounds in other animal models of anxiety and depression will be reported in due course.

Experimental Section

See part 1, the preceding paper for a description of the general synthetic methods.[10e]

General Procedure for the Preparation of the Substituted 4-*N*-(3-{1-[4-(Phenyl)-4-oxobutyl]-4-piperidinyl}phenyl)-acetamides (Method I, 11a−e). A mixture of *N*-[3-(4-piperidinyl)-phenyl]acetamide (1.0 equiv) and an aryl-substituted chlorobutyrophenone (2.0 equiv), K_2CO_3 (5.0 equiv), diisopropylethylamine (3.0 equiv), and tetrabutylammonium iodide (cat. 5−10%) in dioxane (0.5 to 1.0 M) were heated at reflux temperature for 16 h. The reaction mixture was filtered and concentrated in vacuo. The crude product was chromatographed using silica preparative TLC (chloroform/methanol containing 0.5% isopropyl amine) to give the desired product.

***N*-{3-[1-(4-Oxo-4-phenylbutyl)-4-piperidinyl]phenyl}-acetamide (11a).** The desired product was obtained according to method I (16 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−6.80 (m, 10 H), 3.40−2.95 (m, 4 H), 2.85−2.20 (m, 3 H), 2.19 (s, 3 H), 2.15−1.70 (m, 8 H); ESMS *m*/*e* 365.3 $(M + H)^+$; exact mass calcd for $C_{23}H_{29}N_2O_2$ (M + H), 365.2229; found, 365.2231.

***N*-(3-{1-[4-(4-Chlorophenyl)-4-oxobutyl]-4-piperidinyl}phenyl)-acetamide (11b).** The desired product was obtained according to method I (11 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.8 Hz, 2 H), 7.55−7.40 (m, 3 H), 7.35 (m, 2 H), 7.22 (t, J = 8.0 Hz, 1 H), 6.92 (d, J = 8.0 Hz, 1 H), 3.30−3.27 (m, 2 H), 3.09 (t, J = 7.0 Hz, 2 H), 2.76−2.39 (m, 5 H), 2.20 (s, 3 H), 2.17−1.85 (m, 6 H); ESMS *m*/*e* 399.3 $(M + H)^+$; exact mass calcd for $C_{23}H_{28}ClN_2O_2$ (M + H), 399.1839; found, 399.1841.

***N*-(3-{1-[4-(4-Methylphenyl)-4-oxobutyl]-4-piperidinyl}phenyl)-acetamide (11c).** The desired product was obtained according to method I (13 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−6.80 (m, 9 H), 3.10−2.45 (m, 7 H), 2.32 (S, 3 H), 2.02 (s, 3 H), 2.01−1.68 (m, 8 H); ESMS *m*/*e* 379.3 $(M + H)^+$; exact mass calcd for $C_{24}H_{31}N_2O_2$ (M + H), 379.2385; found, 379.2384.

***N*-(3-{1-[4-Oxo-4-(4-phenoxyphenyl)butyl]-4-piperidinyl}-phenyl)acetamide (11d).** The desired product was obtained according to method I (15 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−6.75 (m, 14 H), 3.30−2.80 (m, 4 H), 2.75−2.10 (m, 5 H), 2.03 (s, 3 H), 2.00−1.60 (m, 6 H); ESMS *m*/*e* 457.3 $(M + H)^+$; exact mass calcd for $C_{29}H_{33}N_2O_3$ (M + H), 457.2491; found, 457.2496.

***N*-(3-{1-[4-(3,4-Dimethylphenyl)-4-oxobutyl]-4-piperidinyl}-phenyl)acetamide (11e).** The desired product was obtained according to method I (11 mg, 41%). ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1 H), 7.71 (d, J = 7.6 Hz, 1 H), 7.45 (d, J = 7.2 Hz, 2 H), 7.35 (s, 1 H), 7.26−7.22 (m, 2 H), 6.93 (d, J = 7.6 Hz, 1 H), 3.24−3.21 (m, 2 H), 3.04 (t, J = 7.0 Hz, 2 H), 2.67−2.63 (m, 2 H), 2.59−2.48 (m, 1 H), 2.32 (s, 6 H), 2.30−2.27 (m, 2 H), 2.18 (s, 3 H), 2.14−2.06 (m, 2 H), 2.00−1.80 (m, 4 H); ESMS *m*/*e* 393.3 $(M + H)^+$; exact mass calcd for $C_{25}H_{33}N_2O_2$ (M + H), 393.2542; found, 393.2539.

4-[4-(3-Aminophenyl)-1-piperidinyl]-1-(4-chlorophenyl)-1-butanone (10). A mixture of 3-piperidin-4-yl-phenylamine (2.0 mmol), 4-chloro-1-(4-chloro-phenyl)-butan-1-one (2.4 mmol), potassium carbonate (3.0 mmol), and 18-crown-6 (10 mg) in 5 mL of toluene were heated at 110 °C for 2.5 days. The reaction mixture was concentrated and chromatographed on silica (5% methanol in dichloromethane) to give the desired product (428 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 2 H), 7.44 (d, J = 8.8 Hz, 2 H), 7.08 (t, J = 7.6 Hz, 1 H), 6.60 (d, J = 7.6 Hz, 1 H), 6.53 (m, 2 H), 3.61 (s, 2 H), 3.01−2.97 (m, 4 H), 2.45−2.33 (m, 3 H), 2.05−1.94 (m, 4 H), 1.78−1.75 (m, 2 H), 1.69−1.59 (m, 2 H); ESMS *m*/*e* 357.3 $(M + H)^+$.

General Procedure for the Acylation of 4-[4-(3-Aminophenyl)-1-piperidinyl]-1-(4-chlorophenyl)-1-butanones (Method II, 11f−h). A mixture of 1 equiv of 4-[4-(3-aminophenyl)-1-piperidinyl]-1-(4-chlorophenyl)-1-butanone, 1.5 equiv of an acid chloride, and 5 equiv of diisopropylethylamine in dichloromethane was stirred at room temperature for 2 days. The reaction mixture was applied to a preparative TLC plate and eluted with dichloromethane/methanol (15:1, containing 1% isopropyl amine) to give the desired product.

***N*-(3-{1-[4-(4-Chlorophenyl)-4-oxobutyl]-4-piperidinyl}phenyl)-2-methylpropanamide (11f).** The desired product was obtained according to method II (13 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.93 (d, J = 8.6 Hz, 2 H), 7.45 (d, J = 8.6 Hz, 2 H), 7.39 (d, J = 7.2 Hz, 1 H), 7.32 (m, 2 H), 7.24 (t, J = 7.8 Hz, 1 H), 6.94 (d, J = 8.4 Hz, 1 H), 3.21−3.18 (m, 2 H), 3.05 (t, J = 7.0 Hz, 2 H), 2.64−2.51 (m, 4 H), 2.28−1.86 (m, 8 H), 1.26 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 427.3 $(M + H)^+$; exact mass calcd for $C_{25}H_{32}ClN_2O_2$ (M + H), 427.2152; found, 427.2153.

***N*-(3-{1-[4-(4-Chlorophenyl)-4-oxobutyl]-4-piperidinyl}phenyl)-cyclohexanecarboxamide (11g).** The desired product was obtained according to method II (17 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.4 Hz, 2 H), 7.55−7.19 (m, 6 H), 6.93 (d, J = 7.6 Hz, 1 H), 3.25−3.00 (m, 4 H), 2.65−2.45 (m, 4 H), 2.30−1.50 (m, 18 H); ESMS *m*/*e* 467.3 $(M + H)^+$; exact mass calcd for $C_{28}H_{36}ClN_2O_2$ (M + H), 467.2465; found, 467.2469.

***N*-(3-{1-[4-(4-Chlorophenyl)-4-oxobutyl]-4-piperidinyl}phenyl)-2-phenylacetamide (11h).** The desired product was obtained according to method II (17 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 2 H), 7.46−7.26 (m, 10 H), 7.20 (t, J = 7.6 Hz, 1 H), 6.92 (d, J = 7.6 Hz, 1 H), 3.75 (s, 2 H), 3.15−3.13 (m, 2 H), 3.03 (t, J = 7.0 Hz, 2 H), 2.64−2.46 (m, 3 H), 2.22−1.60 (m, 8 H); ESMS *m*/*e* 475.3 $(M + H)^+$; exact mass calcd for $C_{29}H_{32}ClN_2O_2$ (M + H), 475.2152; found, 475.2166.

General Reductive Amination Procedure for Compounds 15a−h and 16a−g (Method III). A mixture of the aldehyde (1 mol equiv), the piperidine (1 mol equiv), and the acetic acid (1 mol equiv) in 1,2-dichloroethane is stirred with 1.3−1.6 equiv of sodium triacetoxyborohydride under a nitrogen atmosphere at room temperature overnight. The reaction mixture was neutralized with saturated $NaHCO_3$ aqueous solution, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated in vacuo, and purified by preparative TLC using 5% of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired products **15a−h** and **16a−g**.

2-Methyl-*N*-{3-[1-(3-phenoxybenzyl)-4-piperidinyl]phenyl}-propanamide (15a). The desired product was obtained according to method III (81 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1 H), 7.35−7.19 (m, 6 H), 7.11−7.00 (m, 5 H), 6.95 (d, J = 7.6 Hz, 1 H), 6.89 (dd, J = 8.0, 2.4 Hz, 1 H), 3.51 (S, 2 H), 2.97 (d, J = 11.2 Hz, 2 H), 2.53−2.41 (m, 2 H), 2.08−1.99 (m, 2 H), 1.79−1.73 (m, 4 H), 1.23 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 429.2 $(M + H)^+$; exact mass calcd for $C_{28}H_{33}N_2O_2$ (M + H), 429.2542; found, 429.2549.

2-Methyl-*N*-(3-{1-[3-(4-methylphenoxy)benzyl]-4-piperidinyl}-phenyl)propanamide (15b). The desired product was obtained according to method III (62 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1 H), 7.34−7.19 (m, 4 H), 7.14 (d, J = 8.8 Hz, 2 H), 7.06 (d, J = 8.0 Hz, 1 H), 7.02−7.01 (m, 1 H), 6.96 (d, J = 7.6 Hz, 1 H), 6.92 (d, J = 8.8 Hz, 2 H), 6.85 (dd, J = 8.4, 2.4 Hz, 1 H), 3.50 (s, 2 H), 2.98 (d, J = 11.2 Hz, 2 H), 2.53−2.42 (m, 2 H), 2.34 (s, 3 H), 2.09−2.01 (m, 2 H), 1.80−1.74 (m, 4 H), 1.25 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 443.2 $(M + H)^+$; exact mass calcd for $C_{29}H_{35}N_2O_2$ (M + H), 443.2698; found, 443.2697.

***N*-(3-{1-[3-(4-*tert*-Butylphenoxy)benzyl]-4-piperidinyl}phenyl)-2-methylpropanamide (15c).** The desired product was obtained according to method III (63 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1 H), 7.35−7.32 (m, 3 H), 7.28−7.20 (m, 3 H), 7.07 (d, J = 7.6 Hz, 1 H), 7.05 (m, 1 H), 6.97−6.92 (m, 3 H), 6.88 (dd, J = 8.0, 2.4 Hz, 1 H), 3.51 (s, 2 H), 2.98 (d, J = 11.2 Hz, 2 H), 2.53−2.42 (m, 2 H), 2.09−2.02 (m, 2 H), 1.80−1.71 (m, 4 H), 1.32 (s, 9 H), 1.24 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 485.3 $(M + H)^+$; exact mass calcd for $C_{32}H_{41}N_2O_2$ (M + H), 485.3168; found, 485.3182.

***N*-(3-{1-[3-(4-methoxyphenoxy)benzyl]-4-piperidinyl}phenyl)-2-methylpropanamide (15d).** The desired product was obtained according to method III (77 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1 H), 7.35−7.31 (m, 2 H), 7.26−7.20 (m, 2 H), 7.03 (d, J = 7.6 Hz, 1 H), 7.00−6.95 (m, 4 H), 6.90−6.86 (m, 2 H), 6.81 (dd, J = 8.0, 2.4 Hz, 1 H), 3.80 (s, 3 H), 3.49 (s, 2 H), 2.97 (d, J = 11.2 Hz, 2 H), 2.53−2.41 (m, 2 H), 2.08−2.01 (m, 2 H), 1.79−1.72 (m, 4 H), 1.24 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 459.2 $(M + H)^+$; exact mass calcd for $C_{29}H_{35}N_2O_3$ (M + H), 459.2647; found, 459.2660.

***N*-(3-{1-[3-(4-Chlorophenoxy)benzyl]-4-piperidinyl}phenyl)-2-methylpropanamide (15e).** The desired product was obtained according to method III (82 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1 H), 7.38 (s, 1 H), 7.33−7.25 (m, 4 H), 7.21 (t, J = 8.0 Hz, 1 H), 7.11 (d, J = 7.6 Hz, 1 H), 7.03 (s, 1 H), 6.96−6.91 (m, 3 H), 6.87 (dd, J = 8.0, 2.4 Hz, 1 H), 3.50 (s, 2 H), 2.96 (d, J = 11.2 Hz, 2 H), 2.53−2.42 (m, 2 H), 2.08−2.01 (m, 2 H), 1.79−1.72 (m, 4 H), 1.23 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 463.2 $(M + H)^+$; exact mass calcd for $C_{28}H_{32}ClN_2O_2$ (M + H), 463.2152; found, 463.2156.

2-Methyl-*N*-[3-(1-{3-[3-(trifluoromethyl)phenoxy]benzyl}-4-piperidinyl)phenyl]propanamide (15f). The desired product was obtained according to method III (64 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1 H), 7.43 (t, J = 8.0 Hz, 1 H), 7.32 (t, J = 7.6 Hz, 3 H), 7.24 (t, J = 7.6 Hz, 3 H), 7.18−7.14 (m, 2 H), 7.08 (s, 1 H), 6.96 (d, J = 7.6 Hz, 1 H), 6.92 (dd, J = 8.0, 2.0 Hz, 1 H), 3.53 (s, 2 H), 2.98 (d, J = 11.2 Hz, 2 H), 2.53−2.43 (m, 2 H), 2.10−2.03 (m, 2 H), 1.80−1.74 (m, 4 H), 1.24 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 497.2 $(M + H)^+$; exact mass calcd for $C_{29}H_{32}F_3N_2O_2$ (M + H), 497.2416; found, 497.2420.

***N*-(3-{1-[3-(3,4-Dichlorophenoxy)benzyl]-4-piperidinyl}phenyl)-2-methylpropanamide (15g).** The desired product was obtained according to method III (268 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1 H), 7.38 (d, J = 8.8 Hz, 1 H), 7.32 (t, J = 8.0 Hz, 2 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.15 (d, J = 7.6 Hz, 1 H), 7.09 (d, J = 2.8 Hz, 2 H), 7.06 (s, 1 H), 6.97 (d, J = 7.6 Hz, 1 H), 6.90 (dd, J = 7.6, 2.0 Hz, 1 H), 6.86 (dd, J = 8.8, 2.8 Hz, 1 H), 3.52 (s, 2 H), 2.98 (d, J = 11.2 Hz, 2 H), 2.53−2.45 (m, 2 H), 2.11−2.02 (m, 2 H), 1.82−1.79 (m, 4 H), 1.26 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 497.2 $(M + H)^+$; exact mass calcd for $C_{28}H_{31}Cl_2N_2O_2$ (M + H), 497.1762; found, 497.1763.

***N*-(3-{1-[3-(3,5-Dichlorophenoxy)benzyl]-4-piperidinyl}phenyl)-2-methylpropanamide (15h).** The desired product was obtained according to method III (56 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1 H), 7.35−7.30 (m, 2 H), 7.26−7.16 (m, 3 H), 7.08−7.05 (m, 2 H), 6.96 (d, J = 7.6 Hz, 1 H), 6.92 (dd, J = 8.0, 2.4 Hz, 1 H), 6.87−6.86 (m, 2 H), 3.53 (s, 2 H), 2.98 (d, J = 11.2 Hz, 2 H), 2.55−2.44 (m, 2 H), 2.10−2.04 (m, 2 H), 1.81−1.75 (m, 4 H), 1.24 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 497.2 $(M + H)^+$; exact mass calcd for $C_{28}H_{31}Cl_2N_2O_2$ (M + H), 497.1762; found, 497.1770.

2-Methyl-*N*-{3-[1-(4-phenoxybenzyl)-4-piperidinyl]phenyl}-propanamide (16a). The desired product was obtained according to method III (81 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1 H), 7.36−7.29 (m, 6 H), 7.23 (dd, J = 13.6, 6 Hz, 1 H), 7.10 (t, J = 7.6 Hz, 1 H), 7.03−6.94 (m, 5 H), 3.58 (s, 2 H), 3.07 (d, J = 11.6 Hz, 2 H), 2.54−2.45 (m, 2 H), 2.17−2.09 (m, 2 H), 1.87−1.80 (m, 4 H), 1.24 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 429.2 $(M + H)^+$; exact mass calcd for $C_{28}H_{33}N_2O_2$ (M + H), 429.2542; found, 429.2548.

***N*-(3-{1-[4-(4-Chlorophenoxy)benzyl]-4-piperidinyl}phenyl)-2-methylpropanamide (16b).** The desired product was obtained according to method III (151 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1 H), 7.34−7.19 (m, 7 H), 6.98−6.87 (m, 5 H), 3.50 (s, 2 H), 2.98 (d, J = 11.8 Hz, 2 H), 2.58−2.44 (m, 2 H), 2.10−1.98 (m, 2 H), 1.83−1.76 (m, 4 H), 1.24 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 463.2 $(M + H)^+$; exact mass calcd for $C_{28}H_{32}ClN_2O_2$ (M + H), 463.2152; found, 463.2150.

***N*-(3-{1-[4-(4-Methoxyphenoxy)benzyl]-4-piperidinyl}phenyl)-2-methylpropanamide (16c).** The desired product was obtained according to method III (167 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1 H), 7.31−7.20 (m, 4 H), 7.12 (s, 1 H), 7.00−6.96 (m, 3 H), 6.91−6.86 (m, 4 H), 3.80 (s, 3 H), 3.49 (s, 2 H), 2.99 (d, J = 11.6 Hz, 2 H), 2.53−2.44 (m, 2 H), 2.08−2.01 (m, 2 H), 1.82−1.72 (m, 4 H), 1.25 (d, J = 6.8 Hz, 6 H); ESMS *m*/*e* 459.2 $(M + H)^+$; exact mass calcd for $C_{29}H_{35}N_2O_3$ (M + H), 459.2647; found, 459.2657.

***N*-(3-{1-[4-(3,4-Dichlorophenoxy)benzyl]-4-piperidinyl}phenyl)-2-methylpropanamide (16d).** The desired product was obtained

according to method III (422 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1 H), 7.36−7.18 (m, 6 H), 7.08 (d, J = 1.8 Hz, 1 H), 6.96 (d, J = 6.8 Hz, 3 H), 6.84 (dd, J = 2.8, 8.9 Hz, 1 H), 3.51 (s, 2 H), 2.99 (d, J = 11.5 Hz, 2 H), 2.55−2.42 (m, 2 H), 2.12−2.02 (m, 2 H), 1.84−1.73 (m, 4 H), 1.24 (d, J = 7.0 Hz, 6 H); ESMS m/e 497.1 $(M + H)^+$; exact mass calcd for $C_{28}H_{31}Cl_2N_2O_2$ (M + H), 497.1762; found, 497.1767.

***N*-(3-{1-[4-(3,4-Difluorophenoxy)benzyl]-4-piperidinyl}phenyl)-2-methylpropanamide (16e).** The desired product was obtained according to method III (255 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.32 (d, J = 8.4 Hz, 2 H), 7.28−7.21 (m, 2 H), 7.14−7.06 (m, 2 H), 6.98−6.94 (m, 3 H), 6.86−6.79 (m, 1 H), 6.76−6.69 (m, 1 H), 3.51 (s, 2 H), 2.99 (d, J = 11.7 Hz, 2 H), 2.55−2.44 (m, 2 H), 2.12−2.02 (m, 2 H), 1.86−1.74 (m, 4 H), 1.25 (d, J = 7.0 Hz, 6 H); ESMS m/e 465.2 $(M + H)^+$; exact mass calcd for $C_{28}H_{31}F_2N_2O_2$ (M + H), 465.2353; found, 465.2356.

***N*-(5-{1-[4-(3,4-Difluorophenoxy)benzyl]-4-piperidinyl}-2-methylphenyl)-2-methylpropanamide (16f).** The desired product was obtained according to method III (22 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1 H), 7.36 (d, J = 8.4 Hz, 2 H), 7.13 (q, J = 9.2 Hz, 2 H), 6.97−6.93 (m, 4 H), 6.86−6.80 (m, 1 H), 6.74−6.70 (m, 1 H), 3.54 (s, 2 H), 3.03 (d, J = 10.8 Hz, 2 H), 2.61−2.50 (m, 2 H), 2.24 (s, 3 H), 2.20−2.04 (m, 2 H), 1.85−1.83 (m, 4 H), 1.30 (d, J = 6.8 Hz, 6 H); ESMS m/e 479.2 $(M + H)^+$; exact mass calcd for $C_{29}H_{33}F_2N_2O_2$ (M + H), 479.2510; found, 479.2520.

***N*-(3-{1-[4-(3,4-Difluorophenoxy)benzyl]-4-piperidinyl}-4-methylphenyl)-2-methylpropanamide (16g).** The desired product was obtained according to method III (220 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 2 Hz, 1 H), 7.38−7.31 (m, 2 H), 7.27 (dd, J = 8.8, 2.0 Hz, 1 H), 7.14−7.06 (m, 3 H), 7.00−6.93 (m, 2 H), 6.86−6.79 (m, 1 H), 6.75−6.69 (m, 1 H), 3.52 (s, 2 H), 3.01 (d, J = 11.2 Hz, 2 H), 2.73−2.65 (m, 1 H), 2.52−2.43 (m, 1 H), 2.28 (s, 3 H), 2.10 (dt, J = 11.6, 2.8 Hz, 2 H), 1.88−1.71 (m, 4 H), 1.24 (d, J = 6.8 Hz, 6 H); ESMS m/e 479.1 $(M + H)^+$; exact mass calcd for $C_{29}H_{33}F_2N_2O_2$ (M + H), 479.2510; found, 479.2518.

In Vitro, In Vivo and DMPK Procedures: See part 1, the preceding paper, for a description of the in vitro binding assays;[10e] see part 1, the preceding paper, for a description of the in vivo assays: social interaction test (SIT);[10e] see part 1, the preceding paper, for a description of the MCH-induced water intake;[10e] see part 1, the preceding paper, for a description of the rat pharmacokinetic assay;[10e] and see part 1, the preceding paper, for a description of the rat pharmacokinetic screening.[10e]

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Supporting Information Available: IC_{50} values, LCMS purity checks, and high-resolution mass spectrum data for compounds of interest. This material is available free of charge via the Internet at http://pubs.acs.org.

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