Synthesis and SAR Investigations for Novel Melanin-Concentrating Hormone 1 Receptor (MCH_1) Antagonists Part 1. The Discovery of Arylacetamides as Viable Replacements for the Dihydropyrimidinone Moiety of an HTS Hit

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Melanin-concentrating hormone (MCH) is involved in the regulation of feeding, water balance, energy metabolism, general arousal and attention state, memory, cognitive functions, and psychiatric disorders. Herein, two new chemical series exemplified by *N*-[5-(1-{3-[2,2-bis-(4-fluoro-phenyl)-acetylamino]-propyl}-piperidin-4-yl)-2,4-difluoro-phenyl]-isobutyramide (SNAP 102739, **5m**) and *N*-[3-(1-{3-[(*S*)-2-(4-fluoro-phenyl)-propionylamino]-propyl}-piperidin-4-yl)-4-methylphenyl]-isobutyramide (**(*S*)-6b**) are reported. These compounds were designed to improve the pharmacokinetic properties of the high-throughput screening lead compound **1** (SNAP 7941). The MCH_1 receptor antagonists **5m** and **(*S*)-6b** show reasonable pharmacokinetic profiles (rat bioavailability = 48 and 81%, respectively). Compounds **5m** and **(*S*)-6b** demonstrated the inhibition of a centrally administered MCH-evoked drinking effect, and compound **5m** exhibited oral in vivo efficacy in the rat social interaction model of anxiety, with a minimum effective dose = 0.3 mg/kg.

Introduction

Melanin-concentrating hormone (MCH) is a cyclic peptide originally isolated from salmonid pituitaries, where it was named for its ability to cause aggregation of melanin within skin melanophores, resulting in skin lightening.[1] In mammals, MCH is a cyclic 19-amino acid neuropeptide that is produced predominantly by neurons in the lateral hypothalamus and zona incerta, which project broadly throughout the brain.[2] Mammalian MCH is highly conserved between rat, mouse, and human species, exhibiting 100% amino acid identity.[2] The biological function of MCH is mediated by two receptors, MCH_1 receptor and MCH_2 receptor, which have been identified in several species, including human, rhesus monkey, ferret, and dog;[3] however, functional MCH_2 receptor has not been found in rat, mouse, hamster, guinea pig, or rabbit.[4] Recent reports have suggested that the MCH peptide plays a major role in regulation of food intake and stress in rodents.[5] For example, the central administration of MCH stimulates food intake, while fasting results in an increase in MCH expression.[6] Furthermore, mice lacking the gene encoding MCH are lean, hypophagic and maintain elevated metabolic rates.[7] In contrast, mice overexpressing the MCH gene are susceptible to obesity and insulin resistance.[8] In addition, MCH seems to be an activator of the HPA stress axis.[9] These findings suggest that small-molecule antagonists of the MCH_1 receptor can potentially be used in the treatment of obesity and mood disorders.[5]

The promising in vitro and in vivo pharmacology of published MCH_1 receptor antagonists has made the MCH_1 receptor an attractive target for the development of a small molecule antagonist.[10a−k] The progress of MCH_1 receptor research for antagonists acting at the receptor has been summarized by several authors.[11,12] Examples include the first described non-peptide MCH_1 receptor antagonist **2** (T-226296, Figure 1), which suppressed MCH-stimulated food intake in rats at greater than 90% given 30 mg/kg, po.[10a] Compound **1** also reduced the weight gain in young growing rats and in mature rats that were fed a high-fat diet (Diet-Induced Obese rats).[10b] Additionally, compound **4** (GW-803430) showed a 13% dose-dependent weight loss after 12 days when administered to mice at 3 mg/kg.[10c] Furthermore, compound **1** produced effects similar to the clinically used antidepressants and anxiolytics in three different animal models for depression and anxiety: the rat forced-swim test, the rat social interaction assay, and the guinea pig maternal-separation vocalization test.[10b] As well, Taisho and Arena have recently reported a potent orally active MCH_1 receptor antagonist **3** (ATC-0175), with anxiolytic and antidepressant activities in rodents.[10d] Additional MCH_1 receptor publications have recently appeared in the literature describing the pharmacological properties and the control of food intake by the resultant diverse MCH_1 receptor antagonists.[10−12]

The high-throughput screening of Lundbeck GPCR-directed compound collection identified compound **1** as a high affinity and selective MCH_1 receptor antagonist. The in vitro and in vivo properties of compound **1** were described recently.[10b] However, experience with compound **1** as a highly metabolized and hydrolyzed analog resulting in low bioavailability, as well as experience with previously described dihydropyrimidinone-substituted compounds,[13] prompted a search for alternative templates to circumvent hydrolysis and metabolism issues. Studies in the discovery of alternative templates in place of the dihydropyrimidinone moiety of compound **1** as well as the optimization of the resultant MCH_1 receptor antagonists and the in vitro and in vivo properties of the optimal MCH_1 receptor antagonists **5** and **6**, depicted in Figure 2, are described herein.

Synthetic Chemistry

The synthesis of final compounds **5** and **6** required the synthesis of intermediate **7** shown in Scheme 1. The synthesis of compound **7** was accomplished according to the procedures depicted in Scheme 1. Bromobenzenes **8a**/**8b** were treated with nitric acid in the presence of sulfuric acid at <7 °C to afford

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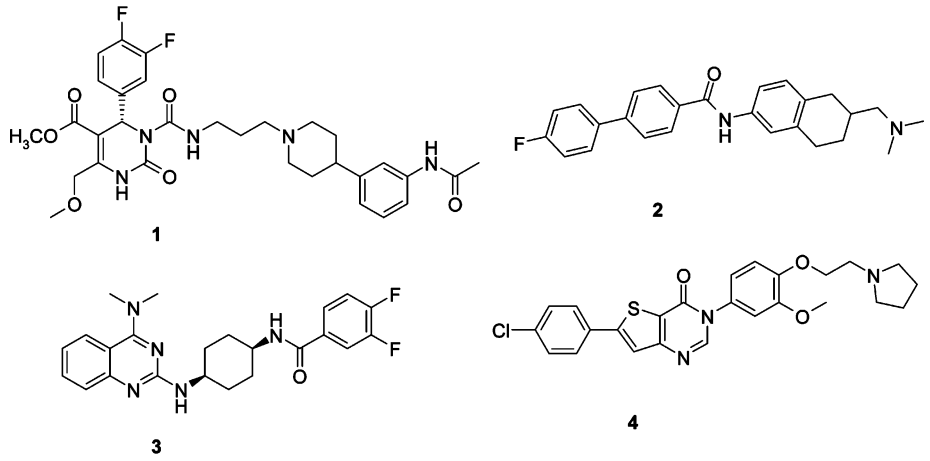
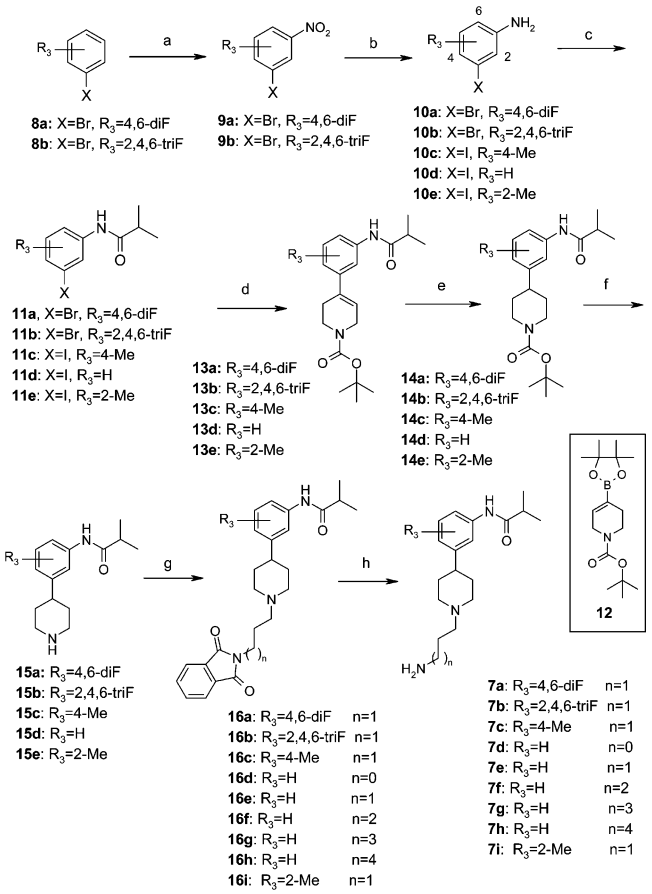


Figure 1. Representative nonpeptide MCH_1 receptor antagonists.

Scheme 1[a]



[a] Reagents and conditions: (a) H_2SO_4, HNO_3, below 7 °C, 45 min; (b) Fe, NH_4Cl, EtOH, reflux, 2 h; (c) acid chloride, base, THF, 0 °C then rt 2−3 h; (d) **12**, $Pd(OAc)_2$, TBAI, Na_2CO_3, H_2O, 150 °C; (e) 10% Pd/C, H_2, EtOH, rt, 24−48 h; (f) 4 M HCl in 1,4-dioxane, rt, 1 h, or TFA, CH_2Cl_2, rt, 1−2 h; (g) *N*-(*n*-bromoalkyl)-phthalimide, K_2CO_3, DMF, 80 °C, 4 h; (h) H_2NNH_2, EtOH, reflux, 5 h. Compounds **10c**/**10d**/**10e** are commercially available from Sigma-Aldrich.

nitrobenzenes **9a**/**9b** in a yield of 99%.[14] Reduction of the nitro group in **9a**/**9b** with iron in the presence of ammonium chloride in ethanol at refluxing temperature afforded anilines **10a**/**10b** in 59% yields. Compounds **11a**−**11e** were synthesized via amidations of compounds **10a**−**10e** using 2-methylpropionyl chloride in the presence of triethylamine (TEA) in yields of about 95%. Suzuki coupling of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (**12**) with iodobenzenes or bromobenzenes **11a**−**11e** in the presence of tetrabutylammonium iodide and palladium acetate in water at 150 °C afforded compounds **13a**−**13e** in 90−95% yields.[15] Hydrogenation of compounds **13a**−**13e** under 200 psi reduced the double bond to yield compounds **14a**−**14e** in a yield of 83−88%. Deprotection of compounds **14a**−**14e** in the presence of trifluoroacetic acid (TFA) in dichloromethane (DCM) or hydrogen chloride in dioxane afforded 4-phenyl piperidines **15a**−**15e** in quantitative yields. The aminoalkyl tether chains of compounds **7a**−**7e** were introduced by sequential reactions of compounds **15a**−**15e** with *N*-(*n*-bromoalkyl)-phthalimides ($n = 0-4$) in the presence of potassium carbonate in *N*,*N*-dimethylformamide at 80 °C to afford compounds **16a**−**16i** in yields of 79−93%. Deprotection of compounds **16a**−**16i** with hydrazine in refluxing ethanol proceeded to give compounds **7a**−**7i** in 91−97% yields. In the case of the 3-carbon tether analogs **7a**−**7c**, **7e**, and **7i**, $n = 1$, an alternative route of the reaction of compounds **16a**−**16i** with (3-bromo-propyl)-carbamic acid *tert*-butyl ester followed by acidic removal of the BOC group gave the desired compounds **7a**−**7c**, **7e**, and **7i** in 70−80% yields.

The intermediate diarylacetic acids **17b** and **17c**, shown in Scheme 2, were synthesized from substituted benzenes and glyoxylic acid monohydrate in acetic acid at 80 °C according to literature procedures.[16] The synthesis of the chiral advanced carboxylic acids **18a**/**18b**, shown in Scheme 3, needed for the synthesis of compounds **6a**/**6b**, followed Evans' protocol to afford a separable mixture of diastereoisomers in a ratio of >98.5:1.5 in 60−80% yields.[17] The chiral purity of the final products **6a**/**6b** were determined via chiral SFC to be >95% ee. A Daicel AD column with diethylamine and methanol modifiers was used in the determinations of the ratios.

As shown in Scheme 2, the amidation of acid chloride **17a** with compounds **7a**−**7e** in the presence of triethylamine in dichloromethane or the coupling of carboxylic acids **17b**−**17g** with compounds **7a**−**7e** in the presence of EDC and DMAP in DCM/DMF at room temperature afforded products **5a**−**5p** in 50−85% yields.

Similarly, the amidation of carboxylic acids **18a**−**18d** with compounds **7a**−**7e** in the presence of EDC and DMAP in DCM/DMF, shown in Scheme 3, at room temperature afforded products **6a**−**6d** in 50−85% yields.

Results and Discussion

An early exploratory library approach to identifying suitable replacements for the dihydropyrimidinone moiety of compound **1** rendered 2,2-diarylacetamides and 2-aryl and 2-alkyl-acetamides as viable surrogates, as depicted for compounds **5** and **6**

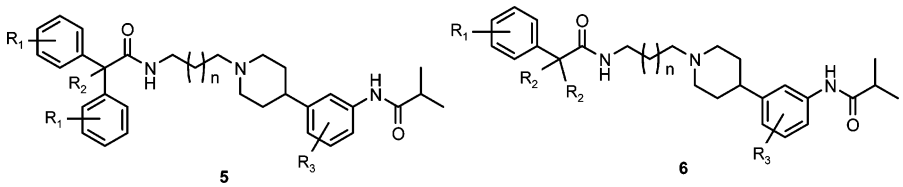
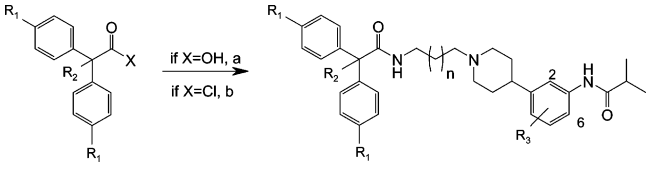


Figure 2. Two novel chemical series **5** and **6** of MCH_1 receptor antagonists.

Scheme 2[a]

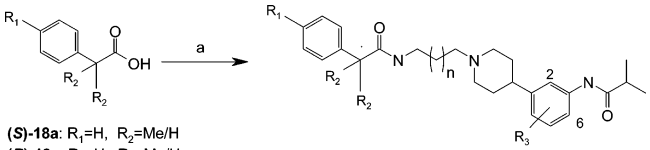


17a: X=Cl, R_1=H, R_2=H
17b: X=OH, R_1=4-F, R_2=H
17c: X=OH, R_1=4-Cl, R_2=H
17d: X=OH, R_1=H, R_2=OH
17e: X=OH, R_1=H, R_2=Me
17f: X=OH, R_1=H, R_2=Et
17g: X=OH, R_1=H, R_2=*n*-Pent

5a: R_1=H, R_2=H, R_3=H, n=0
5b: R_1=H, R_2=H, R_3=H, n=1
5c: R_1=H, R_2=H, R_3=H, n=2
5d: R_1=H, R_2=H, R_3=H, n=3
5e: R_1=H, R_2=H, R_3=H, n=4
5f: R_1=F, R_2=H, R_3=H, n=1
5g: R_1=Cl, R_2=H, R_3=H, n=1
5h: R_1=H, R_2=Me, R_3=H, n=1
5i: R_1=H, R_2=Et, R_3=H, n=1
5j: R_1=H, R_2=*n*-Pent, R_3=H, n=1
5k: R_1=F, R_2=H, R_3=4-Me, n=1
5l: R_1=H, R_2=H, R_3=4-Me, n=1
5m: R_1=F, R_2=H, R_3=4,6-diF, n=1
5n: R_1=F, R_2=H, R_3=2,4,6-triF, n=1
5o: R_1=H, R_2=H, R_3=2-Me, n=1
5p: R_1=H, R_2=OH, R_3=4-Me, n=1

[a] Reagents and conditions: (a) **7**, DMAP, EDC, DCM/DMF, rt, 5 h; (b) **7**, TEA, THF, rt, 5 h. Compounds **17a** and **17d**−**17g** are available from Sigma-Aldrich.

Scheme 3[a]



(*S*)-**18a**: R_1=H, R_2=Me/H
(*R*)-**18a**: R_1=H, R_2=Me/H
(*S*)-**18b**: R_1=F, R_2=Me/H
(*R*)-**18b**: R_1=F, R_2=Me/H
18c: R_1=F, R_2= $(CH_2)_4$
18d: R_1=F, R_2= $(CH_2)_5$

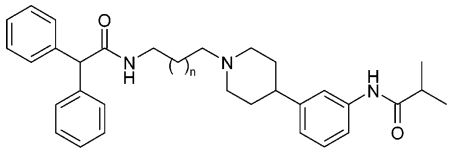
(*S*)-**6a**: R_1=H, R_2=Me/H, R_3=Me,
(*R*)-**6a**: R_1=H, R_2=Me/H, R_3=Me,
(*S*)-**6b**: R_1=F, R_2=Me/H, R_3=Me,
(*R*)-**6b**: R_1=F, R_2=Me/H, R_3=Me,
6c: R_1=F, R_2=$(CH_2)_5$, R_3=Me
6d: R_1=F, R_2=$(CH_2)_4$, R_3=Me

[a] Reagents and conditions: (a) DMAP, EDC, DCM/DMF, rt, 5 h. Compounds **18c**/**18d** are available from Acros Organic U.S.A.

in Schemes 2 and 3. The subsequent medicinal chemistry efforts in the optimization of analogs **5** and **6** are summarized herein. The SAR of the 2,2-diarylacetamide replacements on the MCH_1 receptor affinities of compounds **5a**−**5p** is presented in Tables 1 and 2. Table 1 illustrates the effect of increasing tether length on the MCH_1 receptor affinities of compounds **5a**−**5e**. The optimal tether length for compounds **5a**−**5e** was determined to be two and three carbons, $n = 0$ or 1, both displaying 1.9 nM MCH_1 receptor affinities. Within compounds **5a**−**5e**, as the linker length increased, $n = 2-4$, a drop in affinity was seen at $n = 2$ and 3 (compounds **5c**,**d**), followed by a slight improvement at $n = 4$ (compound **5e**). Due to its favorable MCH_1 receptor affinity profile and synthetic accessibility, compound **5b** ($n = 1$) was selected for further SAR studies. The formation of the two-carbon tether ($n = 0$, step g) outlined in Scheme 1 was accompanied by variable degrees of decomposition.

The substituent effects at the R_1-R_3 positions on the MCH_1 receptor affinities of compounds **5b**−**5p** are summarized in Table 2. The relatively small H, F, and Cl substituents at R_1 (**5b**, **5f**, **5g**) afforded low nanomolar affinity compounds. Minor effects on the MCH_1 receptor affinities of 0.6−14 nM were

Table 1. Effect of the Tether Length on the MCH_1 Receptor Affinities of Compounds **5a**−**5e**[a]



cmpd	*n*[a]	rMCH$_1$[b] $K_i \pm$ SEM (nM)
1	NA	0.25 ± 0.01
5a	0	1.9 ± 0.7
5b	1	1.9 ± 0.2
5c	2	50 ± 10
5d	3	47 ± 19
5e	4	29 ± 1

[a] NA = not applicable. [b] 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.

observed for substitutions at the R_2 position (**5h**, **5i**, **5j**, and **5p**), depending on the substituents (H, alkyl, OH). A comparison of compounds **5b**−**5p** in Table 2 also showed that, while fluorines at 2-, 4-, and 6-R_3 (**5m** and **5n**) and 6-CH_3 positions (**5k** and **5l**) gave high affinity MCH_1 receptor compounds, a 4-CH_3 group weakened the MCH_1 receptor affinity of the desired product (cf. **5b** and **5l** vs **5o**).

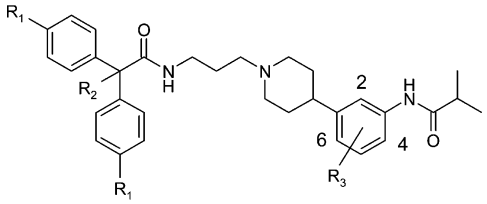
As part of the SAR studies, the effect of 2-aryl-2-alkylacetamide substitution, in place of the 2,2-diarylacetamide group, on the MCH_1 receptor affinity of compound **6** was explored. The effect of the chirality of the acetamide group of compounds **6a** and **6b** on the MCH_1 receptor affinities was initially examined (Table 3). Within the enantiomeric pairs **6a** and **6b**, **(*S*)-6b** was found to have higher affinity of 10 nM.

The effect of 2,2-dialkyl substitution on compounds **6b**−**6d** is shown in Table 4. While the monomethylated analog **(*S*)-6b** exhibited an MCH_1 receptor affinity of 10 nM, the cycloalkyl groups, $(CH_2)_5$ and $(CH_2)_4$, slightly improved the affinity profiles of analogs **6c** and **6d**.

Concurrent with the dihydropyrimidinone replacement studies, blockage of the putative sites of metabolism of compound **1** were also studied, with an anticipated enhancement in the pharmacokinetic (PK) properties of the resultant analogs. The anilide moiety of compound **1** is potentially susceptible to enzymatic hydroxylations and hydrolysis. Hence, the effect of blocking the putative sites of metabolism of the anilides of compounds **5** were investigated by measuring the plasma levels of rats, dosed at 10 mg/kg po, at 1, 2, and 4 h. The brain levels were measured at the conclusion of the plasma monitoring period at 4 h.

The effect of *para*-R_3 substitution (H vs 6-CH_3) on the plasma and the brain levels of compounds **5b** and **5l** is summarized in Table 5. The two analogs **5b** and **5l** were administered po at 10

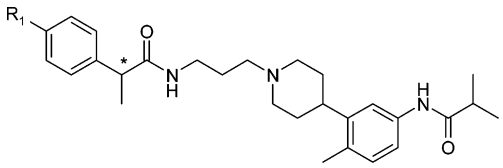
Table 2. Effect of R_1-R_3 Substitutions on the MCH_1 Receptor Affinities of Compounds **5b**−**5p**[a]



cmpd	R_1	R_2	R_3	rMCH$_1$[a] $K_i \pm$ SEM (nM)
5b	H	H	H	1.9 ± 0.2
5f	F	H	H	1.4 ± 0.2
5g	Cl	H	H	2.4 ± 0.1
5h	H	Me	H	7.5 ± 1.3
5i	H	Et	H	14 ± 1
5j	H	*n*-pent	H	8.5 ± 0.5
5k	F	H	6-Me	0.62 ± 0.01
5l	H	H	6-Me	3.0 ± 0.4
5m (SNAP 102739)	F	H	4,6-diF	1.8 ± 0.6
5n	F	H	2,4,6-triF	2.9 ± 1.4
5o	H	H	4-Me	500 ± 50
5p	H	OH	6-Me	0.6 ± 0.2

[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.

Table 3. Effect of Chirality and R_1 on the MCH_1 Receptor Affinities of Compounds **6a**−**6b**[a]

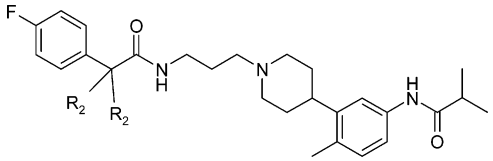


cmpd	R_1	rMCH$_1$[a] $K_i \pm$ SEM (nM)
(*S*)-6a	H	34 ± 7
(*R*)-6a	H	37 ± 8
(*S*)-6b	F	10 ± 1
(*R*)-6b	F	28 ± 6

[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.

mg/kg to rats, and the plasma levels were monitored at $t = 1$, 2, and 4 h. At the conclusion of the plasma monitoring period at 4 h, the rat brain levels were examined as well. Compound **5b** (R_3 = H) shows low but stable plasma levels at $t = 1-4$ h. Compound **5b** was not detected in the brain at $t = 4$ h of the monitoring period. On the other hand, compared to compound **5b**, **5l**, which is substituted at the *para*-anilide position with R_3 = 6-CH_3, showed improved initial plasma levels at $t = 1$, 2, and 4 h. The plasma levels of both analogs **5b** and **5l** were maintained at a steady level throughout the four-hour plasma monitoring period. Additionally, compared to compound **5l**, **5b** also showed improved brain exposure levels at 4 h. Within the

Table 4. Effect of Monosubstitution vs Cyclic Analogs at Benzylic Positions on the MCH_1 Receptor Affinities of Compounds **6b**−**6d**[a]



cmpd	R_2/R_2	rMCH$_1$[a] $K_i \pm$ SEM (nM)
(*S*)-6b	Me/H	10 ± 1
6c	$(CH_2)_5$	1.9 ± 0.5
6d	$(CH_2)_4$	3.8 ± 0.7

[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.

Table 5. Plasma and Brain Levels of Compounds **5b** and **5l**[a]

cmpd	rat plasma at 1 h (ng/mL)	rat plasma at 2 h (ng/mL)	rat plasma at 4 h (ng/mL)	rat brain at 4 h (ng/g)
5b (R_3 = H)	15 ± 2	12 ± 2	15 ± 2	0 ± 2
5l (R_3 = 6-CH_3)	69 ± 2	59 ± 2	75 ± 2	13 ± 2

[a] The data were generated from pooled samples of three rats for each time point, dosed at 10 mg/kg, po. The analytical limit of quantitation for compounds **5b** and **5l** were determined to be ±2 ng/mL for plasma and ±2 ng/g for brain measurements. See the Experimental Section under "Rat Pharmacokinetic Screening" for details.

chemical series of formula **5**, partially described in Table 5, the blockage of the *para*-anilide position appeared to give compounds with more favorable plasma and brain levels.

Compounds **5m** and **(*S*)-6b** were selected for further studies. The PK data for compounds **5m** and **(*S*)-6b** are summarized in Table 6. Both compound **5m** and compound **(*S*)-6b** showed improved rat bioavailability (48−81%) profiles compared with compound **1**, which exhibited a bioavailability of 6% in rats.

Compounds **5m** and **(*S*)-6b** were screened in an in-house panel of 18 receptors as well a broad cross-reactivity panel and were shown to be devoid of any activities that may contribute to the in vivo efficacy studies outlined below.

MCH was recently reported to stimulate water intake independent of food intake.[18] Compounds **5m** and **(*S*)-6b** produced significant inhibition of MCH-evoked drinking when tested at a screening concentration of 10 mg/kg po at 1 h, shown in Figure 3. These data confirmed the specific blockage of a centrally induced MCH-evoked drinking by compounds **5m** and **(*S*)-6b**.

The rat social interaction animal model is used as a predictive tool for anxiolytic activity.[19] The design and procedure for the social interaction test was modified from that previously described by Kennett et al.[20] Animals were treated with either vehicle (20% cyclodextrin), chlordiazepoxide (CDP; 5 mg/kg p.o.), or compound **5m**. When tested in the social interaction test of anxiety, compound **5m**, administered orally 1 h previously, produced a significant increase in social interaction time relative to vehicle-treated rats, with a minimally effective dose = 0.3 mg/kg (basal: 38.3 ± 5.7 s; chlordiazepoxide: 85.1 ± 5.6 s; **5m**: 69.3 ± 9.7 s, $p < 0.05$; Newman−Keuls post-hoc test).

See the Experimental Section under "MCH-induced water intake" for more details.

Table 6. PK[a] Data for Compounds **1**, **5m**, and **(*S*)-6b** in Rats[b]

cmpd	*F*%[c]	CL_b[d] (L/hr/kg)	CL_p[e] (L/hr/kg)	C_{max}[f] (ng/mL)	T_{max}[g] (hr)	$T_{1/2}$[h] (hr)	V_{ss}[i] (L/kg)
1[j]	6	ND[l]	9.2	2.02 ± 0.03[m]	4.0	1.7	24
5m[k]	48	3.6	2.4	80 ± 2[m]	0.6	2.1	3.6
(*S*)-6b[k]	81	3.3	1.5	305 ± 2[m]	2.2	4.2	3.4

[a] PK = pharmacokinetic. [b] See the Experimental Section under "Rat Pharmacokinetic Assay" for details. [c] *F*% = rat bioavailability. [d] CL_b = blood clearance. [e] CL_p = plasma clearance. [f] C_{max} = maximal plasma concentration. [g] T_{max} = time of maximal concentration. [h] $T_{1/2}$ = half-life. [i] V_{ss} = volume of distribution at steady state. [j] The rats were dosed at 1 mg/kg po ($n = 2$) and 1 mg/kg iv ($n = 2$). [k] The rats were dosed at 2 mg/kg po ($n = 2$) and 1 mg/kg iv ($n = 2$). [l] ND = not determined. [m] The analytical limit of quantitation for compound **1** was determined to be ±0.03 ng/mL for plasma measurements (*via* a solid-phase extraction step). The analytical limit of quantitation for compounds **5 m** and **(S)-6b** were determined to be ±2 ng/mL for plasma measurements.

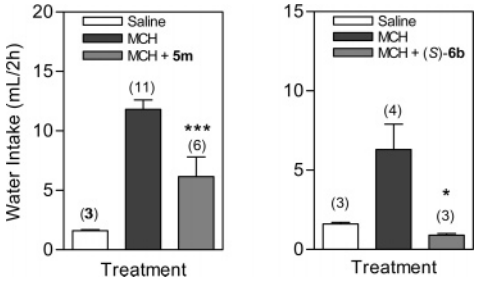


Figure 3. Inhibition of MCH-evoked drinking in rats. MCH peptide was administered icv (10 μg in 5 μL saline). Antagonists (**5 m** or **(*S*)-6b**, 10 mg/kg, p.o.) were given orally before the MCH challenge. Water intake was monitored for 2 h. Results represent the means ± SEM of *N* determinations (*N* in parentheses). *$p < 0.05$; ***$p < 0.001$ vs MCH alone.

Conclusion

In summary, two highly potent replacements for the dihydropyrimidinone moiety of compound **1**, (2,2-diaryl)acetamide, and (2-aryl-2-alkyl)acetamide, represented by compounds **5m** and **(*S*)-6b**, were identified via an initial diversity-based library approach, followed by medicinal chemistry efforts. Compounds **5m** and **(*S*)-6b** exhibited reasonable PK properties. In vivo efficacy experiments demonstrated that *N*-[5-(1-{3-[2,2-bis-(4-fluoro-phenyl)-acetylamino]-propyl}-piperidin-4-yl)-2,4-difluoro-phenyl]-isobutyramide (**5m**) and *N*-[3-(1-{3-[(*S*)-2-(4-fluoro-phenyl)-propionylamino]-propyl}-piperidin-4-yl)-4-methylphenyl]-isobutyramide (**(*S*)-6b**) inhibited a centrally induced MCH-evoked drinking effect. In addition, compound **5m** exhibited an anxiolytic effect in the rat social interaction model of anxiety. An alternative parallel approach that removed the amide moiety in the linker of the compounds **5** and **6** is described in the accompanying paper.

Experimental Section

General Methods. All reactions were performed under a nitrogen atmosphere, and the reagents, neat or in appropriate solvents, were transferred to the reaction vessel via syringe and cannula techniques. Anhydrous solvents were purchased from Aldrich Chemical Co. and used as received. The NMR spectra were recorded at Bruker Avance (400 MHz) or GE QEPlus300 in $CDCl_3$, MeOH-d_4, or DMSO-d_6 as solvent, with tetramethylsilane as the internal standard, unless otherwise noted. Chemical shifts (δ) are expressed in ppm, coupling constants (*J*) are expressed in Hz, and splitting patterns are described as follows: s = singlet; d = doublet; t = triplet; q = quartet; quintet; sextet; septet; br = broad; m = multiplet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; dm = doublet of multiplets; ddd = doublet of doublet of doublets. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. Unless otherwise noted, mass spectra were obtained using electrospray ionization (ESMS, Micromass Platform II or Quattro Micro) and $(M + H)^+$ is reported. Thin-layer chromatography (TLC) was carried out on glass plates precoated with silica gel 60 F_{254} (0.25 mm, EM Separations Tech.). Preparative TLC was carried out on glass sheets precoated with silica gel GF (2 mm, Analtech). Flash column chromatography was performed on Merck silica gel 60 (230−400 mesh). Melting points (mp) were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Reverse phase high-pressure liquid chromatography purification was performed using a Genesis HPLC column (ref 16R10985, 100 mm × 22.5 mm) containing C18−7 μm, 120 Å silica. Microwave experiments were carried out using a Biotage Emyrs Optimizer or Smithcreator. High-resolution MS data was obtained using a Waters Q-TOF and Agilant 1100 system.

***N*-{3-[1-(2-Diphenylacetylamino-ethyl)-piperidin-4-yl]-phenyl}-isobutyramide (5a).** Compound **5a** was prepared from diphenylacetic acid chloride and *N*-{3-[1-(2-aminoethyl)-4-piperidinyl]-phenyl}-2-methylpropanamide according to the general procedure B of **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1 H), 7.42−7.14 (m, 13 H), 6.96−6.89 (m, 1 H), 6.67 (br s, 1 H), 4.97 (s, 1 H), 3.50−3.37 (m, 2 H), 2.61−2.37 (m, 4 H), 2.11 (t, $J = 11.5$ Hz, 2 H), 1.81−1.53 (m, 4 H), 1.25 (d, $J = 6.86$ Hz, 6 H); ESMS *m*/*e* 484.2 $(M + H)^+$; HRMS (FAB) calcd for $C_{31}H_{38}N_3O_2$ $(M + H)^+$, 484.2958; found, 484.2933.

***N*-{3-[1-(3-Diphenylacetylamino-propyl)-piperidin-4-yl]-phenyl}-isobutyramide (5b). (a) General Procedure A for the Synthesis of 5b.** A mixture of 2,2-diphenylpropionic acid (0.200 mmol), *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide (0.200 mmol), 1-[3-(dimethylamino)propyl]3-ethylcarbodiimide (EDC, 0.400 mmol, 62.0 mg). and 4-dimethylaminopyridine (5.00 mg) was dissolved in CH_2Cl_2/DMF (1.00/0.100 mL), and the mixture was shaken on an orbital J-KEM shaker at room temperature for 5 h. The reaction mixture was concentrated in vacuo and purified by preparative TLC [silica, CH_2Cl_2/ammonia (2.0 M in methanol) 100:5] to afford the desired product (78% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 7.33−7.21 (m, 13 H), 6.94 (m, 2 H), 4.88 (s, 1 H), 3.39 (t, $J = 5.6$ Hz, 2 H), 2.93 (d, $J = 11.3$ Hz, 2 H), 2.52−2.36 (m, 4 H), 1.97 (t, $J = 11.3$ Hz, 2 H), 1.83−1.58 (m, 6 H), 1.24 (d, $J = 7.6$ Hz, 6 H); ESMS *m*/*e* 498.4 $(M + H)^+$; HRMS (FAB) calcd for $C_{32}H_{39}N_3O_2$ $(M + H)^+$, 498.3115; found, 498.3088.

(b) General Procedure B for the synthesis of 5a and 5c−5p. A mixture of 2,2-diphenylacetyl chloride (0.300 mmol), *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide (0.250 mmol), and triethylamine (0.500 mmol) was dissolved in THF (2.00 mL), and the mixture was shaken on an Orbital J-KEM shaker at room temperature for 5 h. The reaction mixture was concentrated in vacuo, and the residue was purified by preparative TLC [silica, CH_2Cl_2/ammonia (2.0 M in methanol) 100:5] to afford the desired product.

***N*-{3-[1-(5-Diphenylacetylamino-pentyl)-piperidin-4-yl]-phenyl}-isobutyramide (5c).** Compound **5c** was prepared from diphenylacetic acid chloride and *N*-{3-[1-(4-aminobutyl)-4-piperidinyl]-phenyl}-2-methylpropanamide according to the general procedure B for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.13 (m, 14 H), 6.91−6.85 (m, 1 H), 5.91−5.82 (m, 1 H), 4.93 (s, 1 H), 3.33−3.15 (m, 4 H), 2.62−2.41 (m, 4 H), 2.28 (t, $J = 11.5$ Hz, 2 H), 2.07−1.76 (m, 4 H), 1.65−1.52 (m, 2 H), 1.50−1.36 (m, 2 H), 1.23 (d, $J = 6.86$ Hz, 6 H); ESMS *m*/*e* 512.4 $(M + H)^+$; HRMS (FAB) calcd for $C_{34}H_{42}N_3O_2$ $(M + H)^+$, 512.3271; found, 512.3242.

***N*-{3-[1-(5-Diphenylacetylamino-pentyl)-piperidin-4-yl]-phenyl}-isobutyramide (5d).** Compound **5d** was prepared from diphenylacetic acid chloride and *N*-{3-[1-(5-aminopentyl)-4-piperidinyl]-

phenyl}-2-methylpropanamide according to the general procedure B for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.13 (m, 14 H), 6.92−6.88 (m, 1 H), 5.91−5.82 (m, 1 H), 4.92 (s, 1 H), 3.32−3.25 (m, 4 H), 2.62−2.45 (m, 4 H), 2.28 (t, J = 11.5 Hz, 2 H), 2.07−1.87 (m, 4 H), 1.65−1.54 (m, 2 H), 1.49−1.39 (m, 2 H), 1.28−1.25 (m, 2 H), 1.23 (d, J = 6.86 Hz, 6 H); ESMS *m/e* 526.4 $(M + H)^+$; HRMS (FAB) calcd for $C_{34}H_{44}N_3O_2$ $(M + H)^+$, 526.3428; found, 526.3401.

***N*-{3-[1-(6-Diphenylacetylamino-hexyl)-piperidin-4-yl]-phenyl}-isobutyramide (5e).** Compound **5e** was prepared from diphenylacetic acid chloride and *N*-{3-[1-(6-aminohexyl)-4-piperidinyl]-phenyl}-2-methylpropanamide according to the general procedure B for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.13 (m, 14 H), 6.91−6.85 (m, 1 H), 5.91−5.82 (m, 1 H), 4.93 (s, 1 H), 3.33−3.15 (m, 4 H), 2.62−2.41 (m, 4 H), 2.28 (t, J = 11.5 Hz, 2 H), 2.07−1.76 (m, 4 H), 1.65−1.52 (m, 2 H), 1.50−1.36 (m, 2 H), 1.28−1.25 (m, 2 H), 1.23 (d, J = 6.86 Hz, 6 H), 1.05−1.01 (m, 2 H); ESMS *m/e* 540.8 $(M + H)^+$; HRMS (FAB) calcd for $C_{35}H_{45}N_3O_2$ $(M + H)^+$, 540.3584; found, 540.3557.

***N*-{3-[1-(3-{[Bis(4-fluorophenyl)acetyl]amino}propyl)-4-piperidinyl]phenyl}-2-methylpropanamide (5f).** Compound **5f** was prepared from bis(4-fluorophenyl)acetic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1 H), 7.39−7.31 (m, 3 H), 7.29−7.21 (m, 5 H), 7.02−6.96 (m, 4 H), 4.80 (s, 1 H), 3.40 (q, J = 4.5 Hz, 2 H), 2.94 (d, J = 10.2 Hz, 2 H), 2.51−2.38 (m, 4 H), 1.97 (dt, J = 1.8, 10.4 Hz, 2 H), 1.81 (m, 2 H), 1.68 (quintet, J = 6.8 Hz, 2 H), 1.59 (m, 3 H), 1.23 (d, J = 6.9 Hz, 6 H); ESMS *m/e* 534.3 $(M + H)^+$; HRMS (FAB) calcd for $C_{32}H_{38}F_2N_3O_2$ $(M + H)^+$, 534.2926; found, 534.2899.

***N*-{3-[1-(3-{[Bis(4-chlorophenyl)acetyl]amino}propyl)-4-piperidinyl]phenyl}-2-methylpropanamide (5g).** Compound **5g** was prepared from bis(4-chlorophenyl)acetic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1 H), 7.34−7.13 (m, 12 H), 4.75 (s, 1 H), 3.41 (q, J = 4.5 Hz, 2 H), 2.94 (d, J = 10.2 Hz, 2 H), 2.51−2.40 (m, 4 H), 1.97 (m, 2 H), 1.82 (m, 2 H), 1.68 (quintet, J = 6.8 Hz, 2 H), 1.59 (m, 3 H), 1.25 (d, J = 6.8 Hz, 6 H); ESMS *m/e* 566.2 $(M + H)^+$; HRMS (FAB) calcd for $C_{32}H_{38}Cl_2N_3O_2$ $(M + H)^+$, 566.2335; found, 566.2311.

***N*-(3-{4-[3-(Isobutyrylamino)phenyl]-1-piperidinyl}propyl)-2,2-diphenylpropanamide (5h).** Compound **5h** was prepared from 2,2-diphenylpropanoic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1 H), 7.42 (s, 1 H), 7.39−7.18 (m, 12 H), 6.89 (d, J = 7.7 Hz, 1 H), 6.23 (m, 1 H), 3.35 (q, J = 6.4 Hz, 2 H), 2.85 (d, J = 10.8 Hz, 2 H), 2.5 (quintet, J = 7.4 Hz, 1 H), 2.45−2.36 (m, 1 H), 2.28 (t, J = 6.4 Hz, 2 H), 1.99 (s, 3 H), 1.91−1.82 (m, 2 H), 1.75−1.68 (m, 2 H), 1.65 (t, J = 6.4 Hz, 2 H), 1.60−1.47 (m, 2 H), 1.23 (d, J = 7.0 Hz, 6 H); ESMS *m/e* 512.4 $(M + H)^+$; HRMS (FAB) calcd for $C_{33}H_{42}N_3O_2$ $(M + H)^+$, 512.3271; found, 512.3248.

***N*-{3-[4-(3-Isobutyrylamino-phenyl)-piperidin-1-yl]-propyl}-2,2-diphenyl-butyramide (5i).** Compound **5i** was prepared from 2,2-diphenylbutyric acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$ δ 7.46 (s, 1 H), 7.41 (s, 1 H), 7.40−7.18 (m, 12 H), 6.88 (d, J = 7.6 Hz, 1 H), 6.23 (m, 1 H), 3.35 (q, J = 6.4 Hz, 2 H), 2.85 (d, J = 10.8 Hz, 2 H), 2.5 (quintet, J = 7.4 Hz, 1 H), 2.45−2.36 (m, 1 H), 2.28 (t, J = 6.4 Hz, 2 H), 1.97 (m, 2 H), 1.91−1.82 (m, 2 H), 1.75−1.68 (m, 2 H), 1.65 (t, J = 6.4 Hz, 2 H), 1.60−1.47 (m, 2 H), 1.25−1.23 (m, 3 H), 1.23 (d, J = 7.0 Hz, 6 H); ESMS *m/e* 526.7 $(M + H)^+$; HRMS (FAB) calcd for $C_{34}H_{44}N_3O_2$ $(M + H)^+$, 526.3428; found, 526.3419.

***N*-(3-{4-[3-(Isobutylrylamino)phenyl]-1-piperidinyl}propyl)-2,2-diphenylheptanamide (5j).** Compound **5j** was prepared from 2,2-diphenylheptanoic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1 H), 7.45 (s, 1 H), 7.40 (m, 1 H), 7.37−7.19 (m, 11 H), 6.88 (d, J = 7.3 Hz, 1 H), 6.34 (t, J = 4.5 Hz, 1 H), 3.34−3.27 (m, 3 H), 2.94−2.87 (m, 2 H), 2.52 (septet, J = 6.9 Hz, 1 H), 2.46−2.34 (m, 4 H), 2.27 (t, J = 6.9 Hz, 2 H), 2.00−1.91 (m, 2 H), 1.77−1.69 (m, 2 H), 1.69−1.52, (m, 5 H), 1.30−1.20 (m, 12 H); ESMS *m/e* 568.4 $(M + H)^+$; HRMS (FAB) calcd for $C_{37}H_{50}N_3O_2$ $(M + H)^+$, 568.3897; found, 568.3880.

***N*-{3-[1-(3-{[Bis(4-fluorophenyl)acetyl]amino}propyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide (5k).** Compound **5k** was prepared from bis(4-fluorophenyl)acetic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.98 (s, 1 H), 7.59 (d, J = 1.8 Hz, 1 H), 7.54−7.51 (m, 1 H), 7.32 (m, 3 H), 7.21−7.18 (m, 1 H), 6.99−6.94 (m, 5 H), 4.87 (s, 1 H), 3.36 (q, J = 5.8 Hz, 2 H), 2.92−2.97 (m, 2 H), 2.68−2.58 (m, 1 H), 2.5 (quintet, J = 7.2 Hz, 1 H), 2.37 (t, J = 5.7 Hz, 2 H), 2.25 (s, 3 H), 2.01−1.92 (m, 2 H), 1.71−1.52 (m, 6 H), 1.16 (d, J = 7.2 Hz, 6 H); ESMS *m/e* 548.4 $(M + H)^+$; HRMS (FAB) calcd for $C_{33}H_{40}F_2N_3O_2$ $(M + H)^+$, 548.3083; found, 548.3056.

***N*-[3-(1-{3-[(Diphenylacetyl)amino]propyl}-4-piperidinyl)-4-methylphenyl]-2-methylpropanamide (5l).** Compound **5l** was prepared from diphenylacetyl chloride and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide according to the general procedure B for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.23 (m, 12 H), 7.14 (br, 1 H), 7.08 (d, J = 8.4 Hz, 1 H), 6.90 (br, 1 H), 4.91 (s, 1 H), 3.41 (dd, J = 6.4, 12.4 Hz, 2 H), 2.95 (d, J = 12.4 Hz, 2 H), 2.66 (m, 1 H), 2.47 (m, 1 H), 2.40 (t, J = 6.4 Hz, 2 H), 2.28 (s, 3 H), 2.03−1.97 (m, 2 H), 1.74−1.62 (m, 6 H), 1.22 (d, J = 7.2 Hz, 6 H); ESMS *m/e* 512.3 $(M + H)^+$; HRMS (FAB) calcd for $C_{33}H_{42}N_3O_2$ $(M + H)^+$, 512.3271; found, 512.3247.

***N*-{5-[1-(3-{[Bis(4-fluorophenyl)acetyl]amino}propyl)-4-piperidinyl]-2,4-difluorophenyl}-2-methylpropanamide (5m).** Compound **5m** was prepared from bis(4-fluorophenyl)acetic acid and *N*-{5-[1-(3-aminopropyl)-4-piperidinyl]-2,4-difluorophenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: UV 254 nm, 100%; ELSD, 100%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (t, J = 8.4 Hz, 1 H), 7.67−7.57 (m, 1 H), 7.51 (s, 1 H), 7.36−7.25 (m, 4 H), 7.03−6.91 (m, 4 H), 6.81 (t, J = 9.6 Hz, 1 H), 4.81 (s, 1 H), 3.45−3.31 (m, 2 H), 2.92 (m, 2 H), 2.83−2.67 (m, 1 H), 2.63−2.47 (m, 1 H), 2.47−2.33 (m, 2 H), 2.05−1.90 (m, 2 H), 1.82−1.72 (m, 2 H), 1.72−1.56 (m, 4 H), 1.22 (d, J = 6.8 Hz, 6 H); ESMS *m/e* 570.2 $(M + H)^+$; HRMS (FAB) calcd for $C_{32}H_{36}F_4N_3O_2$ $(M + H)^+$, 570.2738; found, 570.2713.

***N*-{3-[1-(3-{[Bis(4-fluorophenyl)acetyl]amino}propyl)-4-piperidinyl]-2,4,6-trifluorophenyl}-2-methylpropanamide (5n).** Compound **5n** was prepared from bis(4-fluorophenyl)acetic acid and *N*-{5-[1-(3-aminopropyl)-4-piperidinyl]-2,4,6-trifluorophenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1 H), 7.36−7.28 (m, 4 H), 7.02−6.97 (m, 4 H), 6.78−6.70 (m, 2 H), 4.76 (s, 1 H), 3.41−3.39 (m, 2 H), 3.02−2.96 (m, 3 H), 2.65−2.55 (m, 2 H), 2.10−2.09 (m, 4 H), 1.73−1.65 (m, 4 H), 1.23 (d, J = 6.92 Hz, 6 H); ESMS *m/e* 588.3 $(M + H)^+$; HRMS (FAB) calcd for $C_{32}H_{35}F_5N_3O_2$ $(M + H)^+$, 588.2649; found, 588.2652.

***N*-{3-[1-(3-Diphenylacetylamino-propyl)-piperidin-4-yl]-2-methyl-phenyl}-isobutyramide (5o).** Compound **5o** was prepared from diphenylacetyl chloride and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]-2-methylphenyl}-2-methylpropanamide according to the general procedure B for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.0 Hz, 1 H), 7.35−7.19 (m, 11 H), 7.09−7.02 (m, 3 H), 4.90 (s, 1 H), 3.41 (dd, J = 5.6, 11.6 Hz, 2 H), 2.99 (d, J = 12.8 Hz, 2 H), 2.72 (m, 1 H), 2.59 (m, 1 H), 2.43 (t, J = 6.4 Hz, 2 H), 2.19 (s, 3 H), 2.06−2.00 (m, 2 H), 1.75−

1.60 (m, 6 H), 1.30 (d, J = 6.8 Hz, 6 H); ESMS *m/e* 512.5 (M + H)$^+$; HRMS (FAB) calcd for $C_{33}H_{42}F_5N_3O_2$ (M + H)$^+$, 512.3271; found, 512.3248.

***N*-{3-[1-(3-{[Hydroxy(diphenyl)acetyl]amino}propyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide (5p).** A mixture of hydroxy(diphenyl)acetic acid (100 mg, 0.44 mmol) and 1,1′-carbonyldiimidazole (78 mg, 0.48 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 3 h, then a solution of *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]-4-methylphenyl}-2-methyl propanamide (140 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added. The resulting mixture was stirred at room temperature for overnight, evaporated in vacuo, and dissolved in a mixture of EtOAc and 1 N NaOH. The organic layer was separated, washed twice with water, dried over $MgSO_4$, and concentrated. The residue was purified over preparative TLC (10% 2 M NH_3/MeOH in 50% EtOAc/ hexanes) to give 111 mg (0.21 mmol, 48%) of (*N*-{3-[1-(3-{[hydroxy-(diphenyl)acetyl]amino}propyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1 H), 8.14 (s, 1 H), 7.80 (s, 1 H), 7.64−7.48 (m, 4 H), 7.32−7.16 (m, 6 H), 6.95 (d, J = 8.0 Hz, 1 H), 6.64 (d, J = 8.0 Hz, 1 H), 5.83−5.62 (br, 1 H), 3.54−3.38 (m, 2 H), 3.11−2.94 (m, 2 H), 2.79−2.59 (m, 1 H), 2.57−2.41 (m, 2 H), 2.26 (s, 3 H), 2.29−2.16 (m, 1 H), 2.16−1.91 (m, 4 H), 1.74−1.53 (m, 4 H), 0.86 (d, J = 6.8 Hz, 6 H); ESMS *m/e* 528.4 (M + H)$^+$; HRMS (FAB) calcd for $C_{33}H_{42}N_3O_3$ (M + H)$^+$, 528.3220; found, 528.3196.

2-Methyl-*N*-{4-methyl-3-[1-(3-{[(2R)-2-phenylpropanoyl]-amino}propyl)-4-piperidinyl]phenyl}propanamide ((*S*)-6a). Compound **(*S*)-6a** was prepared from (2*S*)-2-phenylpropanoic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1 H), 7.44 (d, J = 2.0 Hz, 1 H), 7.38−7.26 (m, 5 H), 7.26−7.18 (m, 1 H), 7.06 (d, J = 8.0 Hz, 1 H), 6.74−6.63 (m, 1 H), 3.63−3.49 (m, 1 H), 3.38−3.23 (m, 2 H), 2.91 (ABq, 2 H), 2.71−2.58 (m, 1 H), 2.58−2.45 (m, 1 H), 2.32 (t, J = 6.4 Hz, 2 H), 2.26 (s, 3 H), 2.05−1.87 (m, 2 H), 1.77−1.55 (m, 6 H), 1.53 (d, J = 7.2 Hz, 3 H), 1.22 (d, J = 6.8 Hz, 6 H); ESMS *m/e* 450.4 (M + H)$^+$; HCl salt of 2-methyl-*N*-{4-methyl-3-[1-(3-{[(2S)-2-phenylpropanoyl]amino}propyl)-4-piperidinyl]phenyl}-propanamide $[\alpha]_D$ = −34.3° (*c* 1, MeOH); HRMS calcd for $C_{28}H_{40}N_3O_2$ (M + H)$^+$, 450.3120; found, 450.3116.

2-Methyl-*N*-{4-methyl-3-[1-(3-{[(2S)-2-phenylpropanoyl]-amino}propyl)-4-piperidinyl]phenyl}propanamide ((*R*)-6a). Compound **(*R*)-6a** was prepared from (2*R*)-2-phenylpropanoic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1 H), 7.47−7.38 (m, 1 H), 7.37−7.26 (m, 5 H), 7.26−7.18 (m, 1 H), 7.06 (d, J = 8.0 Hz, 1 H), 6.74−6.64 (m, 1 H), 3.64−3.50 (m, 1 H), 3.38−3.23 (m, 2 H), 2.92 (ABq, 2 H), 2.70−2.58 (m, 1 H), 2.58−2.42 (m, 1 H), 2.33 (t, J = 6.4 Hz, 2 H), 2.26 (s, 3 H), 2.02−1.88 (m, 2 H), 1.76−1.55 (m, 6 H), 1.53 (d, J = 7.2 Hz, 3 H), 1.22 (d, J = 6.8 Hz, 6 H); ESMS *m/e* 450.2 (M + H)$^+$; HCl salt of 2-methyl-*N*-{4-methyl-3-[1-(3-{[(2*R*)-2-phenyl propanoyl]-amino}propyl)-4-piperidinyl]phenyl}propanamide $[\alpha]_D$ = + 22.3° (*c* 1, MeOH); HRMS calcd for $C_{28}H_{40}N_3O_2$ (M + H)$^+$, 450.3115; found, 450.3095.

(2*S*)-2-(4-Fluorophenyl)-*N*-(3-{4-[5-(isobutyrylamino)-2-methylphenyl]-1-piperidinyl}propyl)propanamide ((*S*)-6b). Compound **(*S*)-6b** was prepared from (2*S*)-2-(4-fluorophenyl)propanoic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: $[\alpha]_D$ = +13.5° (*c* 1.02, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.49 (m, 2 H), 7.37−7.29 (m, 2 H), 7.26−7.19 (m, 1 H), 7.06 (d, J = 8.0 Hz, 1 H), 7.04−6.92 (m, 3 H), 3.56 (t, J = 6.8 Hz, 1 H), 3.43−3.23 (m, 2 H), 2.95 (ABq, 2 H), 2.63−2.59 (m, 1 H), 2.59−2.45 (m, 1 H), 2.37 (t, J = 6.0 Hz, 2 H), 2.27 (s, 3 H), 2.07−1.90 (m, 2 H), 1.82−1.57 (m, 6 H), 1.50 (d, J = 7.2 Hz, 3 H), 1.22 (d, J = 7.2 Hz, 6 H); ESMS *m/e* 468.3 (M + H)$^+$; HRMS calcd for $C_{28}H_{39}FN_3O_2$ (M + H)$^+$, 468.3020; found, 468.3000.

(2*R*)-2-(4-Fluorophenyl)-*N*-(3-{4-[5-(isobutyrylamino)-2-methylphenyl]-1-piperidinyl}propyl)propanamide ((*R*)-6b). Compound **(*R*)-6b** was prepared from (2R)-2-(4-fluorophenyl)propanoic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: $[\alpha]_D$ = −9.1° (*c* 1.65, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 2.0 Hz, 1 H), 7.37−7.28 (m, 2 H), 7.23−7.14 (m, 2 H), 7.08 (d, J = 8.0 Hz, 1 H), 7.05−6.96 (m, 2 H), 6.90−6.82 (m, 1 H), 3.54 (q, J = 7.2 Hz, 1 H), 3.43−3.23 (m, 2 H), 2.95 (ABq, 2 H), 2.73−2.59 (m, 1 H), 2.57−2.42 (m, 1 H), 2.42−2.32 (m, 2 H), 2.28 (s, 3 H), 2.07−1.91 (m, 2 H), 1.83−1.57 (m, 6 H), 1.51 (d, J = 7.2 Hz, 3 H), 1.23 (d, J = 6.8 Hz, 6 H); ESMS *m/e* 468.3 (M + H)$^+$; HRMS calcd for $C_{28}H_{39}FN_3O_2$ (M + H)$^+$, 468.3026; found, 468.3026.

1-(4-Fluorophenyl)-*N*-(3-{4-[5-(isobutyrylamino)-2-methylphenyl]-1-piperidinyl}propyl)cyclopentanecarboxamide (6c). Compound **6c** was prepared from 1-(4-fluorophenyl)cyclopentanecarboxylic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.37 (m, 3 H), 7.29−7.27 (m, 2 H), 7.09 (d, J = 8.4 Hz, 1 H), 7.04−7.00 (m, 2 H), 6.47 (br s, 1 H), 3.29 (dd, J = 5.6, 12.0 Hz, 2 H), 2.94 (d, J = 12.0 Hz, 2 H), 2.66 (m, 1 H), 2.54−2.48 (m, 3 H), 2.33−2.30 (m, 2 H), 2.29 (s, 3 H), 2.03−1.95 (m, 4 H), 1.84−1.60 (m, 10 H), 1.26 (d, J = 6.8 Hz, 6 H); ESMS *m/e* 522.3 (M + H)$^+$; HRMS calcd for $C_{31}H_{43}FN_3O_2$ (M + H)$^+$, 522.3490; found, 522.3463.

1-(4-Fluorophenyl)-*N*-(3-{4-[5-(isobutylamino)-2-methylphenyl]-1-piperidinyl}propyl)cyclohexanecarboxamide (6d). Compound **6d** was prepared from 1-(4-fluorophenyl)cyclohexanecarboxylic acid and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]-4-methylphenyl}-2-methylpropanamide according to the general procedure A for the synthesis of compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.43 (m, 3 H), 7.26−7.22 (m, 2 H), 7.10 (d, J = 8.4 Hz, 1 H), 7.06−7.01 (m, 2 H), 6.74 (br s, 1 H), 3.31 (dd, J = 6.0, 12.0 Hz, 2 H), 2.96 (d, J = 11.6 Hz, 2 H), 2.68 (m, 1 H), 2.52 (m, 1 H), 2.36−2.32 (m, 4 H), 2.29 (s, 3 H), 2.03−1.90 (m, 4 H), 1.74−1.61 (m, 12 H), 1.27 (d, J = 6.8 Hz, 6 H); ESMS *m/e* 508.3 (M + H)$^+$; HRMS calcd for $C_{31}H_{43}FN_3O_2$ (M + H)$^+$, 508.3333; found, 508.3309.

1-Bromo-2,4-difluoro-5-nitrobenzene (9a). To a 0 °C mixture of 1-bromo-2,4-difluorobenzene (20.0 g; 11.7 mL; 0.100 mol) and H_2SO_4 (76.8 mL) was added HNO_3 (68.0 mL) over 45 min at such a rate that the internal temperature was <7 °C. The resulting mixture was stirred for 1 h at 0 °C, poured into ice water (400 mL), stirred vigorously for 2−3 min, and extracted with CH_2Cl_2 (400 mL). The organic layers were washed with brine (1 × 500 mL), dried over Na_2SO_4, filtered, and evaporated to give the product as a yellow oil (23.5 g, 95%). ^{1}H NMR ($CDCl_3$) δ 8.39 (t, J = 7.2 Hz, 1 H), 7.14 (ddd, J = 0.3, 7.8, 9.9 Hz, 1 H).

1-Bromo-3-nitro-2,4,6-trifluorobenzene (9b). To a cooled (1.3 °C) mixture of 1-bromo-2,4,6-trifluorobenzene (30.0 g; 142 mmol) and H_2SO_4 (115 mL) was added HNO_3 (68%; 102 mL) over 1.5 h at such a rate that the internal temperature was <8 °C. After stirring at 0 °C for 2 h, the resulting mixture was poured into ice water (1850 mL), stirred vigorously for 30 min, and extracted with CH_2Cl_2 (3 × 600 mL). The combined organic layers were washed with water (2 × 600 mL), dried over $MgSO_4$, filtered, and concentrated to give the desired product as a clear yellow oil (35.0 g, 99%). ^{1}H NMR ($CDCl_3$) δ 7.01 (ddd, J = 2.4, 7.8, 9.3 Hz, 1 H); ^{19}F NMR ($CDCl_3$) δ −116.20 to −116.10, −107.73 to −107.71, −93.80 to −93.70.

5-Bromo-2,4-difluoroaniline (10a). To a solution of 1-bromo-2,4-difluoro-5-nitrobenzene (5.04 g, 21.3 mmol) in EtOH (100 mL), THF (50 mL), $NH_4Cl_{(satd)}$ (25 mL), and H_2O (25 mL) was added iron powder (5.00 g, 89.5 mmol). The mixture was refluxed for 2 h and filtered through celite. The filter pad was washed with EtOAc (3 × 50 mL). The filtrate was concentrated and the residue was partitioned between EtOAc and brine. The organic layer was dried over $MgSO_4$ and concentrated. Purification by flash chromatography (5−10% EtOAc/ Hexane) provided 2.60 g (59%) of 5-bromo-2,4-

difluoroaniline. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84−6.77 (m, 2 H), 3.81−3.57 (br, 2 H); ESMS *m*/*e* 208.2 $(M + H)^+$.

3-Bromo-2,4,6-trifluoroaniline (10b). Compound **10b** was prepared from 1-bromo-3-nitro-2,4,6-trifluorobenzene **9b** according to the procedure for the synthesis of compound **10a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85−6.76 (m, 1 H), 3.78−3.51 (br, 2 H).

***N*-(5-Bromo-2,4-difluorophenyl)-2-methylpropanamide (11a).** Into a solution of 2.6 g (12.6 mmol) of 5-bromo-2,4-difluoroaniline **10a** and 2.1 mL (15.1 mmol) of triethylamine in 50 mL THF at 0 °C was slowly added 1.6 mL (15.1 mmol) of isobutyryl chloride. The reaction mixture was stirred at room temperature for 2 h and concentrated in vacuo. The residue was dissolved in EtOAc and washed with H_2O, saturated aqueous Na_2CO_3, and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 3.30 g (11.8 mmol, 94%) of *N*-(5-bromo-2,4-difluorophenyl)-2-methylpropanamide: ESMS *m*/*e* 278.1 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (m, 1 H), 7.27 (m, 1 H), 6.95 (m, 1 H), 2.56 (sept, J = 6.35 Hz, 1 H), 1.29−1.22 (m, 6 H).

***N*-(3-Bromo-2,4,6-trifluorophenyl)-2-methylpropanamide (11b).** Compound **11b** was prepared from 3-bromo-2,4,6-trifluoroaniline **10b** according to the procedure for the synthesis of compound **11a**. ESMS *m*/*e* 296.3 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89−6.82 (m, 1 H), 6.82−6.75 (m, 1 H), 2.63 (sept, J = 6.75 Hz, 1 H), 1.27 (d, J = 6.75 Hz, 6 H).

***N*-(3-Iodo-4-methyl-phenyl)-isobutyramide (11c).** Compound **11c** was prepared from 3-iodo-4-methyl-phenylamine **10c** according to the procedure for the synthesis of compound **11a**. ESMS *m*/*e* 304.2 $(M + H)^+$.

***N*-(3-Iodo-phenyl)-isobutyramide (11d).** Compound **11d** was prepared from 3-iodo-phenylamine **10d** according to the procedure of **11a**. ESMS *m*/*e* 290.2 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1 H), 7.47 (d, J = 8.22 Hz, 1 H), 7.41 (d, J = 8.22 Hz, 1 H), 7.27−7.13 (br, 1 H), 7.00 (t, J = 8.22 Hz, 1 H), 2.48 (sept, J = 7.39 Hz, 1 H), 1.23 (d, J = 7.39 Hz, 6 H).

***N*-(3-Iodo-2-methyl-phenyl)-isobutyramide (11e).** Compound **11e** was prepared from 3-iodo-2-methyl-phenylamine **10e** according to the procedure for the synthesis of compound **11a**. ESMS *m*/*e* 290.2 $(M + H)^+$.

***tert*-Butyl 4-[2,4-Difluoro-5-(isobutyrylamino)phenyl]-3,6-dihydro-1(2*H*)-pyridine carboxylate (13a).** To a 250-mL RB flask containing *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate **12** (3.31 g, 10.7 mmol), K_2CO_3 (4.44 g, 32.1 mmol), and $PdCl_2$dppf (870 mg, 1.07 mmol) was added a solution of *N*-(5-bromo-2,4-difluorophenyl)-2-methylpropanamide **11a** (3.28 g, 11.8 mmol) in DMF (100 mL) at room temperature under argon. The mixture was heated to 80 °C under argon overnight, cooled to room temperature, and filtered through celite, and the celite was washed with EtOAc (3 × 20 mL). The filtrates were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (10−20% EtOAc/hexane) to give 2.40 g (6.31 mmol, 59%) of *tert*-butyl 4-[2,4-difluoro-5-(isobutyrylamino)phenyl]-3,6-dihydro-1(2*H*)-pyridine carboxylate: ESMS *m*/*e* 379.3 $(M - H)^-$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (t, J = 8.78 Hz, 1 H), 7.24 (s, 1 H), 6.83 (t, J = 9.97 Hz, 1 H), 6.00−5.83 (br, 1 H), 4.04 (m, 2 H), 3.58 (m, 2 H), 2.56 (sept, J = 6.78 Hz, 1 H), 2.47 (m, 2 H), 1.49 (s, 9 H), 1.27 (d, J = 6.78 Hz, 6 H).

***tert*-Butyl 4-[2,4,6-Trifluoro-3-(isobutyrylamino)phenyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate (13b).** Compound **13b** was prepared from *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate **12** and *N*-(3-bromo-2,4,6-trifluorophenyl)-2-methylpropanamide **11b** according to the procedure for the synthesis of compound **13a**. ESMS *m*/*e* 397.6 $(M - H)^-$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (m, 1 H), 5.84−5.75 (br, 1 H), 4.05 (m, 2 H), 3.61 (m, 2 H), 2.62 (sept, J = 6.50 Hz, 1 H), 2.37 (m, 2 H), 1.49 (s, 9 H), 1.28 (d, J = 6.50 Hz, 6 H).

4-(5-Isobutyrylamino-2-methyl-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (13c). Compound **13c** was prepared from *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate **12** and *N*-(3-iodo-4-methyl-phenyl)-isobutyramide **11c** according to the procedure for the synthesis of compound **13a**. ESMS *m*/*e* 303.0 $(M - 56 + H)^+$.

4-(3-Isobutyrylamino-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic Acid *tert*-Butyl Ester (13d). Compound **13d** was prepared from *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate **12** and *N*-(3-iodo-phenyl)-isobutyramide **11d** according to the procedure for the synthesis of compound **13a**. ESMS *m*/*e* 343.5 $(M - H)^-$.

4-(3-Isobutyrylamino-2-methyl-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (13e). Compound **13e** was prepared from *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate **12** and *N*-(3-iodo-2-methyl-phenyl)-isobutyramide **11e** according to the procedure for the synthesis of compound **13a**. ESMS *m*/*e* 357.4 $(M - H)^-$.

***tert*-Butyl 4-[2,4-Difluoro-5-(isobutyrylamino)phenyl]-1-piperidinecarboxylate (14a).** A solution of *tert*-butyl 4-[2,4-difluoro-5-(isobutyrylamino)phenyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate **13a** (2.40 g, 6.31 mmol) and 10% Pd/C (500 mg) in EtOAc (40.0 mL) and MeOH (10.0 mL) was hydrogenated (200 psi) at room temperature overnight. The reaction mixture was filtered through celite and washed with ethanol (3 × 10 mL). The combined extracts were concentrated in vacuo to afford 2.04 g (5.34 mmol, 85%) of *tert*-butyl 4-[2,4-difluoro-5-(isobutyrylamino)phenyl]-1-piperidinecarboxylate: ESMS *m*/*e* 383.2 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (t, J = 7.75 Hz, 1 H), 7.35−7.30 (br, 1 H), 6.82 (t, J = 10.0 Hz, 1 H), 4.15−4.08 (m, 2 H), 2.94 (m, 1 H), 2.84−2.73 (m, 2 H), 2.58 (sept, J = 6.89 Hz, 1 H), 1.81−1.72 (m, 2 H), 1.72−1.59 (m, 2 H), 1.48 (s, 9 H), 1.26 (d, J = 6.89 Hz, 6 H).

4-(2,4,6-Trifluoro-3-isobutyrylamino-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (14b). Compound **14b** was prepared from *tert*-butyl 4-[2,4,6-trifluoro-3-(isobutyrylamino)-phenyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate **13b** according to the procedure for the synthesis of compound **14a**. ESMS *m*/*e* 401.4 $(M + H)^+$.

4-(5-Isobutyrylamino-2-methyl-phenyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (14c). Compound **14c** was prepared from 4-(5-isobutyrylamino-2-methyl-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester **13c** according to the procedure for the synthesis of compound **14a**. ESMS *m*/*e* 361.2 $(M + H)^+$.

4-(3-Isobutyrylamino-phenyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (14d). Compound **14d** was prepared from 4-(3-isobutyrylamino-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester **13d** according to the procedure for the synthesis of compound **14a**. ESMS *m*/*e* 347.2 $(M + H)^+$.

4-(3-Isobutyrylamino-2-methyl-phenyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (14e). Compound **14e** was prepared from 4-(3-isobutyrylamino-2-methyl-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester **13e** according to the procedure for the synthesis of compound **14a**. ESMS *m*/*e* 361.2 $(M + H)^+$.

***N*-[2,4-Difluoro-5-(4-piperidinyl)phenyl]-2-methylpropanamide (15a)**. Into a solution of *tert*-butyl 4-[2,4-difluoro-5-(isobutyrylamino)phenyl]-1-piperidinecarboxylate **14a** (6.54 g, 17.1 mmol) in 1,4-dioxane (40.0 mL) was added 4 M HCl in 1,4-dioxane (160 mL) at room temperature. The reaction mixture was stirred for 1 h and concentrated in vacuo. The residue was dissolved in 100 mL of H_2O and was basified with 10% KOH solution (50 mL). The aqueous layer was extracted with $CHCl_3$/*i*-PrOH (3:1, 3 × 150 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 4.72 g (16.7 mmol, 98%) of *N*-[2,4-difluoro-5-(4-piperidinyl)phenyl]-2-methylpropanamide: ESMS *m*/*e* 283.3 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (t, J = 8.24 Hz, 1 H), 6.88 (t, J = 10.9 Hz, 1 H), 3.23−3.13 (m, 2 H), 2.93 (m, 1 H), 2.84−2.73 (m, 2 H), 2.61 (sept, J = 6.76 Hz, 1 H), 1.81−1.74 (m, 2 H), 1.72−1.61 (m, 2 H), 1.10 (d, J = 6.76 Hz, 6 H).

2-Methyl-*N*-[2,4,6-trifluoro-3-(4-piperidinyl)phenyl] propanamide (15b). Compound **15b** was prepared from 4-(2,4,6-trifluoro-3-isobutyrylamino-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester **14b** according to the procedure for the synthesis of compound **15a**. ESMS *m*/*e* 301.2 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ

6.80 (m, 1 H), 3.86−3.76 (m, 1 H), 3.08−2.97 (m, 3 H), 2.67−2.54 (m, 3 H), 2.01−1.87 (m, 2 H), 1.65−1.56 (m, 2 H), 1.10 (d, J = 6.76 Hz, 6 H).

***tert*-Butyl 4-[5-(Isobutyrylamino)-2-methylphenyl]-1-piperidinecarboxylate (15c).** Compound **15c** was prepared from 4-(5-isobutyrylamino-2-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester **14c** according to the procedure for the synthesis of compound **15a**. ESMS *m*/*e* 261.0 $(M + H)^+$.

***N*-(3-Piperidin-4-yl-phenyl)-isobutyramide (15d).** Compound **15d** was prepared from 4-(3-isobutyrylamino-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester **14d** according to the procedure for the synthesis of compound **15a**. ESMS *m*/*e* 247.4 $(M + H)^+$.

***N*-(2-Methyl-3-piperidin-4-yl-phenyl)-isobutyramide (15e).** Compound **15e** was prepared from 4-(3-isobutyrylamino-2-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester **14e** according to the procedure for the synthesis of compound **15a**. ESMS *m*/*e* 261.0 $(M + H)^+$.

General Procedure to Synthesize 16: A mixture of piperidine **15** (1.00 equiv, 0.023 mmol), *N*-(*n*-bromoalkyl)phthalimide (1.50 equiv, 0.034 mmol), Bu_4NI (200 mg), and diisopropylethylamine (5.00 equiv, 0.113 mmol) in dioxane (200 mL) was heated at 99 °C for 24 h. The reaction was monitored by TLC analysis (95:5 CH_2Cl_2/methanol). If necessary, an additional 0.0113 mmol of the appropriate bromoalkylphthalimide was added to the reaction mixture and heating was continued for an additional 48 h. The reaction mixture was cooled to room temperature, the ammonium salts were filtered out, and the solvent was removed under reduced pressure. The crude product was chromatographed (silica) to give the desired *N*-(*n*-phthalimidoalkyl)piperidine **16**.

***N*-(5-{1-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-piperidin-4-yl}-2,4-difluoro-phenyl)-isobutyramide (16a).** Compound **16a** was prepared from *N*-[2,4-difluoro-5-(4-piperidinyl)-phenyl]-2-methylpropanamide **15a** according to the general procedure to synthesize **16**. ESMS *m*/*e* 470.2 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (t, J = 8.97 Hz, 1 H), 7.88−7.82 (m, 2 H), 7.72−7.67 (m, 2 H), 7.29−7.23 (m, 1 H), 6.76 (t, J = 8.97 Hz, 1 H), 3.78 (t, J = 6.96 Hz, 2 H), 2.99−2.92 (m, 2 H), 2.74−2.64 (m, 1 H), 2.56 (sept, J = 6.86 Hz, 1 H), 2.42 (t, J = 6.62 Hz, 2 H), 1.98−1.90 (m, 2 H), 1.90−1.84 (m, 1 H), 1.72−1.65 (m, 2 H), 1.61−1.49 (m, 2 H), 1.27 (d, J = 6.79 Hz, 6 H).

***N*-(3-{1-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-piperidin-4-yl}-2,4,6-trifluoro-phenyl)-isobutyramide (16b).** Compound **16b** was prepared from 2-methyl-*N*-[2,4,6-trifluoro-3-(4-piperidinyl)phenyl] propanamide **15b** according to the general procedure to synthesize compound **16**. ESMS *m*/*e* 488.4 $(M + H)^+$.

***N*-(3-{1-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-piperidin-4-yl}-4-methyl-phenyl)-isobutyramide (16c).** Compound **16c** was prepared from *tert*-butyl 4-[5-(isobutyrylamino)-2-methylphenyl]-1-piperidinecarboxylate **15c** according to the general procedure to synthesize compound **16**. ESMS *m*/*e* 448.2 $(M + H)^+$.

***N*-(3-{1-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-piperidin-4-yl}-phenyl)-isobutyramide (16d).** Compound **16d** was prepared from *N*-(3-piperidin-4-yl-phenyl)-isobutyramide **15d** according to the general procedure to synthesize compound **16**. ESMS *m*/*e* 420.2 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.84−7.70 (m, 4 H), 7.59 (s, 1 H), 7.25−7.17 (m, 2 H), 6.95−6.89 (m, 1 H), 3.74−3.52 (m, 4 H), 3.19−2.97 (m, 4 H), 2.82−2.79 (m, 1 H), 2.56 (sept, J = 6.76 Hz, 1 H), 2.11−1.84 (m, 4 H), 1.72−1.65 (m, 4 H), 1.13 (d, J = 6.76 Hz, 6 H).

***N*-(3-{1-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-piperidin-4-yl}-phenyl)-isobutyramide (16e).** Compound **16e** was prepared from *N*-(3-piperidin-4-yl-phenyl)-isobutyramide **15d** according to the general procedure for the synthesis of compound **16**. ESMS *m*/*e* 434.2 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.84−7.70 (m, 4 H), 7.59 (s, 1 H), 7.25−7.17 (m, 2 H), 6.95−6.89 (m, 1 H), 3.74−3.52 (m, 4 H), 3.19−2.97 (m, 4 H), 2.82−2.79 (m, 1 H), 2.56 (sept, J = 6.76 Hz, 1 H), 2.11−1.84 (m, 4 H), 1.72−1.65 (m, 4 H), 1.13 (d, J = 6.76 Hz, 6 H).

***N*-(3-{1-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-butyl]-piperidin-4-yl}-phenyl)-isobutyramide (16f).** Compound **16f** was prepared from *N*-(3-piperidin-4-yl-phenyl)-isobutyramide **15d** according to the general procedure for the synthesis of compound **16**. ESMS *m*/*e* 448.0 $(M + H)^+$.

***N*-(3-{1-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-pentyl]-piperidin-4-yl}-phenyl)-isobutyramide (16g).** Compound **16g** was prepared from *N*-(3-piperidin-4-yl-phenyl)-isobutyramide **15d** according to the general procedure for the synthesis of compound **16**. ESMS *m*/*e* 462.2 $(M + H)^+$.

***N*-(3-{1-[6-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-hexyl]-piperidin-4-yl}-phenyl)-isobutyramide (16h).** Compound **16h** was prepared from *N*-(3-piperidin-4-yl-phenyl)-isobutyramide **15d** according to the general procedure for the synthesis of compound **16**. ESMS *m*/*e* 476.3 $(M + H)^+$.

***N*-(3-{1-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-piperidin-4-yl}-2-methyl-phenyl)-isobutyramide (16i).** Compound **16i** was prepared from *N*-(2-methyl-3-piperidin-4-yl-phenyl)-isobutyramide **15e** according to the general procedure for the synthesis of compound **16**. ESMS *m*/*e* 448.3 $(M + H)^+$.

General Procedure to Synthesize 7: A solution of phthalimide-protected amine **16a**−**16i** with excess hydrazine hydrate (10 equiv) in ethanol (0.5−1.0 M) was heated at 90 °C for 4 h. The reaction mixture was monitored by TLC to completion. Upon completion of the reaction, the mixture was cooled to room temperature, the insoluble byproducts were removed by filtration through celite, and the filtrate was concentrated in vacuo. The crude product was chromatographed (dichloromethane−methanol−isopropylamine) to give the desired products **7a**−**7i**.

***N*-{5-[1-(3-Amino-propyl)-piperidin-4-yl]-2,4-difluoro-phenyl}-isobutyramide (7a).** Compound **7a** was prepared from *N*-(5-{1-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-piperidin-4-yl}-2,4-difluoro-phenyl)-isobutyramide **16a** according to the general procedure for the synthesis of compound **7**. ESMS *m*/*e* 340.1 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (t, J = 8.17 Hz, 1 H), 6.97 (t, J = 8.17 Hz, 1 H), 3.14−3.08 (m, 2 H), 2.92−2.81 (m, 1 H), 2.73−2.66 (m, 3 H), 2.49−2.45 (m, 2 H), 2.18−2.10 (m, 2 H), 1.87−1.77 (m, 5 H), 1.76−1.68 (m, 1 H), 1.22 (d, J = 6.92 Hz, 6 H).

***N*-{3-[1-(3-Amino-propyl)-piperidin-4-yl]-2,4,6-trifluoro-phenyl}-isobutyramide (7b).** Compound **7b** was prepared from *N*-(3-{1-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-piperidin-4-yl}-2,4,6-trifluoro-phenyl)-isobutyramide **16b** according to the general procedure for the synthesis of compound **7**. ESMS *m*/*e* 358.2 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (t, J = 8.17 Hz, 1 H), 6.97 (t, J = 8.17 Hz, 1 H), 3.14−3.08 (m, 2 H), 2.92−2.81 (m, 1 H), 2.73−2.66 (m, 3 H), 2.49−2.45 (m, 2 H), 2.18−2.10 (m, 2 H), 1.87−1.77 (m, 5 H), 1.76−1.68 (m, 1 H), 1.22 (d, J = 6.92 Hz, 6 H).

***N*-{3-[1-(3-Amino-propyl)-piperidin-4-yl]-4-methyl-phenyl}-isobutyramide (7c).** Compound **7c** was prepared from *N*-(3-{1-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-piperidin-4-yl}-4-methyl-phenyl)-isobutyramide **16c** according to the general procedure for the synthesis of compound **7**. ESMS *m*/*e* 318.2 $(M + H)^+$.

***N*-{3-[1-(2-Amino-ethyl)-piperidin-4-yl]-phenyl}-isobutyramide (7d).** Compound **7d** was prepared from *N*-(3-{1-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-piperidin-4-yl}-phenyl)-isobutyramide **16d** according to the general procedure for the synthesis of compound **7**. ESMS *m*/*e* 318.2 $(M + H)^+$.

***N*-{3-[1-(3-Amino-propyl)-piperidin-4-yl]-phenyl}-isobutyramide (7e).** Compound **7e** was prepared from *N*-(3-{1-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-piperidin-4-yl}-phenyl)-isobutyramide **16e** according to the general procedure for the synthesis of compound **7**. ESMS *m*/*e* 304.3 $(M + H)^+$.

***N*-{3-[1-(4-Amino-butyl)-piperidin-4-yl]-phenyl}-isobutyramide (7f).** Compound **7f** was prepared from *N*-(3-{1-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyl]-piperidin-4-yl}-phenyl)-isobutyramide **16f** according to the general procedure for the synthesis of compound **7**. ESMS *m*/*e* 318.2 $(M + H)^+$.

***N*-{3-[1-(5-Amino-pentyl)-piperidin-4-yl]-phenyl}-isobutyramide (7g).** Compound **7g** was prepared from *N*-(3-{1-[5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentyl]-piperidin-4-yl}-phenyl)-isobutyramide **16g** according to the general procedure for the synthesis of compound **7**. ESMS *m*/*e* 332.2 $(M + H)^+$.

***N*-{3-[1-(6-Amino-hexyl)-piperidin-4-yl]-phenyl}-isobutyramide (7h).** Compound **7h** was prepared from *N*-(3-{1-[6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-hexyl]-piperidin-4-yl}-phenyl)-isobutyramide **16h** according to the general procedure for the synthesis of compound **7**. ESMS *m*/*e* 346.2 $(M + H)^+$.

***N*-{3-[1-(3-Amino-propyl)-piperidin-4-yl]-2-methyl-phenyl}-isobutyramide (7i).** Compound **7i** was prepared from *N*-(3-{1-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-piperidin-4-yl}-2-methyl-phenyl)-isobutyramide **16i** according to the general procedure for the synthesis of compound **7**. ESMS *m*/*e* 318.2 $(M + H)^+$.

Bis-(4-fluoro-phenyl)-acetic Acid (17b). Fluorobenzene (13.6 g, 0.142 mol) and glyoxylic acid monohydrate (2.35 g, 0.026 mol) were dissolved in warm acetic acid (30.0 mL). The mixture was cooled in an ice/water bath and concentrated sulfuric acid (20.0 mL) was added dropwise over 0.5 h. The resulting thick red suspension was stirred at 80 °C for 12 h and then cooled to room temperature. Water (300 mL) was added and the pH was adjusted to 3 with potassium hydroxide pellets and 10% KOH solution. The aqueous solution was extracted with ethyl acetate (3 × 100 mL), and the combined organic extracts were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to give the desired product (5.18 g, 82%) as a red solid, which was used in the subsequent step without further purification: ^{1}H NMR (400 MHz, CD_3OD) δ 9.45 (br s, 1 H), 7.31−7.25 (m, 4 H), 7.06−7.0 (m, 4 H), 5.01 (s, 1 H).

Bis-(4-chloro-phenyl)-acetic Acid (17c). Compound **17c** was prepared from chlorobenzene and glyoxylic acid monohydrate according to the procedure for the synthesis of compound **17b**. ESMS *m*/*e* 279.1 $(M - H)^-$.

(2*S*)-2-(4-Fluorophenyl)propanoic Acid ((*S*)-18b). (4*S*)-3-[(4-Fluorophenyl)acetyl]-4-isopropyl-1,3-oxazolidin-2-one: To a solution of (4*S*)-4-isopropyl-1,3-oxazolidin-2-one (2.0 g, 15.5 mmol) in dry THF (20 mL) at −78 °C under argon was added dropwise a 2.5 M solution of *n*-BuLi in hexanes (6.2 mL, 15.5 mmol). After stirring at −78 °C for 15 min, (4-fluorophenyl)acetyl chloride (2.55 mL, 18.6 mmol) was added. The resulting reaction mixture was stirred at −78 °C for 30 min and 0 °C for 15 min, quenched with saturated NH_4Cl (5 mL), and concentrated in vacuo. The residue was dissolved in EtOAc (100 mL) and washed with saturated Na_2CO_3 followed by brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (10−15% EtOAc/hexane) to give 2.83 g (10.7 mmol, 69%) of (4*S*)-3-[(4-fluorophenyl)acetyl]-4-isopropyl-1,3-oxazolidin-2-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.25 (m, 2 H), 7.10 (t, J = 8.5 Hz, 2 H), 4.46−4.41 (m, 1 H), 4.36−4.15 (m, 4 H), 2.40−2.28 (m, 1 H), 0.88 (d, J = 7.6 Hz, 3 H), 0.79 (d, J = 7.6 Hz, 3 H); ESMS *m*/*e* 266.2 $(M + H)^+$.

(4*S*)-3-[(2*S*)-2-(4-Fluorophenyl)propanoyl]-4-isopropyl-1,3-oxazolidin-2-one. To a solution of (4*S*)-3-[(4-fluorophenyl)acetyl]-4-isopropyl-1,3-oxazolidin-2-one (2.81 g, 10.6 mmol) in dry THF (40 mL) at −78 °C under argon was added dropwise a 1.0 M solution of NaHMDS in THF (11.7 mL, 11.7 mmol) over a period of 10 min. After stirring at −78 °C for 1 h, MeI (3.30 mL, 53.0 mmol) was added. The resulting reaction mixture was stirred at −78 °C for 1 h and −40 °C for 2 h, quenched with HOAc (32 mmol) in ether (20 mL), and filtered over celite. The filtrate was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O followed by brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (5−10% EtOAc in hexane) to give 2.40 g (8.60 mmol, 81%) of (4*S*)-3-[(2*S*)-2-(4-fluorophenyl)-propanoyl]-4-isopropyl-1,3-oxazolidin-2-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.31 (m, 2 H), 7.02−6.96 (m, 2 H), 5.13 (q, J = 7.7 Hz, 1 H), 4.38−4.33 (m, 1 H), 4.18−4.13 (m, 2 H), 2.48−2.37 (m, 1 H), 1.49 (d, J = 7.3 Hz, 3 H), 0.91 (apparent t, J = 6.9 Hz, 6 H); ESMS *m*/*e* 280.2 $(M + H)^+$.

(2*S*)-2-(4-Fluorophenyl)propanoic Acid ((*S*)-18b). To a solution of (4*S*)-3-[(2S)-2-(4-fluorophenyl) propanoyl]-4-isopropyl-1,3-oxazolidin-2-one (2.40 g, 8.60 mmol) in 160 mL of THF/H_2O (3:1) at 0 °C, was added 30% H_2O_2 (7.8 mL, 68.8 mmol) followed by LiOH (722 mg, 17.2 mmol). The resulting mixture was stirred at 0 °C for 2 h, and the excess peroxide was quenched at 0 °C with 1.5 N aqueous Na_2SO_3 (51 mL). After buffering to pH 9−10 with aqueous $NaHCO_3$ and evaporation of the THF, the oxazolidone chiral auxiliary was recovered by EtOAc extraction (50 mL × 3). The aqueous layer was acidified with 3 N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 0.92 g (5.47 mmol, 64%) of (2*S*)-2-(4-fluorophenyl)propanoic acid: $[\alpha]_D$ = +70° (*c* 1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.2−11.4 (br, 1 H), 7.31−7.24 (m, 2 H), 7.04−6.97 (m, 2 H), 3.72 (q, J = 7.3 Hz, 1 H), 1.49 (d, J = 7.3 Hz, 3 H); ESMS *m*/*e* 167.2 $(M - H)^+$.

(2*R*)-2-(4-Fluorophenyl)propanoic Acid ((*R*)-18b). Compound **(*R*)-18b** was prepared accordingly: $[\alpha]_D = -61.5°$ (*c* 1.04, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.2−11.4 (br, 1 H), 7.31−7.24 (m, 2 H), 7.04−6.97 (m, 2 H), 3.72 (q, J = 7.3 Hz, 1 H), 1.49 (d, J = 7.3 Hz, 3 H); ESMS *m*/*e* 167.2 $(M - H)^+$.

Biological Evaluations. In Vitro Binding Assays. Rat MCH_1 receptor binding assays were performed by incubating membranes from modified HEK 293 cells ($PEAK^{RAPID}$ cells, Edge Biosystems, Gaithersburg, MD) transiently transfected with the rat MCH-1 receptor with varying concentrations of [^{3}H]-**1** ([^{3}H]SNAP- 7941) 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. Similarly, α_{1A} and D_2 binding assays were performed in membranes of cells expressing the human recombinant α_{1A} and D_2 receptors using [^{125}I]HEAT and [^{3}H]-spiperone, respectively. Membranes for the D_2 assays were obtained from Packard Bioscience.[10b]

In Vitro Functional Assays. Functional antagonism of the compounds was assessed using FLIPR calcium mobility assay. HEK 293 cells stably expressing rat MCH_1 were seeded on a 386-well poly-D-lysine-coated black plates (Becton Dickinson Labware, Bedford, MA). After 16 h incubation, cells were loaded with 1.5 μM Fluo4 fluorescent dye (Molecular Probs) in Hank's balanced salt solution (HBSS, Wisent Inc) for 60 min. Cells were then washed and varying concentrations of testing compounds were added. After 20 min incubation, MCH peptide was added at 30 nM. Fluorescent intensity in response to changes in intracellular calcium concentration was measured on a FLIPR-384 fluorescent reader. Data analysis was performed using Activity Base software. IC_{50} values were calculated using nonlinear curve fitting.

In Vivo Assays: Social Interaction Test (SIT). Rats were allowed to acclimate to the animal care facility for 5 days and were housed singly for 5 days prior to testing. Animals were handled for 5 min per day. The design and procedure for the SIT was carried out as previously described by Kennett et al. (1997). On the test day, weight matched pairs of rats (±5%), unfamiliar to each other, were given identical treatments and returned to their home cages. Animals were randomly divided into five treatment groups, with five pairs per group, and were given one of the following i.p. treatments: test compound (10, 30, or 100 mg/kg), vehicle (1 mL/kg), or chlordiazepoxide (5 mg/kg). Dosing is 1 h prior to testing. Rats were subsequently placed in a white perspex test box or arena (54 × 37 × 26 cm), whose floor was divided up into 24 equal squares, for 15 min. An air conditioner was used to generate background noise and to keep the room at approximately 74 °F. All sessions were videotaped using a JVC camcorder (model GR-SZ1, Elmwood Park, NJ) with either TDK (HG ultimate brand) or Sony 30 min videocassettes. All sessions were conducted between 1300−1630 h. Active social interaction, defined as grooming, sniffing, biting, boxing, and wrestling, following and crawling over or under, was scored using a stopwatch (Sportsline model no. 226, 1/100 s discriminability). The number of episodes of rearing (animal completely raises up its body on its hind limbs), grooming (licking, biting, scratching of body), face washing (i.e., hands are moved repeatedly over face), and number of squares crossed were scored. Passive social interaction (animals are lying beside or on top of each other) was not scored. All behaviors were assessed later by an observer who was blind as to the treatment of each pair. At the end of each test, the box was thoroughly wiped with moistened paper towels.

MCH−Induced Water Intake. MCH-induced water intake in rats was studied according to the method described by Clegg et al. (2003) with modifications.[16] Briefly, male Sprague−Dawley rats (250-400 g) implanted with a permanent intracerebroventricular (icv) cannula, were procured from Charles River Laboratories and housed individually with free access to rat chow and water under standard husbandry conditions. After a week of acclimatization, the rats were brought to the laboratory in their home cage and were denied access to water for 2 h. Individual rats received either vehicle (20% cyclodextrin) or the test compound at least 1 h prior to administration of either saline or MCH (10 ug in 5 μL saline) icv. The animals were given access to water immediately after the icv administration, and the water consumption was measured at the end of 2 h. To confirm that position as well as specificity of blockade of MCH-induced water intake, rats were administered with 100 ng of angiotensin-II (icv in 5 μL saline) and water consumption was measured for an additional 30 min. Animals that failed to consume at least 3 mL of water following angiotensin-II challenge were excluded from the analysis.

The total water consumption over 2 h following either saline or MCH by different treatement groups was compared for significance by using one way ANOVA followed by Dunnett's post hoc analysis.

Rat Pharmacokinetic Assay. Male Sprague−Dawley male rats with an average body weight of 200−250 g were purchased from Charles River Laboratories. Each test compound was dissolved in an appropriate vehicle and dosed via intravenous (1 mg/kg) and oral administrations (2 mg/kg). The oral administration was performed on the same rat 24 h after the intravenous dosing. An Accusampler (Dilab, Lund, Sweden) was used for blood sample collection. A blood sample containing the test compound at a concentration of 109 ng/mL was prepared to determine blood/plasma distribution. Plasma samples were obtained by centrifuging the blood samples. The plasma samples were analyzed by LC/MS/MS, turbulent flow chromatography (Cohesive 2300, Cohesive Technologies, Franklin, MA), coupled with mass spectrometry (ThermoFinnigan TSQ Quantum, San Jose, CA). Compound concentrations in plasma were quantified using ThermoFinnigan Xcalibur. WinNonlin v. 3.2 (Pharsight Co., Mountain View, CA) was used for pharmacokinetic analysis of the plasma concentration−time profile.

Rat PK for compound **1** was measured at a CRO using 1 mg/kg dosing for both iv and po administrations. Due to the low plasma concentrations of compound **1**, to increase the limit of quantitation (LOQ) for this bioavailability study, the compound was extracted from plasma matrix via solid-phase extraction instead of an acetonitrile precipitation.

Rat Pharmacokinetic Screening. Femoral artery cannulated Sprague−Dawley male rats were purchased from Taconic Laboratories. The average body weight was 300−350 g. Each compound that was dissolved in an appropriate vehicle was orally administered to three rats ($N = 3$) at a dose of 10 mg/kg. Blood samples were collected at four time points: predose (0 h), 1 h, 2 h, and 4 h. The rats were then sacrificed, and the brain tissues were collected and immediately stored at −80 °C. Plasma samples were obtained by centrifuging the blood samples. To increase bioanalysis throughput, an equal amount of $N = 3$ plasma or brain samples at the same time point, which were collected from three different rats, were pooled together. Each pooled rat brain sample was homogenized in an aqueous solution. Protein precipitation of the pooled plasma or homogenized brain sample afforded a supernatant that was analyzed by LC/MS/MS, an Agilent 1100 HPLC (Agilent Technologies, Palo Alto, CA) and a TSQ Quantum MS (ThermoFinnigan, San Jose, CA). Compound concentrations in the plasma and brain matrices were quantified using ThermoFinnigan Xcalibur.

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

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