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Synthesis and In Vitro Opioid Receptor Functional Antagonism of Methyl-Substituted Analogues of (3*R*)-7-Hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl}-2-methylpropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (JDTic)†

Juan Pablo Cueva, Tingwei Bill Cai, S. Wayne Mascarella, James B. Thomas, Hernán A. Navarro, and F. Ivy Carroll*

Center for Organic and Medicinal Chemistry, Research Triangle Institute, Post Office Box 12194, Research Triangle Park, North Carolina 27709-2194

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In previous structure−activity relationship (SAR) studies, (3*R*)-7-hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl}-2-methylpropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (JDTic, **3**) was identified as the first potent and selective κ-opioid receptor antagonist from the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of opioid antagonists. In the present study, we report the synthesis of analogues **8a**−**p** of **3** and present their in vitro opioid receptor functional antagonism using a [^{35}S]GTPγS binding assay. Compounds **8a**−**p** are analogues of **3** containing one, two, or three methyl groups connected to the JDTic structure at five different positions. All the analogues with one and two added methyl groups with the exception of **8k** had subnanomolar K_e values at the κ receptor. The three most potent analogues were the monomethylated (3*R*)-7-hydroxy-*N*-[(1*S*,2*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidine-1-yl]methyl}-2-methylbutyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**8a**) and (3*R*)-7-hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-(2-methylpropyl)]-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**8e**) with K_e values of 0.03 nM at the κ receptor and (3*R*)-7-hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-methoxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**8d**) with K_e = 0.037 nM at the κ receptor. All three compounds were selective for the κ receptor relative to the μ and δ receptors. Overall, the results from this study highlight those areas that are tolerant to substitution on **3**.

Introduction

Stress can induce despair and increase the risk of clinical depression and drug abuse.[1,2] Dynorphin, the endogenous ligand for the κ-opioid receptor, is a stress-related neuropeptide in the brain that may mediate these responses.[3] Activation of the κ-opioid receptor causes place aversion in rodents and dysphoria in humans.[4,5] The dynorphin/κ-opioid receptor system has been reported to be critical for stress-induced depression-like behaviors and reinstatement to drug-seeking behavior.[4,6−10] The results from these studies have led to an increased interest in selective κ-opioid receptor antagonists.

The first nonpeptide, highly selective antagonists of the κ-opioid receptor were nor-BNI[11] (**1**, Figure 1) and GNTI[12] (**2**, Figure 1), which were derived from the nonselective opioid receptor antagonist naltrexone. More recently, JDTic (**3**, Figure 1) was discovered as the first highly potent and selective κ-opioid receptor antagonist from the N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**4**, Figure 1) class of antagonist,[13,14] and arodyn (**5**, Figure 1) was developed from dynorphin.[15] Studies with these compounds have shown that this system is intimately involved in brain processes that relate to stress, fear, and anxiety as well as reward-seeking behavior.[16] Studies have shown that **3** and **1** dose-dependently reduce fear and stress-induced responses in multiple behavioral paradigms with rodents (immobility in the forced-swim assay,[8,10] reduction of exploratory behavior in the elevated plus maze, fear-potentiated startle).[17] Furthermore, selective κ antagonists have been shown to reduce stress-induced reinstatement of cocaine self-administration in rats,[8] block the stress-induced potentiation of cocaine place preference conditioning,[7,9,18] decrease dependence-induced ethanol self-administration,[19] diminish deprivation-induced eating in rats,[20] and prevent prepulse inhibition mediated by the κ agonist U50,488.[21] These observations regarding the behavioral consequences of receptor blockade in several animal tests suggest that κ antagonists might be useful for the treatment of anxiety, depression, schizophrenia, addiction, and eating disorders.

In vivo, **3** has been shown to be more potent at blocking κ-opioid agonist-induced activity than other κ-opioid antagonist.[22] Compound **3** was also shown to have oral activity in antagonizing the antinociceptive activity of the κ agonist enadoline in mice[22] and preventing stress-induced cocaine reinstatement of self-administration in rats.[8] To our knowledge **3** remains the only orally active κ-opioid receptor antagonist.

In a recent structure−activity relationship study, it was reported that **8a**, which has an extra methyl group on the

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*To whom correspondence should be addressed. Phone: 919-541-6679. Fax: 919-541-8868. E-mail: fic@rti.org.

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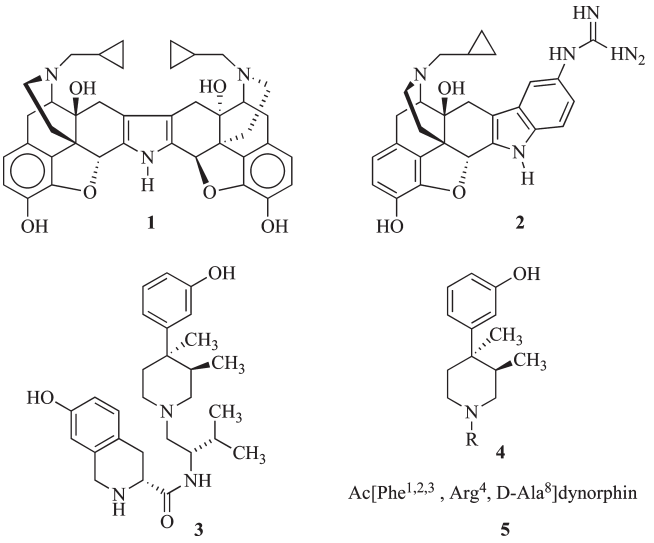


Figure 1

(1*S*)-isopropyl group of **3**, had a K_e value of 0.03 nM at the κ-opioid receptor, relative to 0.02 nM for **3**, and retained 100- and 800-fold κ selectivity relative to the μ and δ opioid receptors, respectively.[23] It was also reported that the methyl ether **8b** was a highly potent antagonist with a K_e value of 0.06 nM at the κ-opioid receptor, making it only 3-fold less potent than **3**. Compound **8b** was 857- and 1970-fold selective for the κ receptor relative to the μ and δ receptors, respectively. The synthesis of the *N*-methyl analogue **8c** has also been reported; however, this analogue had not been evaluated for inhibition of agonist-stimulated [^{35}S]GTPγS[a] binding at cloned μ-, δ-, and κ-opioid receptors in our laboratory.[14] In this study, we report the synthesis of a series of methylated analogues of **3** (**8d**−**p**, see Table 1 for structures) and report results on their ability to inhibit agonist-stimulated [^{35}S]GTPγS binding in cells expressing cloned μ-, δ-, and κ-opioid receptors. Even though **3** has drug-like properties and has performed well in several animal behavioral tests,[8,17,22] we reasoned that analogues **8a**−**d** could have better pharmacokinetic properties and ability to penetrate the brain. All 16 analogues (**8a**−**p**) had calculated logBB values[24] that suggested they would possess better brain penetration than **3**. All the mono- and dimethylated **3** analogues with the exception of **8k** had subnanomolar K_e values at the κ-opioid receptor. The most potent new analogue was **8e** with a K_e value of 0.03 nM for the κ-opioid receptor and 120- and 28000-fold selective relative to the μ- and δ-opioid receptors. However, analogues **8d** and previously reported **8a** and **8b** were also potent and selective κ antagonists.

Chemistry

The structure of **3** was modified to introduce methyl groups at five different sites of the molecule (see Table 1 for structure): at the phenol moieties (R_1, R_2), on the linker of the phenylpiperidine to the tetrahydroisoquinoline carboxamide fragments (R_3), at the position α to the carboxamide moiety (R_4), and at the isoquinoline nitrogen (R_5). Analogues **8a**−**c** were synthesized as previously reported.[14,23] The synthesis of the new analogues **8d**−**p** is shown in Scheme 1. Coupling of the appropriate 1,2,3,4-tetrahydroisoquinoline carboxylic acids **6a**−**e** with **7a**−**d** using benzotriazole-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP) in tetrahydrofuran (THF) or *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) in acetonitrile (followed by removal of the Boc-protecting group with trifluoroacetic acid in methylene chloride when **6a** and **6c** were used) yielded **8d**−**p**.

The tetrahydroisoquinoline carboxylic acids **6a**−**d** needed for the synthesis of **8e**, **8g**, **8h**, **8i**, **8l**, **8m**, **8n**, and **8o** were prepared following the transformations outlined in Scheme 2. D-Alanine (**9**) was converted to the sodium salt using sodium hydroxide in ethanol, followed by conversion to the chiral oxazolidinone **10** by condensation with benzaldehyde under azeotropic distillation conditions and benzoylation using benzoyl chloride.[25] Alkylation of **10** with 4-methoxybenzyl bromide using lithium hexamethyldisilazide as the base at −78 °C proceeded with high diastereomeric selectivity to give the *p*-methoxybenzylated intermediate **11**.[26] Acid hydrolysis of the chiral intermediate **11** gave the amino acid **12**. Formation of the tetrahydroisoquinoline ring system was achieved via the Pictet−Spengler reaction. This was carried out by bromination of **12** to give **13** to protect the ortho positions of the methoxy group, followed by treatment with hydrobromic acid and formaldehyde at 80 °C to give **14**. Compound **14** was converted to **6a** by treatment with concentrated hydrobromic acid to demethylate the 7-methoxy to a phenol, followed by catalytic debromination using palladium on carbon under hydrogen, and finally treatment with di-*tert*-butyl dicarbonate in dimethylformamide containing triethylamine to give **6a**. The *N*-methyl analogue **6b** was obtained by treating **6a** with trifluoroacetic acid to give the free amine followed by reductive methylation using Raney nickel catalyst, hydrogen, and formaldehyde in methanol. Compounds **6c** and **6d** were obtained from **14** by protection as the *tert*-butoxycarbonyl ester using di-*tert*-butyl dicarbonate and then debromination using palladium on carbon as catalyst under hydrogen to give **6c**. Removal of the Boc-protecting group from **6c** using hydrochloric acid followed by reductive methylation using the same conditions as for **6b** gave the *N*-methyl analogue **6d**.

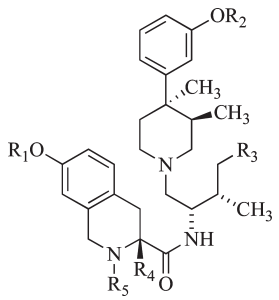
Compound **7b** was synthesized by coupling *N*-Boc-L-valine with (3*R*,4*R*)-4-(3-methoxyphenyl)-3,4-dimethylpiperidine (**16a**)[27] using BOP in tetrahydrofuran followed by reduction with diborane in tetrahydrofuran (Scheme 3). Coupling of **16b** and **16a** with N-Boc-L-isoleucine using HBTU in acetonitrile followed by reduction with diborane gave **7c** and **7d**, respectively. Compound **7a** was synthesized as previously reported.[28]

Pharmacology

Compounds **1**, **3**, and **8a**−**p** were first evaluated at 10 μM for intrinsic activity in the [^{35}*S*]GTPγS binding assay at all three opioid receptors. As none of the compounds displayed measurable intrinsic activity at this concentration, they and the reference compound **1** were evaluated for functional antagonism and selectivity at the opioid receptors. These data were obtained by monitoring the ability of test compounds to inhibit stimulated [^{35}*S*]GTPγS binding produced by the

[a] Abbreviations: GPCRs, G-protein-coupled receptors; cDNAs, cDNA; SAR, structure−activity relationship; [^{35}S]GTPγS, sulfur-35 guanosine-5′-*O*-(3-thio)triphosphate; DAMGO, [D-Ala^2,MePhe^4,Gly-ol^5]enkephalin; DPDPE, [D-Pen^2,D-Pen^5]enkephalin; U69,593, (5α,7α,8β)-(−)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzeneacetamide; CHO, Chinese hamster ovary; GDP, guanosine diphosphate; BOP, benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; HBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; Tic, tetrahydroisoquinolinecarboxylic acid; tPSA, topological polar surface area.

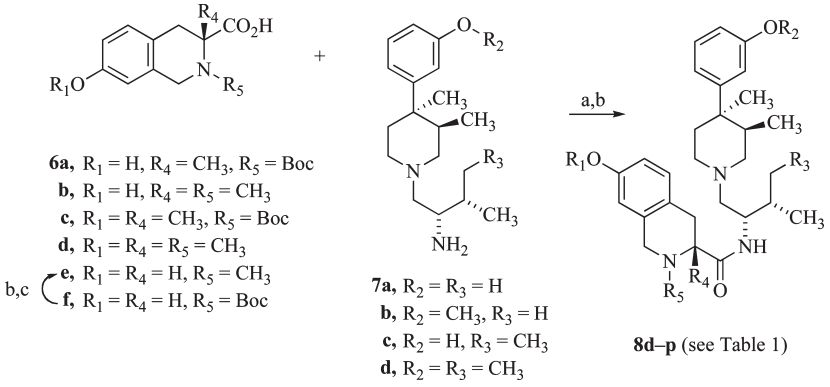
Table 1. Comparison of Inhibition of Agonist Stimulated [^{35}S]GTPγS Binding in Cloned Human μ, δ, and κ-opioid Receptors for Compounds **8a**−**d** to **3** and **1**[a]



compd	R_1	R_2	R_3	R_4	R_5	μ, DAMGO K_e (nM)	δ, DPDPE K_e (nM)	κ, U69,593 K_e (nM)	μ/κ	δ/κ
1						26 ± 7	29 ± 8	0.05 ± 0.02	520	580
3	H	H	H	H	H	25.1 ± 3.5[b]	76.4 ± 2.7[b]	0.02 ± 0.01[b]	1255	3830
8a	H	H	CH_3	H	H	3 ± 1[c]	24 ± 4[c]	0.03 ± 0.02[c]	100	800
8b	CH_3	H	H	H	H	51.4 ± 15[c]	118 ± 45[c]	0.06 ± 0.01[c]	857	1970
8c	H	H	H	H	CH_3	210 ± 60	491 ± 120	0.16 ± 0.06	1313	3070
8d	H	CH_3	H	H	H	24 ± 8	21.2 ± 5	0.037 ± 0.003	649	573
8e	H	H	H	CH_3	H	3.6 ± 1	854 ± 210	0.03 ± 0.008	120	28500
8f	H	CH_3	CH_3	H	H	5.1 ± 2	1170 ± 400	0.96 ± 0.4	5	1220
8g	CH_3	H	H	CH_3	H	3.8 ± 1.1	36.8 ± 6.9	0.93 ± 0.05	4	40
8h	H	CH_3	H	CH_3	H	123 ± 30	2200 ± 900	0.26 ± 0.1	473	8500
8i	H	H	CH_3	CH_3	H	8.7 ± 2.7	149 ± 13	0.11 ± 0.01	79	1350
8j	H	H	CH_3	H	CH_3	7.2 ± 1.8	132 ± 24	0.11 ± 0.03	66	1200
8k	H	CH_3	H	H	CH_3	880 ± 220	2300 ± 900	4.3 ± 2.7	204	535
8l	CH_3	CH_3	H	CH_3	H	1450 ± 490	IA[d]	15.2 ± 3.7	95	
8m	CH_3	H	CH_3	CH_3	H	17.5 ± 3.6	18.7 ± 1.5	3.5 ± 0.8	5	5
8n	H	CH_3	CH_3	CH_3	H	59.1 ± 16	2100 ± 600	0.52 ± 0.2	114	4040
8o	CH_3	H	H	CH_3	CH_3	7.0 ± 1.4	117 ± 30	2.2 ± 0.6	3	53
8p	H	CH_3	CH_3	H	CH_3	360 ± 120	IA[d]	2.03 ± 0.03	180	

[a] The data represent the means ± SE from at least three independent experiments. [b] The K_e values for **3** supplied by the NIDA Opioid Treatment Discovery Program (OTDP) were 3.41, 79.3, and 0.01 nM for the μ, δ, and κ receptors, respectively (ref 14). [c] Data taken from ref 23. [d] Inactive or > 10000 nM.

Scheme 1[a]

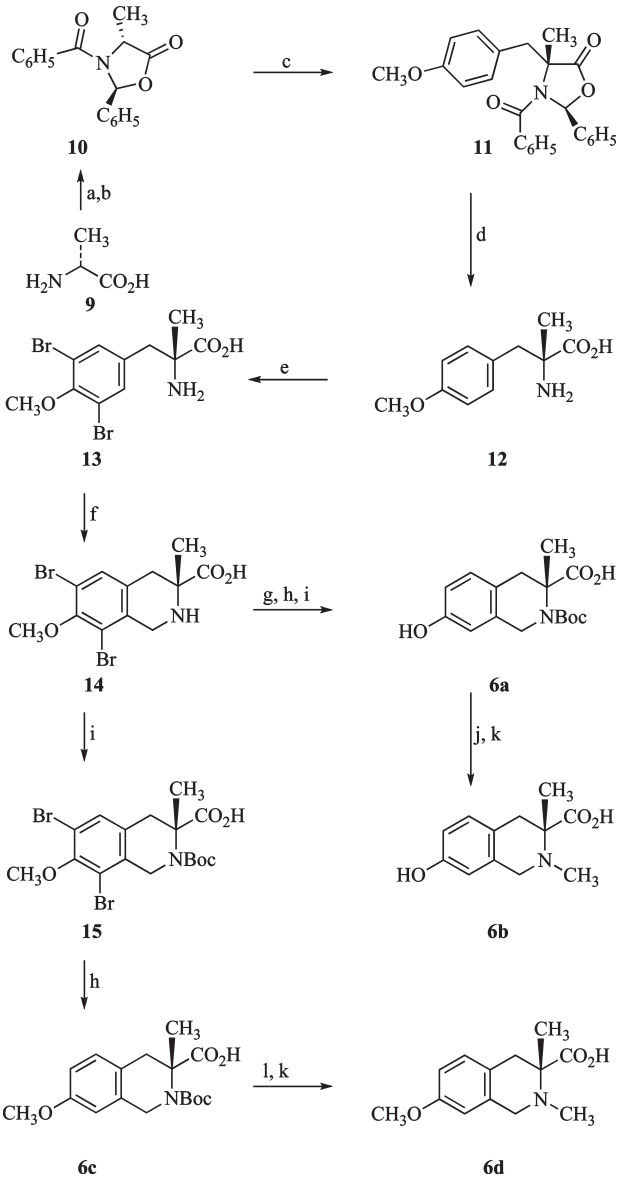


[a] Reagents: (a) BOP, THF, Et_3N (for **8d**, **8f**−**g**, **8i**−**l**, **8n**−**p**), or HBTU, CH_3CN, Et_3N, (for **8e**, **8h**, **8m**) for coupling with **6a** and **6c**; (b) CF_3CO_2H, CH_2Cl_2; (c) Raney Ni, H_2, HCHO, CH_3OH.

selective agonists DAMGO (μ), DPDPE (δ), or U69,593 (κ) using cloned human opioid receptors expressed in CHO cells.[29] Agonist dose response curves were run in the presence or absence of a single concentration of test compound. Test compound assay concentrations ranged from 1−5000 nM, depending on their activity. The K_e values were calculated using the formula: $K_e = [L]/DR - 1$, where [L] is the concentration of test compound and DR is the ratio of agonist EC_{50} value in the presence or absence of test compound, respectively. At least two different concentrations of test compound were used to calculate the K_e, and the concentrations were chosen such that the agonist EC_{50} exhibited at least a 4-fold shift to the right and there was a clear upper asymptote to the agonist + compound concentration response curve. The K_e values along with those for the reference compound **1** are shown in Table 1.

The calculated logP, tPSA, and logBB values for compounds **1**, **3**, and **8a**−**p** are given in Table 2. The logBB values were calculated using eq 6 (the Clark equation) given in ref 24. Topological polar surface areas (tPSA) and logP values were

Scheme 2[a]



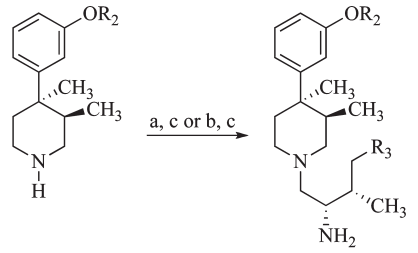
[a] Reagents: (a) NaOH, C_6H_5CHO; (b) C_6H_5COCl; (c) LiHMDS, THF, −78 °C; $CH_3OC_6H_4CH_2Br$; (d) conc HCl; (e) Br_2, HCl; (f) HCHO, HBr, H_2O, CF_3CO_2H; (g) conc HBr, reflux; (h) H_2, Pd/C, CH_3OH; (i) $(Boc)_2O$, DMF, Et_3N; (j) CF_3CO_2H, CH_2Cl_2; (k) Raney Ni, H_2, CH_3OH, HCHO; (l) 12 M HCl, THF.

calculated using ChemAxon's Instant JChem version 5.03 software.

Results and Discussion

Even though **3** (K_e = 0.02 nm) was more potent as a κ-opioid receptor antagonist than any of the methylated analogues studied, many of the analogues were potent and selective κ antagonists. All of the monomethylated analogues **8a**−**8e**, the dimethylated analogues **8f**−**8j**, and the trimethylated analogue **8m** retained subnanomolar potency at the κ-opioid receptor. All of the monomethylated compounds **8a**−**8e**, the dimethylated compounds **8h** and **8k**, and the trimethylated compound **8n** retained greater than 100-fold κ selectivity relative to the μ and δ receptors. The two most potent analogues were **8a** (R_3 = CH_3) and **8e** (R_4 = CH_3), both with K_e values of 0.03 nM at the κ-opioid receptor. Both

Scheme 3[a]



16a, R_2 = CH_3 **7b,** R_2 = CH_3, R_3 = H
b, R_2 = H **c,** R_2 = H, R_3 = CH_3
d, R_2 = R_3 = CH_3

[a] Reagents: (a) N-Boc-L-valine, BOP, THF; (b) N-Boc-L-isoleucine, HBTU, CH_3CN, Et_3N, THF; (c) B_2H_6, THF.

Table 2. Calculated logP, tPSA, and logBB for **1**, **3**, and **8a**−**p**[a]

compd	logP	tPSA	logBB
1	1.57	121.65	−1.42
3	3.75	84.83	−0.55
8a	4.09	84.83	−0.49
8b	4.11	73.83	−0.33
8c	4.12	76.04	−0.36
8d	3.83	73.83	−0.37
8e	3.98	84.83	−0.51
8f	4.18	73.83	−0.32
8g	4.33	73.83	−0.30
8h	4.06	73.83	−0.34
8i	4.32	84.83	−0.46
8j	4.46	76.04	−0.31
8k	4.20	65.04	−0.19
8l	4.74	62.83	−0.07
8m	4.71	73.83	−0.24
8n	4.41	73.83	−0.28
8o	4.69	65.04	−0.11
8p	4.55	65.04	−0.13

[a] logBB was calculated using eq 6 in ref 24.

compounds had 100-fold or greater selectivity for the κ receptor relative to the μ receptor. The κ selectivity for **8a** and **8e** relative to the δ receptor was 800 and 28500, respectively. The *N*-methyl compound **8c** (R_5 = CH_3) with a K_e value of 0.16 nM at the κ-opioid receptor and 1313- and 3070-fold selectivity for the κ receptor relative to the μ and δ receptors was the most κ selective analogue of this new series. Compound **8b** (R_2 = CH_3), with a K_e value of 0.06 nM, was 3 times less potent than **3**, and with μ/κ and μ/δ ratios of 857 and 1970, it was also highly κ selective.

Compound **8d**, with a methyl substituted at the 3-hydroxyl in the phenylpiperidine fragment, had only a 2-fold decrease in potency for the κ receptor (K_e = 0.037 nM) relative to **3**.

Methylation of the alkyl side chain on the linker between the phenylpiperidine and tetrahydroisoquinoline carboxamide fragments (R_3) produced compounds **8a**, **8f**, **8i**, **8j**, and **8m** that had increased potency at μ receptors compared to **3**. This effect was most notable in the monomethyl substituted compound **8a**, which had an 8-fold increase in potency at μ receptors compared to **3**. These observations mirror those seen in previous studies where large substituents at this position increased μ receptor potency.[28]

N-Methylation at the tetrahydroisoquinoline nitrogen to give the *N*-methyl **3** analogue **8c** resulted in a reduction in potency at all receptor subtypes. At κ receptors, this modification consistently gave decreases in potency for all analogues

8j, **8k**, **8o**, and **8p**. Nevertheless, analogues **8c** and **8j**, with K_e values of 0.16 and 0.11 nM, respectively, were still highly potent κ antagonists.

In general, it was observed that introduction of multiple methyl groups into the structure of **3** was detrimental for potency and selectivity at κ receptors. Compounds **8i** and **8j** with K_e values of 0.11 nM each at the κ receptor were the two most potent analogues with multiple methyl groups. The effect was more noticeable for compounds with three methyl substitutions. The most potent analogue containing three methyl groups was **8n**, which had a K_e value of 0.52 nM at the κ receptor.

The calculated logP, tPSA, and logBB values for **1**, **3**, and **8a**−**p** are given in Table 2.[24] In contrast to standard compound **1** (calculated logBB = −1.42), the calculated logBB for **3** and **8a**−**p** (−0.07 to −0.55) are above the threshold proposed by Clark to indicate low blood−brain barrier penetration. The calculated logBB values[24] show that all 16 methylated analogues would be expected to show enhanced brain penetration relative to **3**. In the case of **8b** for instance, monomethylation shifts the calculated logBB value positively by 0.22 log units (calculated logBBs for **3** and **8b** are −0.55 and −0.33, respectively). This change in the relative concentration of drugs implies an approximately 66% increase in the concentration of the drug in the brain.

Conclusions

In summary, 16 analogues of **3** with methyl substituents at five different positions on the **3** structure were synthesized. Eleven of the analogues had subnanomolar K_e values at the κ opioid receptor. The monomethylated analogues **8a**, **8b**, **8d**, and **8e** with K_e values of 0.03−0.06 nM were the most potent compounds. Even though the efficacy at the κ opioid receptor is not as good as that for **3**, the calculated logBB values suggest that these analogues may have activity comparable to that of **3** in vivo. While beyond the scope of this investigation, a pharmacokinetic (PK) study could suggest further development of one or more of these analogues.

Experimental Section

^{1}H NMR spectra were determined on a Bruker 300 spectrometer using tetramethylsilane as an internal standard. Mass spectral data were obtained using a Finnegan LCQ electrospray mass spectrometer in positive ion mode at atmospheric pressure. Medium-pressure flash column chromatography was done on a CombiFlash Companion system using Teledyne Isco prepacked silica gel columns or using EM Science silica gel 60 Å (230−400 mesh). All reactions were followed by thin-layer chromatography using Whatman silica gel 60 TLC plates and were visualized by UV. Optical rotations were measured on an Auto Pol III polarimeter. All solvents were reagent grade. HCl in dry diethyl ether was purchased from Aldrich Chemical Co. and used while fresh before discoloration. CMA-80 is a mixture of 80% chloroform, 18% methanol, and 2% concentrated ammonium hydroxide. Purity of compounds (>95%) was established by elemental analysis. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Care should be used when using BOP in coupling reactions as it yields the carcinogenic byproduct HMPA.

(2*S*,4*R*)-4-(4-Methoxybenzyl)-4-methyl-2-phenyl-3-(phenylcarbonyl)-1,3-oxazolidin-5-one (11). Compound **10**[25] (6.35 g, 0.023 mol) in 50 mL of THF at −78 °C was added over 20 min to a solution of LiHMDS in THF (25 mL of 1 M solution in THF). After 10 min, 1.1 equiv of 4-methoxybenzyl bromide (25 mmol, 5 mL) was added in one portion. The mixture was stirred at −78 °C for 3 h and then at room temperature overnight. Saturated NH_4Cl solution was added, the THF was removed in vacuo, Et_2O (100 mL) was added, and the phases were separated. The organic layer was washed with 50 mL of $NaHCO_3$ solution and brine. After drying (Na_2SO_4), filtration, and removal of the solvent, the residue was purified by chromatography using a silica gel Isco column with 9% EtOAc in hexanes as eluent. Concentration of the product fractions gave 7.4 g (82%) of **11** as a white solid: mp 128−129 °C; $[\alpha]^{25}_D$ = −260 (c 0.8, MeOH). ^{1}H NMR ($CDCl_3$) δ 7.27 (2H, d, J = 8 Hz), 7.19−7.14 (2H, m), 7.09−7.05 (4H, m), 6.94 (d, 2H, J = 8 Hz), 6.76−6.72 (m, 4H), 5.68 (s, 1H), 3.88 (d, 1H, J = 12 Hz), 3.86 (s, 3H), 3.27 (d, 1H, J = 12 Hz), 2.14 (s, 3H). ^{13}C NMR 175.1, 169.4, 159.6, 136.7, 131.5, 130.1, 130.0, 128.8, 128.7, 128.2, 127.2, 126.3, 114.6, 90.7, 65.9, 55.8, 40.5, 24.6. ESIMS: m/z 402 (M + 1, 100).

***O*,α-Dimethyl-D-tyrosine (12).** Compound **11** (2.2 g, 0.0055 mol) was suspended in 20 mL of concentrated HCl solution. After nitrogen flush, the mixture was heated under reflux for 3 h. After filtration and removal of the HCl solution, the white precipitate was dried. ^{1}H NMR (CD_3OD) δ 7.24 (d, 2H, J = 6 Hz), 6.91 (d, 2H, J = 6 Hz), 3.77 (3H, s), 3.26 (d, 1H, J = 14 Hz), 3.13 (d, 1H, J = 14 Hz), 1.66 (s, 3H). ^{13}C NMR 173.8, 161.3, 132.9, 115.9, 62.4, 56.4, 43.5, 23.2. MS (ESI) 210 (M + 1). The product was used in the next step without purification.

3,5-Dibromo-*O*,α-dimethyl-D-tyrosine (13). To a solution of compound **12** from above in distilled water (20 mL), 12 M HCl (4 mL) was added. The reaction mixture was cooled to 5 °C, and bromine (2.1 mL, 41 mmol) was injected into the stirred solution. After 15 min, N_2 gas was passed through the reaction mixture until the product precipitated. APCIMS: m/z 366 (M + 1, 100). The product was used in the next step without purification.

(3*R*)-6,8-Dibromo-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (14). Compound **13** from above (assumed to be 4.8 mmol) was added to trifluoroacetic acid (5 mL). HBr (33% in acetic acid, 0.9 mL, 4.8 mmol) was added dropwise to the reaction mixture under a nitrogen atmosphere. After the addition of the acid, formaldehyde (8.64 mmol, 260 mg, 0.7 mL) was added dropwise and the mixture stirred at 70−80 °C for 17 h. The reaction mixture was cooled, dried, and concentrated. APCIMS: m/z 378 (M + 1). The product was used in the next step without purification.

(3*R*)-6,8-Dibromo-2-(*tert*-butoxycarbonyl)-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (15). The crude compound **14** reported above (assumed to be 4.8 mmol) was dissolved in DMF (7 mL) and water (2 mL). Triethylamine (1.01 g, 0.01 mol) was added, followed by di-*tert*-butyl dicarbonate (1.57 g, 0.007 mol). The reaction mixture was stirred at room temperature for 4 h and then concentrated to dryness. The resulting residue was treated with water (30 mL) and EtOAc (30 mL). $KHSO_4$ (2 g) was added to the mixture (pH = 2), and the organic layer was separated, dried, and concentrated. The product was purified by chromatography on silica gel (Isco column) using 35% EtOAc in hexanes as eluent to afford 500 mg of **15** (22% from **13**) as a syrup. ^{1}H NMR (CD_3OD) δ 7.55 (s, 1H), 4.84 (d, 1H, J = 16 Hz), 4.54 (d, 1H, J = 16 Hz), 3.85 (s, 3H), 3.19 (d, 1H, J = 16 Hz), 2.92 (d, 1H, J = 16 Hz), 1.47 (s, 9H), 1.42 (s, 3H). ^{13}C NMR 177.7, 154.7, 138.1, 135.4, 132.9, 118.6, 117.9, 62.5, 62.0, 46.1, 41.7, 29.1, 28.3, 23.9. ESIMS: m/z 478 (M + 1).

(3*R*)-2-(*tert*-Butoxycarbonyl)-7-hydroxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (6a). A suspension of **14** (5.00 g, 0.012 mol) in 75 mL of 48% aqueous HBr was heated to reflux for 5 h. The solution was then evaporated to dryness under reduced pressure and dissolved in 30 mL of MeOH and 7.00 mL of Et_3N (0.05 mol). This solution was added to 300 mg of 10% Pd on carbon and shaken for 12 h in a Parr hydrogenator under 60 psig H_2. The suspension was filtered and the solvents removed under reduced pressure to leave a solid product

(containing the product and triethylammonium salts) with a mass of 9.77 g. This solid was dissolved in 15 mL of H_2O, 40 mL of DMF, and 4.78 mL (34.29 mmol) of Et_3N. Into this solution, di-*tert*-butyl dicarbonate (2.1 mL, 22.26 mmol) was introduced and the mixture stirred for 10 h. The solution was reduced to 1/10 of its volume under reduced pressure and partitioned between 30 mL of H_2O and 30 mL of EtOAc. The water layer was extracted with EtOAc (3 × 15 mL). The pooled organic extracts were washed once each with 10 mL of H_2O, 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to dryness to yield 3.42 g of **6a** as a foam that was pure by NMR. ^{1}H NMR ($CDCl_3$) δ 7.17 (d, 1H, J = 8.1 Hz), 6.73 (m, 2H), 4.60−4.41 (2d, 2H), 3.12 (d, 1H, J = 14.7 Hz), 2.78 (d, 1H, J = 14.7 Hz), 1.56−1.24 (2s, 12H). ESIMS: m/z 207 (M + 1-Boc).

(*R*)-7-Hydroxy-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (6b) Triethylammonium Salt. The Boc-protected isoquinoline **6a** (534 mg, 1.74 mmol) was dissolved in 5 mL of a 1:1 mixture of CF_3CO_2H/CH_2Cl_2 and stirred overnight. The solvents were removed under reduced pressure and the residue suspended in 2 mL of water. The pH of the solution was adjusted to 7 by addition of saturated $NaHCO_3$. To this solution was added 300 mg of Raney Ni slurry in MeOH using a spatula along with 1 mL of a 37% solution of formaldehyde in water (13.4 mmol), and the resulting suspension was stirred under 1 atm of H_2 overnight. The suspension was filtered, and the solvents were removed under reduced pressure to yield a residue that was subjected to silica gel flash-column chromatography. Elution with $CHCl_3$/MeOH/NH_4OH (60:30:10) afforded 384 mg of the ammonium salt of **6b** after removal of solvents. The triethylammonium salt of **6b** was prepared by addition of 5 mL of Et_3N to a solution of the compound in 2 mL of MeOH, followed by removal of the volatiles: mp > 220 °C. ^{1}H NMR (CD_3OD) δ 7.07 (d, 1H, J = 8 Hz), 7.77 (d, 1H), 6.58 (s, 1H), 4.43 (bd, 1H), 4.31 (bd, 1H), 3.37 (d, 1H), 3.20 (m, 9H), 2.95 (d, 1H, J = 14.7 Hz), 1.52 (s, 3H), 1.25 (t, 9H), 2.88 (m, 1H), 2.75 (m, 1H). ESIMS: m/z 222 (M + 1, 100).

(3*R*)-2-(*tert*-Butoxycarbonyl)-7-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (6c). Triethylamine (3 mmol, 0.42 mL) and 10% Pd/C (20 mg) were added to **15** (337 mg, 1.05 mmol) in MeOH (5 mL). This mixture was shaken for 90 min under 40 psig of H_2 in a Parr apparatus. The mixture was then filtered and concentrated under reduced pressure to give **6c** in quantitative yield. An analytical sample was prepared by recrystallization from EtOAc-hexanes: mp 191 °C dec. ^{1}H NMR (CD_3OD) δ 7.10 (d, 1H, J = 8 Hz), 6.82 (m, 3H), 4.69 (d, 1H), 4.40 (d, 1H), 3.18 (d, 1H, J = 14.7 Hz), 2.79 (d, 1H, J = 14.7 Hz), 1.46 (s, 9H), 1.39 (s, 3H). ESIMS: m/z 322 (M + 1, 100).

(3*R*)-7-Methoxy-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (6d) Triethylammonium Salt. At 0 °C, **6c** (266 mg, 1.13 mmol) was dissolved in 5 mL of THF and 2 mL of 12 M HCl. After this solution was stirred for 4 h, the solvents were removed under reduced pressure. The residue was dissolved in 5 mL of MeOH. Into this solution were added 0.12 mL of Et_3N, 0.5 mL of 37% formaldehyde in H_2O, and 0.3 mL of Raney Ni slurry in MeOH. The mixture was stirred overnight under an atmosphere of H_2, filtered, and the solvents removed under reduced pressure to yield a residue that contained the title compound and $Et_3N\cdot$HCl. This residue was used without further purification. ^{1}H NMR (CD_3OD) δ 7.13 (d, 1H), 6.88 (d, 1H), 6.75 (s, 1H), 4.57 (d, 1H), 4.32 (d, 1H) 3.77 (s, 3H), 3.41 (d, 1H, J = 14.7 Hz), 3.21 (q, 6H), 2.99 (d, 1H), 2.90 (s, 3H), 1.53 (s, 3H), 1.31 (t, 9H). ESIMS: m/z 322 (M + 1, 100).

(3*R*)-7-Hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (6e) Hydrochloride. Compound **6f**[30] (1.087 g, 0.0034 mol) was suspended in 15 mL of CH_2Cl_2, and the mixture was cooled to 0 °C. Into this solution was added 7 mL of CF_3COOH, and the mixture was stirred for 6 h. The solvents were removed under reduced pressure, and the residue was suspended in 100 mL of MeOH and 5 mL of formalin. Into this suspension was added 1 g of a slurry of Raney Ni in MeOH using a spatula. The mixture was stirred under an atmosphere of H_2 for 5 h and was filtered through celite. To the filtered solution was added 10 mL of a 2 M solution of HCl in ethanol. The solvents were removed under reduced pressure, and the residue was recrystallized from MeOH to give 879 mg (64%) of **6e**·HCl as a white powder: mp > 220 °C. ^{1}H NMR (DMSO-d_6) δ 9.59 (s, 1H), 7.09 (d, 1H, J = 8.4 Hz), 6.73 (m, 1H), 6.59 (s, 1H), 4.53 (b, 1H), 4.38 (b, 2H), 3.31 (dd, 1H, J = 5.7 Hz), 3.16−3.07 (m, 1H), 2.91 (s, 3H). ESIMS: m/z 208 (M + 1, 100).

(2*S*)-1-[(3*R*,4*R*)-4-(3-Methoxyphenyl)-3,4-dimethylpiperidin-1-yl]-3-methylbutan-2-amine (7b). To a heterogeneous solution of (3*R*,4*R*)-4-(3-methoxyphenyl)-3,4-dimethylpiperidine[27] (41.1 g, 0.161 mol), N-Boc-L-valine (34.9 g, 0.161 mol), BOP reagent (71.0 g, 0.161 mol) in THF (450 mL) was added triethylamine (51.9 g, 0.513 mol) in THF (50 mL). The reaction mixture became homogeneous within 5 min after addition of Et_3N. The reaction was stirred for 4 h at room temperature and then added to ether (500 mL)/H_2O (300 mL). The organic layer was separated, washed with saturated $NaHCO_3$ and then brine, and separated. The extracts were dried (Na_2SO_4) and concentrated in vacuo to afford an off-white solid. This material was purified by silica gel column chromatography, eluting with 70% hexanes in EtOAc to yield 63.6 g (94%) of a white amorphous solid.

Diborane (260 mL, 1.0 M in THF, 0.260 mol) was added to the material described above (54.6 g, 0.130 mol) in THF (350 mL). The reaction mixture was stirred under N_2 at reflux for 2 h. The slightly heterogeneous reaction mixture was cooled to room temperature, and 6 N HCl was added (initially cautiously). After stirring at reflux for 2 h, the mixture was concentrated in vacuo and diluted with water. The reaction mixture was made basic with solid Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to afford 44 g (100%) of a thick oil. ^{1}H NMR ($CDCl_3$) δ 7.21 (t, 1H), 6.88 (d, 1H, J = 8.1 Hz), 6.83 (s, 1H), 6.71 (d, 1H), 3.81 (s, 3H), 2.77 (m, 1H), 2.63−2.13 (m, 8H), 2.10 (bm, 1H), 2.00 (m, 1H), 1.60 (m, 1H), 1.41 (s, 3H), 0.91 (m, 7H), 0.76 (d, 3H, J = 7.2 Hz). ESIMS: m/z 305 (M + H^+, 100). Anal. ($C_{19}H_{32}N_2O$) C, H, N.

3-{(3*R*,4*R*)-1-[(2*S*,3*S*)-2-Amino-3-methylpentyl]-3,4-dimethylpiperidin-4-yl}phenol (7c).[23] 3-[(3*R*,4*R*)-3,4-Dimethylpiperidin-4-yl]phenol (2.42 g, 11.79 mmol) and L-Boc-Ile (2.73 g, 11.79 mmol) were stirred in 30 mL of CH_3CN and the solution cooled to 0 °C. Into this solution, HBTU (4.47 g, 11.79 mmol) was added followed by Et_3N (3.3 mL, 23.57 mmol). The solution was stirred for 2 h and was then partitioned between 60 mL of EtOAc and 20 mL of H_2O. The organic layer was washed with saturated $NaHCO_3$ (10 mL × 3) and brine (10 mL). The solvent was dried over Na_2SO_4, filtered, and removed under reduced pressure. Flash column chromatography on silica gel eluting with a solvent gradient (80% hexanes in EtOAc to 66% hexanes in EtOAc) gave fractions that contained 3.39 g of pure amide. The amide (3.37 g, 8.33 mmol) was dissolved in 20 mL of dry THF, and 16.67 mL of a 1 M solution of BH_3 in THF was added. The solution was heated at reflux for 3 h, cooled to ambient temperature, and carefully added to 3 mL of H_2O. Then 7 mL of conc HCl was added. The mixture was heated at reflux for 2 h, and the volume of the reaction was reduced to one-third under reduced pressure. The remaining mixture was made basic by addition of solid $NaHCO_3$ and extracted thoroughly with a 4:1 mixture of CH_2Cl_2/THF. The pooled extracts were washed once with 20 mL of H_2O, dried over $MgSO_4$, filtered, and concentrated to give 2.50 g (70%) of a clear oil that slowly crystallized. An analytical sample was prepared by recrystallization from EtOAc: mp 150−153 °C. ^{1}H NMR ($CDCl_3$) δ 7.13 (t, 1H), 6.80 (m, 1H), 6.71 (s, 1H), 6.64 (d, 1H), 2.82−2.78 (m, 3H), 2.74−2.52 (m, 4H), 2.42−2.26 (m, 6H), 1.97 (m, 1H), 1.54 (m, 2H), 1.49−1.38 (m, 1H), 1.31 (s, 3H), 1.27−1.19 (m, 1H), 0.89 (t, 6H), 0.77 (d, 3H, J = 6.9 Hz). ESIMS: m/z 305 (M + H^+, 100). Anal. ($C_{19}H_{32}N_2O$) C, H, N.

(2*S*,3*S*)-1-[(3*R*,4*R*)-4-(3-Methoxyphenyl)-3,4-dimethylpiperidin-1-yl]-3-methylpentan-2-amine (7d). (*3R*,*4R*)-4-(3-Methoxyphenyl)-3,4-dimethylpiperidine[27] (533 mg, 2.43 mmol) and Boc-L-Ile (562 mg, 2.43 mmol) were stirred in 20 mL of CH_3CN, and the solution was cooled to 0 °C. Into this solution was added HBTU (922 mg, 2.43 mmol), followed by Et_3N (0.7 mL, 4.87 mmol). The solution was stirred for 2 h and was then partitioned between 30 mL of EtOAc and 10 mL of H_2O. The organic layer was washed with saturated $NaHCO_3$ (7 mL × 3) and brine (5 mL) solutions. The solvent was dried over Na_2SO_4, filtered, and removed under reduced pressure. Flash column chromatography on silica gel eluting with 83% hexanes in EtOAc gave fractions that after removal of solvent yielded 680 mg of pure amide. The amide (675 mg, 1.56 mmol) was dissolved in 20 mL of dry THF, and 3.12 mL of a 1 M solution of BH_3 in THF was added. The solution was heated at reflux for 3 h, cooled to room temperature, and then 1 mL of H_2O was added carefully, followed by 3 mL of conc HCl. The mixture was heated at reflux for 2 h, and the volume of the reaction was reduced to one-third under reduced pressure. The remaining mixture was made basic by addition of $NaHCO_3$ and extracted thoroughly with CH_2Cl_2. The pooled extracts were washed once with 10 mL of H_2O, dried over $MgSO_4$, filtered, and the solvents removed to give 540 mg (70%) of a clear oil. ^{1}H NMR (CD_3OD) δ 7.20 (t, 1H, ArH), 6.89 (m, 1H, ArH), 6.82 (s, 1H, ArH), 6.72 (m, 1H, ArH), 3.77 (s, 3H, CH_3OAr), 2.88−2.25 (m, 9H), 2.03 (m, 1H), 2.57−2.40 (m, 3H), 1.30 (d, 3H, CH_3, J = 6.6 Hz).), 1.28−1.10 (m, 1H), 0.96−0.89 (m, 7H), 1.60−1.70 (dd, 3H, CH_3). EIMS: m/z 319 ($M + H^+$, 100). Anal. ($C_{20}H_{34}N_2O$) C, H, N.

General Procedures for the Preparation of Compounds 8d−p.

a. BOP Coupling Procedure. A phenylpiperidine **7** (1 equiv) was dissolved along with a tetrahydroisoquinoline **6** (1.05 equiv) in 10 mL of dry THF and cooled to 0 °C. Into this flask was introduced BOP (1.05 equiv) dissolved in 5 mL of dry THF. Immediately afterward, Et_3N (1.05 equiv) was added and the solution was warmed to room temperature and allowed to stir for 3 h. The solution was added to 30 mL of saturated $NaHCO_3$. The resulting mixture was extracted 3× with 10 mL of EtOAc. The pooled organic solvents were washed once with 5 mL of water and dried over $MgSO_4$. The mixture was then separated by flash chromatography on silica gel. For the reactions employing Boc-protected tetrahydroisoquinolines, and the crude coupling mixture was dissolved in 10 mL of a 20% CF_3CO_2H solution in CH_2Cl_2 and stirred overnight. The solvents were removed and the crude product stirred in 10 mL of saturated $NaHCO_3$ and 10 mL of EtOAc. The layers were separated, and the aqueous layer was extracted 2× with 5 mL of EtOAc. The pooled EtOAc extracts were washed once with 3 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield a crude residue. When needed, the impure compound was purified by preparative thick layer chromatography. The dihydrochloride salts were formed by dissolving the freebase in 5 mL of EtOH, followed by addition of 5 mL of 2 M HCl in EtOH and evaporation of the solution under reduced pressure.

b. HBTU Coupling Procedure. A phenylpiperidine **7** (1 equiv) was dissolved along with a tetrahydroisoquinoline **6** (1.05 equiv) in 15 mL of a 50% solution of THF in CH_3CN and cooled to 0 °C. Into this flask was introduced HBTU (1.05 equiv) dissolved in 10 mL of CH_3CN. Immediately afterward, Et_3N (1.05 equiv) was added and the solution was warmed to room temperature and allowed to stir for 3 h. To the reaction solution was added 30 mL of saturated $NaHCO_3$. The resulting mixture was extracted three times with 10 mL of EtOAc. The pooled organic solvents were washed once with 5 mL of water and dried over $MgSO_4$. The mixture was then separated by chromatography. For the reactions employing Boc-protected tetrahydroisoquinolines, the crude coupling mixture was dissolved in 10 mL of a 20% CF_3CO_2H solution in CH_2Cl_2 and stirred overnight. The solvents were removed and the crude product stirred in 10 mL of saturated $NaHCO_3$ and 10 mL of EtOAc. The layers were separated, and the aqueous layer was extracted 2× with 5 mL EtOAc. The pooled EtOAc extracts were washed once with 3 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield a crude residue. When needed, the impure compound was purified by preparative thick layer chromatography. The dihydrochloride salts were formed by dissolving the freebase in 5 mL of EtOH, followed by addition of 5 mL of 2 M HCl in EtOH and evaporation of the solvents under reduced pressure.

(3*R*)-7-Hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-methoxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8d) Dihydrochloride. General procedure (a) was employed using 100 mg (0.328 mmol) of **7b** and 112 mg (0.382 mmol) of **6f** to afford 65 mg (35%) of the freebase. ^{1}H NMR (CD_3OD) δ 7.26 (t, 1H, J = 8.1 Hz), 7.00 (d, 1H, J = 8.1 Hz), 6.91 (d, 1H, J = 8.1 Hz), 6.86−6.75 (m, 2H), 6.63 (s, 1H), 4.30−4.37 (m, 3H), 3.50 (m, 2H), 3.15−3.11 (m, 1H), 2.80−2.71 (m, 1H), 2.45 (m, 1H), 1.93−1.87 (m, 1H), 1.49 (s, 3H), 1.29−1.13 (m, 1H), 1.07 (2d, 6H), 0.85 (d, 3H). The hydrochloride salt synthesized by the general procedure had mp > 220 °C dec $[\alpha]_D^{25}$ +69° (c 0.35, MeOH). ^{1}H NMR (CD_3OD) δ 7.31 (t, 1H, J = 9 Hz), 7.12 (d, 1H, J = 9 Hz), 6.95 (d, 1H), 6.86−6.73 (m, 3H), 6.63 (s, 1H), 4.40 (d, 1H), 4.34 (d, 1H), 4.27 (m, 2H), 3.81 (s, 3H), 3.63 (d, 1H), 3.60−3.24 (m, 6H), 3.20 (d, 1H), 2.63 (dt, 1H), 2.43 (m, 1H), 1.95 (m, 1H), 1.48 (s, 3H), 1.03−0.87 (m, 3H), 0.83 (d, 3H, J = 9 Hz), 0.80−0.68 (m, 6H). ESIMS: m/z 480 (M + 1, 50). Anal. ($C_{29}H_{43}Cl_2N_3O_3 \cdot 2H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*)-1-[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-(2-methylpropyl]-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8e) Dihydrochloride. General procedure (b) was employed using 100 mg (0.344 mmol) of **7a** and 111 mg (0.361 mmol) of **6a** to afford 65 mg (35%) of the freebase after separation by preparative TLC eluting with 1:1 CMA-80/CH_2Cl_2. ^{1}H NMR (CD_3OD) δ 7.09 (t, 1H, J = 8.4 Hz), 6.87 (d, 1H, J = 8.4 Hz), 6.70 (m, 2H), 6.55 (m, 2H), 6.47 (s, 1H), 4.02 (d, 1H), 3.77 (m, 2H), 3.16 (d, 1H), 2.74−2.33 (m, 7H), 2.14 (dt, 1H), 1.89−1.75 (m, 2H), 1.47 (d, 1H), 1.38 (d, 3H), 1.26−1.17 (m, 7H), 0.82 (t, 6H), 0.58 (d, 3H). The hydrochloride salt synthesized by the general procedure had mp > 220 °C dec $[\alpha]_D^{25}$ +47.2° (c 1, MeOH). ^{1}H NMR (CD_3OD) δ 7.18 (m, 2H), 6.75 (m, 3H), 6.62 (m, 1H), 4.42 (d, 1H), 4.27 (d, 1H), 4.25 (m, 1H), 3.67−3.30 (m, 6H), 3.18 (d, 1H), 2.63 (dt, 1H), 2.39 (m, 1H), 1.90 (d, 1H), 1.85−1.60 (m, 1H), 1.79 (s, 3H), 0.85 (d, 3H, J = 9 Hz), 0.68 (2d, 6H). ESIMS: m/z 480 (M + 1, 50). Anal. ($C_{29}H_{41}Cl_2N_3O_3 \cdot 2H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*,2*S*)-1-{[(3*R*,4*R*)-4-(3-methoxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylbutanyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8f) Dihydrochloride. General procedure (a) was employed using 120 mg (0.377 mmol) of **7d** and 116 mg (0.396 mmol) of **6f** to afford 50 mg (27%) of the freebase after separation by preparative TLC eluting with 1:1 CMA-80/Et_2O. ^{1}H NMR (CD_3OD) δ 7.19 (t, 1H), 6.87−6.81 (m, 2H), 6.80 (s, 1H), 6.69 (ds, 1H), 6.58 (ds, 1H), 6.47 (s, 1H), 4.06 (m, 1H), 3.77 (dd, 2H), 3.75 (s, 3H), 3.50 (dd, 1H), 2.82 (dd, 1H), 2.78−2.70 (m, 2H), 2.65−2.39 (m, 5H), 2.27 (dt, 1H), 1.99 (m, 1H), 1.70−1.50 (m, 4H), 1.40 (m, 5H), 1.22−1.03 (m, 2H), 0.8 (m, 9H), 0.69 (d, 3H). The hydrochloride salt synthesized by the general procedure had mp > 220 °C dec $[\alpha]_D^{25}$ +95.9° (c 0.71, MeOH). ^{1}H NMR (CD_3OD) δ 7.30 (t, 1H, J = 9 Hz), 7.12 (d, 1H, J = 9 Hz), 6.91 (d, 1H, J = 9 Hz), 6.89−6.73 (m, 2H), 6.62 (s, 1H), 4.40−4.20 (m, 3H), 3.89 (d, 1H), 3.81 (s, 3H), 3.67−3.23 (m, 7H), 3.12 (m, 1H), 2.82 (dt, 1H), 2.45 (m, 1H), 1.92 (d, 1H), 1.70 (m, 1H), 1.55 (m, 1H), 1.50 (s, 3H), 1.42 (m, 1H), 1.31 (m, 1H), 1.20 (m, 1H), 1.10−0.89 (m, 9H). ESIMS: m/z 494 (M + 1, 80). Anal. ($C_{30}H_{45}Cl_2N_3O_3 \cdot H_2O$) C, H, N.

(3*R*)-7-Methoxy-*N*-[(1*S*)-1-[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-(2-methylpropyl]-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8g) Dihydrochloride.

General procedure (b) was employed using 172 mg (0.593 mmol) of **7a** and 200 mg (0.622 mmol) of **6c** to afford 250 mg of the freebase after isolation (68% yield): mp 210−212 °C. ^{1}H NMR (CD_3OD) δ 7.09 (t, 1H, J = 8.1 Hz), 6.73−6.57 (m, 2H), 4.13 (d, 1H), 3.95−3.87 (m, 2H), 3.64 (s, 3H), 3.25 (d, 2H), 2.68 (m, 1H), 2.65−2.50 (m, 2H), 2.40 (m, 4H), 2.18 (dt, 1H), 1.82 (m, 2H), 1.52 (d, 1H), 1.37 (s, 3H), 1.24 (s, 3H), 0.85 (2d), 0.47 (d, 3H). The hydrochloride salt synthesized by the general procedure had mp 210−212 °C dec $[\alpha]_D^{25}$ +15° (*c* 1.2, MeOH). ^{1}H NMR (CD_3OD) δ 7.17−6.74 (m, 5H), 6.61 (m, 1H), 4.44 (d, 1H), 4.25 (d, 1H), 4.23 (m, 1H), 3.79 (s, 3H), 3.65−3.29 (m, 6H), 3.17 (d, 1H), 2.63 (dt, 1H), 2.40 (m, 1H), 1.91 (d, 1H), 1.84−1.59 (m, 1H), 1.79 (s, 3H), 0.84 (d, 3H, J = 9 Hz), 0.67 (2d, 6H). ESIMS: m/z 494 (M + 1, 100). Anal. ($C_{30}H_{45}Cl_2N_3O_3\cdot H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-methoxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8h) Dihydrochloride. General procedure (b) was employed using 100 mg (0.328 mmol) of **7b** and 120 mg (0.390 mmol) of **6a** to afford 27 mg (17%) of the freebase after separation by preparative TLC eluting with 75:1 EtOAc/Et_3N. ^{1}H NMR (CD_3OD) δ 7.17 (t, 1H), 6.79−6.90 (m, 2H), 6.70 (m, 1H), 6.56 (m, 1H), 6.48 (s, 1H), 4.00 (d, 1H), 3.87 (m, 2H), 3.78 (s, 3H), 3.17 (d, 1H), 2.72−2.28 (m, 7H), 2.15 (dt, 1H), 1.89 (m, 1H), 1.79 (sextet, 1H), 1.50 (d, 1H), 1.38−1.20 (m, 7H), 1.10−0.77 (m, 7H), 0.56 (d, 3H). The hydrochloride salt synthesized by the general procedure had mp >220 °C dec $[\alpha]_D^{25}$ +49.8° (*c* 0.45, MeOH). ^{1}H NMR (CD_3OD) δ 7.30 (t, 1H, J = 9 Hz), 7.13 (d, 1H, J = 9 Hz), 6.94 (d, 1H, J = 9 Hz), 6.85−6.74 (m, 3H), 6.63 (s, 1H), 4.41 (d, 1H), 4.35 (d, 1H), 4.27 (m, 1H), 3.81 (s, 3H), 3.63 (d, 1H), 3.60−3.25 (m, 6H), 3.20 (d, 1H), 2.63 (dt, 1H), 2.45 (m, 1H), 1.95 (m, 1H), 1.78 (s, 3H), 1.48 (s, 3H), 1.05−0.89 (m, 3H), 0.83 (d, 3H, J = 9 Hz), 0.80−0.68 (m, 6H). ESIMS: m/z 494 (M + 1, 80). Anal. ($C_{30}H_{45}Cl_2N_3O_3\cdot H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*,2*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylbutanyl]-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8i) Dihydrochloride. General procedure (a) was employed using 104 mg of **7d** (0.341 mmol) and 110 mg (0.358 mmol) of **6a** to afford 29 mg of the freebase after separation by preparative TLC eluting with 1:1 CMA-80/CH_2Cl_2 (17% yield). ^{1}H NMR (CD_3OD) δ 7.19 (t, 1H), 6.79 (d, 1H, J = 8.1 Hz), 6.77−6.66 (m, 2H), 6.58 (m, 2H), 6.48 (s, 1H), 4.09 (q, 1H), 4.02−3.95 (d, 1H), 3.93−3.8 (m, 2H), 3.15 (d, 2H), 2.70−2.50 (m, 3H), 2.49−2.32 (m, 3H), 2.15 (dt, 1H), 1.88 (m, 1H), 1.62−1.3 (m, 11H), 0.91−0.79 (m, 9H), 0.58 (d, 3H, CH_3). The hydrochloride salt synthesized by the general procedure had mp >220 °C dec $[\alpha]_D^{25}$+42.2° (*c* 0.51, MeOH). ^{1}H NMR (CD_3OD) δ 7.20 (t, 1H, J = 9 Hz), 7.13 (d, 1H, J = 9 Hz), 6.80−6.75 (m, 2H), 6.69−6.64 (m, 2H), 4.41 (d, 1H), 4.30 (d, 1H), 4.28 (m, 1H), 3.64−3.32 (m, 7H), 3.17 (d, 1H), 2.63 (dt, 1H), 2.40 (m, 1H), 1.92 (d, 1H), 1.76 (s, 3H), 1.47 (m, 4H), 1.20 (m, 2H), 0.92−0.71 (m, 9H). ESIMS: m/z 494 (M + 1, 80). Anal. ($C_{30}H_{45}Cl_2N_3O_3\cdot H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*,2*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylbutanyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8j) Dihydrochloride. General procedure (a) was employed using 130 mg (0.427 mmol) of **7c** and 109 mg (0.448 mmol) of **6e to** afford 55 mg (25%) of the freebase after separation by preparative TLC eluting with 2:1 CMA-80/CH_2Cl_2. ^{1}H NMR (CD_3OD) δ 7.19 (t, 1H, J = 8.1 Hz), 6.90 (d, 1H, J = 8.1 Hz), 6.73 (m, 2H), 6.59 (m, 2H), 6.51 (s, 1H), 4.09 (q, 1H), 3.98 (m, 1H), 3.84 (d, 1H), 3.50 (d, 1H), 3.13 (t, 1H), 2.99 (m, 1H), 2.88 (m, 1H), 2.75 (m, 1H), 2.55 (m, 2H), 2.45 (s, 3H), 2.37 (m, 2H), 2.23 (m, 1H) 1.94 (m, 2H), 1.63 (m, 1H), 1.50 (m, 2H), 1.62−1.3 (m, 11H), 0.80−1.0 (m, 9H), 0.7 (d, 3H, CH_3). The hydrochloride salt synthesized by the general procedure had mp 180 °C dec $[\alpha]_D^{25}$ +84.3° (*c* 0.6, MeOH). ^{1}H NMR (CD_3OD) δ 7.19−7.11 (m, 2H), 6.89−6.65 (m, 4H), 4.50 (m, 2H), 4.32 (m, 1H), 3.73 (d, 1H), 3.55−3.16 (m, 8H), 3.08 (s, 3H), 2.78 (dt, 1H), 2.39 (m, 1H), 1.86 (d, 1H, J = 15 Hz), 1.68 (m, 1H), 1.51−1.40 (m, 4H), 1.21 (m, 2H), 1.02 (d, 3H, J = 6 Hz), 0.97−0.80 (m, 6H). ESIMS: m/z 494 (M + 1, 100). Anal. ($C_{30}H_{45}Cl_2N_3O_3\cdot H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-methoxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8k) Dihydrochloride. General procedure (a) was employed using 120 mg (0.394 mmol) of **7b** 86 mg (0.414 mmol) of **6e** to afford 67 mg (35%) of the freebase after separation by preparative TLC eluting with 2:1:1 CMA-80/EtOAc/hexanes. ^{1}H NMR (CD_3OD) δ 7.20 (t, 1H, J = 8.1 Hz), 6.91 (d, 1H, J = 8.1 Hz), 6.86 (d, 1H, J = 8.1 Hz), 6.81 (s, 1H), 6.71 (dd, 1H), 6.59 (dd, 1H), 6.51 (d, 1H), 4.09 (q, 1H), 3.92 (m, 1H), 3.84 (dd, 1H), 3.77 (s, 1H), 3.50 (d, 1H), 3.13 (dd, 1H), 3.05 (dd, 1H), 2.96 (dd, 1H), 2.73 (m, 1H), 2.53 (dd, 1H), 2.50−2.40 (m, 4H), 2.40−2.37 (m, 2H), 2.22 (dt, 1H) 1.98 (m, 2H), 1.84 (m, 1H), 1.57 (t, 1H), 1.33 (m, 5H), 0.94−0.84 (m, 8H), 0.84−075 (dd, 1H), 0.73−0.68 (m, 3H). The hydrochloride salt synthesized by the general procedure had mp 210−215 °C dec $[\alpha]_D^{25}$ +75.7° (*c* 1, MeOH). ^{1}H NMR (CD_3OD) δ 7.29 (t, 1H, J = 9 Hz), 7.12 (d, 1H, J = 9 Hz), 6.91 (d, 1H), 6.87−6.61 (m, 3H), 4.48 (d, 1H), 4.35 (d, 1H), 4.30 (m, 1H), 3.81 (s, 3H), 3.78 (d, 1H), 3.63−3.15 (m, 6H), 3.09 (s, 3H), 3.07 (m, 1H), 2.80 (dt, 1H), 2.45 (m, 1H), 1.91 (m, 2H), 1.49 (s, 3H), 1.08−0.90 (m, 7H), 0.86 (d, 3H, J = 9 Hz). ESIMS: m/z 494 (M + 1, 100). Anal. ($C_{30}H_{45}Cl_2N_3O_3\cdot H_2O$) C, H, N.

(3*R*)-7-Methoxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-methoxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8l) Dihydrochloride. General procedure (a) was employed using 126 mg (0.414 mmol) of **7b** 140 mg (0.435 mmol) of **6c** to afford 51 mg (23%) of the freebase after separation by preparative TLC eluting with 2:1 $CHCl_3$/CMA-80. ^{1}H NMR (CD_3OD) δ 7.39−7.19 (m, 2H), 7.92−6.78 (m, 5H), 4.5−4.32 (q, 2H), 4.25 (m, 1H), 3.70 (d, 6H), 3.6−3.30 (m), 3.20 (d, 1H), 2.67 (dt, 1H), 2.45 (m, 1H), 1.92 (bd, 1H), 1.78 (s, 3H), 1.75−1.60 (m, 1H), 1.47 (s, 3H), 0.86 (d, 3H), 0.70 (t, 6H). The hydrochloride salt synthesized by the general procedure had mp >220 °C dec $[\alpha]_D^{25}$ +49.8° (*c* 1, MeOH). ^{1}H NMR (CD_3OD) δ 7.30 (t, 1H), 7.26 (d, 1H, J = 6 Hz), 6.92−6.80 (m, 2H), 6.84−6.80 (m, 2H), 4.48 (d, 1H), 4.36 (d, 1H), 4.38 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.58 (d, 1H), 3.44−3.25 (m, 6H), 3.23 (d, 1H), 2.64 (dt, 1H), 2.46 (m, 1H), 1.95 (d, 1H), 1.78 (s, 3H), 1.80 (m, 1H), 0.83 (d, 3H, J = 7.5 Hz), 0.79 (m, 6H). ESIMS: m/z 508 (M + 1, 100). Anal. ($C_{31}H_{47}Cl_2N_3O_3\cdot H_2O$) C, H, N.

(3*R*)-7-Methoxy-*N*-[(1*S*,2*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]}-2-methylbutanyl]-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8m) Dihydrochloride. General procedure (b) was employed using 65 mg (0.213 mmol) of **7c** and 46 mg (0.224 mmol) of **6c** to afford 25 mg (25%) of the freebase after separation by preparative TLC eluting with 1:1 CMA-80/CH_2Cl_2. ^{1}H NMR ($CDCl_3$) δ 7.41 (d, 1H), 7.12 (t, 1H), 6.96 (d, 1H), 6.82−6.52 (m, 5H), 4.18−3.77 (m, 4H), 3.73 (s, 3H), 3.11 (d, 1H), 2.82−2.57 (m, 4H), 2.48−2.28 (m, 4H), 2.17−2.02 (m, 2H), 1.91−1.54 (m, 3H), 1.55−1.22 (m, 9H), 0.98−083 (m, 6H), 0.48 (d, 3H). 1.47 (d, 1H), 1.38 (d, 3H), 1.26−1.17 (m, 7H), 0.82 (t, 6H), 0.58 (d, 3H). The hydrochloride salt synthesized by the general procedure had mp >220 °C dec $[\alpha]_D^{25}$ +44.7° (*c* 0.45, MeOH). ^{1}H NMR (CD_3OD) δ 7.24 (d, 1H, J = 9 Hz), 7.18 (t, 1H, J = 9 Hz), 6.92 (m, 1H), 6.80 (s, 1H), 6.76 (m, 1H), 6.68 (m, 1H), 4.48 (d, 1H), 4.38 (d, 1H), 4.30 (m, 1H), 3.79 (s, 3H), 3.70 (d, 1H, J = 15.9 Hz), 3.60−3.31 (m, 5H), 3.20 (d, 1H, J = 15.9 Hz), 2.67 (dt, 1H), 2.40 (m, 1H), 1.91 (d, 1H), 1.79 (s, 3H), 1.46 (bs, 4H), 1.13 (m, 1H), 0.85 (d, 3H), 0.80−0.69 (m, 6H). ESIMS: m/z 508 (M + 1, 100). Anal. ($C_{31}H_{47}Cl_2N_3O_3\cdot 2H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*,2*S*)-1-{[(3*R*,4*R*)-4-(3-methoxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylbutanyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8n) Dihydrochloride. General procedure (a) was employed using 145 mg (0.455 mmol) of **7d** and 146 mg (0.478 mmol) of **6a** to afford

60 mg (26%) of the freebase after separation by preparative TLC eluting with 3:1 $CHCl_3$/CMA-80. ^{1}H NMR (CD_3OD) δ 7.18 (t, 1H, J = 8.1 Hz), 6.88 (d, 1H, J = 8.1 Hz), 6.82 (d, 1H), 6.78 (t, 1H), 6.89 (dd, 1H, J_2 = 5.7 Hz, J_1 = 2.1 Hz), 6.53 (dd, 1H J_2 = 5.7 Hz, J_1 = 2.1 Hz), 6.46 (d, 1H, J = 2.4 Hz), 3.96 (d, 1H), 3.92 (m, 1H), 3.76 (s, 3H), 3.30 (m, 1H), 3.15 (d, 1H, J = 15.9 Hz), 2.69 (m, 1H), 2.64 (d, 1H), 2.54 (b, 1H), 2.47−2.36 (m, 5H), 2.17 (dt, 1H), 1.91 (m, 1H), 1.52−1.35 (m, 5H), 1.32 (s, 3H), 1.26 (m, 4H), 1.15 (d, 1H), 1.06−0.9 (m, 2H), 0.86 (t, 3H, J = 7.2 Hz), 0.81 (d, 3H, J = 6.9 Hz), 0.57 (d, 3H, J = 6.9 Hz). The hydrochloride salt synthesized by the general procedure had mp 210 °C dec $[\alpha]_D^{25}$ +39.7° (c 0.41, MeOH). ^{1}H NMR (CD_3OD) δ 7.27 (t, 1H, J = 9 Hz), 7.11 (d, 1H, J = 9 Hz), 6.90−6.70 (m, 3H), 6.61 (s, 1H), 4.38 (d, 1H), 4.29 (m, 1H), 3.65 (d, 1H), 3.60−3.25 (m, 5H), 3.15 (d, 1H), 2.64 (dt, 1H), 2.42 (m, 1H), 1.92 (d, 1H), 1.76 (s, 3H), 1.46 (bs, 4H), 1.12 (m, 1H), 0.82 (d, 3H, J = 9 Hz), 0.78−0.71 (m, 6H). ESIMS: m/z 508 (M + 1, 100). Anal. ($C_{31}H_{47}Cl_2N_3O_3\cdot 2H_2O$) C, H, N.

(3*R*)-7-Methoxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8o) Dihydrochloride. General procedure (a) was employed using 104 mg (0.358 mmol) of **7a** and 88 mg (0.376 mmol) of **6d** to afford 80 mg (44%) of the freebase after separation by preparative TLC eluting with 3:1 $CHCl_3$/CMA-80. ^{1}H NMR (CD_3OD) δ 7.07 (t, 1H), 6.93 (d, 1H), 6.73−6.52 (m, 5H), 4.86 (s, 3H), 4.07 (d, 1H, J = 16.5 Hz), 3.89 (m, 1H), 3.80 (d, 1H, J = 16.5 Hz), 3.67 (s, 3H), 3.14 (d, 1H, J = 16.5 Hz), 2.72 (m, 1H), 2.62−2.57 (m, 2H), 2.50−2.37 (m, 5H), 2.31 (dd, 1H), 2.18 (dt, 1H), 1.90 (m, 1H), 1.89−1.75 (m, 1H), 1.51 (bd, 1H), 1.37−1.25 (m, 7H), 1.01−0.84 (m, 8H), 0.54 (d, 3H, J = 6.9 Hz). The hydrochloride salt synthesized by the general procedure had mp 199 °C dec $[\alpha]_D^{25}$ +50.2° (c 0.55, MeOH). ^{1}H NMR (CD_3OD) δ 7.29 (d, 1H, J = 9 Hz), 7.18 (t, 1H, J = 9 Hz), 6.95 (d, 1H, J = 9 Hz), 6.83−6.68 (m, 2H), 6.67 (d, 1H), 4.70−4.48 (bm, 2H), 4.33 (bm, 1H), 3.80 (s, 3H), 3.67−3.30 (m, 7H), 2.99 (s, 1H), 2.68 (dt, 1H), 2.42 (m, 1H), 1.92 (d, 1H), 1.48 (s, 3H), 0.99−0.50 (s, 9H). ESIMS: m/z 508 (M + 1, 100). Anal. ($C_{31}H_{47}Cl_2N_3O_3\cdot 2H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*,2*S*)-1-{[(3*R*,4*R*)-4-(3-methoxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl]-2-methylbutanyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8p) Dihydrochloride. General procedure (a) was employed using 100 mg (0.328 mmol) of **7d** and 71 mg (0.345 mmol) of **6e** to afford 40 mg (34%) of the freebase after separation by preparative TLC eluting with 1:1 CMA-80/Et_2O. ^{1}H NMR (CD_3OD) δ 7.19 (t, 1H, J = 7.8 Hz), 6.92−6.84 (m, 2H), 6.82 (s, 1H), 6.71 (d, 1H), 6.59 (m, 1H), 6.21 (m, 1H), 4.09 (q, 1H), 3.98 (m, 1H), 3.87 (m, 1H), 3.77 (s, 3H), 3.49 (d, 1H, J = 15 Hz), 3.14−2.82 (m, 4H), 2.79−2.60 (m, 2H), 2.60−2.28 (m, 9H), 2.23 (dt, 1H) 1.97 (m, 1H), 1.68−1.35 (m, 4H), 1.29 (d, 3H), 1.23 (t, 3H), 0.93 (t, 5H), 0.90−0.77 (m, 2H), 0.70 (t, 3H). The hydrochloride salt, synthesized by the general procedure, had mp 180 °C dec $[\alpha]_D^{25}$ +66.2° (c 0.5, MeOH). ^{1}H NMR (CD_3OD) δ 7.29 (t, 1H, J = 9 Hz), 7.13 (d, 1H, J = 9 Hz), 6.93−6.78 (m, 3H), 6.67 (d, 1H), 6.85−6.74 (m, 3H), 6.67 (d, 1H), 4.48−4.28 (m, 3H), 3.81 (s, 3H), 3.63 (d, 1H), 3.60−3.25 (m, 6H), 3.09−3.01 (m, 4H), 2.78 (dt, 1H), 2.46 (m, 1H), 1.92 (m, 1H), 1.78 (s, 3H), 1.48 (bs, 4H), 1.1−0.8 (m, 10H). ESIMS: m/z 508 (M + 1, 100). Anal. ($C_{31}H_{47}Cl_2N_3O_3\cdot H_2O$) C, H, N.

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Supporting Information Available: Elemental analysis data for compounds **7c**,**d**, **8d**−**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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