Synthesis and In Vitro Opioid Receptor Functional Antagonism of Analogues of the Selective Kappa Opioid Receptor Antagonist (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)

Tingwei Bill Cai, Zhou Zou, James B. Thomas, Larry Brieaddy, Hernán A. Navarro, and F. Ivy Carroll*

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

Received October 26, 2007

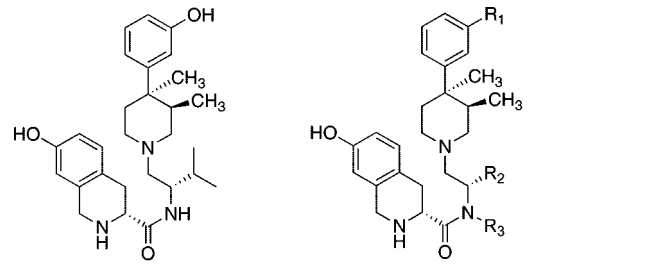
In previous structure–activity relationship (SAR) studies, we identified (3*R*)-7-hydroxy-*N*-((1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl}-2-methylpropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (JDTic, **1**) as the first potent and selective κ opioid receptor antagonist from the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of opioid antagonist. In the present study, we report the synthesis and in vitro opioid receptor functional antagonism of a number of analogues of **1** using a [^{35}S]GTPγS binding assay. The results from the studies better define the pharmacophore for this class of κ opioid receptor antagonist and has identified new potent and selective κ antagonist. (3*R*)-7-Hydroxy-*N*-[(1*S*,2*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylbutyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**3**) with a K_e value of 0.03 nM at the κ receptor and 100- and 793-fold selectivity relative to the μ and δ receptors was the most potent and selective κ opioid receptor antagonist identified.

Introduction

The opioid receptors, μ, δ, and κ, and the opioid-like receptor (ORL-1[a]) belong to the super family of G-protein coupled receptors (GPCRs) that possess seven helical transmembrane spanning domains in their architecture.[1] The majority of research efforts focused upon this group of proteins has been directed toward the μ receptor because it mediates the actions of both the opiate and opioid analgesics, such as morphine and fentanyl, respectively.[2] Over the years, however, it has become increasingly clear that the entire family of proteins are actively involved in a host of biological processes.[2] Furthermore, the advent of selective antagonists has demonstrated that pharmacotherapeutic opportunities exist via both negative and positive modulation of this receptor family.[3–8]

The κ opioid receptor system and its endogenous ligands, the dynorphins, have been linked to numerous physiological conditions, including stress, depression, anxiety, and psychotic behaviors, such as schizophrenia.[9–12] Stress and depression are two key triggers for relapse to addictive behaviors including cocaine abuse, a chronically relapsing disease for which there is no existing pharmacotherapy.[13,14] Kappa receptor antagonists have been shown to modulate the responses to stress in a number of animal models.[9–11] We recently reported that the κ receptor antagonist JDTic (**1**)[6–8] demonstrated dose-dependent reduction of stress-induced relapse to cocaine seeking in abstinent rats.[15] Furthermore, compound **1** demonstrated dose-dependent efficacy in the Porsolt forced swim test that is characteristic of antidepressants.[15] Taken together, these findings suggest that κ receptor antagonists may provide a pharmacological means of managing relapse to cocaine seeking by simultaneous blockade of two key triggers for relapse, stress, and depression. In this article, we report the synthesis and evaluation of **2–5**, **6a–f**, and **7a–k** analogues of **1** (Charts 1–3) for their ability to antagonize in vitro opioid receptor activation in a [^{35}S]GTPγS binding assay. The results from these SAR studies provide a better understanding of the key pharmacophore features associated with κ receptor antagonists related to **1**. In addition, new potent and selective κ opioid receptor antagonists were identified.

Chart 1



(**2**) R_1 = $CONH_2$; R_2 = *i-Pr*; R_3 = H
(**3**) R_1 = OH; R_2 = *s*-butyl; R_3 = H
(**4**) R_1 = OH; R_2 = H; R_3 = $-CH_2CH(CH_3)_2$
(**5**) R_1 = OH; R_2 = H; R_3 = $-CH_2CH_2CH(CH_3)_2$

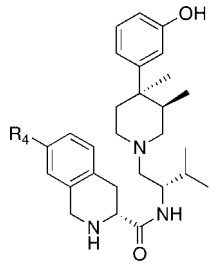
Chemistry. The synthesis of compound **2** is given in Scheme 1. 3-[1-(2*S*-Amino-3-methylbutyl)-3*R*,4*R*-dimethyl-4-piperidinyl]phenol (**8**)[16] was first N-protected with a *tert*-butoxycarbonyl (Boc) group followed by conversion of the phenol to the triflate by treatment with triflic anhydride to afford intermediate **9**. Compound **9** was then converted to the methyl ester **10** in 96% yield by treatment with carbon monoxide and catalytic dichloro-[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) [$PdCl_2$-(dppf)] in a methanol and dimethylsulfoxide solution at 70 °C.[17]

* Telephone: 919-541-6679. Fax: 919-541-8868. E-mail: fic@rti.org.

[a] Abbreviation: GPCRs, G-protein-coupled receptors; cDNAs, complementary deoxyribonucleic acid; ORL-1, opioid receptor like; 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; Tic, tetrahydroisoquinoline; $PdCl_2$ (dppf), dichloro-[1,1′-bis(diphenylphosphino)ferrocene] palladium(II).

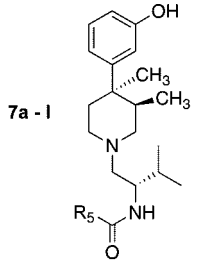
10.1021/jm701344b CCC: $40.75 © 2008 American Chemical Society
Published on Web 02/29/2008

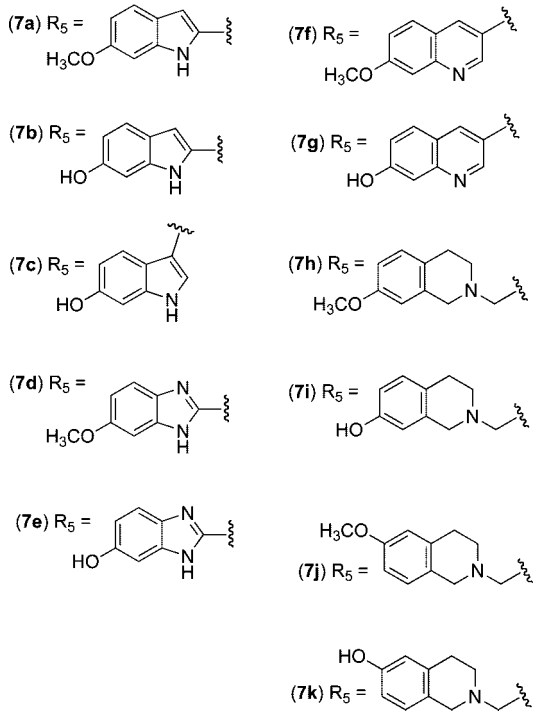
Chart 2



(**6a**) $R_4 = OCH_3$
(**6b**) $R_4 = NO_2$
(**6c**) $R_4 = NH_2$
(**6d**) $R_4 = NHCOCH_3$
(**6e**) $R_4 = NHSO_2CH_3$
(**6f**) $R_4 = H$

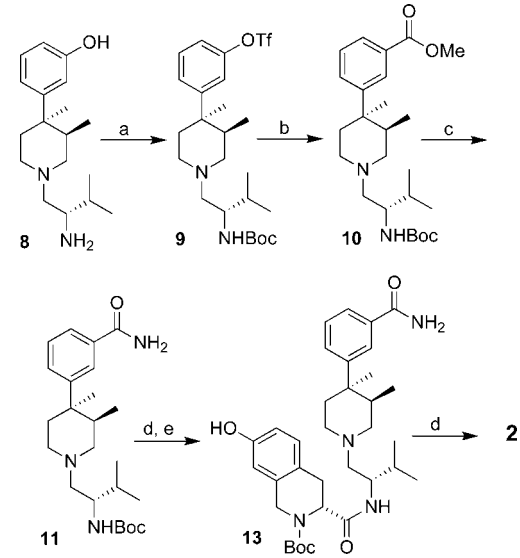
Chart 3





Hydrolysis of the ester to the acid was followed by conversion to amide **11** using ammonium hydrogen carbonate with di-*tert*-butyl pyrocarbonate as an activating agent in acetonitrile containing a small amount of pyridine in 50% yield.[18] Finally, deprotection of **11** with 2N hydrochloric acid in ether followed by coupling with Boc-D-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**12**) using benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) in tetrahydrofuran (THF) and deprotection gave compound **2**.

Scheme 1[a]



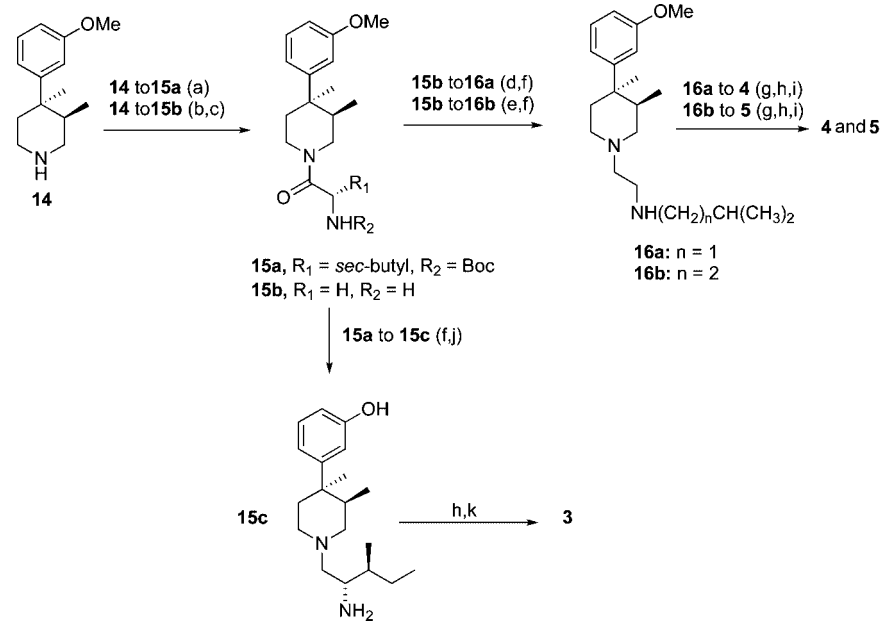
[a] Reagents and conditions: (a) $(Boc)_2O$ then Tf_2O, pyridine; (b) $PdCl_2(dppf)$, CO, MeOH, DMSO; (c) LiOH, H_2O then pyridine, $(Boc)_2O$, NH_4HCO_3, CH_3CN; (d) 2 N HCl in ether, MeOH; (e) Boc-D-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**12**), BOP, Et_3N, THF.

The synthesis of compound **3**, Scheme 2, began with the coupling of piperidine **14** with Boc-protected isoleucine using BOP in THF to give **15a**. This compound was converted to **15c** by reduction with borane in THF followed by refluxing with 48% hydrobromic acid to deprotect the phenol and remove the *tert*-butoxycarbonyl group. Compound **3** was obtained by coupling of **15c** with **12** using BOP in THF followed by deprotection with 6 N HCl. Compounds **4** and **5** were also synthesized as outlined in Scheme 2. Compound **14** was coupled to *N*-Boc-glycine using BOP in THF followed by N-deprotection to give **15b**. This material was coupled with either isobutyric acid chloride or 3-methylbutyryl acid chloride, and the resulting product reduced using borane in THF to give **16a**,**b**. O-Demethylation using boron tribromide in methylene chloride followed by coupling with **12** and N-deprotection using trifluoroacetic acid gave compounds **4** and **5**.

Compounds **6a**−**e** were synthesized by the routes shown in Scheme 3. Intermediate **18**, needed for the synthesis of **6a**, was prepared from **12** by first methylating both the phenol and the carboxylic acid with dimethylsulfate to give **17**. Selective hydrolysis of the methyl ester using lithium hydroxide in aqueous methanol followed by coupling of the resulting acid with **8**, using BOP, provided **18**. N-Deprotection of **18** with trifluoroacetic acid yielded **6a**. The preparation of compounds **6b**, **6d**, and **6e** were obtained by coupling the appropriate Boc-D-7-substituted-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (**19**–**21**)[19–21] with **8** using BOP conditions to give **24**–**26**. Deprotection with trifluoroacetic acid afforded **6b**, **6d**, and **6e**. Reduction of the nitro group in **6b** using 10% palladium on carbon catalyst in methanol afforded **6c**.

The syntheses of compounds **7a**−**k**, depicted in Schemes 4−9, all followed a similar path wherein a specific carboxylic acid was prepared, coupled to **8**, and then N- and O-deprotected. The preparation of indole analogues **7a**,**b** started with 6-methoxy-1*H*-indole-2-carboxylic acid (**27**, Scheme 4). The synthesis of **7c** involved treatment of 6-methoxy-1*H*-indole (**28**) with trichloroacetyl chloride to give 2,2,2-trichloro-1-(6-methoxy-1*H*-indol-3-yl)ethanone that was subsequently hydrolyzed to 6-methoxy-1*H*-indole-3-carboxylic acid (**29**, Scheme 5). This material was carried forward through intermediate **30** to give

Scheme 2[a]



[a] Reagents and conditions: (a) *N*-Boc-isoleucine, BOP, Et_3N, THF; (b) *N*-Boc-glycine, BOP, Et_3N, THF; (c) 2 N HCl, ether, CH_3OH; (d) isobutyric chloride, DIPEA; (e) 3-methylbutanoyl chloride, DIPEA; (f) BH_3, THF, 6 N HCl; (g) BBr_3, CH_2Cl_2, −78 °C; (h) Boc-D-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**12**), BOP, Et_3N, THF; (i) TFA; (j) 48% HBr reflux; (k) 6 N HCl reflux.

7c as described for **7a**,**b**. The synthesis of benzimidazole analogues **7d**,**e** started with 4-methoxybenzene-1,2-diamine (**31**, Scheme 6), which was treated with methyl 2,2-dichloro-2-methoxyacetate followed by saponification with lithium hydroxide to give 6-methoxy-1*H*-benzimidazole-2-carboxylic acid (**32**). This acid was converted to the target compounds **7d**,**e** as described above. Quinoline analogues **7f**,**g** were obtained from 3,3-dimethyloxypropionitrile (**33**) (Scheme 7) by conversion to 3-cyano-7-methoxyquinoline (**34**) followed by hydrolysis to 7-methoxyquinoline-3-carboxylic acid (**35**), which was carried forward as described for **7a** and **7b**. Isoquinoline analogues **7h**,**i** (Scheme 8) were obtained from 2-benzotriazolymethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**36**) via the (7-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)acetic acid ethyl ester intermediate (**37**). Analogues **7j**,**k** (Scheme 9) were prepared from bis(6-methoxy-*N*-1,2,3,4-tetrahydroisoquinolinyl)methane (**39**) obtained via the Pictet−Spengler reaction using 3-methoxyphenethylamine **38**. This material was then converted to the (6-ethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)acetic acid ethyl ester (**40**), as described above. Hydrolysis of the ethyl ester followed by coupling with **8** afforded **7j**. O-Demethylation of **7j** gave **7k**.

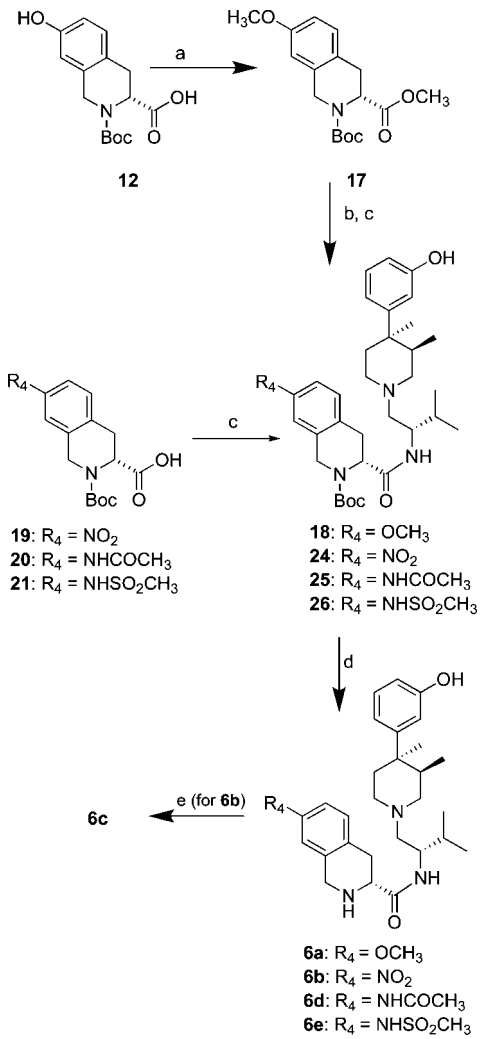
Biology. Compounds **2**–**5**, **6a**−**f**, and **7a**−**k** were first evaluated at 10 μM for intrinsic activity in the [^{35}S]GTPγS binding assay at all three opioid receptors. As none of compounds displayed measurable intrinsic activity at this concentration, they and the reference compound **1** 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 selective agonists DAMGO (μ), DPDPE (δ), or U69,593 (κ) using cloned human opioid receptors expressed in CHO cells.[22] Agonist dose response curves were run in the presence or absence of a single concentration of test compound. The K_e values were calculated using the following formula: $K_e = [L]/\mathrm{DR}-1$, 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 2-fold shift to the right and there was a clear upper asymptote to the agonist + compound concentration response curve. The K_e values for **2**–**5**, **6a**−**f**, and **7a**−**k** along with those for the reference compound **1** are shown in Table 1.

Results and Discussion

The evaluation of analogues **2**–**5** listed in Chart 1 provided insight into changes in in vitro functional antagonism resulting from structural modification of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine-based portion of **1** (Table 1). The data for carboxamido derivative **2** provides information as to the effect of changing to the hydrogen bond donating 3-hydroxyphenyl group in the antagonist "message" fragment of **1** to a 3-carboxamidophenyl group. Such modifications have been successfully employed in other opioid compounds and in some cases have provided compounds with improved biological properties.[23–25] Compound **2** has a $K_e = 0.1$ nM, which is only 5-fold less potent than that of **1**. Compound **2** with K_e values of 21 and 478 at the μ and δ receptors is also selective for the κ opioid receptor. Changing the (1*S*)-isopropyl group of **1** to a (1*S*)-*sec*-butyl group gives **3**, which has a K_e value of 0.03 nM at the κ opioid receptor, which is almost as potent as **1**. With K_e values of 3 and 24 nM at the μ and δ opioid receptors, respectively, **3** also retained good κ selectivity.

Analogues **4** and **5** examined the effect of moving the isopropyl group in **1** from the carbon next to the amide group to the amide nitrogen. The one and two methylene linkers were added to ensure that this group could still reach the same receptor space as that found in **1**. Both of these compounds are antagonists at all three of the opioid receptors, but the potency at the κ receptor was much lower than that found for **1**. Because high potency at the κ receptor has always driven the selectivity in this series of compounds, this change was not favorable and gave compounds that were not selective for the κ versus the μ receptor.

Scheme 3[a]



[a] Reagents and conditions: (a) $(CH_3)_2SO_4$, K_2CO_3, CH_3COCH_3; (b) LiOH, CH_3OH, H_2O; (c) **8**, BOP, Et_3N, THF; (d) TFA; (e) 10% Pd/C, H_2, MeOH.

Compounds **6a**−**e** are analogues where the hydroxy group in the 7-hydroxy-D-Tic part of **1** has been replaced with other groups, Chart 2. The most potent of these groups was the methyl ether **6a**. This compound 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 at the κ receptor relative to **1**. The amino analogue **6c** also had a subnanomolar antagonist potency (K_e = 0.2 nM) and only a 10-fold loss of potency relative to **1**. Changing the amino group to its *N*-acetyl and *N*-sulfonamido derivatives gave **6d** and **6e** with K_e values of 1.4 and 4 nM, respectively. The nitro derivative **6b** gave a 320-fold loss of potency at the κ receptor relative to **1**. The previously reported unsubstituted analogue **6f**[26] was found to have a K_e value of 56 nM for the κ receptor. The high potency of **1**, **6a**, and **6c** relative to **6f** suggests the potential involvement of their hydroxy, methoxy, and amino groups in a hydrogen bond acceptor interaction. Alternatively, the κ potency may be due to electronic effects. Compounds **1**, **6a**, and **6c**, which possess R_4 groups that donate electron density to the aryl ring have higher potency κ antagonism than compounds wherein electron density was removed from the ring, **6b**, or where resonance donation was reduced (**6d**,**e** relative to **6c**). Overall, it is clear that more analogues will be needed to completely resolve this issue.

We also examined replacement of the isoquinoline portion of 7-hydroxy-D-Tic part of **1** with achiral heterocycles (R_5, as depicted in Chart 3). These included a number of 6,5 fused-ring heterocycles such as **7a**–**7e** and 6,6 fused-ring heterocycles like **7f**–**7k**. In each of these cases, we retained representative functional groups found in **1** or **6a**, including an oxygen-substituted (OH or OCH_3) aryl ring fused to a nitrogen-bearing heterocyclic ring. In this modification, we included indole, benzimidazole, quinoline, and tetrahydroisoquinoline examples. The two most potent of these compounds at the κ opioid receptor were **7k** with a K_e value of 3.9 nM and **7c** with a K_e value of 4.5 nM, which represent 195- and 225-fold decreases in antagonist potency relative to **1**. Overall, this suggests that the stereocenter in the D-Tic portion of **1** is important for highly potent antagonist activity at the κ receptor.

Conclusion

This study has identified several potent and selective analogues of **1** and also provided new SAR information, which has shed new light on the κ opioid receptor antagonist pharmacophore. First, compound **2** demonstrated that the hydroxyl group in the phenol ring of the message component of **1** can be substituted by a carboxamido group and still retain high κ potency and selectivity. Changing the isopropyl substituent next to the amide nitrogen in **1** to a *sec*-butyl group to give **3**, and methylating the phenol in the 7-hydroxy-D-Tic portion of **1** to a methyl ether to give **6a** produced potent and selective κ opioid receptor antagonists. In contrast, the addition of large aliphatic groups to the amide nitrogen to give compounds **4** and **5** and elimination of the chiral center with concomitant modification of the isoquinoline group in the D-Tic portion of **1** to give **7a**–**k** all resulted in significant loss of potency at the κ receptor. In addition, changes to the electron density in the aromatic portion of 7-hydroxy-D-Tic fragment (see compounds **6a**–**6f**) strongly influenced antagonist potency suggesting that this ring is an active part of the pharmacophore and not simply a molecular scaffold.

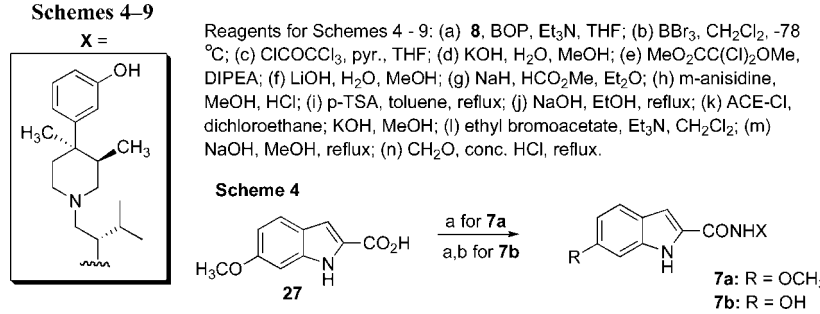
Experimental Section

^{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. Silica gel 60 (230–400 mesh) was used for column chromatography. 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. MMA-80 is a mixture of 80% methylene chloride, 18% methanol, and 2% concentrated ammonium hydroxide. IUPAC nomenclature is used in the Experimental Section to name target compounds and intermediates except **12** and **19**–**21**. The names were generated using ACD software.

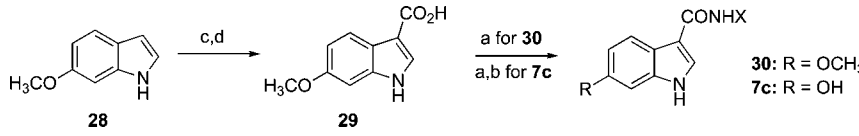
General Procedure for Coupling of Amines and Acids. The subject amine (1 equiv) was coupled with the subject carboxylic acid (1 equiv) by combining with BOP reagent (1 equiv) and triethylamine (2 equiv) in THF (20 mL/g of subject compound) at 0 °C. The mixture was stirred at room temperature for 2 h and diluted with ether. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine, and the organic layer was dried (Na_2SO_4) and concentrated.

General Procedures for N-Deprotection. Method A: The subject compound (50 mg) was dissolved in 1 mL of MeOH and to this was added 10 mL of 2 N HCl in ether. The mixture was stirred at room temperature for 3 h and then concentrated. The

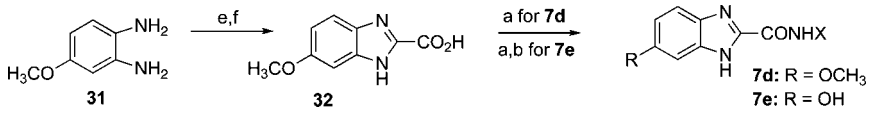
Scheme 4



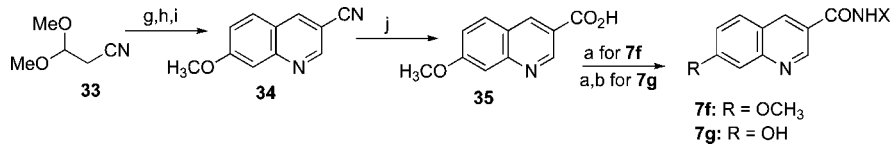
Scheme 5



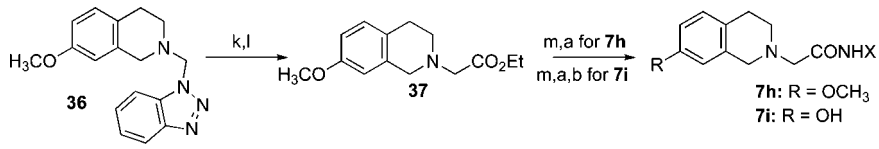
Scheme 6



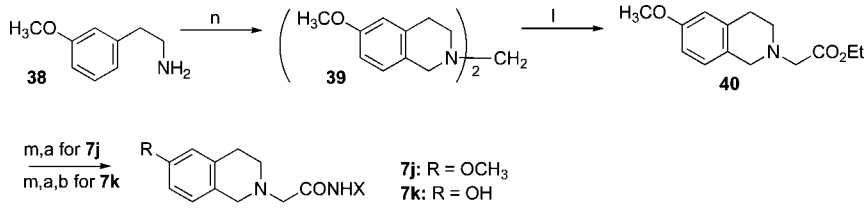
Scheme 7



Scheme 8



Scheme 9



resulting residue was dissolved by CH_2Cl_2 and washed with $NaHCO_3$ solution. The organic layer was separated, dried (Na_2SO_4), and concentrated. **Method B**: The subject compound (50 mg) was dissolved in 5 mL of dry CH_2Cl_2 and cooled to −20 °C. To this was added 5 mL of trifluoroacetic acid in one portion. The mixture was stirred at −20 °C for 30 min, whereupon the bath was removed. When the reaction temperature reached room temperature, the mixture was concentrated. The residue obtained was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), and concentrated.

General Procedure for O-Demethylation. The subject compound (1 equiv) was dissolved in dry CH_2Cl_2 (0.25 mL/mg) under a nitrogen atmosphere and cooled to −78 °C. A solution of BBr_3 in CH_2Cl_2 (13.5 equiv, 1 M BBr_3) was added to this mixture dropwise and stirred for 3 h. After this time, the reaction mixture was washed with saturated $NaHCO_3$ solution, and the organic layer was dried (Na_2SO_4) and concentrated.

3-[(3*R*,4*R*)-1-{(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-methylbutyl}-3,4-dimethylpiperidin-4-yl]phenyl Trifluoromethanesulfonate (9). A solution of 3-[1-(2*S*-amino-3-methylbutyl)-3*R*,4*R*-dimethyl-4-piperidinyl]phenol (**8**, 360 mg, 0.92 mmol) and di-*tert*-butyl dicarbonate (200 mg, 0.92 mmol) in 10 mL of CH_2Cl_2 was stirred at room temperature for 3 h. The reaction mixture was concentrated to dryness and dissolved in a mixture of pyridine (3 mL) and CH_2Cl_2 (10 mL) and cooled to 0 °C. Triflic anhydride (0.5 mL, 3 mmol) dissolved in CH_2Cl_2 (1 mL) was added slowly over 10 min. The mixture was warmed to room temperature and stirred for 3 h. MeOH (2 mL) was added and the mixture stirred for 10 min. The reaction mixture was quenched with 10% NaOH and extracted with CH_2Cl_2. The combined organic layers were

Table 1. Inhibition of Agonist Stimulated [^{35}S]GTPγS Binding by Compounds in Cloned Human μ, δ, and κ Opioid Receptors[a]

cmpd	μ, DAMGO K_e (nM)	δ, DPDPE K_e (nM)	κ, U69,593 K_e (nM)	$\mu\kappa$	$\delta\kappa$
1	25 ± 4[b]	76 ± 3[b]	0.02 ± 0.01[b]	1250	3800
2	21 ± 3	478 ± 75	0.10 ± 0.04	210	4780
3	3 ± 1	24 ± 4	0.03 ± 0.02	100	800
4	1.0 ± 0.2	39 ± 9	1.9 ± 0.4	0.5	21
5	0.5 ± 0.1	9.3 ± 2.1	1.2 ± 0.5	0.4	8
6a	51.4 ± 15	118 ± 45	0.06 ± 0.01	857	1976
6b	7.9 ± 1.4	65 ± 25	6.4 ± 1.7	1.2	10
6c	12.6 ± 2	373 ± 70	0.20 ± 0.03	63	1865
6d	11 ± 4	555 ± 61	1.4 ± 0.4	7.9	396
6e	17.7 ± 6	106 ± 16	4.0 ± 0.3	4.4	27
6f	ND	ND	56 ± 3		
7a	13.7 ± 2.1	282 ± 78	10.9 ± 1.8	1.3	26
7b	23.8 ± 5.7	97 ± 19	34.1 ± 9.9	0.7	3
7c	4.8 ± 1.2	224 ± 90	4.5 ± 0.6	1.1	50
7d	8.5 ± 1.2	102 ± 44	28.4 ± 10.2	0.3	3.6
7e	15.6 ± 1.9	290 ± 50	22.4 ± 10.4	0.7	13
7f	19.5 ± 6.1	158 ± 48	11.4 ± 0.4	1.7	14
7g	48 ± 15	229 ± 85	9.3 ± 2.8	5.2	25
7 h	17.7 ± 6	51.7 ± 10	16.8 ± 3	1.0	3
7i	9.2 ± 4.3	177 ± 27	23.5 ± 11	0.4	7.5
7j	11.4 ± 1.3	76 ± 31	26 ± 9	0.4	3
7k	21.4 ± 5	408 ± 160	3.9 ± 1.6	5.5	105

[a] The data represent the means ± SE from at least three independent experiments. [b] The K_e values for JDTic 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 4).

washed with brine, dried (Na_2SO_4), filtered, and concentrated to yield a brown oil that was purified by flash column chromatography on silica gel using 5% CMA-80 in CH_2Cl_2 as the eluent to afford 450 mg (94%) of **9** as a yellow oil. ^{1}H NMR (CD_3OD) δ 7.4–7.30 (m, 2H), 7.14 (t, 1H, J = 1.8 Hz), 7.08–7.05 (m, 1H), 3.51–3.48 (m, 1H), 2.72 (d, 1H, J = 11 Hz), 2.57 (d, 1H, J = 11 Hz), 2.48–2.42 (m, 1H), 2.39–2.34 (m, 1H), 2.35–2.17 (m, 3H), 1.95–1.93 (m, 1H), 1.70–1.64 (m, 1H), 1.55–1.51 (m, 1H), 1.31 (s, 9H), 1.24 (s, 3H), 0.82 (d, 3H, J = 7 Hz), 0.77 (d, 3H, J = 7 Hz), 0.63 (d, 3H, J = 7 Hz); ^{13}C NMR (CD_3OD) δ 158.9, 155.7, 151.8, 131.6, 127.5, 122.7, 120.3, 119.7, 80.1, 61.5, 56.6, 54.1, 52.1, 40.5, 40.4, 32.8, 32.1, 29.2 28.2, 20.3, 18.2, 17.0; MS (ESI) m/z 523 (M + 1).

Methyl 3-[(3*R*,4*R*)-1-{(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-methylbutyl}-3,4-dimethylpiperidin-4-yl]benzoate (10). A mixture of **9** (150 mg, 0.29 mmol), $PdCl_2$(dppf) (2.5 mg, 0.003 mmol), and MeOH (5 mL) in DMSO (15 mL) was heated at 70 °C for 2 days under an atmosphere of CO gas. The solution was concentrated and purified by flash column chromatography on silica gel using 5% CMA-80 in CH_2Cl_2 as the eluent to afford 120 mg (96%) of **10** as a yellow oil. ^{1}H NMR (CD_3OD) δ 7.86 (t, 1H, J = 1.8 Hz), 7.73 (dt, 1H, J = 7.8, 1.2 Hz), 7.46 (dt, 1H, J = 6.6, 1.5 Hz), 7.32 (t, 1H, J = 7.8 Hz), 3.80 (s, 3H), 3.50 (m, 1H), 2.72 (d, 1H, J = 10.5 Hz), 2.56 (d, 1H, J = 10 Hz), 2.4–2.18 (m, 5H), 1.97 (d, 1H, J = 6 Hz), 1.68 (m, 1H), 1.55 (d, 1H, J = 12 Hz), 1.30 (s, 9H), 1.23 (d, 3H), 0.82 (d, 3H, J = 7 Hz), 0.77 (d, 3H, J = 7 Hz), 0.62 (d, 3H, J = 7 Hz); ^{13}C NMR (CD_3OD) δ 169.3, 158.8, 152.7, 132.2, 131.5, 129.9, 128.1, 80.0, 61.6, 56.7, 54.1, 53.0, 52.2, 50.3, 40.4, 40.2, 32.9, 32.2, 29.3, 28.4, 20.3, 18.2, 17.1; MS (ESI) m/z 433 (M + 1).

***tert*-Butyl [(1*S*)-1-{[(3*R*,4*R*)-4-(3-Carbamoylphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]carbamate (11).** Compound **10** (250 mg, 0.58 mmol) was dissolved in 10 mL of THF and MeOH (3:1). A solution of LiOH monohydrate (73 mg, 1.74 mmol) in water (2 mL) was added, and the mixture was stirred at room temperature overnight. The solution was neutralized with 6 N HCl and concentrated. The product obtained was dissolved in 15 mL of acetonitrile, and pyridine (0.03 mL, 29 mg, 0.37 mmol), $(Boc)_2O$ (164 mg, 0.75 mmol), and ammonium hydrogen carbonate (59 mg, 0.75 mmol) were added. After 10 h at room temperature, the reaction mixture was added to a separatory funnel containing saturated $NaHCO_3$ solution and CH_2Cl_2. After thoroughly mixing, the organic layer was separated and dried (Na_2SO_4). The organic layer was filtered and concentrated, and the residue was purified by flash column chromatography on silica gel using 15% CMA-80 in CH_2Cl_2 to give 120 mg (50%) of **11** as a syrup. ^{1}H NMR (CD_3OD) δ 7.80 (s, 1H), 7.64 (d, 1H, J = 7.5 Hz), 7.46 (d, 1H, J = 7.8 Hz), 7.36 (t, 1H, J = 7.8 Hz), 3.60–3.54 (m, 1H), 2.78 (d, 1H, J = 11 Hz), 2.63 (d, 1H, J = 11 Hz), 2.53–2.49 (m, 1H), 2.44–2.40 (m, 1H), 2.37–2.26 (m, 3H), 2.07–2.05 (m, 1H), 1.78–1.65 (m, 1H), 1.59 (d, 1H, J = 10.5 Hz), 1.36 (s, 9H), 1.30 (s, 3H), 0.88 (d, 3H, J = 7 Hz), 0.83 (d, 3H, J = 7 Hz), 0.68 (d, 3H, J = 7 Hz); ^{13}C NMR (CD_3OD) δ 158.8, 152.7, 135.1, 130.9, 129.7, 126.5, 120.1, 80.0, 61.6, 56.7, 54.0, 52.3, 40.3, 40.2, 32.9, 32.1, 29.3, 28.4, 20.3, 18.2, 17.2; MS (ESI) m/z 419 (M + 1).

***tert*-Butyl (3*R*)-3-{[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Carbamoylphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]carbamoyl}-7-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (13).** Compound **11** (50 mg, 0.12 mmol) was deprotected according to the general procedure (method A), and the impure product was coupled to **12** using the general procedure. The residue was purified by flash column chromatography on silica gel using 13% CMA-80 in CH_2Cl_2 as the eluent to give 60 mg (85%) of **13** as a yellow oil. ^{1}H NMR (CD_3OD) δ 7.71 (s, 1H), 7.57 (d, 1H, J = 7.5 Hz), 7.39 (d, 1H, J = 7.5 Hz), 7.30 (t, 1H, J = 7.8 Hz), 6.83 (d, 1H, J = 7.5 Hz), 6.56–6.49 (m, 2H), 4.64 (br, 1H), 4.47–4.42 (m, 2H), 3.74 (dd, 1H J = 12, 6 Hz), 3.04–2.95 (m, 2H), 2.60–2.55 (m, 1H), 2.37 (m, 2H), 2.25–2.10 (m, 4H), 1.90 (d, 1H, J = 6 Hz), 1.65 (br, 1H), 1.38 (br, 10H), 1.19 (s, 3H), 0.71 (br, 6H), 0.52 (d, 3H, J = 7 Hz); ^{13}C NMR (CD_3OD) δ 174.0, 157.8, 157.4, 152.7, 136.4, 134.9, 131.0, 130.4, 129.7, 126.5, 126.1, 125.2, 115.6, 114.1, 82.5, 61.9, 57.8, 57.3, 53.3, 51.7, 40.4, 40.1, 32.9, 32.5, 32.1, 29.1, 28.3, 20.4, 18.2, 17.2; MS (ESI) m/z 593 (M + 1).

(3*R*)-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Carbamoylphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (2) Dihydrochloride. Compound **13** (60 mg, 0.1 mmol) was deprotected according to the general procedure (method A). The residue was purified by flash column chromatography on silica gel using 20% CMA-80 in CH_2Cl_2 as the eluent to give 40 mg (82%) of **2** as a white solid: ^{1}H NMR (CD_3OD) δ 7.84 (s, 1H), 7.69 (d, 1H, J = 7.5 Hz), 7.51 (d, 1H, J = 8 Hz), 7.41 (t, 1H, J = 7.8 Hz), 6.92 (d, 1H, J = 8 Hz), 6.59 (dd, 1H, J = 8, 2.4 Hz), 6.50 (d, 1H, J = 1.8 Hz), 4.05–4.00 (m, 1H), 3.95–3.93 (m, 2H), 3.55 (dd, 1H, J = 12, 6 Hz), 2.93 (dd, 1H, J = 11, 5 Hz), 2.84–2.80 (m, 2H), 2.70–2.55 (m, 2H), 2.52–2.35 (m, 4H), 2.10 (d, 1H, J = 7 Hz), 1.94–1.88 (m, 1H), 1.68 (d, 1H, J = 12.6 Hz), 1.35 (s, 3H), 0.96 (d, 3H, J = 7 Hz), 0.93 (d, 3H, J = 7 Hz), 0.70 (d, 3H, J = 7 Hz); ^{13}C NMR (CD_3OD) δ 174.3, 155.7, 151.2, 136.4, 133.6, 129.8, 129.6, 128.3, 125.1, 124.7, 124.6, 113.9, 112.1, 73.5, 60.3, 57.1, 55.8, 51.4, 50.8, 46.9, 39.0, 38.8, 31.3, 31.0, 27.0, 19.0, 16.8, 15.7; MS (ESI) 493 (M + 1). The HCl salt prepared using 1.1 equiv of HCl (1.25 N in MeOH) had mp 223–225 °C; $[\alpha]_D$ +86° (c 0.5, CH_3OH). Anal. ($C_{29}H_{42}Cl_2N_4O_3 \cdot 2H_2O$) C, H, N.

***tert*-Butyl [(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]carbonyl}-2-methylpentyl]carbamate (15a).** To a heterogeneous solution of **14** (5.86 g, 0.023 mol), BOP (0.13 g, 0.023 mol), and *N*-Boc-L-isoleucine (5.30 g, 0.023 mol) in THF (120 mL) was added Et_3N (7.40 g, 0.073 mol) in THF (40 mL). The reaction mixture was stirred at room temperature for 90 min to give a cloudy light yellow mixture. To this mixture was added ether (500 mL)/H_2O (200 mL). The organic phase was separated, washed with 10% $NaHCO_3$ (800 mL), and brine (300 mL), dried (Na_2SO_4), and concentrated to yield 9.9 g of a foam. This residue was purified by column chromatography on silica gel, eluting with 70% hexane/EtOAc, to afford 8.25 g (83%) of **15a** as a white amorphous solid. ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 1H), 6.84 (m, 3H), 5.26 (dd, 1H, J = 9.6, 4.2 Hz), 4.73 (d, 1H, J = 12.0 Hz), 4.59 (m, 1H), 4.32 (d, 1H, J = 13.5 Hz), 3.95 (d, 1H, J = 3.3 Hz), 3.80 (s, 3H), 3.65 (q, 1H, J = 2.7 Hz), 3.42 (t, 1H, J = 0.8, 2.7 Hz), 3.15 (dd, 1H, J = 2.7, 10.8 Hz), 2.94 (t, 1H, J = 3.0 Hz), 2.20 (m, 2H),

1.66 (m, 2H), 1.43 (s, 9H), 1.40 (d, 3H, $J = 5.1$ Hz), 1.08 (m, 1H), 0.87 (m, 6H), 0.62 (t, 3H, $J = 6.9$ Hz).

3-[1-(2*S*-Amino-3-methylpentyl)-3*R*,4*R*-dimethyl-4-piperidinyl]phenol (15c). Borane (42 mL, 0.042 moL, 1 M) was added dropwise to **15a** in THF (75 mL). The reaction mixture was heated under reflux for 90 min and cooled, 6 N HCl (10 mL) was added, the mixture was refluxed for 90 min, and then concentrated in vacuo. The resulting residue was dissolved in water (150 mL) and neutralized using solid Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and concentrated to give 6.1 g (>100%) of a thick clear oil; $R_f = 0.50$, silica, 50% CMA-80/CH_2Cl_2. This material was dissolved in 48% HBr (30 mL) and stirred at reflux for 4 h. The residue obtained after concentration was dissolved in water, made basic with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried (Na_2CO_3) and concentrated to afford 4.43 g (77%) of **15c** as a white solid: mp 150–152 °C; $R_f = 0.33$, silica, CMA-80/EtOAc/hexane (2:1:1). ^{1}H NMR ($CDCl_3$) δ 7.15 (t, 1H, $J = 8.1$ Hz), 6.77 (d, 1H, $J = 7.5$ Hz), 6.70 (s, 1H), 6.65 (dd, 1H, $J = 6.0$, 2.1 Hz), 3.85 (s, 3H), 2.82 (m, 2H), 2.56 (m, 2H), 2.26–2.43 (m, 4H), 1.95 (m, 1H), 1.39–1.57 (m, 3H), 1.24 (s, 3H), 1.23 (m, 1H), 0.93 (t, 6H, $J = 4.5$ Hz), 0.73 (d, 3H, $J = 6.9$ Hz).

(3*R*)-7-Hydroxy-*N*-[(1*S*,2*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylbutyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide Dihydrochloride (3). Compound **3** was prepared from **15c** (4.0 g, 14.5 mmol) and Boc-D-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**12**, 4.4 g, 14.5 mmol) according to the general procedure and purified by column chromatography on silica gel using CMA-80 as the eluent to afford 6.6 g (95%) of **3** as a foam. ^{1}H NMR (CD_3OD) δ 7.02 (t, 1H, $J = 8.1$ Hz), 6.85 (d, 1H, $J = 2.4$ Hz), 6.62–6.68 (m, 2H), 6.47–6.52 (m, 2H), 6.43 (d, 1H $J = 2.4$ Hz), 4.02 (m, 1H), 3.88 (d, 2H, $J = 3.6$ Hz), 3.51 (dd, 1H, $J = 8.7$ Hz), 2.56–2.89 (m, 8H), 2.40 (t, 1H, $J = 14.0$ Hz), 2.15 (m, 1H), 1.68 (d, 1H, $J = 14.4$ Hz), 1.55 (d, 2H), 1.50 (m, 1H), 1.23 (s, 3H), 1.07 (t, 3H, $J = 6.9$ Hz), 0.84 (d, 6H, $J = 6.9$ Hz), 0.74 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (CD_3OD) δ 171.5, 164.1, 159.2, 158.5, 150.9, 131.6, 131.0, 130.0, 122.2, 117.8, 117.3, 114.5, 114.1, 62.3, 57.8, 55.3, 53.5, 52.5, 50.4, 45.8, 38.9, 30.2, 29.1, 27.4, 26.4, 16.2, 16.0, 11.7. The HCl salt prepared using ethereal HCl had mp 225–229 °C; $[\alpha]_D$ +108° (*c* 0.61, MeOH). Anal. ($C_{29}H_{43}Cl_2N_3O_3 \cdot 1.5H_2O$), C, H, N.

2-[(3*R*,4*R*)-4-(3-Methoxyphenyl)-3,4-dimethylpiperidin-1-yl]-2-oxoethanamine (15b). (3*R*,4*R*)-3,4-Dimethyl-4-(3-methoxyphenyl)piperidine (**14**, 1 g, 3.9 mmol) and *N*-Boc-glycine (683 mg, 3.9 mmol) were coupled and deprotected (method A) according to the general procedures to yield 1.07 g (99%) of the title compound. The material was used in the next step without purification. ^{1}H NMR (CD_3OD) δ 7.25 (t, 1H, $J = 8$ Hz), 6.92–6.77 (m, 3H), 4.28 (m, 1H), 4.12 (d, 1H, $J = 16$ Hz), 3.98 (d, 1H, $J = 16$ Hz), 3.80 (s, 3H), 3.72 (m, 1H), 3.46 (m, 1H), 3.10 (m, 1H), 2.23–2.19 (m, 2H), 1.72 (d, 1H, $J = 14$ Hz), 1.44 (s, 3H), 0.63 (d, 3H, $J = 7$ Hz).

***N*-{2-[(3*R*,4*R*)-4-(3-Methoxyphenyl)-3,4-dimethylpiperidin-1-yl]ethyl}-2-methylpropan-1-amine (16a).** Compound **15b** (200 mg, 0.64 mmol), *N*,*N*-diisopropylethylamine (412 mg, 0.56 mL, 3.2 mmol), and isobutyric acid chloride (82 mg, 0.08 mL, 0.77 mmol) were stirred in 20 mL of CH_2Cl_2 at room temperature for 3 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated to give the intermediate as a viscous oil. Borane (1 M solution in THF, 3.2 mL, 3.2 mmol) was added in THF (20 mL) under nitrogen, with the reaction flask immersed in a water bath. After the addition, the reaction mixture was stirred at reflux for 1.5 h and cooled to room temperature, followed by the careful addition of 6 N HCl (1 mL). The reaction mixture was concentrated to remove THF, made basic with saturated $NaHCO_3$ and solid Na_2CO_3, and extracted with CH_2Cl_2 (50 mL). The organic layer was dried (Na_2SO_4) and concentrated to give the impure product, which was purified by flash column chromatography on silica gel using 10% CMA-80 in CH_2Cl_2 as the eluent to give 200 mg (98%) of **16a** as a sticky liquid. ^{1}H NMR (CD_3OD) δ 7.10 (t, 1H, $J = 8$ Hz), 6.78–6.64 (m, 2H), 6.60 (dd, 1H, $J = 8$, 2 Hz), 3.67 (s, 3H), 2.71 (m, 1H), 2.58 (t, 2H, $J = 6$ Hz), 2.48 (m, 2H), 2.45–2.20 (m, 5H), 1.93 (br, 1H), 1.70 (m, 1H), 1.55 (d, 1H, $J = 12$ Hz), 1.21 (s, 3H), 0.93 (m, 1H), 0.80 (d, 6H, $J = 7$ Hz), 0.66 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CD_3OD) δ 161.6, 130.5, 130.4, 119.5, 113.6, 111.6, 59.1, 58.4, 57.4, 56.0, 51.9, 47.6, 40.5, 40.1, 32.3, 29.4, 28.5, 21.9, 21.4, 21.3, 17.2; MS (ESI) *m*/*z* 319 (M + 1).

(3*R*)-7-Hydroxy-*N*-{2-[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]ethyl}-*N*-(2-methylpropyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (4) Dihydrochloride. Compound **16a** (70 mg, 0.22 mmol) was O-demethylated according to the general procedure. The residue was coupled with **12** and deprotected (method B) according to the general procedures. Purification by flash column chromatography on silica gel using 15% CMA-80 in CH_2Cl_2 as the eluent gave 27 mg (26%) of **4** as a syrup. ^{1}H NMR (CD_3OD) δ 7.00 (td, 1H, $J = 8$, 5 Hz), 6.80 (dd, 1H, $J = 12$, 8 Hz), 6.69–6.61 (m, 2H), 6.5–6.47 (m, 2H), 6.38 (d, 1H, $J = 2$ Hz), 3.84 (m, 3H), 3.4 (m, 1H), 3.31 (m, 1H), 3.15 (d, 1H, $J = 8$ Hz), 3.00 (m, 1H), 2.7–2.6 (m, 3H), 2.55–2.42 (m, 4H), 2.34 (t, 1H, $J = 12$ Hz), 2.2–2.1 (m, 1H), 1.94–1.88 (m, 2H), 1.47 (t, 1H, $J = 12$ Hz), 1.20 (s, 3H), 0.86–0.82 (m, 6H), 0.67 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CD_3OD) δ 175.6, 158.7, 157.2, 153.2, 137.2, 131.4, 130.4, 125.5, 118.5, 115.4, 114.3, 113.7, 113.4, 59.4, 58.1, 57.4, 56.7, 55.1, 52.1, 47.2, 45.1, 40.6, 39.8, 32.4, 29.6, 28.5, 20.9, 20.4, 17.2; MS (ESI) *m*/*z* 480 (M + 1). The HCl salt prepared using 1 N HCl in ether had mp 209–211 °C; $[\alpha]_D$ +107.7° (*c* 0.9, MeOH). Anal. ($C_{29}H_{43}Cl_2N_3O_3 \cdot H_2O$) C, H, N.

***N*-{2-[(3*R*,4*R*)-4-(3-Methoxyphenyl)-3,4-dimethylpiperidin-1-yl]-2-oxoethyl}-3-methylbutanamide (16b).** Compound **16b** was prepared from **15b** (200 mg, 0.64 mmol) using 3-methylbutanoyl chloride by a procedure similar to that used for compound **16a** to give 210 mg (99%) of **16b**. ^{1}H NMR (CD_3OD) δ 7.38 (t, 1H, $J = 8$ Hz), 7.07 (d, 1H, $J = 8$ Hz), 6.99 (s, 1H), 6.90 (dd, 1H, $J = 8$, 2 Hz), 3.95 (s, 3H), 3.59 (m, 1H), 3.05–2.56 (m, 10H), 2.22 (br, 1H), 182–1.76 (m, 3H), 1.45 (s, 3H), 1.09 (d, 6H, $J = 6$ Hz), 0.94 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CD_3OD) δ 161.7, 153.5, 130.7, 119.8, 113.8, 111.8, 72.2, 63.4, 57.7, 56.1, 51.8, 47.1, 40.7, 38.9, 32.4, 28.6, 27.8, 23.4, 17.2.

(3*R*)-7-Hydroxy-*N*-{2-[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]ethyl}-*N*-(1-methylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (5) Trihydrochloride. Compound **5** was prepared from **16b** (50 mg, 0.15 mmol) using a procedure similar to that described for **4** to give 31 mg (42%) of **5**. ^{1}H NMR (CD_3OD) δ 7.11 (td, 1H, $J = 8$, 5 Hz), 6.95 (t, 1H, $J = 8$ Hz), 6.8–6.73 (m, 2H), 6.67–6.6 (m, 2H), 6.51 (d, 1H, $J = 1.5$ Hz), 4.00 (m, 2H), 3.90 (t, 1H, $J = 8$ Hz), 3.74 (t, 1H, $J = 7$ Hz), 3.53 (t, 1H, $J = 7$ Hz), 3.50–3.36 (m, 2H), 2.95 (m, 1H), 2.83 (d, 2H, $J = 8$ Hz), 2.73 (d, 1H, $J = 3$ Hz), 2.65–2.62 (m, 3H), 2.5–2.48 (m, 1H), 2.47–2.4 (m, 1H), 1.91 (m, 1H), 1.62–1.5 (m, 4H), 1.33 (s, 3H), 0.96 (d, 6H, $J = 7$ Hz), 0.78 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CD_3OD) δ 153.1, 136.8, 131.4, 130.5, 118.4, 115.5, 115.4, 114.3, 113.8, 113.7, 113.4, 64.5, 60.5, 59.5, 58.0, 56.6, 53.7, 46.0, 45.1, 40.6, 39.7, 37.9, 32.3, 28.5, 27.7, 23.3, 23.2, 17.1; MS (ESI) *m*/*z* 494 (M + 1). The HCl salt had mp 213–215 °C; $[\alpha]_D$ +128.3° (*c* 0.24, MeOH). Anal. ($C_{30}H_{46}Cl_3N_3O_3 \cdot 0.5H_2O$) C, H, N.

2-*tert*-Butyl 3-Methyl (3*R*)-7-Methoxy-3,4-dihydroisoquinoline-2,3(1*H*)-dicarboxylate (17). 7-Hydroxy-Boc-D-Tic (**12**, 500 mg, 1.7 mmol), dimethylsulfate (5 mL), and K_2CO_3 (5 g) were stirred in acetone (20 mL) under reflux for 5 h. The filtrate obtained after filtration was concentrated, and the residue was washed with water. This material was purified by flash column chromatography on silica gel, eluting with 50 mL of CH_2Cl_2/EtOAc (3:1) to afford 414 mg (76%) of **17** as a syrup. ^{1}H NMR ($CDCl_3$) δ 7.03 (d, 1H, $J = 7.5$ Hz), 6.72–6.63 (m, 2H), 5.12 (m, 0.5H), 4.77–4.70 (m, 2H), 4.65 (d, 0.5H, $J = 5$ Hz), 4.47 (t, 1H, $J = 17$ Hz), 4.09 (s, 0.5H), 3.75 (s, 3H), 3.63 (s, 1.5H), 3.59 (s, 1.5H), 3.21–3.03 (m, 2H), 2.14 (s, 0.5H), 1.53 (s, 4.5H), 1.45 (s, 4.5H); MS (ESI) *m*/*z* 322 (M + 1).

***tert*-Butyl (3*R*)-3-{[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]carbamoyl}-7-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (18).** Compound **17** (100 mg, 0.3 mmol) was dissolved in 20 mL of MeOH.

LiOH (20 mg, 0.45 mmol) was added, and the reaction mixture was stirred overnight. The reaction mixture was neutralized with 6 N HCl and concentrated to dryness. The impure carboxylic acid was coupled to **12** according to the general procedure to give 65 mg (80%) of **18** as a syrup. ^{1}H NMR (CD_3OD) of selected resonances δ 7.11 (t, 1H, J = 8 Hz), 7.06 (d, 1H, J = 8 Hz), 6.7–6.73 (m, 4H), 6.61 (d, 1H, J = 8 Hz), 3.91 (s, 3H), 1.50 (br, 9H), 1.24 (m, 3H), 0.61 (d, 6H, J = 7 Hz), 0.67 (d, 3H, J = 7 Hz); MS (ESI) m/z 580 (M + 1). This product was used directly in the next step without further purification.

(3*R*)-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-7-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (6a) Dihydrochloride. Compound **18** (60 mg, 0.1 mmol) was deprotected according to the general procedure to give 49 mg (100%) of **6a** (method B). ^{1}H NMR (CD_3OD) δ 7.10 (t, 1H, J = 8 Hz), 6.99 (d, 1H, J = 8 Hz), 6.76–6.74 (m, 2H), 6.70 (dd, 1H, J = 8, 3 Hz), 6.61–6.59 (m, 2H), 4.04–3.89 (m, 3H), 3.72 (s, 3H), 3.55 (q, 1H, J = 5 Hz), 2.96 (dd, 1H, J = 16, 5 Hz), 2.85–2.77 (m, 2H), 2.64 (d, 2H, J = 9 Hz), 2.54–2.35 (m, 4H), 2.25 (td, 1H, J = 13, 4 Hz), 2.00–1.82 (m, 2H), 1.28 (s, 3H), 0.96 (d, 3H, J = 7 Hz), 0.89 (d, 3H, J = 7 Hz), 0.71 (d, 3H, J = 7 Hz); ^{13}C NMR (CD_3OD) δ 174.1, 158.5, 157.3, 152.2, 136.5, 129.9, 129.1, 125.9, 117.0, 112.8, 112.8, 112.3, 110.7, 60.3, 57.0, 55.9, 54.7, 51.4, 50.9, 39.2, 38.5, 31.2, 31.1, 27.2, 19.0, 16.9, 15.8; MS (ESI) m/z 480 (M + 1). The HCl salt prepared using 1 N HCl in ether had mp 201–203 °C; $[\alpha]_D$ +111.9° (c 0.27, MeOH). Anal. ($C_{29}H_{43}Cl_2N_3O_3 \cdot H_2O$) C, H, N.

***tert*-Butyl (3*R*)-3-{[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl] methyl}-2-methylpropyl]carbamoyl}-7-nitro-3,4-dihydroisoquinoline-2(1*H*)carboxylate (24).** Boc-D-7-nitro-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**19**, 150 mg, 0.465 mmol) was coupled to **8** (115 mg, 0.396 mmol) according to the general procedure. The product obtained was purified by flash column chromatography on silica gel using 10–15% CMA-80 in CH_2Cl_2 as the eluent to give 181 mg (77%) of **24** as a white foam. ^{1}H NMR (CD_3OD) δ 8.10–8.02 (m, 2H), 7.39 (d, 1H, J = 8.3 Hz), 7.08 (t, 1H, J = 8.2 Hz), 6.71–6.68 (m, 2H), 6.57 (dd, 1H, J = 7.1, 1.3 Hz), 4.74–4.66 (m, 2H), 3.85–3.79 (m, 1H), 2.45–2.39 (m, 2H), 2.38–2.30 (m, 3H), 2.16–2.12 (m, 1H), 1.88–1.85 (m, 1H), 1.75–1.71 (m, 1H), 1.49 (s, 9H), 1.22 (s, 3H), 0.80 (d, 3H, J = 6.1 Hz), 0.79 (d, 3H, J = 6.4 Hz), 0.58 (d, 3H, J = 6.9 Hz); ^{13}C NMR (CD_3OD) δ 172.9, 158.3, 153.2, 152.0, 148.3, 142.2, 137.5, 130.5, 130.0, 123.0, 122.4, 117.9, 113.8, 113.3, 82.5, 61.6, 56.9, 53.0, 51.6, 51.0, 40.2, 39.4, 37.1, 37.0, 32.2, 32.0, 28.7, 28.0, 20.1, 18.0, 16.7; MS (ESI) m/z 595.8 $(M + H)^+$.

(3*R*)-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-7-nitro-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (6b) Dihydrochloride. Compound **24** (120 mg, 0.2 mmol) was deprotected according to the general procedure (method B). The product was purified by flash column chromatography on silica gel using 10–25% MMA-80 in CH_2Cl_2 as the eluent to give 86 mg (86%) of **6b** as a white foam. ^{1}H NMR (CD_3OD) δ 7.97 (d, 2H, J = 5.9 Hz), 7.33 (d, 1H, J = 9.1 Hz), 7.07 (t, 1H, J = 8.2 Hz), 6.72–6.69 (m, 2H), 6.56 (dd, 1H, J = 7.3, 1.7 Hz), 4.17 (d, 1H, J = 16.8 Hz), 4.04 (s, 1H), 4.03–3.96 (m, 1H), 3.68–3.63 (dd, 1H, J = 8.9, 5.3 Hz), 3.14 (dd, 1H, J = 17.0, 5.2 Hz), 3.01 (dd, 1H, J = 17.1, 8.9 Hz), 2.84–2.76 (m, 1H), 2.51–2.34 (m, 5H), 2.25–2.15 (m, 1H), 1.93–1.81 (m, 2H), 1.53 (d, 1H, J = 13.0 Hz), 1.26 (s, 3H), 0.95 (d, 3H, J = 6.9 Hz), 0.92 (d, 3H, J = 6.9 Hz), 0.62 (d, 3H, J = 6.9 Hz); ^{13}C NMR (CD_3OD) δ 174.9, 158.6, 153.5, 148.1, 143.7, 139.1, 131.6, 130.4, 122.5, 122.3, 118.3, 114.1, 113.6, 61.9, 57.2, 57.1, 52.9, 52.5, 47.6, 40.6, 39.8, 32.8, 32.5, 32.4, 28.4, 20.4, 18.3, 17.0; MS (ESI) m/z 495.6 $(M + H)^+$. The HCl salt prepared using 1.0 N HCl in ether had mp 190–191 °C; $[\alpha]_D^{25}$ +126.3° (c 1, CH_3OH). Anal. ($C_{28}H_{40}Cl_2N_4O_4 \cdot 1.5H_2O$) C, H, N.

(3*R*)-7-Amino-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl] methyl}-2-methylpropyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (6c) Trihydrochloride. Compound **6b** (43 mg, 0.087 mmol) was dissolved in MeOH (8 mL), and 10% Pd/C (8 mg) was added under N_2. The mixture was stirred under H_2 (balloon overnight). The catalyst was removed by filtration, and the filtrate was concentrated to afford 33 mg (82%) of **6c** as a white foam. ^{1}H NMR (CD_3OD) δ 7.09 (t, 1H, J = 7.9 Hz), 6.84 (d, 1H, J = 8.1 Hz), 6.7–6.71 (m, 2H), 6.59–6.52 (m, 2H), 6.44 (d, 1H, J = 2.1 Hz), 4.73 (s, 3H), 4.05–3.96 (m, 1H), 3.90 (d, 2H, J = 6.9 Hz), 3.53 (dd, 1H, J = 10.1, 4.9 Hz), 2.90 (dd, 1H, J = 15.7, 4.8 Hz), 2.83–2.75 (m, 2H), 2.66–2.62 (m, 1H), 2.57–2.48 (m, 1H), 2.45–2.37 (m, 3H), 2.21 (td, 1H, J = 12.6, 4.1 Hz), 1.98–1.93 (m, 1H), 1.92–1.84 (m, 1H), 1.56 (d, 1H, J = 12.2 Hz), 1.28 (s, 3H), 0.94 (d, 3H, J = 6.9 Hz), 0.91 (d, 3H, J = 6.9 Hz), 0.71 (s, 3H); ^{13}C NMR (CD_3OD) δ 175.3, 158.3, 153.2, 146.8, 136.8, 130.5, 130.1, 124.5, 118.1, 115.7, 113.84, 113.77, 113.3, 74.5, 61.4, 58.3, 56.9, 52.4, 51.9, 48.0, 40.3, 39.5, 32.4, 32.1, 28.1, 20.0, 17.8, 16.7; MS (ESI) m/z 465.9 $(M + H)^+$. The HCl salt prepared using 1.0 N HCl in ether had mp 192–194 °C; $[\alpha]_D^{25}$ +121.4° (c 1, CH_3OH). Anal. ($C_{28}H_{43}Cl_3N_4O_2 \cdot 4.25H_2O$) C, H, N.

***tert*-Butyl (3*R*)-7-(Acetylamino)-3-{[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]carbamoyl}-3,4-dihydroisoquinoline-2(1*H*)carboxylate (25).** Boc-D-7-acetylamino-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid[19] (**20**, 80 mg, 0.24 mmol) was coupled to **8** (65 mg, 0.22 mmol) according to the general procedure. The product was purified by flash column chromatography using 10–15% MMA-80 in CH_2Cl_2 as the eluent to give 88 mg (65%) of **25** as a white foam. ^{1}H NMR (CD_3OD) δ 7.47 (s, 1H), 7.38–7.34 (m, 1H), 7.12–7.06 (m, 2H), 6.74–6.69 (m, 2H), 6.57 (dd, 1H, J = 7.9, 1.9 Hz), 4.57 (s, 3H), 4.16–4.14 (m, 1H), 3.81 (d, 1H, J = 5.7 Hz), 3.13 (dd, 2H, J = 13.9, 5.9 Hz), 2.64–2.59 (m, 1H), 2.46 (s, 2H), 2.30–2.28 (m, 3H), 2.13–2.07 (m, 1H), 2.09 (s, 3H), 1.93–1.74 (m, 3H), 1.59–1.48 (m, 2H), 1.48 (s, 9H), 1.21 (s, 3H), 0.80 (d, 6H, J = 5.8 Hz), 0.62 (d, 3H, J = 6.9 Hz); ^{13}C NMR (CD_3OD) δ 173.5, 171.6, 158.2, 153.2, 138.8, 135.6, 130.0, 129.9, 129.5, 119.8, 119.4, 118.7, 118.1, 113.8, 113.3, 82.3, 61.5, 57.0, 56.1, 52.9, 51.2, 40.2, 39.4, 32.4, 32.3, 31.9, 28.8, 28.1, 23.9, 20.0, 17.9, 16.7; MS (ESI) m/z 608.0 $(M + H)^+$.

(3*R*)-7-(Acetylamino)-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (6d) Dihydrochloride. Compound **25** (50 mg, 0.082 mmol) was deprotected according to the general procedure (method B). The product was purified by flash column chromatography on silica gel using 10–25% MMA-80 in CH_2Cl_2 as the eluent to give 34 mg (81%) of **6d** as a white foam. ^{1}H NMR (CD_3OD) δ 7.32 (s, 1H), 7.27–7.21 (m, 1H), 7.11–7.00 (m, 2H), 6.76–6.67 (m, 2H), 6.57 (d, 1H, J = 7.8, 2.0 Hz), 4.32 (s, 1H), 4.04–3.95 (m, 2H), 3.57 (dd, 1H, J = 9.8, 5.0 Hz), 2.98 (dd, 1H, J = 15.9, 4.6 Hz), 2.89–2.77 (m, 1H), 2.64–2.35 (m, 5H), 2.28–2.18 (m, 2H), 2.09 (s, 3H), 1.96–1.77 (m, 3H), 1.54 (d, 1H, J = 12.8 Hz), 1.27 (s, 3H), 0.94 (d, 3H, J = 6.9 Hz), 0.91 (d, 3H, J = 6.8 Hz), 0.70 (d, 3H, J = 6.9 Hz); ^{13}C NMR (CD_3OD) δ 175.5, 171.9, 158.6. 153.6, 138.4, 137.3, 131.2, 130.6, 130.4, 119.9, 118.9, 118.4, 114.2, 113.6, 89.9, 61.8, 58.2, 57.2, 52.8, 52.3, 48.2, 40.6, 39.8, 32.8, 32.4, 28.4, 24.2, 20.3, 18.2, 17.0; MS (ESI) m/z 507.4 $(M + H)^+$. The HCl salt of **6d** prepared using 1.0 N HCl in ether had mp 190 °C (dec); $[\alpha]_D^{25}$ +110.2° (c 0.5, CH_3OH). Anal. ($C_{30}H_{44}Cl_2N_4O_3 \cdot 1.25H_2O \cdot 2CH_3OH$) C, H, N.

(3*R*)-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-7-[(methylsulfonyl)-amino]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (6e) Dihydrochloride. Boc-D-7-[(methylsulfonyl)amino]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid[21] (**21**, 49 mg, 0.13 mmol) was coupled to **8** (43 mg, 0.148 mmol) according to the general procedure. The crude product **26** was deprotected according to the general procedure (method B). The product was purified by flash column chromatography on silica gel using 10–25% CMA-80 in CH_2Cl_2 as the eluent to give 29 mg (40%) of **6e** as a white foam. ^{1}H NMR (CD_3OD) δ 7.13–6.99 (m, 3H), 6.96 (s, 1H), 6.77–6.69 (m, 2H), 6.57 (dd, 1H, J = 7.8, 2.1 Hz), 4.06–3.95 (m, 3H), 3.57 (dd, 1H, J = 9.9, 5.0 Hz), 3.25–3.22 (m, 1H), 3.01 (dd, 1H, J = 16.2, 4.8 Hz), 2.88 (s, 3H), 2.86–2.83 (m, 2H), 2.67–2.63 (m, 1H), 2.55–2.49 (m, 1H), 2.49–2.35 (m, 3H), 2.30–2.20 (m, 1H), 2.01–1.94 (m, 1H), 1.91–1.82 (m, 1H), 1.56 (d, 1H, J = 13.2 Hz), 1.28 (s, 3H), 0.95 (d, 3H, J = 6.9 Hz), 0.91 (d, 3H, J = 6.9 Hz),

0.70 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (CD_3OD) δ 175.1, 158.3, 153.3, 137.8, 137.6, 131.7, 131.0, 130.1, 120.4, 119.3, 118.1, 113.8, 113.3, 74.5, 61.4, 57.8, 56.9, 52.4, 52.0, 47.8, 40.2, 39.0, 32.3, 32.1, 32.0, 28.1, 20.0, 17.9, 16.7; MS (ESI) *m/z* 543.9 $(M + H)^+$. The HCl salt prepared using 1.0 N HCl in ether had mp 182 °C (dec); $[\alpha]_D^{25}$ +93.6° (*c* 0.5, CH_3OH). Anal. ($C_{29}H_{44}Cl_2N_4O_4Cl_2 \cdot CH_3OH$) C, H, N.

***N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}−2-methylpropyl]-6-methoxy-1*H*-indole-2-carboxamide (7a) Hydrochloride.** Commercially available methyl-6-methoxy-2-indolecarboxylate (**27**, 205 mg, 1 mmol) and NaOH (200 mg, 5 mmol) were stirred in a mixture of MeOH (10 mL) and water (1 mL) overnight at room temperature. The reaction solution was neutralized with concentrated HCl and concentrated to dryness. The 6-methoxy-2-indolecarboxylic acid obtained was coupled to **8** according to the general procedure. The product was purified by column chromatography on silica gel using 30% CMA-80 in CH_2Cl_2 as the eluent to give 405 mg (87%) of **7a** as a white foam. ^{1}H NMR (CD_3COCD_3) δ 7.45 (d, 1H, $J = 8$ Hz), 7.14 (s, 1H), 7.06 (t, 1H, $J = 8$ Hz), 7.02 (d, 1H, $J = 2$ Hz), 6.7–6.68 (m, 3H), 6.62 (dd, 1H, $J = 8$, 2 Hz), 4.31 (m, 1H), 3.79 (s, 3H), 3.67 (br, 1H), 2.98–2.84 (m, 2H), 2.73–2.60 (m, 4H), 2.31–2.22 (m, 1H), 2.02–1.91 (m, 2H), 1.58 (d, 1H, $J = 13$ Hz), 1.26 (s, 3H), 1.00 (d, 3H, $J = 7$ Hz), 0.98 (d, 3H, $J = 7$ Hz), 0.63 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CD_3COCD_3) δ 162.7, 158.3, 157.6, 138.3, 138.2, 129.4, 122.7, 122.4, 122.4, 116.9, 112.9, 112.7, 111.8, 103.2, 94.5, 60.3, 55.3, 55.1, 51.8, 51.7, 51.2, 38.9, 38.4, 31.4, 27.2, 19.3, 18.1, 15.7; MS (ESI) *m/z* 465 (M + 1). The HCl salt prepared using 1 N HCl in ether had mp 183–185 °C; $[\alpha]_D$ +74.3° (*c* 1, CH_3OH). Anal. ($C_{28}H_{38}ClN_3O_3 \cdot 1.5H_2O$) C, H, N.

6-Hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-1*H*-indole-2-carboxamide (7b) Hydrochloride. Compound **7a** (300 mg, 0.65 mmol) was O-demethylated according to the general procedure. The product was purified by flash column chromatography on silica gel using 30% CMA-80 in CH_2Cl_2 as the eluent to give 260 mg (90%) of **7b**. ^{1}H NMR (CD_3OD) δ 7.41 (d, 1H, $J = 8.7$ Hz), 7.07 (t, 1H, $J = 8$ Hz), 7.04 (d, 1H, $J = 0.6$ Hz), 6.81 (d, 1H, $J = 2$ Hz), 6.75–6.71 (m, 2H), 6.66 (dd, 1H, $J = 8.7$, 2.4 Hz), 6.55 (dd, 1H, $J = 7.5$, 1.8 Hz), 4.06 (m, 1H), 2.84 (m, 1H), 2.73–2.46 (m, 5H), 2.27 (td, 1H, $J = 12$, 4 Hz), 1.99–1.88 (m, 2H), 1.58 (d, 1H, $J = 12$ Hz), 1.28 (s, 3H), 1.01 (d, 3H, $J = 7$ Hz), 1.00 (d, 3H, $J = 7$ Hz), 0.65 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CD_3OD) δ 164.6, 158.6, 156.7, 153.6, 140.0, 131.5, 130.4, 123.8, 123.3, 118.4, 114.1, 113.6, 112.7, 105.5, 97.8, 61.1, 56.6, 53.0, 52.4, 47.6, 40.5, 33.2, 28.4, 20.3, 18.9, 16.8, 11.1; MS (ESI) *m/z* 451 (M + 1). The HCl salt prepared using 1 N HCl in ether had mp 208–210 °C; $[\alpha]_D$ +89.3° (*c* 0.38, CH_3OH). Anal. ($C_{27}H_{36}ClN_3O_3 \cdot H_2O$) C, H, N.

6-Methoxy-1*H*-indole-3-carboxylic Acid (29). To a solution of 6-methoxyindole (206 mg, 1.4 mmol) in THF (5 mL) was added pyridine (148 μL, 1.8 mmol), and the solution was cooled to 2 °C. Trichloroacetyl chloride (201 μL, 1.8 mmol) was added dropwise over 1 h. The mixture was warmed to room temperature over 16 h and concentrated under reduced pressure. The residue was partitioned between EtOAc and HCl (1 N). The organic layer was separated, dried (Na_2SO_4), and concentrated to give 6-methoxy-3-trichloroacetylindole as an off-white solid.[27] ^{1}H NMR ($CDCl_3$) δ 8.85 (br, 1H), 8.28 (d, 1H, $J = 12$ Hz), 8.27 (s, 1H), 7.01 (dd, 1H, $J = 12$, 2 Hz), 6.93 (d, 1H, $J = 2$ Hz), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.3, 136.8, 133.5, 123.7, 113.4, 107.7, 95.6, 76.7, 56.1; MS (ESI) 292 (M + 1). The residue was dissolved in CH_3OH (10 mL), and to this was added KOH (280 mg, 5 mmol) and water (1 mL). The reaction mixture was heated under reflux for 12 h. The solution was neutralized with 12 N HCl and concentrated to dryness. The 6-methoxy-3-carboxylindole was used in the next step without further purification.

6-Methoxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-1*H*-indole-3-carboxamide (30). Compound **29** (267 mg, 1.4 mmol) was coupled to **8** (406 mg, 1.4 mmol) according to the general procedure to give 520 mg (80%) of **30** as a solid. ^{1}H NMR (CD_3OD) δ 7.94 (d, 1H, $J = 8$ Hz), 7.79 (s, 1H), 7.10–7.06 (m, 1H), 6.92 (d, 1H, $J = 2$ Hz), 6.8–6.7 (m, 3H), 6.60–6.55 (m, 1H), 4.23 (m, 1H), 3.79 (s, 3H), 2.8–2.3 (m, 5H), 2.01–1.93 (m, 3H), 1.53 (d, 1H, $J = 12$ Hz), 1.26 (s, 3H), 0.99 (d, 3H, $J = 7$ Hz), 0.94 (d, 3H, $J = 7$ Hz), 0.61 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CD_3OD) δ 167.4, 157.2, 157.0, 152.2, 137.8, 129.0, 126.7, 121.2, 120.3, 116.9, 112.7, 112.3, 112.2, 111.1, 94.8, 59.5, 55.2, 55.0, 53.4, 51.2, 39.0, 31.7, 27.1, 19.0, 18.9, 15.7; MS (ESI) *m/z* 464 (M + 1).

6-Hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-1*H*-indole-3-carboxamide (7c) Hydrochloride. Compound **30** (115 mg, 0.25 mmol) was O-demethylated according to the general procedure to afford 100 mg (89%) of compound **7c**. ^{1}H NMR (CD_3OD) δ 7.85 (d, 1H, $J = 8$ Hz), 7.73 (s, 1H), 7.06 (t, 1H, $J = 7.8$ Hz), 6.80 (d, 1H, $J = 2$ Hz), 6.73–6.7 (m, 3H), 6.55 (dd, 1H, $J = 8$, 1.5 Hz), 4.22 (m, 1H), 3.72 (m, 1H), 2.91–2.77 (m, 2H), 2.69–2.57 (m, 2H), 2.27 (td, 1H, $J = 12$, 2 Hz), 2.0–1.9 (m, 2H), 1.87 (m, 1H), 1.57 (d, 1H, $J = 12$ Hz), 1.28 (s, 3H), 1.01 (d, 3H, $J = 7$ Hz), 0.99 (d, 3H, $J = 7$ Hz), 0.62 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CD_3OD) δ 167.6, 157.2, 153.8, 151.0, 138.2, 129.0, 126.6, 121.2, 119.7, 116.9, 112.7, 112.2, 112.2, 111.1, 97.0, 59.6, 55.1, 51.2, 51.1, 38.9, 38.4, 31.7, 30.7, 27.0, 18.8, 17.6, 15.4; MS (ESI) 450 (M + 1). The HCl salt prepared using 1 N HCl in ether had mp 213–215 °C; $[\alpha]_D$ +42° (*c* 0.4, CH_3OH). Anal. ($C_{27}H_{36}ClN_3O_3 \cdot H_2O$) C, H, N.

5-Methoxy-1*H*-benzoimidazole-2-carboxylic Acid (32). 4-Methoxy-1,2-phenylendiamine (**31**; 1 g, 7.25 mmol), methyl 2,2-dichloro-2-methoxyacetate (5 g, 29.1 mmol), and DIPEA (7.74 g, 10.4 mL, 60 mmol) were stirred in CH_2Cl_2 (30 mL) at room temperature overnight. The reaction mixture was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The residue obtained on concentration was purified by flash column chromatography on silica gel using hexane/ethyl acetate (1:1) as the eluent to give 1.1 g (73%) of methoxy-1*H*-benzimidazole-2-carboxylic acid methyl ester as a white solid. This compound (300 mg, 1.5 mmol) and LiOH (61 mg, 1.5 mmol) were dissolved in 8 mL of THF and 2 mL of water. The mixture was stirred in a microwave reactor for 4 h at 160 °C. The reaction mixture was concentrated to afford 300 mg (100%) of **32**. ^{1}H NMR (DMSO) δ 12.3 (s, 1H), 7.45 (d, 1H, $J = 9$ Hz), 6.84 (dd, 1H, $J = 9$, 3 Hz), 6.75 (d, 1H, $J = 3$ Hz), 3.95 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (DMSO) δ 158.4, 153.6, 150.9, 131.8, 127.5, 124.7, 111.4, 98.8, 55.8, 54.2; MS (ESI) 207 (M + 1).

***N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-6-methoxy-1*H*-benzimidazole-2-carboxamide (7d) Dihydrochloride.** Compound **32** (288 mg, 1.5 mmol) was coupled to **8** (406 mg, 1.4 mmol) by the general procedure to give 325 mg (50%) of **7d**. ^{1}H NMR (CD_3OD) δ 7.54 (d, 1H, $J = 9$ Hz), 7.07 (m, 2H), 6.97 (dd, 1H, $J = 9$, 2 Hz), 6.71 (m, 2H), 6.56 (d, 1H, $J = 8$ Hz), 4.22 (m, 1H), 3.85 (s, 3H), 2.8–2.63 (m, 6H), 2.30 (m, 1H), 2.00 (m, 2H), 1.58 (d, 1H, $J = 13.5$ Hz), 1.31 (s, 3H), 1.04 (m, 6H), 0.63 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CD_3OD) δ 159.6, 158.2, 157.1, 128.9, 116.8, 114.7, 112.6, 112.2, 59.7, 55.0, 54.9, 51.8, 51.1, 38.2, 35.9, 35.8, 31.2, 26.8, 18.7, 17.1, 15.1; MS (ESI) 465 (M + 1). The HCl salt prepared using 1 N HCl in ether had mp 185–188 °C; $[\alpha]_D$ +71° (*c* 1, CH_3OH). Anal. ($C_{27}H_{38}Cl_2N_4O_3 \cdot 1.25H_2O$) C, H, N.

6-Hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-1*H*-benzimidazole-2-carboxamide (7e) Dihydrochloride. Compound **7e** (14 mg) was prepared in 64% yield from **7d** (15 mg, 0.032 mmol) by the general O-demethylation procedure. ^{1}H NMR (CD_3OD) δ 7.54 (d, 1H, $J = 9$ Hz), 6.95 (t, 1H, $J = 7.8$ Hz), 6.84 (d, 1H, $J = 2$ Hz), 6.76 (dd, 1H, $J = 9$, 2.4 Hz), 6.58 (m, 2H), 6.43 (dd, 1H, $J = 8$, 1.8 Hz), 4.07 (m, 1H), 2.72 (d, 1H, $J = 11$ Hz), 2.61–2.34 (m, 5H), 2.12 (m, 1H), 1.87 (m, 2H), 1.41 (d, 1H, $J = 13$ Hz), 1.17 (s, 3H), 0.92 (d, 3H, $J = 7$ Hz), 0.90 (d, $J = 7$ Hz), 0.49 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CD_3OD) δ 164.3, 161.9, 160.2, 157.0, 149.6, 133.7, 121.6, 119.2, 117.4, 116.9, 64.5, 59.9, 56.7, 55.8, 43.9, 43.1, 36.0, 35.4, 31.6, 23.6, 21.8, 20.0; MS (ESI) *m/z* 451 (M + 1). The HCl salt had mp 211–213 °C; $[\alpha]_D$ +112° (*c* 0.85, CH_3OH). Anal. ($C_{26}H_{36}Cl_2N_4O_3 \cdot 1.5H_2O$) C, H, N.

3-Cyano-7-methoxy-quinoline (34). To a suspension of NaH (50% dispension in oil, 3.0 g, 0.063 mol) in dry ether (75 mL) was added 3,3-dimethyloxypropionitrile (**33**, 6.25 mL, 0.055 mol) and methyl formate (6.85 mL, 0.110 mol). The mixture was stirred at room temperature for 2 days under argon. The resulting precipitate was separated by filtration, washed with ether, and dried under vacuum to yield 7.75 g (86%) of 3,3-dimethyloxy-2-formylpropionitrile sodium salt as a white solid.[28] This compound (520 mg, 3.13 mmol) was added to a solution of *m*-anisidine (308 mg, 2.5 mmol) in methanol (10 mL) followed by 12 N HCl (0.63 mL, 7.5 mmol). The resulting mixture was heated at reflux for 2 h. After cooling, the mixture was filtered, and the precipitate was washed with cooled methanol and dried under vacuum for 3 h to afford a yellow solid. This solid was dissolved in toluene (40 mL), *p*-toluenesulfonic acid (1 g, 5 mmol) was added, and the mixture was heated at reflux for 16 h. After adding 10% Na_2CO_3 solution (40 mL), the organic layer was separated and the aqueous solution was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and purified by flash column chromatography on silica gel using 65% CH_2Cl_2 in hexane as the eluent to give 290 mg (65%) of **34** as a slightly yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.97 (d, 1H, J = 2.1 Hz), 8.42 (d, 1H, J = 2.1 Hz), 7.73 (d, 1H, J = 9.3 Hz), 7.46 (d, 1H, J = 2.4 Hz), 7.32 (dd, 1H, J = 9.3, 2.4 Hz), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.8, 141.0, 129.7, 122.4, 108.1, 101.6, 56.2; MS (ESI) 185 (M + 1).

7-Methoxyquinoline-3-carboxylic Acid (35). Compound **34** (145 mg, 0.79 mmol) and NaOH (90 mg, 2.24 mmol) in ethanol (0.68 mL) were heated under reflux for 1 h. The solution was acidified with 1 N HCl. Concentration afforded 130 mg (100%) of **35** as a white precipitate. ^{1}H NMR (CD_3OD) δ 9.20 (d, 1H, J = 2.1 Hz), 8.64 (d, 1H, J = 2.1 Hz), 7.79 (d, 1H, J = 9.3 Hz), 7.29 (d, 1H, J = 2.4 Hz), 7.15 (dd, 1H, J = 9.3, 2.4 Hz), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.3, 163.9, 152.9, 151.5, 139.2, 131.7, 130.3, 124.5, 121.6, 107.3, 56.5; MS (ESI) 204 (M + 1).

***N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-7-methoxyquinoline-3-carboxamide (7f) Dihydrochloride.** Compound **35** (130 mg, 0.64 mmol) was coupled with **8** (186 mg, 0.64 mmol) according to the general procedure to give 294 mg (97%) of **7f**. ^{1}H NMR ($CDCl_3$) δ 9.18 (d, 1H, J = 2.1 Hz), 8.53 (s, 1H), 7.70 (d, 1H, J = 9 Hz), 7.40 (d, 1H, J = 2.1 Hz), 7.20 (dd, 1H, J = 9, 2.1 Hz), 7.07 (t, 1H, J = 9 Hz), 6.73–6.78 (m, 3H), 6.63 (dd, 1H, J = 7.8, 1.5 Hz), 4.21 (m, 1H), 3.91 (s, 3H), 2.82–2.79 (m, 1H), 2.65–2.62 (m, 2H), 2.55–2.43 (m, 4H), 2.24–2.11 (m, 2H), 1.96–1.84 (m, 1H), 1.53 (d, 1H, J = 13 Hz), 1.24 (s, 3H), 1.00 (d, 6H, J = 7 Hz), 0.49 (d, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 166.5, 162.6, 156.6, 152.2, 151.3, 148.7, 135.8, 130.2, 129.5, 125.8, 122.6, 121.3, 117.8, 113.3, 113.0, 107.4, 58.2, 56.0, 54.9, 52.0, 38.9, 38.7, 31.2, 30.9, 27.7, 18.9, 18.8, 16.5; MS (ESI) 476 (M + 1). The HCl salt prepared using 1 N HCl in ether had mp 181–183 °C; $[\alpha]_D$ +136.9° (*c* 0.8, CH_3OH). Anal. ($C_{29}H_{39}Cl_2N_3O_3 \cdot H_2O$) C, H, N.

7-Hydroxy-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]quinoline-3-carboxamide (7g) Dihydrochloride. Compound **7g** (67 mg) was prepared from **7f** (107 mg, 0.23 mmol) by the general O-demethylation procedure in 64% yield. ^{1}H NMR (CD_3OD) δ 9.08 (d, 1H, J = 2.1 Hz), 8.64 (d, 1H, J = 1.5 Hz), 7.88 (d, 1H, J = 9 Hz), 7.31 (d, 1H, J = 2.1 Hz), 7.24 (dd, 1H, J = 9, 2.1 Hz), 7.06 (t, 1H, J = 9 Hz), 6.70–6.63 (m, 2H), 6.54 (dd, 1H, J = 7.8, 1.5 Hz), 4.26 (m, 1H), 2.87–2.81 (m, 2H), 2.70–2.65 (m, 1H), 2.55–2.51 (m, 3H), 2.26 (td, 1H, J = 12, 4 Hz), 1.98–1.89 (m, 2H), 1.56 (d, 1H, J = 13 Hz), 1.28 (s, 3H), 1.03 (d, 3H, J = 7 Hz), 1.01 (d, 3H, J = 7 Hz), 0.49 (d, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 168.8, 162.9, 158.6, 153.5, 152.0, 137.7, 132.1, 130.4, 126.8, 123.3, 122.2, 118.3, 114.1, 113.6, 110.5, 61.3, 56.3, 53.7, 52.8, 40.5, 39.9, 33.3, 32.2, 28.4, 20.5, 19.1, 17.0; MS (ESI) 462 (M + 1). The HCl salt had mp 211–213 °C; $[\alpha]_D$ +137.8° (*c* 2.7, CH_3OH). Anal. ($C_{28}H_{37}Cl_2N_3O_3 \cdot 2H_2O$) C, H, N.

(7-Methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-acetic Acid Ethyl Ester (37). 2-Benzotriazolymethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**36**, 100 mg, 0.34 mmol), prepared according to the literature procedure,[29] 1-chloroethyl chloroformate (243 mg, 1.7 mmol) and $NaHCO_3$ (142 mg, 1.7 mmol) were refluxed in $ClCH_2CH_2Cl$ (5 mL) overnight. The reaction mixture was cooled and filtered. The filtrate was dried (Na_2SO_4), KOH (100 mg) in CH_3OH (5 mL) was added, and the reaction mixture was refluxed overnight. After concentration, the residue was extracted with CH_2Cl_2. The organic layer was washed (2 N NaOH), dried (Na_2SO_4), and concentrated. The impure product was purified by column chromatography on silica gel using 10% CMA-80 in CH_2Cl_2 as the eluent to give 39 mg (71%) of 7-methoxy-1,2,3,4-tetrahydroisoquinoline. ^{1}H NMR (CD_3OD) δ 7.07 (d, 1H, 8 Hz), 6.82 (d, 1H, J = 8 Hz), 6.60 (s, 1H), 4.26 (s, 2H), 3.78 (s, 3H), 3.41 (t, 2H, J = 6 Hz), 3.01 (t, 2H, J = 6 Hz). 7-Methoxy-1,2,3,4-tetrahydroisoquinoline (515 mg, 3.16 mmol) was dissolved in CH_2Cl_2, triethylamine (0.73 mL) was added, followed by ethyl bromoacetate (528 mg, 3.16 mmol). The reaction mixture was stirred for 30 min at room temperature, poured into CH_2Cl_2, and washed with saturated $NaHCO_3$ solution. The organic layer was concentrated and purified by column chromatography on silica gel using hexane/EtOAc/Et_3N (5:4:1) as the eluent to give 787 mg (92%) of **37** as a liquid. ^{1}H NMR (CD_3OD) δ 7.02 (d, 1H, J = 7 Hz), 6.73 (dd, 1H, J = 7, 2 Hz), 6.60 (d, 1H, J = 2 Hz), 4.21 (q, 2H, J = 7 Hz), 3.75 (s, 3H), 3.74 (s, 2H), 3.46 (s, 2H), 2.81 (s, 4H), 1.25 (t, 3H, J = 7 Hz).

***N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-2-(7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)acetamide (7h) Dihydrochloride.** A portion of **37** (255 mg, 1.02 mmol) was dissolved in MeOH (20 mL) and 40% NaOH (0.3 mL) and heated for 2 h. The solution was neutralized with concentrated HCl and concentrated to afford the acid. This material was coupled with **8** according to the general procedure to afford **7h** in 50% yield. ^{1}H NMR (CD_3OD) δ 7.13 (t, 1H, J = 8 Hz), 7.99 (d, 1H, J = 8 Hz), 6.75–6.71 (m, 3H), 6.57 (dd, 1H, J = 8, 3 Hz), 6.50 (d, 1H, J = 3 Hz), 4.00 (p, 1H, J = 5 Hz), 3.72 (s, 3H), 3.68 (q, 2H, J = 15 Hz), 3.16 (q, 1H, J = 17 Hz), 2.95–2.68 (m, 6H), 2.51–2.42 (m, 3H), 2.31 (m, 2H), 1.96 (m, 1H), 1.84 (m, 1H), 1.56 (d, 1H, J = 13 Hz), 1.28 (s, 3H), 0.95 (d, 3H, J = 7 Hz), 0.89 (d, 3H, J = 7 Hz), 0.69 (d, 3H, J = 7 Hz); ^{13}C NMR (CD_3OD) δ 171.5, 158.3, 157.3, 152.3, 135.5, 129.7, 129.1, 125.9, 116.9, 113.0, 112.8, 112.3, 111.0, 61.1, 60.3, 56.1, 55.2, 54.7, 51.6, 51.3, 39.1, 38.5, 31.0, 28.3, 27.1, 19.0, 17.3, 15.9; MS (ESI) 494 (M + 1). The HCl salt prepared using 1 N HCl in ether had mp 183–185 °C; $[\alpha]_D$ +48° (*c* 1.2, CH_3OH). Anal. ($C_{30}H_{45}Cl_2N_3O_3 \cdot H_2O$) C, H, N.

2-(7-Hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]-methyl}−2-methylpropyl]acetamide (7i) Dihydrochloride. Compound **7i** was prepared from **7h** (140 mg, 0.284 mmol) using the general O-demethylation procedure to give 106 mg (78%). ^{1}H NMR (CD_3OD) δ 6.99 (t, 1H, J = 8 Hz), 6.85 (d, 1H, J = 8 Hz), 6.65–6.63 (m, 2H), 6.49 (td, 1H, J = 8, 3 Hz), 6.35 (d, 1H, J = 3 Hz), 3.88 (p, 1H, J = 5 Hz), 3.52 (d, 2H, J = 5 Hz), 3.01 (dd, 2H, J = 26, 16 Hz), 2.71–2.55 (m, 6H), 2.37–2.30 (m, 3H), 2.25–2.19 (m, 2H), 1.74 (m, 1H), 1.72 (m, 1H), 1.44 (d, 1H, J = 13 Hz), 1.17 (s, 3H), 0.83 (d, 3H, J = 7 Hz), 0.78 (d, 3H, J = 7 Hz), 0.60 (d, 3H, J = 7 Hz); ^{13}C NMR (CD_3OD) δ 171.6, 157.2, 155.4, 152.3, 135.4, 129.7, 129.1, 124.6, 117.0, 114.1, 112.8, 112.6, 112.3, 78.5, 61.2, 60.3, 56.1, 55.3, 51.7, 51.6, 51.3, 39.1, 38.5, 31.0, 28.4, 27.1, 19.1, 17.2, 15.9; MS (ESI) 480 (M + 1). The HCl salt had mp 195–197 °C; $[\alpha]_D$ +106° (*c* 0.55, CH_3OH). Anal. ($C_{29}H_{43}Cl_2N_3O_3 \cdot H_2O$) C, H, N.

Bis(6-methoxy-*N*-1,2,3,4-tetrahydroisoquinolinyl)methane (39). Formaldehyde (37% solution, 2.2 g, 27 mmol) was added dropwise to the 3-methoxyphenethylamine **38** (4 g, 26.5 mmol). The reaction mixture was heated at 100 °C for 1 h. The oil was extracted with CH_2Cl_2, and the extract was washed with water. Concentration of the extract afforded a viscous oil that was dissolved in HCl (2.45 mL of 37% solution, 29.2 mmol) and concentrated. The residue was made alkaline with NaOH solution and extracted with ether. Concentration of the dried (Na_2SO_4) ether extracts yielded 4.45 g (99%) of **39** as a white solid. ^{1}H NMR ($CDCl_3$) δ 6.94 (d, 1H, J

= 9 Hz), 6.75–6.63 (m, 2H), 3.75 (s, 3H), 3.66 (s, 2H), 3.23 (s, 1H), 2.88–2.80 (m, 4H).

(6-Methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)acetic Acid Ethyl Ester (40). The preparation of **40** from **39** was carried out using a procedure similar to that described for **37**. ^{1}H NMR ($CDCl_3$) δ 6.90 (d, 1H, J = 8 Hz), 6.69–6.62 (m, 2H), 4.23 (q, 2H, J = 8 Hz), 3.77 (s, 3H), 3.37 (s, 2H), 2.90–2.77 (m, 4H), 1.28 (t, 3H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 170.9, 158.4, 135.4, 127.8, 126.7, 113.6, 112.5, 61.0, 59.4, 55.6, 55.2, 51.0, 29.6, 14.7; MS (ESI) 250 (M + 1).

***N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-2-(6-methoxyl-3,4-dihydroisoquinolin-2(1*H*)-yl)acetamide (7j) Dihydrochloride.** Compound **40** (130 mg, 0.52 mmol) was hydrolyzed as described for the synthesis of **7h** and coupled with **8** according to the general procedure to give 257 mg (100%) of **7j**. ^{1}H NMR (CD_3OD) δ 7.11 (t, 1H, J = 8 Hz), 6.69 (d, 1H, J = 8 Hz), 6.7–6.70 (m, 4H), 6.61–6.58 (m, 1H), 4.00 (m, 1H), 3.76 (s, 3H), 3.68 (d, 1H, J = 15 Hz), 3.65 (d, 1H, J = 15 Hz), 3.28 (d, 1H, J = 16 Hz), 3.10 (d, 1H, J = 16 Hz), 2.92–2.74 (m, 6H), 2.51–2.20 (m, 5H), 2.45–2.25 (m, 5H), 1.98–1.83 (m, 2H), 1.57 (d, 1H, J = 13 Hz), 1.29 (s, 3H), 0.95 (d, 3H, J = 7 Hz), 0.89 (d, 3H, J = 7 Hz), 0.69 (d, 3H, J = 7 Hz); ^{13}C NMR (CD_3OD) δ 171.6, 158.7, 157.3, 152.2, 135.0, 129.1, 127.4, 126.6, 117.0, 113.3, 112.8, 112.4, 112.3, 78.5, 61.3, 60.3, 55.5, 55.3, 54.7, 51.6, 51.3, 39.1, 38.4, 31.0, 29.4, 27.0, 19.0, 17.2, 15.8; MS (ESI) 494 (M + 1). The HCl salt prepared using 1 N HCl in ether had mp 184–186 °C; $[\alpha]_D$ +50° (*c* 1, CH_3OH). Anal. ($C_{29}H_{43}Cl_2N_3O_2 \cdot CH_3OH$) C, H, N.

2-(6-Hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-2-methylpropyl]acetamide (7k) Dihydrochloride. Compound **7j** (147 mg, 0.29 mmol) was O-demethylated according to the general procedure to give 120 mg (86%) of **7k**. ^{1}H NMR (CD_3OD) δ 7.01 (t, 1H, J = 8 Hz), 6.73 (d, 1H, J = 8 Hz), 6.6–.63 (m, 2H), 6.52–6.43 (m, 3H), 3.90–3.88 (m, 1H), 3.54 (d, 1H, J = 15 Hz) 3.51 (d, 1H, J = 15 Hz), 2.92–2.68 (m, 6H), 2.37–2.25 (m, 5H), 2.45–2.25 (m, 5H), 1.98–1.83 (m, 2H), 1.57 (d, 1H, J = 13 Hz), 1.18 (s, 3H), 0.84 (d, 3H, J = 7 Hz), 0.78 (d, 3H, J = 7 Hz), 0.61 (d, 3H, J = 7 Hz); ^{13}C NMR (CD_3OD) δ 171.6, 157.2, 155.9, 152.2, 135.0, 129.0, 127.4, 125.4, 117.0, 114.8, 113.4, 112.7, 112.2, 78.4, 61.3, 60.2, 55.6, 55.3, 51.6, 51.4, 39.1, 38.4, 31.0, 29.3, 27.0, 18.9, 17.1, 15.8; MS (ESI) 480 (M + 1). The HCl salt had mp 222–224 °C; $[\alpha]_D$ +48° (*c* 0.85, CH_3OH). Anal. ($C_{29}H_{43}Cl_2N_3O_2 \cdot 0.25H_2O$) C, H, N.

Acknowledgment. This research was supported by the National Institute on Drug Abuse, Grant DA 09045.

Supporting Information Available: Elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Dhawan, B. N.; Cesselin, F.; Raghubir, R.; Reisine, T.; Bradley, P. B.; Portoghese, P. S.; Hamon, M. International Union of Pharmacology. XII. Classification of opioid receptors. *Pharmacol. Rev.* **1996**, *48*, 567–592.

(2) Aldrich, J. V.; Vigil-Cruz, S. C. Narcotic Analgesics. *Burger's Medicinal Chemistry and Drug Discovery*, 6th ed.; John Wiley & Sons: New York, NY, 2003; pp 329–481..

(3) Husbands, S. M. Kappa-opioid receptor ligands. *Expert Opin. Ther. Pat.* **2004**, *14*, 1725–1741.

(4) Prisinzano, T. E.; Tidgewell, K.; Harding, W. W. Kappa opioids as potential treatments for stimulant dependence. *AAPS J.* **2005**, *7*, E592–E599.

(5) Metcalf, M. D.; Coop, A. Kappa opioid antagonists: past successes and future prospects. *AAPS J.* **2005**, *7*, E704–E722.

(6) Carroll, F. I.; Thomas, J. B.; Dykstra, L. A.; Granger, A. L.; Allen, R. M.; Howard, J. L.; Pollard, G. T.; Aceto, M. D.; Harris, L. S. Pharmacological properties of JDTic: A novel κ-opioid receptor antagonist. *Eur. J. Pharmacol.* **2004**, *501*, 111–119.

(7) Thomas, J. B.; Atkinson, R. N.; Vinson, N. A.; Catanzaro, J. L.; Perretta, C. L.; Fix, S. E.; Mascarella, S. W.; Rothman, R. B.; Xu, H.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification 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 as a novel potent and selective opioid kappa receptor antagonist. *J. Med. Chem.* **2003**, *46*, 3127–3137.

(8) Thomas, J. B.; Atkinson, R. N.; Rothman, R. B.; Fix, S. E.; Mascarella, S. W.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Lu, Y.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of the first *trans*-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine derivative to possess highly potent and selective opioid kappa receptor antagonist activity. *J. Med. Chem.* **2001**, *44*, 2687–2690.

(9) Mague, S. D.; Pliakas, A. M.; Todtenkopf, M. S.; Tomasiewicz, H. C.; Zhang, Y.; Stevens, W. C., Jr.; Jones, R. M.; Portoghese, P. S.; Carlezon, W. A., Jr. Antidepressant-like Effects of kappa-opioid receptor antagonists in the forced swim test in rats. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 323–330.

(10) McLaughlin, J. P.; Marton-Popovici, M.; Chavkin, C. Kappa opioid receptor antagonism and prodynorphin gene disruption block stress-induced behavioral responses. *J. Neurosci.* **2003**, *23*, 5674–5683.

(11) Bortolato, M.; Aru, G. N.; Frau, R.; Orru, M.; Fa, M.; Manunta, M.; Puddu, M.; Mereu, G.; Gessa, G. L. Kappa opioid receptor activation disrupts prepulse inhibition of the acoustic startle in rats. *Biol. Psychiatry* **2005**, *57*, 1550–1558.

(12) Knoll, A. T.; Meloni, E. G.; Thomas, J. B.; Carroll, F. I.; Carlezon, W. A. Anxiolytic-like effects of k-opioid receptor antagonists in models of unlearned and learned fear in rats. *J. Pharmacol. Exp. Ther.* **2007**, *323*, 838–845.

(13) Weiss, F. Neurobiology of craving, conditioned reward and relapse. *Curr. Opin. Pharmacol.* **2005**, *5*, 9–19.

(14) Kreek, M. J.; Nielsen, D. A.; Butelman, E. R.; LaForge, K. S. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nat. Neurosci.* **2005**, *8*, 1450–1457.

(15) Beardsley, P. M.; Howard, J. L.; Shelton, K. L.; Carroll, F. I. Differential effects of the novel kappa opioid receptor antagonist, JDTic, on reinstatement of cocaine-seeking induced by footshock stressors vs cocaine primes and its antidepressant-like effects in rats. *Psychopharmacology (Berlin)* **2005**, *183*, 118–126.

(16) Thomas, J. B.; Fall, M. J.; Cooper, J. B.; Rothman, R. B.; Mascarella, S. W.; Xu, H.; Partilla, J. S.; Dersch, C. M.; McCullough, K. B.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of an opioid k receptor subtype-selective N-substituent for (+)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine. *J. Med. Chem.* **1998**, *41*, 5188–5197.

(17) Liu, Y.; Yu, H.; Svensson, B. E.; Cortizo, L.; Lewander, T.; Hacksell, U. Derivatives of 2-(dipropylamino)tetralin: Effect of the C8-substituent on the interaction with 5-HT1A receptors. *J. Med. Chem.* **1993**, *36*, 4221–4229.

(18) Pozdnev, V. F. Activation of carboxylic acids by pyrocarbonates. Application of di-tert-butyl pyrocarbonate as condensing reagent in the synthesis of amides of protected amino acids and peptides. *Tetrahedron Lett.* **1995**, *36*, 7115–7118.

(19) Tramontano, A.; Ammann, A. A.; Lerner, R. A. Antibody catalysis approaching the activity of enzymes. *J. Am. Chem. Soc.* **1988**, *110*, 2282–2286.

(20) Matter, H.; Schudok, M.; Schwab, W.; Thorwart, W.; Barbier, D.; Billen, G.; Haase, B.; Neises, B.; Weithmann, K.; Wollmann, T. Tetrahydroisoquinoline-3-carboxylate based matrix-metalloproteinase inhibitors: Design, synthesis and structure−activity relationship. *Bioorg. Med. Chem.* **2002**, *10*, 3529–3544.

(21) Johnson, R. E.; Silver, P. J.; Becker, R.; Birsner, N. C.; Bohnet, E. A.; Briggs, G. M.; Busacca, C. A.; Canniff, P.; Carabateas, P. M.; Chadwick, C. C.; D'Ambra, T.; Dundore, R. L.; Dung, J.; Ezrin, A. M.; Gorczyca, W.; Habeeb, P. G.; Horan, P.; Krafte, D. S.; Pilling, G. M.; O'Connor, B.; Saindane, M. T.; Schlegel, D. C.; Stankus, G. P.; Swestock, J.; Volberg, W. A. 4,5-Dihydro-3-(methanesulfonamidophenyl)-1-phenyl-1*H*-2,4-benzodiazepines: A novel class III antiarrhythmic agents. *J. Med. Chem.* **1995**, *38*, 2551–2556.

(22) Carroll, F. I.; Chaudhari, S.; Thomas, J. B.; Mascarella, S. W.; Gigstad, K. M.; Deschamps, J.; Navarro, H. A. N-substituted cis-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines are opioid receptor pure antagonists. *J. Med. Chem.* **2005**, *48*, 8182–8193.

(23) Diaz, N.; Benvenga, M.; Emmerson, P.; Favors, R.; Mangold, M.; McKinzie, J.; Patel, N.; Peters, S.; Quimby, S.; Shannon, H.; Siegel, M.; Statnick, M.; Thomas, E.; Woodland, J.; Surface, P.; Mitch, C. SAR and biological evaluation of novel *trans*-3,4-dimethyl-4-arylpiperidine derivatives as opioid antagonists. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3844–3848.

(24) Bidlack, J. M.; Cohen, D. J.; McLaughlin, J. P.; Lou, R.; Ye, Y.; Wentland, M. P. 8-Carboxamidocyclazocine: a long-acting, novel benzomorphan. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 374–380.

(25) Wentland, M. P.; Lou, R.; Ye, Y.; Cohen, D. J.; Richardson, G. P.; Bidlack, J. M. 8-Carboxamidocyclazocine analogues: redefining

the structure-activity relationships of 2,6-methano-3-benzazocines. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 623–626.

(26) Thomas, J. B.; Fix, S. E.; Rothman, R. B.; Mascarella, S. W.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Importance of phenolic address groups in opioid kappa receptor selective antagonists. *J. Med. Chem.* **2004**, *47*, 1070–1073.

(27) Fedouloff, M.; Hossner, F.; Voyle, M.; Ranson, J.; Powles, J.; Riley, G.; Sanger, G. Synthesis and pharmacological activity of metabolites of the 5-HT(4) receptor antagonist SB-207266. *Bioorg. Med. Chem.* **2001**, *9*, 2119–2128.

(28) Benoit, R.; Dupas, G.; Bourguignon, J.; Quéguiner, G. Facile synthesis of annelated NADH model precursors. *Synthesis* **1987**, *12*, 1124–1126.

(29) Locher, C. Convenient preparation of some N-substituted 1,2,3,4-tetrahydroisoquinolines lacking electron-donating substituents. *Synth. Commun.* **2001**, *31*, 2895–2911.

JM701344B