N-Substituted 4β-Methyl-5-(3-hydroxyphenyl)-7α-amidomorphans Are Potent, Selective κ Opioid Receptor Antagonists

F. Ivy Carroll,* Matt S. Melvin, Michel C. Nuckols, S. Wayne Mascarella, Hernán A. Navarro, and James B. Thomas

Organic and Medicinal Chemistry, Research Triangle Institute, Research Triangle Park, North Carolina 27709

Received August 26, 2005

In a previous study, we identified (−)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(1-piperidinyl)propanamide (**5a**, KAA-1) as the first potent and selective κ opioid receptor antagonist from the 5-(3-hydroxyphenyl)morphan class of opioids. In this study we report an improved synthesis of this class of compounds. The new synthetic method was used to prepare analogues **5b**−**r** where the morphan N-substituent and 7α-amido group were varied. Most of the analogues showed sub-nanomolar potency for the κ opioid receptor and were highly selective relative to the μ and δ opioid receptors. (−)-3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-{(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-[2-(2-methylphenyl)ethyl]-2-azabicyclo[3.3.1]non-7-yl}propanamide (**5n**, MTHQ) is at least as potent and selective as nor-BNI as a κ opioid receptor antagonist in the [^{35}S]GTP-γ-S in vitro functional test.

N-Substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1**) are a structurally unique class of opioid receptor antagonist.[1] Unlike naloxone (**2a**) and naltrexone (**2b**) as well as the κ opioid receptor selective nor-BNI (**3**) and GNTI (**4**), where the antagonist activity is dependent on the *N*-allyl or *N*-cyclopropylmethyl substituent, all N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1**) including the *N*-methyl analogue **1a** are opioid receptor pure antagonists (Chart 1).[1−5] A few of the more interesting analogues include alvimopan (**1b**),[4−7] which has reached the NDA stage for GI motility disorder, LY255 582 (**1c**),[4,8] which was developed to treat obesity, and the selective κ opioid receptor antagonist JDTic (**1d**),[9−12] which is active in rat models of stress-induced cocaine relapse and antidepression.[13]

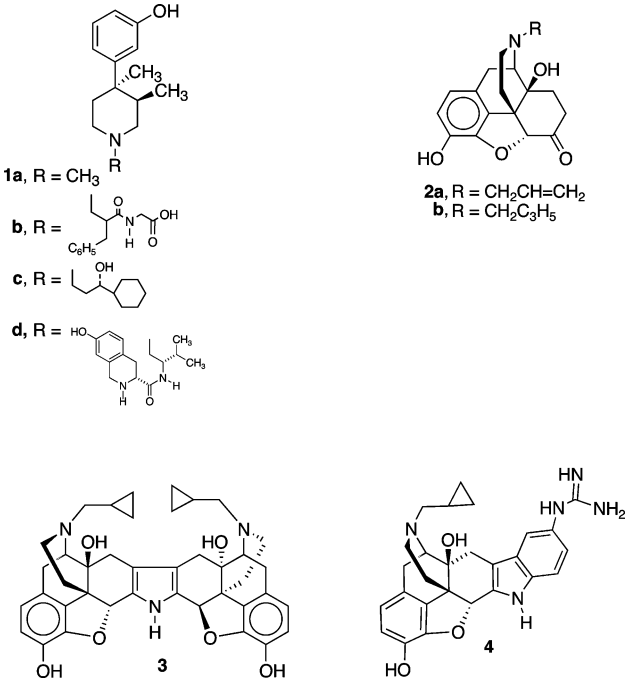
In recent studies, we reported that N-substituted 4β-methyl-5-(3-hydroxyphenyl)morphans (**5**, Chart 2) were opioid receptor pure antagonists with in vitro pharmacological properties similar to those of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1**).[14,15] The morphans can be viewed as conformationally rigid analogues of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1**). These studies identified (−)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(1-piperidinyl)propanamide (**5a**) as a potent and selective κ opioid receptor antagonist.[15]

In this study, we report an improved synthesis for this class of compounds, which provided analogues **5b**−**r**. Several compounds are more potent and selective κ opioid receptor antagonists than **5a**. (−)-3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-{(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-[2-(2-methylphenyl)ethyl]-2-azabicyclo[3.3.1]non-7-yl}propanamide, **5n** (MTHQ), is at least as potent and selective as nor-BNI for the κ opioid receptor relative to the μ and δ opioid receptors in the [^{35}S]GTP-γ-S functional assay.

Chemistry

Compounds **5b**−**k** were synthesized as outlined in Scheme 1. This procedure is much improved over that previously used to prepare **5a**.[15] Condensation of optically pure ketone **6**[15] with hydroxylamine hydrochloride in ethanol at reflux for 3 h provided oxime **7** in 88% yield. Reduction of **7** using sodium and 2-propanol in refluxing toluene gave amine **8** as one isomer in 95% yield. Condensation of **8** with phthalic anhydride in refluxing toluene under a Dean−Stark trap provided a 62% yield of protected amine **9**. Treatment of **9** with 1-chloroethyl chloroformate (ACE-Cl) followed by refluxing the resulting carbamate in methanol afforded the N-demethylated product, **10**. Reductive alkylation of **10** with hydrocinnamaldehyde and sodium triacetoxyborohydride in dichloroethane gave **11** in 84% yield. Removal of the phthalimide protecting group with hydrazine in refluxing ethanol gave amino compound **12** in 97% yield. Two slightly different procedures were used to convert **12** to the desired final products **5b**−**k**. For analogues **5b**−**e**, **5g**, and **5i**−**k**, compound **12** was first treated with 48% hydrobromic acid in acetic acid to give amino phenol **13**. Coupling **13** with the appropriate 3-substituted propionic acid using benzotriazol-1-yloxy-tris(dimethylamino)phosphonium

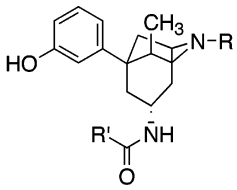
Chart 1

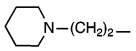


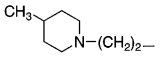
* Corresponding author. Telephone: 919-541-6679. Fax: 919-541-8868. E-mail: fic@rti.org.

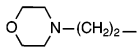
10.1021/jm058264p CCC: $33.50
Published on Web 02/07/2006

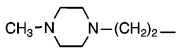
Chart 2

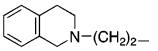


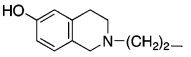
5a, R = $C_6H_5(CH_2)_3$, R' = 

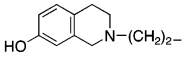
5b, R = $C_6H_5(CH_2)_3$, R' = 

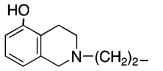
5c, R = $C_6H_5(CH_2)_3$, R' = 

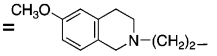
5d, R = $C_6H_5(CH_2)_3$, R' = 

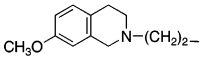
5e, R = $C_6H_5(CH_2)_3$, R' = 

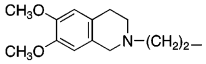
5f, R = $C_6H_5(CH_2)_3$, R' = 

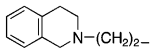
5g, R = $C_6H_5(CH_2)_3$, R' = 

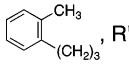
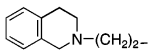
5h, R = $C_6H_5(CH_2)_3$, R' = 

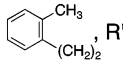
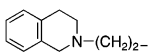
5i, R = $C_6H_5(CH_2)_3$, R' = 

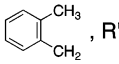
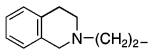
5j, R = $C_6H_5(CH_2)_3$, R ' = 

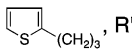
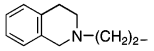
5k, R = $C_6H_5(CH_2)_3$, R' = 

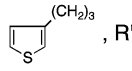
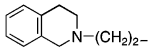
5l, R = $CH_3(CH_2)_5$, R' = 

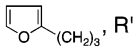
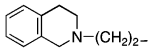
5m, R =  , R' = 

5n, R =  , R' = 

5o, R =  , R' = 

5p, R =  , R' = 

5q, R =  , R' = 

5r, R =  , R' = 

hexafluorophosphate (BOP) in tetrahydrofuran containing triethylamine or diisopropylethylamine yielded compounds **5b**−**e**, **5g**, and **5i**−**k**. Compounds **5f** and **5h** were synthesized by first coupling **12** with the appropriate acid using 1-ethyl-3-(dimethylaminopropyl)carbodiimide (EDCI) to give the isopropyl-protected intermediates **14a**,**b**. Treatment of **14a**,**b** with boron tribromide in methylene chloride yielded the desired **5f** and **5h**. The 3-substituted propionic acids were either commercially available or prepared by addition of acrylic acid to the appropriate substituted tetrahydroisoquinoline (THIQ). The 6-methoxy-, 7-methoxy-, and 7-hydroxy-THIQ were synthesized by reported methods (see Experimental Section).[16−18] THIQ, 5-methoxy-, and 6,7-dimethoxy-THIQ were commercially available.

Scheme 2 shows the methods used to synthesize compounds **5l**−**r**. Compound **10** was converted to the *tert*-butylcarbonyl-protected intermediate **15** using di-*tert*-butyl dicarbonate in methylene chloride containing triethylamine. Removal of the phthalimide-protecting group in **15** with hydrazine in refluxing ethanol yielded amine **16**. Coupling **16** with 3-(3,4-dihydro-1*H*-isoquinolin-2-yl)propionic acid using BOP in tetrahydrofuran afforded amide **17**. Treatment of **17** with boron tribromide in methylene chloride at −78 °C effected removal of both the phenolic isopropyl and the *tert*-butylcarbonyl groups to give **18**. Reductive amination of **18** with the appropriate aldehyde using sodium triacetoxyborohydride in dichloroethane gave the desired compounds **5l**−**r**. The aldehydes were all known compounds.[19−21] However, 2-(2-methylphenyl)acetaldehyde, 3-(2-thienyl)propanal, and 3-(3-thienyl)propanal were synthesized by new procedures (details are given in the Experimental Section).

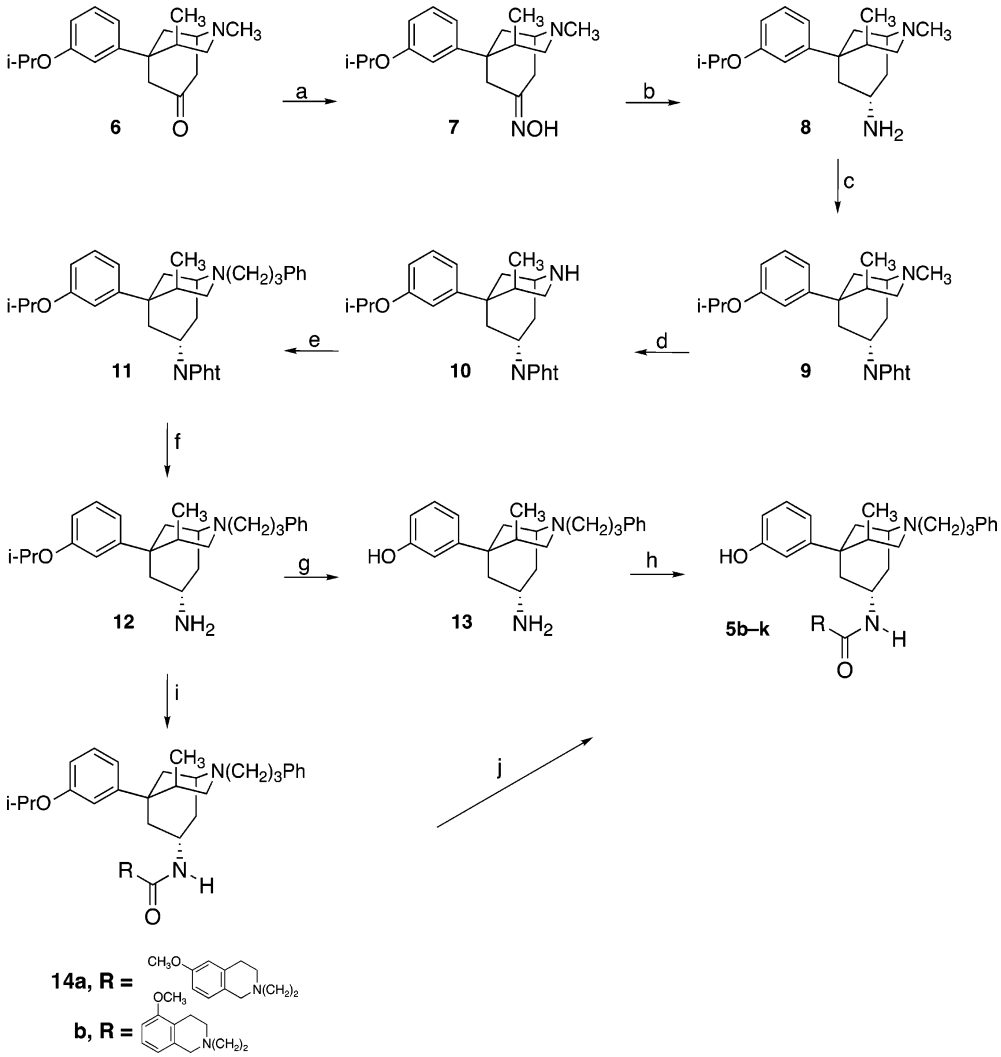
Biology

Measures of functional antagonism and selectivity of **5a**−**r** were obtained by monitoring the ability of test compounds to inhibit stimulated [^{35}S]GTP-γ-S 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 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. The K_e values for **5a**−**r** along with those for the reference compounds, JDTic and nor-BNI, are shown in Table 1.

Results and Discussion

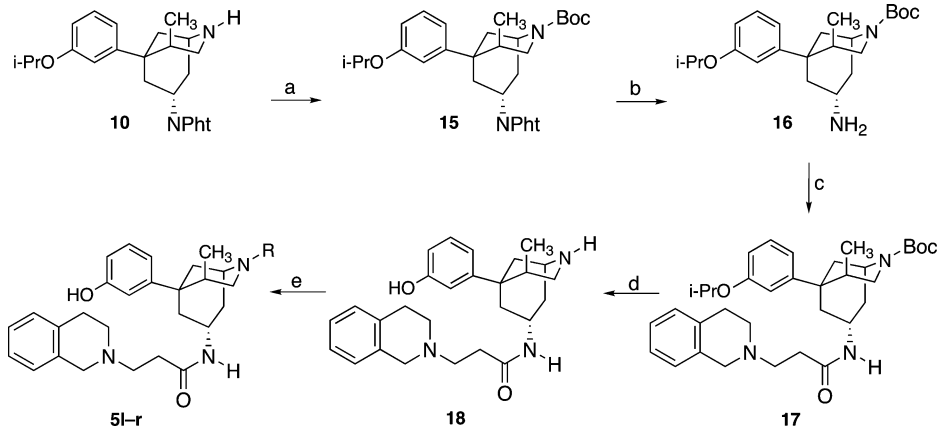
In the design of novel and selective antagonists for opioid receptors, we have found the conceptual framework illustrated in Figure 1 useful for comparing the prototypical oxymorphone (**2**−**4**) antagonists to the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1a**−**d**). This is supported by a comparison of the structure−activity relationship (SAR) displayed by the two scaffolds. The assumptions made based on SAR are (1) both prototypes associate with a hydrogen bond acceptor (H) for high potency antagonist activity; (2) the protonated basic nitrogen of both prototypes associates with the receptor via a salt bridge (S); (3) fitting the two antagonist scaffolds between the S and H domains orients the N-substituents of the two prototypical scaffolds into different binding domains NS1 and NS2, respectively. The latter follows as a consequence of the 3-hydroxyphenyl axial or 3-hydroxyphenyl equatorial piperidine chair structure or substructure present in both systems. In the case of the oxymorphones, a phenyl axial arrangement is present due to physical constraint, whereas in the phenylpiperidines, the equatorial phenyl orientation results from a conformational preference. Importantly, the SAR of the N-substituents of the two types of antagonists is divergent and can best be explained by interactions at different receptor domains (NS1**,** NS2). The oxymorphones display pure antagonist activity within a very limited number of N-substituents (cyclopropylmethyl, allyl),

Scheme 1[a]



[a] Reagents: (a) $NH_2OH{\cdot}HCl$, EtOH; (b) *i*PrOH, toluene, Na; (c) phthalic anhydride, toluene, D−S trap: (d) ACE-Cl, dichloroethane and then CH_3OH reflux; (e) $NaBH(OAc)_3$, $C_6H_5(CH_2)_2CHO$; (f) H_2NNH_2, EtOH, reflux; (g) 48% HBr, HOAc, reflux; (h) BOP, Et_3N, THF, RCO_2H; (i) EDCI, RCO_2H, HOBT, CH_2Cl_2; (j) BBr_3, CH_2Cl_2.

Scheme 2[a]



[a] Reagents: (a) Boc_2O, Et_3N, CH_2Cl_2; (b) H_2NNH_2, EtOH, reflux: (c) BOP, 3-(3,4-dihydro-1*H*-isoquinolin-2-yl)propionic acid, Et_3N, THF; (d) BBr_3, CH_2Cl_2; (e) RCHO, $NaBH(OAc)_3$, CH_2Cl_2.

whereas all N-substituent derivatives of *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines are pure antagonists.

In our initial study of the 4β-methyl-5-(3-hydroxyphenyl)-morphan class of antagonist, we reported that the lead compound **5a** (KAA-1) possessed a $K_e = 0.24$ nM at the κ opioid receptor and was 174- and 137-fold selective for the κ receptor relative to the μ and the δ receptors, respectively. Parts C and D of Figure 1 illustrate how the κ-selective oxymorphone derivative GNTI compares to the κ-selective 5-(3-hydroxyphenyl)morphan (**5a**). Note that for both cases the proposed κ receptor address elements, that is, the guanidine group of GNTI and the 7-amido group of KAA-1, are oriented in a common direction (space).

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

compound	μ, DAMGO K_e (nM)	δ, DPDPE K_e (nM)	κ, U69 593 K_e (nM)	μ/κ	δ/κ
JDTic[b]	25 ± 4 (3.41)	76 ± 3 (79.3)	0.02 ± 0.01 (0.01)	1250	3800
nor-BNI[b]	26 ± 7 (19)	29 ± 8 (4.4)	0.05 ± 0.02 (0.04)	520	580
5a (KAA1)	42 ± 4	33 ± 2.7	0.24 ± 0.01	175	138
5b	176 ± 53	313 ± 34	0.47 ± 0.14	374	666
5c	259 ± 89	77 ± 14	2.2 ± 0.3	118	35
5d	82 ± 2	186 ± 58	0.87 ± 0.33	94	214
5e	48 ± 13	13 ± 0.1	0.09 ± 0.03	533	144
5f	26 ± 7	32 ± 7	0.30 ± 0.17	87	107
5g	52 ± 22	62 ± 20	0.09 ± 0.04	578	689
5h	4.6 ± 1.2	25 ± 9	0.07 ± 0.02	66	357
5i	261 ± 112	42 ± 10	0.12 ± 0.03	2175	350
5j	28 ± 6	35 ± 12	0.28 ± 0.09	100	125
5k	218 ± 72	40 ± 11	0.54 ± 0.04	404	74
5l	103 ± 36	145 ± 100	0.20 ± 0.06	515	725
5m	41 ± 5	20 ± 5	0.20 ± 0.07	205	100
5n	28 ± 9	25 ± 9	0.04 ± 0.01	700	625
5o	>500	>500	6.1 ± 1.3	>82	>82
5p	25 ± 8	19 ± 6	1.8 ± 0.4	14	11
5q	52 ± 17	29 ± 6	1.1 ± 0.3	47	26
5r	35 ± 8	52 ± 8	0.32 ± 0.05	109	163

[a] The data represent the mean ± SE from at least three independent experiments. [b] Data in parentheses for JDTic and nor-BNI were taken from ref 10 and were originally supplied by the NIDA Opioid Treatment Discovery Program.

The purpose of the present study was to further explore the effect of structural diversity in the 7-amido address element of the phenylmorphans as well as to explore its relationship to concomitant changes in the morphan N-substituent (NS2).

Modification of the 7-amido group by addition of a methyl group to the 4-position of the piperidine ring in **5a** to give **5b** resulted in an overall loss of affinity for all receptors with the greatest impact seen at μ (4-fold) and δ (10-fold). However, the fact that the κ potency of **5b** was reduced only 2-fold resulted in a more selective compound relative to **5a**. Changing the piperidine in **5a** to the morpholine group in **5c** was not productive since the resulting compound was not nearly as potent and was not selective. This followed from 10- and 6-fold losses in activity for κ and μ, respectively, but only a 2-fold change at δ. An *N*-methyl piperazine modification (**5d**) did not lead to improved potency or selectivity. There was less of a loss in κ potency relative to **5a** (3.6-fold) compared to that found for the morpholine **5c,** but this change did not appear to be promising. The lower potency and selectivity for these two derivatives indicate that the addition of polar substituents to the 7-amido piperidine ring of **5a** is less favored compared with the addition to that of the hydrophobic moieties.

Changing the 7-amido group from piperidine to THIQ (**5e**) afforded a shift toward greater antagonist potency at κ (2.7-fold, K_e = 0.09 nM) and δ (2.5-fold, 13 nM) while leaving μ activity unchanged. This combination of factors revealed an enhanced selectivity relative to **5a** (533-fold κ/μ). Adding hydroxyl groups to the isoquinoline ring to assess potential similarities with the hydroxy-Tic group in JDTic (**1d**) gave mixed results. All of the compounds (**5f**, **5g**, and **5h**) were potent antagonists for the κ receptor (K_e's of 0.3, 0.09, and 0.07 nM, respectively) and in the range of the unsubstituted **5e** with **5h** being the most similar (7-fold less potent) and **5f** the most disparate at 30-fold less potent. Curiously these two compounds were also more active at the μ receptor such that only **5g** retained both κ versus μ and κ versus δ selectivity. It is interesting to note that **5g** has the same 7-hydroxy-THIQ functionality as JDTic.

As a group, compounds substituted with methoxy in the aromatic THIQ ring provided enhanced κ/μ selectivity. However, this was not true for **5j** the direct analogue of the better hydroxy derivative **5g**. In this case, the potency at κ was shifted lower by 3-fold while μ and δ activity doubled. The compound was still potent and selective, but these attributes were clearly diminished by the change. In this group, the best overall compound was **5i**, the methoxy analogue of the 6-hydroxy analogue, **5f**, which displayed improved potency for κ (K_e = 0.12 versus 0.30 nM) and much lower potency for μ (K_e = 261 versus 26 nM). The potency for δ was similar in both cases. The resulting **5i** has one of the best potency/selectivity profiles ever reported for any κ ligand and certainly for any κ antagonist. The dimethoxy derivative **5k** was the least potent at κ (K_e = 0.54 nM), and given that it retained reasonable δ potency (K_e = 40 nM), there was a loss of κ/δ selectivity. Viewed collectively, this set of analogues demonstrates that changes to the 7-amido address group in the 5-(3-hydroxyphenyl)morphan series have a relatively small effect on κ opioid receptor antagonist potency but can dramatically impact the selectivity of the resulting target compounds due to large changes in potency at the μ and δ opioid receptors.

The set of compounds **5l**−**r** had a fixed 7-amido group and focused on changes to the morphan amino group. Within the set of compounds studied, this strategy did not yield as many potent and selective compounds compared with changes to the 7-amido group, but it clearly demonstrated that modifications in this domain have an influence on ligand potency. The *N*-hexyl derivative **5l** for example was found to be 2-fold less potent than aryl−alkyl derivative **5e** but was still very potent at κ with a K_e of 0.2 nM. Combined with its low activities at μ (K_e = 103) and δ (K_e = 145), the linear alkane provided a well-rounded selectivity profile of 515 and 725 for κ/μ and κ/δ, respectively. Adding a single ortho methyl to **5e** to give **5m** results in a 2-fold loss in κ activity with little change in selectivity. The truncated version of **5m** (i.e., the 2-methylphenylethyl derivative, **5n**) is more potent at κ than **5e** and has selectivities of 700 and 625 for κ versus μ and δ. Shortening the chain further to 2-methylbenzyl (**5o**) results in a 74-fold drop in κ potency from **5e** as well as a loss of selectivity. Thus, small changes to aryl−alkyl morphan nitrogen substituents can lead to shifts in ligand potency and considerable loss in selectivity.

Heteroaromatic replacement of the distal phenyl ring of **5e** as in **5p**−**r** gave mixed results with both the 2- and 3-thiophene analogues **5p** and **5q** showing a loss of κ potency (K_e = 1.8 and 1.1 nM, respectively) and concomitantly lower selectivities. The furan derivative **5r** on the other hand retained potency with a K_e of 0.32 nM and selectivity ratios of 109 and 163 for κ relative to μ and δ. Taken together, the changes to the morphan amino substituent can result in compounds of significantly lower potency when compared to the potency of others with a fixed 7-amido group. In this respect, it seems clear that the phenylpropyl group was a reasonable choice to explore changes to the 7-amido domain. Furthermore, the dramatic swings in potency between **5b**−**r** illustrate that both groups influence a ligand's antagonist activity. This suggests that further manipulation at these positions could result in even more potent and selective compounds than were found in this study.

In summary, an improved synthesis of the N-substituted 4β-methyl-5-(3-hydroxyphenyl)-7α-amidomorphans was developed and used to prepare a series of analogues of our original lead compound **5a**, where the 7α-amido address and the N-substituted groups were varied. Several compounds were

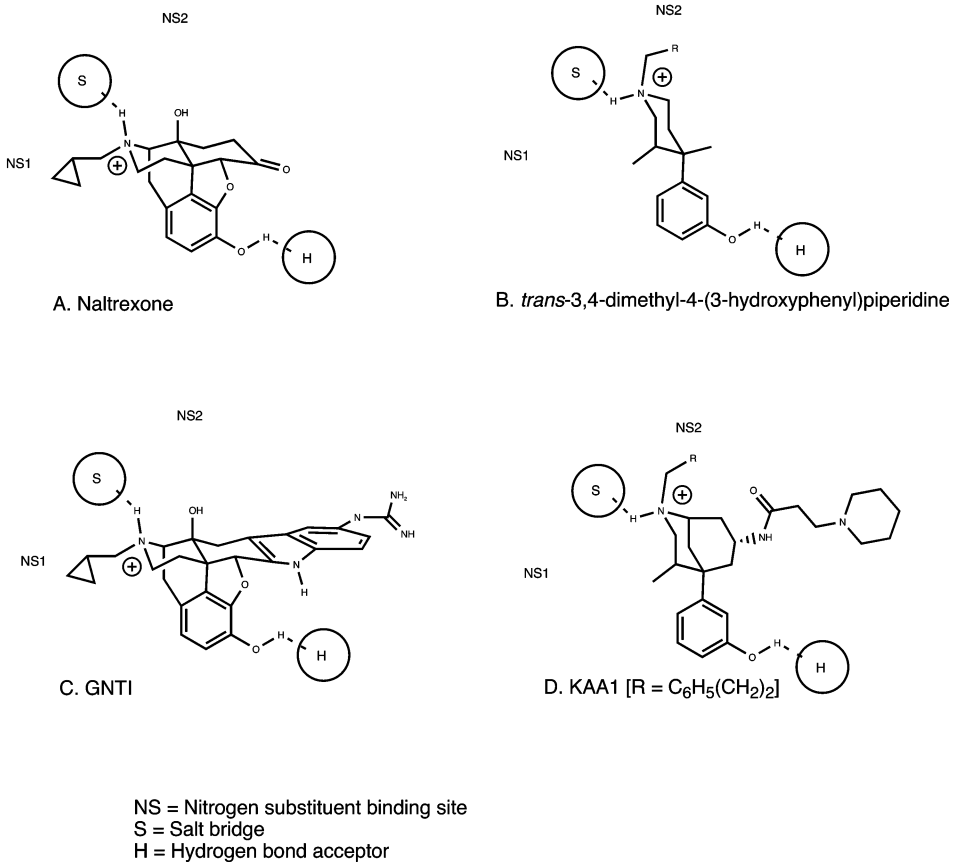


Figure 1. Comparison of the κ opioid receptor binding domains for naltrexone, *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine, GNTI, and KAA1.

developed that showed greater κ opioid receptor potency and selectivity relative to **5a**. The most κ potent and selective compound was (−)-3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-{(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-[2-(2-methylphenyl)ethyl]-2-azabicyclo[3.3.1]non-7-yl}propanamide (**5n**). While the data set is limited, it appears that the addition of lipophilic aryl groups to the 7α-amido address group improves κ opioid receptor potency and selectivity. Similar to the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of opioid antagonist, all N-substituted 4β-methyl-5-(3-hydroxyphenyl)-7α-amidomorphans studied were opioid antagonists at all three receptors.

Experimental Section

^{1}H NMR 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 or by charring with the use of 5% phosphomolybdic acid in ethanol. Optical rotations were measured on an Auto Pol III polarimeter. All solvents were reagent grade. Tetrahydrofuran and diethyl ether were dried over sodium benzophenone ketyl and distilled prior to use. Methylene chloride and chloroform were distilled from calcium hydride if used as reaction solvents. HCl in dry diethyl ether was purchased from Aldrich Chemical Co. and used while fresh before discoloration.

DAMGO, DPDPE, and U69 593 were obtained via the Research Technology Branch, NIDA, and were prepared by Multiple Peptide Systems (San Diego, CA). [^{35}S]GTP-γ-S was obtained from Perkin-Elmer Life Sciences (Boston, MA). GTP-γ-S and GDP were obtained from Sigma Chemical Company (St. Louis, MO). CMA-80 is a mixture of 80% chloroform, 18% methanol, and 2% concentrated ammonium hydroxide. IUPAC nomenclature is used in the Experimental Section to name target compounds and intermediates. Common nomenclature is used for reagents. Common opioid nomenclature is used in the Results and Discussion.

(1*R*,4*S*,5*R*)-5-(3-Isopropoxyphenyl)-2,4-dimethyl-2-azabicyclo-[3.3.1]nonan-7-one Oxime (7). Ketone (**6**) (3.11 g, 0.013 mol) and hydroxylamine hydrochloride (4.50 g, 0.065 mol) in EtOH (absolute, 195 mL) were heated to reflux for 3 h. The reaction mixture was allowed to cool to room temperature, and the EtOH was removed under reduced pressure. The crude oil was dissolved in 2 N NaOH (100 mL) and extracted with 3:1 CH_2Cl_2−THF (4 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure yielding crude product. The crude product was purified by flash chromatography (neutral alumina, Brockman activity II−III) and was eluted with 9:1 EtOAc−hexane to afford 3.68 g (88%) of the title compound as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 0.76 (d, 3H, J = 6.9 Hz), 1.33 (d, 6H, J = 6.0 Hz), 2.05−1.87 (m, 5H), 2.44−2.40 (m, 4H), 2.51 (d, 1H, J = 15.9 Hz), 2.94−2.85 (m, 2H), 3.29 (br, 1H), 3.63 (d, 1H, J = 17 Hz), 4.54 (m, 1H), 7.00−6.72 (m, 3H), 7.23 (t, 1H, J = 7.8 Hz), 8.47 (br, 1H).

(1*R*,4*S*,5*S*,7*R*)-5-(3-Isopropoxyphenyl)-2,4-dimethyl-2-azabicyclo[3.3.1]nonan-7-amine (8). Oxime (**7**) (4.87 g, 0.015 mol) in dry $(CH_3)_2CHOH$ was added dropwise over 1 h to a refluxing suspension of Na (51.3 g, 2.23 mol) in dry toluene (450 mL). After complete addition of the oxime, two portions of $(CH_3)_2CHOH$ (250 mL) were added dropwise over 30 min. The reaction mixture was heated to reflux until all of the Na was consumed followed by cooling to 50 °C and quenching by the careful addition of H_2O (750 mL). The toluene layer was separated, and the aqueous layer was extracted with $CHCl_3$ (4 × 500 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield crude product. The crude product was purified by flash chromatography (neutral alumina, Brockman activity II−III) and was eluted with 9:1 EtOAc−EtOH to afford 4.42 g (95%)

of the title compound as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 0.73 (d, 3H, $J = 6.9$ Hz), 0.94 (m, 1H), 1.15 (m, 1H), 1.31 (d, 6H, $J = 6.0$ Hz), 1.67 (m, 2H), 2.11 (m, 1H), 2.23 (s, 1H), 2.45−2.32 (m, 4H), 2.62 (m, 1H), 2.96 (m, 1H), 3.15 (m, 1H), 3.51 (m, 1H), 4.52 (sept, 1H, $J = 6.1$ Hz), 7.00−6.72 (m, 3H), 7.23 (t, 1H, $J = 7.8$).

2-[(1*R*,4*S*,5*R*,7*R*)-5-(3-Isopropoxyphenyl)-2,4-dimethyl-2-azabicyclo[3.3.1]non-7-yl]-1*H*-isoindole-1,3(2*H*)-dione (9). Amine (**8**) (1.69 g, 0.0056 mol) was dissolved in toluene followed by the addition of phthalic anhydride (2.5 g, 0.017 mol), and the reaction mixture was heated at reflux under a Dean−Stark trap overnight. The solution was cooled, diluted with EtOAc, and filtered into a separatory funnel. The organic layer was washed with 1 N NaOH (3×30 mL) and H_2O. The organic layer was collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product obtained was purified by filtering through a short column of neutral alumina (Brockman activity II−III) and was eluted with EtOAc to afford 1.5 g, (62%) of the title compound as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 0.73 (d, 3H, $J = 6.9$ Hz), 0.94 (m, 1H), 1.15 (m, 1H), 1.31 (d, 6H, $J = 6.0$ Hz), 1.67 (m, 2H), 2.11 (m, 1H), 2.23 (s, 1H), 2.45−2.32 (m, 4H), 2.62 (m, 1H), 2.96 (m, 1H), 3.15 (m, 1H), 4.52 (sept, 1H, $J = 6.1$ Hz), 5.08 (m, 1H), 7.00−6.72 (m, 3H), 7.23 (t, 1H, $J = 7.8$), 7.65 (m, 2H), 7.76 (m, 2H).

2-[(1*R*,4*S*,5*R*,7*R*)-5-(3-Isopropoxyphenyl)-4-methyl-2-azabicyclo-[3.3.1]non-7-yl]-1*H*-isoindole-1,3(2*H*)-dione (10). Phthalimide (**9**) (1.50 g, 0.0035 mol) was dissolved in CH_2Cl_2 and heated to reflux followed by the addition of 1-chloroethyl chloroformate (0.410 mL, 3.8 mmol). This solution was allowed to reflux for 3.5 h. The mixture was cooled, and the solvent was removed under reduced pressure. The crude material was dissolved in EtOAc and washed with a saturated $NaHCO_3$ solution (3×30 mL). The organic layer was collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue obtained was dissolved in CH_3OH and heated at reflux overnight. The CH_3OH was removed, and the crude product was dissolved in 1 N NaOH. The aqueous was extracted with 3:1 CH_2Cl_2−THF. The combined organic layers were collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure. This product was used without further purification in the next step.

2-[(1*R*,4*S*,5*R*,7*R*)-5-(3-Isopropoxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-1*H*-isoindole-1,3(2*H*)-dione (11). Amine (**10**) (2.92 g, 0.007 mol) and hydrocinamaldehyde (1.12 g, 0.0083 mol) were dissolved in CH_2Cl_2 (115 mL) followed by the addition of sodium triacetoxyborohydride (2.1 g, 0.0097 mol) and allowed to react at room temperature overnight. The reaction was quenched by the addition of a saturated sodium $NaHCO_3$ solution (200 mL), and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$. The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on an aluminum oxide (neutral, Brockman activity II−III) column and was eluted with 8:2 hexanes−EtOAc giving 3.16 g (84%) of the desired product: ^{1}H NMR ($CDCl_3$) δ 0.78 (d, 3H, $J = 6.9$), 1.31 (d, 6H, $J = 6$), 1.96−1.78 (m, 4H), 2.25−2.16 (m, 5H), 2.78−2.52 (m, 6H), 3.08 (dd, 1H, $J_1 = 6$ Hz, $J_2 = 3$ Hz), 3.27 (br, 1H), 4.52 (sept, 1H, $J = 6.0$ Hz), 5.15 (m, 1H), 6.68 (d, 1H, $J = 7.8$), 6.79 (m, 2H), 7.25 (m, 5H), 7.64 (m, 2H), 7.75 (m, 2H).

(1*R*,4*S*,5*S*,7*R*)-5-(3-Isopropoxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]nonan-7-amine (12). Phthalimide (**11**) (3.16 g, 0.0078 mol) and hydrazine (1.4 g, 0.044 mol) were dissolved in EtOH (150 mL) and refluxed overnight. The solution was cooled, and the white precipitate was separated by filtration and washed with cold EtOH. The solution was concentrated under vacuum, and the crude material was dissolved in 3:1 CH_2Cl_2−THF. The resulting white precipitate was separated by filtration and washed with cold CH_2Cl_2. The organic layer was concentrated to yield 3.07 g (97%) of the desired product as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 0.71 (d, 3H, $J = 7.2$), 0.90 (m, 2H), 1.29 (d, 6H, $J = 6$ Hz), 1.80 (m, 1H), 1.82 (m, 2H), 2.11 (m, 1H), 2.34 (m, 3H), 2.50 (m, 2H), 2.66 (m, 3H), 2.82 (m, 1H), 3.19 (br, 1H), 3.51 (m, 1H), 4.56 (sept, 1H, $J = 6$), 6.71 (m, 3H), 7.18 (m, 6H).

3-[(1*R*,4*S*,5*S*,7*R*)-7-Amino-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-5-yl]phenol (13). Amine (**12**) (3.07 g, 0.0078 mol) was dissolved in glacial AcOH (20 mL). A 48% HBr (32.5 mL) solution was added, and the mixture was heated to reflux for 15 h. The reaction mixture was allowed to cool to room temperature and poured into ice (100 g), and the pH was raised to 10 with 50% NaOH. The aqueous layer was extracted with 3:1 CH_2Cl_2−THF (3×100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel and then eluted with 65:35 CH_2Cl_2−CMA-80 to yield 2.8 g (88%) of the desired product as an off-white solid. Analytical samples were prepared by dissolving the free base in $CHCl_3$, acidifying with HCl in Et_2O, and precipitating with Et_2O. The Et_2O−$CHCl_3$ mixture was decanted, and the precipitate was dissolved in MeOH. The product was then precipitated out of the MeOH with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: $[\alpha]^{20}_D$ −21° (*c* 1.03, MeOH); ^{1}H NMR ($CDC1_3$) δ 0.70 (d, 3H, $J = 6.9$ Hz), 0.98 (m, 1H), 1.14 (m, 1H), 1.53 (m, 1H), 1.77 (t, 2H, $J = 7.2$), 2.04 (br, 1H), 2.31 (m, 3H), 2.46 (t, 2H, $J = 7.0$ Hz), 2.66−2.53 (m, 3H), 2.79 (m, 1H), 3.54 (br, 1H), 4.33 (br, 2H), 6.65−6.58 (m, 3H), 7.27−7.07 (m, 6H); ^{13}C NMR (CD_3OD) δ 18.5, 27.4, 28.4, 30.6, 34.0, 37.4, 38.4, 40.1, 44.1, 45.0, 46.8, 51.4, 55.1, 55.8, 56.2, 57.1, 89.9, 113.4, 113.6, 114.9, 115.1, 117.5, 127.9, 129.9, 130.1, 131.4, 141.9, 149.3. Anal. ($C_{24}H_{34}Cl_2N_2O\cdot H_2O$) C, H, N.

(−)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(4-methylpiperidin-1-yl)propanamide (5b) Dihydrochloride. Amine (**13**) (52.5 mg, 0.14 mmol), 3-(4-methylpiperidin-1-yl)propionic acid (55.7 mg, 0.29 mmol), and triethylamine (72.9 mg, 0.72 mmol) were dissolved in THF. BOP reagent (70.1 mg, 0.16 mmol) was added, and the mixture was allowed to stir at room temperature for 4 h. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ (3×15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) eluting with 65:35 $CHCl_3$−CMA-80 to yield 25.4 mg (34.0%) of the desired product. The analytical sample was prepared by dissolving the free base in $CHCl_3$, acidifying with HCl in Et_2O, and precipitating with Et_2O. The Et_2O−$CHCl_3$ mixture was decanted, and the precipitate was dissolved in MeOH. The product was then precipitated out of the MeOH with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: mp 205−228 °C dec; $[\alpha]^{23}_D$ −58° (*c* 0.92, MeOH); ^{1}H NMR (CD_3OD) δ 0.73 (d, 3H, $J = 6.9$), 0.90 (d, 3H, $J = 2.4$), 1.29−1.14 (m, 6H), 1.69−1.55 (m, 3H), 1.92−1.88 (m, 2H), 2.07−1.95 (m, 2H), 2.34−2.15 (m, 5H), 2.65−2.56 (m, 7H), 2.85−2.80 (m, 2H), 3.08−2.95 (m, 1H), 3.21 (s, 1H), 4.62−4.49 (m, 1H), 6.68−6.58 (m, 3H), 7.25−7.08 (m, 6H); ^{13}C NMR (CD_3OD) δ 19.0, 28.0, 30.9, 31.6, 31.7, 34.6, 38.1, 40.9, 43.8, 45.8, 47.0, 56.6, 58.2, 58.3, 62.9, 113.9, 128.4, 130.4, 130.6, 131.8, 142.4, 150.7, 159.9, 171.4. Anal. ($C_{33}H_{49}Cl_2N_3O_2\cdot 2H_2O$) C, H, N.

(−)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(morpholin-4-yl)-propanamide (5c) Dihydrochloride. Amine (**13**) (55.6 mg, 0.15 mmol), 3-(morpholin-4-yl)propionic acid (55.3 mg, 0.31 mmol), and diisopropylethylamine (0.132 mL, 0.70 mmol) were dissolved in THF. BOP reagent (74.2 mg, 0.17 mmol) was added, and the mixture was allowed to stir at room temperature for 4 h. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ (3×15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) eluting with 65:35 $CHCl_3$−CMA-80 to yield 35.4 mg (46%) of the desired product. Analytical samples were prepared by dissolving the free base in $CHCl_3$, acidifying with HCl in Et_2O, and precipitating with Et_2O. The Et_2O−$CHCl_3$ mixture was decanted, and the precipitate was dissolved in MeOH. The product was then precipitated out of the

MeOH with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: mp 215−225 °C dec; $[\alpha]^{23}_D$ −42° (*c* 0.745, MeOH); ^{1}H NMR (CD_3OD) δ 0.73 (d, J = 7.2, 3H), 1.24−1.14 (m, 3H), 1.92−1.55 (m, 3H), 2.68−2.30 (m, 23H), 3.08 (dd, J1 = 6.5, J2 = 2.5), 3.18 (bs, 1H), 3.63 (t, J = 4.5, 4H), 4.62−4.49 (m, 1H), 6.60 (d, J = 8.1 hz, 1H), 6.69 (bs, 2H), 7.36−7.08 (m, 6H); ^{13}C NMR (CD_3OD) δ 21.6, 30.9, 33.6, 34.3, 34.4, 34.5, 37.3, 40.9, 43.7, 48.4, 57.4, 58.5, 59.2, 61.0, 61.1, 69.5, 131.3, 133.2, 133.5, 133.6, 139.0, 145.2. Anal. ($C_{31}H_{45}Cl_2N_3O_3\cdot 3.5H_2O$) C, H, N.

(−)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(4-methylpiperazin-1-yl)propanamide (5d) Dihydrochloride. Amine (**13**) (112.6 mg, 0.31 mmol), 3-(4-methylpiperidin-1-yl)propionic acid (120.0 mg, 0.62 mmol), and triethylamine (117.6 mg, 1.54 mmol) were dissolved in THF. BOP reagent (150.3 mg, 0.34 mmol) was added, and the mixture was allowed to stir at room temperature for 4 h. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) and eluted with 65:35 $CHCl_3$−CMA-80 to yield 41.3 mg (26%) of the desired product. The analytical sample was prepared by dissolving the free base in $CHCl_3$, acidifying with HCl in Et_2O, and precipitating with Et_2O. The Et_2O−$CHCl_3$ mixture was decanted, and the precipitate was dissolved in MeOH. The product was then precipitated out of the MeOH with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: mp 230−255 °C dec; $[\alpha]^{23}_D$ −44° (*c* 0.64, MeOH); ^{1}H NMR (CD_3OD) δ 0.78 (d, 3H, J = 7.5), 1.52−1.31 (m, 1H), 1.72−1.56 (m, 1H), 2.21−1.95 (m, 3H), 2.15−2.09 (m, 7H), 2.80−2.73 (m, 7H), 3.34−2.90 (m, 10H), 3.68−3.52 (m, 1H), 3.96 (s, 1H), 4.62−4.49 (m, 1H), 6.67−6.65 (m, 3H), 7.31−7.14 (m, 6H); ^{13}C NMR (CD_3OD) δ 17.0, 20.3, 26.1, 28.8, 28.9, 29.6, 29.7, 31.6, 32.7, 36.2, 38.9, 43.8, 45.1, 53.6, 54.8, 56.3, 68.0, 111.8, 126.4, 128.5, 128.6, 128.7, 129.8, 131.3, 140.4, 148.6, 157.9, 169.9. Anal. ($C_{32}H_{49}Cl_3N_4O_2\cdot 1.5H_2O$) C, H, N.

(−)-3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo-[3.3.1]non-7-yl]propanamide (5e) Dihydrochloride. Amine (**13**) (55.5 mg, 0.15 mmol), 3-(3,4-dihydro-1*H*-isoquinolin-2-yl)propionic acid (69.2 mg, 0.30 mmol), and Et_3N (77.0 mg, 0.76 mmol) were dissolved in THF. BOP reagent (74.1 mg, 0.17 mmol) was added, and the mixture was allowed to stir at room temperature for 4 h. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) and was eluted with 65:35 $CHCl_3$−CMA-80 to yield 25.6 mg (31%) of the desired product. The analytical sample was prepared by dissolving the free base in $CHCl_3$, acidifying with HCl in Et_2O, and precipitating with Et_2O. The Et_2O−$CHCl_3$ mixture was decanted, and the precipitate was dissolved in MeOH. The product was then precipitated out of the MeOH with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: mp 197−240 °C; $[\alpha]^{20}_D$ −50° (*c* 0.97, MeOH); ^{1}H NMR (CD_3OD) δ 0.78 (d, 3H, J = 7.5), 2.09−2.04 (m, 3H), 2.48−2.32 (m, 1H), 2.54−2.50 (m, 4H), 2.75−2.55 (m, 1H), 2.84−2.73 (m, 4H), 3.60−3.19 (m, 9H), 3.89−3.78 (m, 1H), 3.96 (s, 1H), 4.42−4.25 (m, 1H), 4.68−4.51 (m, 2H), 6.67−6.65 (m, 3H), 7.46−7.14 (m, 10H); ^{13}C NMR (CD_3OD) δ 18.3, 26.7, 27.5, 30.0, 31.1, 34.0, 37.6, 40.4, 45.2, 46.2, 51.7, 53.2, 54.8, 55.9, 57.6, 57.7, 113.3, 127.9, 128.3, 128.8, 129.0, 129.8, 130.0, 130.1, 130.3, 131.3, 132.4, 141.8, 150.1, 171.4. 18.3, 26.7, 27.5, 30.0, 31.1, 34.0, 37.6, 40.4, 45.2, 46.2, 51.7, 53.2, 54.8, 55.9, 57.6, 57.7, 113.3, 127.9, 128.3, 128.8, 129.0, 129.8, 130.0, 130.1, 130.3, 131.3, 132.4, 141.8, 150.1, 171.4. Anal. ($C_{36}H_{47}Cl_2N_3O_2\cdot 4H_2O$) C, H, N.

(−)-3-(7-Hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]propanamide (5g) Dihydrochloride. Amine (**13**) (66.0 mg, 0.18 mmol), 3-(7-hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic acid (93.3 mg, 0.36 mmol), and Et_3N (92.1 mg, 091 mmol) were dissolved in THF. BOP reagent (88.1 mg, 0.20 mmol) was added, and the mixture was allowed to stir at room temperature for 4 h. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) and was eluted with 65:35 $CHCl_3$−CMA-80 to yield 32.0 mg (31%) of the desired product. The analytical sample was prepared by dissolving the free base in $CHCl_3$, acidifying with HCl in Et_2O, and precipitating with Et_2O. The Et_2O−$CHCl_3$ mixture was decanted, and the precipitate was dissolved in MeOH. The product was then precipitated out of the MeOH with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: mp 210−218 °C dec; $[\alpha]^{23}_D$ −57° (*c* 0.07, MeOH); ^{1}H NMR (CD_3OD) δ 0.78 (d, 3H, J = 7.2), 1.52−1.38 (m, 1H), 1.72−1.58 (m, 1H), 2.21−1.95 (m, 3H), 2.53−2.51 (m, 3H), 2.80−2.72 (m, 4H), 3.10 (br, 1H), 3.34−3.30 (m, 5H), 3.57−3.46 (m, 5H), 3.95 (s, 1H), 4.40 (br, 2H), 4.65−4.47(m, 1H), 6.77−6.61 (m, 5H), 7.10−7.07 (m, 1H), 7.30−7.16 (m, 6H); ^{13}C NMR (CD_3OD) δ 17.1, 24.6, 26.1, 28.2, 29.8, 32.7, 36.3, 39.1, 43.9, 45.0, 47.2, 50.7, 52.3, 53.6, 54.6, 56.3, 112.0, 112.9, 116.2, 121.4, 126.6, 128.5, 128.7, 128.8, 129.9, 130.1, 140.5, 148.8, 156.9, 158.1, 170.2. Anal. ($C_{36}H_{47}Cl_2N_3O_2\cdot 3H_2O$) C, H, N.

(−)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanamide (5i) Dihydrochloride. Amine (**13**) (64.3 mg, 0.18 mmol), 3-(6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic acid (85.8 mg, 0.35 mmol), and Et_3N (89.3 mg, 0.88 mmol) were dissolved in THF. BOP reagent (85.8 mg, 0.19 mmol) was added, and the mixture was allowed to stir at room temperature for 4 h. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) eluting with 65:35 $CHCl_3$−CMA-80 to yield 54.8 mg (52%) of the desired product. The analytical sample was prepared by dissolving the free base in $CHCl_3$, acidifying with HCl in Et_2O, and precipitating with Et_2O. The Et_2O−$CHCl_3$ mixture was decanted, and the precipitate was dissolved in MeOH. The product was then precipitated out of the MeOH with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: mp 235−245 °C; $[\alpha]^{20}_D$ −52° (*c* 0.20, MeOH); ^{1}H NMR (CD_3OD) δ 0.72 (d, 3H, J = 6.9), 1.28−1.02 (m, 3H), 1.69−1.51 (m, 1H), 1.87−1.71 (m, 2H), 2.19−2.11 (m, 1H), 2.43−2.33 (m, 5H), 2.55−2.52 (m, 2H), 2.84−2.62 (m, 8H), 3.07−2.96 (m, 1H), 3.20 (s, 1H), 3.55 (s, 2H), 3.72 (s, 3H), 4.68−4.51 (m, 1H), 6.67−6.60 (m, 5H), 6.89−6.86 (m, 1H), 7.43−7.08 (m, 6H); ^{13}C NMR (CD_3OD) δ 19.5, 30.3, 30.4, 32.8, 33.6, 34.9, 39.1, 41.6, 46.3, 52.1, 55.2, 55.5, 55.9, 56.0, 56.5, 113.6, 113.8, 114.5, 127.2, 127.7, 127.9, 128.9, 129.0, 129.7, 129.9, 130.3, 130.7, 136.5, 143.9, 153.0, 158.9, 160.1, 174.0. Anal. ($C_{37}H_{49}Cl_2N_3O_2\cdot 2H_2O$) C, H, N.

(−)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanamide (5j) Dihydrochloride. Amine (**13**) (239.7 mg, 0.59 mmol), 3-(7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic acid (160.2 mg, 0.59 mmol), and Et_3N (131.2 mg, 1.29 mmol) were dissolved in THF. BOP reagent (259.4 mg, 0.59 mmol) was added, and the mixture was allowed to stir at room temperature for 4 h. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) and was eluted with 65:35 $CHCl_3$−CMA-80 to yield 141.3 mg (41%) of the desired product. The analytical sample was prepared by dissolving the free base in $CHCl_3$, acidifying with HCl in Et_2O, and precipitating with Et_2O. The Et_2O−$CHCl_3$ mixture was decanted, and the precipitate was dissolved in MeOH. The product was then precipitated out of the MeOH with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: mp 232−241 °C dec; $[\alpha]^{23}_D$ −56° (*c* 0.20,

MeOH); ^{1}H NMR (CD_3OD) δ 0.72 (d, 3H, J = 6.9), 1.28−1.02 (m, 3H), 1.69−1.51 (m, 1H), 1.87−1.71 (m, 2H), 2.19−2.11 (m, 1H), 2.43−2.33 (m, 5H), 2.55−2.52 (m, 2H), 2.84−2.62 (m, 8H), 3.07−2.96 (m, 1H), 3.20 (s, 1H), 3.55 (s, 2H), 3.72 (s, 3H), 4.68−4.51 (m, 1H), 6.67−6.60 (m, 5H), 6.89−6.86 (m, 1H), 7.43−7.08 (m, 6H); ^{13}C NMR (CD_3OD) δ 19.5, 30.3, 30.4, 32.8, 33.6, 34.9, 39.1, 41.6, 46.3, 52.1, 55.2, 55.5, 55.9, 56.0, 56.5, 113.6, 113.8, 114.5, 127.2, 127.7, 127.9, 128.9, 129.0, 129.7, 129.9, 130.3, 130.7, 136.5, 143.9, 153.0, 158.9, 160.1, 174.0. Anal. ($C_{37}H_{49}Cl_2N_3O_3\cdot 4H_2O$) C, H, N.

(−)-3-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]propanamide (5k) Dihydrochloride. Amine (**13**) (63.5 mg, 0.17 mmol), 3-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic acid (92.4 mg, 0.35 mmol), and Et_3N (88.1 mg, 091 mmol) were dissolved in THF. BOP reagent (154.1 mg, 0.35 mmol) was added, and the mixture was allowed to stir at room temperature for 4 h. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) and was eluted with 65:35 $CHCl_3$−CMA-80 to yield 94.5 mg (89%) of the desired product. The analytical sample was prepared by dissolving the free base in $CHCl_3$, acidifying with HCl in Et_2O, and precipitating with Et_2O. The Et_2O−$CHCl_3$ mixture was decanted, and the precipitate was dissolved in MeOH. The product was then precipitated out of the MeOH with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: mp 240−252 °C dec; $[\alpha]^{23}_D$ −54° (*c* 0.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.70 (d, 3H, J = 7.2), 0.80−0.66 (m, 1H), 1.09−0.09 (m, 1H), 1.56 (d, J = 12.0 Hz), 1.77−1.73 (m, 2H), 2.26 (bs, 1H), 2.30 (m, 2H), 2.44−2.47 (m, 5H), 2.66−2.50 (m, 3H), 2.75−2.73 (m, 7H), 2.75 (m, 1H), 3.02 (bs, 1H), 3.55 (br, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 4.65−4.47(m, 1H), 6.48 (s, 1H), 6.57 (s, 1H), 6.73−6.65 (m, 3H), 7.26−7.10 (m, 6H); ^{13}C NMR (CD_3OD) δ 17.3, 25.2, 26.4, 29.2, 30.0, 30.1, 33.0, 36.5, 39.3, 44.2, 45.4, 52.5, 53.5, 54.9, 55.8, 55.9, 56.5, 56.6, 110.3, 112.1, 112.2, 119.8, 123.6, 126.9, 128.8, 129.0, 130.2, 140.8, 149.0, 149.3, 150.2, 158.4, 170.4. Anal. ($C_{39}H_{51}Cl_2N_3O_4\cdot 3.5H_2O$) C, H, N.

***N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-Isopropoxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanamide (14a).** Amine (**12**) (202.3 mg, 0.50 mmol) was dissolved in CH_2Cl_2 (30 mL) followed by 3-(6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic acid (202.8 mg, 0.75 mmol). Triethylamine was added in excess to the required number of equivalents (0.118.9 mL, 0.85 mmol), and the mixture was allowed to stir for 20 min. EDCI (162.1 mg, 0.85 mmol) and HOBt (114.3 mg, 0.85 mmol) were added, and the reaction was stirred for 4 h. The reaction was quenched with the addition of H_2O, and the organic layer was washed with H_2O. The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) and was eluted with 80:20 $CHCl_3$−CMA-80 to yield 88.0 mg (28%) of the desired product: ^{1}H NMR (CD_3OD) δ 0.72 (d, 3H, J = 6.9), 1.28−1.02 (m, 3H), 1.69−1.51 (m, 1H), 1.87−1.71 (m, 2H), 2.19−2.11 (m, 1H), 2.43−2.33 (m, 5H), 2.55−2.52 (m, 2H), 2.84−2.62 (m, 8H), 3.07−2.96 (m, 1H), 3.20 (s, 1H), 3.59 (s, 2H), 3.80 (s, 3H), 4.51 (sept, J = 6 Hz, 1H), 4.68−4.59 (m, 1H), 6.67−6.60 (m, 5H), 6.89−6.86 (m, 1H), 7.86−7.17 (m, 6H).

(−)-3-(6-Hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]propanamide (5f) Dihydrochloride. Amide (**14a**) (88.0 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (30 mL), cooled to −78 °C, and BBr_3 (3.0 mL, 21.0 mmol, 10 equiv per protecting group added). The mixture was allowed to stir at −78 °C for 30 min and at room temperature for 2 h. The mixture was cooled to 0 °C, quenched with $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) and was eluted with 65:35 $CHCl_3$−CMA-80 to yield 67.8 mg (85%) of the desired product. The analytical sample was prepared by dissolving the free base in MeOH, acidifying with HCl in Et_2O, and precipitating with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: mp 240−247 °C dec; $[\alpha]^{23}_D$ −57° (*c* 0.20, MeOH); ^{1}H NMR (CD_3OD) δ 0.72 (d, 3H, J = 6.9), 1.28−1.02 (m, 3H), 1.69−1.51 (m, 1H), 1.87−1.71 (m, 2H), 2.19−2.11 (m, 1H), 2.43−2.33 (m, 5H), 2.55−2.52 (m, 2H), 2.84−2.62 (m, 8H), 3.07−2.96 (m, 1H), 3.20 (s, 1H), 3.54 (s, 2H), 4.68−4.51 (m, 1H), 6.62−6.50 (m, 5H), 6.81−6.78 (m, 1H), 7.38−7.11 (m, 6H); ^{13}C NMR (CD_3OD) δ 19.40, 30.15, 30.28, 34.87, 39.04, 41.51, 46.23, 50.24, 52.18, 55.34, 55.51, 55.93, 56.60, 57.54, 113.5, 114.9, 116.0, 126.5, 127.2, 128.9, 129.7, 129.9, 130.8, 136.4, 143.8, 152.8, 157.3, 159.0, 174.0. Anal. ($C_{36}H_{47}Cl_2N_3O_3\cdot 2H_2O$) C, H, N.

***N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-Isopropoxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(5-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanamide (14b).** Amine (**12**) (122.3 mg, 0.30 mmol) was dissolved in CH_2Cl_2 (5 mL) followed by 3-(5-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic acid (122.6 mg, 0.45 mmol). Triethylamine was added in excess to the required number of equivalents (0.71 mL, 0.51 mmol), and the mixture was allowed to stir for 20 min. EDCI (98.0 mg, 0.51 mmol) and HOBt (69.1 mg, 0.51 mmol) were added, and the reaction was stirred for 4 h. The reaction was quenched with the addition of H_2O, and the organic layer was washed with H_2O. The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) and was eluted with 80:20 $CHCl_3$−CMA-80 to yield 141.0 mg (71%) of the desired product: ^{1}H NMR (CD_3OD) δ 0.72 (d, 3H, J = 6.9), 1.28−1.02 (m, 3H), 1.69−1.51 (m, 1H), 1.87−1.71 (m, 2H), 2.19−2.11 (m, 1H), 2.43−2.33 (m, 5H), 2.55−2.52 (m, 2H), 2.84−2.62 (m, 8H), 3.07−2.96 (m, 1H), 3.20 (s, 1H), 3.59 (s, 2H), 3.80 (s, 3H), 4.52 (sept, J = 6 Hz, 1H), 4.68−4.59 (m, 1H), 6.67−6.60 (m, 5H), 6.89−6.86 (m, 1H), 7.43−7.08 (m, 6H).

(−)-3-(5-Hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]propanamide (5h) Dihydrochloride. Amide (**14b**) (116.9 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (30 mL), cooled to −78 °C, and BBr_3 (4.0 mL, 21.0 mmol, 10 equiv per protecting group) added. The mixture was allowed to stir at −78 °C for 30 min and at room temperature for 2 h. The mixture was cooled to 0 °C, quenched with $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified using preparative TLC (SiO_2) and was eluted with 65:35 $CHCl_3$−CMA-80 to yield 44.1 mg (41%) of the desired product. The analytical sample was prepared by dissolving the free base in MeOH, acidifying with HCl in Et_2O, and precipitating with Et_2O. The solvent was decanted, and the resulting material was dried under vacuum at 50 °C overnight: mp 242−248 °C dec; $[\alpha]^{23}_D$ −55° (*c* 0.20, MeOH); ^{1}H NMR (CD_3OD) δ 0.72 (d, 3H, J = 6.9), 1.28−1.02 (m, 3H), 1.69−1.51 (m, 1H), 1.87−1.71 (m, 2H), 2.19−2.11 (m, 1H), 2.43−2.33 (m, 5H), 2.55−2.52 (m, 2H), 2.84−2.62 (m, 8H), 3.07−2.96 (m, 1H), 3.20 (s, 1H), 3.55 (s, 2H), 4.68−4.51 (m, 1H), 6.67−6.60 (m, 5H), 6.89−6.86 (m, 1H), 7.43−7.08 (m, 6H); ^{13}C NMR (CD_3OD) δ 19.24, 24.71, 29.71, 34.716, 38.72, 41.27, 46.00, 52.07, 55.36, 55.76, 55.96, 57.00, 57.59, 113.5, 113.7, 114.2, 119.0, 122.4, 127.4, 128.0, 129.8, 129.9, 130.9, 136.7, 143.4, 152.2, 156.4, 159.0, 164.1, 174.0. Anal. ($C_{36}H_{4479}Cl_2N_3O_2\cdot 3.5H_2O$) C, H, N.

3-(6-Methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic Acid Hydrochloride. 6-Methoxy-1,2,3,4-tetrahydroisoquinoline (10.2 g, 54.0 mmol) was dissolved in MeOH followed by the addition of acrylic acid (4.7 g, 64.8 mmol) and diisopropylethylamine (cat.) and heated to reflux for 4 h. The solution was diluted with H_2O and extracted with $CHCl_3$ (3 × 50 mL). The pH of the aqueous layer was adjusted to 6.5 with concentrated HCl by measurement with a pH meter. The water was removed under reduced pressure to yield the zwitterion and NaCl. The zwitterion was dissolved in $(CH_3)_2CO$, filtered to remove the NaCl, and converted to the HCl salt by addition of 1 N HCl (5 mL). The solvent was removed

under reduced pressure to yield 11.2 g (76.5%) of the HCl salt as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 2.51 (t, 2H, J = 6.3 Hz), 2.74 (t, 2H, J = 6.3 Hz), 2.81 (m, 2H), 2.86 (m, 2H), 3.34 (s, 2H), 3.85 (s, 3H), 7.01 (m, 1H), 7.11 (m, 2H).

3-(7-Hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic Acid. 7-Hydroxy-1,2,3,4-tetrahydroisoquinoline (6.3 g, 30.2 mmol) was dissolved in MeOH (50 mL) followed by the addition of acrylic acid (3.1 mL, 45.3 mmol) and diisopropylethylamine (200 μL, 1.1 mmol) and heated to reflux for 4 h. The mixture was cooled to room temperature, and the CH_3OH was removed under reduced pressure. The crude material was then dissolved in $NaHCO_2$ and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The crude material was purified by use of flash chromatography (neutral alumina, Brockman activity II−III) with 8:2 hexanes−EtOAc as the eluent. The combined organic fractions yielded 5.0 g (75%) of the title compound as an off-white solid: ^{1}H NMR (CD_3OD) δ 2.96 (t, 2H, J = 6.3 Hz), 3.40−3.30 (m, 4H), 3.54 (t, 2H, J = 6.3 Hz), 3.49 (m, 2H), 6.62−6.61 (m, 1H), 6.77−6.73 (m, 1H), 7.09−7.02 (m, 1H).

3-(7-Methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic Acid. 7-Methoxy-1,2,3,4-tetrahydroisoquinoline (7.0 g, 46.7 mmol) was dissolved in MeOH (50 mL) followed by the addition of acrylic acid (3.2 mL, 46.7 mmol) and diisopropylethylamine (200 μL, 1.1 mmol) and heated to reflux for 4 h. The mixture was cooled to room temperature, and the CH_3OH was removed under reduced pressure. The crude material was then dissolved in $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The crude material was purified using flash chromatography (neutral alumina, Brockman activity II−III) with 8:2 hexanes−EtOAc as the eluent. The combined organic fractions yielded 9.1 g (83%) of the title compound as an off-white solid: ^{1}H NMR (CD_3OD) δ 2.96 (t, 2H, J = 6.3 Hz), 3.40−3.30 (m, 4H), 3.54 (t, 2H, J = 6.3 Hz), 3.49 (m, 2H), 3.81 (s, 3H), 6.62−6.61 (m, 1H), 6.77−6.73 (m, 1H), 7.09−7.02 (m, 1H).

3-(5-Methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic Acid Hydrochloride. 5-Methoxy-1,2,3,4-tetrahydroisoquinoline (2.3 g, 10.8 mmol) was dissolved in MeOH (100 mL) followed by the addition of acrylic acid (1.2 mL, 16.2 mmol) and diisopropylethylamine (200 μL, 1.1 mmol) and heated to reflux for 4 h. The solution was diluted with H_2O and extracted with $CHCl_3$ (3 × 50 mL). The pH of the aqueous layer was adjusted to 6.5 with concentrated HCl by measurement with a pH meter. The H_2O was removed under reduced pressure to yield the zwitterion and NaCl. The zwitterion was dissolved in $(CH_3)_2CO$, filtered to remove the NaCl, and converted to the HCl salt by addition of 1 N HCl (5 mL). The solvent was removed under reduced pressure to yield 2.0 g (84%) of the HCl salt of the title compound as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 2.55−2.49 (m, 2H), 2.84−2.82 (m, 2H), 2.96−2.93 (m, 4H), 3.78 (s, 3H), 3.81 (s, 2H), 6.67−6.51 (m, 2H), 7.02−6.93 (m, 1H).

3-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic Acid Hydrochloride. 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (1.34 g, 5.8 mmol), diisopropylethylamine (cat.), and acrylic acid (501.5 mg, 6.5 mmol) were dissolved in CH_3OH (20 mL) and heated at reflux overnight. The solution was cooled to room temperature, and a white precipitate formed. This precipitate was filtered and washed with cold CH_3OH to yield 1.43 g (93%) of the title compound as the HCl salt: ^{1}H NMR (CD_3OD + 2 drops NaOD) δ 2.49 (m, 2H), 2.87−2.70 (m, 6H), 3.46 (s, 2H), 3.70 (s, 6H), 6.28 (s, 1H), 6.34 (s, 1H).

***tert*-Butyl (1*R*,4*S*,5*S*,7*R*)-7-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-(3-isopropoxyphenyl)-4-methyl-2-azabicyclo[3.3.1]nonane-2-carboxylate (15).** In a 1000-mL round-bottomed flask, the amine (**10**) (5.30 g, 0.013 mmol) was dissolved in 50 mL of CH_2Cl_2 followed by the addition of Et_3N (1.94 mL, 13.93 mmol) and solid (still cold) di-*tert*-butyl dicarbonate (2.90 g, 0.013 mol). Upon addition of the Boc_2O the reaction immediately began to evolve gas. After 1 h, only a faint starting material spot could be seen by TLC analysis (basic alumina, 5% EtOAc−hexane). The solvent was removed by rotary evaporation to give a dark brown oil. Purification by flash chromatography on silica eluting with 1:1 EtOAc−petroleum ether gave 6.49 g (99%) of **15** as a colorless oil that gave a white foam under vacuum: recrystallized from hexanes, mp 141−143 °C; ^{1}H NMR ($CDCl_3$) δ 0.64 (d, 3H, J = 7.2 Hz), 1.32 (d, 6H, J = 6.0 Hz), 1.48 (d, 9H, J = 3.0 Hz), 1.81−1.98 (m, 1H), 1.99−2.15 (m, 1H), 2.16−2.46 (m, 4H), 2.53 (td, 1H, J = 12.9, 3.6 Hz), 3.65 (td, 1H, J = 15.6, 3.4 Hz), 3.75−3.87 (m, 1H), 4.52 (dt, 2H, J = 12.1, 6.0 Hz), 4.70−4.79 (m, 1H), 5.07 (ddd, 1H, J = 19.4, 12.8, 6.2 Hz), 6.71 (dd, 1H, J = 7.9, 2.3 Hz), 6.74−6.83 (m, 2H), 7.19 (t, 1H, J = 7.9 Hz), 7.68 (dd, 2H, J = 5.7, 3.0 Hz), 7.78 (dd, 2H, J = 5.8, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 17.7, 22.0, 28.4, 30.7, 32.9, 37.1, 40.1, 41.9, 45.5, 47.3, 48.3, 69.6, 79.5, 79.6, 112.6, 113.8, 117.5, 123.0, 129.1, 131.8, 133.8, 149.9, 155.5, 157.8, 168.1; MS (ESI) 518 $(M)^+$.

***tert*-Butyl (1*R*,4*S*,5*S*,7*R*)-7-Amino-5-(3-isopropoxyphenyl)-4-methyl-2-azabicyclo[3.3.1]nonane-2-carboxylate (16).** Phthalimide (**15**) (6.91 g, 0.019 mmol) was dissolved in 330 mL of 95% EtOH in a 1000-mL three-neck round-bottom flask with magnetic stirrer and reflux condenser. Hydrazine hydrate (3.63 mL, 0.075 mmol) was added, and the mixture was heated to reflux and monitored by TLC (silica 1:4 EtOAc−hexane), which showed the reaction progressing quickly and was complete in approximately 1 h. The mixture was allowed to cool to room temperature. Upon slow cooling, the phthalic hydrazide byproduct precipitated out, the mixture was filtered, and the solvent was removed. The solid residue was dissolved in 3:1 CH_2Cl_2−THF, and the remaining phthalic hydrazide was, again, filtered off. The solvent was removed to give very clean product **16** as a thick yellow oil, 5.03 g (97%) which was used directly in the next step: ^{1}H NMR ($CDCl_3$) $\boldsymbol{\delta}$ 0.60 (d, 3H, J = 7.2 Hz), 1.16−1.30 (m, 2H), 1.33 (d, 6H, J = 6.0 Hz), 1.47 (d, 9H, J = 7.2 Hz), 1.58 (t, 1H, J = 12.2 Hz), 2.06−2.36 (m, 4H), 2.41 (dd, 1H, J = 13.6, 5.3 Hz), 3.45−3.62 (m, 3H), 4.51 (br s, 2H, J = 54.6 Hz), 4.54 (dt, 1H, J = 12.3, 6.1 Hz), 6.66−6.88 (m, 3H), 7.15−7.26 (m, 1H); ^{13}C NMR ($CDCl_3$) $\boldsymbol{\delta}$ 17.8, 22.0, 28.5, 31.2, 36.9, 40.3, 41.0, 46.0, 47.6, 48.4, 50.4, 69.8, 79.5, 112.5, 113.8, 117.4, 129.1, 150.5, 155.7, 157.9; MS (ESI) 389.9 $(M + H)^+$.

***tert*-Butyl (1*R*,4*S*,5*S*,7*R*)-7-{[3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)propanoyl]amino}-5-(3-isopropoxyphenyl)-4-methyl-2-azabicyclo[3.3.1]nonane-2-carboxylate (17).** The amine (**16**) (1.38 g, 0.0036 mol) was dissolved in 90 mL of anhydrous THF in a 250-mL round-bottom flask. 3-(3,4-Dihydro-1*H*-isoquinoline-2-yl)-propionic acid HCl salt (1.29 g, 0.0054 mol) and Et_3N (2.47 mL, 17.8 mmol) were added and stirred at room temperature for 1.5 h. The BOP reagent (1.73 g, 0.0039 mol) was added, and the mixture was monitored by TLC (silica 1:1 $CHCl_3$−CMA-80). The reaction was complete in 1 h. EtOAc (20 mL) and saturated $NaHCO_3$ (30 mL) were added to the mixture. The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (2 × 20 mL). The aqueous layers were back extracted with Et_2O (20 mL), and the combined organic layers were washed with 1 N NaOH (20 mL), dried over Na_2SO_4, and concentrated to give 2.35 g of a colorless oil/foam. This material was purified by CombiFlash chromatography (silica $CHCl_3$ to 85:15 $CHCl_3$−CMA-80) to give 1.84 g (85%): ^{1}H NMR ($CDCl_3$) δ 0.56 (d, 3H, J = 6.8 Hz), 0.99−1.18 (m, 2H), 1.32 (d, 6H, J = 6.0 Hz), 1.40−1.54 (m, 9H), 2.04−3.08 (m, 11H), 3.48−3.81 (m, 4H), 4.30−4.77 (m, 3H), 6.54−7.25 (m, 7H), 7.88−8.14 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.6, 22.0, 28.4, 30.8, 31.2, 32.5, 36.5, 37.2, 39.9, 43.3, 46.7, 47.2, 47.7, 48.2, 49.8, 53.7, 55.3, 69.7, 79.5, 112.6, 113.6, 117.4, 125.8, 126.3, 126.4, 128.6, 129.1, 133.6, 150.3, 155.6, 157.8, 171.6; MS (ESI) 576.8 $(M + H)^+$.

3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*R*,4*S*,5*R*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-azabicyclo[3.3.1]non-7-yl]propanamide (18). The starting material (**17**) (1.47 g, 0.0026 mol) was dissolved in 100 mL of CH_2Cl_2 and cooled to −78 °C in a 250-mL round-bottom flask. (As the solution cooled, it became cloudy.) BBr_3 (12.77 mL, 1 M in CH_2Cl_2, 12.77 mmol) was added dropwise resulting in a turbid solution with a light brown hue. TLC analysis (silica 1:1 $CHCl_3$−CMA-80) showed the starting material was consumed within 4 min. The cooling bath was removed, and the mixture was allowed to warm. Around 0 °C (judging by frost

melting) water (40 mL) was added to the reaction mixture. The aqueous layer was acidified by adding a small amount of 6 N HCl. The layers were separated, and the organic layer was extracted with 1 N HCl (50 mL). The acid layer was washed with a small amount of CH_2Cl_2. The combined acid layers were made basic (pH 9−10) while they were stirred in an Erlenmeyer flask with 50% NaOH. This mixture was transferred to a separatory funnel using 1 N HCl (50 mL). EtOAc (100 mL) was added, and while the mixture was rapidly stirred, the pH was adjusted to 9−10 with 50% NaOH. This mixture was transferred to the separatory funnel. The layers were separated, and the basic layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give 100% of the product: ^{1}H NMR ($CDCl_3$) δ 0.60 (d, 3H, J = 6.8 Hz), 1.09 (t, 1H, J = 12.6 Hz), 1.26 (d, 1H, J = 2.6 Hz), 1.46 (d, 1H, J = 11.7 Hz), 2.03 (s, 1H), 2.15 (d, 2H, J = 8.3 Hz), 2.41 (d, 2H, J = 3.0 Hz), 2.51 (d, 1H, J = 7.9 Hz), 2.62−2.77 (m, 4H), 2.81 (d, 2H, J = 5.7 Hz), 3.34−3.45 (m, 2H), 3.53−3.66 (m, 2H), 4.81 (d, 1H, J = 6.0 Hz), 5.28 (br s, 1H), 6.53−6.74 (m, 3H), 6.92−7.01 (m, 1H), 7.00−7.20 (m, 4H), 7.81−8.05 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.2, 28.7, 31.4, 32.5, 36.7, 38.3, 39.8, 44.6, 46.9, 48.1, 48.7, 49.9, 53.6, 55.2, 112.2, 113.0, 115.7, 125.7, 126.3, 126.4, 128.5, 129.2, 133.5, 133.6, 151.1, 157.3, 171.9; MS (ESI) 434.6 $(M + H)^+$.

(−)-3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*R*,4*S*,5*S*,7*R*)-2-hexyl-5-(3-hydroxyphenyl)-4-methyl-2-azabicyclo[3.3.1]non-7-yl]propanamide (5l) Dihydrochloride. Amine **18** (0.038 mg, 0.088 mmol) was dissolved in 11 mL of anhydrous CH_2Cl_2 in a 100-mL round-bottom flask. The solution remained cloudy and was slow to dissolve. Hexanal (0.013 mL, 0.105 mmol) was added followed by sodium triacetoxyborohydride (26 mg, 0.123 mmol). This mixture was stirred at room temperature and monitored by TLC (silica 1:1 $CHCl_3$−CMA-80), which showed the starting material was consumed in 1 h. Aqueous saturated $NaHCO_3$ (30 mL) and $CHCl_3$ (15 mL) were added and stirred for about 5 min. The layers were separated, and the aqueous layer was washed with $CHCl_3$ (20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The product was isolated by column chromatography (silica 1:4 $CHCl_3$−CMA-80). The purified product was dissolved in anhydrous Et_2O (1 mL) and anhydrous MeOH (4 drops), and 1 M HCl in Et_2O (1 mL) was added dropwise with rapid stirring resulting in a white precipitate. The solvent was evaporated with nitrogen, and the residual solid was pumped on high vacuum for 1.5 h. The salt was triturated with Et_2O (4 × 2.5 mL) to give 24 mg (46%) of the hydrochloride salt: $[\alpha]^{20}_D$ −44° (*c* 0.75, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.70 (d, 3H, J = 9 Hz), 0.77−0.96 (m, 4H), 1.06 (t, 1H, J = 15 Hz), 1.24 (s, 8H), 1.14 (s, 2H), 1.57 (d, 1H, J = 12 Hz), 2.13 (s, 1H), 2.31 (m, 2H), 2.45 (m, 5H), 2.60−2.91 (m, 7H), 2.91−3.10 (m, 1H), 3.17 (s, 1H), 3.50−3.75 (m, 2H), 4.60 (m, 1H), 6.38−6.79 (m, 3H), 6.90−7.22 (m, 5H), 8.0 (bs, 1H). Anal. ($C_{33}H_{49}Cl_2N_3O_2\cdot H_2O$) C, H, N. MS (ESI) 518.8 $(M + H)^+$.

(−)-3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-{(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-[3-(2-methylphenyl)propyl]-2-azabicyclo[3.3.1]non-7-yl}propanamide (5m) Dihydrochloride. The title compound was prepared in 63% yield using a procedure similar to that described for **5l** starting from amine **18** and 3-(2-methoxyphenyl)propanal: $[\alpha]^{20}_D$ −47° (*c* 1.1, CH_3OH); ^{1}H NMR ($CDCl_3$) 0.69 (d, 3H, J = 6 Hz), 0.88 (dd, 1H, J = 15 Hz, J = 15 Hz), 1.07 (dd, 1H, J = 12 Hz, J = 12 Hz), 1.55 (d, 1H, J = 12 Hz), 1.71 (m, 2H), 2.12 (s, 1H), 2.25 (s, 3H), 2.28−2.961 (series of m, 16H), 3.05 (dd, 1H, J = 12 Hz, J = 3 Hz), 3.16 (s, 1H), 3.62 (m, 2H), 4.63 (m, 1H), 6.49−6.82 (m, 3H), 6.98 (d, 1H, J = 9 Hz), 7.01−7.21 (m, 8H), 8.10 (bs, 1H); MS (ESI) 566.5 $(M + H)^+$. Anal. ($C_{37}H_{49}Cl_2N_3O_2\cdot 1.5H_2O$) C, H, N.

(−)-3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-{(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-[2-(2-methylphenyl)ethyl]-2-azabicyclo[3.3.1]non-7-yl}propanamide (5n) Dihydrochloride. The title compound was prepared in 45% yield using a procedure similar to that described in **5l** starting from amine **18** and 2-(2-methylphenyl)acetaldehyde: $[\alpha]^{20}_D$ −26° (*c* 0.95, CH_3OH); ^{1}H NMR ($CDCl_3$) 0.74 (d, 3H, J = 6 Hz), 0.93 (m, 1H), 1.08 (m, 1H), 1.58 (m, 1H), 2.11−2.59 (m, 9H), 2.60−2.96 (m, 10H), 3.12 (dd, 1H, J = 12 Hz, J = 3 Hz), 3.29 (s, 1H), 3.63 (m, 2H), 4.60 (m, 1H), 5.75 (bs, 1H), 6.48−6.85 (m, 3H), 6.98 (m, 1H), 7.02−7.23 (m, 8H), 8.0 (bs, 1H); MS (ESI) 552.9 $(M + H)^+$. Anal. ($C_{36}H_{47}Cl_2N_3O_2\cdot 2H_2O$) C, H, N.

(−)-3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-(2-methylbenzyl)-2-azabicyclo-[3.3.1]non-7-yl]propanamide (5o) Dihydrochloride. The title compound was prepared in 72% yield using a procedure similar to that described in **5l** starting from amine **18** and *o*-tolylacetaldehyde: $[\alpha]^{20}_D$ −54.8° (*c* 1.15, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.62 (d, 3H, J = 6 Hz), 0.89 (m, 2H), 1.04 (dd, 1H, J = 12 Hz, J = 12 Hz), 1.26 (m, 2H), 1.45 (d, 1H, J = 6 Hz), 2.04 (m, 1H), 2.22 (d, 1H, J = 12 Hz), 2.32 (s, 3H), 2.36−2.60 (m, 4H), 2.65−2.92 (m, 5H), 3.01 (s, 1H), 3.11 (dd, 1H, J = 12 Hz, J = 3 Hz), 3.42−3.78 (m, 4H), 4.75 (m, 1H), 6.52−6.92 (m, 3H), 6.97 (d, 1H, J = 6 Hz), 7.02−7.23 (m, 8H), 7.80 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 18.7, 19.5, 29.1, 31.9, 33.0, 33.1, 37.9, 40.7, 45.2, 47.7, 50.5, 52.7, 54.1, 55.6, 56.0, 57.9, 112.9, 113.7, 116.7 (113.7 and 116.7 show up as broad signals with a poor S/N ratio.), 125.7, 126.4, 126.9, 127.0, 127.3, 129.1, 129.6, 129.8, 130.6, 133.8, 134.0, 137.6, 138.1, 152.0, 157.3, 172.4. MS (ESI) 538.6 $(M + H)^+$. Anal. ($C_{35}H_{45}Cl_2N_3O_2\cdot 1.5H_2O$) C, H, N.

(−)-3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-{(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-[3-(2-thienyl)propyl]-2-azabicyclo-[3.3.1]non-7-yl}propanamide (5p) Dihydrochloride. The title compound was prepared in 43% yield using a procedure similar to that described in **5l** starting from amine **18** and 3-(2-thienyl)-propanal: $[\alpha]^{20}_D$ −45° (*c* 1.05, CH_3OH). ^{1}H NMR ($CDCl_3$) δ 0.68 (d, 3H, J = 9 Hz), 0.86 (dd, 1H, J = 12 Hz, J = 12 Hz), 1.05 (dd, 1H, J = 12 Hz, J = 12 Hz), 1.53 (d, 1H, J = 12 Hz), 1.74 (m, 2H), 2.10 (bs, 1H), 2.28 (dd, 2H, J = 12 Hz, J = 12 Hz), 2.36−2.54 (m, 5H), 2.61 (m, 3H), 2.66−2.88 (m, 7H), 3.01 (dd, 1H, J = 12 Hz, J = 3 Hz), 3.13 (s, 1H), 3.61 (s, 2H), 4.60 (m, 1H), 6.49−6.77 (m, 3H), 6.88 (d, 1H, J = 3 Hz), 6.97 (m, 1H), 7.02−7.15 (m, 4H), 7.19 (dd, 1H, J = 6 Hz), 7.96 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 19.09, 28.22, 28.33, 28.46, 29.36, 31.90, 32.87, 37.84, 40.53, 45.10, 47.72, 50.51, 53.59, 54.16, 54.66, 55.73, 56.26, 112.89, 113.49, 116.59, 120.50, 125.59, 126.39, 126.90, 127.01, 128.75, 129.13, 129.79, 134.13, 142.97, 151.68, 157.59, 172.61; MS (ESI) 558.7 $(M + H)^+$. Anal. ($C_{34}H_{45}Cl_2N_3O_2S\cdot H_2O$) C, H, N.

(−)-3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-{(1*R*,4*S*,5*S*,7*R*)-5-(3-hydroxyphenyl)-4-methyl-2-[3-(3-thienyl)propyl]-2-azabicyclo-[3.3.1]non-7-yl}propanamide (5q) Dihydrochloride. The title compound was prepared in 64% yield using a procedure similar to that described in **5l** starting from amine **18** and 3-(3-thienyl)-propanal: $[\alpha]^{20}_D$ −41° (*c* 1.2, CH_3OH); ^{1}H NMR ($CDCl_3$) 0.70 (d, 3H, J = 6 Hz), 0.86 (m, 1H), 1.05 (dd, 1H, J = 12 Hz, J = 12 Hz), 1.53 (d, 1H, J = 12 Hz), 1.79 (m, 2H), 2.12 (s, 1H), 2.28 (m, 2H), 2.37−2.59 (m, 5H), 2.59−2.91 (m, 10H), 3.03 (dd, 1H, J = 12 Hz, J = 3 Hz), 3.12 (s, 1H), 3.62 (s, 2H), 4.61 (m, 1H), 6.50−6.82 (m, 4H), 6.89 (dd, 1H, J = 6 Hz, J = 3 Hz), 6.98 (m, 1H), 7.02−7.21 (m, 5H), 8.05 (bs, 1H); ^{13}C NMR ($CDCl_3$) 19.06, 27.73, 29.35, 29.67, 32.00, 32.92, 37.86, 40.57, 45.11, 47.75, 50.50, 53.73, 54.16, 55.73, 56.08, 112.88, 113.59, 116.69, 123.32, 124.62, 126.38, 126.89, 126.99, 127.11, 129.12, 129.75, 134.12, 145.58, 151.74, 157.51, 172.56; MS (ESI) 558.8 $(M + H)^+$. Anal. ($C_{34}H_{45}Cl_2N_3O_2S\cdot 1.5H_2O$) C, H, N.

(−)-3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-[(1*R*,4*S*,5*S*,7*R*)-2-[3-(2-furyl)propyl]-5-(3-hydroxyphenyl)-4-methyl-2-azabicyclo-[3.3.1]non-7-yl]propanamide (5r) Dihydrochloride. The title compound was prepared in 47% yield using a procedure similar to that described in **5l** starting from amine **18** and 3-(2-furyl)-propanal: $[\alpha]^{20}_D$ −35° (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.72 (d, 3H, J = 6 Hz), 0.78−0.96 (m, 2H), 0.98−1.14 (m, 1H), 1.25 (m, 2H), 1.55 (d, 1H, J = 6 Hz), 1.77 (m, 2H), 2.07−2.20 (m, 1H), 2.20−2.37 (m, 2H), 2.38−2.57 (m, 4H), 2.59−2.71 (m, 3H), 2.71−2.79 (m, 3H), 2.79−2.89 (m, 2H), 3.07 (dd, 1H, J = 12 Hz, J = 3 Hz), 3.21 (s, 1H), 3.64 (m, 2H), 4.59 (m, 1H), 5.98 (d, 1H, J = 3 Hz), 6.25 (d, 1H, J = 3 Hz), 6.50−6.81 (m, 3H), 6.98 (m,

1H), 7.02−7.21 (m, 4H), 7.27 (d, 1H, J = 3 Hz), 8.10 (bs, 1H); MS (ESI) 542.8 $(M + H)^+$. Anal. ($C_{34}H_{45}Cl_2N_3O_3 \cdot 2H_2O$) C, H, N.

(2-Methylphenyl)acetaldehyde. To *o*-tolylacetic acid (1.22 g, 8.12 mmol) in 20 mL of absolute EtOH was added 2 drops of concentrated H_2SO_4, and the mixture was heated under reflux overnight. The solvent was then removed by rotary distillation. The residue was dissolved in Et_2O (40 mL), washed with saturated aqueous $NaHCO_3$ (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a colorless oil in near quantitative yield. The crude product was reduced to 2-methylphenylacetaldehyde following Mandell's procedure.[19]

3-(2-Thienyl)propanal. Methyl (*E*)-3-(2-thiophenyl)acrylate was made as described by Mouloungui[20] and was reduced to methyl 3-(2-thiophenyl)propionate as described by Robertson.[21] The methyl 3-(2-thiophenyl)propionate (0.467 g, 2.74 mmol) was dissolved in Et_2O (8 mL) and cooled to −78 °C. Diisobutylaluminum hydride (4.57 mL, 6.85 mmol, 1.5 M in toluene) was added and stirred at −78 °C for 1 h. The cooling bath was removed, H_2O (5 mL) was added, and the mixture was stirred vigorously for 15 min. The reaction mixture was filtered through a coarse sintered glass frit, and the solids were washed generously with Et_2O and H_2O. The layers were separated, and the organic layer was washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to a colorless oil giving 0.36 g (92%).

Oxalyl chloride (0.173 g, 1.36 mmol, 0.117 mL) was dissolved in CH_2Cl_2 (8 mL) and cooled to −78 °C. DMSO (0.212 g, 2.72 mmol, 0.193 mL) was added and stirred at −78 °C for 10 min. 3-(2-Thiophenyl)propanol (0.176 g, 1.23 mmol) was added dropwise as a 1 mL solution in CH_2Cl_2. The mixture was stirred at −78 °C for 1 h at which point Et_3N (0.163 g, 1.61 mmol, 0.224 mL) was added. The mixture was allowed to warm to room temperature. Water (10 mL) and CH_2Cl_2 (10 mL) were added, the layers were separated, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure giving the product as short white needles, 0.145 g (83%).

3-(3-Thienyl)propanal and 3-(2-furyl)propanal were prepared from 3-thiophene carboxaldehyde and 2-furanaldehyde, respectively, in the same manner as 3-(2-thienyl)propanal. 3-(2-Methylphenyl)-propanal was also prepared in this manner from ethyl 2-methyl-cinnamate.

Acknowledgment. This work was supported by the National Institute on Drug Abuse, Grant DA09045. The CHO cells expressing the human opioid receptors were kind gifts of Dr. Lawrence Toll (SRI, Menlo Park, CA; hMOR and hDOR) and Dr. Liu-Chen (Temple University, Philadelphia, PA; hKOR).

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

References

(1) Zimmerman, D. M.; Nickander, R.; Horng, J. S.; Wong, D. T. New structural concepts for narcotic antagonists defined in a 4-phenylpiperidine series. *Nature* **1978**, *275*, 332−334.
(2) Thomas, J. B.; Mascarella, S. W.; Rothman, R. B.; Partilla, J. S.; Xu, H.; McCullough, K. B.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Investigation of the N-substituent conformation governing potency and μ receptor subtype-selectivity in (+)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonists. *J. Med. Chem.* **1998**, *41*, 1980−1990.
(3) Zimmerman, D. M.; Leander, J. D.; Cantrell, B. E.; Reel, J. K.; Snoddy, J.; Mendelsohn, L. G.; Johnson, B. G.; Mitch, C. H. Structure−activity relationships of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine antagonists for μ and κ opioid receptors. *J. Med. Chem.* **1993**, *36*, 2833−2841.
(4) Mitch, C. H.; Leander, J. D.; Mendelsohn, L. G.; Shaw, W. N.; Wong, D. T.; Cantrell, B. E.; Johnson, B. G.; Reel, J. K.; Snoddy, J. D.; Takemori, A. E.; Zimmerman, D. M. 3,4-Dimethyl-4-(3-hydroxyphenyl)piperidines: Opioid antagonists with potent anorectant activity. *J. Med. Chem.* **1993**, *36*, 2842−2850.
(5) Zimmerman, D. M.; Gidda, J. S.; Cantrell, B. E.; Schoepp, D. D.; Johnson, B. G.; Leander, J. D. Discovery of a potent, peripherally selective *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonist for the treatment of gastrointestinal motility disorders. *J. Med. Chem.* **1994**, *37*, 2262−2265.
(6) Schmidt, W. K. Alvimopan* (ADL 8-2698) is a novel peripheral opioid antagonist. *Am. J. Surg.* **2001**, *182*, 27S−38S.
(7) Leone, N.; Wentz, L. News Release from Adolor Corporation−FDA Accepts Entereg(TM) (alvimopan) New Drug Application (NDA) for Review. http://phx.corporate-ir.net/phoenix.zhtml?c=120919&p=irol-newsArticle&t=Regular&id=611171& (accessed 2004).
(8) Statnick, M. A.; Suter, T. M.; Gackenheimer, S. L.; Emmerson, P. J.; Quimby, S. J.; Gehlert, D. R.; Wheeler, W. J.; Mitch, C. H. Na^+-dependent high affinity binding of [3H]LY515300, a 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid receptor inverse agonist. *Eur. J. Pharmacol.* **2003**, *482*, 139−150.
(9) 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 κ receptor subtype-selective N-substituent for (+)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine. *J. Med. Chem.* **1998**, *41*, 5188−5197.
(10) 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.
(11) 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.
(12) 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.
(13) 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.
(14) Thomas, J. B.; Gigstad, K. M.; Fix, S. E.; Burgess, J. P.; Cooper, J. B.; Mascarella, S. W.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. A stereoselective synthetic approach to *N*-alkyl-4β-methyl-5-phenylmorphans. *Tetrahedron Lett.* **1999**, *40*, 403−406.
(15) Thomas, J. B.; Atkinson, R. N.; Namdev, N.; Rothman, R. B.; Gigstad, K. M.; Fix, S. E.; Mascarella, S. W.; Burgess, J. P.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Discovery of an opioid kappa receptor selective pure antagonist from a library of N-substituted 4β-methyl-5-(3-hydroxyphenyl)morphans. *J. Med. Chem.* **2002**, *45*, 3524−3530.
(16) Buck, J. S. Some Substituted Tetrahydroisoquinoline Hydrochlorides. *J. Am. Chem. Soc.* **1934**, *56*, 1769−1771.
(17) Kucznierz, R.; Grams, F.; Leinert, H.; Marzenell, K.; Engh, R. A.; von der Saal, W. Tetrahydro-isoquinoline-based factor Xa inhibitors. *J. Med. Chem.* **1998**, *41*, 4983−4994.
(18) Katritzky, A. R.; He, H.-Y.; Jiang, R.; Long, Q. 2-Substituted-1,2,3,4-tetrahydroisoquinolines and chiral 3-carboxyl analogues from *N*-benzotriazolylmethyl-*N*-phenethylamines. *Tetrahedron: Asymmetry* **2001**, *12*, 2427−2434.
(19) Mandell, L.; Lee, D. E.; Courtney, L. F. Protection of a substituted catechol whose derivatives are subject to steric labilization. *J. Org. Chem.* **1982**, *47*, 731−734.
(20) Mouloungui, Z.; Elmestour, R.; Delmas, M.; Gaset, A. Reactions de Wittig−Horner et de transesterification en une operation par activation anionique de liaisons C−H et O−H en milieu heterogene carbonate de potassium/alcool (Wittig−Horner reactions and transesterification by anionic activation of C−H and O−H in heterogeneous potassium carbonate/alcohol). *Tetrahedron* **1992**, *48*, 1219−1232.
(21) Robertson, A.; Philp, D.; Neil Spencer, N. Recognition-induced control of a Diels−Alder cycloaddition. *Tetrahedron* **1999**, *55*, 11365−11384.
(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.

JM058264P