# Highly Potent and Selective Phenylmorphan-Based Inverse Agonists of the Opioid δ Receptor

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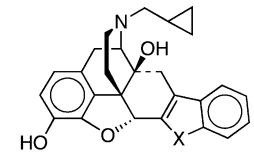
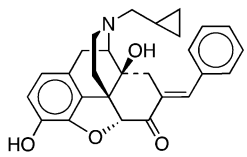
We recently reported the discovery of (+)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo-[3.3.1]non-7-yl-(1-phenyl-1-cyclopentane)carboxamide [(+)-KF4, (+)-**5**] as a novel chemotype possessing potent antagonist activity at the δ opioid receptor. Additional SAR studies involving changes to both the 2-amino and 7-amido N-substituents using this same (+)-morphan scaffold have revealed compounds with improved potency and selectivity for the δ opioid receptor. The highly potent and selective 2,2-dimethylphenylacetamide analogue (+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-2-methyl-2-phenylpropanamide (**13d**, delmorphan-A) showed picomolar inhibitory potency ($K_e$ = 0.1 nM) in the [$^{35}$S]GTPγS functional assay with δ opioid receptor selectivity ratios of 103- and 132-fold versus the μ and κ opioid receptors, respectively. The compounds showed no agonist activity at any of the three opioid receptors; however, measurements of δ inverse agonist activity within this series illustrated a broad range of negative efficacy and $IC_{50}$ values 650-fold more potent than the prototypical δ opioid receptor inverse agonist ICI 174 864 (**22**).

It is now well established that opioid receptors belong to the superfamily of G-protein-coupled receptors (GPCRs[a]). Distinct cDNAs encoding the μ, δ, κ, and ORL-1 receptors have been cloned, and studies with opioid receptor knockout mice have clarified the role each receptor type plays in mediating effects of morphine.[1,2] Since the discovery of the three distinct opioid receptors and the ORL-1 orphan receptor, researchers studying the underlying mechanisms of opioid activity have sought highly potent and selective agonists and antagonists.[3] In recent years, the δ opioid receptor has received considerable attention. Numerous studies have been directed toward the development of δ agonists as potentially new analgesics with reduced side effects relative to μ opioid agonists.[4−7] In addition, studies have also suggested that δ opioid receptor antagonists can modulate a number of biological processes.[8] For example, δ opioid receptor antagonists might be useful in the treatment of L-DOPA-induced dyskinesia in Parkinson's disease[9] and alcohol abuse,[10] as antitussive drugs,[11] and in the regulation of tumor cell growth.[12−14] Most importantly, however, are the continued reports that indicate an intimate involvement of the δ opioid receptor system in morphine tolerance and dependence.[15−17]

Very few opioid receptor pure antagonists selective for the δ receptor have been reported. By applying the message−address concept of Schwyzer[18] to naltrexone, Portoghese developed antagonists selective for the δ receptor. Attachment of a properly aligned phenyl ring (δ address) to the nonselective opioid antagonist naltrexone (the opioid message) to act as a mimic for Phe[4] of the enkephalins provided the δ opioid receptor selective antagonists naltrindole (**1a**) and naltriben (**1b**).[19] Compounds **1a** and **1b** have proven to be highly useful for the characterization of the δ opioid receptor, even though Takemori et al. reported that they showed some agonist effects.[20,21] A significant amount of work from several research groups has been reported with the goal of providing optimal alignment of the message and address moieties. Two different approaches to this are illustrated by benzylidenenaltrexone (BNTX, **2**) and the nonopiate SK 205588 (**3**).[22−24] The latter is remarkable not only because it showed significant enhancement of selectivity versus **1a** but also because it broke tradition using a nonclassical N-substituent structure to induce antagonist behavior in a nonopiate scaffold. Beyond this, the SAR of **1a** proper has been surveyed including N-substituent modification, alkylation of the 14-position, alkylation of the indole nitrogen, and substitution or heterocyclic replacement of the phenyl address ring.[25−29]




**1a**: X = NH
**1b**: X = O

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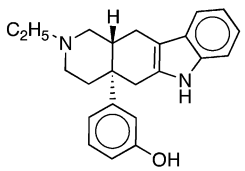


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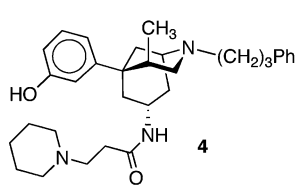


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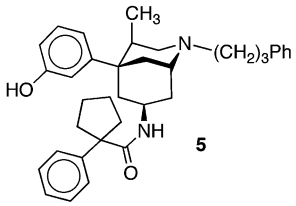


**5**

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[a] Abbreviations: GPCRs, G-protein-coupled receptors; cDNAs, complementary deoxyribonucleic acids; ORL-1, opioid-receptor-like; BNTX, benzylidenenaltrexone; SAR, structure−activity relationship; ACE-Cl, α-chloroethyl chloroformate; ICI 174,864, $(C_3H_5)_2$Tyr-AiG-Aib-Phe-Leu (**22**); [$^{35}$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 (**23**); CHO, Chinese hamster ovary; GDP, guanosine diphosphate; GFB, glass fiber B filter; PTX, pertussis toxin; SK 205583, 3-(2-ethyl-1,2,3,4,5,6,11,11a-octahydro-4aH-pyrido[4,3-*b*]carbazol-4a-yl)phenol (**3**); BOP, (dimethylamino)phosphonium hexafluorophosphate.

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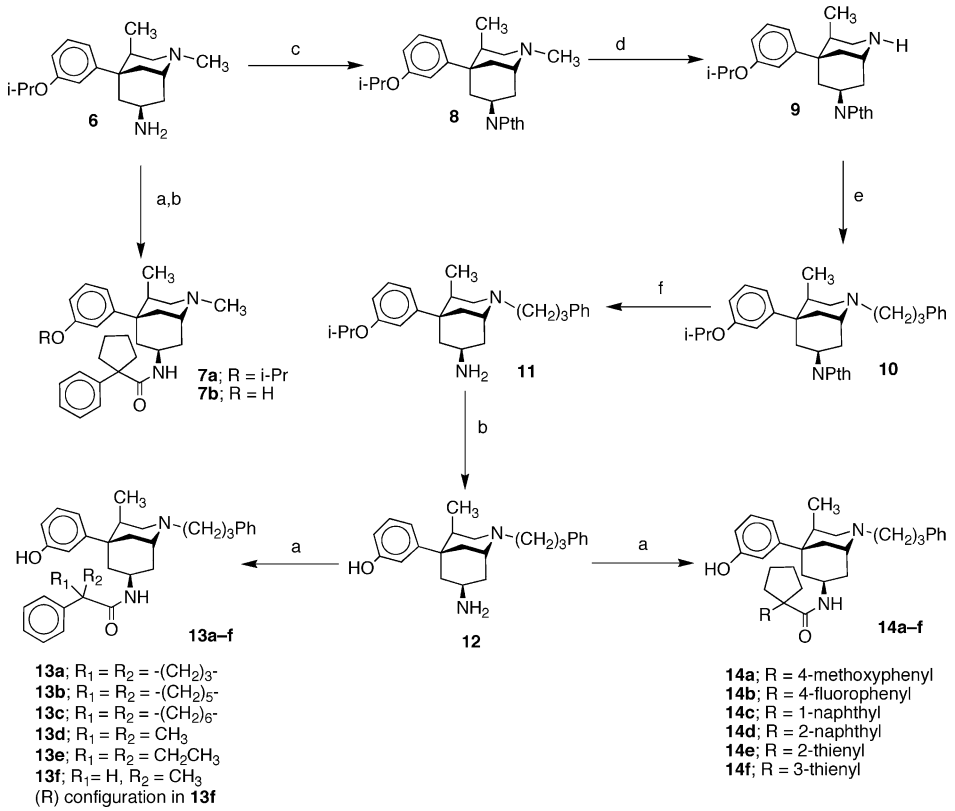
**Scheme 1**[a]




[a] Reagents: (a) appropriate carboxylic acid, BOP, $Et_3N$, THF; (b) 48% HBr, HOAc, reflux; (c) phthalic anhydride, toluene, Dean−Stark trap; (d) ACE-Cl, $CH_2Cl_2$, MeOH, reflux; (e) $NaBH(OAc)_3$, $Ph(CH_2)_2CHO$, $CH_2Cl_2$; (f) $H_2NNH_2$, EtOH, reflux.

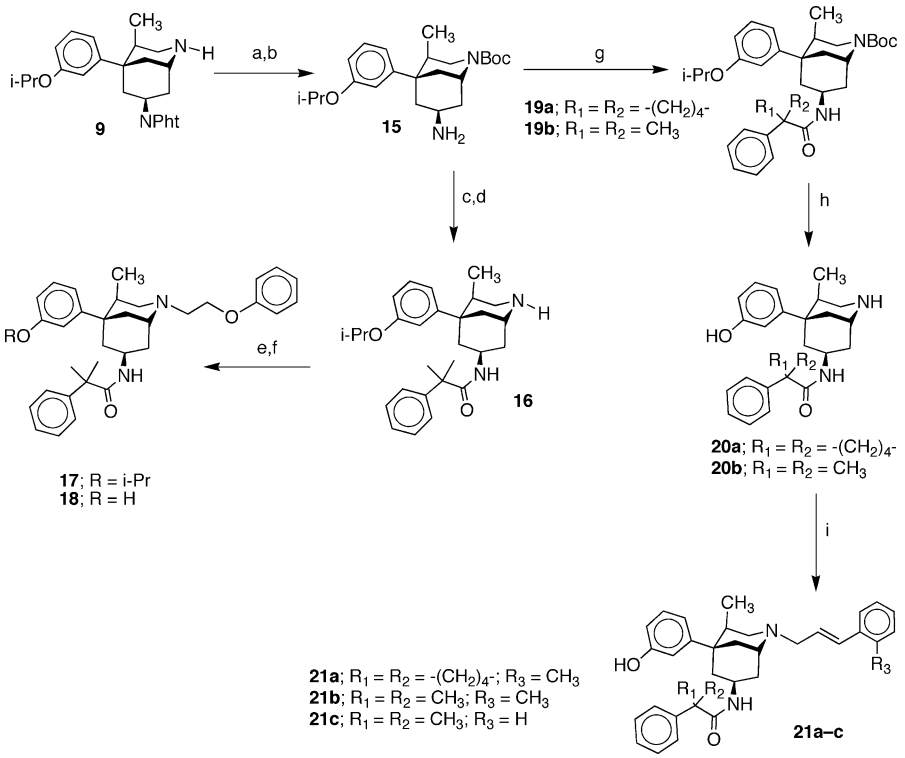
The phenylmorphans are a class of opioid compounds first described by Ong and May over 30 years ago.[30] In recent years we have shown that this scaffold can produce potent opioid pure antagonists and can assume the role of "antagonist message" similar to naltrexone. Furthermore, we have shown that introduction of appropriate 7-amido-linked "address" elements to this nonselective scaffold confers opioid receptor selectivity to the resulting ligand. In line with the findings of Portoghese and co-workers, $\kappa$ selectivity was achieved with address elements containing a basic amino group as in **4** [(−)-KAA1] and $\delta$ selectivity was obtained using a phenyl ring as the address element as in **5** [(+)-KF4].[31−33] Herein we report an expanded SAR survey with the same (+)-phenylmorphan scaffold, which has revealed analogues with enhanced potency and selectivity for the $\delta$ opioid receptor as well as potent inverse agonist activity.

## Chemistry

Preparation of the target compounds began with optically pure 7-aminomorphan **6** prepared as previously described (Scheme 1).[34] The *N*-methyl derivative of **5**, compound **7b**, was prepared directly from **6** by coupling with 1-cyclopentanecarboxylic acid using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP, Castro's reagent) followed by removal of the isopropyl group with hydrogen bromide and acetic acid. Target compounds **13a**−**f** and **14a**−**f** required a change to the phenylpropyl N-substituent. This conversion was accomplished via protection of the 7-amine as the phthalimide (**8**) followed by treatment with α-chloroethyl chloroformate (ACE-Cl) and then refluxing methanol to give N-demethylated **9**. Reductive alkylation of **9** with hydrocinnamldehyde using sodium triacetoxyborohydride gave *N*-phenylpropyl derivative **10**. Protection of **6** as the phthalimide was required because 7-amido derivatives of **6** failed to react with ACE-Cl or any other chloroformate N-demethylating reagent. Deprotection of **10** with hydrazine gave the 7-amino derivative **11**, which was converted to the seminal intermediate **12** by treatment with hydrogen bromide in glacial acetic acid. Preparation of target compounds from **12** utilized BOP coupling with the appropriate carboxylic acid. Target compounds **13a**−**f** expanded the SAR of **5** by introducing diversity in the α and α′ positions of the phenylacetamide side chain, whereas target compounds **14a**−**f** incorporated diversity in the aromatic fragment.

Target compounds **18** and **21a**−**c** explored the SAR of the N-substituent of the 2-amine in **5** and were accessed from intermediate **9** as shown in Scheme 2. Differentiation of the amino groups was accomplished by blocking the 2-amino position as a *tert*-butyl carbamate followed by selective removal of the phthalimide from the 7-position to give intermediate **15**. Target compound **18** was prepared by coupling with 2,2-dimethylphenylacetic acid followed by removing the carbamate with trifluoroacetic acid to give **16** followed by N-alkylation with $\beta$-bromophenetole to give **17** and finally phenol deprotection with boron tribromide. Target compounds **21a**−**c** were obtained from **15** by first coupling with the appropriate carboxylic acid derivatives using BOP to give the 7-amido side chain intermediates **19a**,**b**. Removal of both the isopropyl and *tert*-butyloxycarbonyl groups was accomplished with hydrogen bromide and acetic acid to give secondary amines **20a**,**b**, which were subsequently converted to the desired target compounds **21a**−**c** via reductive alkylation using sodium triacetoxyborohydride and the appropriate aldehyde.

**Scheme 2**[a]




[a] Reagents: (a) $Boc_2O$, $Et_3N$, $CH_2Cl_2$; (b) $H_2NNH_2$, EtOH, reflux; (c) 2,2-dimethylphenylacetic acid, BOP, $Et_3N$, THF; (d) TFA, $CH_2Cl_2$; (e) $PhOCH_2CH_2Br$, $Bu_4NI$; (f) $BBr_3$, $CH_2Cl_2$; (g) $PhR_1R_2CO_2H$, BOP, $Et_3N$, THF; (h) 48% HBr, HOAc; (i) $NaBH(OAc)_3$, appropriate aldehyde, $CH_2Cl$.

## Biology

Measures of functional antagonism and selectivity of the target compounds and standards, **1a** and ICI 174 864 (**22**), were obtained by monitoring the ability of test compounds to inhibit stimulated [$^{35}$S]GTP$\gamma$S binding produced by the selective agonist DAMGO ($\mu$), DPDPE ($\delta$), or U69 593 (**23**, $\kappa$) using cloned human opioid receptors expressed in CHO cells (Table 1).[31] The assays were run in a 96-well array in 1.4 mL polypropylene tubes. In a final volume of 0.5 mL, each assay contained 0.5 nM [$^{35}$S]GTP$\gamma$S, 20−40 $\mu$g of membrane protein, one of seven concentrations of agonist (0.32−32 000 nM), 1 or 10 $\mu$M GDP, test compound, and 1% dimethyl sulfoxide. The assay concentration of the test compounds were 3−300, 1−50, and 50−300 nM for the $\mu$, $\delta$, and $\kappa$ assays, respectively. The assays were run in a 20 mM Hepes buffer (pH 7.4) containing 100 mM NaCl, 10 mM $MgCl_2$, and incubated at room temperature for 1 h. The assay was started by the addition of the membrane homogenate, and it was terminated by rapid vacuum filtration over GF/B filter plates and washing with three volumes of ice-cold buffer. The plates were dried, and trapped radioactivity was determined using a TopCount scintillation counter. The average (±SEM) percent stimulation of basal binding for DAMGO, DPDPE, and **23** was 292 ± 10, 246 ± 11, and 285 ± 9, respectively. Receptor expression for these cell lines ranged between 0.4 and 0.6 pmol/mg protein.

Agonist concentration response curves were run in the presence or absence of a single concentration of test compound and in the presence of 10 $\mu$M GDP. This concentration of GDP was used to reduce the basal or unstimulated binding of [$^{35}$S]GTP$\gamma$S in order to increase the agonist signal-to-background ratio. The concentration of test compound was chosen such that it caused at least a 2-fold increase in the agonist $EC_{50}$ value. The apparent affinity or $K_e$ values were calculated using the formula $K_e = [L]/\{(A'/A) - 1\}$, where [L] is the concentration of test compound and $A'$ and $A$ are the agonist $EC_{50}$ values in the presence and absence of antagonist, respectively. No agonist activity was observed at the $\delta$ opioid receptor with any of the test compounds (maximum assay concentration of 31.6 $\mu$M), and none of the compounds displayed intrinsic activity (agonist or inverse agonist) at either the $\mu$ or $\kappa$ receptor.

**Table 1.** Apparent Affinity ($K_e$) at Cloned Human $\mu$, $\delta$, and $\kappa$ Opioid Receptors[a]

| | $K_e$ (nM) | | | | |
|---|---|---|---|---|---|
| compd | $\mu$[b] | $\delta$[c] | $\kappa$[d] | $\mu/\delta$ | $\kappa/\delta$ |
| **5** | 8.7 ± 2.7 | 0.15 ± 0.03 | 17.9 ± 6.3 | 58 | 119 |
| **7b** | 43.2 ± 5.9 | 76.8 ± 31 | 61 ± 16 | 0.6 | 0.8 |
| **13a** | 10.6 ± 4.8 | 0.17 ± 0.04 | 16.0 ± 5.7 | 62 | 94 |
| **13b** | 22.8 ± 6.2 | 0.34 ± 0.14 | 10.2 ± 1.5 | 67 | 30 |
| **13c** | 24.4 ± 3.97 | 0.26 ± 0.16 | 17.5 ± 4.5 | 93 | 67 |
| **13d** | 10.3 ± 3.7 | 0.10 ± 0.02 | 13.2 ± 2.6 | 103 | 132 |
| **13e** | 11.7 ± 3.6 | 0.20 ± 0.13 | 14.6 ± 4.7 | 59 | 74 |
| **13f** | 9.6 ± 2.5 | 0.14 ± 0.04 | 8.1 ± 1.5 | 69 | 58 |
| **14a** | 12.0 ± 3.6 | 0.67 ± 0.3 | 2.43 ± 0.02 | 18 | 3.6 |
| **14b** | 9.1 ± 4.6 | 0.26 ± 0.06 | 4.5 ± 1.3 | 35 | 17 |
| **14c** | 27.2 ± 12.8 | 1.42 ± 0.3 | 43.6 ± 20.2 | 19 | 31 |
| **14d** | 35.0 ± 15.4 | 0.75 ± 0.23 | 56.1 ± 13.4 | 47 | 75 |
| **14e** | 2.19 ± 0.86 | 0.31 ± 0.091 | 24.0 ± 8.4 | 7.1 | 77 |
| **14f** | 2.07 ± 0.91 | 0.24 ± 0.09 | 7.77 ± 1.46 | 8.8 | 33 |
| **18** | 11.4 ± 0.7 | 0.87 ± 0.24 | 96.3 ± 27.8 | 13 | 111 |
| **21a** | 2.51 ± 0.90 | 0.33 ± 0.12 | 5.6 ± 2.8 | 7.6 | 22 |
| **21b** | 1.02 ± 0.27 | 0.47 ± 0.16 | 6.7 ± 1.8 | 2.2 | 14 |
| **21c** | 1.9 ± 0.3 | 0.81 ± 0.45 | 15.8 ± 5.0 | 2.4 | 20 |
| **1a** | 33 ± 23 | 0.21 ± 0.06 | 16.1 ± 5.3 | 157 | 77 |
| **22** | 42 ± 16 | 7.9 ± 3.3 | 339 ± 179 | 5.3 | 43 |

[a] The data represent the mean ± SE from at least three independent experiments. The final GDP assay concentration was 10 $\mu$M. [b] The $\mu$ assay used (D-Ala$^2$,MePhe$^4$,Gly-ol$^5$)enkephalin. Agonist selective for $\mu$ opioid receptor. [c] The $\delta$ assay used [D-Pen$^2$,D-Pen$^5$]enkephalin. Agonist selective for $\delta$ opioid receptor. [d] The $\kappa$ assay used [(5$\alpha$,7$\alpha$,8$\beta$)-(−)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzeneacetamide] (**23**). Agonist selective for $\kappa$ opioid receptor.

**Table 2.** Inverse Agonist Potencies and Efficacies of Compounds at the Cloned Human δ Receptor

| compd | $IC_{50}$ (nM) | % of basal binding |
|---|---|---|
| **5** | 1.8 ± 0.6 | 70 ± 10 |
| **7b** | 95 ± 28 | 79 ± 3.2 |
| **13a** | 0.42 ± 0.10 | 65 ± 4.3 |
| **13b** | 0.68 ± 0.21 | 65 ± 4.6 |
| **13c** | 0.39 ± 0.15 | 70 ± 7 |
| **13d** | 0.40 ± 0.23 | 64 ± 7 |
| **13e** | 1.8 ± 1.0 | 61 ± 17 |
| **13f** | 0.15 ± 0.01 | 78 ± 6 |
| **14a** | 0.48 ± 0.05 | 72 ± 7 |
| **14b** | 0.45 ± 0.03 | 72 ± 4 |
| **14c** | 16 ± 7.5 | 46 ± 1.4 |
| **14d** | 7.7 ± 2.84 | 69 ± 13 |
| **14e** | 0.80 ± 0.33 | 54 ± 6 |
| **14f** | 0.45 ± 0.18 | 86 ± 5 |
| **18** | 1.4 ± 1.1 | 83 ± 2 |
| **21a** | 0.50 ± 0.12 | 70 ± 4 |
| **21b** | 0.12 ± 0.01 | 70 ± 5 |
| **21c** | 0.72 ± 0.32 | 78 ± 4 |
| naltrexone | NA[b] | |
| **1a** | NA[b] | |
| **22** | 83 ± 35 | 75 ± 4 |
| PTX | | 61 ± 7 |

[a] The data represent the mean ± SE from at least three independent experiments. The assays were exactly as described above except the final GDP assay concentration was 1 μM. See text for rationale. DPDPE typically caused a 2-fold increase in basal binding under these assay conditions.[b] No intrinsic activity.

The potencies and efficacies of the target compounds as inverse agonists were determined in the [$^{35}$S]GTPγS binding assay using wild-type human δ opioid receptors and compared to the prototypical inverse agonist (**22**) as well as the oxymorphone-based antagonists naltrexone and **1a** (Table 2). Intrinsic activity at all receptors was determined using a final concentration of 1 μM GDP. In our test system this concentration of GDP results in an approximate 5-fold increase in basal [$^{35}$S]GTPγS binding. This increase in basal binding provides a greater signal range over which the effect of an inverse agonist can be detected. A DPDPE concentration response curve was run on each assay plate to control for the performance of the assay. It is noted that although the compounds were inverse agonists, their influence on the basal binding in the δ opioid $K_e$ experiments was minor because they were reducing an already low basal activity (~400 cpm) and it had no apparent effect on the upper asymptote of the DPDPE curve.

## Results and Discussion

The results obtained for the measures of [$^{35}$S]GTPγS in vitro antagonist potency at the μ, δ, and κ receptors are listed in Table 1 and are described in comparison to the lead compound **5**. The 2-(*N*-methyl) derivative of **5**, compound **7b**, showed a significant loss of potency (512-fold) for the δ receptor (76.8 versus 0.15 nM), but as expected, the compound retained its antagonist activity. Typically, antagonists of this and related phenylpiperidine-based systems show much greater potency with N-substituent groups larger than methyl.[33] Compound **7b** showed no receptor preference, suggesting that both the 7-amido and the basic 2-amino substituent contribute to receptor selectivity. The phenylacetamide analogues **13a**−**f** on the other hand showed subnanomolar potency at the δ receptor with $K_e$ of 0.10−0.26 nM compared to 0.21 nM for **1a**. All six compounds showed much improved selectivity relative to **7b**. Compounds **13a**−**c** are α,α′-cyclic systems like **5**, having fewer (**13a**) or more methylene groups (**13b**,**c**) in the ring. The four-membered ring analogue **13a** was of equal potency compared with **5** at nearly all of the opioid receptors and as a consequence was nearly as selective with μ/δ and κ/δ ratios of 62 and 94, respectively. Increasing the ring size to a six-membered ring as in **13b**, however, resulted in a 2-fold loss of potency for μ and δ but an increase in potency at κ. The selectivity as a consequence was maintained at μ but was decreased for κ to 30-fold versus δ. Increasing the ring size to seven members gave results similar to those of the six-membered ring but showed lower potency for κ, which combined to improve the δ/κ selectivity. Overall, changing the size of the cyclopentyl ring in **5** did not provide any significant improvements in either the potency or the selectivity of the target compounds.

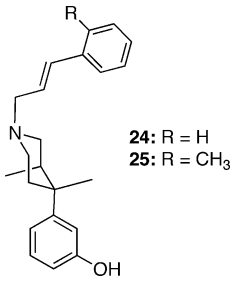
Three acyclic analogues of **5** were investigated, including the dimethyl (**13d**, delmorphan-A), diethyl (**13e**), and monomethyl (**13f**) derivatives. The dimethyl analogue was the most potent and selective of the three with a $K_e$ of 0.1 nM for the δ receptor and μ/δ and κ/δ ratios of 103 and 132, respectively. Overall, this compound represents one of the most potent and selective δ opioid receptor antagonists yet identified and exceeded the lead compound **5** in both potency and selectivity. The diethyl derivative on the other hand was 2-fold less potent than **13d** at roughly 0.2 nM, whereas the monomethyl derivative was only slightly less potent relative to **13d** but equally potent compared with **5**. From a selectivity standpoint, however, neither of the last two compounds showed the high level of selectivity of **13d**. Together with the cyclic analogues, the results obtained with this set of compounds indicates that dimethyl substitution has the best overall combination of potency and selectivity and is from this standpoint the best compound yet identified in this series of antagonists.

Target compounds **14a**−**f** retained the cyclopentyl ring found in **5** and focused on variation of the aromatic fragment of the 7-amido side chain substructure. The first two members of this set explored the electronic character of the aromatic ring looking at both ends of the spectrum, para fluoro (**14b**) and para methoxy (**14a**) substitution. Remarkably, addition of the methoxy group to **5** imparts a 7.5-fold increase in potency for the κ opioid receptor while maintaining roughly the same potency at μ. Combined with a 5-fold decrease in potency for the δ receptor, the methoxy group virtually eliminates the selectivity seen in **5**. Interestingly, fluoro substitution has a similar effect, though in this case, the δ potency decreases less than 2-fold and is still very potent at 0.26 nM. However, **14b** was also more potent at both μ and κ receptors with selectivity ratios of 35 and 17, respectively, and thus is not a δ selective compound.

Target compounds **14c**−**f** include the naphthyl and thienyl replacement analogues for the phenyl ring in **5** with each of these being represented by two regioisomeric variations. Target compound **14c**, the 1-naphthyl analogue, showed potency decreases at all opioid receptors relative to **5**. The biggest drop was at the δ receptor at roughly 10-fold, which resulted in a nonselective compound. The 2-naphthyl derivative (**14d**) on the other hand showed only half as much decrease in δ potency but relatively greater losses in potency for the remaining receptors. Overall, however, neither of the naphthyl compounds represented an improvement compared with **5** toward either potency or selectivity. The 2-thienyl compound **14e** was found to be very potent for the δ receptor with a $K_e$ of 0.31 nM, but relative to **5**, the μ potency improved roughly 4-fold, thus eliminating selectivity. The 3-thienyl compound was also very potent in the δ assay but was not selective because of relatively good potencies for the μ and κ receptors. On the whole, changes to either the size or electron density of the side chain aromatic ring in **5** did not lead to improved compounds but showed a significant ability to affect both the potency and selectivity of

the target compounds. In general, the analogues possessing an unsubstituted phenyl ring show greater in vitro potency and selectivity for the δ opioid receptor.

Changes to the N-substituent of **5** and **13d** were also examined in this study. This included a phenetole derivative (**18**) as well as cinnamyl and 2-methyl cinnamyl (**21a**−**c**) derivatives. Target compound **18** was 9-fold less potent than compound **13d** in the δ assay but showed little change for μ. The compound also lost significant potency (7.6-fold) in the κ assay. Compound **21a** was not selective for the δ receptor because the compound showed improved potency at both μ and κ. Thus, while the δ potency was only 2-fold less than **5**, its μ and κ $K_e$ values were 3.5- and 3.2-fold greater. Similar results were obtained in **21b** and **21c** where the δ potency decreased in parallel with improvements in potency for both μ and κ. It is noted, however, that the cinnamyl N-substituents (as in **21a**−**c**) had previously shown strong potency for the μ receptor in the phenylpiperidine analogues [(+)-*N*-(*trans*-3′-phenyl-2′-propenyl)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine (RTI-5989-1, **24**) and (+)-*N*-[*trans*-3′-(2-methylphenyl)-2′-propenyl]-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine (RTI-5989-25, **25**)].[31,35,36] Thus, it is not surprising that these compounds showed a lack of μ/δ receptor selectivity. The significant decrease in μ receptor potency for **21a**,**b**, however, relative to the corresponding phenylpiperidines **24** and **25** reveals that the 7-amido side chain moiety exerts a substantial influence over potency for the μ. However, it is very interesting that all of the compounds showed subnanomolar potency for the δ receptor, since the related phenylpiperidines **24** and **25** identified in previous work showed high μ potency ($K_e$ values at μ are 0.039 and 0.013 nM) for **24** and **25**, respectively.[35] Similar to the prototype, all the target compounds were inverse agonists for the δ receptor. Compound **7b** showed very low activity with an $IC_{50}$ of 95 nM, which is consistent with the low $K_e$ found as a δ antagonist. In the other examples studied, the $K_e$ for δ antagonist activity was usually very similar to the $IC_{50}$ seen for inverse agonism. Reduction in the percent of basal binding was similar for most compounds, with many examples showing levels equal to that found with PTX (100 ng/mL). The lead compound **5** with an $IC_{50}$ value of 1.8 nM was 46 times more potent than the prototype **22**. The most potent inverse agonist discovered, however, was **21b** (delmorphan-B) ($IC_{50}$ = 0.12 nM), which was ∼650 times as potent as **22**.




**24:** R = H
**25:** R = $CH_3$

We have demonstrated in recent years that the addition of a 4β-methyl substituent to the parent N-substituted 5-(3-hydroxyphenyl)morphans resulted in compounds that showed pure, albeit nonselective, opioid antagonist activity.[32] In addition to this, we have demonstrated that this class of antagonist conforms to the message−address model that Portoghese used to explain the δ selective properties of **1a**.[19] In the present case, we found that the addition of phenyl "address" groups to the (+)-*N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)morphan "message" fragment resulted in δ selective compounds. Viewed from this perspective, the phenylmorphan-based compounds are similar to their naltrexone-based counterparts. In terms of inverse agonist behavior, however, the data available in the [$^{35}$S]GTPγS assay using wild-type human δ opioid receptors suggest that the two classes of compounds behave differently. As shown earlier, all of the phenylmorphans tested in this study were found to be inverse agonists. This trait is also shared by the structurally related phenylpiperidine-based antagonists such as **24** and **25**, which have also been found to be inverse agonists.[35,37,38] In contrast, neither **1a** nor naltrexone showed inverse agonist activity. Others using wild-type δ receptors showed that naltrexone-based compounds did not demonstrate inverse agonist activity.[39]

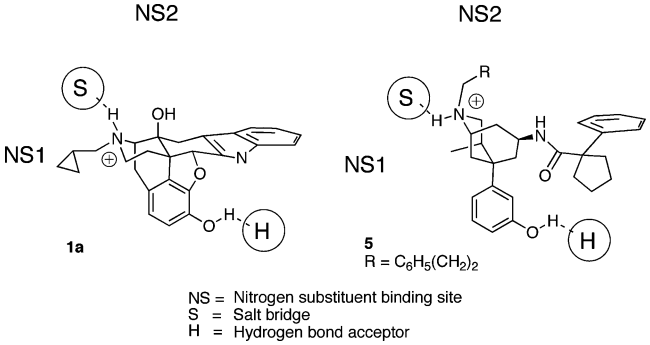



**Figure 1.** Comparison of the relative δ opioid receptor binding for **1a** and **5**.

In a recent article, we related our interpretation of the similarities and differences observed in the SAR for these two types of antagonist structures as arising from different ways of binding to the opioid receptors, as depicted in Figure 1.[34] As illustrated, the phenol and protonated amino groups of the two classes of antagonist were believed to bind to common domains represented by H and S, respectively. This implied that the N-substituents would occupy different domains NS1 versus NS2. Using this comparative analysis as a guide, we were able to correctly position the phenyl "address" ring on the nonselective phenylmorphan scaffold to obtain numerous δ opioid receptor selective compounds. These positive results support our initial hypothesis regarding the different relative modes of receptor binding presented by the two classes of antagonist. This in turn offers a means of rationalizing why one observes inverse agonist activity in the phenylmorphan series but not in the compounds derived from naltrexone. In short, the dichotomy in behavior between the two series could arise from the different modes by which they interact with the receptor. More specifically, the analysis suggests that the inverse agonist behavior arises as a consequence of the interaction of the receptor region NS2 by the 2-amino N-substituent of the phenylmorphan ligand. Though speculative, this notion is supported by the observation of inverse agonist activity in the phenylpiperidine series (**24** and **25**) and these compounds are believed to occupy the receptor in a manner similar to that depicted for the phenylmorphans. Collectively, the potent and selective phenylmorphan-based inverse agonists such as **13d** not only will provide tools for elucidating the biological role of constitutive activity but also are a valuable set of compounds that can provide an understanding of the mechanistic aspects leading to inverse agonist activity.

## Conclusion

This study suggests that using the hypothetical binding model that compared the receptor binding of phenylmorphan-based compounds to that of naltrexone-based antagonists such as **1a** can accurately predict structural modifications that impart δ

opioid receptor selectivity to nonselective phenylmorphan-based compounds. Interestingly, however, the set of analogues of (+)-**5** examined revealed that in every instance the compounds are actually inverse agonists for the $\delta$ receptor. While this activity was narrowly defined within a specific set of structural elements, we did find that (+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-2-methyl-2-phenylpropanamide (**13d**), the dimethylphenylacetamido analogue of **5**, is both more potent and more selective for the $\delta$ opioid receptor than the lead compound, showing picomolar activity ($K_e = 0.1$ nM) in the [$^{35}$S]GTP$\gamma$S functional assay and selectivity ratios of 103- and 132-fold for $\delta$ versus the $\mu$ and $\kappa$ opioid receptors, respectively. Finally, the success of the model in predicting the relative relationship between the two classes of "antagonists" may be further interpreted to suggest that it is the occupation of different receptor domains by the 2-amino N-substituents of these two classes of compounds that underlies the observation of neutral antagonist activity for the naltrexone-based series and inverse agonist activity in the phenylmorphan series.

## 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 or by charring using 5% phosphomolybdic acid in ethanol. 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 **23** were obtained from NIDA and were prepared by Multiple Peptide Systems (San Diego, CA). [$^{35}$S]-GTP$\gamma$S was obtained from Perkin-Elmer Inc. (Boston, MA). GTP$\gamma$S and GDP were obtained from Sigma Chemical Company (St. Louis, MO).

***N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Isopropoxyphenyl)-2,4-dimethyl-2-azabicyclo[3.3.1]non-7-yl]-1-phenylcyclopentanecarboxamide (7a).** A 250 mL three-neck round-bottom flask was charged with (+)-(1*S*,4*R*,5*R*,7*S*)-5-(3-isopropoxyphenyl)-2,4-dimethyl-2-azabicyclo-[3.3.1]nonan-7-amine (**6**) (820 mg, 2.71 mmol), 1-cyclopentanecarboxylic acid (1.03 g, 0.0054 mol), and dry THF (70 mL), followed by the addition of triethylamine (1.9 mL, 13.55 mmol) and BOP reagent (1.32 g, 2.98 mmol). The reaction mixture was stirred under $N_2$ at room temperature overnight. The mixture was diluted with diethyl ether (70 mL), washed consecutively with water (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by flash chromatography [silica gel, 20% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as a white foam (1.01 g, 78%): $^1$H NMR ($CDCl_3$) $\delta$ 7.38−7.16 (m, 6H), 6.71−6.65 (m, 3H), 4.71−4.46 (m, 3H), 3.13−3.08 (m, 2H), 2.64−1.52 (m, 18H), 1.32 (d, 6H, $J = 6.0$ Hz), 0.99−0.90 (m, 1H), 0.70 (d, 3H, $J = 6.9$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.9, 158.0, 151.3, 144.2, 129.2, 128.7, 126.85, 126.81, 117.4, 113.6, 112.2, 69.7, 59.1, 58.0, 54.9, 46.7, 44.8, 43.0, 39.8, 37.4, 37.0, 36.9, 32.7, 31.2, 29.7, 24.1, 22.1, 18.6.

**(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-2,4-dimethyl-2-azabicyclo[3.3.1]non-7-yl]-1-phenylcyclopentanecarboxamide (7b).** A solution of **7a** (107 mg, 0.225 mmol) in glacial acetic acid (3 mL) and 48% HBr (3 mL) was heated to reflux overnight. The reaction mixture was allowed to cool to room temperature, added to ice (10 g), and adjusted to pH 14 with 50% NaOH. The aqueous layer was extracted with 3:1 $CH_2Cl_2$−THF (30 mL × 3), the organic layer was collected and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The product was purified by preparative TLC [silica gel plate, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound (55.1 mg, 57%) as a white foam: $^1$H NMR ($CDCl_3$) $\delta$ 7.35−7.18 (m, 5H), 7.09 (t, 1H, $J = 7.8$ Hz), 6.60 (m, 3H), 4.78 (d, 1H, $J = 7.8$ Hz), 4.57 (m, 1H), 3.12−3.06 (m, 2H), 2.65 (d, 1H, $J = 12.3$ Hz), 2.50−2.21 (m, 8H), 2.14−1.94 (m, 3H), 1.82−1.51 (m, 5H), 0.94−0.72 (m, 2H), 0.63 (d, 3H, $J = 6.6$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 176.4, 157.1, 151.1, 144.1, 129.6, 128.9, 127.2, 127.0, 116.6, 113.2, 112.7, 59.8, 58.5, 55.5, 47.0, 45.5, 43.5, 40.1, 38.0, 37.64, 37.60, 33.1, 31.6, 24.71, 24.68, 19.2; MS (APCI) *m*/*z* 433.5 $(M + H)^+$. The free base (43.2 mg, 0.1 mmol) was dissolved in $CH_2Cl_2$. HCl (1 M in diethyl ether, 110 $\mu$L, 1.1 equiv) solution was added to this, and the salt was precipitated from the solution by adding diethyl ether (5 mL), filtered, and dried in the vacuum oven at 50 °C overnight: mp 194−200 °C; $[\alpha]^{20}_D$ +43.6° (*c* 0.50, MeOH). Anal. ($C_{28}H_{37}ClN_2O_2 \cdot H_2O$) C, H, N.

**2-[(1*S*,4*R*,5*S*,7*S*)-5-(3-Isopropoxyphenyl)-2,4-dimethyl-2-azabicyclo[3.3.1]non-7-yl]-1*H*-isoindole-1,3(2*H*)-dione (8).** Amine **6** (800 mg, 2.64 mmol) was dissolved in toluene (25 mL), followed by the addition of phthalic anhydride (1.19 g, 0.008 mol) and refluxed under a Dean−Stark trap overnight. The solution was cooled, washed with 1 N NaOH (25 mL × 3) and water (25 mL) and dried ($Na_2SO_4$). The solvent was removed under reduced pressure yielding crude product, which was purified by filtering through a short column of neutral alumina (Brockman activity II-II), eluting with 50% ethyl acetate in hexanes to afford the title compound (0.726 g, 64%) as a white solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.80−7.75 (m, 2H), 7.68−7.66 (m, 2H), 7.19 (t, 1H, $J = 7.8$ Hz), 6.81−6.76 (m, 2H), 6.70−6.68 (m, 1H), 5.07 (m, 1H), 4.52 (sept, 1H, $J = 6.0$ Hz), 3.27−3.18 (m, 2H), 2.73 (d, 1H, $J = 12.3$ Hz), 2.48−2.41 (m, 4H), 2.30−2.11 (m, 5H), 2.00−1.96 (m, 1H), 1.32 (d, 6H, $J = 6.0$ Hz), 0.78 (d, 3H, $J = 6.9$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.4, 158.2, 151.3, 134.0, 132.1, 129.3, 123.2, 117.6, 113.8, 112.5, 69.9, 58.6, 55.4, 46.6, 43.4, 42.7, 40.1, 38.0, 32.1, 26.6, 22.3, 18.9; LCMS (APCI) *m*/*z* 433.5 $(M + H)^+$.

**2-[(1*S*,4*R*,5*S*,7*S*)-5-(3-Isopropoxyphenyl)-4-methyl-2-azabicyclo-[3.3.1]non-7-yl]-1*H*-isoindole-1,3(2*H*)-dione (9).** Phthalimide **8** (2.67 g, 0.0062 mol) was dissolved in dichloroethane and heated to reflux under $N_2$ followed by the addition of 1-chloroethyl chloroformate (0.80 mL, 8.11 mmol). This solution was allowed to reflux for 4 h. The reaction mixture was allowed to cool to room temperature and then washed with a saturated sodium bicarbonate solution (150 mL) and water (250 mL). The solvent was removed under reduced pressure. The residue was dissolved in methanol (150 mL) and refluxed under $N_2$ overnight. The methanol was removed, and the crude product was not purified but carried directly to the next step: $^1$H NMR ($CDCl_3$) $\delta$ 7.78−7.76 (m, 2H), 7.67−7.65 (m, 2H), 7.19 (t, 1H, $J = 7.8$ Hz), 6.80−6.68 (m, 3H), 5.33 (m, 1H), 4.52 (sept, 1H, $J = 6.0$ Hz), 3.76 (dd, 1H, $J = 13.8$, 4.8 Hz), 3.58 (br, 1H), 2.86 (d, 1H, $J = 13.8$ Hz), 2.63 (td, 1H, $J = 12.9$, 4.2 Hz), 2.18−2.32 (m, 5H), 1.92−1.96 (m, 2H), 1.32 (d, 6H, $J = 6.0$ Hz), 0.72 (d, 3H, $J = 6.9$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.1, 157.9, 151.3, 133.8, 131.8, 129.1, 122.9, 117.1, 113.4, 112.4, 69.6, 49.5, 48.6, 46.6, 42.3, 40.4, 37.4, 34.6, 31.0, 22.0, 17.1; LCMS (APCI) *m*/*z* 419.9 $(M + H)^+$.

**2-[(1*S*,4*R*,5*S*,7*S*)-5-(3-Isopropoxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-1*H*-isoindole-1,3(2*H*)-dione (10).** To a solution of amine **9** (2.66 mmol) in anhydrous 1,2-dichloroethane (60 mL) was added hydrocinnamaldehyde (0.34 mL, 2.32 mmol) and $NaBH(OAc)_3$ (736 mg, 3.47 mmol), and the resulting mixture was stirred overnight. The reaction mixture was washed with saturated $NaHCO_3$ (45 mL), and the aqueous layer was back-extracted with ethyl acetate (45 mL × 2). The combined organic layers were dried over $MgSO_4$, and the solvent was removed at reduced pressure. This material was purified by flash chromatography ($Al_2O_3$, 5% EtOAc in hexanes) to afford the title compound as a white solid (1.07 g, 75% yield from **8**): $^1$H NMR ($CDCl_3$) $\delta$ 7.78−7.76 (m, 2H), 7.68−7.65 (m, 2H), 7.30−

7.16 (m, 6H), 6.81−6.77 (m, 2H), 6.70−6.67 (m, 1H), 5.11 (m, 1H), 4.52 (sept, 1H, $J$ = 6.0 Hz), 3.27 (br, 1H), 3.11 (dd, 1H, $J$ = 12, 4.8 Hz), 2.77 (d, 1H, $J$ = 11.4 Hz), 2.67 (m, 2H), 2.58−2.52 (m, 2H), 2.46−2.41 (m, 1H), 2.29−2.14 (m, 5H), 1.94 (d, 1H, $J$ = 12.3 Hz), 1.80 (pentet, 2H, $J$ = 7.5 Hz), 1.32 (d, 6H, $J$ = 6.0 Hz), 0.77 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) δ 168.2, 157.9, 151.2, 142.5, 133.8, 132.0, 129.1, 128.5, 128.2, 125.6, 123.0, 117.5, 113.7, 112.4, 69.7, 55.7, 54.4, 54.0, 46.5, 42.5, 40.5, 37.9, 33.3, 31.9, 29.4, 27.6, 22.1, 18.6; LCMS (APCI) $m/z$ 537.5 $(M + H)^+$.

**(1*S*,4*R*,5*R*,7*S*)-5-(3-Isopropoxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]nonan-7-amine (11).** Hydrazine (295 μL, 9.40 mmol) was added to a solution of phthalimide **10** (1.01 g, 0.0019 mol) in ethanol (70 mL), and the reaction mixture was refluxed under $N_2$ for 4.5 h. The reaction mixture was allowed to cool to room temperature. Removal of the solvent yielded a white solid crude product, which was dissolved in $CH_2Cl_2$ (15 mL). The heterogeneous solution was filtered through a fritted funnel with several $CH_2Cl_2$ washes. The filtrate was concentrated and dried on the vacuum pump to afford the title compound as a yellow oil in almost quantitative yield: $^1$H NMR ($CDCl_3$) δ 7.30−7.18 (m, 6H), 6.81−6.70 (m, 3H), 4.54 (sept, 1H, $J$ = 6.0 Hz), 3.53 (m, 1H), 3.16 (m, 1H), 2.89 (dd, 1H, $J$ = 12.0, 4.8 Hz), 2.68−2.62 (m, 3H), 2.52−2.47 (m, 2H), 2.37−2.32 (m, 3H), 2.13 (m, 1H), 1.84−1.59 (m, 5H), 1.33 (d, 6H, $J$ = 6.0 Hz), 1.17 (dd, 1H, $J$ = 13.8, 11.4 Hz), 0.97 (m, 1H), 0.74 (d, 3H, $J$ = 7.2 Hz); LCMS (APCI) $m/z$ 407.7 $(M + H)^+$.

**3-[(1*S*,4*R*,5*R*,7*S*)-7-Amino-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-5-yl]phenol (12).** A solution of amine **11** (2.41 mmol) in glacial acetic acid (11 mL) and 48% HBr (11 mL) was heated to reflux for 17 h. The reaction mixture was allowed to cool to room temperature. Ice (40 g) was added to the mixture, and the pH of the mixture was adjusted to 14 with 50% NaOH. This mixture was extracted with 3:1 $CH_2Cl_2$−THF (70 mL × 3), the organic layer was collected and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The product was purified by flash chromatography [silica gel, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as an off-white foam (0.546 g, 62%): $^1$H NMR ($CDCl_3$) δ 7.29−7.24 (m, 2H), 7.19−7.11 (m, 4H), 6.68−6.60 (m, 3H), 3.59 (m, 1H), 3.17 (br, 2H), 2.86 (dd, 1H, $J$ = 7.2, 4.8 Hz), 2.69−2.61 (m, 3H), 2.51−2.46 (m, 2H), 2.42−2.32 (m, 4H), 2.10 (m, 1H), 1.79 (m, 2H), 1.58 (d, 1H, $J$ = 12.0 Hz), 1.26−1.16 (m, 1H), 1.06−0.98 (m, 1H), 0.72 (d, 3H, $J$ = 6.9 Hz).

**(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-1-phenyl-1-cyclobutanecarboxamide (13a).** A 50 mL round-bottom flask was charged with amine **12** (48 mg, 0.132 mmol) and 1-phenyl-1-cyclobutanecarboxylic acid (25.6 mg, 0.145 mmol), and then the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (40 μL, 0.290 mmol) and BOP reagent (64.1 mg, 0.145 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 2.5 h. The mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by preparative TLC [silica gel plate, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as an off-white solid (50 mg, 73%): $^1$H NMR ($CDCl_3$) δ 7.35−7.11 (m, 11H), 6.68−6.65 (m, 3H), 4.68−4.60 (m, 2H), 3.12 (br, 1H), 3.02 (dd, 1H, $J$ = 7.8, 4.5 Hz), 2.84−2.80 (m, 1H), 2.74−2.67 (m, 2H), 2.60 (t, 2H, $J$ = 7.8 Hz), 2.52−2.40 (m, 4H), 2.37−2.30 (m, 3H), 2.17−2.11 (m, 2H), 1.89−1.75 (m, 3H), 1.51 (d, 1H, $J$ = 12.0 Hz), 0.92 (m, 1H), 0.76−0.67 (m, 4H); $^{13}$C NMR ($CDCl_3$) δ 175.8, 156.4, 151.5, 144.4, 142.4, 129.4, 128.8, 128.5, 128.2, 126.9, 126.3, 125.6, 116.8, 112.9, 112.4, 55.6, 54.2, 53.3, 52.7, 46.7, 45.0, 40.3, 37.4, 33.4, 32.6, 32.2, 31.8, 29.2, 18.6, 16.6; LCMS (APCI) $m/z$ 523.8 $(M + H)^+$. The free base (49 mg, 0.0937 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this solution was added HCl (1 M in diethyl ether, 103 μL, 1.1 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 45 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (51.3 mg, 98%): mp 157.5−159.5 °C; $[\alpha]^{20}_D$ +36.5° ($c$ 3.80, $CHCl_3$). Anal. ($C_{35}H_{43}ClN_2O_2 \cdot H_2O$) C, H, N.

**(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-1-phenyl-1-cyclohexanecarboxamide (13b).** A 50 mL round-bottom flask was charged with amine **12** (48 mg, 0.132 mmol) and 1-phenyl-1-cyclohexanecarboxylic acid (29.6 mg, 0.145 mmol), and the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (40 μL, 0.290 mmol) and BOP reagent (64.1 mg, 0.145 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 2.5 h. The mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by preparative TLC [silica gel plate, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$ and then silica gel plate 49% hexanes/49% acetone/2% $Et_3N$] to afford the title compound as an off-white solid (42.9 mg, 59%): $^1$H NMR ($CDCl_3$) δ 7.33−7.31 (m, 4H), 7.28−7.21 (m, 3H), 7.17−7.11 (m, 4H), 6.71−6.64 (m, 3H), 4.78 (d, 1H, $J$ = 7.8 Hz), 4.63 (m, 1H), 3.10 (br, 1H), 3.01 (m, 1H), 2.69−2.58 (m, 3H), 2.55−2.44 (m, 2H), 2.32−2.12 (m, 6H), 1.98 (m, 2H), 1.79−1.71 (m, 2H), 1.63−1.36 (m, 8H), 0.92 (m, 1H), 0.75−0.67 (m, 4H); $^{13}$C NMR ($CDCl_3$) δ 175.8, 156.7, 151.7, 143.4, 142.6, 129.6, 129.1, 128.7, 128.5, 127.0, 126.9, 125.8, 116.9, 113.2, 112.7, 55.7, 54.4, 53.6, 51.0, 46.8, 46.1, 45.1, 40.5, 37.6, 34.7, 34.5, 33.6, 32.8, 32.0, 29.4, 26.0, 23.0, 18.8; LCMS (APCI) $m/z$ 551.8 $(M + H)^+$. The free base (42.9 mg, 0.078 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M in diethyl ether, 86 μL, 1.1 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (43.7 mg, 93%): mp 157.0−159.0 °C; $[\alpha]^{20}_D$ +32.0° ($c$ 1.11, $CHCl_3$). Anal. ($C_{37}H_{47}ClN_2O_2 \cdot H_2O$) C, H, N.

**(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-1-phenyl-1-cycloheptanecarboxamide (13c).** A 50 mL round-bottom flask was charged with amine **12** (37.4 mg, 0.102 mmol) and 1-phenyl-1-cycloheptanecarboxylic acid (24.6 mg, 0.112 mmol), and the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (32 μL, 0.224 mmol) and BOP reagent (51 mg, 0.112 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 1.5 h. The mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified twice by preparative TLC (silica gel plate, hexanes−acetone−triethylamine, 65:33:2) and [silica gel plate, 33% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as a white solid (37.9 mg, 66%): $^1$H NMR ($CDCl_3$) δ 7.33−7.31 (m, 4H), 7.28−7.20 (m, 3H), 7.17−7.11 (m, 4H), 6.69−6.64 (m, 3H), 4.78 (d, 1H, $J$ = 7.8 Hz), 4.63 (m, 1H), 3.10 (br, 1H), 3.01 (m, 1H), 2.69−2.58 (m, 3H), 2.53−2.40 (m, 2H), 2.32−2.10 (m, 6H), 1.98 (m, 2H), 1.79−1.71 (m, 3H), 1.60−1.36 (m, 8H), 0.92 (m, 1H), 0.75−0.67 (m, 4H); $^{13}$C NMR ($CDCl_3$) δ 177.4, 156.1, 151.7, 145.2, 142.5, 129.4, 128.7, 128.5, 128.2, 126.8, 126.7, 125.6, 117.0, 112.8, 112.4, 55.5, 54.2, 53.4, 46.5, 44.8, 40.3, 37.47, 37.42, 37.2, 33.4, 32.6, 31.8, 29.9, 29.3, 24.18, 24.14, 18.6; LCMS (APCI) $m/z$ 565.6 $(M + H)^+$. The free base (37.9 mg, 0.0671 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M in diethyl ether, 80.5 μL, 1.2 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (41.2 mg, 99.9%): mp 152−155 °C; $[\alpha]^{20}_D$ +28.5° ($c$ 0.88, $CH_2Cl_2$). Anal. ($C_{38}H_{49}ClN_2O_2 \cdot 0.75H_2O$) C, H, N.

**(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-2-methyl-2-phenylpropanamide (13d).** A 50 mL round-bottom flask was charged with amine **12** (35.5 mg, 0.0974 mmol) and 2-methyl-2-phenyl-

propionic acid (17.6 mg, 0.107 mmol), and the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (30 $\mu$L, 0.214 mmol) and BOP reagent (47.3 mg, 0.107 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 2.5 h. TLC showed complete consumption of the starting material (**12**). The reaction mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by preparative TLC [silica gel plate, 49% hexanes/49% acetone/2% $Et_3N$ and then silica gel plate 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as an off-white solid (37.0 mg, 74%): $^1$H NMR ($CDCl_3$) $\delta$ 7.31−7.10 (m, 11H), 6.66 (m, 3H), 4.75−7.63 (m, 2H), 3.15 (br, 1H), 3.04 (dd, 1H, $J$ = 12, 4.2 Hz), 2.73−2.53 (m, 5H), 2.53 (m, 3H), 2.14 (m, 1H), 1.77 (m, 2H), 1.53 (d, 7H, $J$ = 6.0 Hz), 0.93 (m, 1H), 0.81−0.69 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.1, 156.3, 151.4, 144.8, 142.3, 129.4, 128.7, 128.5, 128.2, 127.1, 126.4, 125.7, 116.9, 112.9, 112.4, 55.6, 54.2, 53.4, 46.9, 46.5, 45.0, 40.2, 37.4, 33.3, 32.5, 31.7, 29.0, 27.2, 27.0, 18.6; LCMS (APCI) $m/z$ 511.5 $(M + H)^+$. The free base (37.0 mg, 0.0724 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M in diethyl ether, 80 $\mu$L, 1.1 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (40.4 mg, 99%): mp 147.5−149.5 °C; $[\alpha]^{20}_D$ +36.5° ($c$ 1.03, $CHCl_3$). Anal. ($C_{34}H_{43}ClN_2O_2 \cdot H_2O$) C, H, N.

**(+)-2-Ethyl-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-2-phenylbutanamide (13e).** A 50 mL round-bottom flask was charged with amine **12** (39.4 mg, 0.108 mmol) and 2-ethyl-2-phenylbutyric acid (22.8 mg, 0.118 mmol), and the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (33 $\mu$L, 0.236 mmol) and BOP reagent (53.8 mg, 0.118 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 1.5 h. The mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified twice by preparative TLC [silica gel plate, hexanes−acetone−ammonium hydroxide, 49:49:2, and silica gel plate 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as a white solid (37.7 mg, 65%): $^1$H NMR ($CDCl_3$) $\delta$ 7.32−7.10 (m, 11H), 6.66 (m, 3H), 4.74 (m, 2H), 3.14 (br, 1H), 3.06 (dd, 1H, $J$ = 11.7, 3.3 Hz), 2.72−2.53 (m, 5H), 2.37−2.28 (m, 3H), 2.14 (m, 1H), 2.05−1.88 (m, 4H), 1.77 (m, 2H), 1.52 (d, 1H, $J$ = 12 Hz), 0.97 (t, 1H, $J$ = 12 Hz), 0.79−0.61 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.9, 156.4, 151.4, 143.1, 142.4, 129.4, 128.5, 128.4, 128.3, 127.4, 126.8, 125.7, 116.7, 113.0, 112.4, 55.6, 54.5, 54.2, 53.5, 46.6, 44.9, 40.3, 37.5, 33.4, 32.5, 31.9, 29.1, 27.41, 27.35, 18.6, 8.5, 8.3; LCMS (APCI) $m/z$ 539.7 $(M + H)^+$. The free base (37.7 mg, 0.07 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M in diethyl ether, 84 $\mu$L, 1.2 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (39.9 mg, 94%): mp 150−152 °C; $[\alpha]^{20}_D$ +31.9° ($c$ 1.03, $CH_2Cl_2$). Anal. ($C_{36}H_{47}ClN_2O_2 \cdot 1.75H_2O$) C, H, N.

**(+)-(2*R*)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-2-phenylpropanamide (13f).** A 50 mL round-bottom flask was charged with amine **12** (77.9 mg, 0.214 mmol) and (*R*)-2-phenylpropanoic acid (36.4 mg, 0.235 mmol), and the mixture was dissolved in dry THF (20 mL), followed by the addition of triethylamine (66 $\mu$L, 0.47 mmol) and BOP reagent (103.9 mg, 0.235 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 2.5 h. The mixture was diluted with diethyl ether (20 mL), washed consecutively with water (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by silica gel chromatography using an ISCO chromatography system [0−50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as a white foam (68 mg, 64%): $^1$H NMR ($CDCl_3$) $\delta$ 7.30−7.07 (m, 11H), 6.66−6.60 (m, 3H), 5.05 (d, 1H, $J$ = 6.0 Hz), 4.62 (m, 1H), 3.49 (q, 1H, $J$ = 7.2 Hz), 3.15 (br, 1H), 2.99 (dd, 1H, $J$ = 12.3, 4.8 Hz), 2.69−2.48 (m, 5H), 2.32−2.04 (m, 4H), 1.78−1.72 (m, 2H), 1.49 (d, 4H, $J$ = 6.9 Hz), 0.85 (m, 2H), 0.66 (d, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.2, 156.9, 151.5, 142.5, 141.1, 129.6, 129.2, 128.7, 128.4, 127.8, 127.6, 125.9, 116.7, 113.2, 112.7, 55.9, 54.4, 53.4, 47.4, 46.8, 45.2, 40.4, 37.5, 33.6, 32.6, 32.0, 29.2, 18.8; LCMS (APCI) $m/z$ 498.0 $(M + H)^+$. The free base (68 mg, 0.137 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M in diethyl ether, 164 $\mu$L, 1.2 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (75 mg, 99.9%): mp 162−165 °C; $[\alpha]^{20}_D$ +43.9° ($c$ 0.84, MeOH). Anal. ($C_{33}H_{41}ClN_2O_2 \cdot 0.75H_2O$) C, H, N.

**(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-1-(4-methoxyphenyl)-1-cyclopentanecarboxamide (14a).** A 50 mL round-bottom flask was charged with amine **12** (53.8 mg, 0.148 mmol) and 1-(4-methoxyphenyl)-1-cyclopentanecarboxylic acid (38.0 mg, 0.164 mmol), and the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (45 $\mu$L, 0.326 mmol) and BOP reagent (73.8 mg, 0.162 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 2.5 h. The mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by preparative TLC [silica gel, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound (82 mg, 98%) as a white foam: $^1$H NMR ($CDCl_3$) $\delta$ 7.31−7.08 (m, 8H), 6.83−6.80 (m, 2H), 6.68−6.63 (m, 3H), 4.81−4.79 (m, 1H), 4.58 (m, 1H), 3.76 (s, 3H), 3.14 (br, 1H), 3.01 (dd, 1H, $J$ = 12.0, 4.5 Hz), 2.70−1.52 (m, 21H), 0.90 (t, 1H, $J$ = 12.3 Hz), 0.731 (m, 1H), 0.67 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 176.7, 158.4, 156.7, 151.4, 142.3, 135.7, 129.3, 128.5, 128.2, 128.0, 125.6, 116.5, 114.1, 112.9, 112.5, 58.4, 55.6, 55.2, 54.2, 53.3, 46.6, 45.0, 40.2, 37.4, 37.15, 37.11, 36.9, 33.4, 32.5, 31.7, 29.0, 24.0, 18.6; MS (APCI) $m/z$ 567.6 $(M + H)^+$. The free base was dissolved in $CH_2Cl_2$, and to this was added HCl (1 M in diethyl ether, 160 $\mu$L, 1.1 equiv). The solvent was removed under reduced pressure to yield an off-white solid. This product was purified by dissolving in $CH_2Cl_2$, then precipitated from the solution by adding diethyl ether, filtered, and dried in the vacuum oven at 50 °C overnight: mp 142.5−144.5 °C; $[\alpha]^{20}_D$ +24.5° ($c$ 0.84, $CHCl_3$). Anal. ($C_{37}H_{47}ClN_2O_3 \cdot 1.25H_2O$) C, H, N.

**(+)-1-(4-Fluorophenyl)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-1-cyclopentanecarboxamide (14b).** A 50 mL round-bottom flask was charged with amine **12** (62.5 mg, 0.171 mmol) and 1-(4-fluorophenyl)-1-cyclopentanecarboxylic acid (40.7 mg, 0.192 mmol), and the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (52 $\mu$L, 0.376 mmol) and BOP reagent (85.8 mg, 0.188 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 2.5 h. The mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by preparative TLC [silica gel, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound (88.3 mg, 93%) as a white foam: $^1$H NMR ($CDCl_3$) $\delta$ 7.36−6.86 (m, 10H), 6.68−6.62 (m, 3H), 4.81 (m, 1H), 4.59 (m, 1H), 3.15 (br, 1H), 2.98 (m, 1H), 2.71−2.30 (m, 10H), 2.08−1.49 (m, 11H), 0.93 (t, 2H, $J$ = 12.0 Hz), 0.75 (t, 1H, $J$ = 12.0 Hz), 0.67 (d, 3H, $J$ = 6.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.9, 161.6 (d, $J_{CF}$ = 246.0 Hz), 156.7, 151.2, 142.2, 139.5, 129.3, 128.4, 128.3, 128.2, 125.6, 116.6, 115.5 (d, $J_{CF}$ = 21.1 Hz), 112.9, 112.5, 58.6, 55.6, 54.2, 53.2, 46.5, 45.1, 40.1, 37.3, 37.04, 36.99, 33.3, 32.3, 31.6, 28.9, 23.84, 23.81, 18.6; MS (APCI) $m/z$ 556.0 $(M + H)^+$. The free base was dissolved in $CH_2Cl_2$, and to this was added HCl (1 M in diethyl

ether, 175 μL, 1.1 equiv). The solvent was removed under reduced pressure to yield an off-white solid. This product was purified by dissolving in $CH_2Cl_2$, then precipitated from the solution by adding diethyl ether, filtered, and dried in the vacuum oven at 50 °C overnight: mp 148−152 °C; $[\alpha]^{20}_D$ +25.1° (*c* 0.75, $CHCl_3$). Anal. ($C_{36}H_{44}ClFN_2O_2 \cdot 1.25H_2O$) C, H, N.

**(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-1-(1-naphthyl)cyclopentanecarboxamide (14c).** A 50 mL round-bottom flask was charged with amine **12** (34.1 mg, 0.0933 mmol) and 1-(1-naphthyl)-cyclopentanecarboxylic acid (24.3 mg, 0.103 mmol), and the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (29 μL, 0.206 mmol) and BOP reagent (45.4 mg, 0.103 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 3 h. The mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by preparative TLC [silica gel plate, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as a white solid (45 mg, 82%): $^1$H NMR ($CDCl_3$) δ 7.93−7.90 (m, 1H), 7.81−7.78 (m, 1H), 7.73 (d, 1H, *J* = 8.1 Hz), 7.48−7.35 (m, 4H), 2.27−2.22 (m, 2H), 7.16 (m, 3H), 7.07 (m, 1H), 6.63−6.56 (m, 3H), 6.02 (br, 1H), 4.63−4.58 (m, 2H), 2.97 (m, 2H), 2.73−2.45 (m, 7H), 2.27−2.10 (m, 6H), 1.87 (m, 2H), 1.74−1.58 (m, 4H), 1.31 (d, 1H, *J* = 12.1 Hz), 0.64 (d, 4H, *J* = 6.75 Hz), 0.38 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 177.4, 156.1, 151.4, 142.4, 139.7, 134.6, 131.5, 129.3, 129.0, 128.9, 128.5, 128.2, 126.0, 125.8, 125.7, 125.6, 124.9, 123.6, 117.0, 112.7, 112.3, 58.4, 55.4, 54.1, 53.3, 46.3, 45.0, 40.1, 38.0, 37.5, 37.4, 33.3, 32.4, 31.4, 29.2, 25.0, 24.8, 18.5; LCMS (APCI) *m*/*z* 587.4 (M + H)$^+$. The free base (45 mg, 0.0767 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M in diethyl ether, 84 μL, 1.1 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (47.1 mg, 99%): mp 159−161 °C; $[\alpha]^{20}_D$ +18.7° (*c* 0.98, $CHCl_3$). Anal. ($C_{40}H_{47}ClN_2O_2 \cdot 1.5H_2O$) C, H, N.

**(−)-*N*-(1*S*,4*R*,5*R*,7*S*)-{5-(3-Hydroxy)phenyl-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl}-1-(naphthalen-2-yl)-cyclopentanecarboxamide (14d).** A 50 mL round-bottom flask was charged with amine **12** (39.1 mg, 0.107 mmol) and 1-(naphthalen-2-yl)cyclopentanecarboxylic acid (28.3 mg, 0.118 mmol), and the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (35 μL, 0.236 mmol) and BOP reagent (54 mg, 0.118 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 3 h. The mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified twice by preparative TLC [silica gel plate, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$ and silica gel plate hexanes−acetone−triethylamine, 65:33:2] to afford the title compound as a white solid (40.0 mg, 64%): $^1$H NMR ($CDCl_3$) δ 7.81−7.76 (m, 3H), 7.72 (s, 1H), 7.50−7.42 (m, 2H), 7.35 (dd, 1H, *J* = 8.7, 1.5 Hz), 7.25−7.22 (m, 2H), 7.17−7.05 (m, 4H), 6.62−6.56 (m, 3H), 4.77−4.74 (m, 1H), 4.60 (m, 1H), 3.07 (br, 1H), 2.98 (m, 1H), 2.67−2.41 (m, 7H), 2.27−2.01 (m, 6H), 1.87−1.68 (m, 6H), 4.41 (d, 1H, *J* = 11.7 Hz), 0.79−0.63 (m, 5H); $^{13}$C NMR ($CDCl_3$) δ 176.0, 156.2, 151.5, 142.4, 141.3, 133.2, 132.3, 129.4, 128.6, 128.5, 128.2, 128.0, 127.6, 126.4, 126.1, 125.9, 125.6, 124.6, 116.8, 112.8, 112.4, 59.3, 55.5, 54.2, 53.3, 46.5, 45.1, 40.2, 37.3, 37.0, 33.4, 32.4, 31.6, 29.2, 24.2, 18.6; LCMS (APCI) *m*/*z* 587.7 (M + H)$^+$. The free base (40 mg, 0.0682 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M in diethyl ether, 75 μL, 1.1 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (41.6 mg, 95%): mp 159−162 °C; $[\alpha]^{20}_D$ −74.3° (*c* 1.09, $CHCl_3$). Anal. ($C_{40}H_{47}ClN_2O_2 \cdot H_2O$) C, H, N.

**(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-1-(2-thienyl)cyclopentanecarboxamide (14e).** A 50 mL round-bottom flask was charged with amine **12** (35.4 mg, 0.0971 mmol) and 1-(2-thienyl)-cyclopentanecarboxylic acid (20.96 mg, 0.107 mmol), and the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (30 μL, 0.214 mmol) and BOP reagent (47.32 mg, 0.107 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 3 h. The mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by preparative TLC [silica gel plate, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as a white foam (42.9 mg, 81%): $^1$H NMR ($CDCl_3$) δ 7.28−7.11 (m, 7H), 6.94−6.89 (m, 2H), 6.68−6.65 (m, 3H), 5.08 (d, 1H, *J* = 7.8 Hz), 4.60 (m, 1H), 3.17 (br, 1H), 3.04 (dd, 1H, *J* = 12, 3.9 Hz), 2.73−2.31 (m, 10H), 2.12−2.06 (m, 3H), 1.84−1.52 (m, 8H), 0.97 (t, 1H, *J* = 12.6 Hz), 0.84−0.76 (m, 1H), 0.70 (d, 3H, *J* = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) δ 175.1, 156.4, 151.3, 148.4, 142.3, 129.4, 128.5, 128.2, 127.1, 125.7, 125.1, 124.8, 116.8, 112.9, 112.4, 56.6, 55.6, 54.2, 53.4, 46.5, 45.1, 40.2, 39.3, 39.2, 37.4, 33.3, 32.4, 31.6, 29.0, 24.3, 18.6; LCMS (APCI) *m*/*z* 543.4 (M + H)$^+$. The free base (42.9 mg, 0.0790 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M in diethyl ether, 87 μL, 1.1 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (45.5 mg, 96%): mp 154.0−156.0 °C; $[\alpha]^{20}_D$ +35.8° (*c* 1.06, $CHCl_3$). Anal. ($C_{34}H_{43}ClN_2O_2S \cdot H_2O$) C, H, N.

**(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-1-(3-thienyl)cyclopentanecarboxamide (14f).** A 50 mL round-bottom flask was charged with amine **12** (36.3 mg, 0.0996 mmol) and 1-(3-thienyl)-cyclopentanecarboxylic acid (21.5 mg, 0.109 mmol), and the mixture was dissolved in dry THF (10 mL), followed by the addition of triethylamine (30 μL, 0.214 mmol) and BOP reagent (48.8 mg, 0.110 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 3 h. The mixture was diluted with diethyl ether (10 mL), washed consecutively with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by preparative TLC [silica gel plate, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as an off-white solid (42 mg, 78%): $^1$H NMR ($CDCl_3$) δ 7.29−7.23 (m, 3H), 7.17−7.12 (m, 4H), 7.06 (m, 1H), 6.92 (dd, 1H, *J* = 4.8, 0.9 Hz), 6.66 (m, 3H), 4.88 (d, 1H, *J* = 7.8 Hz), 4.61 (m, 1H), 3.14 (br, 1H), 3.28 (dd, 1H, *J* = 12.0, 3.9 Hz), 2.71−2.51 (m, 5H), 2.43−2.24 (m, 5H), 2.14 (m, 1H), 2.02−1.97 (m, 2H), 1.80−1.76 (m, 4H), 1.67−1.51 (m, 3H), 0.95 (t, 1H, *J* = 12.6 Hz), 0.76 (t, 1H, *J* = 12 Hz), 0.69 (d, 3H, *J* = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) δ 175.7, 156.3, 151.5, 145.0, 142.4, 129.4, 128.5, 128.4, 128.2, 127.2, 126.7, 125.6, 120.9, 112.9, 112.4, 56.4, 55.5, 54.2, 53.4, 46.6, 45.0, 40.2, 37.6, 37.5, 37.4, 33.3, 32.5, 31.8, 29.1, 24.3, 18.6; LCMS (APCI) *m*/*z* 543.4 (M + H)$^+$. The free base (42 mg, 0.0774 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M in diethyl ether, 85 μL, 1.1 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (46.0 mg, 99%): mp 151.0−153.0 °C; $[\alpha]^{20}_D$ +26.2° (*c* 0.97, $CHCl_3$). Anal. ($C_{34}H_{43}ClN_2O_2 \cdot 1.25H_2O$) C, H, N.

***tert*-Butyl (1*S*,4*R*,5*R*,7*S*)-7-Amino-5-(3-isopropoxyphenyl)-4-methyl-2-azabicyclo[3.3.1]nonane-2-carboxylate (15).** Triethylamine (5.25 mL, 37.7 mmol) and di-*tert*-butyl dicarbonate (8.48 g, 0.038 mol) were added to a solution of **9** (7.88 g, 0.019 mol) in dichloromethane (250 mL). The reaction mixture was stirred at room temperature for an hour. TLC showed complete consumption of the starting material. Removal of the solvent under reduced pressure afforded a solid crude product. This material was dissolved in diethyl ether, and the insoluble solid was filtered and washed several

times with diethyl ether. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography using an ISCO chromatography system (silica gel, 0−50% ethyl acetate in hexanes) to give **15** as a white solid (7.92 g, 81%). Rotamers of this compound were observed in the $^1$H and $^{13}$C NMR spectra: $^1$H NMR ($CDCl_3$) $\delta$ 7.85−7.78 (m, 2H), 7.70−7.67 (m, 2H), 7.19 (t, 1H, $J$ = 7.8 Hz), 6.80−6.69 (m, 3H), 5.07 (m, 1H), 4.74−4.48 (m, 2H), 3.84−3.59 (m, 2H), 2.52 (ddd, 1H, $J_1 = J_2$ = 12.9 Hz, $J_3$ = 3.6 Hz), 2.43−2.24 (m, 4H), 2.11−2.02 (m, 1H), 1.89 (m, 1H), 1.48 (d, 9H, $J$ = 2.7 Hz), 1.32 (d, 6H, $J$ = 6.0 Hz), 0.63 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.6, 158.3, 156.0, 150.4/150.2, 134.3, 132.3, 129.5, 123.5, 117.9, 114.4/114.2, 113.1, 80.0, 70.2, 48.8/48.6, 47.8/47.5, 46.0/45.8, 42.4, 40.6/40.3, 37.5/37.2, 33.3/32.8, 31.2/30.7, 28.9, 22.5, 18.2/17.9.

Hydrazine (2.9 mL, 91.2 mmol) was added to a solution of the phthalimide (9.46 g, 0.018 mol) in ethanol (500 mL), and the reaction mixture was refluxed under $N_2$ for 2.5 h. The reaction mixture was cooled to room temperature, and TLC [silica gel, 25% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] showed complete consumption of compound **9**. Removal of the solvent under reduced pressure yielded a white solid residue, which was dissolved in $CH_2Cl_2$ (150 mL). The heterogeneous solution was filtered through a fritted funnel, and the solid was washed several times with $CH_2Cl_2$. The filtrate was concentrated under reduced pressure, and the residue was dried on vacuum pump to afford the title compound (6.94 g, 98%) as a white foam. Rotamers of this compound were observed in the $^1$H and $^{13}$C NMR spectra: $^1$H NMR ($CDCl_3$) $\delta$ 7.21 (t, 1H, $J$ = 7.8 Hz), 6.80−6.71 (m, 3H), 4.60−4.41 (m, 2H), 3.59−3.43 (m, 3H), 2.44−2.12 (m, 4H), 1.63−1.42 (m, 11H), 1.33 (d, 6H, $J$ = 6.0 Hz), 1.26−1.12 (m, 3H), 0.60 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.2, 155.9, 150.8/150.6, 129.4, 117.7, 114.1, 112.9, 79.7, 70.0, 50.3/50.1, 48.6/48.4, 47.8/47.3, 46.4/46.0, 41.0, 40.6/40.4, 37.2/37.0, 31.5/31.2, 28.7, 22.3, 18.1/18.0.

***N*-[(1*S*,4*R*,5*S*,7*S*)-5-(3-Isopropoxyphenyl)-4-methyl-2-azabicyclo-[3.3.1]non-7-yl]-2-methyl-2-phenylpropanamide (16).** A 500 mL round-bottom flask was charged with amine **15** (2.02 g, 0.052 mol) and 2-methyl-2-phenylpropionic acid (1.73 g, 0.01 mol) followed by dry THF (130 mL), triethylamine (3.60 mL, 26.0 mmol), and BOP reagent (2.60 g, 0.0057 mol). The reaction mixture was stirred under $N_2$ at room temperature for 4 h. TLC showed that the starting material was consumed completely. The mixture was diluted with diethyl ether (130 mL), washed consecutively with water (150 mL), saturated $NaHCO_3$ (150 mL), and brine (150 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by Combi Flash chromatography (silica gel, 10−25% ethyl acetate in hexanes) to afford the title compound (2.60 g, 93%) as a white foam. Rotamers in $^1$H and $^{13}$C NMR spectra were observed: $^1$H NMR ($CDCl_3$) $\delta$ 7.36−7.17 (m, 6H), 6.72−6.64 (m, 3H), 4.76−4.63 (m, 2H), 4.58−4.40 (m, 2H), 3.75−3.57 (m, 2H), 2.47−2.42 (m, 1H), 2.22−2.13 (m, 3H), 1.52 (m, 7H), 1.46 (s, 9H), 1.32 (d, 6H, $J$ = 6.0 Hz), 1.04−0.96 (m, 2H), 0.58 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.1/176.9, 158.2, 155.9/155.5, 150.6/150.5, 145.1, 129.4, 128.9, 127.2, 126.6, 117.6, 113.8, 112.9/112.6, 79.8/79.7, 70.0, 48.4, 47.8/47.4, 47.1/46.8, 46.3, 44.2, 40.3/40.2, 37.4, 36.8/36.7, 31.4/31.0, 28.7, 27.4/27.2, 22.3, 17.8; MS (APCI) $m/z$ 535.7 $(M + H)^+$.

To a solution of the amide (105 mg, 0.196 mmol) in $CH_2Cl_2$ (3 mL) at room temperature was added trifluoroacetic acid (230 $\mu$L, 2.98 mmol). After 1.5 h, TLC [25% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] showed complete consumption of the starting material. The solvent and excess TFA were removed under vacuum, the residue was dissolved in $CH_2Cl_2$ (10 mL) and made basic with saturated $Na_2CO_3$. The organic layer was dried ($Na_2SO_4$) and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, 0−50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to give the title compound as a colorless film (52.4 mg, 62%): $^1$H NMR ($CDCl_3$) $\delta$ 7.31−7.17 (m, 6H), 6.71 (m, 3H), 4.77 (m, 2H), 4.52 (hep, 1H, $J$ = 6.0 Hz), 3.73−3.66 (m, 2H), 2.94 (d, 1H, $J$ = 13.8 Hz), 2.51−2.21 (m, 4H), 1.58−1.51 (m, 7H), 1.32 (d, 6H, $J$ = 6.0 Hz), 1.26−1.16, (m, 1H), 1.05 (m, 1H), 0.74 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.0, 158.3, 150.4, 145.1, 129.6, 128.9, 127.2, 126.6, 117.2, 113.5, 112.7, 70.0, 48.7, 48.0, 47.1, 46.4, 44.8, 40.0, 36.5, 30.4, 27.3, 27.2, 22.3, 22.2, 17.6; MS (APCI) $m/z$ 435.6 $(M + H)^+$.

***N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Isopropoxyphenyl)-4-methyl-2-(2-phenoxyethyl)-2-azabicyclo[3.3.1]non-7-yl]-2-methyl-2-phenylpropanamide (17).** To a solution of amine **16** (125 mg, 0.288 mmol) in THF (anhydrous, 3 mL) was added $\beta$-bromophenetole (57.6 mg, 0.288 mmol), triethylamine (48 $\mu$L, 0.346 mmol), and tetrabutylammonium iodide (106 mg, 0.288 mmol). The reaction mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with $CH_2Cl_2$ (10 mL), washed with 1 N HCl and water, and dried over $NaSO_4$. This solution was concentrated under vacuum, and the residue was purified by flash chromatography [silica gel, 0−50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound as a yellow oil (81 mg, 51%) and the starting material (56 mg): $^1$H NMR ($CDCl_3$) $\delta$ 7.32−7.17 (m, 8H), 6.97−6.89 (m, 3H), 6.70 (m, 3H), 4.76−4.62 (m, 2H), 4.52 (hep, 1H, $J$ = 6.0 Hz), 4.22 (br, 2H), 3.40 (br, 1H), 3.31 (dd, 1H, $J$ = 12.6, 4.8 Hz), 3.08 (m, 2H), 2.92 (d, 1H, $J$ = 12.0 Hz), 2.34 (m, 2H), 2.40−2.34 (m, 1H), 2.22 (pet, 1H, $J$ = 6.0 Hz), 1.60 (m, 1H), 1.54 (d, 6H, $J$ = 3.6 Hz), 1.32 (d, 6H, $J$ = 6.0 Hz), 1.06−0.88 (m, 2H), 0.76 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.1, 158.8, 158.2, 150.7, 145.1, 129.7, 129.5, 128.9, 127.2, 126.6, 121.1, 117.2, 114.9, 113.7, 70.0, 66.2, 56.5, 55.0, 54.6, 47.1, 46.5, 44.8, 40.0, 37.5, 32.2, 27.4, 27.2, 22.3, 18.9; LCMS (APCI) $m/z$ 555.8 $(M + H)^+$.

**(+)-*N*-[(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-(2-phenoxyethyl)-2-azabicyclo[3.3.1]non-7-yl]-2-methyl-2-phenylpropanamide (18).** A solution of compound **17** (81 mg, 0.146 mmol) in $CH_2Cl_2$ (anhydrous, 20 mL) at −78 °C was treated with $BBr_3$ (1 M solution in $CH_2Cl_2$, 1.5 mL). After 30 min, the reaction mixture was warmed to room temperature and was kept stirring for an additional 2 h. The reaction mixture was cooled to 0 °C, and the reaction was quenched with saturated $NaHCO_3$ (25 mL). The aqueous layer was separated and extracted with $CH_2Cl_2$ (10 mL × 2). The combined organic layers were washed with water (30 mL × 2), dried over $NaSO_4$, and concentrated under vacuum. The residue was purified by preparative TLC [silica gel plate, 25% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to give the title compound as a white solid (44.4 mg, 59%): $^1$H NMR ($CDCl_3$) $\delta$ 7.32−7.23 (m, 7H), 7.12 (t, 1H, $J$ = 7.8 Hz), 6.93−6.85 (m, 3H), 6.68−6.65 (m, 3H), 4.78−4.66 (m, 2H), 4.06 (t, 2H, $J$ = 5.4 Hz), 3.22−3.17 (m, 2H), 3.03−2.86 (m, 2H), 2.75 (d, 1H, $J$ = 12.3 Hz), 2.42−2.30 (m, 3H), 2.14 (m, 1H), 1.54 (d, 7H, $J$ = 6.9 Hz), 0.97−0.76 (m, 2H), 0.67 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.4, 159.0, 156.6, 151.5, 145.1, 129.6, 129.0, 127.4, 126.6, 120.9, 117.0, 114.9, 113.2, 112.6, 66.7, 56.5, 54.4, 54.3, 47.1, 46.7, 45.2, 40.1, 37.6, 32.6, 32.3, 27.4, 27.2, 18.7; LCMS (APCI) $m/z$ 513.6 $(M + H)^+$. The free base (44.4 mg, 0.0866 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M in diethyl ether, 104 $\mu$L, 1.2 equiv). The solvent was removed under reduced pressure, and the product was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white solid (41.4 mg, 84%): mp 147−150 °C; $[\alpha]^{20}_D$ + 37.1° (*c* 0.84, MeOH). Anal. ($C_{33}H_{41}ClN_2O_3 \cdot H_2O$) C, H, N.

***tert*-Butyl (1*S*,4*R*,5*R*,7*S*)-5-(3-Isopropoxyphenyl)-4-methyl-7-{[(1-phenyl-1-cyclopentyl)carbonyl]amino}-2-azabicyclo[3.3.1]-nonane-2-carboxylate (19a).** A 100 mL round-bottom flask was charged with amine **15** (459 mg, 1.18 mmol) and 1-phenyl-1-cyclopentanecarboxylic acid (449 mg, 2.36 mmol), and the mixture was dissolved in dry THF (30 mL), followed by the addition of triethylamine (0.82 mL, 5.9 mmol) and BOP reagent (574 mg, 1.3 mmol). The reaction mixture was stirred under $N_2$ at room temperature for 4 h. The mixture was diluted with diethyl ether (50 mL), washed consecutively with water (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by flash chromatography (silica gel, 20% ethyl acetate in hexanes) to afford the title compound (0.606 g, 92%) as a white

foam. Rotamers of this compound were observed in the $^1$H and $^{13}$C NMR spectra: $^1$H NMR ($CDCl_3$) $\delta$ 7.34−7.14 (m, 6H), 6.72−6.63 (m, 3H), 4.77−4.39 (m, 4H), 3.73−3.57 (m, 2H), 2.43−1.45 (m, 22H), 1.32 (d, 6H, $J$ = 6.0 Hz), 0.97 (t, 2H, $J$ = 12.5 Hz), 0.57 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 176.0/175.8, 157.9, 155.6/155.3, 150.4, 144.1/144.0, 129.2, 128.7, 126.9, 126.8, 117.4, 113.6, 112.7/112.4, 79.6/79.4, 69.8, 59.1, 48.2, 47.6/47.1, 46.5/46.0, 44.0, 40.1/39.9, 37.2, 37.0/36.9, 36.7/36.6, 36.5, 31.1, 30.8, 28.4, 24.1, 22.0, 17.6.

***tert*-Butyl (1*S*,4*R*,5*R*,7*S*)-5-(3-Isopropoxyphenyl)-4-methyl-7-[(2-methyl-2-phenylpropanoyl)amino]-2-azabicyclo[3.3.1]nonane-2-carboxylate (19b).** A 500 mL round-bottom flask was charged with **15** (2.02 g, 0.0052 mol) and 2-methyl-2-phenylpropionic acid (1.73 g, 0.01 mol), and the mixture was dissolved in dry THF (130 mL), followed by the addition of triethylamine (3.60 mL, 26.0 mmol) and BOP reagent (2.60 g, 0.0057 mol). The reaction mixture was stirred under $N_2$ at room temperature for 4 h. TLC showed that the starting material was completely consumed. The mixture was diluted with diethyl ether (130 mL), washed consecutively with water (150 mL), saturated $NaHCO_3$ (150 mL), and brine (150 mL × 2), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the product was purified by flash chromatography (silica gel, 10−25% ethyl acetate in hexanes) to afford the title compound (2.60 g, 93%) as a white foam. Rotamers of this compound were observed in the $^1$H and $^{13}$C NMR spectra: $^1$H NMR ($CDCl_3$) $\delta$ 7.36−7.17 (m, 6H), 6.72−6.64 (m, 3H), 4.76−4.63 (m, 2H), 4.58−4.40 (m, 2H), 3.75−3.57 (m, 2H), 2.47−2.42 (m, 1H), 2.22−2.13 (m, 3H), 1.52 (m, 7H), 1.46 (s, 9H), 1.32 (d, 6H, $J$ = 6.0 Hz), 1.04−0.96 (m, 2H), 0.58 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.1/176.9, 158.2, 155.9/155.5, 150.6/150.5, 145.1, 129.4, 128.9, 127.2, 126.6, 117.6, 113.8, 112.9/112.6, 79.8/79.7, 70.0, 48.4, 47.8/47.4, 47.1/46.8, 46.3, 44.2, 40.3/40.2, 37.4, 36.8/36.7, 31.4/31.0, 28.7, 27.4/27.2, 22.3, 17.8; MS (APCI) *m*/*z* 535.7 $(M + H)^+$.

***N*-[(1*S*,4*R*,5*S*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-azabicyclo-[3.3.1]non-7-yl]-1-phenyl-1-cyclopentanecarboxamide (20a).** A solution of amide **19a** (231 mg, 0.412 mmol) in glacial acetic acid (4 mL) and 48% HBr (4 mL) was heated to reflux for 15 h. The reaction mixture was allowed to cool to room temperature, and ice (10 g) was added. The pH of the reaction mixture was adjusted to 14 with 50% NaOH. The aqueous layer was extracted with 3:1 $CH_2Cl_2$−THF (30 mL × 3). The organic layer was collected and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The product was purified by flash chromatography [silica gel, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound (0.126 g, 73%) as a white solid: $^1$H NMR ($CD_3OD$) $\delta$ 7.38−7.06 (m, 6H), 6.62−6.57 (m, 3H), 4.79 (m, 1H), 3.60 (dd, 1H, $J$ = 9.0 Hz, 5.1 Hz), 3.31 (m, 1H), 2.72 (d, 1H, $J$ = 14.1 Hz), 2.49−2.40 (m, 2H), 2.25−1.87 (m, 6H), 1.70−1.56 (m, 5H), 1.48−1.40 (m, 1H), 1.28−1.15 (m, 2H), 0.64 (d, 3H, $J$ = 7.2 Hz); $^{13}$C NMR ($CD_3OD$) $\delta$ 177.9, 158.6, 152.7, 145.4, 130.3, 129.4, 127.6, 127.6, 117.0, 113.8, 113.0, 60.7, 49.6, 46.9, 46.3, 41.0, 38.1, 37.9, 37.3, 37.2, 32.0, 24.39, 24.37, 17.6; MS (APCI) *m*/*z* 419.7 $(M + H)^+$.

***N*-[(1*S*,4*R*,5*S*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-azabicyclo-[3.3.1]non-7-yl]-2-methyl-2-phenylpropanamide (20b).** A solution of amide **19b** (530 mg, 0.991 mmol) in glacial acetic acid (9 mL) and 48% HBr (9 mL) was heated to reflux for 17.5 h. The reaction mixture was allowed to cool to room temperature, and ice (25 g) was added. The pH of the reaction mixture was adjusted to 14 with 50% NaOH. The aqueous layer was extracted with 3:1 $CH_2Cl_2$−THF (50 mL × 3). The organic layer was collected and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The product was purified by flash chromatography [silica gel, 50% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound (0.164 g, 42%) as a white solid. The $^1$H NMR and $^{13}$C NMR spectra showed several small peaks, indicating pyridine impurities: $^1$H NMR ($C_5D_5N$) $\delta$ 7.53−7.48 (m, 2H), 7.33−7.28 (m, 3H), 7.24−7.22 (m, 1H), 7.10−7.05 (m, 2H), 6.79 (m, 1H), 6.69 (d, 1H, $J$ = 8.1 Hz), 5.43−5.28 (m, 1H), 3.78 (dd, 1H, $J$ = 13.5, 4.8 Hz), 3.34 (br, 1H), 2.72−2.62 (m, 2H), 2.36−2.30 (m, 1H), 2.18 (d, 1H, $J$ = 12.0 Hz), 2.09 (m, 1H), 1.70 (d, 7H), 1.48−1.39 (m, 4H), 0.79 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($C_5D_5N$) $\delta$ 176.7, 159.6, 153.4, 147.5, 130.3, 129.3, 127.3, 127.2, 116.8, 113.9, 113.8, 50.0, 49.4, 47.62, 47.58, 46.2, 41.4, 40.1, 38.2, 32.6, 28.5, 27.8, 18.0.

**(+)-*N*-{(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-[3-(2-methylphenyl)prop-2-en-1-yl]-2-azabicyclo[3.3.1]non-7-yl}-1-phenylcyclopentanecarboxamide (21a).** Amine **20a** (126 mg, 0.301 mmol) was suspended in DCE (15 mL) under $N_2$. Then *trans*-2-methylcinnamaldehyde (46 mg, 0.301 mmol) and sodium triacetoxyborohydride (82.9 mg, 0.391 mmol) were added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 days and became a clear solution. The reaction mixture was transferred to a separatory funnel and washed with saturated $NaHCO_3$. The aqueous layer was extracted with 3:1 $CH_2Cl_2$−THF (15 mL × 2). The combined organic layers were dried ($MgSO_4$) and concentrated to give a solid crude product. The crude product was purified by preparative TLC [silica gel plate, 35% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound (0.126 g, 76%) as a white solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.38−7.07 (m, 10H), 6.76 (d, 1H, $J$ = 15.9 Hz), 6.66−6.60 (m, 3H), 6.14−6.04 (m, 1H), 4.79−4.63 (m, 2H), 3.35−2.24 (m, 3H), 3.08−3.03 (m, 1H), 2.75 (d, 1H, $J$ = 12.3 Hz), 2.52−2.22 (m, 8H), 2.10−1.95 (m, 3H), 1.83−1.65 (m, 4H), 1.50−1.46 (m, 1H), 0.87−0.64 (m, 5H). $^{13}$C NMR ($CDCl_3$) $\delta$ 176.8, 157.1, 151.5, 144.3, 136.5, 135.7, 130.6, 129.8, 129.2, 127.7, 127.4, 127.2, 126.4, 126.2, 126.1, 117.1, 113.4, 112.9, 59.6, 58.4, 56.4, 53.6, 46.8, 45.4, 40.5, 37.8, 37.42, 37.38, 32.8, 31.9, 24.5, 24.4, 20.2, 19.0; MS (APCI) *m*/*z* 549.7 $(M + H)^+$. The free base (126 mg, 0.230 mmol) was dissolved in $CH_2Cl_2$ (8 mL), and to this was added HCl (1 M solution in diethyl ether, 255 $\mu$L, 0.255 mmol). The reaction mixture was stirred for 15 min, and the solvent was removed under vacuum. The salt was purified twice by adding diethyl ether (8 mL) to its $CH_2Cl_2$ (3 mL) solution. The precipitate was filtered and dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as a white powder (98.5 mg, yield 73%): mp 168.5−170.5 °C; $[\alpha]^{20}_D$ +25.6° (*c* 1.04, $CHCl_3$). Anal. ($C_{37}H_{45}ClN_2O_2 \cdot H_2O$) C, H, N.

**(+)-*N*-{(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-[3-(2-methylphenyl)prop-2-en-1-yl]-2-azabicyclo[3.3.1]non-7-yl}-2-methyl-2-phenylpropanamide (21b).** Amine **20b** (50 mg, 0.127 mmol) was suspended in DCE (5 mL) under $N_2$, and then *trans*-2-methylcinnamaldehyde (18.6 mg, 0.127 mmol) and sodium triacetoxyborohydride (41 mg, 0.19 mmol) were added to the reaction mixture. The reaction mixture was stirred at room temperature for 3 h, when it became a clear solution. The reaction mixture was diluted with $CH_2Cl_2$ and washed with saturated $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$ (10 mL × 2). The combined organic layers were dried ($Na_2SO_4$) and concentrated under vacuum. The residue was purified by preparative TLC [silica gel plate, 33% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound (52 mg, 78%) as a white solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.40−7.08 (m, 10H), 6.78 (d, 1H, $J$ = 15.9 Hz), 6.64 (m, 3H), 6.11 (dt, 1H, $J$ = 15.6, 6.3 Hz), 4.78−4.68 (m, 2H), 4.78−4.68 (m, 2H), 3.36 (m, 2H), 3.27 (br, 1H), 3.08 (m, 1H), 2.78 (d, 1H, $J$ = 12.0 Hz), 2.43−2.43 (m, 6H), 2.14 (m, 1H), 1.59−1.50 (m, 8H), 0.91 (t, 1H, $J$ = 12.0 Hz), 0.78 (t, 1H, $J$ = 12.0 Hz), 0.68 (d, 3H, $J$ = 6.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.4, 156.7, 151.4, 145.1, 136.4, 135.5, 130.4, 129.7, 129.0, 128.8, 127.5, 127.3, 126.6, 126.3, 125.9, 117.0, 113.7, 113.1, 112.6, 58.2, 56.2, 53.5, 47.2, 46.8, 45.2, 40.4, 37.7, 32.7, 31.8, 27.4, 27.3, 20.1, 18.8; MS (APCI) *m*/*z* 523.4 $(M + H)^+$. The free base (42 mg, 0.080 mmol) was dissolved in $CH_2Cl_2$ (3 mL), and to this was added HCl (1 M solution in diethyl ether, 96 $\mu$L, 0.096 mmol). The reaction mixture was stirred for 15 min, and the solvent was removed under vacuum. The residue was dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as an off-white powder (40.1 mg, yield 87%): mp 148.5−151.5 °C; $[\alpha]^{20}_D$ +27.8° (*c* 0.74, MeOH). Anal. ($C_{35}H_{43}ClN_2O_2 \cdot H_2O$) C, H, N.

**(+)-*N*-{(1*S*,4*R*,5*R*,7*S*)-5-(3-Hydroxyphenyl)-4-methyl-2-[3-phenylprop-2-en-1-yl]-2-azabicyclo[3.3.1]non-7-yl}-2-methyl-2-phenylpropanamide (21c).** Amine **20b** (51.8 mg, 0.132 mmol) was suspended in DCE (5 mL) under $N_2$, and then cinnamaldehyde (17 $\mu$L, 0.132 mmol) and sodium triacetoxyborohydride (42 mg, 0.198 mmol) were added to the reaction mixture. The reaction mixture was stirred at room temperature overnight and became a clear solution. The reaction mixture was diluted with $CH_2Cl_2$ and washed with saturated $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$ (10 mL × 2). The combined organic layers were dried ($Na_2SO_4$) and concentrated under vacuum. The residue was purified by preparative TLC [silica gel plate, 25% (80% $CHCl_3$, 18% $CH_3OH$, 2% $NH_4OH$) in $CHCl_3$] to afford the title compound (60.2 mg, 90%) as a white solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.33−7.06 9m, 11H), 6.66−6.51 (m, 4H), 6.20 (dt, 1H, $J$ = 8.7, 6.6 Hz), 4.78−4.65 (m, 2H), 3.34−3.30 (m, 2h), 3.23 (br, 1H), 3.07 (dd, 1H), $J$ = 12.3, 4.8 Hz), 2.74 (d, 1H, $J$ = 12.6 Hz), 2.40−2.10 (m, 4H), 1.57−1.45 (m, 7H), 0.83−0.62 (d, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.5, 156.8, 151.4, 145.0, 137.2, 132.6, 129.6, 129.0, 128.8, 128.4, 127.6, 127.3, 126.62, 126.55, 116.8, 113.2, 112.7, 57.9, 56.4, 53.1, 47.2, 46.7, 45.2, 40.3, 37.6, 32.6, 31.7, 27.4, 27.3, 18.8; MS (APCI) $m/z$ 509.6 $(M + H)^+$. The free base (60.2 mg, 0.118 mmol) was dissolved in $CH_2Cl_2$ (4 mL), and to this was added HCl (1 M solution in diethyl ether, 142 $\mu$L, 0.142 mmol). The reaction mixture was stirred for 15 min, and the solvent was removed under vacuum. The salt was purified twice by adding diethyl ether (8 mL) to its MeOH (3 mL) solution. The precipitate was filtered and dried in the vacuum oven at 50 °C overnight to afford the hydrochloride salt of the title compound as a white powder (52.2 mg, yield 78%): mp 152.5−155 °C; $[\alpha]^{20}_D$ +28.8° (*c* 0.82, MeOH). Anal. ($C_{34}H_{41}ClN_2O_2 \cdot 1.25H_2O$).

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

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