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Modulation of Opioid Receptor Affinity and Efficacy via N-Substitution of 9 β -Hydroxy-5-(3-hydroxyphenyl)morphan: Synthesis and Computer Simulation Study

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Abstract

The enantiomers of a variety of N-alkyl-, N-aralkyl-, and N-cyclopropylalkyl-9 β -hydroxy-5-(3-hydroxyphenyl)morphans were synthesized employing cyanogen bromide and K₂CO₃ to improve the original N-demethylation procedure. Their binding affinity to the μ -, δ -, and κ -opioid receptors (ORs) was determined and functional (GTP γ ³⁵S) assays were carried out on those with reasonable affinity. The 1*R*,5*R*,9*S*-enantiomers (1*R*,5*R*,9*S*)-(-)-5-(3-hydroxyphenyl)-2-(4-nitrophenethyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-**16**), (1*R*,5*R*,9*S*)-(-)-2-cinnamyl-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-**20**), and (1*R*,5*R*,9*S*)-(-)-5-(3-hydroxyphenyl)-2-(4-(trifluoromethyl)phenethyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-**15**), had high affinity for

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A. Supplementary data

¹H and ¹³C NMRs of novel compounds, X-ray crystallographic data, molecular modeling and simulations.

the μ -opioid receptor (e.g., **1R,5R,9S-16**: $K_i = 0.073, 0.74$, and 1.99 nM, respectively). The **1R,5R,9S-16** and **1R,5R,9S-15** were full, high efficacy μ -agonists ($EC_{50} = 0.74$ and 18.5 nM, respectively) and the former was found to be a partial agonist at δ -OR and an antagonist at κ -OR, while the latter was a partial agonist at δ -OR and κ -OR in the $GTP\gamma^{35}S$ assay. The enantiomer of **1R,5R,9S-16**, (+)-**1S,5S,9R-16** was unusual, it had good affinity for the μ -OR ($K_i = 26.5$ nM) and was an efficacious μ -antagonist ($Ke = 29.1$ nM). Molecular dynamics simulations of the μ -OR were carried out with the **1R,5R,9S-16** μ -agonist and the previously synthesized (1*R*,5*R*,9*S*)-(–)-5-(9-hydroxy-5-(3-hydroxyphenyl-2-phenylethyl)-2-azabicyclo[3.3.1]nonane (1*R*,5*R*,9*S*)-(–)-NIH 11289) to provide a structural basis for the observed high affinities and efficacies. The critical roles of both the 9 β -OH and the *p*-nitro group are elucidated, with the latter forming direct, persistent hydrogen bonds with residues deep in the binding cavity, and the former interacting with specific residues via highly structured water bridges.

Graphical abstract

Keywords

Opioid agonists and antagonists; μ -, δ - and κ -opioid receptors; molecular dynamics simulations for an atomic-level rationale; opioid receptor binding affinity; $GTP\gamma^{35}S$ functional studies

1. Introduction

Opioid ligands are known to interact with G-protein coupled opioid receptors (ORs) in several ways, and those interactions have been noted to occur through different mechanisms. They can exert effects via binding to orthosteric sites producing an unbiased or biased signal, or through biased agonism with β -arrestins. Their effects may be influenced by interaction with an allosteric site that can modulate the orthosteric sites effects.^{1–2} Efforts have been made to synthesize opioids that interact either singly or via orthosteric¹³ and allosteric mechanisms.¹⁴ Bivalent ligands¹⁵ have been synthesized that interact with μ - and κ -ORs¹⁴ that may exist as receptor dimers.¹⁶ Many non-selective opioids interact with two or all three of the main types of ORs by any, or several, of these routes. NOP (nociception/orphanin FQ opioid peptide receptor) activation has been found to exert a modulatory role in μ -OR mediated actions. Moreover, transmembrane conformational changes occur during μ -receptor activation¹⁸ that further complicates our ability to fully characterize the ligand-receptor interaction.

Most of the concepts referred to above are the results of the 21st century re-evaluation of the pharmacology of opioids. The increased complexity has resulted from the evaluation of both old and novel molecules that act as opioids. Explication of the complex ligand - OR interaction can be aided by the synthesis of sets of new ligands interacting with ORs by selective mechanisms. Among our goals is the synthesis of enantiomeric ligands that function as potent antinociceptives or as “pure” opioid antagonists through specific interactions with ORs.

Molecular modification of the N-substituent in the 5-phenylmorphans class of opioids, as well as many of the other classes of opioids, has been found to induce functional changes in the action of ligands, e.g., from agonist to antagonist,¹⁹ as well as modifying their interactions with the μ -, δ -, and κ -ORs. We previously found that a compound with an *N*-phenethyl substituent on a 9 β -OH substituted 5-phenylmorphans (Fig. 1, (1*R*,5*R*,9*S*)-(-)-9-hydroxy-5-(3-hydroxyphenyl)-2-phenylethyl-2-azabicyclo[3.3.1]nonane)) was a high affinity μ -agonist, a moderate affinity δ -agonist, and acted as a potent antinociceptive in mice (ca 470 times more potent than morphine).²⁰ Notably, the 9 β -OH substitution changed the μ -antagonist activity of 5-(3-hydroxyphenyl)-*N*-phenylethylmorphans²¹ to a potent μ -agonist. In a different study,²² we also pointed out that 5-phenylmorphans enantiomers with some restrained N-substituents could act as very potent μ -antagonists while others were inverse agonists. The conformational restraint was introduced by a cyclopropyl ring or through introduction of unsaturation in an N-substituent's alkyl chain.

We have also examined the effect of substituents on the aromatic ring in the *N*-phenethyl sidechain of a 5-phenylmorphans enantiomer²³ and found that the addition of a nitro moiety in the *para* position of the aromatic ring of 5-(3-hydroxyphenyl)-*N*-phenylethylmorphans yielded a compound that had high affinity for the μ -OR, moderate affinity for the δ -OR, and acted as a μ -agonist, δ -antagonist in the [³⁵S]GTP γ S functional assay. The compound was also ca. 50 times more potent than morphine in mice antinociceptive assays. In the present work, we have further modified the *N*-phenethyl substituent of the (1*R*,5*R*,9*S*)-(-)-9-hydroxy-5-(3-hydroxyphenyl)-2-phenylethyl-2-azabicyclo[3.3.1]nonane (NIH 11289) molecular template²⁰ as indicated by Cheng et al.^{25,26} The effect of these modifications were then assessed in both receptor binding assays and functional studies. In addition, molecular dynamics simulations were carried out with 1*R*,5*R*,9*S*-(-)-**16** and NIH 11289 in the binding pocket of the μ -OR (inactive, X-ray crystal structure PDB 4DKL). These simulations were done to provide an atomic-level rationale for transforming the μ -antagonist activity of 5-(3-hydroxyphenyl)-*N*-phenylethylmorphans to potent μ -agonism upon 9 β -OH substitution, as well as a rationale for the enhanced binding affinity and μ -agonist potency upon *p*-NO₂ group substitution.

2. Results and Discussion

2.1 Chemistry

Our strategy to get to the target compounds (Scheme 1) was based on well-known methodology.^{20,24,25}

Starting with the *1S,5S* 9-oxo and the *1R,5R* 9-oxo compounds **1**, prepared essentially according to the literature,^{24,25} N-demethylation, N-alkylation, and selective reduction followed by O-demethylation, are reactions that were likely to provide the desired compounds. The *N*-methyl compound **1** was reacted with ethyl chloroformate, followed by TMSI, to give **2** in 63% yield over the two steps. An alternate route that eliminated column chromatography could also be used, as shown with the racemate of **2**. The application of this method employed cyanogen bromide to form an intermediate N-cyano compound that on acid hydrolysis gave the N-demethylated compound **2.HCl**. The latter was converted to its free base and purified through recrystallization of its salt. No chromatography was needed to obtain racemic **2** in 72% yield.

With the enantiomeric piperidines **2** in hand, N-alkylation with variety of alkyl and allyl bromides was carried out (Scheme 3).

In general, reaction between piperidine **2** and an alkyl bromide (**3–7**) required an excess amount of the alkyl bromide and heating at 80 °C overnight (Scheme 3). On the other hand, the allyl bromide derivatives (**8**) were much more reactive with piperidine **2**, needed less of the reagent allyl bromide and quickly formed a salt at lower temperatures. Superhydride (lithium triethylborohydride) reduction of the ketones **3–8** to the corresponding alcohols **9–14** provided high diastereoselectivity and excellent yields, as shown for the *1S,5S,9R*- and *1R,5R,9S*-products in Scheme 4.

The relative stereochemistry of the products were assigned based on the literature.²⁰

O-Demethylation of the methyl ethers **9 – 14** to the phenolic products **15 – 20** proceeded smoothly and in good yield. Each of the enantiomers (+)-*1S,5S,9R* and (–)-*1R,5R,9S* was converted to its salt form for pharmacological evaluation.

We then turned our attention to partially hindered N-side chains through the introduction of chiral phenylcyclopropylmethyl moieties.²² As shown in Scheme 6, coupling of ketone **2** with a chiral cyclopropyl carboxylic acid generated the intermediate methoxyphenyl amides (Scheme 7). Subsequent stereoselective reduction of the 9-oxo to the alcohol (Scheme 8), followed by reduction of the amide and conversion to the phenol, should provide the desired products.

Thus the *1S,5S*-amides **21 – 24** were prepared from *1S,5S*-**2** and the *1R,5R*-amides **21 – 24** were prepared from *1R,5R*-**2** through reaction with 4 isomers of chiral 2-phenylcyclopropane-1-carboxylic acid. They were obtained in good yield (Scheme 7) and appeared to be mixtures of rotamers by ¹H and ¹³C NMR analysis.

Reduction of the 9-oxo-phenylmorphans *1S,5S*-**21–24** with Superhydride (LiEt₃BH) proceeded stereoselectively (Scheme 8), but unfortunately gave the *9S*-OH products **25–28**, albeit in high yield, rather than the anticipated *9R* products. This reaction proceeded differently from the reduction of the enantiomers **3–8** with Superhydride (Scheme 4) that gave compounds with the *9R*-OH (Scheme 4). Possibly, the reversal of stereochemistry at C9 was caused by coordination between the amide group and the hydride reagent. Thus, the stereochemical configuration of the compounds **25–28** did not correspond to the

configuration of the very potent *1R,5R,9S*-compound shown in Figure 1. The obtained compounds (**25–28**) existed as a mixture of rotamers based on ^1H and ^{13}C NMR analysis. Our previous NMR and quantum chemical study characterized such rotamers.²⁶

The phenolic final products **29–32** were obtained by reduction of the amide group and O-demethylation of the phenyl ether. The intermediate formed from the reduction with lithium aluminum hydride (LAH) after aqueous work-up was subjected to the BBr_3 demethylation reaction without further purification (Scheme 9). All of the final products were purified through their oxalate salt. The stereochemistry of *1S,5S,9S*-**30**.oxalate was confirmed by X-ray crystallographic analysis (Fig. 2).

2.2 Binding affinity for opioid receptors

Opioid receptor binding studies were carried out on **15–20** and **29–32**. Initial exploratory assays for interaction with μ , δ , and κ -opioid receptors were used to determine the more promising compounds, i.e., those that displaced >50% of the specific binding of the radioligand (average of two assays) at a 100 nM concentration of the tested compounds. Full assays at the indicated receptor(s) were run on those compounds that produced more than 50% displacement. Only four of the compounds (Table 1) had appreciable affinity ($K_i < \sim 10$ nM) for the μ -OR (*1R,5R,9S*-**16**.oxalate, *1R,5R,9S*-**20**.oxalate, *1R,5R,9S*-**15**.HCl, and *1R,5R,9R*) (*1'R,2'S*)-**31**.oxalate) and two for the δ -OR (*1R,5R,9S*-**16**.oxalate and *1R,5R,9S*-**20**.oxalate). The *1R,5R,9S*-stereochemistry was necessary for the receptor affinity of compounds **15**, **16**, **20**, and **31**. The (–)-*1R,5R,9S*-**16** had 350 times greater affinity than its enantiomer, (+)-*1S,5S,9R*-**16**. It also had four times greater affinity at the μ -OR than the (–)-*1R,5R,9S*-*N*-phenethyl compound **NTH 11289** in Fig. 1.

Among the rotationally hindered *N*-substituents, only (*1R,5R,9R*) (*1'R,2'S*)-**31**.oxalate had moderate affinity for any opioid receptor. The relative lack of affinity of these rotationally hindered compounds can be ascribed to their *9R* configuration. Compounds with the *9S* configuration would likely have high affinity for ORs.

2.3. Functional studies

The stimulation of $\text{GTP}\gamma^{35}\text{S}$ binding by compounds with affinity for the various ORs (Table 1) is shown in Table 2. *1R,5R,9S*-**16** was found to be a high-potency full agonist at μ -OR, with lower potency but full agonist effects at δ -OR and no efficacy (an antagonist) at the κ -OR (i.e., no stimulation of $\text{GTP}\gamma^{35}\text{S}$ binding, Table 2). *1R,5R,9S*-**16** was much more potent as a μ -agonist and far more selective for the μ -OR ($\delta\text{-OR}/\mu\text{-OR} = \text{ca. } 850$) than any of the other compounds. In contrast, the (–)-*1R,5R,9S*-*N*-phenethyl compound (**NIH 11289**) was found to be a potent μ -agonist and a lower potency δ -agonist in a similar $\text{GTP}\gamma^{35}\text{S}$ assay²⁰ and was less selective for μ -OR than *1R,5R,9S*-**16**. *1R,5R,9S*-**20** was found to be a high potency partial agonist at μ -OR, with greater efficacy at δ -OR than at μ -OR. It was found to be less selective at μ -OR ($\delta\text{-OR}/\mu\text{-OR}$ selectivity = 133, based on the $\text{GTP}\gamma^{35}\text{S}$ potency data) than *1R,5R,9S*-**16**. *1R,5R,9S*-**15** was found to have higher efficacy and potency at μ -OR than at δ -OR (partial agonist at δ -OR) and it was less potent and had lower efficacy at κ -OR than at the other two receptors. The selectivity of *1R,5R,9S*-**15** based on the $\text{GTP}\gamma^{35}\text{S}$ potency data was: $\delta\text{-OR}/\mu\text{-OR} = 47$, $\kappa\text{-OR}/\mu\text{-OR} = 40$; it was less selective at μ -OR than *1R*,

5R,9S-20 or **1R,5R,9S-16**. **1R,5R,9S-17** was a low potency μ -OR partial agonist. (**1R,5R,9R**) (**1' R,2' S**)-**31** had low efficacy and potency. **1S,5S,9R-16**, **1S,5S,9R-20**, (**1R,5R,9R**) (**1' R,2' R**)-**29** and (**1R,5R,9R**) (**1' S,2' R**)-**32**, had effects consistent with designation as selective μ -OR antagonists (i.e. no stimulation of $\text{GTP}\gamma^{35}\text{S}$ and low activity in binding to δ -OR and κ -OR).

It is interesting to note that (–)-**1R,5R,9S-16** and (+)-**1S,5S,9R-16** in Tables 1 and 2 are enantiomers. The former is a high affinity μ -agonist and a δ -agonist whereas the (+)-enantiomer was found to be a selective μ -antagonist. As measured by the shift in the DAMGO concentration-effect curve in the [^{35}S]GTP γS assay a K_e of 31.5 ± 3.3 nM ($n = 3$) (Fig. 3) was calculated for (+)-**1S,5S,9R-16** which is in agreement with its binding affinity ($K_i = 26.5$ nM).

These two enantiomers display a considerable difference in binding affinity; that affinity difference would be anticipated with enantiomers. However, their functional difference is unusual and has not been commonly found with other opioids. Enantiomers are different compounds and there is no a priori reason to expect one to be functionally different from the other. Usually (although not always), the enantiomer of an opioid-like compound has little or no affinity for opioid receptors. However, in an early study by Ong et al.,²⁷ the (+)-enantiomer of an *N*-methyl-substituted phenylmorphane was found to be three times more potent than morphine in antinociceptive assays in mice; its (–)-enantiomer was comparable to morphine as an antinociceptive and it was nalorphine-like as an antagonist in morphine-dependent monkeys. This was discovered (in 1974) before opioid receptor assays were widely available, and it is difficult to compare the results from animal assays to contemporary receptor assays; nevertheless, one of the phenylmorphane enantiomers of Ong et al.,²⁷ was found to be a potent agonist, and the other enantiomer had (weak) antagonist properties, albeit agonist properties as well in vivo. This is reminiscent of the activities of the enantiomers of compound **16**.

2.4 Computational studies

Molecular dynamics (MD) simulations were conducted with the all-atom CHARMM force field, at 35 °C and 1 atm, with standard protonation states at pH 7. The μ -receptor was embedded in a model of a lipid bilayer and the system immersed in water. The conformations of the loops connecting TM5 and TM6 were modeled using an *ab initio* methodology described previously (see Supplementary Data).^{28,29} NIH 11289 was constructed based on the X-ray structure²⁰ and **1R,5R,9S-16** was modeled by chemical analogy, with atomic charges and other parameters obtained from quantum chemical calculations at the level of B3LYP/6-31G* (see Supplementary Data). In a previous study, prior to the elucidation of the X-ray structure of ORs, phenylmorphans were overlaid onto NIH 11289^{20,30} or morphine³¹ to define the structural requirements for high μ -OR binding affinity, as well as their agonist or antagonist properties. In the present study, the putative binding modes of both NIH 11289 and **1R,5R,9S-16** in the μ -receptor were initially modeled as in those previous studies. For comparison, simulations of the μ -OR in the absence of ligands and with morphine were also carried out. Additional details of the simulations and modeling are given in the Supplementary Data.

Fig. 4 summarizes the main results schematically. In the absence of a ligand, the binding cavity is filled with (~ 20) water molecules, and a few residues at the bottom of the cavity, mainly W229, prevent water from further hydrating the protein interior. These residues move away when a ligand enters the cavity, and a structural accommodation is made to allow the phenyl or the 4-nitrophenyl group to interact favorably with nearby residues via dispersion and H-bond interactions. Upon binding, both ligands displace about half the number of water molecules in the cavity. For the NIH 11289 compound, however, unlike **1R,5R,9S-16**, two water molecules find their way deeper into the binding pocket, and H-bond to residues that were not fully intra-receptor H-bonded prior to binding. For **1R,5R,9S-16** an analogous net gain in energy is provided not by water but by the nitro group, which now H-bonds to some of the same residues as water does in the NIH 11289 case. Statistical analysis shows that the -NO_2 group forms a persistent H-bonding interaction with N264 located on TM7, which helps stabilize the ligand. Several other polar interactions of the nitro group are observed frequently over the course of the simulation, specifically with the donor groups of S265 (in TM7) and of N86 and S90 (both in TM3). These $\text{-NO}_2 \cdots \text{H-}$ close contacts, generally of $\sim 2 - 3.5 \text{ \AA}$, could be exploited in further modifications of the phenyl ring to either enhance the affinity through H-bonds or to modify the $\mu\text{-OR}$ function. For both compounds, close nonpolar packing of the aromatic ring also helps stabilize the complex through non-polar (mainly dispersion) interactions, but these appear to be different in each case, involving both T-shaped (W229) and stacking (Y262) interactions with the NIH 11289 compound, and stacking (W229) with **1R,5R,9S-16**. In both ligands the protonated -NH group remains H-bonded to D83 throughout the entire length of the simulation, although for **1R,5R,9S-16** this interaction seems to be more persistent, probably due to the overall structural stabilization provided by the -NO_2 group. In contrast, NIH 11289, lacking such a strong anchoring interaction to the receptor, tends to fluctuate more and move upwards ($\sim 1 \text{ \AA}$ in average), thus weakening this H-bond interaction.

The additional H-bonds of the NO_2 group of **1R,5R,9S-16** with the $\mu\text{-OR}$ explain its higher binding affinity ($K_i \approx 0.073 \text{ nM}$) as compared to that of NIH 11289 ($K_i \approx 0.27 \text{ nM}$). Likewise, the dispersion interaction of the phenyl ring and the additional H-bond of water in the cavity may in turn explain the enhanced affinity of NIH 11289 relative to morphine. Considering that OR activity likely involves changes in the relative conformation of TM helices (e.g., TM6 of the β_2 adrenergic receptor-G protein complex undergoes significant restructuring upon activation),³² the extra interactions of **1R,5R,9S-16** with residues in both TM3 and TM7 may affect the structure and dynamics of these helices, as well as those of adjacent TM5 and TM6, hence the interaction of the receptor with the G proteins. Further computer simulations need to be conducted to quantify and elucidate these effects as they are expected to occur in longer time frames. From the current simulations it can be expected, however, that OR function is quite sensitive to strong perturbations introduced in the deeper regions of the binding cavity, as indicated with **1R,5R,9S-16** and NIH 11289. This may explain the 30 times higher full agonist activity of **1R,5R,9S-16** at $\mu\text{-OR}$ than NIH 11289, which was found to be ca 470 fold more potent than morphine in mouse antinociceptive assays.²⁰ As to the functional difference between the enantiomers of **16**, the unusually potent $\mu\text{-antagonist}$ assay result ($K_e = 29.1 \text{ nM}$) for (+)-**1S,5S,9R-16** may arise from the deeply anchored $p\text{-NO}_2$ group. While in general the enantiomer of an opioid-like compound has

significantly lower affinity for ORs, these H-bonding interactions provided by the *p*-NO₂ moiety of (+)-1*S*,5*S*,9*R*-**16** may also increase the binding affinity ($K_i = 26.5$ nM) of the (+)-enantiomer. It remains uncertain, however, why it should function as a μ -antagonist.

The present simulations also show that the 9 β -OH of both NIH 11289 and 1*R*,5*R*,9*S*-**16** make no direct H-bonds with the receptor but are bridged through highly-structured water chains to Q60 (TM2), Y64 (TM2), D83 (TM3), and Y262 (TM7); the water network is more complex for NIH 11289, which on average contains two water molecules, whereas 1*R*,5*R*,9*S*-**16** is bridged by a single water molecule (see Supplementary Data, Fig. S3). This highlights the importance of the 9 β -OH of the phenylmorphin in terms of higher K_i and also as a potent μ -agonist, since compounds without such hydroxyl group have a significantly lower K_i and μ -antagonist activity.²¹ These observations are consistent with our previous proposal that the 9 β -OH of NIH 11289 H-bonds with a water molecule and plays an importing role in enhancing the binding affinity and efficacy for the μ -receptor.^{20,30} Taken together, these observations suggest that judicious modifications of this group to either enhance (e.g., via direct H-bond) or weaken its interactions with TM2, TM3, or TM7 may affect the μ -OR activity in specific ways to be assessed.

3. Conclusion

The newly synthesized *N*-substituents on a C9 β -OH substituted 5-phenylmorphin (Fig. 1, (1*R*,5*R*,9*S*)-(–)-9-hydroxy-5-(3-hydroxyphenyl-2-phenylethyl-2-azabicyclo[3.3.1]nonane)) have provided insight into the structural requirements of the μ -OR for the assorted ligands. The 1*R*,5*R*,9*S*-configuration is critical for binding to the μ -OR and to potentiate its agonist activity. Compounds with the epimeric 1*R*,5*R*,9*R*-configuration are either unable to interact with the μ -OR, or as in the case of the 1*S*,5*S*,9*R*-**16** enantiomer, function as μ -antagonists. The 9 β -OH moiety imparts a potent μ -agonist activity (the 1*R*,5*R*-enantiomer in the *N*-phenethyl series without a C9 β -OH moiety (1*R*,5*R*)-(–)-5-(3-hydroxyphenyl-2-phenylethyl-2-azabicyclo[3.3.1]nonane was determined to be a μ -antagonist). The simulations indicate that a network of highly-structured water-mediated ligand-OR interactions involving the 9 β -OH group is responsible for this change in function. Further, a *p*-nitro addition to the *N*-phenethyl substituent enhances binding affinity and efficacy for the μ -receptor. As shown by MD simulations a net gain in energy is provided by the nitro group in 1*R*,5*R*,9*S*-**16** rather than by water in NIH 11289, although several of the same residues deep in the receptor are involved. Accordingly, the OR function is likely to be sensitive to strong perturbations introduced in the deeper regions of the binding cavity. This may explain the 30 times higher full agonist activity of 1*R*,5*R*,9*S*-**16** at μ -OR than NIH 11289, which was found experimentally to be ca 470 fold more potent than morphine in mouse antinociceptive assays. These perturbations are stronger in 1*R*,5*R*,9*S*-**16** with the *p*-nitrophenethyl moiety than in NIH 11289. Finally, the present simulations have identified a few critical residues in “hot spots” of the μ -OR that should be targeted in-modulating the binding affinity and efficacy of OR ligands.

4. Experimental

4.1. Chemistry

Melting points were determined on a Thomas Hoover Melting Point Apparatus and are uncorrected. Proton nuclear magnetic resonance (^1H NMR, 400 MHz) and carbon nuclear magnetic resonance (^{13}C NMR, 100 MHz) spectra were recorded on a Varian Model XXX wide-bore spectrometer in CDCl_3 (unless otherwise noted) with the values given in ppm and $J(\text{Hz})$ assignments of ^1H resonance coupling. For ^1H NMR spectra (CDCl_3), the residual solvent peak was used as the reference (7.27 ppm). For proton coupling: br = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, comp = complex multiplet of magnetically non-equivalent protons. The central solvent peak was used as the ^{13}C NMR reference (77.0 ppm in CDCl_3). The high resolution electrospray ionization (ESI) mass spectra were obtained on a Waters LCT Premier Time-of-flight (TOF) mass spectrometer. Thin-layer chromatography (TLC) was performed on 0.25 mm Analtech GHLF silica gel, using a CHCl_3 :MeOH:conc NH_4OH (CMA), 95:4.5:0.5 solvent system, which was used to determine the completion of the reaction. Gas chromatography (GC) was performed on an Agilent Technologies 6850 Series system equipped with Agilent Technologies 7683B series injector and Agilent Technologies 5975C VL MSD Triple-Axis detector. Flash column chromatography was performed with Bodman silica gel LC 60 A. Elemental analyses were performed by Micro-Analysis, Inc, Wilmington, DE, and were within 0.4% for C, H, and N.

4.1.1. *rac*-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-one (2)—To a solution of *rac*-1 (free base) (12 g, 46 mmol, 1 equiv) in anhydrous CH_3CN (100 mL) was added K_2CO_3 (6.34 g, 46, 1 equiv) and cyanogen bromide (CNBr) (13.8 mL, 5.0 M, 69 mmol, 1.5 equiv), respectively. The reaction mixture was stirred at room temperature for 2 h. After evaporation of solvent, the residue was dissolved in CHCl_3 (100 mL) and H_2O (100 mL), then basified with 28% NH_4OH to pH > 9. The aqueous layer was separated and extracted with CHCl_3 (50 mL $\times$ 3). The combined organic layers were washed with brine and evaporated. The residue was dissolved in MeOH (20 mL) and 3 M HCl (150 mL), and heated to 100 °C overnight. The reaction was cool to room temperature and basified with 28% NH_4OH to pH > 9. The mixture was extracted with CHCl_3 (100 mL $\times$ 3). The combined organic layers were washed with brine, dried over MgSO_4 , and evaporated. The residue was dissolved in 2-propanol (100 mL) and 37% HCl (10 mL) was added dropwise over 5 min. The mixture was stirred at room temperature for 3 h and at 0 °C for 1 h. The solid was filtered and then free-based with 28% NH_4OH to provide **2** (10.651 g, 72% yield) as a gray solid. Recrystallization from CH_2Cl_2 /hexanes provided colorless crystals, mp 62 – 64 °C. This compound was previously reported as a liquid. The enantiomers of this compound have been previously described.²⁰

4.1.2. General procedures for the alkylation of the enantiomeric secondary amines 1*S*,5*S*-2 and 1*R*,5*R*-2

Method A: To a solution of 1*S*,5*S*-2 or 1*R*,5*R*-2 (490 mg, 2.0 mmol, 1 equiv) in anhydrous CH_3CN (5 mL) was added K_2CO_3 (550 mg, 4.0 mmol, 2.0 equiv) and alkyl bromide (3.0 mmol, 1.5 equiv), respectively. The reaction was stirred at 80 °C for 16 h. After cooling to

room temperature, the solid was filtered off and the solvent was evaporated. The residue was purified by flash column chromatography eluting with hexane/EtOAc.

Method B: A mixture of 1*S*,5*S*-**2** or 1*R*,5*R*-**2** (490 mg, 2.0 mmol, 1.0 equiv) and K₂CO₃ (550 mg, 4.0 mmol, 2.0 equiv) in anhydrous CH₃CN (5 mL) was cooled to 0 °C (ice bath). Then a solution of (*E*)-(3-bromoprop-1-en-1-yl)benzene (2.0 mmol, 1.0 equiv) in CH₃CN (1 mL) was added via a syringe pump over 1 h. The reaction was further stirred for 1 h at room temperature. The solid was filtered off and the solvent was evaporated. The residue was purified by flash column chromatography eluting with hexane/EtOAc.

4.1.2.1. (1*S*,5*S*)-(-)-5-(3-Methoxyphenyl)-2-(4-(trifluoromethyl)phenethyl)-2-azabicyclo[3.3.1]nonan-9-one (1*S*,5*S*-3)

Method A: Reaction between 1*S*,5*S*-**2** and 1-(2-bromoethyl)-4-(trifluoromethyl)benzene provided 1*S*,5*S*-**3** in 74% yield as colorless liquid. The product was purified with flash column chromatography (SiO₂) by eluting with hexane/EtOAc (4:1); [α]_D²⁰ -22.9 (*c* 1.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.23 (m, 1H), 6.87 – 6.77 (m, 3H), 3.80 (s, 3H), 3.32 (t, *J* = 3.2 Hz, 1H), 3.28 – 3.19 (m, 1H), 2.95 – 2.81 (comp, 4H), 2.80 – 2.71 (m, 1H), 2.52 – 2.26 (comp, 4H), 2.12 – 2.20 (m, 2H), 1.80 – 1.61 (m, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 214.1, 159.1, 145.9, 144.2, 129.0, 128.8, 128.6, 125.6, 125.2, 119.6, 113.7, 111.1, 68.9, 58.2, 55.1, 52.8, 48.7, 40.5, 39.1, 34.1, 34.1, 18.8; HRMS (ESI) *m/z* 418.1989 [C₂₄H₂₇F₃NO₂ (M+H)⁺ requires 418.1994].

4.1.2.2. (1*R*,5*R*)-(+)-5-(3-Methoxyphenyl)-2-(4-(trifluoromethyl)phenethyl)-2-azabicyclo[3.3.1]nonan-9-one (1*R*,5*R*-3)

Method A: 68% yield; [α]_D²⁰ +23.7 (*c* 1.4, CHCl₃).

4.1.2.3. (1*S*,5*S*)-(-)-5-(3-Methoxyphenyl)-2-(4-nitrophenethyl)-2-azabicyclo[3.3.1]nonan-9-one (1*S*,5*S*-4)

Method A: Reaction between 1*S*,5*S*-**2** and 1-(2-bromoethyl)-4-nitrobenzene provided 1*S*,5*S*-**4** in 61% yield as a yellow solid. The product was purified with flash column chromatography (SiO₂) by eluting with hexane/EtOAc (7:3); mp 75 – 76 °C; [α]_D²⁰ -16.61 (*c* 1.15, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.31 – 7.24 (m, 1H), 6.87 – 6.75 (m, 3H), 3.80 (s, 3H), 3.30 (t, *J* = 3.2 Hz, 1H), 3.29 – 3.21 (m, 1H), 3.00 – 2.83 (m, 4H), 2.80 – 2.71 (m, 1H), 2.50 – 2.08 (comp, 6H), 1.82 – 1.61 (comp, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 213.9, 159.1, 148.0, 146.4, 145.8, 129.5, 128.8, 123.5, 119.6, 113.7, 111.1, 68.9, 57.7, 55.1, 52.7, 48.6, 40.4, 39.1, 34.1, 34.0, 18.8; HRMS (ESI) *m/z* 395.1966 [C₂₃H₂₇N₂O₄ (M+H)⁺ requires 395.1971].

4.1.2.4. (1*R*,5*R*)-(+)-5-(3-Methoxyphenyl)-2-(4-nitrophenethyl)-2-azabicyclo[3.3.1]nonan-9-one (1*R*,5*R*-4)

Method A: 49% yield; [α]_D²⁰ +17.1 (*c* 1.0, CHCl₃).

4.1.2.5. (1*S*,5*S*)-(-)-2-Allyl-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-one (1*S*,5*S*-5)

Method A: Reaction between 1*S*,5*S*-2 and allylbromide provided 1*S*,5*S*-5 in 68% yield as a clear viscous liquid. The product was purified with flash column chromatography (SiO₂) by eluting with hexane/EtOAc (4:1); [α]_D²⁰ -34.8 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.26 (t, *J* = 8.0 Hz, 1H), 6.91 – 6.68 (comp, 3H), 5.81 – 5.92(m, 1H), 5.28 – 5.07 (m, 2H), 3.80 (s, 3H), 3.15 – 3.32 (comp, 4H) 2.69 – 2.75 (m, 1H), 2.15 – 2.45, (comp, 6H), 1.82 – 1.63 (m, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 214.2, 159.1, 145.9, 135.2, 128.8, 119.6, 117.8, 113.6, 111.1, 67.9, 59.8, 55.1, 52.8, 48.5, 40.6, 39.2, 33.5, 19.2. HRMS (ESI) *m/z* 286.1805 [C₁₈H₂₄NO₂ (M+H)⁺ requires 286.1807].

4.1.2.6. (1*R*,5*R*)-(+)-2-Allyl-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-one (1*R*,5*R*-5)

Method A: 87% yield; [α]_D²⁰ +36.9 (*c* 1.0, CHCl₃)

4.1.2.72. (1*S*,5*S*)-(-)-2-(Cyclobutylmethyl)-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-one (1*S*,5*S*-6)

Method A: Reaction between 1*S*,5*S*-2 and (bromomethyl)cyclobutane provided 1*S*,5*S*-6 in 62% yield as a colorless liquid. The product was purified with flash column chromatography (SiO₂) by eluting with hexanes:ethyl acetate (4:1); [α]_D²⁰ -38.0 (*c* 1.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.26 (t, *J* = 8 Hz, 1H), 6.86 – 6.75 (m, 3H), 3.79 (s, 2H), 3.19 (t, *J* = 3.0 Hz, 1H), 3.14 (quin, *J* = 4.0 Hz, 1H), 2.62 – 2.68 (m, 3H), 2.32 – 2.53 (comp, 5H), 2.24 – 2.02 (comp, 4H), 1.96 – 1.61 (comp, 6H). ¹³C NMR (400 MHz, CDCl₃) δ 214.7, 159.1, 146.2, 128.8, 119.7, 113.7, 111.1, 68.9, 63.2, 55.1, 52.8, 49.0, 40.6, 39.4, 34.2, 34.0, 27.2, 27.1, 19.0, 18.7; HRMS (ESI) *m/z* 314.2119 [C₂₀H₂₈NO₂ (M+H)⁺ requires 314.2120].

4.1.2.8. (1*R*,5*R*)-(+)-2-(Cyclobutylmethyl)-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-one (1*R*,5*R*-6)

Method A: 73% yield; [α]_D²⁰ -37.9 (*c* 1.3, CHCl₃)

4.1.2.9. (1*S*,5*S*)-(-)-2-(Cyclopropylmethyl)-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-one (1*S*,5*S*-7)

Method A: Reaction between 1*S*,5*S*-2 and (bromomethyl)cyclopropane provided 1*S*,5*S*-7 in 75% yield as a colorless oil. The product was purified with flash column chromatography (SiO₂) by eluting with hexane/EtOAc (4:1); [α]_D²⁰ -26.6 (*c* 1.15, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.26 (t, *J* = 8.0, 1H), 6.90 – 6.71 (m, 3H), 3.80 (s, 3H), 3.41 – 3.39 (t, *J* = 3 Hz, 1H), 3.26 (quin, *J* = 5.5 Hz, 1H), 2.84 – 2.78 (m, 1H), 2.60 (dd, *J* = 12.7, 6.2 Hz, 1H), 2.49 – 2.13 (comp, 7H), 1.83 – 1.62 (m, 2H), 0.94 – 0.82 (m, 1H), 0.52 (dd, *J* = 8.2, 1.6 Hz, 2H), 0.15 (dd, *J* = 8.6, 5.0 Hz, 2H); ¹³C NMR (400 MHz, CDCl₃) δ 214.6, 159.1, 146.1, 128.8, 119.7, 113.7, 111.1, 68.4, 61.5, 55.1, 52.8, 48.7, 40.6, 39.4, 33.5, 19.3, 9.3, 4.0, 3.6; HRMS (ESI) *m/z* 300.1958 [C₁₉H₂₆NO₂ (M+H)⁺ requires 300.1964].

4.1.2.10. (1*R*,5*R*)-(+)-2-(Cyclopropylmethyl)-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-one (1*R*,5*R*-7)

Method A: 74% yield; $[\alpha]^{20}_{\text{D}} +24.5$ (c 1.35, CHCl_3)

4.1.3. (1*S*,5*S*)-(-)-2-Cinnamyl-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-one (1*S*,5*S*-8)

Method B: Reaction between 1*S*,5*S*-2 and (*E*)-(3-bromoprop-1-en-1-yl)benzene provided 1*S*,5*S*-8 with 92% yield as a light yellow oil. The product was purified with flash column chromatography (SiO_2) by eluting with hexane/EtOAc (4:1); $[\alpha]^{20}_{\text{D}} -32.4$ (c 1.05, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.20 – 7.40 (comp, 6H), 6.75 – 6.85 (comp, 3H), 6.56 (d, $J = 15.9$ Hz, 1H), 6.20 – 6.30 (m, 1H), 3.79 (s, 3H), 3.52 – 3.33 (comp, 3H), 3.32 – 3.23 (m, 1H), 2.82 – 2.70 (m, 1H), 2.49 – 2.13 (comp, 6H), 1.84 – 1.65 (m, 2H); ^{13}C NMR (400 MHz, CDCl_3) δ 214.2, 159.1, 145.8, 136.7, 132.8, 128.8, 128.5, 127.5, 126.7, 126.3, 119.6, 113.6, 111.1, 68.1, 59.1, 55.1, 52.8, 48.6, 40.6, 39.2, 33.5, 19.2; HRMS (ESI) m/z 362.2116 [$\text{C}_{24}\text{H}_{28}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$ requires 362.2120].

4.1.3.1. (1*R*,5*R*)-(+)-2-Cinnamyl-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-one (1*R*,5*R*-8)

Method B: 88% yield; $[\alpha]^{20}_{\text{D}} -30.76$ (c 1.01, CHCl_3)

4.1.4. General procedure for selective reduction of 1*S*,5*S*,9*R*-3– 8 and 1*R*,5*R*,9*S*-3 – 8 using Superhydride (lithium triethylborohydride)—The starting material (1*S*,5*S*,9*R*-3– 8 or 1*R*,5*R*,9*S*-3– 8) (0.50 mmol, 1.0 equiv) was dissolved in anhydrous THF (5 mL) and cooled to -78°C . A solution of Superhydride; 1.0 M in DCM, 0.75 mL, 0.75 mmol, 1.5 equiv) was added dropwise, and the resulting mixture was stirred for 3 h at -78°C . The reaction was quenched with sat. NH_4Cl (2 mL) and basified with 28% NH_4OH to pH ~ 9.5 . The aqueous layer was extracted with Et_2O (10 mL $\times$ 3). The combined extracts were washed with brine, dried over anhyd MgSO_4 , and evaporated. The residue was purified by flash column chromatography (SiO_2) by eluting with $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ (95/4.5/0.5)

4.1.4.1. (1*S*,5*S*,9*R*)-(+)-5-(3-Methoxyphenyl)-2-(4-(trifluoromethyl)phenethyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*R*-9): Using general procedure 4.1.4: Reaction between 1*S*,5*S*,9*R*-3 and Superhydride provided 1*S*,5*S*,9*R*-9 as pale yellow liquid in 96% yield; $[\alpha]^{20}_{\text{D}} +35.4$ (c 1.25, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.27 – 7.22 (m, 1H), 7.00 (dd, $J = 7.9, 0.9$ Hz, 1H), 6.94 (t, $J = 2.1$ Hz, 1H), 6.72 (dd, $J = 8.1, 2.1$ Hz, 1H), 4.08 (d, $J = 3.5$ Hz, 1H), 3.79 (s, 3H), 3.12 – 3.01 (comp, 2H), 2.97 – 2.82 (comp, 4H), 2.35 – 2.21 (m, 2H), 2.06 (dd, $J = 13.5, 4.7$ Hz, 1H), 1.94 – 1.78 (m, 2H), 1.71 – 1.47 (comp, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ 159.4, 150.4, 144.3, 129.1, 128.8, 128.4, 125.5, 125.2, 117.7, 112.0, 110.3, 71.3, 58.5, 55.6, 55.0, 48.1, 40.7, 40.5, 33.9, 29.5, 24.6, 22.6; HRMS (ESI) m/z 420.2141 [$\text{C}_{24}\text{H}_{30}\text{F}_3\text{NO}_2$ ($\text{M}+\text{H}$) $^+$ requires 420.2150].

4.1.4.2 (1*R*,5*R*,9*S*)-(-)-5-(3-Methoxyphenyl)-2-(4-(trifluoromethyl)phenethyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-9): Using general procedure 4.1.4: 94% yield; $[\alpha]^{20}_{\text{D}} -57.7$ (c 1.3, CHCl_3)

4.1.4.3. (1*S*,5*S*,9*R*)-(+)-5-(3-Methoxyphenyl)-2-(4-nitrophenethyl)-2-

azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*R*-10): Using general procedure 4.1.4: Reaction between 1*S*,5*S*,9*R*-4 and Superhydride provided 1*S*,5*S*,9*R*-10 as yellow solid in 91% yield; mp = 105 – 106 °C (recrystallized from CH₂Cl₂ and hexanes); [α]_D²⁰ +42.2 (*c* 1.55, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.01 – 6.96 (m, 1H), 6.95 – 6.91 (m, 1H), 6.72 (ddd, *J* = 8.2, 2.4, 0.6 Hz, 1H), 4.06 (d, *J* = 3.4 Hz, 1H), 3.79 (s, 3H), 3.09 (td, *J* = 12.2, 5.3 Hz, 1H), 3.00 (br, 1H), 2.97 – 2.85 (comp, 5H), 2.33 – 2.21 (m, 2H), 2.06 (dd, *J* = 13.6, 4.9 Hz, 1H), 1.95 – 1.49 (comp, 5H); ¹³C NMR (400 MHz, CDCl₃) δ 159.4, 150.3, 148.1, 146.3, 129.3, 129.1, 123.5, 117.6, 112.0, 110.3, 71.3, 58.6, 55.2, 55.0, 48.0, 40.6, 40.5, 33.9, 29.5, 24.6, 22.5; HRMS (ESI) *m/z* 397.2120 [C₂₃H₃₀N₂O₄ (M+H)⁺ requires 397.2127].

4.1.4.4. (1*R*,5*R*,9*S*)-(-)-5-(3-Methoxyphenyl)-2-(4-nitrophenethyl)-2-

azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-10): Using general procedure 4.1.4: 91% yield; [α]_D²⁰ -37 (*c* 1.2, CHCl₃).

4.1.4.5. (1*S*,5*S*,9*R*)-(+)-2-Allyl-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*S*,

5*S*,9*R*-11): Using general procedure 4.1.4: Reaction between 1*S*,5*S*,9*R*-5 and Superhydride provided 1*S*,5*S*,9*R*-11 as a colorless oil in 87% yield; [α]_D²⁰ +78.1 (*c* 1.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.25 (t, *J* = 8.0 Hz, 1H), 7.05 – 7.00 (m, 1H), 6.97 (t, *J* = 2.1 Hz, 1H), 6.72 (dd, *J* = 8.0, 2.0 Hz, 1H), 5.86 – 5.76 (m, 1H), 5.26 – 5.08 (comp, 2H), 4.09 (d, *J* = 2.8 Hz, 1H), 3.79 (s, 3H), 3.65 (br, 1H), 3.22 (dd, *J* = 6.4, 1.2 Hz, 2H), 3.06 (d, *J* = 2.7 Hz, 1H), 2.98 (td, *J* = 12.3, 5.2 Hz, 1H), 2.86 (dd, *J* = 11.7, 7.9 Hz, 1H), 2.40 – 2.19 (m, 2H), 2.04 (dd, *J* = 13.8, 5.1 Hz, 1H), 1.96 – 1.77 (comp, 2H), 1.73 – 1.45 (comp, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 159.4, 150.6, 135.9, 129.0, 117.7, 116.9, 112.0, 110.2, 71.4, 57.8, 57.7, 55.0, 48.1, 40.7, 40.6, 29.6, 24.3, 22.6; HRMS (ESI) *m/z* 288.1955 [C₁₈H₂₇NO₂ (M+H)⁺ requires 288.1963].

4.1.4.6. (1*R*,5*R*,9*S*)-(-)-2-Allyl-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-11): Using general procedure 4.1.4: 92% yield; [α]_D²⁰ -65.1 (*c* 1.0, CHCl₃)

4.1.4.7. (1*S*,5*S*,9*R*)-(+)-2-(Cyclobutylmethyl)-5-(3-methoxyphenyl)-2-

azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*R*-12): Using general procedure 4.1.4: Reaction between 1*S*,5*S*,9*R*-6 and Superhydride provided 1*S*,5*S*,9*R*-12 as a pale yellow solid in 68% yield; [α]_D²⁰ +68.4 (*c* 1.15, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.24 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.98 – 6.94 (m, 1H), 6.72 (dd, *J* = 7.9, 2.1 Hz, 1H), 4.06 (br, 1H), 3.79 (s, 3H), 3.05 – 2.91 (comp, 2H), 2.78 (t, *J* = 8.3 Hz, 1H), 2.59 (d, *J* = 7.6 Hz, 2H), 2.55 – 2.45 (m, 1H), 2.36 – 2.19 (comp, 2H), 2.11 – 1.95 (comp, 3H), 1.95 – 1.75 (comp, 4H), 1.73 – 1.40 (comp, 5H). ¹³C NMR (400 MHz, CDCl₃) δ 159.5, 150.9, 129.1, 117.8, 112.0, 110.4, 71.3, 60.7, 58.2, 55.1, 48.5, 40.8, 40.7, 33.9, 29.9, 26.9, 24.4, 22.7, 18.7. HRMS (ESI) *m/z* 316.2268 [C₂₀H₃₁NO₂ (M+H)⁺ requires 316.2276].

4.1.4.8. (1*R*,5*R*,9*S*)-(-)-2-(Cyclobutylmethyl)-5-(3-methoxyphenyl)-2-

azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-12): Using general procedure 4.1.4.: 87% yield; [α]_D²⁰ +62.5 (*c* 1.1, CHCl₃)

4.1.4.9. (1*S*,5*S*,9*R*)-(+)-2-(Cyclopropylmethyl)-5-(3-methoxyphenyl)-2-

azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*R*-13): Using general procedure 4.1.4: reaction between 1*S*,5*S*,9*R*-7 and Superhydride provided 1*S*,5*S*,9*R*-13 as a pale yellow solid in 93% yield; mp = 61–62 °C; $[\alpha]_D^{20} +84.9$ (*c* 1.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.25 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.98 (t, *J* = 2.1 Hz, 1H), 6.73 (dd, *J* = 8.1, 2.4 Hz, 1H), 4.09 (d, *J* = 3.4 Hz, 1H), 3.80 (s, 3H), 3.21 (d, *J* = 2.5 Hz, 1H), 2.99 (dd, *J* = 11.3, 3.8 Hz, 2H), 2.51 (dd, *J* = 12.6, 6.4 Hz, 1H), 2.41 (dd, *J* = 12.5, 6.7 Hz, 1H), 2.37 – 2.19 (comp, 2H), 2.07 – 2.02 (m, 1H), 1.92 – 1.45 (comp, 5H), 0.90 – 0.79 (m, 1H), 0.55 – 0.45 (m, 2H), 0.12 (dd, *J* = 4.8, 1.1 Hz, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 159.4, 150.8, 129.0, 117.8, 112.0, 110.3, 71.3, 59.5, 57.7, 55.0, 48.4, 40.8, 40.6, 29.8, 24.3, 22.6, 9.4, 3.9, 3.5; HRMS (ESI) *m/z* 302.2114 [C₁₉H₂₉NO₂ (M+H)⁺ requires 302.2120].

4.1.4.10. (1*R*,5*R*,9*S*)-(-)-2-(Cyclopropylmethyl)-5-(3-methoxyphenyl)-2-

azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-13): Using general procedure 4.1.4: 91% yield; $[\alpha]_D^{20} -85.1$ (*c* 1.0, CHCl₃)

4.1.4.11. (1*S*,5*S*,9*R*)-(+)-2-Cinnamyl-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-

ol (1*S*,5*S*,9*R*-14): Using general procedure 4.1.4: reaction between 1*S*,5*S*,9*R*-8 and Superhydride provided 1*S*,5*S*,9*R*-14 as a yellow foam in 89% yield; $[\alpha]_D^{20} +62.0$ (*c* 1.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.19 (comp, 6H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.99 – 6.95 (m, 1H), 6.75 – 6.68 (m, 1H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.24 – 6.17 (m, 1H), 4.10 (d, *J* = 2.7 Hz, 1H), 3.79 (s, 3H), 3.61 (s, 1H), 3.62 (br, 1H), 3.38 (d, *J* = 6.6 Hz, 2H), 3.12 (d, *J* = 2.5 Hz, 1H), 3.03 (td, *J* = 12.3, 5.2 Hz, 1H), 2.91 (dd, *J* = 11.6, 8.0 Hz, 1H), 2.329 – 2.27 (m, 2H), 2.04 (dd, *J* = 13.8, 5.0 Hz, 1H), 1.95 – 1.80 (comp, 2H), 1.74 – 1.47 (comp, 3H). ¹³C NMR (400 MHz, CDCl₃) δ 159.5, 150.7, 136.9, 132.1, 129.1, 128.5, 127.6, 127.4, 126.2, 117.8, 112.2, 110.4, 71.6, 58.0, 57.3, 55.1, 48.3, 40.8, 40.6, 29.8, 24.6, 22.7. HRMS (ESI) *m/z* 364.2271 [C₂₄H₂₉NO₂ (M+H)⁺ requires 364.2277].

4.1.4.12. (1*R*,5*R*,9*S*)-(-)-2-Cinnamyl-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-9-

ol (1*R*,5*R*,9*S*-14): Using general procedure 4.1.4: 84% yield; $[\alpha]_D^{20} -63.8$ (*c* 1.15, CHCl₃)

4.1.5. General procedure for demethylation of the aryl methylethers 1*S*,5*S*, 9*R*-9 – 14 and 1*R*,5*R*,9*S*-9 – 14—1*S*,5*S*,9*R*-9 – 14 or 1*R*,5*R*,9*S*-9 – 14 (0.5 mmol, 1.0 equiv) was dissolved in anhydrous CH₂Cl₂ (3 mL) and cooled to –78 °C. A solution of BBr₃ (1.0 M) (2.5 mL, 2.5 mmol, 5.0 equiv) was added dropwise. The dry-ice/acetone cooling bath was removed, and the reaction was stirred for 45 minutes. The reaction was cooled to –78 °C, then quenched with concentrated NH₄OH (3 mL) and H₂O (5 mL). The cloudy reaction mixture was heated until all the CH₂Cl₂ evaporated. The mixture was extracted with CH₂Cl₂ (15 mL × 3). The combined organic layers were washed with brine, dried over MgSO₄, and evaporated. The residue was purified by column chromatography (SiO₂) by eluting with CHCl₃:MeOH:28% NH₄OH (95:4:1) to afford the desired product.

4.1.5.1. (1*S*,5*S*,9*R*)-(+)-5-(3-hydroxyphenyl)-2-(4-(trifluoromethyl)phenethyl)-2-

azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*R*-15): Using general procedure 4.1.5: Reaction between 1*S*,5*S*,9*R*-9 and BBr₃ gave 1*S*,5*S*,9*R*-15 in 90% yield as white foam; $[\alpha]_D^{20} +24.7$

(*c* 1.4, CHCl₃). HRMS (ESI) *m/z* 406.1988 [C₂₃H₂₇F₃NO₂ (M+H)⁺ requires 406.1994]. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.84 (t, *J* = 2.0 Hz, 1H), 6.56 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.73 (br, 2H), 4.07 (d, *J* = 3.5 Hz, 1H), 3.11 – 3.00 (comp, 2H), 2.91 (dd, *J* = 11.5, 7.8 Hz, 1H), 2.87 – 2.81 (comp, 4H), 2.01 (dd, *J* = 13.9, 5.1 Hz, 1H), 1.90 – 1.76 (comp, 2H), 1.68 – 1.46 (comp, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 155.9, 150.3, 144.3 (d, 1.3 Hz), 144.3, 129.2, 128.8, 128.6 (t, 65.7 Hz), 125.59 (t, 271.9 Hz), 125.2 (q, 3.8 Hz), 117.34, 112.95, 112.81, 71.60, 58.51, 55.78, 48.17, 40.57, 40.55, 34.09, 29.60, 24.62, 22.57.

4.1.5.2. 1*S*,5*S*,9*R*-15.HCl: **4.1.5.2. 1*S*,5*S*,9*R*-15.HCl:** salt was formed with 2-propanol, EtOAc, and 37% HCl; mp 160 – 164 °C. Calcd for C₂₃H₂₆F₃NO₂•HCl•0.75H₂O: C, 60.66; H, 6.31; N, 3.08; found: C, 60.55; H, 6.35; N, 3.06.

4.1.5.3. (1*R*,5*R*,9*S*)-(-)-5-(3-Hydroxyphenyl)-2-(4-(trifluoromethyl)phenethyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-15): Using general procedure 4.1.5: 83% yield; [α]_D²⁰ -24.3 (*c* 1.4, CHCl₃).

4.1.5.4. 1*R*,5*R*,9*S*-15.HCl: Calcd for C₂₃H₂₆F₃NO₂•HCl: C, 62.51; H, 6.16; N, 3.17; found: C, 62.18; H, 6.23; N, 3.17.

4.1.5.5. (1*S*,5*S*,9*R*)-(+)-5-(3-hydroxyphenyl)-2-(4-nitrophenethyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*R*-16): Using general procedure 4.1.5: reaction between 1*S*,5*S*,9*R*-10 and BBr₃ gave 1*S*,5*S*,9*R*-16 in 94% yield as light green liquid. [α]_D²⁰ +45.5 (*c* 1.1, CHCl₃); HRMS (ESI) *m/z* 383.1966 [C₂₂H₂₇N₂O₄ (M+H)⁺ requires 383.1971]. ¹H NMR (400 MHz, CHCl₃) δ 8.11 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.92 – 6.79 (comp, 2H), 6.55 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.87 (br, 2H), 4.05 (d, *J* = 3.5 Hz, 1H), 3.13 – 2.97 (comp, 2H), 2.95 – 2.80 (comp, 5H), 2.3 – 2.19 (comp, *J* = 16.9, 8.5 Hz, 2H), 2.01 (dd, *J* = 13.9, 4.8 Hz, 1H), 1.88 – 1.75 (comp, 2H), 1.65 – 1.45 (comp, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 155.9, 150.1, 148.1, 146.3, 129.3, 129.2, 123.5, 117.1, 112.9, 112.6, 71.5, 58.4, 55.3, 48.0, 40.4, 33.9, 29.4, 24.5, 22.4. (One carbon is missing due to overlap).

4.1.5.6. 1*S*,5*S*,9*R*-16.oxalate: The oxalate salt was formed with oxalic acid in 2-propanol; mp 178– 180°C. Calcd for C₂₂H₂₆N₂O₄•C₂H₂O₄: C, 61.01; H, 5.97; N, 5.93; found: C, 60.72; H, 6.31; N, 5.98.

4.1.5.7. (1*R*,5*R*,9*S*)-(-)-5-(3-Hydroxyphenyl)-2-(4-nitrophenethyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-16): Using general procedure 4.1.5: 87% yield; [α]_D²⁰ -45.3 (*c* 1.1, CHCl₃).

4.1.5.8. 1*R*,5*R*,9*S*-16.oxalate: Calcd for C₂₂H₂₆N₂O₄•C₂H₂O₄•0.3 C₃H₈O: C, 60.97; H, 6.25; N, 5.71; found: C, 60.97; H, 6.42; N, 5.89.

4.1.5.9. (1*S*,5*S*,9*R*)-(+)-2-Allyl-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*R*-17): Using general procedure 4.1.5: Reaction between 1*S*,5*S*,9*R*-11 and BBr₃ gave 1*S*,5*S*,9*R*-17 in 92% yield as white foam. [α]_D²⁰ +75.0 (*c* 1.6, CHCl₃). HRMS (ESI) *m/z*

274.1802 [C₁₇H₂₄NO₂ (M+H)⁺ requires 274.1807]. ¹H NMR (400 MHz, CDCl₃) δ 7.08 (t, *J* = 7.9 Hz, 1H), 6.90 – 6.82 (m, 2H), 6.57 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.93 – 5.65 (comp, 2H), 5.21 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.13 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.09 (d, *J* = 3.5 Hz, 1H), 3.23 (d, *J* = 5.8 Hz, 2H), 3.08 (br, 1H), 3.0 – 2.82 (comp, 2H), 2.32 – 2.15 (comp, 2H), 1.97 (dd, *J* = 13.8, 4.8 Hz, 1H), 1.85 – 1.72 (comp, 2H), 1.67 – 1.42 (comp, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 156.2, 149.9, 135.0, 129.1, 117.7, 116.8, 113.0, 112.8, 71.4, 57.7, 57.6, 48.2, 40.4, 40.3, 29.2, 24.0, 22.3.

4.1.5.10. 1*S*,5*S*,9*R*-17.HCl: The salt was formed with 2-propanol, EtOAc and 37% HCl; mp 218 – 220 °C. Calcd for C₁₇H₂₃NO₂•Ha•0.25 H₂O: C, 64.96; H, 7.86; N, 4.46; found: C, 65.02; H, 7.97; N, 4.47.

4.1.5.11. (1*R*,5*R*,9*S*)-(-)-2-Allyl-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-17): Using general procedure 4.1.5: 84% yield; [α]_D²⁰ -77.5 (*c* 1.6, CHCl₃).

4.1.5.12. 1*R*,5*R*,9*S*-17.HCl: Calcd. for C₁₇H₂₃NO₂•HCl: C, 65.90; H, 7.81; N, 4.52; found: C, 65.79; H, 8.02; N, 4.46.

4.1.5.13. (1*S*,5*S*,9*R*)-(+)-2-(Cyclobutylmethyl)-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*R*-18): Using general procedure 4.1.5: reaction between 1*S*,5*S*,9*R*-12 and BBr₃ gave 1*S*,5*S*,9*R*-18 in 83% yield as light green liquid. [α]_D²⁰ +54.6 (*c* 1.3, CHCl₃); HRMS (ESI) *m/z* 302.2115 [C₁₉H₂₈NO₂ (M+H)⁺ requires 302.2120]. ¹H NMR (400 MHz, CDCl₃) δ 7.08 (t, *J* = 7.9 Hz, 1H), 6.87 – 8.83 (m, 2H), 6.53 (dd, *J* = 8.1, 1.7 Hz, 1H), 5.54 (s, 2H), 4.08 (d, *J* = 3.7 Hz, 1H), 3.01 – 2.91 (m, 2H), 2.76 (dd, *J* = 11.6, 8.0 Hz, 1H), 2.63 – 2.45 (comp, 3H), 2.30 – 2.18 (comp, *J* = 13.9, 8.0 Hz, 2H), 2.10 – 1.73 (comp, 5H), 1.72 – 1.41 (comp, 5H); ¹³C NMR (400 MHz, CDCl₃) δ 156.1, 150.3, 129.0, 116.9, 112.9, 112.7, 71.4, 60.6, 58.0, 48.4, 40.5, 40.3, 33.8, 29.5, 26.9, 26.9, 24.2, 22.5, 18.6.

4.1.5.14. 1*S*,5*S*,9*R*-18.HCl: The salt was formed with 2-propanol, EtOAc and 37% HCl; mp 136 – 140 °C. Calcd for C₁₉H₂₇NO₂•HCl•H₂O•0.25 C₃H₈O: C, 63.95; H, 8.70; N, 3.78; found: C, 64.01; H, 8.96; N, 3.95.

4.1.5.15. (1*R*,5*R*,9*S*)-(-)-2-(Cyclobutylmethyl)-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*S*-18): Using general procedure 4.1.5: 89% yield; [α]_D²⁰ -55.3 (*c* 1.3, CHCl₃).

4.1.5.16. 1*R*,5*R*,9*S*-18.HCl: Calcd for C₁₉H₂₇NO₂•HCl•H₂O: C, 64.12; H, 8.50; N, 3.94; Found: C, 63.96; H, 8.80; N, 3.94.

4.1.5.16. (1*S*,5*S*,9*R*)-(+)-2-(Cyclopropylmethyl)-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*R*-19): Using general procedure 4.1.5: reaction between 1*S*,5*S*,9*R*-13 and BBr₃ gave 1*S*,5*S*,9*R*-19 in 95% yield as a white foam. [α]_D²⁰ +73.4 (*c* 0.7, CHCl₃). HRMS (ESI) *m/z* 288.1956 [C₁₈H₂₆NO₂ (M+H)⁺ requires 288.1963]; ¹H NMR (400 MHz, CDCl₃) δ 7.09 (t, *J* = 8.1 Hz, 1H), 6.89 – 6.85 (m, 2H), 6.54 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.61 (br, 2H), 4.11 (d, *J* = 3.5 Hz, 1H), 3.24 – 3.19 (m, *J* = Hz,

1H), 3.02 – 2.91 (m, 2H), 2.51 (dd, $J = 12.6, 6.4$ Hz, 1H), 2.41 (dd, $J = 12.6, 6.8$ Hz, 1H), 2.37 – 2.26 (m, 1H), 2.21 (d, $J = 13.8$ Hz, 1H), 1.99 (dd, $J = 13.2, 3.6$ Hz, 1H), 1.86 – 1.71 (comp, 2H), 1.66 – 1.42 (comp, 3H), 0.90 – 0.77 (m, 1H), 0.55 – 0.46 (m, 2H), 0.15 – 0.11 (m, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ 156.2, 150.4, 129.1, 117.0, 113.0, 112.9, 71.6, 59.6, 57.7, 48.5, 40.6, 40.6, 29.6, 24.3, 22.6, 9.4, 3.6.

4.1.5.17. 1S,5S,9R-19. (+)-camphoric acid: The salt was formed with (+)-camphoric acid in EtOAc; mp 118–124 °C. Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2 \cdot \text{C}_{10}\text{H}_{16}\text{O}_4 \cdot \text{H}_2\text{O}$: C, 66.51; H, 8.57; N, 2.77; found: C, 66.69; H, 8.94; N, 2.74.

4.1.5.18. (1R,5R,9S)-(-)-2-(Cyclopropylmethyl)-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1R,5R,9S-19): Using general procedure 4.1.5: 88% yield; $[\alpha]_{\text{D}}^{20}$ -74.4 (c 0.7, CHCl_3).

4.1.5.19. 1R,5R,9S-19.(+)-Camphoric acid: Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2 \cdot \text{C}_{10}\text{H}_{16}\text{O}_4 \cdot \text{H}_2\text{O}$: C, 66.51; H, 8.57; N, 2.77; Found: C, 66.64; H, 8.74; N, 2.55.

4.1.5.20. (1S,5S,9R)-(+)-2-Cinnamyl-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1S,5S,9R-20): Using general procedure 4.1.5: reaction between 1S,5S,9R-14 and BBr_3 gave 1S,5S,9R-20 in 61% yield as white foam; $[\alpha]_{\text{D}}^{20}$ +69.4 (c 1.0, CHCl_3). HRMS (ESI) m/z 350.2114 [$\text{C}_{23}\text{H}_{28}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$ requires 305.2120]. ^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.12 (comp, 7H), 6.95 (d, $J = 7.8$ Hz, 1H), 6.91 – 6.88 (m, 1H), 6.62 (dd, $J = 7.7, 2.0$ Hz, 1H), 6.55 (d, $J = 15.9$ Hz, 1H), 6.21 (dt, $J = 15.8, 6.6$ Hz, 1H), 4.09 (d, $J = 3.4$ Hz, 1H), 3.39 (d, $J = 6.5$ Hz, 2H), 3.13 (d, $J = 2.6$ Hz, 1H), 3.03 (td, $J = 12.3, 5.1$ Hz, 1H), 2.92 (dd, $J = 11.6, 7.9$ Hz, 1H), 2.40 – 2.25 (comp, 2H), 2.03 (dd, $J = 13.7, 4.9$ Hz, 1H), 1.94 – 1.79 (comp, 2H), 1.71 – 1.46 (comp, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ 156.0, 150.4, 136.8, 132.3, 129.2, 128.5, 127.4, 127.3, 126.3, 117.2, 113.0, 112.9, 71.7, 57.9, 57.3, 48.3, 40.6, 40.5, 29.6, 24.4, 22.60.

4.1.5.21. 1S,5S,9R-20.oxalate: The oxalic acid salt was formed in 2-propanol; mp 176–181 °C. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_2 \cdot \text{C}_2\text{H}_2\text{O}_4 \cdot 0.5 \text{ C}_3\text{H}_8\text{O}$: C, 67.79; H, 7.08; N, 2.98; found: C, 67.62; H, 7.21; N, 3.14.

4.1.5.22. (1R,5R,9S)-(-) 2-Cinnamyl-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-9-ol (1R,5R,9S-20): Using general procedure 4.1.5: 54% yield; $[\alpha]_{\text{D}}^{20}$ -71.0 (c 1.0, CHCl_3).

4.1.5.23. 1R,5R,9S-20.oxalate: The oxalic acid salt was formed in 2-propanol. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_2 \cdot \text{C}_2\text{H}_2\text{O}_4 \cdot 0.75 \text{ C}_3\text{H}_8\text{O}$: C, 67.54; H, 7.28; N, 2.89; found: C, 67.70; H, 7.55; N, 3.07.

4.1.6. General procedure for the synthesis of amides 1S,5S and 1R,5R-21–24—
To a solution of 1S,5S-or 1R,5R-2 (0.122 g, 0.5 mmol) in DCM (3 mL) was added 2-phenylcyclopropane-1-carboxylic acid (0.097 g, 0.6 mmol, 1.2 equiv), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (0.192 g, 0.6 mmol, 1.2 equiv), and trimethylamine (Et_3N) (0.21 mL, 1.5 mmol, 3.0 equiv), respectively. After stirring at room temperature for 4 h, the reaction was quenched with saturated NaCO_3H . The

mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, evaporated and purified with flash column chromatography by eluting with hexane and ethyl acetate.

4.1.6.1. (1*S*,5*S*)-(+)-5-(3-Methoxyphenyl)-2-((1*S*,2*S*)-2-phenylcyclopropane-1-carbonyl)-2-azabicyclo[3.3.1]nonan-9-one ((1*S*,5*S*) (1'*S*,2'*S*)-21): Using general procedure **4.1.6**: reaction between 1*S*,5*S*-2 and (1*S*,2*S*)-2-phenylcyclopropane-1-carboxylic acid gave (1*S*,5*S*) (1'*S*,2'*S*)-21 in 92% yield as white foam. $[\alpha]^{20}_{\text{D}} +81.5$ (*c* 1.35, CHCl₃); HRMS (ESI) *m/z* 390.2066 [C₂₂H₂₇N₂O₄ (M+H)⁺ requires 390.2069]. A mixture of rotamers (1:1) ratio: ¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.04 (comp, 9H), 6.85 – 6.71 (comp, 4H), 4.68 (s, 1H), 4.59 – 4.46 (comp, 2H), 4.23 (dt, *J* = 13.4, 4.7 Hz, 1H), 3.76 (d, *J* = 3.4 Hz, 4H), 3.47 – 3.27 (m, 2H), 2.77 – 2.64 (m, 1H), 2.61 – 1.98 (comp, 12H), 1.89 – 1.63 (comp, 6H), 1.32 – 1.28 (comp, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 211.1, 210.1, 171.6, 170.8, 159.2, 145.2, 144.8, 140.4, 140.2, 128.9, 128.9, 128.4, 128.3, 126.2, 126.2, 125.9, 125.7, 119.2, 113.4, 111.3, 111.2, 63.3, 63.0, 55.0, 53.1, 52.6, 43.3, 40.5, 40.2, 40.1, 38.4, 37.2, 36.4, 34.2, 26.2, 25.5, 23.9, 23.5, 17.7, 17.5, 16.4, 15.6.

4.1.6.2. (1*R*,5*R*)-(-)-5-(3-Methoxyphenyl)-2-((1*R*,2*R*)-2-phenylcyclopropane-1-carbonyl)-2-azabicyclo[3.3.1]nonan-9-one ((1*R*,5*R*) (1'*R*,2'*R*)-21): Using general procedure **4.1.6**: 89% yield; $[\alpha]^{20}_{\text{D}} -82.38$ (*c* 1.3, CHCl₃).

4.1.6.3. (1*R*,5*R*)-(+)-5-(3-methoxyphenyl)-2-((1*S*,2*S*)-2-phenylcyclopropane-1-carbonyl)-2-azabicyclo[3.3.1]nonan-9-one ((1*R*,5*R*) (1'*S*,2'*S*)-22): Using general procedure **4.1.6**: reaction between 1*R*,5*R*-2 and (1*S*,2*S*)-2-phenylcyclopropane-1-carboxylic acid gave (1*R*,5*R*) (1'*S*,2'*S*)-22 in 90% yield as a white foam. $[\alpha]^{20}_{\text{D}} +149.8$ (*c* 1.1, CHCl₃); HRMS (ESI) *m/z* 390.2063 [C₂₂H₂₇N₂O₄ (M+H)⁺ requires 390.2069]. A mixture of rotamers (1:1) ratio; ¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.09 (comp, 10H), 6.84 – 6.75 (comp, 4H), 4.68 – 4.66 (m, 1H), 4.58 – 4.47 (m, 2H), 4.31 – 4.21 (m, 1H), 3.79 (s, 5H), 3.53 – 3.43 (m, 1H), 3.41 – 3.31 (m, 1H), 2.77 – 2.71 (m, 1H), 2.64 – 2.53 (comp, 4H), 2.45 – 2.33 (comp, 3H), 2.30 – 2.17 (comp, 2H), 2.13 – 1.94 (comp, 2H), 1.88 – 1.60 (comp, 5H), 1.37 – 1.30 (comp, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 211.2, 210.1, 172.0, 171.1, 159.3, 145.2, 144.9, 140.7, 140.2, 129.0, 128.4, 128.4, 126.4, 126.3, 126.2, 125.9, 119.3, 113.6, 113.5, 111.4, 111.3, 63.4, 63.2, 55.1, 53.1, 52.7, 43.4, 40.6, 40.3, 40.2, 38.5, 37.3, 36.4, 34.3, 26.3, 25.3, 23.8, 23.2, 17.8, 16.8, 16.5.

4.1.6.4. (1*S*,5*S*)-(-)-5-(3-methoxyphenyl)-2-((1*R*,2*R*)-2-phenylcyclopropane-1-carbonyl)-2-azabicyclo[3.3.1]nonan-9-one ((1*S*,5*S*) (1'*R*,2'*R*)-22): Using general procedure **4.1.6**: 84% yield; $[\alpha]^{20}_{\text{D}} -143.9$ (*c* 1.1, CHCl₃);

4.1.6.5. (1*S*,5*S*)-(-)-5-(3-Methoxyphenyl)-2-((1*S*,2*R*)-2-phenylcyclopropane-1-carbonyl)-2-azabicyclo[3.3.1]nonan-9-one ((1*S*,5*S*) (1'*S*,2'*R*)-23): Using general procedure **4.1.6**: 92% yield; white foam; $[\alpha]^{20}_{\text{D}} -157.5$ (*c* 1.4, CHCl₃); HRMS (ESI) *m/z* 390.0262 [C₂₂H₂₇N₂O₄ (M+H)⁺ requires 390.2069]. A mixture of 2 rotamers with 2:3 ratio; ¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.06 (m, 16H), 6.82 – 6.61 (m, 8H), 4.61 – 4.59 (t, *J* = 3.0 Hz, 1H), 4.37 (t, *J* = 3.0 Hz, 1.6H), 4.34 – 4.16 (comp, 3.4H), 3.77 (s, 8H), 3.44 –

3.36 (m, 1.5H), 3.17 – 3.09 (m, 2H), 2.69 – 2.65 (m, 2H), 2.56 – 1.53 (m, 25H), 1.41 – 1.29 (m, 3H). ¹³C NMR (400 MHz, CDCl₃) δ 210.9, 210.4, 168.4, 168.0, 159.2, 145.3, 144.7, 136.7, 136.7, 129.0, 128.1, 128.1, 127.9, 127.4, 126.6, 126.4, 119.3, 113.6, 113.6, 111.4, 111.1, 63.5, 62.5, 55.1, 53.2, 52.7, 43.2, 40.5, 40.4, 39.8, 38.9, 38.0, 35.6, 34.0, 25.9, 24.6, 24.3, 23.4, 18.0, 17.9, 11.3, 10.2.

4.1.6.6. (1*R*,5*R*)-(+)-5-(3-Methoxyphenyl)-2-((1*R*,2*S*)-2-phenylcyclopropane-1-carbonyl)-2-azabicyclo[3.3.1]nonan-9-one ((1*R*,5*R*) (1'*R*,2'*S*)-23): Using general procedure 54.1.6: 92% yield; [α]_D²⁰ +154.3 (c 1.15, CHCl₃).

4.1.6.7. (1*R*,5*R*)-(-)-5-(3-methoxyphenyl)-2-((1*S*,2*R*)-2-phenylcyclopropane-1-carbonyl)-2-azabicyclo[3.3.1]nonan-9-one ((1*R*,5*R*) (1'*S*,2'*R*)-24): Using general procedure 4.1.6: 95% yield: white crystals; mp 155 – 156 °C; [α]_D -56.6 (c 1.5, CHCl₃); HRMS (ESI) *m/z* 390.2064 [C₂₂H₂₇N₂O₄ (M+H)⁺ requires 390.2069]. A mixture 2 rotamers with 1:5 ratio; major rotamer: ¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.15 (comp, 6H), 6.80 – 6.66 (comp, 3H), 4.40 (t, *J* = 3.0 Hz, 1H), 4.19 – 4.11 (m, 1H), 3.76 (s, 3H), 3.40 – 3.28 (m, 1H), 2.53 – 2.48 (m, 1H), 2.24 – 2.14 (comp, 3H), 2.10 – 1.99 (comp, 2H), 1.98 – 1.88 (comp, 2H), 1.50 – 1.42 (m, 1H), 1.36 – 1.29 (m, 1H), 1.16 – 1.08 (m, 1H), 0.77 – 0.66 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 211.5, 167.6, 159.2, 145.4, 137.0, 129.0, 128.1, 127.3, 126.5, 119.2, 113.4, 111.2, 62.9, 55.1, 53.0, 42.6, 40.4, 38.2, 34.0, 25.3, 23.4, 16.4, 9.5.

4.1.6.8. (1*S*,5*S*)-(+)-5-(3-methoxyphenyl)-2-((1*R*,2*S*)-2-phenylcyclopropane-1-carbonyl)-2-azabicyclo[3.3.1]nonan-9-one ((1*S*,5*S*) (1'*R*,2'*S*)-24): Using general procedure 4.1.6: 97% yield; [α]_D²⁰ -55.1 (c 1.4, CHCl₃).

4.1.7. General procedure for the synthesis of amido alcohols 1*S*,5*S*,9*S*-25 – 28 and 1*R*,5*R*,9*R*-25 – 28—A solution of amides 1*S*,5*S*-or 1*R*,5*R*-21-24 (0.156 g, 0.40 mmol) in THF (3 mL) at –78 °C was added Superhydride (LiEt₃BH, 1.0 M in THF) (0.8 mL, 0.8 mmol, 2 equiv). The reaction was stirred at –78 °C for 1 h, then warmed-up to room temperature. The reaction was further stirred for 1 h at room temperature. The reaction mixture was quenched with H₂O and then basified with 28% NH₄OH until pH ~ 9. The reaction was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, evaporated, and purified with flash column chromatography by eluting with hexane:ethyl acetate (3:1).

4.1.7.1. ((1*S*,5*S*,9*S*)-(+)-(9-hydroxy-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)((1*S*,2*S*)-2-phenylcyclopropyl)methanone ((1*S*,5*S*,9*S*) (1'*S*,2'*S*)-25): Using general procedure 4.1.7: reduction of 1*S*,5*S*-21 with Superhydride gave (1*S*,5*S*,9*S*) (1'*S*,2'*S*)-25 in 96% yield as a color less liquid. [α]_D²⁰ +103.1 (c 1.0, CHCl₃); HRMS (ESI) *m/z* 392.2220 [C₂₅H₃₀NO₃ (M+H)⁺ requires 392.2225]. Complex proton and carbon NMR spectra were obtained due to mixture of more than two rotamers.

4.1.7.2. ((1*R*,5*R*,9*R*)-(-)-(9-hydroxy-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)((1*R*,2*R*)-2-phenylcyclopropyl)methanone ((1*R*,5*R*,9*R*) (1'*R*,2'*R*)-25): Using general procedure 4.1.7: 84% yield; [α]_D²⁰ -100.9 (c 1.0, CHCl₃).

4.1.7.3. ((1*R*,5*R*,9*R*)-(+)-9-hydroxy-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl) ((1*S*,2*S*)-2-phenylcyclopropyl)methanone (1*R*,5*R*,9*R*) (1'*S*,2'*S*)-26: Using general procedure 4.1.7: reduction of 1*R*,5*R*-22 with Superhydride gave (1*R*,5*R*,9*R*) (1'*S*,2'*S*)-26 in 94% yield as a colorless liquid. $[\alpha]_D^{20} +107.1$ (*c* 1.0, CHCl₃); HRMS (ESI) *m/z* 392.2220 [C₂₅H₃₀NO₃ (M+H)⁺ requires 392.2225]. Complex proton and carbon NMR spectra were obtained due to mixture of more than two rotamers.

4.1.7.4. ((1*S*,5*S*,9*S*)-(-)-9-hydroxy-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl) ((1*R*,2*R*)-2-phenylcyclopropyl)methanone ((1*S*,5*S*,9*S*) (1'*R*,2'*R*)-26: Using general procedure 4.1.7: 90% yield; $[\alpha]_D^{20} -101.1$ (*c* 1.0, CHCl₃).

4.1.7.5. ((1*S*,5*S*,9*S*)-(-)-9-Hydroxy-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl) ((1*S*,2*R*)-2-phenylcyclopropyl)methanone (1*S*,5*S*,9*S*) (1'*S*,2'*R*)-27: Using general procedure 4.1.7: reduction of 1*S*,5*R*-23 with Superhydride gave (1*S*,5*S*,9*S*) (1'*S*,2'*R*)-27 in 70% yield as a colorless liquid; $[\alpha]_D^{20} -45.1$ (*c* 1.4, CHCl₃); HRMS (ESI) *m/z* 392.2221 [C₂₅H₃₀NO₃ (M+H)⁺ requires 392.2225]. Complex proton and carbon NMR spectra were obtained due to mixture of more than two rotamers.

4.1.7.6. ((1*R*,5*R*,9*R*)-(-)-9-Hydroxy-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl) ((1*R*,2*S*)-2-phenylcyclopropyl)methanone (1*R*,5*R*,9*R*) (1'*R*,2'*S*)-27: Using general procedure 4.1.7: 66% yield; $[\alpha]_D^{20} +50.1$ (*c* 1.3, CHCl₃)

4.1.7.7. ((1*R*,5*R*,9*R*)-(-)-9-Hydroxy-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl) ((1*S*,2*R*)-2-phenylcyclopropyl)methanone (1*R*,5*R*,9*R*) (1'*S*,2'*R*)-28: Using general procedure 4.1.7: reduction of 1*R*,5*R*-24 with Superhydride gave (1*R*,5*R*,9*R*) (1'*S*,2'*R*)-28 in 75% yield as a colorless liquid; $[\alpha]_D^{20} -75.7$ (*c* 1.2, CHCl₃); HRMS (ESI) *m/z* 392.2228 [C₂₅H₃₀NO₃ (M+H)⁺ requires 392.2225]. Mixture of 2 rotamers with 1:1 ratio; ¹H NMR (400 MHz, cdcl₃) δ 7.32 – 7.11 (comp, 12H), 6.95 – 6.87 (comp, 2H), 6.77 – 6.62 (comp, 4H), 4.45 (dd, *J* = 6.8, 3.3 Hz, 1H), 4.40 – 4.35 (m, 1H), 4.12 – 4.02 (m, 2H), 3.86 – 3.73 (comp, 7H), 3.54 3.49 (m, 1H), 3.29 – 2.23 (m, 1H), 2.95 (s, 1H), 2.78 (s, 1H), 2.51 – 2.39 (m, 2H), 2.23 – 1.54 (comp, 19H), 1.50 – 1.19 (comp, 5H), 0.99 – 0.94 (m, *J* = 16.1 Hz, 1H), 0.89 – 0.69 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 168.3, 168.0, 159.8, 159.7, 149.5, 148.3, 137.9, 137.0, 129.4, 127.9, 127.9, 127.4, 127.1, 126.3, 126.2, 117.8, 117.6, 112.4, 112.3, 110.9, 110.8, 71.6, 70.6, 55.1, 55.0, 51.9, 50.1, 41.5, 39.9, 39.7, 39.4, 38.5, 37.5, 37.5, 28.3, 27.8, 25.4, 24.9, 23.9, 23.9, 23.3, 21.9, 20.3, 18.6, 10.7, 9.7.

4.1.7.8. ((1*S*,5*S*,9*S*)-(+)-9-Hydroxy-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl) ((1*R*,2*S*)-2-phenylcyclopropyl)methanone (1*S*,5*S*,9*S*) (1'*R*,2'*S*)-28: Using general procedure 4.1.7: 92% yield; $[\alpha]_D^{20} +84.4$ (*c* 1.3, CHCl₃)

4.1.8. A general reduction and demethylation procedure for the synthesis of phenolic phenylmorphans—To a solution of alcohol 1*S*,5*S*,9*S*-25-28 or 1*R*,5*R*,9*R*-25-28 (165 mg, 0.42 mmol) in anhydrous THF (3 mL) was added LAH (32 mg, 0.84 mmol, 2.0 equiv). The reaction mixture was heated at 55 °C for 4 h, cooled to room temperature and quenched with H₂O (2 mL) and 6M NaOH (2 mL), respectively. The cloudy solution was heated at 55 °C for 10 min until it became clear. The solution was

extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated. The crude residue was dissolved in DCM (4 mL) and cooled to -78 °C (dry-ice/acetone). Then a solution of BBr₃ (1.0 M) (1.68 mL, 1.68 mmol) was added dropwise to the reaction mixture. The dry-ice/acetone cooling bath was removed right after the addition of the BBr₃ solution, and the reaction was further stirred for 1 h. The reaction was cooled to 0 °C, then quenched with 28% NH₄OH (4 mL) and H₂O (5 mL). The cloudy reaction mixture was heated until most the DCM evaporated. The mixture was extracted with DCM (10 mL × 3). The combined organic layers were washed with brine, dried over MgSO₄, and evaporated. The residue was purified by column chromatography (SiO₂) by eluting with CHCl₃:MeOH:28% NH₄OH (95:4:1) to afford the corresponding phenolic phenylmorphans.

4.1.8.1 (1*S*,5*S*,9*S*)-(+)-5-(3-Hydroxyphenyl)-2-(((1*S*,2*S*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*S*) (1'*S*,2'*S*)-29: Using general procedure 4.1.8:

Reduction and demethylation of (1*S*,5*S*,9*S*) (1'*S*,2'*S*)-25 gave (1*S*,5*S*,9*S*) (1'*S*,2'*S*)-29 in 78% yield as a white foam. $[\alpha]_D^{20} +35.4$ (*c* 1.1, CHCl₃); HRMS (ESI) *m/z* 364.2269 [C₂₄H₃₀NO₂ (M+H)⁺ requires 364.2277]. ¹H NMR (400 MHz, CDCl₃) δ 7.24 – 7.20 (m, 2H), 7.15 – 6.98 (comp, 4H), 6.84 – 6.83 (comp, 2H), 6.67 – 6.55 (m, 1H), 4.24 (d, *J* = 3.6 Hz, 1H), 3.17 (br, 1H), 2.99 – 2.86 (m, 2H), 2.78 (dd, *J* = 12.7, 6.2 Hz, 1H), 2.57 (dd, *J* = 12.7, 6.8 Hz, 1H), 2.24 – 2.00 (comp, 2H), 1.85 – 1.65 (comp, 7H), 1.33 – 1.24 (m, 1H), 0.98 (dt, *J* = 8.5, 5.1 Hz, 1H), 0.88 (dt, *J* = 8.8, 5.3 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 156.5, 149.5, 142.6, 129.4, 128.3, 125.6, 125.5, 117.6, 114.0, 113.7, 72.4, 59.2, 56.5, 49.5, 40.0, 38.7, 28.3, 22.4, 21.7, 21.0, 17.9, 15.4.

4.2.2. (1*S*,5*S*,9*S*) (1'*S*,2'*S*)-29.oxalate: The salt was formed with oxalic acid in 2-propanol; mp 128– 132 °C; Calcd for C₂₄H₂₉NO₂•C₂H₂O₄•0.5 C₃H₈O: C, 68.30; H, 7.30; N, 2.90; found: C, 67.91; H, 7.34; N, 3.02.

4.1.8.2. (1*R*,5*R*,9*R*)-(-)-5-(3-Hydroxyphenyl)-2-(((1*R*,2*R*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*R*) (1'*R*,2'*R*)-29: Using general procedure 4.1.8: 69% yield; $[\alpha]_D^{20} -34.5$ (*c* 1.1, CHCl₃)

(1*R*,5*R*,9*R*) (1'*R*,2'*R*)-29.Oxalate: Calcd for C₂₄H₂₉NO₂•C₂H₂O₄•0.5 C₃H₈O: C, 68.30; H, 7.30; N, 2.90; found: C, 68.02; H, 7.37; N, 2.84.

4.1.8.3. (1*R*,5*R*,9*R*)-(+)-5-(3-hydroxyphenyl)-2-(((1*S*,2*S*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*R*) (1'*S*,2'*S*)-30: Using general procedure 4.1.8: reduction and demethylation of (1*R*,5*R*,9*R*) (1'*S*,2'*S*)-26 gave (1*R*,5*R*,9*R*) (1'*S*,2'*S*)-30 in 77% yield as a white foam. $[\alpha]_D^{20} +52.4$ (*c* 1.2, CHCl₃); HRMS (ESI) *m/z* 364.2274 [C₂₄H₃₀NO₂ (M+H)⁺ requires 364.2277]. ¹H NMR (400 MHz, CDCl₃) δ 7.25 – 6.93 (comp, 6H), 6.779 – 6.77 (m, 2H), 6.60 – 6.50 (m, 1H), 4.21 (d, *J* = 3.6 Hz, 1H), 3.17 (br, 1H), 2.96 – 2.85 (m, 2H), 2.80 (dd, *J* = 12.7, 5.6 Hz, 1H), 2.53 (dd, *J* = 12.7, 7.3 Hz, 1H), 2.20 – 2.10 (m, 1H), 1.98 (dd, *J* = 22.4, 11.2 Hz, 1H), 1.89 – 1.63 (comp, 7H), 1.32 – 1.27 (1H), 0.96 – 0.89 (m, 1H), 0.87 – 0.82 (m, 1H). ¹³C NMR (400

MHz, CDCl₃) δ 156.4, 149.3, 142.5, 129.4, 128.2, 125.6, 125.4, 117.5, 114.1, 113.9, 72.4, 59.5, 56.8, 49.3, 40.0, 38.6, 28.3, 22.9, 21.7, 20.8, 17.9, 14.9.

4.1.8.4. (1*R*,5*R*,9*R*)-(1'*S*,2'*S*)-30.Oxalate: The salt was formed with oxalic acid in isopropanol; mp 123–126 °C; Calcd for C₂₄H₂₉NO₂•C₂H₂O₄•0.5 C₃H₈O: C, 68.30; H, 7.30; N, 2.90; found: C, 68.36; H, 7.26; N, 2.87.

4.1.8.5. (1*S*,5*S*,9*S*)-(-)-5-(3-hydroxyphenyl)-2-(((1*R*,2*R*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*S*) (1'*R*,2'*R*)-30: Using general procedure 4.1.8: 9% yield; [α]_D²⁰ -61.9 (c 1.24, CHCl₃).

4.1.8.6. (1*S*,5*S*,9*S*) (1'*R*,2'*R*)-30.Oxalate: Calcd for C₂₄H₂₉NO₂•C₂H₂O₄•0.5 C₃H₈O: C, 68.30; H, 7.30; N, 2.90; found: C, 68.47; H, 7.53; N, 3.04.

4.1.8.7. (1*S*,5*S*,9*S*)-(+)-5-(3-hydroxyphenyl)-2-(((1*S*,2*R*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*S*) (1'*S*,2'*R*)-31: Using general procedure 4.1.8: reduction and demethylation of 1*S*,5*S*,9*S* (1'*S*,2'*R*)-27 gave (1*S*,5*S*,9*S*) (1'*S*,2'*R*)-31 in 43% yield as a white foam. [α]_D²⁰ +39.1 (c 0.9, MeOH); HRMS (ESI) *m/z* 364.2271 [C₂₄H₃₀NO₂ (M+H)⁺ requires 364.2277]. ¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.06 (comp, 6H), 6.90 – 6.79 (comp, 2H), 6.52 (dd, *J* = 7.9, 2.1 Hz, 1H), 5.02 (br, 2H), 3.97 (d, *J* = 3.6 Hz, 1H), 3.03 – 2.85 (m, 2H), 2.74 (d, *J* = 2.1 Hz, 1H), 2.41 – 2.15 (m, 4H), 1.97 (dd, *J* = 13.8, 4.9 Hz, 1H), 1.89 – 1.63 (m, 3H), 1.59 – 1.54 (m, 1H), 1.50 – 1.40 (m, 1H), 1.37 – 1.17 (m, 2H), 1.07 (td, *J* = 8.4, 5.2 Hz, 1H), 0.83 (dd, *J* = 11.4, 5.7 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 156.0, 150.5, 138.8, 129.1, 128.6, 128.0, 125.8, 117.2, 112.8, 112.7, 71.4, 58.0, 53.7, 47.9, 40.6, 40.5, 29.6, 24.2, 22.5, 20.7, 17.7, 9.0.

4.1.8.8. (1*S*,5*S*,9*S*) (1'*S*,2'*R*)-31.oxalate: The salt was formed with oxalic acid in isopropanol:ethylacetate (20:1); mp 145–150 °C; Calcd for C₂₄H₂₉NO₂•0.25 H₂O: C, 68.18; H, 6.931; N, 3.06; Found: C, 68.28; H, 6.98; N, 3.03.

4.1.8.9. (1*R*,5*R*,9*R*)-(-)-5-(3-hydroxyphenyl)-2-(((1*R*,2*S*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*R*) (1'*R*,2'*S*)-31: Using general procedure 4.1.8: (52% yield; [α]_D²⁰ -39.0 (c 1.0, MeOH).

4.1.8.10. (1*R*,5*R*,9*R*) (1'*R*,2'*S*)-31.oxalate: Calcd for C₂₉H₃₁NO₆•0.75 C₄H₈O₂: C, 67.03; H, 7.18; N, 2.70; Found: C, 67.01; H, 7.09; N, 3.02.

4.1.8.11. (1*R*,5*R*,9*R*)-(+)-5-(3-hydroxyphenyl)-2-(((1*S*,2*R*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*R*,5*R*,9*R*) (1'*S*,2'*R*)-32: Using general procedure 4.1.8: reduction and demethylation of (1*R*,5*R*,9*R*) (1'*S*,2'*R*)-28 gave (1*R*,5*R*,9*R*) (1'*S*,2'*R*)-32 in 38% yield as a white foam. [α]_D²⁰ +28.1 (c 0.7, CHCl₃); HRMS (ESI) *m/z* 364.2274 [C₂₄H₃₀NO₂ (M+H)⁺ requires 364.2277]. ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.07 (comp, 6H), 6.93 (s, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.66 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.37 (d, *J* = 2.4 Hz, 1H), 3.33 (s, 1H), 2.81 (dd, *J* = 11.9, 7.1 Hz, 1H), 2.68 – 2.57 (m, 2H), 2.30 – 2.01 (comp, 3H), 1.89 – 1.36 (comp, 7H), 1.13 (dt, *J* = 8.3, 4.2 Hz, 1H), 0.88 (dd, *J* = 11.5, 5.8 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 156.6, 149.1,

138.3, 129.4, 128.8, 128.0, 126.0, 117.5, 114.1, 113.6, 71.8, 56.4, 53.9, 49.1, 39.9, 38.2, 28.2, 21.3, 20.3, 17.6, 16.1, 9.5.

4.1.8.12. (1*R*,5*R*,9*R*) (1'*S*,2'*R*)-32.oxalate: The salt was formed with oxalic acid in EtOAc; mp 124–130 °C. Calcd for C₂₉H₃₁NO₆•0.25 H₂O: C, 68.18; H, 6.93; N, 3.06; Found: C, 68.04; H, 7.28; N, 3.01.

4.1.8.13. (1*S*,5*S*,9*S*)-(-)-(5-(3-hydroxyphenyl)-2-(((1*R*,2*S*)-2-phenylkypodpropyl)methyl)-2-azabicyclo[3.3.1]nonan-9-ol (1*S*,5*S*,9*S*) (1*R*,2*S*)-32: Using general procedure 4.1.8: 47% yield; [α]_D²⁰ -28.5 (c 1.0, CHCl₃).

4.1.8.14. (1*S*,5*S*,9*S*) (1*R*,2*S*)-32.oxalate: Calcd for C₂₉H₃₁NO₆•0.75 H₂O: C, 66.86; H, 7.01; N, 3.00; Found: C, 66.75; H, 7.00; N, 3.03.

4.2. Pharmacology

4.2.1. Opioid Binding Affinity—Whole rat brains excluding cerebellum were thawed on ice, homogenized in 50 mM Tris HCl, pH 7.5 using a Brinkman Polytron (setting 6 for 20 sec), and centrifuged at 30,000 × *g* for 10 min at 4 °C. The supernatant was discarded and the pellet was re-suspended in fresh buffer and spun at 30,000 × *g* for 10 min. The supernatant was discarded and the pellet was re-suspended to give 100 mg/mL original wet weight. Ligand binding experiments were conducted in polypropylene assay tubes containing 0.5 mL Tris HCl buffer for 60 min at room temperature. [³H]DADLE (final concentration 1 nM, PolyPeptide Laboratories, San Diego, CA), [³H]DAMGO (final concentration 1 nM, PolyPeptide Laboratories, San Diego, CA) or [³H]U69,593 (final concentration 1 nM, Perkin Elmer Life Sciences, Waltham MA) were used to determine binding at δ-, μ- and κ-opioid receptor sites, respectively. Unlabeled DAMGO (final concentration, 30 nM) was added to the delta assay tubes to block mu receptor binding. All assay tubes contained 100 μL homogenate suspension. Nonspecific binding was determined in all assays using 0.01 mM naloxone. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.1% polyethyleneimine, using a Brandel R48 filtering manifold (Brandel Instruments Gaithersburg, Maryland). The filters were washed twice with 5 mL cold buffer and transferred to scintillation vials. Cytoscint (MP Biologicals) (3.0 mL) was added and the vials were counted the next day using a Perkin Elmer TriCarb liquid scintillation counter. Data were analyzed with GraphPad Prism software (San Diego, California).

4.2.2. Stimulation of [³⁵S]GTPγS Binding—All tissue culture reagents were purchased from Gibco Life Sciences (Grand Island, NY, U.S.). C6-rat glioma cells stably transfected with a rat μ (C6-MOR) or rat δ (C6-DOR) opioid receptor and Chinese hamster ovary (CHO) cells stably expressing a human κ (CHO-KOR) opioid receptor³⁴ were used for all in vitro assays. Cells were grown to confluence at 37 °C in 5% CO₂ in Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum and 5% penicillin/streptomycin. Membranes were prepared by washing confluent cells three times with ice-cold phosphate buffered saline (0.9% NaCl, 0.61 mM Na₂HPO₄, 0.38 mM KH₂PO₄, pH 7.4). Cells were detached from the plates by incubation in warm harvesting buffer (20 mM

HEPES, 150 mM NaCl, 0.68 mM EDTA, pH 7.4) and pelleted by centrifugation at 1600 rpm for 3 min. The cell pellet was suspended in ice-cold 50 mM Tris-HCl buffer, pH 7.4, and homogenized with a Tissue Tearor (Biospec Products, Inc., Bartlesville, OK, U.S.) for 20 sec. The homogenate was centrifuged at 15000 rpm for 20 min at 4 °C. The pellet was re-homogenized in 50 mM Tris-HCl with a Tissue Tearor for 10 sec, followed by re-centrifugation. The final pellet was re-suspended in 50 mM Tris-HCl and frozen in aliquots at 80 °C. Protein concentration was determined via a BCA protein assay (Thermo Scientific Pierce, Waltham, MA, U.S.) using bovine serum albumin as the standard.

Agonist stimulation of [³⁵S]guanosine 5'-O-[γ-thio]triphosphate ([³⁵S]GTPγS, 1250 Ci, 46.2 TBq/mmol) binding to G-protein was measured as described previously. Briefly, membranes (10–20 μg of protein/tube) were incubated 1 h at 25 °C in GTPγS buffer (50 mM Tris-HCl, 100 mM NaCl, 5 mM MgCl₂, pH 7.4) containing 0.1 nM [³⁵S]GTPγS, 30 μM guanosine diphosphate (GDP), and varying concentrations of test compound. G-Protein activation following receptor stimulation of [³⁵S]GTPγS (% stimulation) with test compound was compared with 10 μM of the standard compounds [D-Ala²,N-MePhe⁴,Gly-ol]-enkephalin (DAMGO) at μ-OR, D-Pen²,5-enkephalin (DPDPE) at δ-OR, or U69,593 at κ-OR. The reaction was terminated by vacuum filtration of GF/C filters that were washed 10 times with GTPγS buffer. Bound radioactivity on dried filters was determined by liquid scintillation counting, after saturation with EcoLume liquid scintillation cocktail, in a Wallac 1450 MicroBeta (PerkinElmer, Waltham, MA, U.S.). The results are presented as the mean ± standard error (SEM) from at least three separate assays performed in duplicate; potency (EC₅₀ (nM)) and % stimulation were determined using nonlinear regression analysis with GraphPad Prism.

4.3. Computational studies

Details of the modeling and simulations are given in the Supplementary Data.

4.4. X-ray crystallographic study

Single-crystal X-ray diffraction data on **30.oxalate** was collected using MoKα radiation ($\lambda = 0.71073\text{\AA}$) and a Bruker APEX-2 CCD area detector. The crystal was prepared for data collection by coating with high viscosity microscope oil. The oil-coated crystal was mounted on a micro-mesh mount (Mitegen, Inc.) and transferred to the cold stream on the diffractometer and a diffraction data collected at 150°K. The $0.461 \times 0.399 \times 0.389\text{ mm}^3$ data crystal of **30.oxalate** was monoclinic in space group $P2_1$, with unit cell dimensions $a = 10.2374(4)$, $b = 9.0649(3)$, $c = 12.3716(7)\text{ \AA}$, and $\beta = 94.888(1)^\circ$. The data was 99.7% complete to $29.13^\circ \theta$ ($\sim 0.73\text{ \AA}$) with an average redundancy of 6.13. The final anisotropic full matrix least-squares refinement on F^2 with 96 variables and one constraint converged at $R1 = 3.26\%$, for the observed data and $wR2 = 10.29\%$ for all data.

The structure was solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Corrections were applied for Lorentz, polarization, and absorption effects. Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a

riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 Å. The absolute configuration was set based on the known configuration of unvarying chiral centers. Complete information on data collection and refinement is available in the supplemental material.

Atomic coordinates have been deposited with the Cambridge Crystallographic Data Centre (deposition number 1521496). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- N-Substituted-9 β -hydroxy-5-(3-hydroxyphenyl)morphan enantiomers.
- *1R,5R,9S-16* and *1R,5R,9S-15* - full, high efficacy μ -agonists.
- *1S,5S,9R-16*, the enantiomer of *1R,5R,9S-16*, was an efficacious μ -antagonist.
- μ -OR molecular dynamics simulations with *1R,5R,9S-16*.
- *p*-Nitro group critical, forming direct, persistent hydrogen bonds.

Figure 1.
 Effect of N-substituents in 5-phenylmorphans; an aromatic electron-withdrawing substituent, and introduction of conformational restraint.

Figure 2.
X-ray crystallographic structure of (1*S*,5*S*,9*S*)-5-(3-hydroxyphenyl)-2-(((1*R*,2*R*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-9-ol.oxalate (**30**.oxalate). Displacement ellipsoids are shown at the 50% level.

Figure 3. Shift in the DAMGO concentration-effect curve in the [^{35}S]GTP γ S assay for (+)-1*S*,5*S*,9*R*-16

Figure 4.

Schematic representation of the main, direct ligand-OR interactions observed in the simulations; water-involved H-bond interactions are not shown. Dashed red lines indicate persistent H- bonds; other polar interactions of the nitro group in 1R,5R,9S-16 are also statistically significant (see text). Non-polar interactions include aromatic T-shaped (W229 in NIH 11289) and stacking (Y262 in NIH 11289 and W229 in 1R,5R,9S-16) with the phenyl ring of the ligands.

Scheme 1.
Strategy for the target compounds

Scheme 2.
Improved N-demethylation procedure

Scheme 3.

N-Alkylation procedures: **Method A**: 1.5 equiv of aryl, alkyl, or alkenyl bromide, at 80 °C for 16 h. **Method B**: slow addition of 1.0 equiv of (*E*)-(3-bromoprop-1-en-1-yl)benzene, at 0 °C to room temperature.

Scheme 4.

Selective reduction of **3–8** to give alcohols **9–14**.

Scheme 5.

O-Demethylation of methyl ethers **9 – 14** to give phenols **15 – 20**

Scheme 6.
Installation of the chiral cyclopropyl side chain

Scheme 7.

Coupling reaction between C9-keto-phenylmorphans and chiral carboxylic acids

Scheme 8.

Stereoselective reduction of the C9-oxo phenylmorphans with Superhydride.

Scheme 9.

Reduction and O-demethylation to the phenolic amines.

Table 1

Opioid receptor binding studies^a

Compound	$K_i \pm \text{SEM}$ (nM)			
	μ (DAMGO)	δ (DADLE)	κ (U-69, 593)	
(-)-1 <i>R</i> ,5 <i>R</i> ,9 <i>S</i> - 16 .oxalate	0.073 $\pm$ 0.008	9.81 $\pm$ 1.16	54.5 $\pm$ 7.26	
1 <i>R</i> ,5 <i>R</i> ,9 <i>S</i> - 20 .oxalate	0.741 $\pm$ 0.059	17.8 $\pm$ 1.35	I	
1 <i>R</i> ,5 <i>R</i> ,9 <i>S</i> - 15 .HCl	1.99 $\pm$ 0.239	161 $\pm$ 9.12	29.9 $\pm$ 4.1	
1 <i>R</i> ,5 <i>R</i> ,9 <i>R</i> ,1', <i>R</i> ,2', <i>S</i> '- 31 .oxalate	11.6 $\pm$ 1.58	I	I	
1 <i>S</i> ,5 <i>S</i> ,9 <i>R</i> - 20 .oxalate	25.0 $\pm$ 3.60	I	I	

Compound		$K_i \pm \text{SEM (nM)}$			κ (U-69, 593)
		μ (DAMGO)	δ (DADLE)		
(+)-1,5,5,9R-16,oxalate		26.5 $\pm$ 1.10	I		I
1R,5R,9S-17.HCl		29.2 $\pm$ 1.62	I		I
(1R,5R,9R) (1',2',R)-29,oxalate		44.5 $\pm$ 1.93	I		I
(1R,5R,9R) (1',S,2',R)-32,oxalate		51.8 $\pm$ 7.24	I		I
NIH 11289(-)-(1R,5R,9S)		0.265 $\pm$ 0.018	19.2 $\pm$ 1.50		Not tested
Morphine. HBr		2.33 $\pm$ 0.261			
SNC 80			3.53 $\pm$ 0.428		
U69,593					3.98 ^b

^a Assays were typically conducted in at least three independent experiments, each performed with triplicate observations using rat tissue; $K_i \pm \text{SEM (nM)}$; I = < 50% activity at 100 nM concentration (displaced less than half of radioligand) in exploratory assay.

^b K_d value obtained by homologous competition with three independent replicates modeled together to provide 95% confidence limits of 2.77–5.71 nM.

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DAMGO: [D-Ala², N-MePhe⁴, Gly^{-ol}]-enkephalin; DADLE: [D-Ala², D-Leu⁵]-enkephalin; U-69,593: (+)-(5a,7a,8 β)-N-methyl-N-[7-(1-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl)-benzeneacetamide

Table 2

Stimulation of GTP γ S³⁵ binding at μ -, δ - and κ -opioid receptors

Compound		μ -OR % stimulation (EC50, nM)	δ -OR % stimulation (EC50, nM)	κ -OR % stimulation (EC50, nM)
1 <i>R</i> ,5 <i>R</i> ,9 <i>S</i> - 16 .oxalate		104 ± 4.10 (0.74 ± 0.17)	104 ± 10.8 (630 ± 45.3)	DNS
1 <i>R</i> ,5 <i>R</i> ,9 <i>S</i> - 20 . oxalate		20 ± 6.0 (1.9 ± 0.82)	51 ± 3.7 (253 ± 77.6)	NT
1 <i>R</i> ,5 <i>R</i> ,9 <i>S</i> - 15 .HCl		83 ± 7.8 (19 ± 9.9)	50 ± 2.8 (901 ± 54.8)	18 ± 3.5 (761±274)
1 <i>R</i> ,5 <i>R</i> ,9 <i>R</i>) (1' <i>R</i> ,2' <i>S</i>)- 31 . oxalate		22 ± 3.4 (797.1 ± 573)	NT	NT
1 <i>S</i> ,5 <i>S</i> ,9 <i>R</i> - 20 .oxalate		DNS	NT	NT
1 <i>S</i> ,5 <i>S</i> ,9 <i>R</i> - 16 .oxalate		DNS	NT	NT
1 <i>R</i> ,5 <i>R</i> ,9 <i>S</i> - 17 .HCl		67 ± 5.9 (2056 ± 409)	NT	NT
(1 <i>R</i> ,5 <i>R</i> ,9 <i>R</i>) (1' <i>R</i> ,2' <i>R</i>)- 29 .oxalate		DNS	NT	NT

Compound		μ -OR % stimulation (EC50, nM)	δ -OR % stimulation (EC50, nM)	κ -OR % stimulation (EC50, nM)
(1 <i>R</i> ,5 <i>R</i> ,9 <i>R</i>) (1' <i>S</i> ,2' <i>R</i>)-32.oxalate		DNS	NT	NT
NIH 11289; (-)-(1 <i>R</i> ,5 <i>R</i> ,9 <i>S</i>)		120 ± 3.70 (22 ± 1.7)	100 ± 5.30 (1084 ± 118)	NT
DAMGO ^a		101 ± 0.10 (146 ± 25.0)		
DPDPE ^b			99 ± 1.5 (368 ± 60.0)	
EKC ^c				93 ± 1.3 (2.2 ± 0.70)

% stimulation compared to standard maximal at each receptor (μ -OR = DAMGO; δ -OR = DPDPE; κ -OR = U60593) in C6 cells expressing μ -OR or δ -OR or CHO cells expressing κ -OR. All experiments were repeated on three separate occasions in duplicate. Values are given as means ± SEM. DNS = no stimulation (antagonist). NT = Not tested.

^a ([D-Ala2, N-MePhe4, Gly-ol]-enkephalin);

^b [D-Pen2,5]-enkephalin;

^c ethylketocyclazocine.