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Further Optimization and Evaluation of Bioavailable, Mixed-Efficacy μ-Opioid Receptor (MOR) Agonists/δ-Opioid Receptor (DOR) Antagonists: Balancing MOR and DOR Affinities

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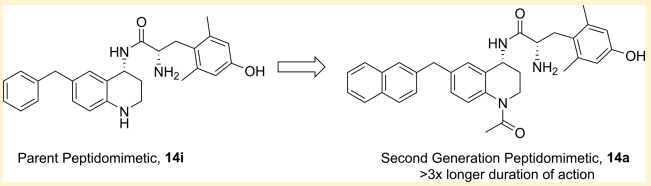
Supporting Information

ABSTRACT: In a previously described peptidomimetic series, we reported the development of bifunctional μ-opioid receptor (MOR) agonist and δ-opioid receptor (DOR) antagonist ligands with a lead compound that produced antinociception for 1 h after intraperitoneal administration in mice. In this paper, we expand on our original series by presenting two modifications, both of which were designed with the following objectives: (1) probing bioavailability and improving metabolic stability, (2) balancing affinities between MOR and DOR while reducing affinity and efficacy at the κ-opioid receptor (KOR), and (3) improving in vivo efficacy. Here, we establish that, through *N*-acetylation of our original peptidomimetic series, we are able to improve DOR affinity and increase selectivity relative to KOR while maintaining the desired MOR agonist/DOR antagonist profile. From initial in vivo studies, one compound (**14a**) was found to produce dose-dependent antinociception after peripheral administration with an improved duration of action of longer than 3 h.



INTRODUCTION

Several studies have reported the utility and application of compounds with μ-opioid receptor (MOR) activation and reduced δ-opioid receptor (DOR) signaling.[1−5] Co-administration of a MOR agonist with a DOR antagonist[6−8] produces antinociception with reduced risk of tolerance and dependence, implicating the importance of reduced DOR signaling in mitigating these undesired properties. However, multidrug regimens may produce pharmacokinetic complications and lead to low patient compliance.[9−11] Thus, we[1,2,12−14] and others[3−5,15,16] have pursued the development of bifunctional, mixed-efficacy MOR agonist/DOR antagonist ligands. We first reported the synthesis of a high-affinity (nanomolar binding) opioid receptor peptidomimetic with selectivity for MOR in 1998. In this initial report, a tetrahydroquinoline (THQ) scaffold was implemented to mimic the binding conformations of the high-affinity tetrapeptide JOM-13 (Tyr-c[D-Cys-Phe-D-Pen]OH) and related peptides while eliminating the disulfide-containing moiety of the peptide.[17] Since then, we have developed several additional mixed-efficacy peptides that have helped elucidate which functionalities yield high affinity binding across the receptor subtypes.[13,14,18,19] For example, we have found that, in our peptides, bulky aromatics (1-naphthyl, 2-naphthyl, and 2-indanyl groups) are especially useful for obtaining a more balanced MOR agonist/DOR antagonist profile.[13,14] Given the promising results from the peptide series, we sought to transfer the key binding elements from a peptide scaffold to a more bioavailable peptidomimetic scaffold that incorporated the bulky aromatic moieties that enhanced the MOR agonist/DOR antagonist profile we desired. We reported a series of mixed-efficacy opioid peptidomimetics employing a THQ scaffold that displayed a MOR agonist/DOR antagonist profile and whose lead compound produced antinociception for a duration of approximately 1 h in a mouse warm water tail withdrawal (WWTW) assay after peripheral (intraperitoneal, ip) administration.[1] Although our original opioid peptidomimetic series displayed the desired profile and validated our THQ scaffold as being a suitable and bioavailable template, there remained opportunity to improve the in vitro and in vivo properties. For example, compounds in the original series displayed a 10- to 130-fold binding affinity preference for MOR over DOR, and many also exhibited considerable affinity and efficacy at the κ-opioid receptor (KOR). In the subsequent generation of compounds, we explored two different modifications to our original series in an attempt to (1) probe and improve bioavailability and metabolic stability, (2) balance the affinity at MOR and DOR while reducing KOR affinity and efficacy, and (3) increase in vivo efficacy and duration of action. Here, we display our findings from two parallel series of analogues, which include replacement of our THQ scaffold with a tetrahydronaphthalene (THN) scaffold or *N*-acetylation of the nitrogen in the THQ core of our original series (Figure 1).

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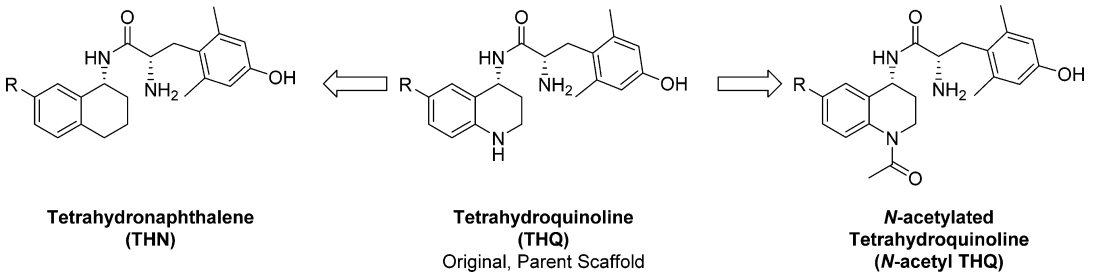


Figure 1. Modifications to the THQ scaffold.

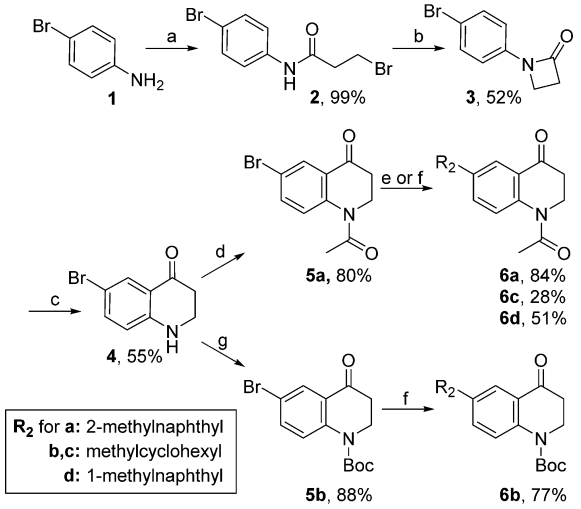
Through both of these modifications, our goal was to reduce the metabolic lability associated with the nitrogen heteroatom in the THQ ring, as two common metabolic concerns associated with this moiety include *N*-oxidation and oxidation α to the heteroatom.[20−24] Furthermore, the amine in the THQ core is also part of an aniline system, which is susceptible to aromatization, not only in vivo,[25] but potentially in ambient atmosphere with trace acid present.[26] As described below, we observed that *N*-acetylation of our parent compound **14i** to form **14e** improved DOR affinity without altering MOR affinity, resulting in a better balance of MOR and DOR binding. Consequently, we decided to explore parallel series with variable substituent R (Figure 1) with and without *N*-acetylation of the core THQ nitrogen to examine effects on bioavailability and relative MOR and DOR affinities. We also explored the effect of eliminating the aniline nitrogen entirely by replacing the THQ scaffold with THN. As described below, the *N*-acetylation of the THQ scaffold improved DOR affinity across our parallel series without significantly altering efficacy profiles or binding at MOR, thereby creating bifunctional ligands with a more balanced MOR agonist/DOR antagonist profile. In addition, one of the new analogues, **14a**, displays full antinociception in the mouse WWTW assay for a duration of longer than 3 h after peripheral administration, a significant improvement on our original in vivo results for parent **14i**.

RESULTS

Diversification of THQ-Containing Analogues via Suzuki Coupling. The core THQ intermediate **4** (Scheme 1) was synthesized using the methodology developed by Schmidt et al.[27] and described in our previous paper[1] with the single modification of using *p*-bromoaniline as the starting material. Briefly, *p*-bromoaniline **1** was acylated using 3-bromopropionyl chloride to yield **2**, cyclized under basic conditions to form lactam **3**, and then treated with trifluoromethanesulfonic acid to form intermediate **4**. The nitrogen of **4** was protected with a *tert*-butyloxycarbonyl (Boc) group or an acetyl group (later referred to as "R_1") to form intermediates **5a** and **5b**, which were then subjected to Suzuki cross-coupling[28,29] to yield compounds **6a−d** with diverse R_2 substituents.

Diversification of THQ-Containing Analogues via Condensation Chemistry. Although starting material for **7e**, which bears a benzyl R_2 substituent, was commercially available, compounds containing a THQ core with a 1- or 2-methylindanyl substituent were synthesized by incorporating the R_2 substituent during the first synthetic step via a condensation reaction. Specifically, the 2-methylindanyl analogue was synthesized via an aldol condensation followed by a hydrogenation as previously described[1] to form aniline intermediate **7f**. The 1-methylindanyl analogues were synthesized as a racemic mixture using a slight modification to the methodology originally developed by Kolanos et al.[30] that begins with a condensation reaction between indene and 4-acetamidobenzaldehyde, the product of which was hydrogenated and deprotected to yield aniline intermediate **7g**. The aniline intermediates **7e−g** were then acylated, cyclized to form lactams **9e−g**, and treated with trifluoromethanesulfonic acid to form **10e−g**, as shown previously[1,27] (Scheme 2). Intermediates **10e−g** were then protected with Boc or an acetyl group (later referred to as "R_1") to form intermediates **6e−h** with diverse substituents.

Scheme 1. Synthesis of THQ-Containing Analogues Diversified via Suzuki Coupling



[a]3-Bromopropionyl chloride (1.02 equiv), K_2CO_3 (2.05 equiv), DCM, RT. [b]NaO*t*Bu (1.05 equiv), DMF, RT. [c]TfOH (3 equiv), DCE, RT. [d]Neat Ac_2O (excess), reflux. [e]For synthesis of **6a** and **6d**: R_2-Bpin (2 equiv), Pd(dppf)Cl_2 (0.1 equiv), K_2CO_3 (3 equiv), 3:1 acetone:H_2O, MW 100 °C, 300 W. [f]For synthesis of **6c** and **6d**: R_2-B(OH)$_2$ (2 equiv), Ag_2O (2.5 equiv), Pd(dppf)Cl_2 (0.1 equiv), K_2CO_3 (3 equiv), THF, MW 100 °C, 300 W. [g]Boc_2O (1.2−2 equiv), DMAP (0.1 equiv), DIPEA (1.2−2 equiv), DCM, 60 °C.

Completion of Synthesis of THQ-Containing Analogues from a Common Intermediate. Once the R_2 substituent was implemented in the THQ scaffold, the synthesis of final compounds **14a−h** converged beginning with **6a−h** (Scheme 3). Intermediates **6a−h** were treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to yield imines **11a−h**, which were reduced in situ with $NaBH_4$ to form the desired *R*-stereochemistry of intermediates **12a−h**.[31−33] The Ellman auxiliary was cleaved using concentrated hydrochloric acid, forming primary amines **13a−h**,[31−33] which were then coupled to di-Boc-protected 2,6-dimethyl-L-tyrosine (diBoc-DMT) and

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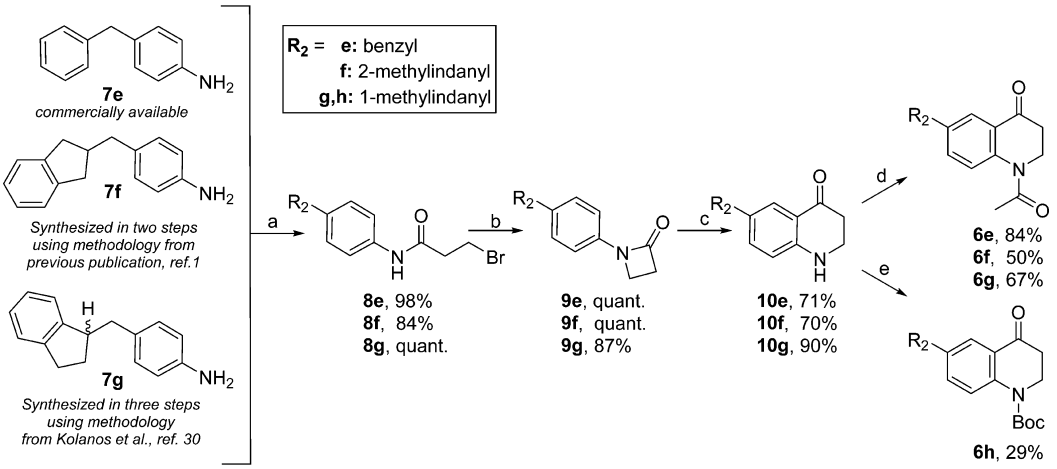
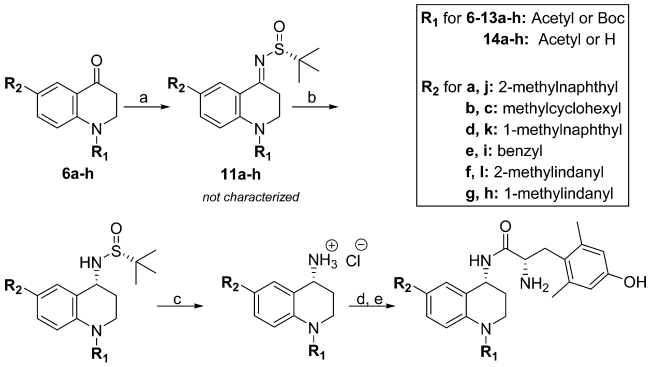
Scheme 2. Synthesis of THQ-Containing Analogues via Condensation Reactions



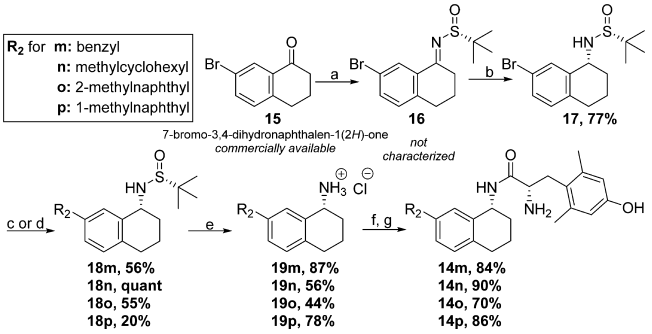
[a]3-Bromopropionyl chloride (1.02 equiv), K_2CO_3(2.05 equiv), DCM, RT. [b]NaO*t*Bu (1.05 equiv), DMF, RT. [c]TfOH (3 equiv), DCE, RT. [d]For synthesis of **6e**, **6g**, and **6g**: neat Ac_2O (excess), reflux. [e]For synthesis of **6h**: Boc_2O (1.2−2 equiv), DMAP (0.1 equiv), DIPEA (1.2−2 equiv), DCM, 60 °C.

Scheme 3. Completion of Synthesis of THQ-Containing Analogues



[a]Dihydroquinolinone intermediate, **6a−h** (1 equiv), (*R*)-*t*-butanesulfinamide (2−3 equiv), THF, $Ti(OEt)_4$ (4−6 equiv), 0 °C, then reflux at 75 °C. [b]$NaBH_4$ (6 equiv), THF, −50 °C to RT, then MeOH, RT. [c]HCl (6 equiv), dioxane, RT. [d]diBoc-DMT (1.05 equiv), PyBOP (1 equiv), 6Cl-HOBt (1 equiv), DIPEA (10 equiv), DMF, RT. [e]1:1 TFA:DCM (excess). Compounds **14i−14l** previously published, see ref 1. * indicates starting material was recovered, but not included in yield calculation.

Scheme 4. Synthesis of THN-Containing Analogues



[a]**15** (1 equiv), (R)-*t*-butanesulfinamide (2−3 equiv), THF, $Ti(OEt)_4$ (4−6 equiv) 0 °C, then reflux at 75 °C. [b]$NaBH_4$ (4−6 equiv), THF, −50 °C to RT, then MeOH, RT. [c]For synthesis of **18m**, **18o**, and **18p**: R_2-Bpin (1 equiv), $Pd(dppf)Cl_2$ (0.1 equiv), K_2CO_3 (3 equiv), 3:1 acetone:H_2O, MW 110 °C, 300 W. [d]For synthesis of **18n**: R_2-$B(OH)_2$(2 equiv), Ag_2O (2.5 equiv), $Pd(dppf)Cl_2$ (0.1 equiv), K_2CO_3 (3 equiv), THF, MW 80 °C, 300 W. [e]HCl (6 equiv), dioxane, RT. [f]diBoc-DMT (1.05 equiv), PyBOP (1 equiv), 6Cl-HOBt (1 equiv), DIPEA (10 equiv), DMF, RT. [g]1:1 TFA:DCM (excess).

deprotected to yield compounds **14a−h**. The syntheses for analogues **14i−l**, which also contain a THQ core, were previously published.[1]

Complete Synthesis of THN Peptidomimetic Analogues. Synthesis of THN compounds **14m−p** began by converting the ketone of commercially available 7-bromo-dihydronaphthalenone **15** to chiral imine **16** using (*R*)-*t*-butanesulfinamide and $Ti(OEt)_4$, followed by in situ reduction to form **17** using $NaBH_4$ to afford the desired *R*-stereochemistry of the sulfonamide[31−33] (Scheme 4). Next, various R_2 substituents were incorporated via Suzuki coupling to form intermediates **18m−p**.[28,29] Intermediates **18m−p** were then treated with concentrated hydrochloric acid to cleave the Ellman auxiliary, affording primary amines **19m−p**.[31−33] In the final step, amines **19m−p** were coupled to diBoc-DMT and deprotected to yield compounds **14m−p**.

Opioid Receptor Binding and Efficacy. Binding affinities (K_i) for the final compounds were determined from competitive displacement of radiolabeled [^{3}H]diprenorphine in membrane preparations from C6 cells stably expressing MOR (C6-MOR) or DOR (C6-DOR) or CHO cells stably expressing KOR (CHO-KOR), as previously described[34,35] (Table 1). Efficacy of the compounds was assessed by agonist-stimulated [^{35}S]GTPγS binding to G protein[36] in cell membrane preparations of C6-MOR, C6-DOR, and CHO-KOR (Table 1).

Although a total of six compound sets were synthesized (each set defined by the R_2 substituent), only four of these sets incorporated all three of the different scaffolds; these sets include analogues in which the R_2 substituent is a benzyl, a 1-

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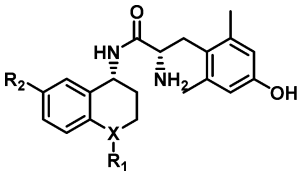
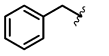
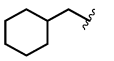
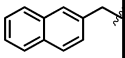
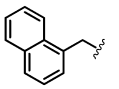
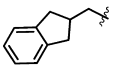
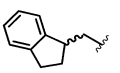
Table 1. Opioid Receptor Binding Affinities and Efficacies of Peptidomimetics



				Binding, K_i (nM)[a,c]			DOR K_i/MOR K_i Ratio	EC_{50} (nM)[b,c]			% stimulation[b,c]		
Cpd	X	R_1	R_2	MOR	DOR	KOR		MOR	DOR	KOR	MOR	DOR	KOR
14i[e]	N	H		0.22 (0.02)	9.4 (0.8)	68 (2)	43	1.6 (0.3)	110 (6)	540 (70)	81 (2)	16 (2)	22 (2)
14e	N			0.13 (0.02)	1.8 (0.1)	87 (10)	14	6.0 (1)	68 (2)	>1300 (90)	76 (4)	26 (3)	29 (5)
14m	CH_2	--		0.045 (0.03)	4.0 (1)	19 (7)	89	2.9 (0.6)	dns	dns	64 (9)	dns	dns
14b	N	H		0.043 (0.01)	3.4 (1)	6.2 (1)	79	2.6 (1)	dns	97 (30)	57 (5)	dns	36 (4)
14c	N			0.03 (0.01)	0.32 (0.1)	8.4 (2)	11	0.61 (0.2)	14 (8)	240 (70)	70 (6)	26 (5)	33 (6)
14n	CH_2	--		0.12 (0.02)	14 (6)	20 (5)	117	dns	dns	350 (80)	dns	dns	25 (6)
14j[e]	N	H		0.078 (0.01)	10 (2)	54 (7)	128	0.53 (0.08)	dns	dns	96 (3)	dns	dns
14a	N			0.04 (0.01)	0.23 (0.02)	48 (20)	6	0.93 (0.2)	dns	dns[d]	87 (3)	dns	dns[d]
14o	CH_2	--		0.06 (0.01)	12 (4)	92 (20)	140	4.4 (2)	dns	dns	72 (4)	dns	dns
14k[e]	N	H		0.76 (0.1)	6.0 (0.7)	17 (1)	8	0.84 (0.4)	69 (40)	dns	93 (5)	15 (1)	dns
14d	N			0.06 (0.02)	1.3 (0.4)	4.3 (2)	22	0.48 (0.2)	dns	dns[d]	70 (4)	dns	dns[d]
14p	CH_2	--		0.39 (0.08)	5.0 (0.3)	63 (20)	13	14 (7)	dns	dns[d]	58 (2)	dns	dns[d]
14l[e]	N	H		0.16 (0.04)	4.1 (2)	1.2 (0.4)	26	0.24 (0.03)	dns	dns	86 (1)	dns	38 (2)
14f	N			0.05 (0.00)	0.44 (0.07)	12 (4)	9	0.56 (0.1)	dns	610 (250)	84 (2)	dns	60 (10)
14h	N	H		0.05 (0.02)	6.8 (2)	19 (10)	136	9.0 (6)	dns	180 (80)	16 (8)	dns	52 (7)
14g	N			0.03 (0.00)	0.84 (0.13)	15 (0.2)	28	15 (10)	dns	340 (100)	39 (10)	dns	26 (8)

[a]Binding affinities (K_i (nM)) were obtained by competitive displacement of radiolabeled [^{3}H]diprenorphine in membrane preparations. [b]Efficacy data were obtained using agonist-induced stimulation of [^{35}S]GTPγS binding; efficacy is represented as percent maximal stimulation relative to standard agonist DAMGO (MOR), DPDPE (DOR), or U69,593 (KOR) at 10 μM. [c]All values are expressed as the mean with SEM in parentheses for n = 3 independent assays in duplicate unless otherwise noted. [d]In duplicate, n = 2 independent assays; dns: does not stimulate. [e]Syntheses and data for these compounds were previously published (see ref 1).

methylnaphthyl, a 2- methylnaphthyl, or a methylcyclohexyl. The effects of both scaffold modifications on the binding affinities are shown in Table 1. The most noticeable trend across these four sets of compounds is seen with the *N*-acetylated THQ series at DOR. This *N*-acetylated series (regardless of R_2) shows a significantly higher affinity at DOR than the unsubstituted THQ counterpart. Additionally, *N*-acetylation maintains, and in some cases slightly improves, affinity at MOR and slightly decreases affinity at KOR. The effect of the *N*-acetylated THQ scaffold on efficacy (Table 1) across all receptors is minimal with most compounds retaining similar efficacy as seen with the parent THQ series. When considering the effects of the *N*-acetylation on the THQ scaffold as a whole, this modification appears to balance the MOR/DOR binding profile while maintaining the desired MOR agonist/DOR antagonist efficacy profile.

In contrast, the effect of the THN scaffold on binding affinities at all three receptors (Table 1), when compared with the parent THQ scaffold, showed no consistent or advantageous trends. For example, when comparing **14m** (THN scaffold) with **14i** (THQ scaffold), **14m** shows increased affinity across all three receptors. Additionally, when comparing **14n** (THN scaffold) with **14b** (THQ scaffold), **14n** has decreased affinity across all three receptors. Furthermore, a decrease in efficacy is seen at MOR regardless of the R_2 substituent when compared to the THQ scaffold. Because the THN scaffold presented no apparent advantage, the 1- and 2-indanyl THN analogues were not pursued.

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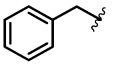
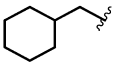
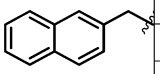
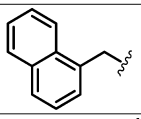
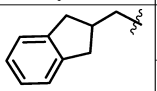
Table 2. In Vivo Activity of Select Peptidomimetics[a]

Cpd	Scaffold	R_2 substituent	*In vivo* Activity following *ip* administration[c]
14i[b]	THQ		Full antinociception at 10 mg/kg with duration of action >1h
14e	*N*-acetyl THQ		No activity up to 10 mg/kg
14m	THN		Partial antinociception with latency of 14 sec at 10 mg/kg
14b	THQ		No activity up to 10 mg/kg
14c	*N*-acetyl THQ		No activity up to 10 mg/kg
14j	THQ		Partial antinociception with latency of 10 sec at 10 mg/kg
14a	*N*-acetyl THQ		Full antinociception at 10 mg/kg with duration of action of >3 h
14o	THN		No activity up to 10 mg/kg
14d	*N*-acetyl THQ		No activity up to 10 mg/kg
14p	THN		No activity up to 10 mg/kg
14l	THQ		No activity up to 10 mg/kg
14f	*N*-acetyl THQ		Partial antinociception with latency of 11 sec at 10 mg/kg

[a]Summary of antinociceptive effects of select analogues (n = 3 for all analogues, except for **14a** n = 6) in mouse WWTW assay following intraperitoneal (ip) administration with a cutoff time of 20 s. [b]See ref 1. [c]Full antinociception indicates that the cutoff time was reached.

In Vivo WWTW Assay. Several compounds were chosen based on in vitro data to be assayed for antinociception in the mouse WWTW assay following intraperitoneal (ip) injection.[37] Of the compounds assayed (Table 2, Figure 2), only three

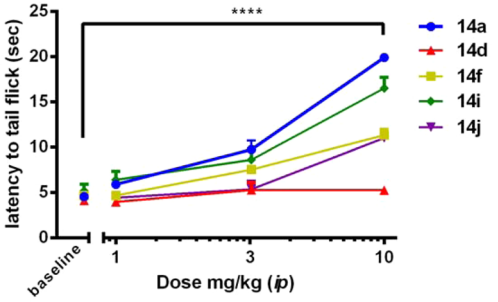


Figure 2. Cumulative antinociceptive dose response curves of select analogues (n = 3 for all analogues, except for **14a** where n = 6) in the mouse WWTW assay following ip administration. Plotted as average ± SEM ****, p < 0.0001 for **14a**, **14f**, **14i**, and **14j** for the 10 mg/kg dose when compared to baseline. Data for **14i** from ref 1.

compounds displayed dose-dependent antinociceptive activity. Compounds **14f** and **14j** displayed partial antinociception at the maximum dose tested, whereas **14a** displayed full antinociception with ED_{50} = 4.72 ± 0.01 mg/kg. By comparison, the ED_{50} of morphine, under the same conditions, was 4.73 ± 0.001 mg/kg. Because compound **14a** displayed full antinociception at 10 mg/kg in the initial WWTW assay, a time course study was completed to determine the duration of action (Figure 3). As can be seen in Figure 3, **14a** produces maximal antinociception with a rapid onset, which is maintained for approximately 200 min. This 200 min duration of action is greater than 3-times longer compared to the duration of action of our original lead peptidomimetic **14i**[1] (and similar to that observed for the same dose of morphine[1]), suggesting better bioavailability or metabolic stability. Interestingly, despite being structural isomers with a similar in vitro profile, **14a** and **14d** displayed drastically different in vivo results when administered via ip injection (Figure 2). Although **14a** displayed full

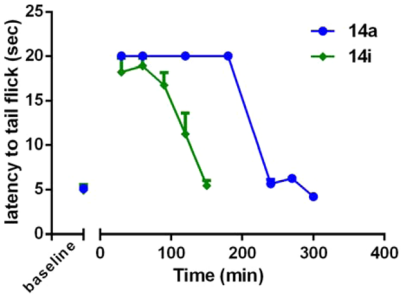


Figure 3. Time course of antinociception of **14a** and **14i** (n = 6) in the mouse WWTW assay following ip administration of 10 mg/kg. Plotted as average ± SEM. Data for **14i** from ref 1.

antinociception after ip administration, **14d** displayed no antinociception at the same dose after ip administration, suggesting that subtle differences in chemical structure create substantial differences in pharmacokinetics.

DISCUSSION AND CONCLUSIONS

Our previously described results[1] were promising in that we were able to transfer pharmacophore elements from a MOR agonist/DOR antagonist peptide to a peptidomimetic scaffold, as seen in our parent peptidomimetic **14i**, which was shown to have antinociceptive activity after peripheral administration in mice. Although our original series of compounds displayed the desired MOR agonist/DOR antagonist profile, there remained opportunity to improve the balance of binding affinities at MOR and DOR and reduce any remaining KOR binding and efficacy. Although the optimal balance of "MOR agonism" with "DOR antagonism" is yet to be determined, we reasoned that a low nanomolar, balanced affinity profile (~1:1 MOR K_i:DOR K_i) was a logical place to start, because this would ensure that both MOR agonist and DOR antagonist character would be represented in the in vivo outcome and would provide useful information for future studies. Our initial series displayed relatively unbalanced MOR and DOR affinities, where our compounds were 10- to 130-fold more selective for MOR over DOR (Table 1). In the present study, we set out to improve

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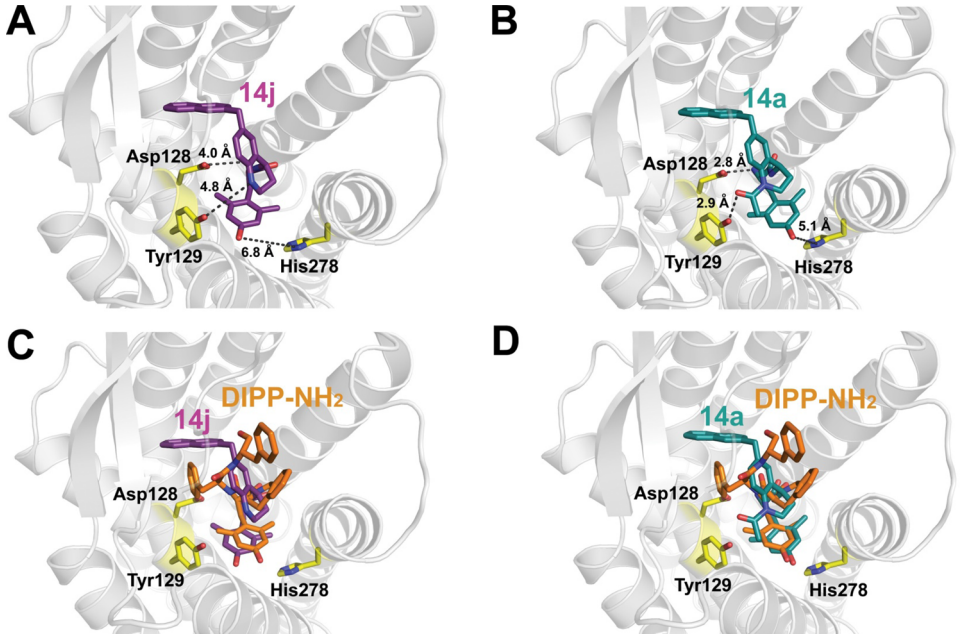

Figure 4. (A) **14j** (purple) in DORinactive (DORi) with key residues shown. (B) **14a** (teal) in DORi with key residues shown. Dashed lines represent calculated distances between ligand and receptor residues, indicating a possible interaction between *N*-acetyl moiety and Tyr^{129} that may increase binding affinity at DORi. (C) Overlay of **14j** (purple) and DIPP-NH_2 (orange) in DORi. (D) Overlay of **14a** (teal) and DIPP-NH_2 (orange) in DORi.

upon our initial compounds in two ways. First, we wished to explore modification of the THQ scaffold to avoid metabolic susceptibility due to the THQ ring nitrogen while also examining the effect of these modifications on binding affinity and efficacy. Second, we wished to explore the additional effect of modifying the R_2 substituent in the search for a MOR agonist/DOR antagonist with a better MOR/DOR affinity balance.

The initial in vitro results for the parallel series of scaffold modifications yield interesting insight into both the electronic and steric requirements for optimal binding. The data in Table 1 indicates that the series incorporating the THN scaffold, when compared to the unsubstituted THQ scaffold, leads to greater disparity in the binding affinities at MOR and DOR. These disparities are caused by either increasing affinity at MOR more so than at DOR or by decreasing affinity at DOR more than at MOR relative to the parallel analogue with a THQ core. Both of these effects result in a less desirable affinity profile and sometimes result in a profile with reduced affinity at both MOR and DOR. Furthermore, the THN scaffold does not improve selectivity over KOR across all sets of compounds. In addition to the effects that the THN scaffold has on the binding affinities at MOR, DOR, and KOR, the THN core also results in reduced efficacy at MOR when compared to our parent THQ series. In contrast, the *N*-acetylated THQ series appears to be superior to both the THN series and the original THQ series. When compared to the original THQ scaffold, the corresponding *N*-acetylated analogues not only maintain MOR agonist activity and DOR antagonism but also show increased DOR binding affinity (regardless of R_2 substituent), whereas MOR affinity remains relatively unchanged, thereby creating a series of ligands with more balanced MOR and DOR affinities (Table 1). The only exception to this trend is in the case of compound **14d**, where the MOR and DOR affinity both increase, with the MOR affinity increasing to a greater extent, resulting in a higher preference for MOR over DOR.

To explain the results of the *N*-acetylated THQ series, we looked at computational docking of one of the THQ/*N*-acetylated ligand pairs docked in the binding pocket of the inactive state of DOR (DORi), as previously described.[13,38] Modeling **14j** and **14a** in the DORi binding pocket (Figure 4), as a representative example, it can be seen that the *N*-acetyl of **14a** extends further into the DORi binding pocket to create a polar contact with Tyr^{129} in transmembrane helix 3 (TM3) of the receptor (Figure 4, panel B), an interaction that appears to be unavailable with the unsubstituted THQ core (Figure 4, panel A). It seems that the *N*-acetyl can increase DORi binding through three modes: (1) the carbonyl of the *N*-acetyl forms a hydrogen bond with the hydroxyl in Tyr^{129}, and once the hydrogen bond is formed, this could orient the ligand in the receptor to form a tighter hydrogen bonding network between (2) the primary amine of the 2,6-dimethyl tyrosine (Dmt) moiety of the ligand and Asp^{128} of the receptor, and (3) the Dmt hydroxyl moiety of the ligand and His^{278}. It has been previously reported[39−44] that ligand interaction with His^{278} and Asp^{128} is important for opioid ligand binding in all three classical receptors. Although the DOR Tyr^{129} residue is conserved in MOR (Tyr^{148}), the *N*-acetylation does not appear to have as profound of an effect in the MOR binding pocket with the measured distance between **14j** and **14a** to the Tyr residue 4.7 to 4.3 Å, respectively (not pictured). When both **14j** and **14a** are overlaid with the crystal structure of the recently reported[44] MOR agonist/DOR antagonist, DIPP-NH_2 (Figure 4, panels C and D, respectively) in DORi, it can be seen that **14a** aligns better with the Dmt and free amine moiety of DIPP-NH_2 than **14j**. This suggests that the *N*-acetyl moiety has a subtle, yet impactful effect on the orientation of the ligand resulting in increased binding affinity at DORi. We hypothesize that the interaction between Tyr^{129} in the binding pocket of DORi and *N*-acetylated ligand **14a** (and other *N*-acetylated analogues) may bring **14a** into closer proximity to His^{278} and Asp^{128}, facilitating a better binding network within the DORi

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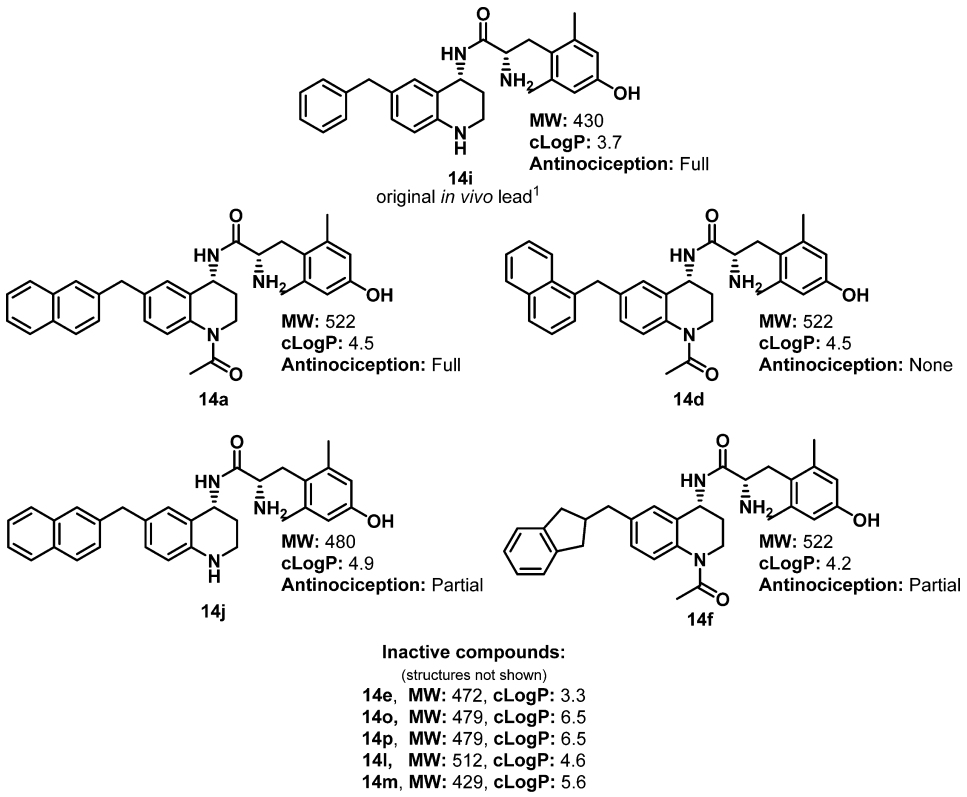

Figure 5. Summary of in vivo activity following ip administration, cLogP, and molecular weight (MW, g/mol) for select compounds. Compounds **14e**, **14o**, **14p**, **14l**, and **14m** do not display antinociception following ip administration, and structures are not shown. [1]See ref 1 for in vivo activity.

binding pocket. Although the increase in DOR affinity across the *N*-acetylated analogues is the most apparent trend when considering the in vitro data in their entirety, it is clear that some substituents display superior profiles over others. For example, the methylcyclohexyl (**14b**, **14c**, **14n**) and 1- and 2-methylindanyl (**14h**, **14g**, and **14l**, **14f**, respectively) analogues pick up considerable undesired KOR affinity and agonism, whereas the 1- and 2-methylnaphthyl analogues (**14k**, **14d**, **14p**, and **14j**, **14a**, **14o**, respectively) display agonist activity at MOR, little or no agonist activity at DOR, and significantly reduced binding and efficacy at KOR, suggesting that these compounds behave as functional antagonists at DOR. To confirm antagonist activity at DOR, we tested **14a** and **14d** against the DOR agonist DPDPE, and as expected from the high binding affinity and lack of stimulation of [^{35}S]GTPγS binding at DOR, **14a** and **14d** both antagonized the DOR agonist with antagonist affinity constants (K_e) of 1.98 nM and 27.5 nM, respectively (data not shown).

On the basis of the results from our initial in vitro screening, we chose 12 candidates for in vivo screening evaluation in the mouse WWTW assay. As seen in Figure 5, the in vitro results and cLogP calculations were both poor predictors of in vivo activity. Surprisingly, **14d** displayed no in vivo activity at 10 mg/kg ip whereas **14a**, a structural isomer of **14d**, displayed full antinociception at 10 mg/kg ip. To explore this unexpected result, we submitted both **14a** and **14d** for plasma stability testing performed by Quintara Discovery (San Francisco, CA, USA). These results revealed that both analogues tested were fully stable in plasma after 30 min, suggesting that compound degradation in the plasma does not account for the differing activities in vivo. Planned pharmacokinetic studies on **14a** and **14d** will be helpful for understanding the basis of the disparate in vivo results.

In summary, we have expanded upon our original THQ scaffold by incorporating a THN and an *N*-acetylated THQ scaffold with the intention of (1) probing and improving bioavailability and metabolic stability, (2) balancing further the affinity at MOR and DOR while reducing KOR affinity and efficacy, and (3) increasing in vivo activity and duration of action. Through *N*-acetylation of the THQ nitrogen, not only were we able to better balance the affinity at MOR and DOR while maintaining the desired MOR agonist/DOR antagonist profile, but we were also able to decrease binding affinity and efficacy at KOR, thereby creating a more desirable compound profile. Furthermore, three of the compounds presented in this paper show in vivo activity when administered peripherally, one of which (**14a**) displays full antinociception in the mouse WWTW assay for >3 h, a promising improvement upon our original lead compound.[1]

EXPERIMENTAL SECTION

Chemistry. All reagents and solvents were obtained from commercial sources and used without additional purification. Suzuki couplings were performed on a Discover S-class (CEM) microwave in a closed vessel with maximum power input of 300 W and temperature set at 110 °C for 10−60 min under the standard method from their Synergy software. Hydrogenations were performed on a Parr hydrogenator apparatus from Parr Instrument Company, model 3916EA, at the pressures specified using 10% of Pd/C as the catalyst. Flash column chromatography was carried out using P60 silica gel (230−400 mesh). Purification of final compounds was performed using a Waters semipreparative HPLC with a Vydac protein and peptide C18 reverse phase column, using a linear gradient of 15% of solvent B (0.1% of TFA in acetonitrile) in solvent A (0.1% of TFA in water) to 50% of solvent B in solvent A at a rate of either 0.5% or 1%

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per minute and monitoring UV absorbance at 230 nm. Purity of synthesized compounds was determined on a Waters Alliance 2690 analytical HPLC instrument and a Vydac protein and peptide C18 reverse phase column, using a linear gradient of 0% of solvent B in solvent A to 45, 70, or 90% of solvent B in solvent A in 45, 70, or 90 min, respectively, and UV absorbance at 230 nm (gradient A). Purities of the final compounds used for testing were ≥95% as determined by HPLC. ^{1}H NMR and ^{13}C NMR data were obtained on either a 400 or 500 MHz Varian spectrometer using $CDCl_3$ or CD_3OD solvents. The identity of each compound was verified by mass spectrometry using an Agilent 6130 LC−MS mass spectrometer in positive mode.

General Procedure A for the Synthesis of the 3-Bromo-*N*-propanamides.[1,27] To a flame-dried round-bottom flask under Ar were added the aniline compound (1.0 equiv) and K_2CO_3 (2.05 equiv). The reaction vessel was placed back under vacuum, and anhyd DCE was added via syringe. The reaction solution was stirred under vacuum for 5 min. After 5 min, the reaction vessel was then flooded with Ar, and 3-bromopropionyl chloride (1.02 equiv) was added via syringe. The reaction was stirred under Ar at RT for 1 h and was monitored by TLC using a ninhydrin stain for disappearance of the aniline compound. Once the reaction was complete, it was quenched with dI H_2O, and the layers were separated. The organic layer was washed with dI H_2O (1 × 50 mL) followed by brine (1 × 30 mL) and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the pure product.

General Procedure B for the Synthesis of Phenylazetidin-2-ones.[1,27] To a round-bottom flask already containing the dried, desiccated 3-bromo-*N*-propanamide (1.0 equiv) was added NaO*t*Bu (1.05 equiv). The reaction vessel was placed under vacuum, and anhyd DMF was added via syringe. The solution was stirred under vacuum for 5 min and was then flooded with Ar. The reaction was stirred under Ar at RT for up to 3 h and was monitored by TLC. Once complete, the solvent was removed under reduced pressure; the resulting crude residue was resuspended in DCM and dI H_2O, and the layers were separated. The organic layer was washed once with dI H_2O (1 × 30 mL) and then brine (1 × 30 mL) and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product, which was then purified using silica gel chromatography to yield the pure product.

General Procedure C for the Synthesis of 2,3-Dihydroquinolin-4(1*H*)-ones.[1,27] To a round-bottom flask already containing the dried, desiccated phenylazetidin-2-ones (1.0 equiv) was added anhyd DCE under vacuum. The reaction vessel was stirred under vacuum for 5 min and then flooded with Ar. Next, triflic acid (TfOH) (3.0 equiv) was added via syringe. The reaction was stirred under Ar at RT for up to 3 h and was monitored by TLC. Once complete, the reaction was quenched with dI H_2O (20 mL) and solid K_2CO_3 (one spatula full), and the layers were separated. The organic layer was washed once with dI H_2O (1 × 30 mL), sat. $NaHCO_3$ (1 × 30 mL), and brine (1 × 30 mL) and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product, which was then purified using silica gel chromatography to yield the pure product.

General Procedure D for the Synthesis of 1-Acetyl-2,3-dihydroquinolin-4(1*H*)-ones. To a flame-dried round-bottom flask under Ar was added 2,3-dihydroquinolin-4(1*H*)-one. The reaction vessel was placed under vacuum for 5 min; then, excess Ac_2O was added via syringe, and the solution was stirred for 5 min. The round-bottom flask was flooded with Ar, equipped with a condenser, and placed in an oil bath at 100 °C. The reaction was stirred at reflux for 12−20 h under Ar and was monitored by TLC. Once the reaction was complete, the solvent was removed under reduced pressure, yielding a crude yellow oil that was purified using silica gel chromatography to obtain the pure product.

General Procedure E for the Synthesis of *tert*-Butyl 4-Oxo-3,4-dihydroquinoline-1(2*H*)-carboxylates. To a flame-dried round-bottom flask under Ar were added 2,3-dihydroquinolin-4(1*H*)-one (1.0 equiv), Boc_2O (1.2−2.0 equiv), and DMAP (0.1 equiv). The reaction vessel was placed under vacuum for 5 min; then, anhyd DCM was added via syringe, and the solution was stirred for 5 min under vacuum. The round-bottom flask was flooded with Ar, and DIPEA (1.2−2.0 equiv) was added via syringe. The reaction vessel was equipped with a condenser and placed in an oil bath at 60 °C. The reaction was stirred at reflux for 12−16 h under Ar and was monitored by TLC. Once significant conversion to product was seen, the reaction was quenched using dI H_2O (20 mL), and the layers were separated. The organic layer was washed with sat. $NaHCO_3$ solution (1 × 20 mL) and brine (1 × 20 mL) and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a crude yellow oil that was purified using silica gel chromatography to obtain the pure product.

General Procedure F for Suzuki Coupling Using an Aromatic Boronic Ester. A solution of 3:1 acetone:dI H_2O was degassed for 1 h, and then Ar was bubbled through the solution for 1 h to ensure removal and displacement of ambient oxygen. When all the reagents are *solid*: aromatic bromide (1.0 equiv), boronic ester (2.0 equiv), K_2CO_3 (3.0 equiv), and $Pd(dppf)Cl_2$ (0.1 equiv) were added to a microwave tube, and the tube was placed under vacuum for 15 min and then flooded with Ar. Roughly 1−2 mL of the 3:1 acetone:dI H_2O solution was added to the tube via syringe; then, the tube was placed in a microwave for 30−60 min with a maximum power of 300 W and a maximum temperature of 100 °C with the "PowerMax" option enabled. When the boronic ester is *liquid*: aromatic bromide (1.0 equiv), K_2CO_3 (3.0 equiv), and $Pd(dppf)Cl_2$ (0.1 equiv) were added to a microwave tube, and the tube was placed under vacuum for 15 min and then flooded with Ar. Roughly 1−2 mL of the 3:1 acetone:dI H_2O solution was added to the tube via syringe, followed by addition of the boronic ester (2.0 equiv) via syringe. The tube was placed in a microwave for 30−60 min with a maximum power of 300 W and a maximum temperature of 100 °C with the "PowerMax" option enabled. Once the microwave reaction was complete, the reaction mixture was filtered through a pad of Celite to remove palladium, and solvents were removed under reduced pressure to yield a crude brown residue that was purified using silica gel chromatography to obtain the pure product. This procedure was adapted from ref 28.

General Procedure G for Suzuki Coupling Using an Aliphatic Boronic Acid. The aromatic bromide (1.0 equiv), boronic acid (1.1−2.0 equiv), K_2CO_3 (3.0 equiv), Ag_2O (2.5 equiv), and $Pd(dppf)Cl_2$ (0.1 equiv) were added to a microwave tube, and the tube was placed under vacuum for 15 min and then flooded with Ar. Roughly 1−2 mL of anhyd THF was added to the tube via syringe, and then the tube was placed in a microwave for 1 h with a maximum power of 300 W and a maximum temperature of 80 °C with the "PowerMax" option enabled. Once the microwave reaction was complete, the reaction mixture was filtered through a pad of Celite to remove palladium, and the solvents were removed under reduced pressure to yield a crude brown residue that was purified using silica gel chromatography to obtain the pure product. This procedure was adapted from ref 29.

General Procedure H for the Synthesis of (*R, R*) THQ and THN Sulfinamides.[31−33] To a round-bottom flask already containing dried, desiccated 6-substituted dihydroquinolinone intermediate (1.0 equiv) was added (*R*)-2-methylpropane-2-sulfinamide (2.0−3.0 equiv); then, the round-bottom flask was placed under vacuum for 10 min. Meanwhile, a reflux condenser was flame-dried under vacuum and then flooded with Ar. Next, anhyd THF (∼20 mL) was added to the reaction vessel containing starting reagents via syringe. The reaction solution was allowed to stir under vacuum for ∼5 min and was then flooded with Ar. The round-bottom flask was placed in an ice bath and allowed to equilibrate. Next, $Ti(OEt)_4$ (4.0−6.0 equiv) was added slowly via syringe. Once the addition was complete, the reaction vessel was taken out of the ice bath and placed in an oil bath at 70−75 °C, equipped with condenser, and stirred for 16−40 h under Ar. The reaction was monitored by TLC for loss of ketone. Once sufficient conversion to the *tert*-butanesulfinyl imine was observed, the reaction vessel was taken out of the oil bath and cooled to ambient temperature. Meanwhile, an additional round-bottom flask containing a stir bar was flame-dried under vacuum and then flooded with Ar; then, $NaBH_4$ was added quickly, and then the reaction vessel was placed back under vacuum for 5 min. Minimal anhyd THF was added (∼5 mL), and the vessel was allowed to stir under vacuum for ∼5 min

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and then flooded with Ar. The round-bottom flask was placed in a dry ice/xylene bath and allowed to equilibrate. Contents from the round-bottom flask containing the imine intermediate were transferred to a round-bottom flask containing $NaBH_4$ via cannula. Once the contents were completely added, the reaction was taken out of the dry ice/xylene bath and allowed to warm to room temperature. The reaction was stirred at ambient temperature for 2−3 h. Once the reaction was complete, MeOH was added for quenching. The solvent was removed under reduced pressure, yielding a solid residue. The residue was resuspended in DCM and the remaining solid was removed by filtration through a cotton plug, and the mother liquor was concentrated and purified using silica gel chromatography to yield pure sulfinamide.

General Procedure I for the Synthesis of (*R*)-1,2,3,4-Tetrahydroquinolin-4-amines and (*R*)-1,2,3,4-Tetrahydronaphthalen-1-amines. To a round-bottom flask already containing the sulfinamide intermediate was added 15−20 mL of dioxane followed by concd HCl (6.0 equiv). The reaction was stirred at RT for up to 3 h. Solvent was removed under reduced pressure to yield a slightly yellow, clear residue. The residue was resuspended in Et_2O. If a white solid precipitated (the HCl salt of the amine): the solid was removed via filtration as product without any further purification necessary. If a white solid did not precipitate, but a residue remained as a film on the flask: the residue was washed with fresh Et_2O (3 × 5 mL) and dried without any further purification necessary.

General Procedure J for diBoc-DMT Coupling to Form Final Product. The (*R*)-amine intermediate, diBoc-DMT (1.05 equiv), and the coupling reagents PyBOP (1.0 equiv) and HOBt-Cl (1.0 equiv) were dissolved in DMF (10−15 mL) followed by the addition of DIPEA (10.0 equiv). The reaction mixture was stirred for 18 h at room temperature. After being concentrated under reduced pressure, the crude residue was dissolved in a 1:1 mixture of DCM and TFA (10 mL) and stirred for 1 h. The mixture was concentrated and purified by semipreparative HPLC to yield the final compound. Note that although other coupling reagents could be used, the coupling reagents used here were chosen to minimize racemization. Additionally, diBoc-DMT was used instead of monoBoc-DMT to prevent any possible ester formation at the phenol of tyrosine that might occur under these coupling conditions, especially at longer reaction times.

*3-Bromo-N-(4-bromophenyl)propanamide (**2**).* This compound was synthesized following general procedure A starting from commercially available **1** (2.0 g, 11.6 mmol, 1.0 equiv), K_2CO_3 (3.29 g, 23.8 mmol, 2.05 equiv), and 3-bromopropionyl chloride (1.20 mL, 11.9 mmol, 1.02 equiv) to yield the title compound as an off-white solid (3.53 g, 98.9%) with no additional purification necessary after quenching and workup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47−7.39 (m, 4H), 3.70 (t, J = 6.5 Hz, 2H), 2.94 (t, J = 6.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.9, 136.4, 132.0, 128.3, 121.6, 40.7, 26.8.

*1-(4-Bromophenyl)azetidin-2-one (**3**).* This compound was synthesized following general procedure B starting with **2** (3.53 g, 11.5 mmol, 1.0 equiv) and NaO*t*Bu (1.16 g, 12.1 mmol, 1.05 equiv). Following solvent removal and workup, the crude product was chromatographed on silica gel (equilibrated in 100% hex, run in 1:4 EA:hex) to yield the title compound as a pure white flaky solid (1.36 g, 52.1%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46−7.42 (m, 2H), 7.27−7.22 (m, 2H), 3.62 (td, J = 4.6, 2.0 Hz, 2H), 3.13 (td, J = 4.6, 1.9 Hz, 2H). No ^{13}C spectrum acquired.

*6-Bromo-2,3-dihydroquinolin-4(1H)-one (**4**).* This compound was synthesized following general procedure C starting with **3** (1.36 g, 6 mmol, 1.0 equiv) and TfOH (1.60 mL, 18.0 mmol, 3.0 equiv) to yield a crude yellow oil. Following workup, the crude material was chromatographed on silica gel (equilibrated in 100% hex, run in 2:3 EA:hex) to yield the title compound as a pure yellow powder (739 mg, 54.5%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 2.4 Hz, 1H), 7.35 (dd, J = 8.7, 2.4 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 4.43 (s, 1H), 3.58 (t, 2H), 2.69 (t, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.3, 150.6, 137.6, 130.0, 120.5, 117.7, 110.2, 42.0, 37.6.

*1-Acetyl-6-bromo-2,3-dihydroquinolin-4(1H)-one (**5a**).* This compound was synthesized following general procedure D starting with **4** (739 mg, 3.27 mmol, 1.0 equiv) for 16 h. Following removal of solvent, the resulting crude yellow oil was purified using silica gel chromatography (equilibrated in 100%, run in 1:3 EA:hex) to yield the title compound as a white waxy solid (704 mg, 80.4%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 2.4 Hz, 1H), 7.64 (dd, J = 8.7, 2.5 Hz, 1H), 7.47 (s, 1H), 4.21 (t, J = 6.3 Hz, 2H), 2.81 (t, J = 6.3 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.4, 169.0, 142.6, 136.6, 130.3, 127.0, 125.8, 118.7, 44.2, 39.1, 23.1.

*tert-Butyl 6-Bromo-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (**5b**).* This compound was synthesized following general procedure E using **4** (300 mg, 1.33 mmol, 1.0 equiv), Boc_2O (348 mg, 1.59 mmol, 1.2 equiv), DMAP (16.2 mg, 0.13 mmol, 0.1 equiv), and DIPEA (0.277 mL, 1.59 mmol, 1.2 equiv). Following the quenching and workup, the crude product was chromatographed on silica gel (equilibrated in 100% hex, run in 2:3 EA:hex) to yield pure product as a white solid (380 mg, 87.8%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 2.4 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.57 (dd, J = 9.0, 2.4 Hz, 1H), 4.15 (t, J = 6.3 Hz, 2H), 2.77 (t, J = 6.3 Hz, 2H), 1.55 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.8, 152.4, 143.1, 136.6, 129.9, 126.1, 125.5, 117.1, 82.6, 44.2, 38.7, 28.3.

*1-Acetyl-6-(naphthalen-2-ylmethyl)-2,3-dihydroquinolin-4(1H)-one (**6a**).* This compound was synthesized following general procedure F using **5a** (50 mg, 0.19 mmol, 1.0 equiv), 4,4,5,5-tetramethyl-2-(naphthalen-2-ylmethyl)-1,3,2-dioxaborolane (100 mg, 0.37 mmol, 2.0 equiv), K_2CO_3 (78 mg, 0.56 mmol, 3.0 equiv), and Pd(dppf)Cl_2 (14 mg, 0.019 mmol, 0.1 equiv). The contents were placed in a microwave tube and reacted in a microwave with a max temp of 110 °C and max power of 250 W for 30 min with the "Powermax" option enabled. Once the crude mixture was filtered through Celite, the solvent was removed, and the residue was purified via silica gel chromatography (equilibrated in 100% hex, run in 1:1 EA:hex) to yield the title compound (51 mg, 83.6%) as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.80−7.74 (m, 3H), 7.63 (s, 1H), 7.48−7.36 (m, 3H), 7.31−7.26 (m, 1H), 4.24−4.15 (m, 2H), 4.13 (s, 2H), 2.80−2.69 (m, 2H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.0, 169.2, 142.1, 138.6, 137.4, 134.6, 133.5, 132.1, 128.3, 127.60, 127.57, 127.5, 127.3, 127.2, 127.1, 126.1, 125.9, 125.5, 124.2, 43.9, 41.3, 39.4, 23.0.

*tert-Butyl 6-(Cyclohexylmethyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (**6b**).* This compound was synthesized following general procedure G using **5b** (100 mg, 0.31 mmol, 1.0 equiv), (cyclohexylmethyl)boronic acid (87 mg, 0.61 mmol, 2.0 equiv), K_2CO_3 (127 mg, 0.92 mmol, 3.0 equiv), Ag_2O (178 mg, 0.77 mmol, 2.5 equiv), and Pd(dppf)Cl_2 (22 mg, 0.031 mmol, 0.1 equiv). The contents were placed in a microwave tube and reacted in a microwave with a max temp of 80 °C and max power of 300 W for 60 min with the "Powermax" option disabled. Once filtered through Celite, the solvent was removed, and the crude residue purified via silica gel chromatography (equilibrated in 100% petroleum ether, run in 5:1 petroleum ether:Et_2O) to yield the title compound as a clear, colorless oil (81 mg, 77.1%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 2.2 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.28 (d, J = 2.3 Hz, 1H), 4.19−4.08 (m, 2H), 2.82−2.71 (m, 2H), 2.47 (d, J = 7.1 Hz, 2H), 1.77−1.59 (m, 5H), 1.55 (s, 9H), 1.51 (s, 1H), 1.18−1.12 (m, 2H), 0.97−0.90 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.5, 152.8, 137.1, 135.0, 133.9, 125.5, 124.6, 123.3, 82.0, 44.3, 43.2, 39.6, 39.1, 36.0, 33.0, 28.3, 26.2.

*1-Acetyl-6-(cyclohexylmethyl)-2,3-dihydroquinolin-4(1H)-one (**6c**).* This compound was synthesized following general procedure G using **5a** (100 mg, 0.37 mmol, 1.0 equiv), (cyclohexylmethyl)boronic acid (58 mg, 0.41 mmol, 1.1 equiv), K_2CO_3 (155 mg, 1.12 mmol, 3.0 equiv), Ag_2O (216 mg, 0.93 mmol, 2.5 equiv), and Pd(dppf)Cl_2 (27 mg, 0.37 mmol, 0.1 equiv). The contents were placed in a microwave tube and reacted in a microwave with a max temp of 80 °C and max power of 300 W for 60 min with the "Powermax" option disabled. Once filtered through Celite, the crude residue was purified via silica gel chromatography (equilibrated in 100% hex, run in 1:3 EA:hex) to yield the title compound as a clear, colorless oil (30 mg, 28.3%). Additionally, 51 mg of **5a** was recovered; this was not considered when calculating the percent yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.33 (d, J = 6.8 Hz, 1H), 4.29−4.19 (m, 2H), 2.79 (t, J = 6.2 Hz,

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2H), 2.50 (d, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.73−1.59 (m, 5H), 1.52 (m, 1H), 1.19−1.14 (m, 3H), 0.99−0.90 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.4, 169.3, 141.7, 139.1, 135.0, 127.8, 125.7, 123.8, 43.2, 39.6, 35.3, 34.1, 33.0, 26.4, 26.2, 23.1.

*1-Acetyl-6-(naphthalen-1-ylmethyl)-2,3-dihydroquinolin-4(1H)-one (**6d**).* This compound was synthesized following general procedure F using **5a** (50 mg, 0.19 mmol, 1.0 equiv), 4,4,5,5-tetramethyl-2-(naphthalen-1-ylmethyl)-1,3,2-dioxaborolane (100 mg, 0.37 mmol, 2.0 equiv), K_2CO_3 (78 mg, 0.56 mmol, 3.0 equiv), and $Pd(dppf)Cl_2$ (14 mg, 0.019 mmol, 0.1 equiv). Contents were placed in a microwave tube and reacted in a microwave with a max temp of 110 °C and max power of 250 W for 30 min with "Powermax" enabled. Once the crude mixture was filtered through Celite, the residue was purified via silica gel chromatography (equilibrated in 100% hex, run in 9:1 EA:hex) to yield the title compound as a clear, colorless oil (31 mg, 50.8%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96−7.90 (m, 2H), 7.89−7.83 (m, 1H), 7.80−7.75 (m, 1H), 7.49−7.40 (m, 3H), 7.32 (d, J = 7.1 Hz, 2H), 4.44 (s, 2H), 4.23−4.13 (m, 2H), 2.75 (t, J = 6.2 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.0, 169.2, 142.1, 138.3, 135.4, 134.2, 134.0, 133.6, 131.8, 128.8, 127.6, 127.5, 127.4, 126.1, 125.7, 125.5, 124.2, 124.0, 43.9, 39.5, 38.3, 23.0.

*1-Acetyl-6-benzyl-2,3-dihydroquinolin-4(1H)-one (**6e**).* This compound was synthesized following general procedure D using **10e** (170 mg, 0.72 mmol, 1.0 equiv) and excess Ac_2O. The reaction was stirred at 100 °C for 16 h. Once complete, the solvent was removed under reduced pressure, and the crude product was chromatographed on silica gel (equilibrated in 100% hexane (hex), run in 3:2 EA:hex) to yield the title compound as a clear, colorless oil (168 mg, 84.0%) ^{1}H NMR (400 MHz$CDCl_3$): δ 7.87−7.84 (bs, 1H), 7.37−7.33 (m, 2H), 7.31−7.24 (m, 2H), 7.23−7.15 (m, 3H), 4.20 (t, J = 6.2 Hz, 2H), 3.98 (s, 2H), 2.76 (t, J = 6.2 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.0, 169.3, 142.1, 140.0, 138.9, 134.6, 128.8, 128.7, 127.6, 126.4, 126.0, 124.2, 43.9, 41.2, 39.5, 23.1.

*1-Acetyl-6-((2,3-dihydro-1H-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1H)-one (**6f**).* This compound was synthesized following general procedure D using **10f** (55 mg, 0.24 mmol, 1.0 equiv). The reaction was stirred at reflux for 20 h. Once the reaction was complete, the solvent was removed, and the crude residue was purified using silica gel chromatography (equilibrated in 100% hex, run in 2:3 EA:hex) to yield the title compound as a clear oil (39 mg, 50.4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.41 (d, J = 6.7 Hz, 2H), 7.20−7.07 (m, 4H), 4.24 (t, J = 6.3 Hz, 2H), 3.00 (dd, J = 15.3, 6.3 Hz, 2H), 2.87−2.76 (m, 5H), 2.67 (dd, J = 15.4, 6.2 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.2, 169.4, 142.7, 141.9, 139.0, 134.7, 127.5, 126.2, 125.9, 124.4, 124.0, 43.9, 41.1, 40.7, 39.4, 38.7, 23.1.

*1-Acetyl-6-((2,3-dihydro-1H-inden-1-yl)methyl)-2,3-dihydroquinolin-4(1H)-one (**6g**).* This compound was synthesized following general procedure D using **10g** (245 mg, 0.88 mmol, 1.0 equiv). The reaction was stirred at reflux for 16 h. Once the reaction was complete, the solvent was removed, and the crude residue was purified using silica gel chromatography (equilibrated in 100% hex, run in 2:3 EA:hex) to yield the title compound as a clear, colorless oil (190 mg, 67.4%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.36 (d, J = 6.2 Hz, 1H), 7.21 (d, J = 5.7 Hz, 1H), 7.18−7.09 (m, 4H), 4.23 (s, 2H), 3.44 (p, J = 7.0 Hz, 1H), 3.15 (dd, J = 13.7, 5.5 Hz, 1H), 2.88 (ddd, J = 14.1, 8.2, 5.5 Hz, 2H), 2.84−2.75 (m, 4H), 2.69 (dd, J = 13.7, 9.5 Hz, 1H), 2.34 (s, 3H), 2.13 (ddd, J = 13.0, 10.4, 6.7 Hz, 1H), 1.81−1.67 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.0, 169.1, 146.1, 143.8, 141.9, 138.3, 134.7, 127.5, 126.5, 125.9, 125.7, 124.5, 123.9, 123.5, 46.0, 43.8, 40.4, 39.4, 31.5, 30.9, 23.0.

*tert-Butyl 6-((2,3-Dihydro-1H-inden-1-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (**6h**).* This compound was synthesized following general procedure E using **10g** (214 mg, 0.77 mmol, 1.0 equiv), Boc_2O (337 mg, 1.54 mmol, 2.0 equiv), DMAP (9 mg, 0.077 mmol, 0.1 equiv), and DIPEA (0.268 mL, 1.54 mmol, 2.0 equiv). The reaction was stirred at reflux for 16 h. Once enough starting material was converted to product, the crude yellow oil was purified using silica gel chromatography (equilibrated in 100% hex, run in 2:3 EA:hex) to yield the title compound as a yellow oil (83 mg, 28.5%). Additionally, 122 mg of starting material **10g** was recovered; this was not considered when calculating the percent yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 5.9 Hz, 2H), 7.15 (d, J = 8.3 Hz, 4H), 4.16 (t, J = 6.3 Hz, 2H), 3.43 (p, J = 6.9 Hz, 1H), 3.13 (dd, J = 13.7, 5.4 Hz, 1H), 2.88−2.83 (m, 1H), 2.83−2.78 (m, 1H), 2.78−2.74 (t, J = 6.3 Hz, 2H), 2.67 (dd, J = 13.6, 9.5 Hz, 1H), 2.13 (dq, J = 13.1, 7.8 Hz, 1H), 1.74 (dq, J = 13.9, 7.3 Hz, 1H), 1.56 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.3, 152.1, 146.4, 144.0, 142.2, 136.5, 134.8, 127.2, 126.5, 126.0, 124.6, 124.5, 123.6, 123.5, 82.0, 77.3, 77.0, 76.8, 46.2, 44.3, 40.5, 39.0, 31.6, 31.0, 28.3.

*4-((2,3-Dihydro-1H-inden-2-yl)methyl)aniline (**7f**).* This compound was synthesized according to a published procedure[1] to yield the title compound. NMR data matched previously reported literature values.[1]

*4-((2,3-Dihydro-1H-inden-1-yl)methyl)aniline (**7g**).* This compound was synthesized according to a published procedure[26] to yield the title compound. NMR data matched previously reported literature values.[26]

*N-(4-Benzylphenyl)-3-bromopropanamide (**8e**).* This compound was synthesized according to general procedure A using commercially available **7e** (2.15 g, 11.7 mmol, 1.0 equiv) to yield the title compound as a tan solid (2.63 g, 98.0%) with no additional purification necessary. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 7.4 Hz, 2H), 7.22−7.12 (5H, m), 3.95 (s, 2H), 3.71 (t, J = 6.6 Hz, 2H), 2.92 (t, J = 6.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.7, 141.9, 137.7, 135.4, 129.5, 128.9, 128.5, 126.1, 120.3, 41.3, 40.7, 27.1.

*3-Bromo-N-(4-((2,3-dihydro-1H-inden-2-yl)methyl)phenyl)-propanamide (**8f**).* This compound was synthesized following general procedure A using **7f** (2.1 g, 9.5 mmol, 1.0 equiv) to yield the title compound as a brown solid (2.87 g, 84.4%) with no additional purification necessary to yield the title compound. NMR data matched previously reported values.[1]

*3-Bromo-N-(4-((2,3-dihydro-1H-inden-1-yl)methyl)phenyl)-propanamide (**8g**).* This compound was synthesized following general procedure A using **7g** (473 mg, 2.1 mmol, 1.0 equiv), K_2CO_3 (600 mg, 4.3 mmol, 2.05 equiv), and 3-bromopropionyl chloride (220 mL, 2.2 mmol, 1.02 equiv) to yield the title compound as an off-white solid (759 mg, quant.) with no additional purification necessary. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 7.0 Hz, 2H), 7.34 (s, 1H), 7.26 (d, J = 1.5 Hz, 0H), 7.22 (d, J = 6.8 Hz, 1H), 7.14 (dd, J = 19.7, 9.8 Hz, 6H), 5.29 (d, J = 1.5 Hz, 2H), 3.71 (t, J = 6.5 Hz, 2H), 3.41 (p, J = 7.1 Hz, 1H), 3.09 (dd, J = 13.7, 5.6 Hz, 1H), 2.94 (d, J = 6.6 Hz, 1H), 2.90−2.84 (m, 1H), 2.79 (dt, J = 15.7, 7.7 Hz, 1H), 2.66 (dd, J = 13.6, 9.2 Hz, 1H), 2.17−2.08 (m, 1H), 1.74 (dq, J = 15.1, 8.0, 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.8, 146.7, 144.1, 137.4, 135.3, 129.6, 126.5, 126.0, 124.5, 123.7, 120.0, 53.4, 46.4, 40.8, 31.8, 31.1, 27.1.

*1-(4-Benzylphenyl)azetidin-2-one (**9e**).* This compound was synthesized following general procedure B using **8e** (3.63 g, 1.1 mmol, 1.0 equiv) and NaOtBu (1.15 g, 1.2 mmol, 1.05 equiv) in anhyd DMF. Following aqueous washes, the title compound was isolated as a tan solid (2.70 g, quant.) and was taken ahead to the next step (formation of **10e**) without purification, isolation, or characterization.

*1-(4-((2,3-Dihydro-1H-inden-2-yl)methyl)phenyl)azetidin-2-one (**9f**).* This compound was synthesized following general procedure B using **8f** (2.87 g, 8.0 mmol, 1.0 equiv) and NaO*t*Bu (808 mg, 8.41 mmol, 1.05 equiv) to yield the title compound as a brown solid (2.22 g, quant.) with no additional purification necessary. NMR data matched previously reported values.[1]

*1-(4-((2,3-Dihydro-1H-inden-1-yl)methyl)phenyl)azetidin-2-one (**9g**).* This compound was synthesized following general procedure B using **8g** (759 mg, 2.12 mmol, 1.0 equiv) and NaO*t*Bu (214 mg, 2.22 mmol, 1.05 equiv) to yield the title compound as a light tan solid (512 mg, 87.4%) with no additional purification necessary. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, J = 8.3 Hz, 2H), 7.25−7.05 (m, 8H), 3.60 (t, J = 4.4 Hz, 2H), 3.40 (p, J = 7.1 Hz, 1H), 3.09 (t, J = 4.5 Hz, 3H), 3.06 (d, J = 6.0 Hz, 1H), 2.90−2.73 (m, 3H), 2.66 (dd, J = 13.6, 9.0 Hz, 1H), 2.11 (ddd, J = 15.9, 7.9, 5.4 Hz, 1H), 1.73 (dq, J = 15.1, 7.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.2, 146.6, 144.0, 136.6,

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136.4, 129.6, 126.4, 125.9, 124.5, 123.7, 116.0, 46.4, 40.8, 38.0, 36.0, 31.7, 31.1.

*6-Benzyl-2,3-dihydroquinolin-4(1H)-one (**10e**).* This compound was synthesized following general procedure C using **9e** (2.70 g, 1.1 mmol, 1.0 equiv) and TfOH (3.0 mL, 3.4 mmol, 3.0 equiv). Following column purification (equilibrated in 100% hex, run in 2:3 EA:hex), the title compound was isolated as a yellow solid (1.91 g, 70.7%). NMR data matched previously reported values.[1]

*6-((2,3-Dihydro-1H-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1H)-one (**10f**).* This compound was synthesized following general procedure C using **9f** (2.22 g, 8.00 mmol, 1.0 equiv) and TfOH (2.12 mL, 24.0 mmol, 3.0 equiv) to yield a crude dark red oil. Crude residue was purified using silica gel chromatography (equilibrated in 100%, run in 1:3 EA:hex) to yield the title compound as a yellow powder (1.55 g, 69.7%). NMR data matched previously reported values.[1]

*6-((2,3-Dihydro-1H-inden-1-yl)methyl)-2,3-dihydroquinolin-4(1H)-one (**10g**).* This compound was synthesized following general procedure C using **9g** (512 mg, 1.85 mmol, 1.0 equiv) and TfOH (0.490 mL, 5.54 mmol, 3.0 equiv) to yield the title compound as a slightly impure yellow solid (459 mg, 89.6%) with no additional purification necessary. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.19 (s, 1H), 7.11 (m, 4H), 6.60 (d, J = 8.3 Hz, 1H), 3.52 (t, J = 6.5 Hz, 2H), 3.37−3.32 (m, 1H), 3.01 (dd, J = 13.7, 5.0 Hz, 1H), 2.85 (m, 1H), 2.77 (m, 1H), 2.67 (m, 2H), 2.56 (m, 1H), 2.11 (dt, J = 12.3, 6.5 Hz, 1H), 1.72 (dq, J = 13.8, 7.4, 6.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.9, 150.5, 146.6, 144.0, 136.2, 130.2, 127.1, 126.3, 125.9, 124.4, 123.6, 119.0, 115.8, 46.3, 42.3, 40.2, 38.1, 31.5, 31.0.

*(R)-N-((R)-1-Acetyl-6-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (**12a**).* This compound was synthesized following general procedure H from **6a** (51 mg, 0.155 mmol, 1.0 equiv), (*R*)-2-methylpropane-2-sulfinamide (56 mg, 0.464 mmol, 3.0 equiv), and $Ti(OEt)_4$ (0.195 mL, 0.929 mmol, 6.0 equiv) to form the (*R*)-*tert*-butanesulfinyl imine intermediate (**11a**) in situ. Once sufficient ketone was converted to imine intermediate (after 40 h), the reaction mixture was transferred to a round-bottom flask containing $NaBH_4$ (35 mg, 0.929 mmol, 6.0 equiv) and stirred at room temperature for 3 h before being quenched with MeOH. Once the resultant solid was removed, the crude residue was purified using silica gel chromatography (equilibrated in 100% hex, run in 100% EA) to yield the title compound as a clear, colorless oil (67 mg, quant. from **6a**), which was taken ahead to the next step (formation of **13a**) without further characterization.

*tert-Butyl(R)-4-(((R)-tert-butylsulfinyl)amino)-6-(cyclohexylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**12b**).* This compound was synthesized following general procedure H using **6b** (78 mg, 0.227 mmol, 1.0 equiv), (*R*)-2-methylpropane-2-sulfinamide (55 mg, 0.454 mmol, 2.0 equiv), and $Ti(OEt)_4$ (0.191 mL, 0.909 mmol, 4.0 equiv) to form the (*R*)-*tert*-butanesulfinyl imine intermediate (**11b**) in situ. Once sufficient ketone was converted to imine intermediate (after 40 h), the reaction mixture was transferred to a round-bottom flask containing $NaBH_4$ (34 mg, 0.909 mmol, 4.0 equiv) and stirred at room temperature for 3 h before being quenched with MeOH. Once the resultant solid was removed, the crude residue was purified using silica gel chromatography (equilibrated in 100% hex, run in 1:3 EA:hex) to yield the title compound as a dark, yellow oil (102 mg, 23.5% from **6b**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 8.6 Hz, 1H), 7.10 (s, 1H), 7.02 (d, J = 8.5 Hz, 1H), 4.55 (s, 1H), 3.99 (d, J = 12.8 Hz, 1H), 3.55 (t, J = 12.1 Hz, 1H), 3.27 (s, 1H), 2.46−2.37 (m, 2H), 2.17 (d, J = 13.3 Hz, 1H), 1.97 (t, J = 12.8 Hz, 1H), 1.71−1.59 (m, 5H), 1.52 (s, 9H), 1.46 (d, J = 7.5 Hz, 1H), 1.22 (s, 9H), 1.17−1.12 (m, 2H), 0.99−0.87 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.6, 136.9, 136.1, 129.3, 128.9, 128.0, 123.5, 81.0, 55.6, 50.3, 43.2, 40.0, 39.6, 33.1, 33.0, 29.6, 28.3, 26.5, 26.2, 22.6.

*(R)-N-((R)-1-Acetyl-6-(cyclohexylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (**12c**).* This compound was synthesized following general procedure H using **6c** (56 mg, 0.196 mmol, 1.0 equiv), (*R*)-2-methylpropane-2-sulfinamide (48 mg, 0.392 mmol, 2.0 equiv), and $Ti(OEt)_4$ (0.165 mL, 0.785 mmol, 4.0 equiv) to form the (*R*)-*tert*-butanesulfinyl imine intermediate (**11c**) in situ. Once sufficient ketone was converted to imine intermediate (after 40 h), the reaction mixture was transferred to a round-bottom flask containing $NaBH_4$ (30 mg, 0.785 mmol, 4.0 equiv) and stirred at room temperature for 3 h before being quenched with MeOH. Once the resultant solid was removed, the crude residue was purified using silica gel chromatography (equilibrated in 100% hex, run in 4:1 EA:hex) to yield the title compound as a clear, yellow oil (20 mg, 26.1% from **6c**) that was taken ahead to the next step (formation of **13c**) without further characterization.

*(R)-N-((R)-1-Acetyl-6-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (**12d**).* This compound was synthesized following general procedure H using **6d** (31 mg, 0.0941 mmol, 1.0 equiv), (*R*)-2-methylpropane-2-sulfinamide (34 mg, 0.282 mmol, 3.0 equiv), and $Ti(OEt)_4$ (0.118 mL, 0.565 mmol, 6.0 equiv) to form the (*R*)-*tert*-butanesulfinyl imine intermediate (**11d**) in situ. Once sufficient ketone was converted to imine intermediate (after 40 h), the reaction mixture was transferred to a round-bottom flask containing $NaBH_4$ (21 mg, 0.565 mmol, 6.0 equiv) and stirred at room temperature for 3 h before being quenched with MeOH. The resultant solid was removed to yield a clear, colorless residue (41 mg, quant.) that was taken ahead to the next step (formation of **13d**) without further purification, isolation, or characterization.

*(R)-N-((R)-1-Acetyl-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (**12e**).* This compound was synthesized following general procedure H using **6e** (168 mg, 0.601 mmol, 1.0 equiv), (*R*)-2-methylpropane-2-sulfinamide (219 mg, 1.80 mmol, 3.0 equiv), and $Ti(OEt)_4$ (0.757 mL, 3.61 mmol, 6.0 equiv) to form the (*R*)-*tert*-butanesulfinyl imine intermediate (**11e**) in situ. Once sufficient ketone was converted to imine intermediate (after 40 h), the reaction mixture was transferred to a round-bottom flask containing $NaBH_4$ (137 mg, 3.61 mmol, 6.0 equiv) and stirred at room temperature for 3 h before being quenched with MeOH. Once the resultant solid was removed, the crude residue was purified using silica gel chromatography (4:1 EA:hex) to yield the title compound as a clear, colorless oil (105 mg, 45.5% from **6e**), which was taken ahead to the next step (formation of **13e**) without further characterization.

*(R)-N-((R)-1-Acetyl-6-((2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (**12f**).* This compound was synthesized following general procedure H using **6f** (39 mg, 0.122 mmol, 1.0 equiv), (*R*)-2-methylpropane-2-sulfinamide (30 mg, 0.244 mmol, 2.0 equiv), and $Ti(OEt)_4$ (0.102 mL, 0.488 mmol, 4.0 equiv) to form the (*R*)-*tert*-butanesulfinyl imine intermediate (**11f**) in situ. Once sufficient ketone was converted to imine intermediate (after 24 h), the reaction mixture was transferred to a round-bottom flask containing $NaBH_4$ (19 mg, 0.488 mmol, 4.0 equiv) and stirred at room temperature for 3 h before being quenched with MeOH. Once the resultant solid was removed, the crude residue was purified using silica gel chromatography (equilibrated in 100% hex, run in 9:1 EA:hex) to yield the title compound as a clear, colorless oil (46 mg, 88.9% from **6f**). ^{1}H NMR (500 MHz, $CDCl^3$): δ 7.40 (s, 1H), 7.29 (s, 1H), 7.21−7.15 (m, 2H), 7.15−7.09 (m, 3H), 4.77−4.66 (m, 1H), 4.57 (bs, 1H), 3.01 (dd, J = 15.3, 6.0 Hz, 2H), 2.83−2.72 (m, 3H), 2.67 (dd, J = 15.2, 5.7 Hz, 2H), 2.43−2.34 (m, 1H), 2.28−2.20 (m, 4H), 2.13−2.02 (m, 1H), 1.22 (s, 9H). No ^{13}C spectrum acquired.

*(R)-N-((4R)-1-Acetyl-6-((2,3-dihydro-1H-inden-1-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (**12g**).* This compound was synthesized as a mixture of diastereomers following general procedure H using **6g** (176 mg, 0.551 mmol, 1.0 equiv), (*R*)-2-methylpropane-2-sulfinamide (200 mg, 1.65 mmol, 3.0 equiv), and $Ti(OEt)_4$ (0.693 mL, 3.31 mmol, 6.0 equiv) to form the (*R*)-*tert*-butanesulfinyl imine intermediate (**11g**) in situ. Once sufficient ketone was converted to imine intermediate (after 16 h), the reaction mixture was transferred to a round-bottom flask containing $NaBH_4$ (125 mg, 3.31 mmol, 6.0 equiv) and stirred at room temperature for 3 h before being quenched with MeOH. Once the resultant solid was removed, the crude residue was purified using silica gel chromatography (equilibrated and run in 100% EA) to yield the title compound as a clear, colorless oil of a mixture of diastereomers (219 mg, 93.6% from **6g**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29−7.25 (m, 1H), 7.24−7.19 (m, 1H), 7.17−7.09 (m,

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4H), 7.09−7.05 (m, 1H), 4.54 (bs, 1H), 3.99−3.87 (m, 2H), 3.84−3.72 (m, 1H), 3.44 (bs, 1H), 3.19−3.04 (m, 1H), 2.96−2.75 (m, 2H), 2.68 (q, J = 12.4 Hz, 1H), 2.25 (s, 3H), 2.23−2.19 (m, 1H), 2.19−2.12 (m, 1H) 2.12−2.05 (m, 1H), 1.84−1.71 (m, 1H), 1.24−1.14 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.7, 146.3, 143.8, 138.1, 136.4, 128.7, 128.6, 126.4, 125.9, 125.8, 124.4, 124.3, 123.6, 123.5, 55.6, 55.0, 50.9, 46.1, 46.0, 40.6, 40.5, 31.7, 31.6, 30.9, 30.9, 30.5, 23.2, 22.4, 22.0, 20.9, 14.0.

*tert-Butyl(4R)-4-(((R)-tert-butylsulfinyl)amino)-6-((2,3-dihydro-1H-inden-1-yl)methyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**12h**).* This compound was synthesized as a mixture of diastereomers following general procedure H using **6h** (83 mg, 0.220 mmol, 1.0 equiv), (*R*)-2-methylpropane-2-sulfinamide (80 mg, 0.660 mmol, 3.0 equiv), and $Ti(OEt)_4$ (0.277 mL, 0.132 mmol, 6.0 equiv) to form the (*R*)-*tert*-butanesulfinyl imine intermediate (**11h**) in situ. Once sufficient ketone was converted to imine intermediate (after 16 h), the reaction mixture was transferred to a round-bottom flask containing $NaBH_4$ (50 mg, 0.132 mmol, 6.0 equiv) and stirred at room temperature for 3 h before being quenched with MeOH. Once the resultant solid was removed, the crude residue was purified using silica gel chromatography (equilibrated in 100%, run in 2:3 EA:hex) to yield the title compound as a clear, colorless oil of a mixture of diastereomers (27 mg, 25.7% from **6h**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0 Hz, 1H), 7.31−7.03 (m, 7H), 4.55 (s, 1H), 4.00 (d, J = 12.8 Hz, 1H), 3.58 (t, J = 12.0 Hz, 1H), 3.44−3.35 (m, 1H), 3.28 (s, 1H), 3.07 (ddd, J = 29.4, 13.6, 5.2 Hz, 1H), 2.94−2.84 (m, 1H), 2.83−2.74 (m, 1H), 2.64 (ddd, J = 19.0, 13.7, 9.6 Hz, 1H), 2.23−2.10 (m, 2H), 1.99 (dd, J = 23.8, 10.6 Hz, 1H), 1.76 (tt, J = 14.4, 7.6 Hz, 2H), 1.53 (s, 9H), 1.44 (bs, 3H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.6, 146.7, 144.1, 136.41, 136.37, 136.3, 129.22, 129.16, 128.9, 128.8, 128.31, 128.28, 126.5, 126.0, 125.9, 124.49, 124.46, 123.8, 123.72, 123.69, 81.1, 55.6, 50.3, 46.4, 46.3, 40.6, 40.5, 40.03, 39.99, 31.9, 31.7, 31.06, 31.05, 29.5, 28.4, 24.2, 22.6.

*(R)-1-Acetyl-6-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-aminium Chloride (**13a**).* This compound was synthesized following general procedure I using **12a** (56 mg, 0.135 mmol, 1.0 equiv). After removing the solvent, the residue was resuspended in Et_2O, and the solid did not crash out. The residue was washed 3× with fresh Et_2O and dried to yield the product as a clear, yellow oil (56 mg, quant.). ^{1}H NMR (500 MHz, CD_3OD): δ 7.83−7.67 (m, 4H), 7.54−7.24 (m, 6H), 4.56 (dd, J = 7.7, 4.0 Hz, 1H), 4.16 (s, 2H), 3.96−3.81 (m, 2H), 2.46−2.35 (m, 1H), 2.26 (s, 3H), 2.13−2.09 (m, 1H). ^{13}C NMR (126 MHz, CD_3OD): δ 172.5, 140.8, 139.6, 138.1, 135.1, 133.6, 130.8, 129.2, 128.6, 128.5, 128.4, 128.1, 127.1, 126.5, 48.2, 42.3, 29.8, 23.3, 21.5.

*(R)-1-(tert-Butoxycarbonyl)-6-(cyclohexylmethyl)-1,2,3,4-tetrahydroquinolin-4-aminium Chloride (**13b**).* This compound was synthesized following general procedure I using **12b** (22 mg, 0.0490 mmol, 1.0 equiv). After removing the solvent, the residue was resuspended in Et_2O, and the solid crashed out. After washing the solid 3× with fresh Et_2O, the remaining Et_2O was decanted, yielding the title compound as an off-white solid (10 mg, 53.5%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.79 (s, 3H), 7.70 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 4.39 (s, 1H), 4.08 (d, J = 13.5 Hz, 1H), 3.64−3.54 (m, 1H), 2.40 (d, J = 7.0 Hz, 2H), 2.19 (s, 2H), 1.70−1.56 (m, 5H), 1.51 (s, 10H), 1.19−1.08 (m, 3H), 0.98−0.85 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.1, 137.1, 136.3, 130.0, 129.4, 123.9, 122.1, 81.4, 47.6, 43.2, 39.9, 39.5, 33.1, 33.0, 28.3, 27.8, 26.5, 26.3, 26.3.

*(R)-1-Acetyl-6-(cyclohexylmethyl)-1,2,3,4-tetrahydroquinolin-4-aminium Chloride (**13c**).* This compound was synthesized following general procedure I using **12c** (20 mg, 0.0512 mmol, 1.0 equiv) and concd HCl (7.5 μL, 0.31 mmol, 6.0 equiv). After removing the solvent, the residue was resuspended in Et_2O, and the solid crashed out. After washing the solid 3× with fresh Et_2O, the remaining Et_2O was decanted, yielding an off-white solid (12 mg, 72.7%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.27 (s, 1H), 7.21 (d, J = 8.2 Hz, 1H), 4.58 (t, J = 6.7 Hz, 1H), 3.91 (h, J = 8.3, 7.9 Hz, 2H), 2.53 (d, J = 7.1 Hz, 2H), 2.48−2.39 (m, 1H), 2.28 (s, 3H), 2.10−1.99 (m, 1H), 1.75−1.65 (m, 5H), 1.61−1.53 (m, 1H), 1.26−1.19 (m, 3H), 1.02−0.94 (m, 2H). No ^{13}C spectrum acquired.

*(R)-1-Acetyl-6-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-aminium Chloride (**13d**).* This compound was synthesized following general procedure I using **12d** (41 mg (from theoretical yield of **12d**), 0.0943 mmol, 1.0 equiv) and concd HCl (14 μL, 0.566 mmol, 6.0 equiv). After removing the solvent, the residue was resuspended in Et_2O, and the solid crashed out. The solid was filtered off, washed 3× with fresh Et_2O, and dried to yield the product as a white solid (22 mg, 62.9%). ^{1}H NMR (500 MHz, CD_3OD): δ 8.02 (d, J = 7.1 Hz, 1H), 7.87 (d, J = 8.1, 1H), 7.78 (d, J = 7.1 Hz, 1H), 7.50−7.43 (m, 4H), 7.43−7.39 (m, 2H), 7.30−7.23 (m, 1H), 4.53 (t, J = 6.7 Hz, 1H), 4.49 (s, 2H), 3.87 (dtd, J = 8.8, 6.7, 6.2, 3.4 Hz, 2H), 2.39 (dq, J = 12.5, 5.7 Hz, 1H), 2.25 (s, 3H), 2.04 (dd, J = 14.2, 7.1 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD): δ 172.5, 137.3, 135.6, 134.6, 133.3, 130.5, 129.8, 128.8, 128.7, 128.5, 127.08, 127.07, 126.71, 126.70, 126.6, 126.5, 125.3, 48.2, 39.4, 29.9, 23.3.

*(R)-1-Acetyl-6-benzyl-1,2,3,4-tetrahydroquinolin-4-aminium Chloride (**13e**).* This compound was synthesized following general procedure I using **12e** (105 mg 0.273 mmol, 1.0 equiv) and concd HCl (40 μL, 1.64 mmol, 6.0 equiv). After removing the solvent, the residue was resuspended in Et_2O, and the solid crashed out. The solid was filtered off, washed 3× with fresh Et_2O, and dried to yield the product as a white solid (68 mg, 78.2%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.43−7.37 (m, 1H), 7.32−7.21 (m, 4H), 7.20−7.15 (m, 1H), 4.62−4.53 (m, 1H), 4.01 (s, 2H), 3.95−3.86 (m, 2H), 2.49−2.38 (m, 1H), 2.28 (s, 3H), 2.07 (s, 1H). ^{13}C NMR (126 MHz, CD_3OD): δ 172.4, 142.1, 140.9, 138.1, 130.7, 129.9, 129.6, 129.0, 127.3, 126.5, 48.3, 42.2, 29.9, 23.3.

*(R)-1-Acetyl-6-((2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-aminium Chloride (**13f**).* This compound was synthesized following general procedure I using **12f** (46 mg 0.108 mmol, 1.0 equiv) and concd HCl (16 μL, 0.650 mmol, 6.0 equiv). After removing the solvent, the residue was resuspended in Et_2O, and the residue crashed out. The residue was gummy and sticky so it was washed 3× with fresh Et_2O and dried to yield the product as a tan solid (39 mg, quant.). The solid was taken ahead to the next reaction (formation of **14f**) without further isolation, purification, or characterization.

*(4R)-1-Acetyl-6-((2,3-dihydro-1H-inden-1-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-aminium Chloride (**13g**).* This compound was synthesized as a mixture of diastereomers following general procedure I using **12g** (219 mg 0.516 mmol, 1.0 equiv) and concd HCl (76 μL, 3.10 mmol, 6.0 equiv). After removing the solvent, the residue was resuspended in Et_2O, and the solid crashed out. The solid was filtered off, washed 3× with fresh Et_2O, and dried to yield the title compound as a white solid (135 mg, 73.4%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.46−7.38 (1H), 7.27 (bs, 1 H), 7.22−7.17 (m, 1H), 7.16−7.08 (m, 3H), 4.60 (s, 1H), 3.93 (qt, J = 8.3, 4.4 Hz, 2H), 3.53−3.44 (m, 1H), 3.17 (dt, J = 13.4, 6.6 Hz, 1H), 2.94−2.84 (m, 1H), 2.84−2.74 (m, 1H), 2.74−2.67 (m, 1H), 2.46 (dq, J = 11.5, 4.7 Hz, 1H), 2.30 (s, 3H), 2.18−2.05 (m, 2H), 1.78 (dp, J = 13.2, 6.6 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD): δ 172.43, 172.41, 147.7, 147.6, 145.11, 145.08, 138.1, 131.0, 129.44, 129.37, 127.7, 127.10, 127.06, 126.3, 125.48, 125.47, 124.73, 124.70, 48.3, 47.6, 41.8, 41.8, 32.9, 32.8, 31.9, 30.0, 23.4, 23.3.

*(4R)-1-(tert-Butoxycarbonyl)-6-((2,3-dihydro-1H-inden-1-yl)-methyl)-1,2,3,4-tetrahydroquinolin-4-aminium Chloride (**13h**).* This compound was synthesized as a mixture of diastereomers following general procedure I using **12h** (27 mg 0.0559 mmol, 1.0 equiv) and concd HCl (8 μL, 0.336 mmol, 6.0 equiv). After removing the solvent, the residue was resuspended in Et_2O, and the solid crashed out. The solid was filtered off, washed 3× with fresh Et_2O, and dried to yield the title compound as a white solid (10 mg, 43.5%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.71 (d, J = 8.5 Hz, 1H), 7.28 (s, 1H), 7.24−7.17 (m, 2H), 7.10 (m, 3H), 4.56 (d, J = 4.7 Hz, 1H), 3.95−3.78 (m, 2H), 3.51−3.40 (m, 1H), 3.13 (dt, J = 12.8, 6.4 Hz, 1H), 2.95−2.74 (m, 2H), 2.68 (dd, J = 13.5, 9.2 Hz, 1H), 2.39−2.30 (d, J = 4.1 Hz, 1H), 2.18−2.03 (m, 2H), 1.78 (dp, J = 13.2, 6.5 Hz, 1H), 1.54 (d, J = 1.4 Hz, 9H). ^{13}C NMR (126 MHz, CD_3OD): δ 154.8, 147.7, 145.1,

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138.41, 138.37, 138.0, 131.0, 130.9, 129.5, 129.4, 127.7, 127.1, 127.0, 125.7, 125.5, 124.7, 83.0, 47.6, 41.9, 41.7, 32.8, 31.9, 29.2, 28.5.

*(S)-N-((R)-1-Acetyl-6-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14a**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **13a** (56 mg, 0.153 mmol, 1.0 equiv) to yield crude product, which was purified by semipreparative HPLC and then lyophilized to yield the title compound as a TFA salt (17 mg, 30.4%). Starting material **13a** was recovered but not considered when calculating percent yield. ^{1}H NMR (500 MHz, CD_3OD): δ 7.80−7.71 (m, 4H), 7.60 (s, 1H), 7.47−7.36 (m, 2H), 7.28 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.19 (s, 1H), 7.12 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.51 (s, 2H), 4.94 (q, *J* = 6.8 Hz, 1H), 4.07 (s, 2H), 3.87 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.24 (dd, *J* = 13.7, 11.5 Hz, 1H), 3.04 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.26 (s, 6H), 2.17 (s, 3H), 1.89−1.79 (m, 1H), 1.51−1.41 (m, 1H). ^{13}C NMR (126 MHz, CD_3OD): δ 172.5, 169.2, 157.4, 151.9, 140.1, 139.8, 135.1, 133.6, 129.5, 129.1, 128.6, 128.5, 128.4, 127.9, 127.1, 126.5, 125.8, 123.3, 116.5, 53.5, 47.2, 47.1, 42.3, 31.9, 31.2, 23.4, 20.4. HPLC (gradient A): retention time = 38.8. ESI-MS: 522.3 $[M + H]^+$.

*(S)-2-Amino-N-((R)-6-(cyclohexylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14b**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **13b** (10 mg, 0.0262 mmol, 1.0 equiv) to yield crude product, which was purified by semipreparative HPLC and then lyophilized to yield the title compound as a TFA salt (9 mg, 63.2%). ^{1}H NMR (500 MHz, CD_3OD): δ 8.09 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 2.0 Hz, 1H), 6.83 (s, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.39 (s, 2H), 4.89 (q, *J* = 5.0 Hz, 1H), 3.78 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.16 (dd, *J* = 13.6, 11.6 Hz, 1H), 2.99 (dt, *J* = 12.5, 4.3 Hz, 1H), 2.93 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.52 (td, *J* = 11.7, 2.6 Hz, 1H), 2.31−2.22 (m, 2H), 2.18 (s, 6H), 1.77−1.67 (m, 1H), 1.61−1.48 (m, 5H), 1.47−1.40 (m, 1H), 1.37−1.27 (m, 1H), 1.12−1.02 (m, 3H), 0.87−0.74 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD): δ 168.6, 157.4, 140.0, 136.3, 131.8, 131.0, 123.3, 118.9, 116.4, 53.4, 45.8, 44.3, 41.2, 39.0, 34.3, 34.1, 31.9, 28.7, 27.6, 27.38, 27.36, 20.5. HPLC (gradient A): retention time = 31.0. ESI-MS: 458.2 $[M + Na]^+$.

*(S)-N-((R)-1-Acetyl-6-(cyclohexylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14c**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **13c** (12 mg, 0.0372 mmol, 1.0 equiv) to yield crude product, which was purified by semipreparative HPLC and then lyophilized to yield the title compound as a TFA salt (12 mg, 55.5%). ^{1}H NMR (500 MHz, CD_3OD): δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.06−7.00 (m, 2H), 6.51 (s, 2H), 4.99−4.93 (m, 1H), 3.88 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.79 (s, 1H), 3.26 (dd, *J* = 13.6, 11.5 Hz, 1H), 3.22−3.10 (m, 1H), 3.05 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.48−2.38 (m, 2H), 2.28 (s, 6H), 2.19 (s, 3H), 1.90−1.82 (m, 1H), 1.74−1.59 (m, 5H), 1.53−1.37 (m, 2H), 1.26−1.12 (m, 3H), 0.99−0.87 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD): δ 172.5, 169.2, 157.5, 140.1, 129.5, 125.4, 123.3, 116.5, 53.5, 47.0, 44.4, 41.0, 34.3, 34.2, 32.0, 31.3, 27.6, 27.36, 27.35, 23.33, 20.44. HPLC (gradient A): retention time = 39.5. ESI-MS: 478.3 $[M + Na]^+$.

*(S)-N-((R)-1-Acetyl-6-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14d**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **13d** (22 mg, 0.060 mmol, 1.0 equiv) to yield crude product, which was purified by semipreparative HPLC and then lyophilized to yield the title compound as a TFA salt (4 mg, 12.9%). Starting material **13d** was recovered but not considered when calculating the percent yield. ^{1}H NMR (500 MHz, CD_3OD): δ 7.99−7.95 (m, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.78−7.74 (m, 1H), 7.48−7.37 (m, 4H), 7.27 (d, *J* = 7.0 Hz, 1H), 7.22−7.17 (m, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.51 (s, 2H), 4.93 (bs, 1H) 4.40 (s, 2H), 3.84 (dd, *J* = 11.4, 5.0 Hz, 1H), 3.24 (t, *J* = 12.6 Hz, 1H), 3.05−2.98 (m, 1H), 2.27 (d, *J* = 1.4 Hz, 6H), 2.17 (s, 3H), 1.86 (dt, *J* = 11.6, 5.7 Hz, 1H), 1.49 (bs, 1H). No ^{13}C NMR spectrum acquired. HPLC (gradient A): retention time = 38.3. ESI-MS: 544.3 $[M + Na]^+$.

*(S)-N-((R)-1-Acetyl-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14e**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **13e** (68 mg, 0.215 mmol, 1.0 equiv) to yield crude product, which was purified by semipreparative HPLC and then lyophilized to yield the title compound as a TFA salt (16 mg, 12.7%). Starting material **13e** was recovered but not considered when calculating the percent yield. ^{1}H NMR (500 MHz, CD_3OD): δ 7.26−7.20 (m, 2H), 7.18−7.12 (m, 4H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.51 (s, 2H), 4.94 (t, *J* = 6.0 Hz, 1H), 3.94−3.83 (m, 3H), 3.27−3.22 (m, 2H), 3.16 (m, 1H), 3.05 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.27 (s, 6H), 2.18 (s, 3H). No ^{13}C NMR spectrum acquired. HPLC (gradient A): retention time = 32.7. ESI-MS: 494.3 $[M + Na]^+$.

*(S)-N-((R)-1-Acetyl-6-((2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14f**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **13f** (39 mg, 0.108 mmol, 1.0 equiv) to yield crude product, which was purified by semipreparative HPLC and then lyophilized to yield the title compound as a TFA salt (14 mg, 20.6%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.12 (s, 4H), 7.09−7.04 (m, 2H), 6.51 (s, 2H), 4.97 (s, 1H), 3.85 (dd, *J* = 11.2, 4.3 Hz, 1H), 3.29−3.19 (m, 2H), 3.04 (dd, *J* = 13.7, 4.1 Hz, 2H), 2.98−2.87 (m, 2H), 2.73 (d, *J* = 10.3 Hz, 3H), 2.62 (d, *J* = 15.6 Hz, 2H), 2.28 (s, 6H), 2.21 (s, 3H). No ^{13}C NMR spectrum acquired. HPLC (gradient A): retention time = 38.4. ESI-MS: 534.3 $[M + Na]^+$.

*(S)-N-((R)-1-Acetyl-6-(((R/S)-2,3-dihydro-1H-inden-1-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14g**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **13g** (20 mg, 0.056 mmol, 1.0 equiv) to yield crude product, which was purified by semipreparative HPLC and then lyophilized to yield the title compound as the TFA salt of a mixture of diastereomers (8 mg, 22.9%). Starting material **13g** was recovered but not considered when calculating the percent yield. ^{1}H NMR (500 MHz, CD_3OD): δ 7.21−6.98 (m, 7H), 6.52 (s, 2H), 5.03−4.93 (1, 2H), 3.87 (dt, *J* = 10.5, 4.9 Hz, 1H), 3.81 (s, 1H), 3.40 (q, *J* = 7.3 Hz, 1H), 3.30−3.21 (m, 1H), 3.08−3.00 (m, 2H), 2.90−2.81 (m, 1H), 2.80−2.70 (m, 1H), 2.67−2.55 (m, 1H), 2.28 (s, 6H), 2.21 (s, 3H), 2.15−2.03 (m, 1H), 1.94−1.82 (m, 1H), 1.71 (dq, *J* = 14.3, 7.4 Hz, 1H), 1.45 (s, 1H). No ^{13}C NMR spectrum acquired. HPLC (gradient A): retention time = 38.4. ESI-MS: 534.3 $[M + Na]^+$.

*(S)-2-Amino-N-((R)-6-(((R/S)-2,3-dihydro-1H-inden-1-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14h**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **13h** (10 mg, 0.0241 mmol, 1.0 equiv) as a mixture of diastereomers to yield crude product, which was purified by semipreparative HPLC and then lyophilized to yield the title compound as the TFA salt of a mixture of diastereomers (5 mg, 35.7%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.18−7.14 (m, 1H), 7.12−7.06 (m, 2H), 7.05−7.00 (m, 1H), 6.97−6.91 (m, 2H), 6.62 (dd, *J* = 8.4, 3.4 Hz, 1H), 6.49 (s, 2H), 4.97 (t, *J* = 4.7 Hz, 1H), 3.86 (dt, *J* = 11.7, 4.8 Hz, 1H), 3.38−3.31 (m, 1H) 3.29−3.22 (m, 1H), 3.09−2.97 (m, 3H), 2.88−2.79 (m, 1H), 2.78−2.69 (m, 1H), 2.64−2.43 (m, 3H), 2.28 (s, 6H), 2.13−1.98 (m, 1H), 1.79 (t, *J* = 12.6 Hz, 1H), 1.69 (ddd, *J* = 15.1, 13.0, 7.0 Hz, 1H), 1.58−1.49 (m, 1H). No ^{13}C NMR spectrum acquired. HPLC (gradient A): retention time = 30.7. ESI-MS: 492.2 $[M + Na]^+$.

*(S)-2-Amino-N-((R)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14i**).* This compound was previously synthesized; see ref 1 for characterization details.

*(S)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (**14j**).* This compound was previously synthesized; see ref 1 for characterization details.

*(S)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (**14k**).* This compound was previously synthesized; see ref 1 for characterization details.

*(S)-2-Amino-N-((R)-6-((2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14l**).* This compound was previously synthesized; see ref 1 for characterization details.

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*(S)-2-Amino-N-((R)-7-benzyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-hydroxy-2,6-dimethylphenyl) propanamide (**14m**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **19m** (44 mg, 0.161 mmol) to yield crude product, which was purified by semipreparative HPLC and lyophilized to yield the title compound as a TFA salt (58 mg, 84%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.09 (d, J = 8.4 Hz, 1H), 7.19 (dd, J = 8.8, 6.8 Hz, 2H), 7.16−7.07 (m, 3H), 7.04 (s, 1H), 6.91 (d, J = 1.2 Hz, 2H), 6.47 (s, 2H), 4.92 (s, 1H), 3.87 (d, J = 4.9 Hz, 1H), 3.83 (s, 2H), 3.24 (dd, J = 13.6, 11.5 Hz, 1H), 3.01 (dd, J = 13.7, 5.0 Hz, 1H), 2.62−2.51 (m, 2H), 2.26 (s, 6H), 1.69−1.45 (m, 2H), 1.45−1.34 (m, 1H), 1.32−1.19 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD): δ 167.4, 155.9, 141.3, 138.8, 138.5, 135.14, 135.10, 135.0, 129.2, 128.8, 128.3, 127.9, 127.8, 125.5, 121.8, 115.0, 52.1, 48.2, 48.0, 47.8, 47.6, 47.4, 47.3, 47.2, 47.0, 40.9, 30.6, 29.2, 28.1, 19.1, 18.9. HPLC (gradient A): retention time = 40.6 ESI-MS: 451.2 $[M + Na]^+$.

*(S)-2-Amino-N-((R)-7-(cyclohexylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (**14n**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **19n** (20 mg, 0.0715 mmol) to yield crude product, which was purified by semipreparative HPLC and lyophilized to yield the title compound as a TFA salt (35 mg, 89.7%). ^{1}H NMR (500 MHz, CD_3OD): δ 8.08−8.02 (m, 1H), 6.95−6.89 (m, 3H), 6.49 (s, 2H), 4.98−4.93 (m, 1H), 3.92−3.81 (m, 1H), 3.25 (d, J = 12.2 Hz, 1H), 3.01 (d, J = 14.1 Hz, 1H), 2.60−2.54 (bs, 2H), 2.40−4.33 (bs, 2H), 2.28 (s, 6H), 1.73−1.59 (m, 6H), 1.58−1.52 (m, 1H), 1.47−1.37 (m, 2H), 1.33−1.24 (m, 1H), 1.22−1.12 (m, 3H), 0.92 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD): δ 168.7, 157.3, 140.1, 139.9, 136.2, 136.0, 130.7, 129.8, 129.5, 123.2, 116.5, 53.53, 53.49, 48.8, 44.7, 41.1, 34.4, 34.2, 32.0, 30.7, 29.6, 27.7, 27.39, 27.38, 20.5, 20.3. HPLC (gradient A): retention time = 47.3. ESI-MS: 457.3 $[M + H]^+$.

*(S)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-7-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-propanamide (**14o**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **19o** (11 mg, 0.034 mmol) to yield crude product, which was purified by semipreparative HPLC and lyophilized to yield the title compound as a TFA salt (14 mg, 69.7%). ^{1}H NMR (500 MHz, CD_3OD): δ 8.09 (d, J = 8.2 Hz, 1H), 7.74 (dd, J = 25.4, 7.7 Hz, 4H), 7.56 (s, 1H), 7.40 (p, J = 7.0 Hz, 3H), 7.26 (d, J = 8.3 Hz, 1H), 7.11 (s, 1H), 7.03−6.94 (m, 3H), 6.49 (s, 2H), 5.01−4.93 (m, 1H), 4.03 (s, 2H), 3.85 (dd, J = 11.2, 4.7 Hz, 1H), 3.24 (t, J = 12.5 Hz, 1H), 3.00 (dd, J = 13.5, 4.7 Hz, 1H), 2.65−2.55 (m, 2H), 2.27 (s, 6H), 1.69−1.60 (m, 1H), 1.59−1.52 (m, 1H), 1.47−1.37 (m, 1H), 1.33−1.24 (bs, 1H). ^{13}C NMR (126 MHz, CD_3OD): δ 168.8, 157.3, 140.3, 140.0, 139.9, 136.7, 136.6, 135.1, 133.5, 130.7, 130.4, 129.5, 128.9, 128.6, 128.4, 127.7, 127.0, 126.4, 123.2, 116.5, 111.4, 53.5, 48.7, 42.5, 32.0, 30.6, 29.6, 20.5, 20.3. HPLC (gradient A): retention time = 45.6. ESI-MS: 479.3 $[M + H]^+$.

*(S)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-7-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-propanamide (**14p**).* This compound was synthesized following general procedure J starting from the (*R*) amine intermediate **19p** (7 mg, 0.0216 mmol) to yield crude product, which was purified by semipreparative HPLC and lyophilized to yield the title compound as a TFA salt (11 mg, 85.9%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.97 (d, J = 8.1 Hz, 1H), 7.87−7.82 (m, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.49−7.34 (m, 3H), 7.22 (d, J = 7.0 Hz, 1H), 7.13 (s, 1H), 6.95−6.84 (m, 2H), 6.49 (d, J = 1.8 Hz, 2H), 4.99−4.91 (m, 1H), 4.35 (s, 2H), 3.84 (ddd, J = 11.5, 5.1, 1.8 Hz, 1H), 3.25 (ddd, J = 13.5, 11.4, 1.9 Hz, 1H), 3.00 (ddd, J = 13.9, 5.1, 1.7 Hz, 1H), 2.64−2.56 (m, 2H), 2.27 (s, 6H), 1.68−1.59 (m, 1H), 1.59−1.51 (m, 1H), 1.46−1.38 (m, 1H), 1.33−1.24 (m, 1H). ^{13}C NMR (126 MHz, CD_3OD): δ 167.2, 155.9, 138.5, 138.3, 136.6, 135.2, 135.1, 134.1, 131.9, 129.0, 128.8, 128.2, 127.6, 126.71, 126.69, 125.4, 125.1, 125.0, 123.8, 121.8, 115.0, 52.1, 47.4, 38.1, 30.6, 29.2, 28.1, 19.1, 18.9. No HPLC retention time data was obtained. ESI-MS: 501.1 $[M + Na]^+$.

*(R)-N-((R)-7-Bromo-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methylpropane-2-sulfinamide (**17**).* This compound was synthesized following general procedure H using commercially available **15** (1.0 g, 4.44 mmol, 1 equiv), (*R*)-2-methylpropane-2-sulfinamide (1076 mg, 8.88 mmol, 2.0 equiv), and $Ti(OEt)_4$ (3.73 mL, 17.771 mmol, 4 equiv) to form the (*R*)-*tert*-butanesulfinyl imine intermediate (**16**) in situ. Once sufficient ketone was converted to imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round-bottom flask containing $NaBH_4$ (671.7 mg, 17.76 mmol, 4 equiv) and 13 mL of THF in a xylene dry ice bath; after this addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once the resultant solid was removed, the crude residue was purified using silica gel chromatography (1:9 EA:hex) to yield the title compound as a clear, colorless oil (1126 mg, 77%) (from **15**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, J = 2.1 Hz, 1H), 7.24 (dd, J = 8.2, 2.1 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 4.46 (q, J = 4.4 Hz, 1H), 3.31 (d, J = 4.0 Hz, 1H), 2.72 (dt, J = 17.0, 5.2 Hz, 1H), 2.61 (ddd, J = 17.0, 8.9, 5.7 Hz, 1H), 2.00−1.92 (m, 1H), 1.92−1.79 (m, 2H), 1.76−1.67 (m, 1H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.9, 138.0, 132.07, 132.06, 130.8, 130.5, 119.6, 77.3, 77.0, 76.7, 55.4, 52.5, 30.2, 28.4, 22.5, 18.0.

*(R)-N-((R)-7-Benzyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methylpropane-2-sulfinamide (**18m**).* This compound was synthesized following general procedure F using **17** (110 mg, 0.33 mmol, 1.0 equiv), 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (148.2 uL, 0.66 mmol, 2.0 equiv), K_2CO_3 (138 mg, 0.99 mmol, 3.0 equiv), and $Pd(dppf)Cl_2$ (24.4 mg, 0.033 mmol, 0.1 equiv). The reagents were placed in a microwave tube followed by 1−2 mL of the previously degassed 3:1 acetone:water solvent system and reacted in a microwave with a max temp of 110 °C and max power of 300 W for 60 min with "Powermax" enabled. Once the crude mixture was filtered through Celite, the residue was purified via silica gel chromatography (1:1 EA:hex) to yield the title compound (64 mg, 56%) as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.31 (m, 1H), 7.31−7.24 (m, 2H), 7.23−7.15 (m, 3H), 7.02 (t, J = 1.4 Hz, 2H), 4.56 (d, J = 3.9 Hz, 1H), 3.95 (s, 2H), 3.23 (d, J = 3.2 Hz, 1H), 2.78 (dt, J = 16.9, 4.9 Hz, 1H), 2.69 (ddd, J = 16.5, 9.5, 5.6 Hz, 1H), 2.08−1.99 (m, 1H), 1.99−1.82 (m, 2H), 1.80−1.70 (m, 1H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.2, 139.5, 136.8, 135.5, 129.9, 129.5, 128.83, 128.82, 128.5, 128.2, 126.0, 77.3, 77.1, 76.8, 55.4, 52.5, 41.6, 30.3, 28.7, 22.6, 18.1.

*(R)-N-((R)-7-(Cyclohexylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methylpropane-2-sulfinamide (**18n**).* This compound was synthesized following general procedure G using **17** (100 mg, 0.30 mmol, 1.0 equiv), (cyclohexylmethyl)boronic acid (86 mg, 0.61 mmol, 2.0 equiv), K_2CO_3 (126 mg, 0.91 mmol, 3.0 equiv), Ag_2O (175 mg, 0.76 mmol, 2.5 equiv), and $Pd(dppf)Cl_2$ (22 mg, 0.031 mmol, 0.1 equiv). The reagents were placed in a microwave tube followed by 1.5 mL of anhyd THF and reacted in a microwave with a max temp of 80 °C and max power of 300 W for 60 min with the "Powermax" option disabled. Once the crude mixture was filtered through Celite, the residue purified via silica gel chromatography (equilibrated in 100% hex, run in 2:3 EA:hex) to yield the title compound as a clear, colorless oil (105 mg, quant), which was taken to the next step (formation of **19n**) without further characterization.

*(R)-2-Methyl-N-((R)-7-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propane-2-sulfinamide (**18o**).* This compound was synthesized following general procedure F using **17** (49 mg, 0.15 mmol, 1.0 equiv), 4,4,5,5-tetramethyl-2-(naphthalen-2-ylmethyl)-1,3,2-dioxaborolane (80 mg, 3.0 mmol, 2.0 equiv), K_2CO_3 (58 mg, 0.42 mmol, 3.0 equiv), and $Pd(dppf)Cl_2$ (11 mg, 0.015 mmol, 0.1 equiv). The reagents were placed in a microwave tube followed by 1−2 mL of the previously degassed 3:1 acetone:water solvent system and reacted in a microwave with a max temp of 110 °C and max power of 300 W for 60 min with "Powermax" enabled. Once the crude mixture was filtered through Celite, the residue was purified via silica gel chromatography (equilibrated in 100% hex, run in 1:1 EA:hex) to yield the title compound (32 mg, 55.2%) as a clear, colorless oil, which was taken ahead.

*(R)-2-Methyl-N-((R)-7-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propane-2-sulfinamide (**18p**).* This compound was synthesized following general procedure F using **17** (46 mg, 0.14 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-(naphthalen-1-ylmethyl)-1,3,2-dioxaborolane (75 mg, 0.28 mmol, 2 equiv), K_2CO_3 (58 mg, 0.42

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mmol, 3 equiv), and Pd(dppf)Cl_2 (10 mg, 0.014 mmol, 0.1 equiv). The reagents were placed in a microwave tube followed by the previously degassed 3:1 acetone:water solvent system and reacted in a microwave with a max temp of 110 °C and max power of 250 W for 30 min with "Powermax" enabled. Once the crude mixture was filtered through Celite, the residue was purified via silica gel chromatography (equilibrated in 100% hex, run in 1:4 EA:hex) to yield the title compound (11 mg, 20.2%) as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03−7.97 (m, 1H), 7.87−7.81 (m, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.48−7.38 (m, 3H), 7.37 (s, 1H), 7.31 (d, J = 6.9 Hz, 1H), 6.96 (s, 2H), 4.53 (q, J = 3.4 Hz, 1H), 4.40 (s, 2H), 3.20 (s, 1H), 2.79−2.71 (m, 1H), 2.70−2.60 (m, 1H), 2.05−1.97 (m, 1H), 1.94−1.79 (m, 2H), 1.77−1.65 (m, 1H), 1.17 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.9, 136.8, 136.6, 135.5, 133.9, 132.0, 129.7, 129.4, 128.6, 127.9, 127.2, 127.1, 125.9, 125.54, 125.47, 124.2, 55.4, 52.4, 38.6, 30.3, 28.7, 22.6, 18.1.

*(R)-7-Benzyl-1,2,3,4-tetrahydronaphthalen-1-aminium Chloride (**19m**).* This compound was synthesized following general procedure I using **18m** (112 mg, 0.33 mmol, 1.0 equiv) and 5 mL of 2 M HCl in dioxane. The hydrochloride salt crashed out after the addition of the acid. The Et_2O was filtered off, leaving a white, flaky precipitate that was washed with cold Et_2O and dried under vacuum without any further purification to yield the title compound (78 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 3H), 7.56 (s, 1H), 7.30−7.05 (m, 5H), 7.01 (s, 2H), 4.39 (dd, J = 6.7 Hz, 1H), 3.86 (s, 2H), 2.87−2.74 (m, 1H), 2.73−2.57 (m, 1H), 2.19−1.89 (m, 3H), 1.72 (dd, J = 14.7, 6.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.0, 139.5, 135.3, 131.1, 129.8, 129.5, 129.3, 128.9, 128.4, 126.0, 77.3, 77.0, 76.7, 49.6, 41.5, 28.3, 27.9, 18.7.

*(R)-7-(Cyclohexylmethyl)-1,2,3,4-tetrahydronaphthalen-1-aminium Chloride (**19n**).* This compound was synthesized following general procedure I using **18n** (100 mg, 0.29 mmol, 1.0 equiv) and concd HCl (42 μL, 1.7 mmol, 6.0 equiv). After removal of the solvent, the residue was resuspended in Et_2O, and a white solid crashed out. The Et_2O was filtered off, leaving a white, flaky precipitate that was washed with cold Et_2O and dried under vacuum without any further purification to yield the title compound (45 mg, 55.9%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 3H), 7.38 (s, 1H), 7.00 (s, 2H), 4.40 (q, J = 5.4 Hz, 1H), 2.81 (dt, J = 16.7, 5.4 Hz, 1H), 2.71−2.61 (m, 1H), 2.40 (d, J = 7.1 Hz, 2H), 2.18−2.07 (m, 2H), 2.05−1.94(m, 1H), 1.79−1.69 (m, 1H), 1.68−1.55 (m, 5H), 1.54−1.46 m, 1H), 1.22−1.08 (m, 3H), 1.01−0.84 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.7, 134.7, 130.6, 129.7, 129.6, 129.3, 49.7, 43.5, 39.5, 33.11, 33.09, 28.3, 27.93, 27.91, 26.6, 26.3, 26.3.

*(R)-7-(Naphthalen-2-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-aminium Chloride (**19o**).* This compound was synthesized following general procedure I using **18o** (30 mg, 0.077 mmol, 1.0 equiv) and concd HCl (11 μL, 0.46 mmol, 6.0 equiv). After removal of the solvent, the residue was resuspended in Et_2O, and the solid did not crash out. The residue was washed 3× with fresh Et_2O and then dried to yield the title compound as an off-white, sticky solid (11 mg, 44.3%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.83−7.74 (m, 3H), 7.66 (s, 1H), 7.43 (p, J = 7.0 Hz, 2H), 7.35−7.29 (m, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 4.45 (t, J = 5.6 Hz, 1H), 4.14 (s, 2H), 2.92−2.74 (m, 2H), 2.22−2.11 (m, 1H), 2.04−1.82 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD): δ 141.2, 140.0, 136.9, 135.1, 133.6, 133.0, 131.2, 130.9, 129.8, 129.1, 128.6, 128.5, 128.4, 128.0, 127.1, 126.5, 50.3, 42.5, 29.4, 29.1, 19.6.

*(R)-7-(Naphthalen-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-aminium Chloride (**19p**).* This compound was synthesized following general procedure I using **18p** (11 mg, 0.028 mmol, 1.0 equiv) and concd HCl (4 μL, 0.17 mmol, 6.0 equiv). After removing the solvent, the residue was resuspended in Et_2O, and the solid crashed out. After washing the solid 3× with fresh Et_2O, the remaining Et_2O was decanted, yielding the title compound as a white solid (7 mg, 77.8%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.05−7.96 (m, 1H), 7.86 (dd, J = 7.0, 2.3 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.47−7.39 (m, 3H), 7.36 (d, J = 7.0 Hz, 1H), 7.30 (s, 1H), 7.17−7.07 (m, 2H), 4.47−3.38 (m, 3H), 2.90−2.69 (m, 2H), 2.14 (ddt, J = 14.5, 9.6, 4.6 Hz, 1H), 1.92 (ddt, J = 43.3, 20.4, 8.1 Hz, 3H). No ^{13}C NMR spectrum acquired.

In Vitro Pharmacology: Cell Lines and Membrane Preparations. 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[30] and Chinese hamster ovary (CHO) cells stably expressing a human κ (CHO-KOR) opioid receptor[31] were used for all in vitro assays. Cells were grown to confluence at 37 °C in 5% CO_2 in Dulbecco's modified Eagle medium (DMEM) containing 10% fetal bovine serum and 5% penicillin/streptomycin. Membranes were prepared by washing confluent cells 3× with ice cold phosphate buffered saline (0.9% NaCl, 0.61 mM Na_2HPO_4, 0.38 mM KH_2PO_4, 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, Incorporated; Bartlesville, OK, USA) for 20 s. The homogenate was centrifuged at 15,000 rpm for 20 min at 4 °C. The pellet was rehomogenized in 50 mM Tris-HCl with a Tissue Tearor for 10 s followed by recentrifugation. The final pellet was resuspended 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, USA) using bovine serum albumin as the standard.

Radioligand Binding Assays. Radiolabeled compounds were purchased from PerkinElmer (Waltham, MA, USA). Opioid ligand binding assays were performed by competitive displacement of 0.2 nM [^{3}H]diprenorphine (250 μCi, 1.85 TBq/mmol) by the peptidomimetic from membrane preparations containing opioid receptors as described above. The assay mixture, containing membranes (20 μg protein/tube) in 50 mM Tris-HCl buffer (pH 7.4), [^{3}H]-diprenorphine, and various concentrations of test peptidomimetic, was incubated at room temperature for 1 h to allow binding to reach equilibrium. The samples were rapidly filtered through Whatman GF/C filters using a Brandel harvester (Brandel; Gaithersburg, MD, USA) and washed 5× with 50 mM Tris-HCl 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, USA). Nonspecific binding was determined using 10 μM naloxone. The results presented are the mean ± standard error (S.E.M.) from at least three separate assays performed in duplicate. K_i (nM) values were calculated using nonlinear regression analysis to fit a logistic equation to the competition data using GraphPad Prism, version 6.0c, for Mac OS X (GraphPad Software Incorporated; La Jolla, CA, USA).

Stimulation of [^{35}S]GTPγS Binding. Agonist stimulation of [^{35}S]guanosine 5′-O-[γ-thio]triphosphate ([^{35}S]GTPγS, 1250 Ci, 46.2 TBq/mmol) binding to G-protein was measured as described previously.[32] Briefly, membranes (10−20 μg of protein/tube) were incubated for 1 h at 25 °C in GTPγS buffer (50 mM Tris-HCl, 100 mM NaCl, 5 mM $MgCl_2$, pH 7.4) containing 0.1 nM [^{35}S]GTPγS, 30 μM guanosine diphosphate (GDP), and varying concentrations of test peptidomimetic. G-protein activation following receptor stimulation of [^{35}S]GTPγS (% stimulation) with peptidomimetic was compared with 10 μM of the standard compounds [D-Ala2,N-MePhe4,Gly-ol]-enkephalin (DAMGO) at MOR, D-Pen2,5-enkephalin (DPDPE) at DOR, or U69,593 at KOR. The reaction was terminated by vacuum filtration of GF/C filters that were washed 10× with GTPγS buffer. Bound radioactivity was measured as described above. The results are presented as the mean ± standard error (S.E.M.) from at least three separate assays performed in duplicate; potency (EC_{50} (nM)) and % stimulation were determined using nonlinear regression analysis with GraphPad Prism, as above.

In Vivo Pharmacology. *Animals.* Adult male C57BL/6 mice weighing between 20 and 30 g at 8−16 weeks old were purchased from Harlan (Indianapolis, IN, USA). Mice were group-housed and had free access to food and water at all times. Experiments were conducted in the housing room, which was maintained on a 12 h light/dark cycle (with lights on at 0700). Each mouse was used only once, and experiments were conducted between 10 a.m. and 5 p.m. Studies were performed in accordance with the University of Michigan

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Committee on the Use and Care of Animals and the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011 publication).

Antinociception. The antinociceptive effects of select peptidomimetics were evaluated in the WWTW assay using a cumulative dosing procedure.[33] For determination of the tail withdrawal latencies, each mouse was placed briefly into a plastic, cylindrical restrainer, and 2−3 cm of the tail tip was placed into a water bath maintained at 50 °C. The latency to withdraw of the tail was recorded with a maximum cutoff time of 20 s. If the mouse did not remove its tail by the cutoff time, the experimenter removed its tail from the water to prevent tissue damage. Each animal received an injection of saline (intraperitoneal, ip), and then, 30 min later, the baseline withdrawal latencies were recorded and ranged between 3 and 6 s. Following baseline determinations, three increasing doses (1, 2.2, and 6.8 mg/kg) of a final compound **14** analogue was given at 30 min intervals to provide final doses of 1, 3.2, and 10 mg/kg. Thirty minutes after each injection, the tail withdrawal latency was measured as described above. To determine the duration of antinociceptive action, the tail-withdrawal test was performed at varying times following administration of a final compound **14** analogue (10 mg/kg, ip). To confirm that **14a** produces antinociception via the opioid receptors, we repeated the cumulative dose response over the doses 3.2, 10, and 32 mg/kg following a 30 min pretreatment with 1 mg/kg naltrexone or saline (ip). The ED_{50} for mice receiving saline pretreatment is 4.73 ± 0.08 mg/kg **14a**, and the ED_{50} for the mice receiving 1 mg/kg naltrexone is 15.07 ±1.03 mg/kg **14a**, suggesting that the antinociception **14a** produces is MOR-mediated.

Computational Modeling. Three-dimensional models of opioid receptors in inactive conformation were produced as previously described[39] using X-ray structures of the mouse MOR (PDB ID: 4DKL),[41] the human DOR (PDB ID: 4N6H),[45] and the human KOR (PDB ID: 4DJH)[43] as structural templates. The recently obtained crystal structure of mouse MOR in the active conformation (PDB ID: 5C1M)[46] was used as a template for homology modeling of active conformations of DOR and KOR. Structures of receptor loops in the active state were kept similar to those in the crystal structures of corresponding receptors in the inactive state. N-termini of DOR (residues 33−45) and KOR (residues 45−57) were modeled using the structure of MOR N-terminus in the active conformation with a few adjustment to satisfy the formation of Zn-binding centers involving D216 (H54−D216) and H319 (C57−H319), which were previously suggested for MOR.[47] Structures of peptidomimetic ligands were generated using 3D-Builder Application of QUANTA (Accelrys, Inc.) followed by the Conformational Search included in the program package. Ligand conformations that demonstrated the best superposition of aromatic substituents of the THQ core with the pharmacophore elements (Tyr^1 and Phe^3) of receptor-bound conformations of cyclic tetrapeptides[40,48] were selected and minimized with CHARMm implemented in QUANTA (adopted-basis Newton−Raphson method, 100 steps, ε = 10). Low energy conformations (within 2 kcal/mol) were manually positioned inside the receptor binding cavity to reproduce the binding modes of cyclic tetrapeptides. The docking pose of each ligand was subsequently refined using the solid docking module of QUANTA. Models of opioid ligand−receptor complexes are available upon request.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.5b01270.

Ki, EC_{50}, and percent stimulation for MOR, DOR, and KOR for **14a−p** (CSV)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

MOR, μ-opioid receptor; DOR, δ-opioid receptor; KOR, κ-opioid receptor; THQ, tetrahydroquinoline; THN, tetrahydronaphthalene; CHO, Chinese hamster ovary; GTPγS, guanosine 5′-O-[γ-thio]triphosphate; WWTW, warm water tail withdrawal; TM, transmembrane; Boc_2O, di-*tert*-butyldicarbonate; Boc, *tert*-butyldicarbonate; DIPEA, *N*,*N*- diisopropylethylamine; EA, ethyl acetate; hex, hexanes; TfOH, triflic acid; PyBOP, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; HOBt-Cl, 6-chlorohydroxybenzotriazole; diBoc-Dmt, *tert*-butyloxycarbonyl-protected 2,6-dimethyltyrosine

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