Design, synthesis, and optimization of opioid receptor peptidomimetics

by

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6Cl-HOBt: 1-hydroxy-6-chloro-benzotriazole

[^{35}S]GTPγS: [^{35}S]guanosine 5′-O-[γ-thio]triphosphate

Ac$_2$O: acetic anhydride

AcOH: acetic acid

Ag$_2$O: silver (I) oxide

anhyd: anhydrous

Asp: aspartic acid

ATP: adenosine triphosphate

BBB: blood brain barrier

BBr$_3$: boron tribromide

Boc: *tert*-butyloxycarbonyl

Boc$_2$O: di-*tert*-butyl dicarbonate

cAMP: cyclic adenosine monophosphate

CCl$_4$: carbon tetrachloride.

CD$_3$OD: deuterated methanol

CDCl$_3$: deuterated chloroform

Cha: cyclohexylalanine

CH$_3$CN: acetonitrile

CHO: Chinese hamster ovary

CsF: cesium fluoride

DAMGO: $_D$-Ala^2,*N*-MePhe^4,Gly-ol]enkephalin

DCE: 1,2-dichloroethane

DCM: dichloromethane

diBoc-Dmt: di-boc protected 2,6-dimethyl-$_L$-tyrosine

DIPEA: *N,N*-diisopropylethylamine

DIPP-NH$_2$: H-Dmt-Tic-Phe-NH$_2$

DIPP-NH$_2$[Ψ]: H-Dmt-TicΨ[CH$_2$NH]-Phe-Phe-NH$_2$

DMAP: 4-dimethylaminopyridine

DMF: dimethylformamide

Dmt: 2,6-dimethyl-L-tyrosine

[Dmt^1]DALDA: H-Dmt-D-Arg-Phe-Lys-NH$_2$

dns: does not stimulate

DOR: δ-opioid receptor, delta opioid receptor

DORi: delta opioid receptor in the inactive conformation

DPDPE: D-Pen2,5-enkephalin

EA: ethyl acetate

EC$_{50}$: concentration of a drug that gives half-maximal response

ED$_{50}$: dose that produces a quantal effect in 50% of the population receiving a dose

Et$_3$N: triethylamine

EtOH: ethanol

GDP: guanosine diphosphate

GIRK: G protein inwardly rectifying potassium channels

GPCR: G protein-coupled receptor

Glu: glutamic acid

GTP: guanosine triphosphate

H$_2$: hydrogen gas

H$_2$SO$_4$: sulfuric acid

HCl: hydrochloric acid

hex: hexanes

His: histidine

icv: intracerebroventricular

ip: intraperitoneal

K$_2$CO$_3$: potassium carbonate

K$_i$: binding affinity symbol

KOH: potassium hydroxide

KOR: κ-opioid receptor, kappa opioid receptor

LiOH: lithium hydroxide

Lys: lysine

MeCOOCl: methyl chloroformate

MeOH: methanol

MgSO$_4$: magnesium sulfate

MOR: μ-opioid receptor, mu opioid receptor

MW: microwave

***n*-BuLi**: *n*-butyl lithium

NaBH$_4$: sodium borohydride

NaI: sodium iodide

NaHCO$_3$: sodium bicarbonate

NaOAc•H$_2$O: sodium acetate monohydrate

NaOH: sodium hydroxide

NaO*t*Bu: sodium *tert*-butoxide

NBS: *N*-bromosuccinimide

NH$_4$Cl: ammonium chloride

NH$_2$OH$_2$•HCl: hydroxylamine hydrochloride

nyt: not yet tested

OR: opioid receptor

Pd/C: palladium on carbon, 10% wt

Pd(dppf)Cl$_2$: bis(diphenylphosphino)ferrocene]palladium(II) dichloride

Pgp: P-glycoprotein.

Phe: phenylalanine

PPA: polyphosphoric acid

PyBOP: (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate)

quant.: quantitative

R-B(OH)$_2$: boronic acid

R-Bpin: pinacol borane ester

R-COCl: acid chloride

RT: room temperature

SAR: Structure-Activity Relationship

S.E.M.: standard error mean

TFA: trifluoroacetic acid

TfOH: trifluoromethanesulfonic acid, triflic acid

Tic: tetrahydroisoquinoline-3-carboxylic acid

TICP[Ψ]: H-Tyr-TicΨ[CH$_2$NH]-Cha-Phe-OH

Ti(OEt)$_4$: titanium (IV) ethoxide

TIPP-NH$_2$: H-Tyr-Tic-Phe-Phe-NH$_2$

THF: tetrahydrofuran

THN: tetrahydronaphthalene

THQ: tetrahydroquinoline

TM: transmembrane

Trp: tryptophan

Tyr: tyrosine

WWTW: warm water tail withdrawal

ABSTRACT

Opioids have been used to produce analgesia, euphoria, sleep, and relief from diarrhea and cough. However, opioid use is associated with several negative neurochemical adaptions including tolerance, dependence, and respiratory depression. Studies have shown that selective delta-opioid receptor (DOR) antagonism in the presence of a mu-opioid receptor (MOR) agonist greatly reduces the development of MOR-mediated morphine tolerance and dependence. Unfortunately, multi-drug regimens have complicated pharmacokinetics (PK) and are often impractical to implement in clinical practice due decreased patient compliance stemming from these PK issues.

This work describes the design and synthesis of a peptidomimetic series of bi-functional ligands with a mixed-efficacy profile that display MOR agonism and DOR antagonism. These ligands retain the analgesic effect (mediated via MOR agonism) while reducing side effects (mediated via DOR antagonism). In particular, three parallel series of peptidomimetics series were synthesized that retain the key opioid binding elements and orientation of lead peptides, but that eliminate the metabolically labile moieties of the lead peptides, thereby creating more bioavailable ligands. The three parallel series of ligands utilized a tetrahydroquinoline (THQ) core, a tetrahydronaphthalene (THN) core, or an *N*-acetylated THQ core. *N*-acetylation increased the affinity of the peptidomimetics for DOR, without significantly altering the subnanomolar affinity and efficacy at MOR, and improved selectivity over the κ-opioid receptor (KOR). Using computational modeling, it was determined that the increase in DOR affinity could be through an interaction between the carbonyl moiety of *N*-acetylated group and a tyrosine residue in DOR. Additional analogue series were synthesized, including series with 1) various *N*-substitutions, all of which contain a carbonyl to maintain DOR affinity, 2) several methoxy and hydroxyl moieties to explore SAR, 3) stereochemistry around the THQ and THN core to explore SAR, and 4.)

fluorine incorporated to increase bioavailabilty. Of all analogues synthesized and screened for *in vivo* activity, **54** emerged as having *in vivo* activity in the Warm Water Tail Withdrawal assay after intraperitoneal administration at 10 mg/kg. Importantly, this compound had a similar duration of action to morphine at the same 10 mg/kg dose and, however unlike morphine, **54** did not produce tolerance upon chronic administration.

CHAPTER 1

Introduction

1.1 Opioid receptors: structure and function

Opioids have been used recreationally and medically for thousands of years for a variety of ailments including headache, coughs, shortness of breath, insomnia, antidiarrheal, euphoric properties and analgesic properties. Morphine and codeine, the two principal active ingredients of opium that produce the characteristic euphoria and analgesia, along with thebaine (which is not itself used therapeutically, but can be converted to other clinically useful agents such as: oxycodone, oxymorphone, and naloxone) were isolated and characterized in the 18th and 19th centuries (Figure 1.1).
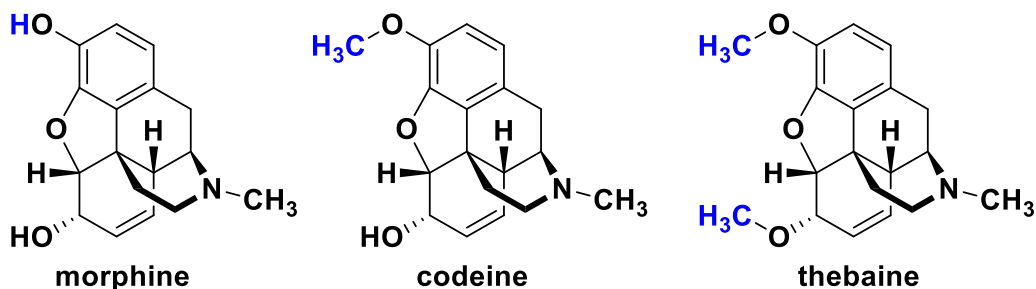
Figure 1.1. Chemical structures of the opiates found in the opium extract. Structural differences highlighted in blue.

Since its isolation and characterization, morphine has been used as the premier treatment for severe pain. Although opioids are irreplaceable as pain-relieving agents, their use is often associated with several side effects including constipation and respiratory depression, which can limit their clinical utility. Furthermore, both acute and chronic use of opioids can result in

neurochemical adaptations that result in physiological tolerance and dependence.[1-4] While there are many theories as to how tolerance develops including theories concerning receptor down regulation and desensitization mechanisms,[1-4] these all most likely reflect a common adaptive response to increased levels of opioid ligand in the body. When sustained administration of opioid drug leads to a decrease in effect or analgesia in the case of opioids, then tolerance has developed. Essentially, in order to achieve the same effect (or level of analgesia in the case of opioids) an escalating drug dosage needs to be administered. On the other hand, dependence is the result of an altered state of biology induced by a drug. In other words, continued use of a drug results in a new "normal" state of cellular functioning, where drug is necessary to maintain the new state of homeostasis, and removal of drug results in withdrawal symptoms. With these side effects in mind, the development of clinically effective opioid analgesics devoid of abuse potential is a critical goal. However, in order to achieve this goal, an understanding of how opioid analgesics exert their analgesic effects through interactions with opioid receptors (ORs) located in the brain and spinal cord is necessary.

Opioid receptors belong to the large family of class A, rhodopsin-like G protein-coupled receptors (GPCRs) and are comprised of seven transmembrane (7TM) spanning alpha helices connected by three extracellular and three intracellular loops with an extracellular N-terminus and an intracellular C-terminus.[5] All GPCRs couple with heterotrimeric guanine nucleotide binding proteins (G proteins) which are composed of an α, and a dimeric βγ subunit. Upon ligand binding to a GPCR, specific conformations of the receptor are stabilized, a signal is transmitted from extracellular space to the intracellular space and second messengers are activated to initiate downstream signaling. When an agonist binds, a conformational change in the transmembrane helices occurs which in turn favors the exchange of a guanosine diphosphate (GDP) for guanosine triphosphate (GTP). This exchange allows for the dissociation of the G protein from the receptor as well as the dissociation of the α subunit from the βγ subunit. These subunits go on to effect downstream signaling partners and alter cell signaling. Eventually the signal is terminated and the receptor is reset for subsequent signaling by hydrolysis of GTP to GDP allowing for the re-association of the α and βγ subunits with each other and the receptor.[5]

There are three classical types of opioid receptors, μ (MOR), δ (DOR) and κ (KOR), each of which is coupled to an inhibitory G protein, $G\alpha_{i/o}$, which when dissociated from the receptor via the aforementioned process can: (1) inhibit the conversion of adenosine triphosphate (ATP) to

cyclic adenosine monophosphate (cAMP) via adenylyl cyclase, (2) shut down voltage-gated Ca^{2+} channels, and (3) open K+ channels via G protein inwardly rectifying potassium channels (GIRKs). The overall effects on nerve cell function when an agonist binds to an opioid receptor includes the reduction of membrane excitability and subsequent decrease in cell firing culminating in the inhibition of neurotransmitter release.[5]

Despite all opioid receptors being coupled to the same G protein, $G\alpha_{i/o}$, each displays unique physiological effects upon agonist binding. For example, the treatment of severe pain relies on μ-opioid receptor (MOR) agonists, such as morphine, which also produce most of the undesired side effects limiting their use in pain treatment.[6] Despite their ability to also produce analgesia, KOR agonists produce dysphoric and psychomimetic effects, thus their use as pain relievers has been discouraged.[6] While DOR agonists have also been shown to produce analgesia with a lesser risk of dependence, they are less efficacious than the commonly used analgesics, and can produce seizures.[6]

While MOR agonists, like morphine, are the gold standard in the treatment of severe pain, their therapeutic use is often limited due to unfortunate side effects including tolerance, dependence, respiratory depression, and constipation. However, several studies have explored the simultaneous administration of a δ-opioid receptor (DOR) ligands as a means to mitigate the negative side effects of purely MOR selective compounds. Recently there has been a shift in drug design methodology that has moved from administering "cocktails" with multiple drug components, each component with a different therapeutic target, to designing a single compound that hits multiple targets. In the opioid community, this paradigm has prompted the design and synthesis of ligands with varying mixed-efficacy profiles.

While several mixed-efficacy profiles exist, of particular interest to our lab is the design and synthesis of ligands showing MOR agonism and DOR antagonism, a profile that has been shown to elicit the desired analgesia of a pure MOR agonist but with reduced risk of tolerance and dependence in a number of preclinical models of analgesia.

1.2 Opioid receptor ligands

In order to design and tailor ligands that specifically bind to opioid receptors, it is necessary to understand the structural motifs present in the natural opiates and in the endogenous opioid ligands that are responsible for facilitating certain interactions with the GPCR that result in

ligand binding. There is a set of endogenous opioid peptides that preferentially binds to each of the opioid receptor subtypes: endorphins and endomorphins for MOR, dynorphins for KOR, and enkephalins for DOR. All of these ligands are peptides of varying length that incorporate a Tyrosine (Tyr) residue in the first position and a phenylalanine (Phe) in the fourth position when going from N to C terminus (Figure 1.2). The conservation of these amino acids across the endogenous peptides highlights the importance of these moieties in the binding of the ligand to each of the opioid receptor types.
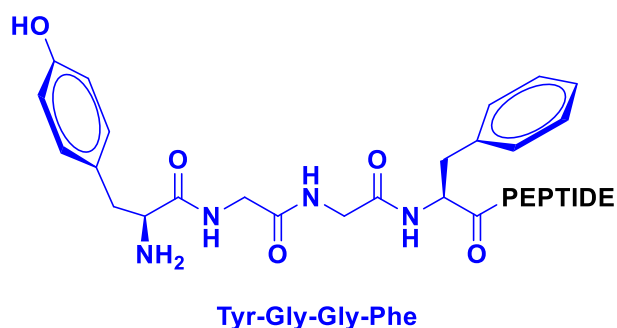
Tyr-Gly-Gly-Phe

Endogenous Opioid Receptor Ligands

MOR
endorphins: **Tyr-Gly-Gly-Phe**-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr (*α-endorphin*)
endomorphins: **Tyr**-Pro-Phe-**Phe**-NH$_2$ (*endomorphin-1*)

DOR
enkephalins: **Tyr-Gly-Gly-Phe**-Met (*met-enkephalin*)

KOR
dynorphins: **Tyr-Gly-Gly-Phe**-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asn-Asn-Gln (*dynorphin A*)

Figure 1.2. Structures of the endogenous opioid receptor ligands. Examples of endogenous peptide in parentheses. Common structural motif highlighted in blue.

1.3 Development of mixed-efficacy opioid ligands

The first reported MOR agonist/DOR antagonist mixed-efficacy ligand for the opioid receptors was a tetrapeptide containing Tyr in the first position and Phe in the fourth position, reported by Schiller in 1992.[7] This peptide, H-Tyr-Tic-Phe-Phe-NH$_2$ (TIPP-NH$_2$; Tic = tetrahydroisoquinoline-3-carboxylic acid, Figure 1.3), produced moderate MOR agonist activity and potent DOR antagonist activity. [7] Shortly after the discovery of TIPP-NH$_2$, several other mixed-efficacy peptides were synthesized from various groups, all producing various degrees of MOR agonism/DOR antagonism.[8-18] Particularly noteworthy was the synthesis and evaluation of DIPP-NH$_2$[Ψ] (H-Dmt-TicΨ[CH$_2$NH]-Phe-Phe-NH$_2$) in 1995[9] (Figure 1.3), which incorporated

4

a reduced peptide bond between the Tic and Phe residues and is the 2,6 –dimethyltyrosine analogue (Dmt) of TIPP-NH$_2$. DIPP-NH$_2$[Ψ] displayed balanced subnanomolar affinity at MOR and DOR and produced no physical dependence and less acute tolerance than morphine upon chronic administration of high doses when given intracerebroventricularly (i.c.v.).[10] However, DIPP-NH$_2$[Ψ] displayed restricted blood brain barrier (BBB) permeability which severely limited its therapeutic potential.[10] Therefore, in an attempt to develop a MOR agonist/DOR antagonist capable of crossing the BBB, the bifunctional ligand consisting of the highly potent MOR agonist [Dmt^1]DALDA (H-Dmt-D-Arg-Phe-Lys-NH$_2$) and the potent and selective DOR antagonistTICP[Ψ] (H-Tyr-TicΨ[CH$_2$NH]-Cha-Phe-OH; Cha = cyclohexylalanine) was synthesized in 2004.[14] It was hypothesized that this compound, [Dmt^1]DALDA→CH$_2$CH$_2$NH←TICP[Ψ] , would cross the BBB through conferred permeability via the [Dmt^1]DALDA portion, which alone is capable of penetrating the BBB. As expected, this bifunctional ligand displayed the desired MOR agonist/DOR antagonist profile *in vitro*. Additionally, this compound produced analgesic potency similar to that of morphine in the mouse tail-flick assay after subcutaneous (s.c.) administration, displayed a longer duration of action than morphine, and elicited less analgesic tolerance than morphine, suggesting that this compound is capable of crossing the BBB. Although [Dmt^1]DALDA→CH$_2$CH$_2$NH←TICP[Ψ] (Figure 1.3) displayed favorable *in vitro* and *in vivo* profiles, one potential drawback of this compound is that the [Dmt^1]DALDA portion, when administered to animals alone, it produced profound tolerance after chronic intrathecal (i.th.) administration.[19] Thus, while this compound is one of the first MOR agonists/DOR antagonists that is suggested to cross the BBB, it is not the ideal drug candidate due to the potential to risk of tolerance via the [Dmt^1]DALDA portion.

H-Tyr-Tic-Phe-Phe-NH$_2$ **TIPP-NH$_2$**
Schiller
1992

H-Dmt-TicΨ[CH$_2$NH]-Phe-Phe-NH$_2$, **DIPP-NH$_2$[Ψ]**
Schiller
1995

[Dmt^1]DALDA→CH$_2$CH$_2$NH←TICP[Ψ]
Weltrowska
2004
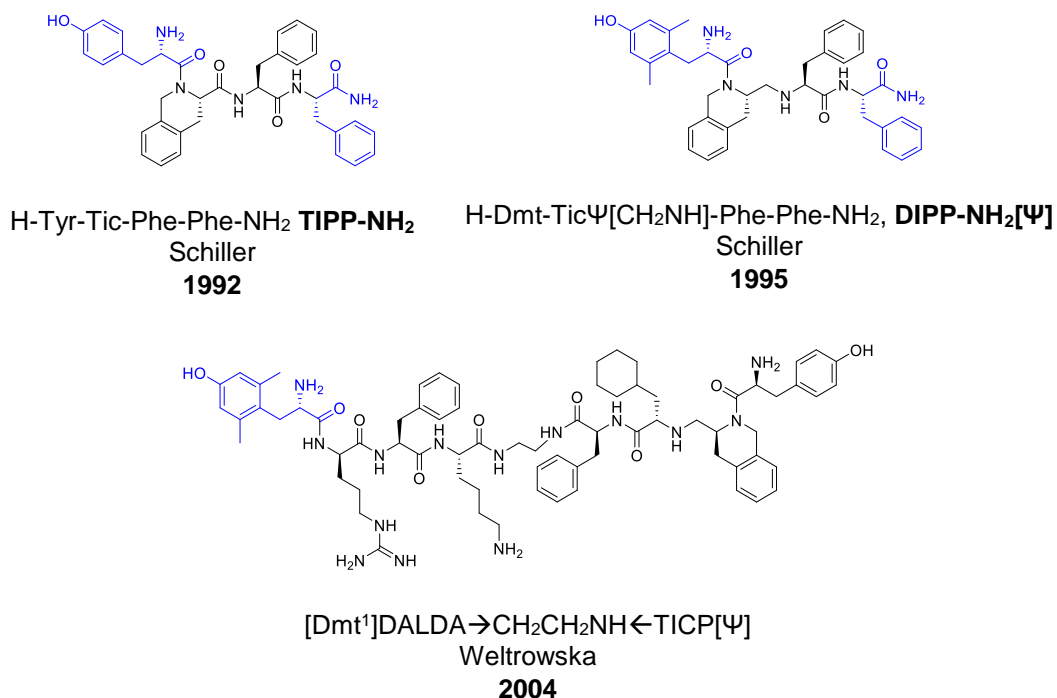
Figure 1.3 Structures of select MOR agonist/DOR antagonist ligands

To summarize, small opioid receptor peptides displaying mixed-efficacy MOR agonist/DOR antagonist profiles have been developed. Unfortunately, although the *in vitro* profiles for all of these mixed-efficacy ligands produce the desired MOR agonism/DOR antagonism profile, many of these compounds have difficulty crossing the BBB *in vivo*, and if and when they do cross the BBB these compounds still produce tolerance. Thus, there remains an unmet need of opioid analgesics devoid of tolerance and dependence liability that have the potential to be formulated for therapeutic use.

1.4 Development of mixed-efficacy opioid peptidomimetics

The majority of the mixed-efficacy MOR agonist/DOR antagonist ligands that have been synthesized are either peptide mimics of the endogenous ligands or modified morphine-like compounds. Two additional approaches that have been taken in order to create mixed-efficacy opioid ligands that cross the BBB include glycosylating lead peptides and generating peptidomimetics.

For the latter approach, a former member of the Mosberg lab synthesized one of the first sets of peptidomimetic ligands that displayed a MOR agonist/DOR antagonist profile *in vitro*. This peptidomimetic (synthesized as a mixture of diastereomers) was designed using computational modeling of the high affinity cyclic tetrapeptide JOM-13(Tyr-c(S-S)[D-Cys-Phe-D-Pen]OH) and

structurally-related compounds (Figure 1.4). Peptidomimetic **1** utilizes a tetrahydroquinoline (THQ) core to eliminate the peptidic, disulfide-containing cycle of JOM-13, while retaining the key binding elements including a dimethyl tyrosine (Dmt mimics the Tyr of JOM-13 and has been empirically shown to increase binding affinity across all three opioid receptors), and a benzyl side chain (mimics Phe of JOM-13).[20] The pharmacological results for both diastereomers of **1** indicate that the stereochemistry at position 4 (Figure 1.4) plays an important role in the orientation of the ligand in the receptors, as the *in vitro* profiles for both diastereomers are quite disparate, with one diastereomer showing tighter binding (Ki = 0.22 nM at MOR, 9.4 nM at DOR, 68 nM at KOR) across all three receptors relative to the other diastereomer (Ki = 2.6 nM at MOR, 56 nM at DOR, 220 nM at KOR).[21] However, one drawback seen with the "good" diastereomer of **1**, is that it still displays nanomolar binding affinity at KOR, which is problematic when trying to design MOR agonist/DOR antagonist ligands. In a subsequent study, it was determined that the stereochemistry at position 4 that resulted in tighter binding across the opioid receptors is *R*.[21] However, despite the unequal binding profiles of both diastereomers of **1**, both of these ligands had binding affinity profiles similar to that of JOM-13 and other related compounds indicating that the THQ core was a good mimic for the cyclic peptide JOM-13. Futhermore, conformational analysis of both diastereomers of the peptidomimetic display good superposition with JOM-6 (a structurally-related peptide to JOM-13). The *in vitro* results along with the computational analysis indicate that **1** serves as a "proof of concept" that key binding elements seen in opioid peptide ligands can be transferred onto a more bioavailable scaffold.

Figure 1.4 Evolution of the peptiomimetic

1.5 Objectives

Despite all of the advances in the design and synthesis of mixed-efficacy MOR agonist/DOR antagonist ligands, there remains an unmet need for opioid analgesics that cross the BBB and are devoid of tolerance, dependence, and other undesirable side effects. For my thesis project, I designed, synthesized, and modified our peptidomimetic scaffold in order to: 1) balance affinities between MOR and DOR while reducing affinity and efficacy at KOR to create a more selective MOR agonist/DOR antagonist profile, 2) probe bioavailability and improve metabolic stability, and 3) penetrate the BBB and improve *in vivo* efficacy. Chapter 2, discusses the results from three parallel series of peptidomimetics that led to the discovery of an *N*-acetylated tetrahydroquinoline core-containing compound with more balanced MOR and DOR affinities (relative to **1**, Figure 1.4), that acts as an agonist at MOR and an antagonist at DOR and produces

antinociception for longer than 3 h after intraperitoneal (*ip*) administration. Chapter 3, explores the effects of additional *N*-substitutions on the THQ core in an attempt to probe the effect of various modifications on the binding affinity and efficacy at DOR. Chapter 4 describes the incorporation of methoxy and hydroxyl moieties at various positions around the core and pendant region to probe steric and electronic requirements and limitations across the opioid receptors and to potentially expose key differences that confer selectivity to one receptor type over the others. Chapter 5 describes efforts to synthesize compounds that probe the effects of different stereochemistry on ligand binding. Chapter 6 highlights efforts to increase metabolic stability through incorporation of a fluorine moiety at various locations on the peptidomimetic core. Finally, Chapter 7 summarizes all the studies and SAR campaigns completed and offers future directions.

CHAPTER 2

Structure-activity relationship studies on three parallel series of mixed-efficacy μ-opioid receptor agonist/δ-opioid receptor antagonist peptidomimetics

2.1 Introduction

The successful transfer of key binding elements from a peptide scaffold to **1** expanded the chemical space that could be altered and modified in order to tailor ligands to specific opioid receptors. While **1** was designed from the tetrapeptide JOM-13, a parallel cyclic pentapeptide series also revealed promising leads toward bifunctional MOR agonist/DOR antagonist ligands. The subsequent series of peptidomimetics are based on a series of cyclic, mixed-efficacy MOR agonist/DOR antagonist pentapeptides with the general formula Tyr-c[D-Cys-X^3-X^4-Cys]NH$_2$,[22] where cyclization occurs through either a disulfide bond or an methylene dithioether bond and X^3 or X^4 represents phenylalanine (Phe), 3-(1-Naphtyhl)alanine (1-Nal), or a 3-(2-Naphtyhl)alanine (2-Nal) amino acids. Briefly, using Tyr-c[D-Cys-Phe-Phe-Cys]NH$_2$ as the parent compound, it was shown that peptides substituting either a 1-Nal or a 2-Nal in the X^3 position decreased DOR binding, while the same substitutions in position X^4 displayed increased affinity binding at DOR, when compared to the parent compound. Additionally, the compounds containing 1-Nal or 2-Nal in the X^4 position were fully efficacious at MOR and displayed

reduced efficacy at DOR,[22] thus fitting the desired MOR agonist/DOR antagonist profile. Furthermore, in the case of the peptides containing of the formula Tyr-c[D-Cys-Phe-2-Nal-Cys]NH₂, DOR efficacy was essentially eliminated.[22] The finding that bulkier aromatics can potentially enhance our desired MOR agonist/DOR antagonist profile served as the foundation for the initial SAR study of our peptidomimetics which included substitution of the benzyl pendant with 1- and 2- methylnapthyl pendants, among other pendants.

2.2 Design and synthesis of the three parallel peptidomimetic series

The first series of peptidomimetics (which includes **1**) utilized a THQ core and incorporated Dmt and various aromatic moieties (benzyl, phenethyl, 1-naphthyl, 2-naphthyl, and 2-indanyl) that mimic the Tyr[1] and Phe[4] residues seen in the peptide series and also in the endogenous ligands, respectively (Figure 2.1, Panel A). Additionally, this first peptidomimetic series was not synthesized asymmetrically, unlike subsequent series, resulting in a set of diastereomers for final products. Later, it was determined that stereochemistry that resulted in a higher affinity binding profile had *R*-stereochemistry at position 4 (Refer to Figure 1.4, structure of **1** for numbering system)[21] and thus after this finding, the synthesis of the peptidomimetics was completed asymmetrically to yield compounds with the desired *R*-stereochemistry at position 4. This original opioid peptidomimetic series displayed the desired profile (as seen in Table 2.1)[21] and confirmed that the THQ scaffold is a suitable and bioavailable template, but there remained opportunity to improve *in vitro* and *in vivo* properties. For example, compounds in the original THQ series displayed 10-130-fold binding affinity preference for MOR over DOR (Table 2.2), and many also exhibited considerable affinity and efficacy at KOR (Table 2.1). Additionally, **1** was submitted to the Pharmacokinetics Core at the University of Michigan to determine the metabolic stability of THQ peptidomimetic series and to provide some insight into possible metabolic routes. Through this study, it was discovered that there were three likely metabolism routes for our peptidomimetics, one of which was oxidation of the THQ core (Figure 2.1, Panel B). Using SMARTCyp, an online metabolic site predictor, the top 10 metabolic labilities were determined and four were predicted to be on the THQ core (Figure 2.1, Panel C). In the subsequent generation of two parallel series of compounds, two different modifications to the THQ series were explored. These modifications included the replacement of the THQ scaffold

with a tetrahydronaphthalene (THN) scaffold or *N*-acetylation of the nitrogen in the THQ core of the original series (Figure 2.1). These modifications were designed 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.[23]
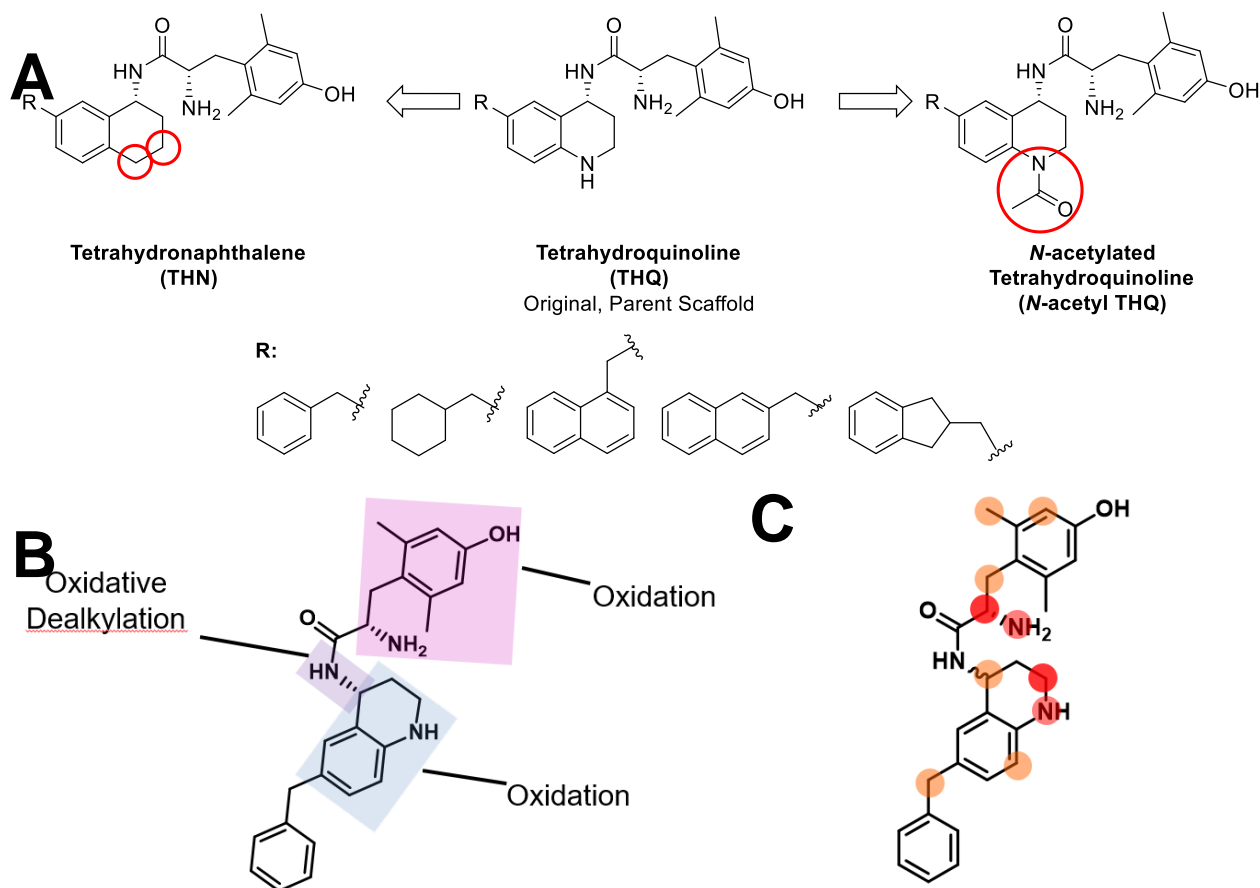
Figure 2.1 Structures and potential metabolism routes for peptidomimetics. **A.** Structures of the three parallel series of peptidomimetics. **B.** Metabolic routes determined by the PK Core at the Univeristy of Michigan. **C.** Metabolic liabilities as predicted by SMARTCyp. Red indicates highly labile, pink indicates moderately labile, orange fairly labile

Through both of these modifications, the goal was to reduce the metabolic lability associated with the nitrogen heteroatom in the THQ ring, as two common metabolic concerns associated with a nitrogen heteroatom include *N*-oxidation and oxidation α to a heteroatom.[24-28] Furthermore, the amine in the THQ core is also part of an aniline system, which is susceptible to aromatization, not only *in vivo*, but potentially in ambient atmosphere with trace acid present.[29]

Through acetylation of the THQ nitrogen, *N*-oxidation would be blocked, however oxidation α to a heteroatom was still of concern. Incorporating a THN scaffold would eliminate both the *N*-

oxidation and oxidation α to a heteroatom completely, by eliminating the problematic nitrogen atom from the scaffold all together. Additionally, it was observed that *N*-acetylation of the parent compound **1** to form **52** improved DOR affinity (DOR K_i = 9.4 nM vs. 1.8 nM, respectively), without altering MOR affinity (MOR K_i = 0.22 nM vs. 0.13 nM, respectively), resulting in an overall better balance of MOR and DOR binding. Consequently, two parallel series, with variable pendant R (Figure 2.1) and an *N*-acetylated THQ core or THN core were explored to examine effects on bioavailability and relative MOR and DOR affinities.

2.2.1 Synthesis of the 2-methylindanyl THQ analogue

The 2-methylindanyl analogue was one of the first analogues of the THQ series to be synthesized. As such, this synthesis was not completed asymmetrically, unlike other analogues in the subsequent parallel series.[21] The core THQ intermediate **6** (Scheme 2.1) was synthesized using the methodology developed by Schmidt et al and described in ref, 21 and 30. In this synthesis, the pendant moiety is incorporated in the first step through an aldol condensation between 1-indanone and *p*-nitrobenzaldeyde to yield **2** which was hydrogenated to yield the aniline **3**. The amine in **3** was acylated with 3-bromopropionyl chloride to give **4**, cyclized to form lactam **5**, and then treated with trifluoromethanesulfonic acid (TfOH) to promote a Fries-Rearrangement and yield **6**. Treatment of **6** with hydroxylamine yielded **7**, which was hydrogenated to form the racemic amine **8**. Amine **8** was coupled to di-Boc protected 2,6-dimethyl-L-tyrosine (diBoc-Dmt) and deprotected to yield diastereomers **9** and **9'**(Scheme 2.1).
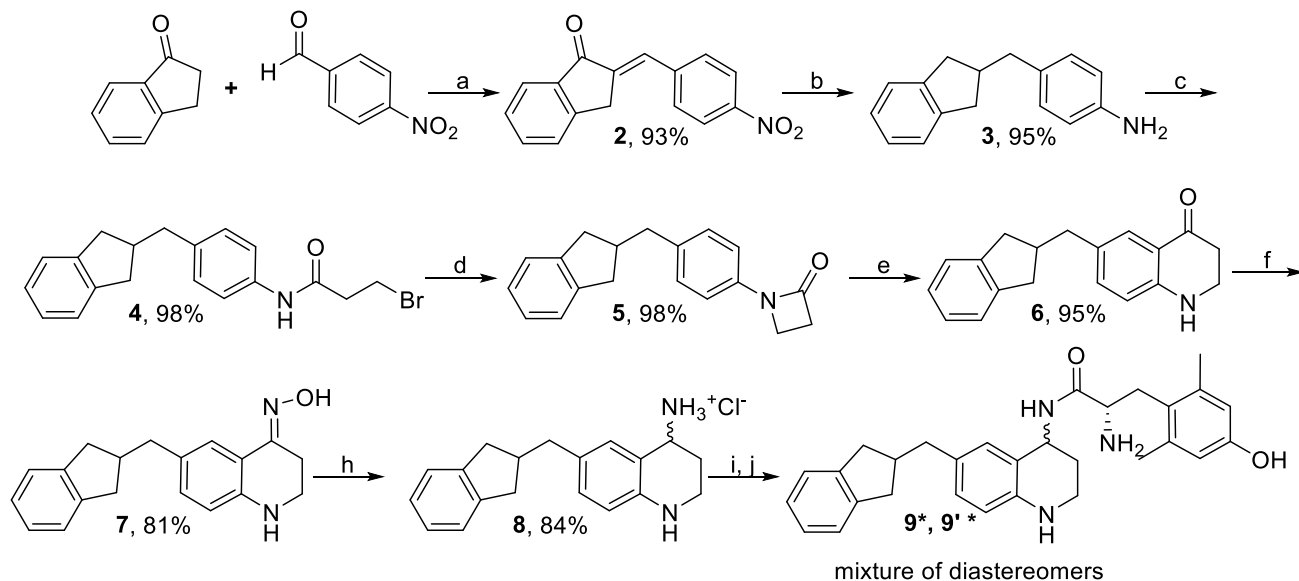
(a) KOH, MeOH, RT, 1 h (b) H_2, Pd/C, 50 psi, 2-3 drops HCl, MeOH, RT, 24 h (c) 3-bromopropionyl chloride, K_2CO_3, DCM, RT, 3 h (d) NaO*t*Bu, DMF, RT, 3 h (e) TfOH, DCE, RT, 3 h (f) $NH_2OH \cdot HCl$, EtOH, reflux, 16 h (h) H_2, Pd/C, 35 psi, 2-3 drops AcOH, MeOH, RT, 16 h (i) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT, 6 h (j) 1:1 TFA:DCM, RT, 1 h. *no final yield calculated because only a portion of crude product was purified.

Scheme 2.1 Synthesis of the 2-methylindanyl THQ analogue

2.2.2 Synthesis of the 1-methylindanyl THQ analogue

Like the 2-methylindanyl analogue, the 1-methylindanyl analogue incorporated the pendant diversity in the first step and was synthesized as a racemic mixture using a slight modification of methodology originally developed by Kolanos et al.[31] The synthesis began with a condensation reaction between indene and 4-acetamidobenzaldehyde, to form **10**, which was hydrogenated to form a racemic mixture of **11**, then deprotected to yield aniline **12**. Intermediate **12** was acylated with 3-bromopropionyl chloride to give **13**, cyclized to form lactam **14**, and then treated with TfOH to promote a Fries-Rearrangement and yield **15**. Intermediate **15** was Boc-protected using di-*tert*-butyl dicarbonate to yield **16**. Instead of using hydroxylamine like in the synthesis of the 2-indanyl analogue, the 1-methylindanyl analogue was synthesiszed asymmetrically utilizing chemistry developed by the Ellman group.[32-34] For the asymmetric synthesis, **16** was treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to form a chiral imine *in situ* which was reduced with NaBH$_4$ to form the desired *R*-stereochemistry for intermediate **17**. The Ellman auxillary was cleaved using concentrated hydrochloric acid (HCl) forming primary amine **18** which was then coupled to diBoc-Dmt and deprotected to yield compound **19** as an inseparable mixture of diastereomers (Scheme 2.2).
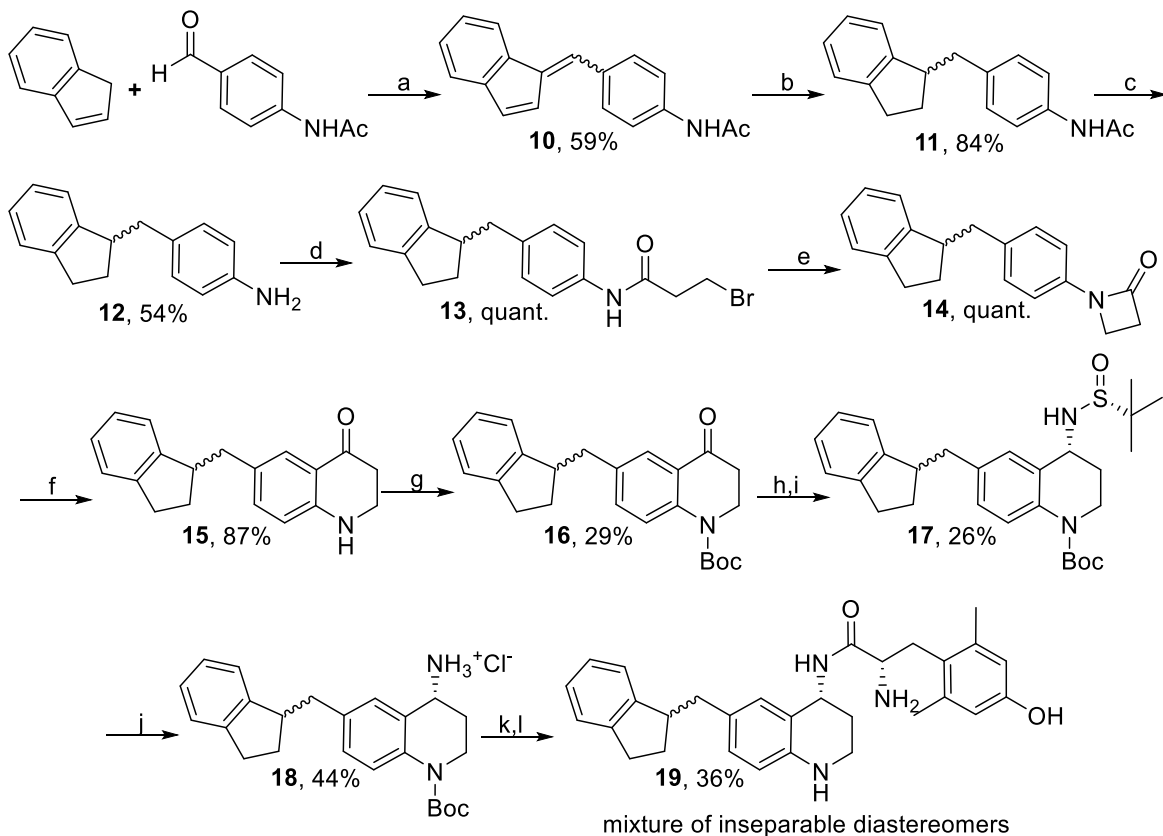
(a) KOH, anhyd EtOH, RT, 1 h (b) H$_2$, Pd/C, 50 psi, MeOH, RT, 24 h (c) HCl, anhyd EtOH, MW (d) 3-bromopropionyl chloride, K$_2$CO$_3$, DCM, RT, 3 h (e) NaOtBu, DMF, RT, 3 h (f) TfOH, DCE, RT, 3 h (g) Boc$_2$O, DMAP, DIPEA, DCM, 60°C (h) (R)-t-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (i) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (j) HCl, dioxane, RT, 3 h (k) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (l) 1:1 TFA:DCM

Scheme 2.2 Synthesis of the 1-methylindanyl THQ analogue

2.2.3 Synthesis of the methylcyclohexyl THQ analogue

The synthesis of the methylcyclohexyl THQ analogue began with the acylation of *p*-bromoaniline using 3-bromopropionyl chloride to yield **20**. Intermediate **20** is cyclized under basic conditions to form lactam **21**, and is then treated with TfOH to form intermediate **22**.[30] The nitrogen of **22** was protected with a *tert*-butyloxycarbonyl (Boc) group forming **23**, which was subjected to Suzuki cross-coupling[35] to incorporate the methylcyclohexyl moiety and yield **24**. Intermediate **24** was treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to form a chiral imine *in situ* which was reduced with NaBH$_4$ to form the desired *R*-stereochemistry for intermediate **25**.[32-34] The Ellman auxillary was cleaved using concentrated HCl forming primary amine **26** which was then coupled to diBoc-Dmt and deprotected to yield compound **27** (Scheme 2.3).
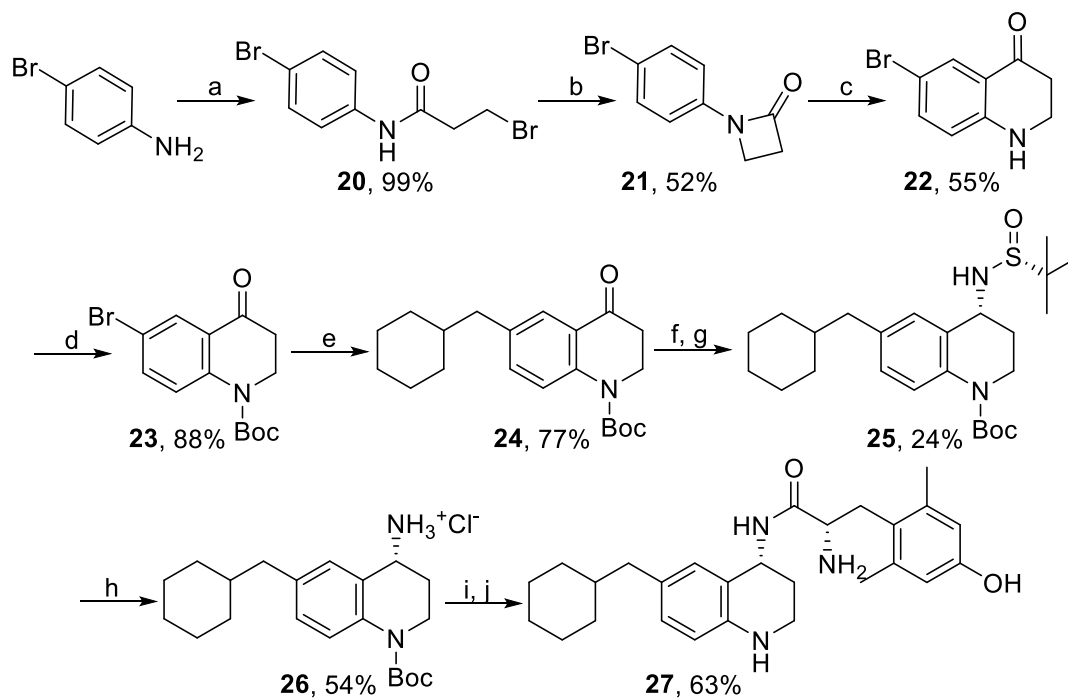
(a) 3-bromopropionyl chloride, K$_2$CO$_3$, DCM, RT, 3 h (b) NaO*t*Bu, DMF, RT, 3 h (c) TfOH, DCE, RT, 3 h (d) Boc$_2$O, DMAP, DIPEA, DCM, reflux, 16 h (e) R$_2$-B(OH)$_2$, Ag$_2$O, Pd(dppf)Cl$_2$, K$_2$CO$_3$, THF (f) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C, 24 h (g) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (h) HCl, dioxane, RT, 3 h (i) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT, 6-24 h (j) 1:1 TFA:DCM

Scheme 2.3 Synthesis of the methylcyclohexyl THQ analogue

2.2.4 Forming the N-acetylated dihydroquinolinone intermediates

The synthesis of the *N*-acetylated analogue of **1** began with acylation of the commercially available benzyl aniline with 3-bromopropionyl chloride to give **28**, followed by cyclization in the presence of base to form lactam **29**. Treatment of **29** with TfOH promoted a Fries-Rearrangement and yielded **30**[30] (Scheme 2.4, A). With the dihydroquinolinone core constructed, intermediates **6**, **15**, and **30**, were treated with acetic anhydride (Ac$_2$O) to form the *N*-acetylated intermediates, **31-33** (Scheme 2.4, B)
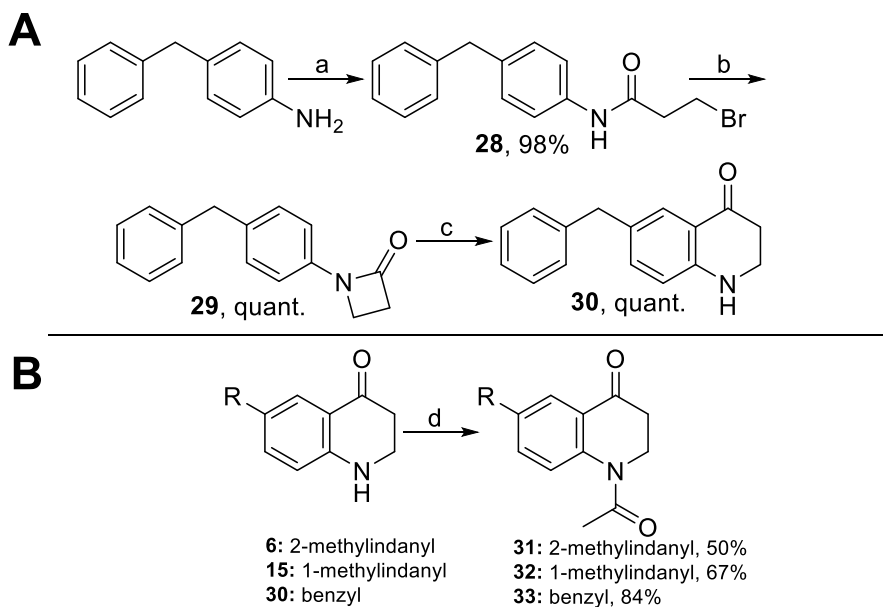
(a) 3-bromopropionyl chloride, K$_2$CO$_3$, DCM, RT, 3 h (b) NaO*t*Bu, DMF, RT, 3 h (c) TfOH, DCE, RT, 3 h (d) neat Ac$_2$O, reflux, 24 h

Scheme 2.4. A. Synthesis of the benzyl dihydroquinolinone core B. Acetylation of the benzyl, 1- and 2-methylindanyl analogues

In order to synthesize the *N*-acetylated dihydroquinolinone intermediates with the methylcyclohexyl-, 1-methylnaphthyl-, and 2-methylnaphthyl- pendants, **22** was acetylated using Ac₂O to form **34** which was then subjected to Suzuki coupling to form intermediates **35-37** (Scheme 2.5).[23,36]
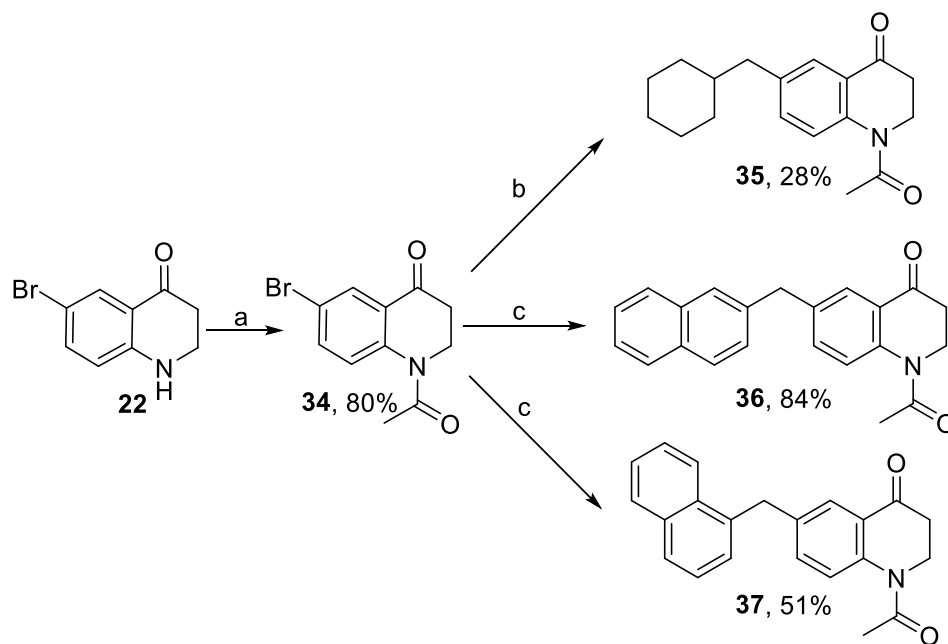
(a) neat Ac₂O, reflux, 24 h (b) cyclohexylmethyl-B(OH)₂, Ag₂O, Pd(dppf)Cl₂, K₂CO₃, THF, MW 100°C, 300 W (c) 1- or 2-methylnaphthyl-Bpin, Pd(dppf)Cl₂, K₂CO₃, 3:1 acetone:H₂O, MW 100°C, 300 W

Scheme 2.5 Synthesis of the *N*-acetylated dihyroquinolinone intermediates containing the methylcyclohexyl, 2-methylnapthyl, and 1-methylnaphthyl pendants

2.2.5 Completing the synthesis of the N-acetylated THQ Series

Once all of the desired pendants were incorporated onto the *N*-acetylated dihydroquinolinone core, the syntheses converged. Intermediates **31-33** and **35-37** were treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to form imines *in situ*, which were reduced *in situ* with NaBH$_4$ to form the desired *R*-stereochemistry of intermediates **38-43**.[32-34] The Ellman auxiliary was cleaved using concentrated HCl forming primary amines **44-49**, which were then coupled to diBoc-Dmt and deprotected to yield final compounds **50-55** (Scheme 2.6).[23]

31: 2-methylindanyl	**38**: 2-methylindanyl, 89%	**44**: 2-methylindanyl, quant.	**50**: 2-methylindanyl, 21%
32: 1-methylindanyl	**39**: 1-methylindanyl, 94%	**45**: 1-methylindanyl, 73%	**51**: 1-methylindanyl, 23%
33: benzyl	**40**: benzyl, 46%	**46**: benzyl, 78%	**52**: benzyl, 13%
35: methylcyclohexyl	**41**: methylcyclohexyl, 26%	**47**: methylcyclohexyl, 73%	**53**: methylcyclohexyl, 56%
36: 2-methylnaphthyl	**42**: 2-methylnaphthyl, quant.	**48**: 2-methylnaphthyl, quant.	**54**: 2-methylnaphthyl, 30%
37: 1-methylnaphthyl	**43**: 1-methylnaphthyl, quant.	**49**: 1-methylnaphthyl, 63%	**55**: 1-methylnaphthyl, 13%

(a) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C, 24 h (b) NaBH$_4$ THF, -50°C to RT, 3 h, then MeOH, RT (c) HCl, dioxane, RT, 3 h (d) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT, 6-24 h (e) 1:1 TFA:DCM

Scheme 2.6 Completion of the *N*-acetylated analogues

2.2.6 Synthesis of the THN Series

Synthesis of THN compounds **65-67** began by converting the ketone of commercially available 7-bromo-dihydronaphthalenone to the chiral imine using (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ followed by *in situ* reduction to form **58** using NaBH$_4$ to afford the desired *R*-stereochemistry of the sulfonamide. Next, the pendant substituents were incorporated via Suzuki coupling[35,36] to form intermediates **59-61**. Intermediates **59-61** were then treated with concentrated HCl to cleave the Ellman auxiliary affording primary amines **62-64**.[31-33] In the final step, the amines **19m-p** were coupled to diBoc-Dmt and deprotected to yield compounds **65-67** (Scheme 2.7).[23]

59: methylcyclohexyl, quant.
60: 2-methylnaphthyl, 55%
61: 1-methylnaphthyl, 20%

58, 77%

62: methylcyclohexyl, 56%
63: 2-methylnaphthyl, 44%
64: 1-methylnaphthyl, 78%

65: methylcyclohexyl, 90%
66: 2-methylnaphthyl, 70%
67: 1-methylnaphthyl, 86%
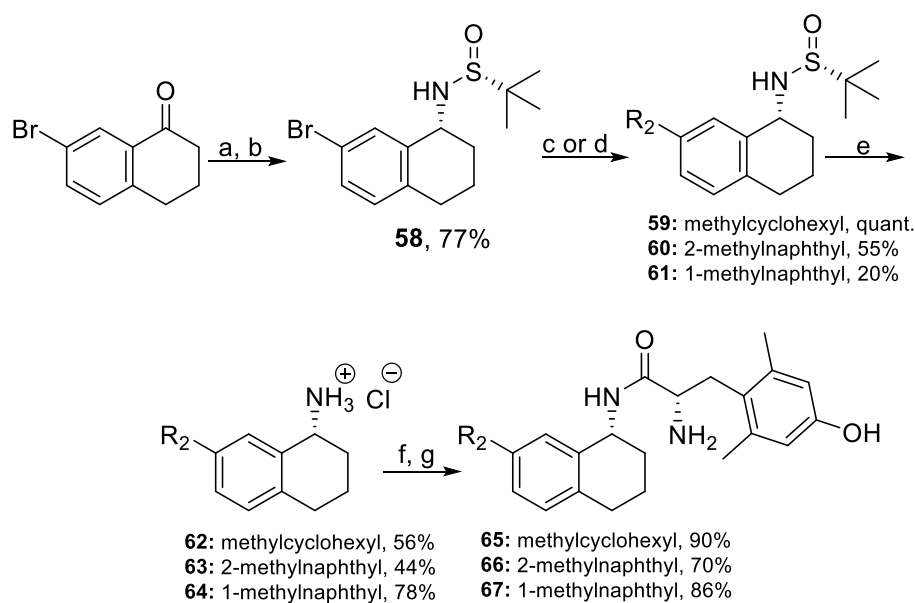
(a) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (b) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (c) cyclohexylmethyl-B(OH)$_2$, Ag$_2$O, Pd(dppf)Cl$_2$, K$_2$CO$_3$, THF, MW 80°C, 300 W (for **59**) (d) 2-methylnaphthyl, or 1-methylnaphthyl-Bpin, Pd(dppf)Cl$_2$, K$_2$CO$_3$, 3:1 acetone:H$_2$O, MW 110°C, 300 W (for **60** and **61**) (e) HCl, dioxane, RT, 3 h (f) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (g) 1:1 TFA:DCM

Scheme 2.7 Synthesis of the THN analogues

2.3 Results

Binding and Efficacy Assays.

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[37,38](Table 2.1). Efficacy of the compounds was assessed by agonist-stimulated [^{35}S]GTPγS binding to G protein[39] in cell membrane preparations of C6-MOR, C6-DOR, and CHO-KOR (Table 2.1). These assays are described in full in **8.2**. In order to determine the effects of the modifications on MOR and DOR selectivity, the DOR K_i value was divided by the MOR K_i value resulting in a relative selectivity for a peptidomimetic to bind to MOR over DOR (Table 2.2). As the relative fold data suggests, the *N*-acetylated series appeared to bring the ratio of MOR to DOR binding closer to 1:1, when compared to the THQ series. In contrast, the THN series created a larger disparity between MOR and DOR binding, with most THN-containing peptidomimetics significantly preferring MOR over DOR.

Table 2.1 Opioid Receptor Binding Affinities and Efficacies of Peptidomimetics[21,23]
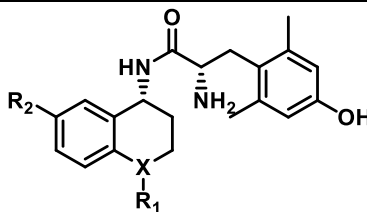
Cpd	X	R_1	R_2	Binding, K_i (nM)[a,c]			EC_{50} (nM)[b,c]			% stimulation[b,c]		
				MOR	DOR	KOR	MOR	DOR	KOR	MOR	DOR	KOR
1[f]	N	H		0.22 (0.02)	9.4 (0.8)	68 (2)	1.6 (0.3)	110 (6)	540 (70)	81 (2)	16 (2)	22 (2)
52	N	acetyl	benzyl	0.13 (0.02)	1.8 (0.1)	87 (10)	6.0 (1)	68 (2)	>1300	76 (4)	26 (3)	29 (5)
68[e]	CH_2	--		0.045 (0.03)	4.0 (1)	19 (7)	2.9 (0.6)	dns	dns	64 (9)	dns	dns
27	N	H	cyclohexylmethyl	0.043 (0.005)	3.4 (1)	6.2 (1)	2.6 (1)	dns	97 (30)	57 (5)	dns	36 (4)
53	N	acetyl		0.03 (0.01)	0.32 (0.1)	8.4 (2)	0.61 (0.2)	14 (8)	240 (70)	70 (6)	26 (5)	33 (6)
65	CH_2	--		0.12 (0.02)	14 (6)	20 (5)	dns	dns	350 (80)	dns	dns	25 (6)
56[e]	N	H	naphthalen-2-ylmethyl	0.078 (0.007)	10 (2)	54 (7)	0.53 (0.08)	dns	dns	96 (3)	dns	dns
54	N	acetyl		0.04 (0.01)	0.23 (0.02)	48 (20)	0.93 (0.2)	dns	dns[d]	87 (3)	dns	dns[d]
66	CH_2	--		0.06 (0.01)	12 (4)	92 (20)	4.4 (2)	dns	dns	72 (4)	dns	dns
57[e]	N	H	naphthalen-1-ylmethyl	0.76 (0.1)	6.0 (0.7)	17 (1)	0.84 (0.4)	69 (40)	dns	93 (5)	15 (1)	dns
55	N	acetyl		0.06 (0.02)	1.3 (0.4)	4.3 (2)	0.48 (0.2)	dns	dns[d]	70 (4)	dns	dns[d]
67	CH_2	--		0.39 (0.08)	5.0 (0.3)	63 (20)	14 (7)	dns	dns[d]	58 (2)	dns	dns[d]
9	N	H	indanylmethyl	0.16 (0.04)	4.1 (2)	1.2 (0.4)	0.24 (0.03)	dns	dns	86 (1)	dns	38 (2)
50	N	acetyl		0.05 (0.00)	0.44 (0.07)	12 (4)	0.56 (0.1)	dns	610 (250)	84 (2)	dns	60 (10)
19	N	H	indanyl	0.05 (0.02)	6.8 (2)	19 (10)	9.0 (6)	dns	180 (80)	16 (8)	dns	52 (7)
51	N	acetyl		0.03 (0.00)	0.84 (0.13)	15 (0.2)	15 (10)	dns	>1000	39 (10)	dns	26 (8)

[a]Binding affinities (K_i (nM)) were obtained by competitive displacement of radiolabeled [³H]diprenorphine in membrane preparations. [b]Efficacy data were obtained using agonist induced stimulation of [³⁵S]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 S.E.M. in parentheses for n=3 independent assays in duplicate, unless otherwise noted. [d]n=2 independent assays in duplicate. dns: does not stimulate. [e]synthesized by Larisa Yeomans. [f]synthesized by Kate Kojiro.

Table 2.2 Binding Affinity Ratios of Peptidomimetics[23]
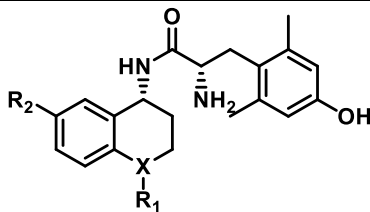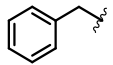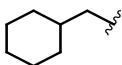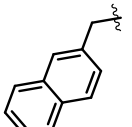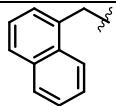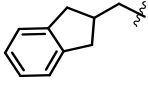
Cpd	X	R_1	R_2	DOR K_i/MOR K_i Ratio
1	N	H		43
52	N	(acetyl)		14
68	CH₂	--		89
27	N	H		79
53	N	(acetyl)		11
65	CH₂	--		117
56	N	H		128
54	N	(acetyl)		6
66	CH₂	--		140
57	N	H		8
55	N	(acetyl)		22
67	CH₂	--		13
9	N	H		26
50	N	(acetyl)		9
19	N	H		136
51	N	(acetyl)		28

***In vivo* WWTW Assay.**

      Several compounds were chosen based on *in vitro* data to be assayed for antinociception in the mouse Warm Water Tail Withdrawal (WWTW) assay following intraperitoneal (*ip*) injection (description of assay in **8.3**). Of the compounds assayed (Table 2.3, Figure 2.3), only three compounds displayed dose-dependent antinociceptive activity. Compounds **50** and **56** displayed partial antinociception at the maximum dose tested, whereas **54** displayed full antinociception with $ED_{50} = 4.72 \pm 0.01$ mg/kg. By comparison, the ED_{50} of morphine, under the same conditions, was 4.73 ± 0.001 mg/kg. Because compound **54** displayed full antinociception at 10 mg/kg in the initial WWTW assay, a time course study was completed to determine duration of action (Figure 2.4, Panel A). As can be seen in Figure 2.4, **54** produced maximal antinociception with a rapid on-set 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 the original lead peptidomimetic **1**[21], and similar to that observed for the same dose of morphine (Figure 2.4 B)[21] suggesting better bioavailability or metabolic stability. Additionally, despite being structural isomers with a similar *in vitro* profile, **54** and **55** displayed drastically different *in vivo* results when administered via *ip* injection (Figure 2.3). While **54** displayed full antinociception after *ip* administration, **55** displayed no antinociception at the same dose after *ip* administration. To further explore this unexpected result, both **54** and **55** via intracerebroventricular (*icv*) injection, then the WWTW assay was performed. Both **54** and **55** displayed full antinociception at a dose of 300 ng/3 μL at 5 min and 15 min post *icv* injection (Figure 2.5), indicating that **55** is indeed capable of producing antinociception when administered centrally, but not when administered via *ip* injection, suggesting that subtle differences in chemical structure create substantial differences in pharmacokinetics.

Table 2.3 *In vivo* Activity of Select Peptidomimetics

Cpd	Scaffold	R₂	*In vivo* **Activity following** *ip* **administration**[b]
1[a]	THQ		Full antinociception at 10 mg/kg with duration of action >1h
52	*N*-acetyl THQ		No activity up to 10 mg/kg
68	THN		Partial antinociception with latency of 14 sec at 10 mg/kg
27	THQ		No activity up to 10 mg/kg
53	*N*-acetyl THQ		No activity up to 10 mg/kg
56	THQ		Partial antinociception with latency of 10 sec at 10 mg/kg
54	*N*-acetyl THQ		Full antinociception at 10 mg/kg with duration of action of >3 h
66	THN		No activity up to 10 mg/kg
55	*N*-acetyl THQ		No activity up to 10 mg/kg
67	THN		No activity up to 10 mg/kg
9	THQ		No activity up to 10 mg/kg
50	*N*-acetyl THQ		Partial antinociception with latency of 11 sec at 10 mg/kg

Summary of antinociceptive effects of select analogues (n=3 for all analogues, except for **54** n=6) in mouse WWTW assay following intraperitoneal (*ip*) administration, with a cut-off time of 20 sec. [a]see ref. 21.[b]Full antinociception indicates that the cut-off time was reached.
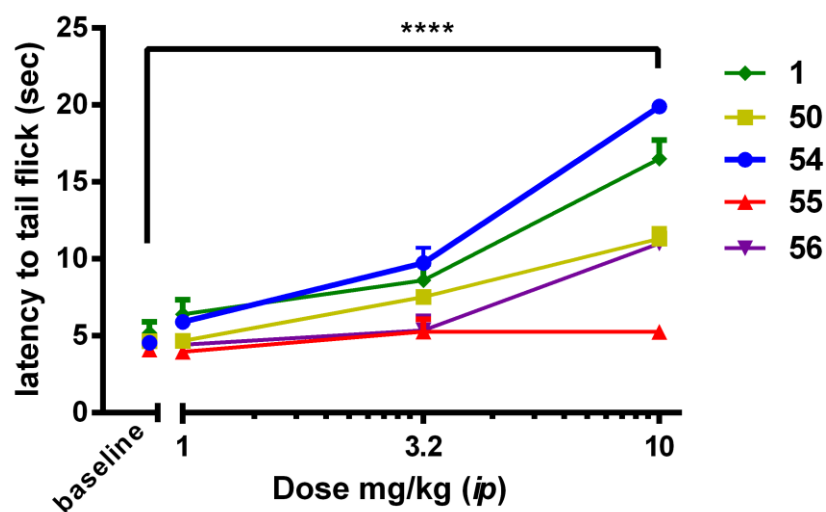
Figure 2.3 Cumulative antinociceptive dose response curves of select analogues **1**, **50**, **54**, **55**, and **56** in the mouse WWTW assay following *ip* administration. n=3 for all analogues, except for **54** where n=6. Plotted as average ± S.E.M. ****, p < 0.0001 for **1**, **50**, **54**, **56** for the 10 mg/kg dose when compared to baseline. [21, 23]
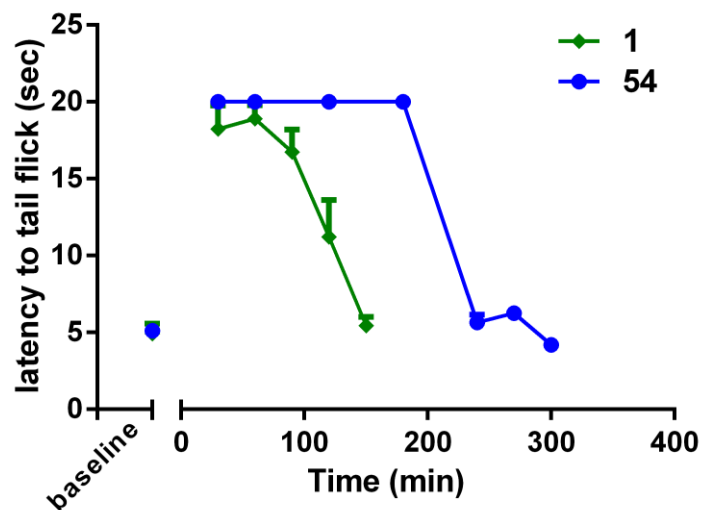
Figure 2.4 Time course of antinociception of **1** and **54** in the mouse WWTW assay following *ip* administration of 10 mg/kg. n=6 for both peptidomimetics, plotted as average ± S.E.M. [21, 23]
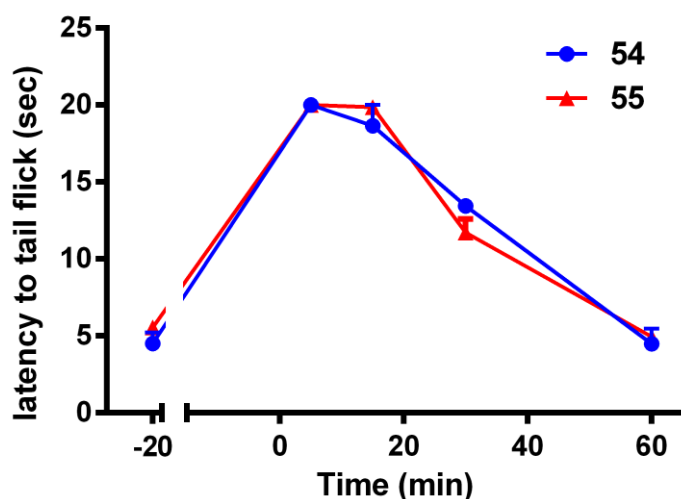
Figure 2.5 Time course antinociception of **54** and **55** in mouse WWTW assay following intracerebroventricular (*icv*) administration of 300 ng/3 μL. n=2, plotted as average +/- SEM.

In Vivo Assay for Chronic Tolerance.

Peptidomimetic **54** produced a MOR agonist/DOR antagonist profile with selectivity over KOR and relatively balanced binding affinities at MOR and DOR *in vitro* (Table 2.1 and 2.2) and produced antinociception for over 3 h after *ip* administration. Because of these promising results, **54** was tested to see if it produced chronic tolerance in mice. In this assay, a dose-response curve for **54** was determined for all mice described in **8.2**. Mice were then separated into two groups: one of which was treated twice daily with saline (*ip*), while the second group was treated twice daily with escalating doses of **54** such that the mice received 10 mg/kg/injection (inj) on day 1, 20 mg/kg/inj on day 2, 30 mg/kg/inj on day 3, 40 mg/kg/inj on day 4, and 50 mg/kg/inj on day 5 (*ip*). On day 6, increasing cumulative doses of **54** was administered to all mice and a second dose response-curve was determined for both groups of mice (chronic saline or chronic **54**). As expected, the dose-response curves on day 1 and day 6 for mice receiving chronic saline do not shift, which indicates that a 10 mg/kg dose of **54** was fully efficacious on day 1 and on day 6. Additionally, in Figure 2.6 Panel A, **54** was fully efficacious at a 10 mg/kg dosage both before and after chronic treatment with **54** This was demonstrated in no shift in the ED_{50} values on day 1 and day 6 which were both 4.73±0.001. This indicates that under these conditions **54** did not produce antinociceptive tolerance in mice. For comparison, the same assay was done with morphine, as expected produced roughly a 4-fold

rightward, parallel shift in the dose-response indicating that mice became tolerant to this treatment regime.
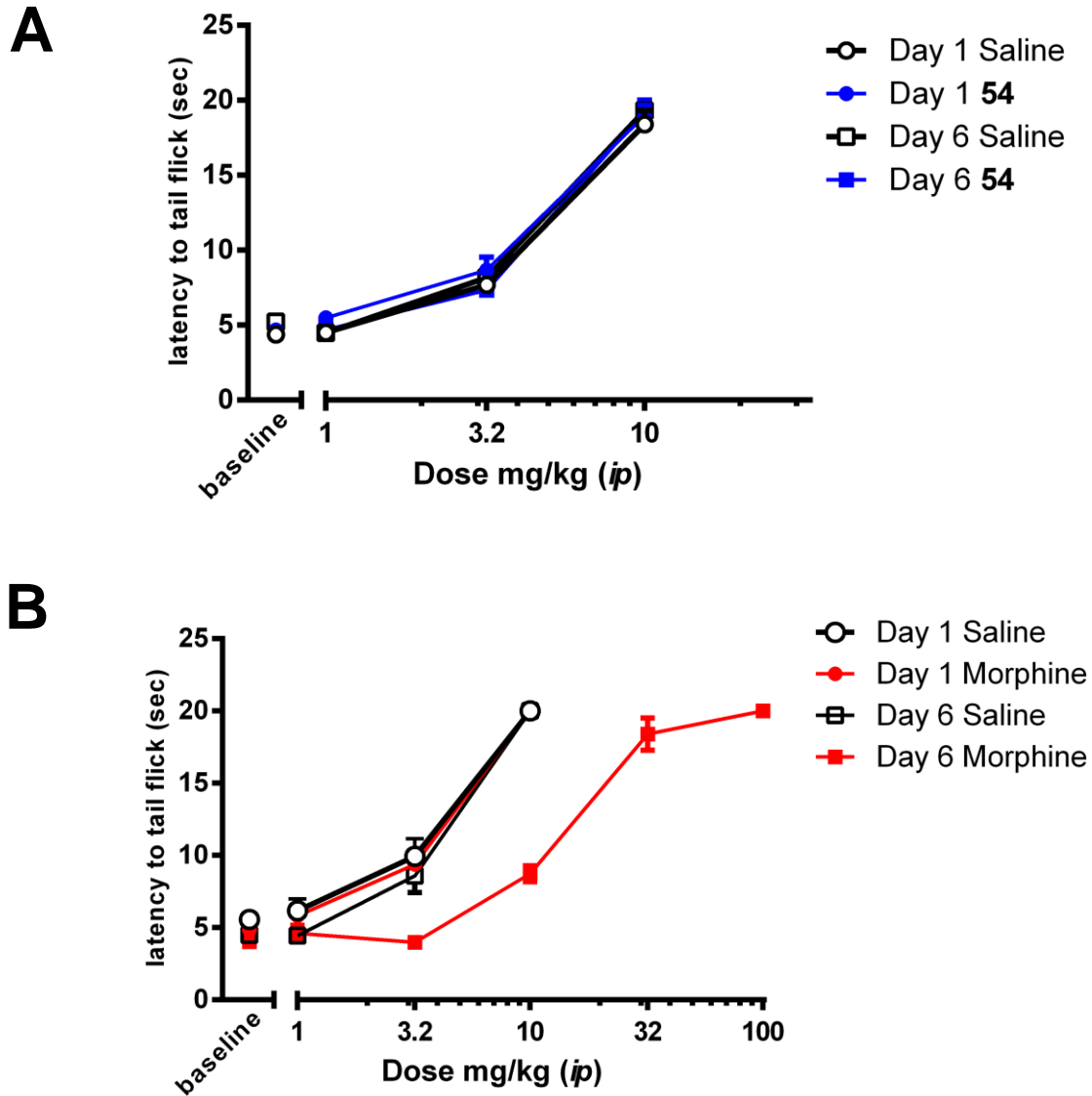
Figure 2.6 Determination of chronic tolerance to antinociceptive effect (mouse WWTW assay) of **54** (**A**) and morphine (**B**). After baseline withdrawal latency was determined, mice were treated with cumulative doses of drug (1.0, 3.2, or 10 mg/kg) to determine dose-reponse curves (open circle for saline, closed circle for **54**) on day 1. After receiving either saline or escalating doses of for five days, a second dose-response curve was determined on day 6 (open square for saline, closed square for **54**). Plotted as average ± S.E.M, n=4-6 mice for each group.

2.4 Discussion

The analogues presented above reiterate that it is possible to transfer key pharmacophore elements from a MOR agonist/DOR antagonist peptide to a peptidomimetic scaffold, with the original parent peptidomimetic, **1**, showing antinociceptive activity after peripheral administration in mice. While the THQ 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, a low nanomolar, balanced affinity profile (~1:1 MOR K_i: DOR K_i) was a logical place to start, since 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. The THQ series displayed relatively unbalanced MOR and DOR affinities, where compounds were 10- to 130-fold selective for MOR over DOR (Table 2.1). In order to optimize the initial compounds, effects of *N*-acetylation of the THQ nitrogen and utilization of THN scaffold instead of a THQ scaffold were explored. Through these modifications of the THQ scaffold, the goal was to reduce or eliminate metabolic susceptibility associated with the THQ ring nitrogen, while also examining the effect of these modifications on binding affinity and efficacy across all three opioid receptors. Additionally, 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.

While a total of six compound sets were synthesized, (each set defined by the pendant substituent), only four of these sets incorporated all three of the different scaffolds; these sets include analogues in which the pendant substituent is a benzyl, a 1-methylnaphthyl, a 2-methylnaphthyl, or a methylcyclohexyl. 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 effects of both scaffold modifications on the binding affinities are shown in Table 2.1. 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 pendant) 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 while slightly decreasing affinity at KOR. The effect of the *N*-acetylated THQ scaffold on efficacy (Table 2.1)

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 as determined by the DOR Ki/MOR K_i ratio (Table 2.2) while maintaining the desired MOR agonist/DOR antagonist efficacy profile. The only exception to this trend is in the case of compound **55**, 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.

In contrast, the effect of the THN scaffold on binding affinities at all three receptors (Table 2.1), when compared with the parent THQ scaffold, showed no consistent or advantageous trends. The data in Tables 2.1 and 2.2 indicate 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. Because the THN scaffold presented no apparent advantage, the 1- and 2-methylindanyl THN analogues were not pursued.

In order to explain the results of the *N*-acetylated THQ series, computational docking of one of the THQ/*N*-acetylated ligand pairs docked in the binding pocket of the inactive state of DOR (DORi) was completed, as previously described. Modeling **54** and **56** in the DORi binding pocket (Figure 2.7) as a representative example, it can be seen that the *N*-acetyl of **54** extends further into the DORi binding pocket to create a polar contact with Tyr[129] in transmembrane helix 3 (TM3) of the receptor (Figure 2.7, Panel B), an interaction that appears to be unavailable with the unsubstituted THQ core (Figure 2.7, 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-L-

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[60-66] that ligand interaction with His[278] and Asp[128] are important for opioid ligand binding in all three classical receptors. While 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 **56** and **54** to the Tyr residue 4.7 Å to 4.3 Å, respectively (not pictured). When both **56** and **54** are overlaid with the crystal structure of the recently reported[66] MOR agonist/DOR antagonist, DIPP-NH$_2$, (Figure 2.7, Panels C and D, respectively) in DORi, it can be seen that **54** aligns better with the Dmt and free amine moiety of DIPP-NH$_2$ than **56**. 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 the *N*-acetylated ligand **54** (and other *N*-acetylated analogues) may bring **14a** into closer proximity to His[279] and Asp[128], facilitating a better binding network within the DORi binding pocket.

While 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 displayed superior profiles over others. For example, the methylcyclohexyl (**27**, **53**, **65**) and 1- and 2-methylindanyl (**19**, **51**, and **9**, **50**) analogues picked up considerable undesired KOR affinity and agonism, while the 1- and 2-methylnaphthyl analogues (**57**, **55**, **67**, and **56**, **54**, **66**) display agonist activity at MOR, little or no agonist activity at DOR, and significantly reduced binding and efficacy at KOR, suggesting that these compounds behaved as functional antagonists at DOR. To confirm antagonist activity at DOR, **54** and **55** were tested against DPDPE, and as expected from the high binding affinity and lack of stimulation of [^{35}S]GTPγS binding at DOR, **54** and **55** both antagonized the DOR agonist DPDPE, with antagonist affinity constants (K_e) of 1.98 nM and 27.5 nM, respectively (data not shown). Lastly, **54** stood out as a compound with one of the best *in vitro* profiles for the desired MOR agonist/DOR antagonist profile across all three series. Analogue **54** displays subnanomolar affinity at both MOR and DOR (K_i = 0.04 nM and 0.23 nM, respectively), indicating that there is only a 6-fold selectivity preference for MOR over DOR. Additionally, when comparing MOR and DOR binding affinities to KOR binding affinity, **54** displayed 200-fold selectivity for DOR and 1200-fold selectively for MOR, relative to KOR. Finally, **54** produced 87% stimulation at MOR, acted as an antagonist at DOR, and

displayed no efficacy and a lower relative affinity at KOR, indicating that any KOR-mediated effects would be minimal.
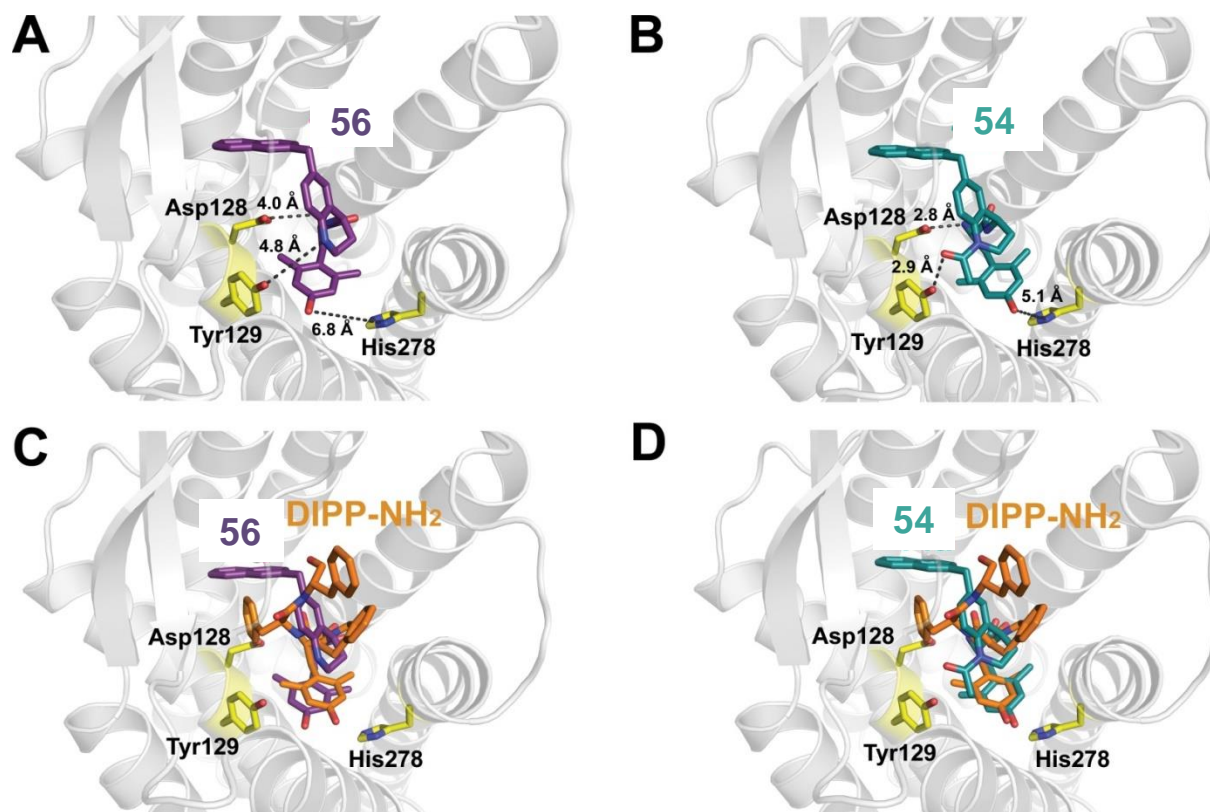
Figure 2.7 Docking of **54**, **56** and DIPP-NH₂ in DORinactive (DORi). **A. 56** (purple) in DORi with key residues shown. **B. 54** (teal) in DORi with key residues shown. Dashed lines represent calculated distances between ligand and receptor residues, indicating a possible interaction between *N*-acetyl moiety and Tyr[129] that may increase binding affinity at DORi. (C) overlay of **56** (purple) and DIPP-NH₂ (orange) in DORi. (D) Overlay of **54** (teal) and DIPP-NH₂ (orange) in DORi.

Because **54** displayed one of the best *in vitro* profiles, this analogue, along with 11 other compounds were tested for *in vivo* activity in mice using the WWTW assay. As seen in Figures 2.3 and 2.8, the *in vitro* results and cLogP calculations were both poor predictors of *in vivo* activity. Surprisingly, **55** displayed no *in vivo* activity at 10 mg/kg *ip* while **54**, a structural isomer of **55**, displayed full antinociception at 10 mg/kg *ip*. Consequently, both **54** and **55** were administered centrally via intracerebroventricular (*icv*) injection, then performed the WWTW assay was performed. Both **54** and **55** displayed full antinociception at 300 ng/3 μL at 5 min and 15 min post *icv* injection (Figure 2.5). As both **54** and **55** were active after *icv* administration, this indicates that the difference in *in vivo* activity following *ip* administration is a matter of

pharmacokinetics and not pharmacodynamics. In order to explore this unexpected result, both **54** and **55** were submitted for plasma stability testing performed by Quintara Discovery (San Francisco, CA, U.S.). These results revealed that both analogues tested were fully stable in plasma after 30 min, suggesting compound degradation in the plasma does not account for the differing activities *in vivo.* As such, **54** and **55** were both tested to see if they were substrates for the P-glycoprotein (Pgp) transporter. The Pgp transporter is a protein located in the capillary endothelial cells of BBB, among other locations in the body, and is responsible for pumping xenobiotics out of cells. The results from the Pgp assay suggest that neither **54** nor **55** are substrates for the Pgp transporter. Additional pharmacokinetic studies on **54** and **55** will be helpful for understanding the basis of the disparate *in vivo* results.

In order to determine the duration of action for **54**, a time course assay was completed. Antinociception produced by **54** (10 mg/kg) lasted over 3 h (Figure 2.4) which is a significant increase over the original lead, **1**, and comparable to morphine at the same 10 mg/kg dose (Data not shown). Additionally, **54** was screened to determine if chronic administration would produce tolerance. As can be seen in Figure 2.6 Panel A, the dose-response curve following twice daily administration of increasing doses of **54** does not produce a rightward-shift and does not differ from animals receiving saline over the duration of the experiment. In contrast, morphine produces a rightward-shift indicating the development of tolerance because an increased dose on day 6 is necessary to produce the same response as seen in day 1 (Figure 2.6, Panel B).
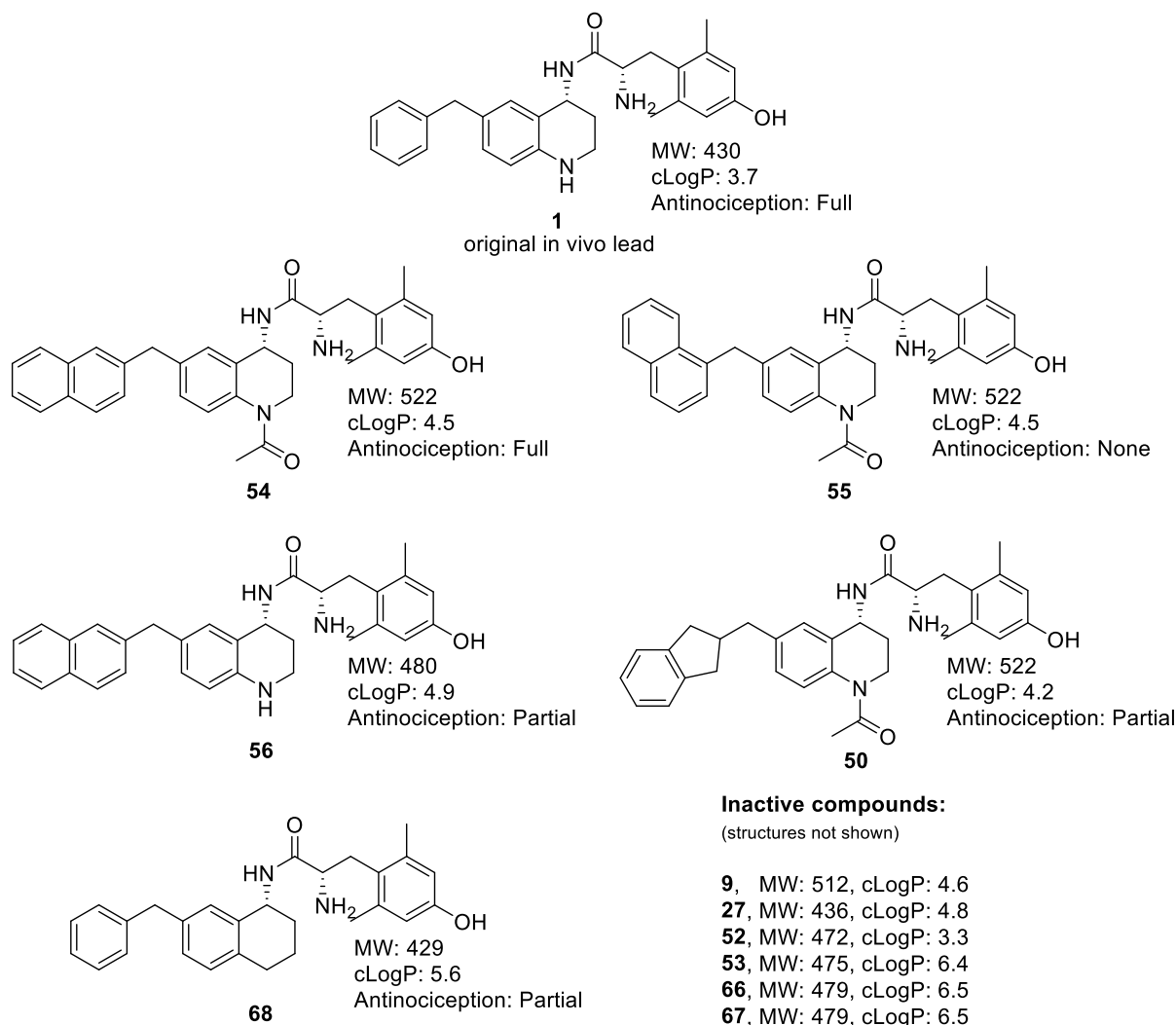
Figure 2.8 Summary of *in vivo* activity following *ip* administration, cLogP, and molecular weight (MW, g/mol) for select compounds. Compounds **9**, **27**, **52**, **53**, **66**, **67** do not display antinociception following *ip* administration and structures are not shown.

In summary, three parallel series of peptidomimetics were synthesized. The original THQ scaffold was modified to incorporate 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. A better balance in affinity at MOR and DOR was achieved through maintaining MOR affinity while increasing DOR affinity via *N*-acetylation. This increase in DOR affinity could be due to an interaction between the carbonyl moiety of the acetyl group and Tyr[129] in DOR. Additionally, *N*-acetylation decreased binding affinity and efficacy at KOR, thereby creating a more selective MOR agonist/DOR antagonist compound profile. Furthermore, three of the compounds produced *in vivo* activity when administered peripherally.

Analogue **54** produced one of the more balanced MOR agonist/DOR antagonist profiles *in vivo*, reduced KOR affinity and efficacy, full antinociception in the mouse WWTW assay for >3 h, a promising improvement upon the original lead compound, **1**,[21] and did not produce chronic tolerance in the mouse model. Additional *in vivo* studies for **54** are planned, including studies to determine if chronic administration of **54** produces dependence.

CHAPTER 3

Effects of various *N*-substitutions on opioid receptor affinity and efficacy

3.1 Introduction

As described above, *N*-acetylation of the THQ core of the mixed-efficacy MOR agonist/DOR antagonist peptidomimetics improves DOR affinity, which results in an overall better balance of affinities at MOR and DOR and thereby creates a MOR agonist/DOR antagonist profile, more selective over KOR. The hypothesis is that an additional polar contact between the carbonyl of the *N*-acetyl moiety and Tyr^{129} of DOR in transmembrane 3 (TM3) helix could be responsible for this increase in affinity (Figure 2.6). In an effort to explore this region of the receptor binding pocket and determine the optimal R-group on the THQ nitrogen, a series of *N*-substituted THQ analogues that incorporate various aliphatic, cyclic, aromatic, and acidic functionalities was synthesized. Through this synthetic campaign, the goal was to empirically probe and "map" the region of the binding pocket where the *N*-substitutions interact and define the steric and electronic requirements and limits. Analogues in the present SAR campaign were therefore designed to (1) include a carbonyl moiety in order to try and maintain the high DOR affinity seen in the initial compounds, and (2) incorporate various aliphatic, cyclic, aromatic, and heteroatom-containing functionalities (Figure 3.1) in order to probe the effect of such modifications on the binding affinity and efficacy not only at DOR, but also at MOR and KOR.

Figure 3.1 Peptidomimetic scaffold, pendants, and *N*-substitutions

3.2 Design and synthesis

All the *N*-substitution moieties shown in Figure 3.1 were incorporated onto the parent peptidomimetic, **1**, where R_1 is a benzyl pendant. The *N*-substitutions that produced the most promising *in vitro* and *in vivo* profiles were integrated onto **9**, where R_1 is a 2-methylindanyl and ont**o 56**, where R_1 is a 2-methylnaphthyl pendant. Compound **9** was chosen as a candidate for additional *N*-substitutions because it was shown to increase selectivity over KOR with the addition of the acetyl group with a K_i = 1.2 nM at KOR for **9** and 12 nM for **50**. Additional *N*-substitutions on **9** could help elucidate what types of moieties confer selectivity and efficacy to either DOR or KOR. Compound **56** was chosen as a candidate for additional *N*-substitutions because **54**, the *N*-acetylated version of **56**, displayed one of the best *in vitro* profiles among the *N*-acetylated series and produced *in vivo* activity. Incorporation of other carbonyl-containing *N*-substitutions might affect the MOR agonist/DOR antagonist profile of an already promising lead or how the *N*-substitutions might influence *in vivo* duration of action.

3.2.1 Synthesis of N-acylated Analogues Containing the Benzyl Pendant

The majority of the peptidomimetics containing the benzyl pendant, **77-80**, were prepared in four steps starting from the dihydroquinolinone intermediate **30** which was subjected to acylation using either an acid anhydride or acyl chloride to form intermediates **69-72**. Intermediates **69-72** were treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to yield imines *in situ*, which were reduced with NaBH$_4$ to form the desired *R*-stereochemistry of intermediates **73-76**.[32-34] The Ellman auxiliary was cleaved using concentrated HCl, forming primary amine salts, which were then coupled to diBoc-Dmt and subsequently deprotected to yield compounds **77-80** (Scheme 3.1).
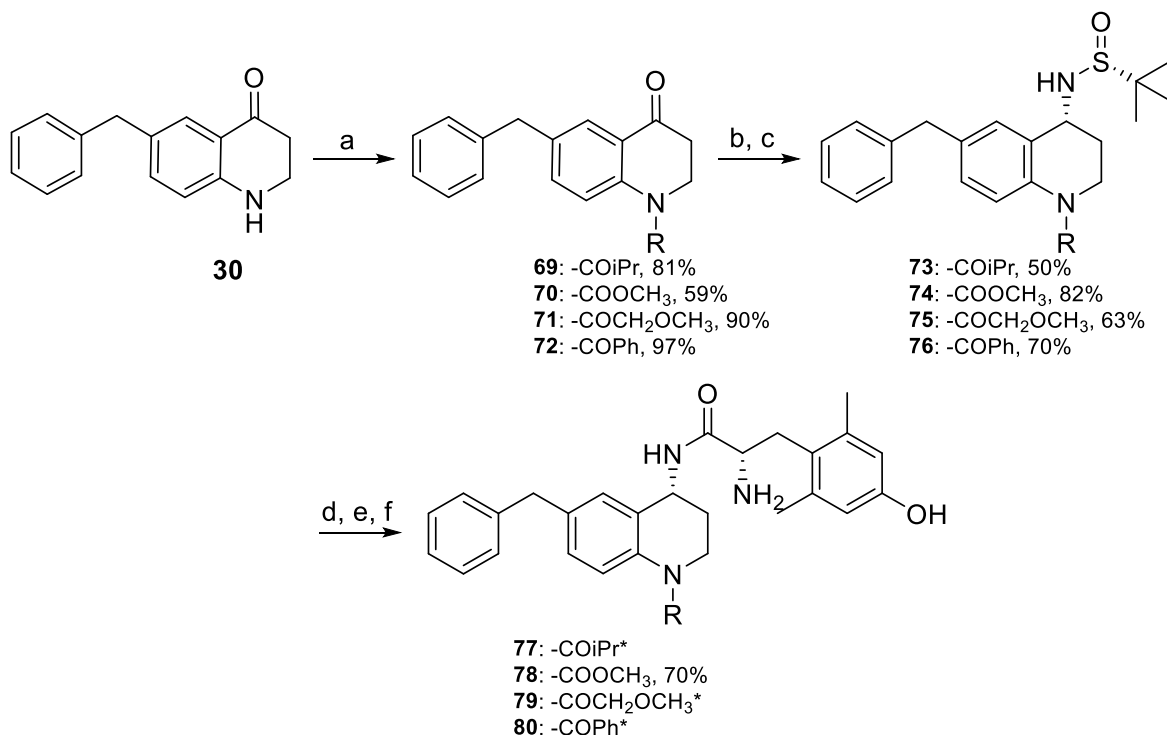
(a) R-COCl, DCM, (b) (R)-t-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (c) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (d) HCl, dioxane, RT, 3 h (e) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (f) 1:1 TFA:DCM. *not all crude product was purified so a yield was not calculated.

Scheme 3.1 Synthesis of *N*-acylated analogues containing the benzyl pendant

3.2.2 Synthesis of additional N-substituted analogues containing the benzyl pendant

The synthesis of compounds **88-90** began by protecting the nitrogen in **30** with a *tert*-butyloxycarbonyl (Boc) group forming **81**. Intermediate **81** was treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to yield an imine *in situ*, which was reduced with NaBH$_4$ to give the desired *R*-stereochemistry of intermediate **82**. [32-34] To ensure both the cleavage of the Ellman auxiliary and the removal of the Boc group, **82** was treated first with TFA then with conc. HCl in dioxane to ultimately yield the hydrochloride salt **83**. Intermediate **83** was coupled to diBoc-Dmt forming **84**. From this intermediate, **84**, the syntheses of **88**, **89**, and **90** diverged. The synthesis of **88** was completed by first performing a Finkelstein reaction on 2-chloroacetamide to form 2-iodoacetamide which was cannulated into a solution containing **84** and *N,N*-diisopropylethylamine (DIPEA) to give **85**. Intermediate **85** was treated with TFA to remove the Boc groups, yielding **88**. To complete the syntheses of **89** and **90**, ethyl 2-bromoacetate was

added to intermediate **84** in the presence of potassium carbonate to give **86**. Intermediate **86** was then treated with TFA to remove Boc groups and afford compound **89**. Compound **90** was completed by saponification of the ester of **86** with lithium hydroxide (LiOH) yielding **87**, which was subsequently treated with TFA to remove the Boc groups and yield compound **90** (Scheme 3.2)
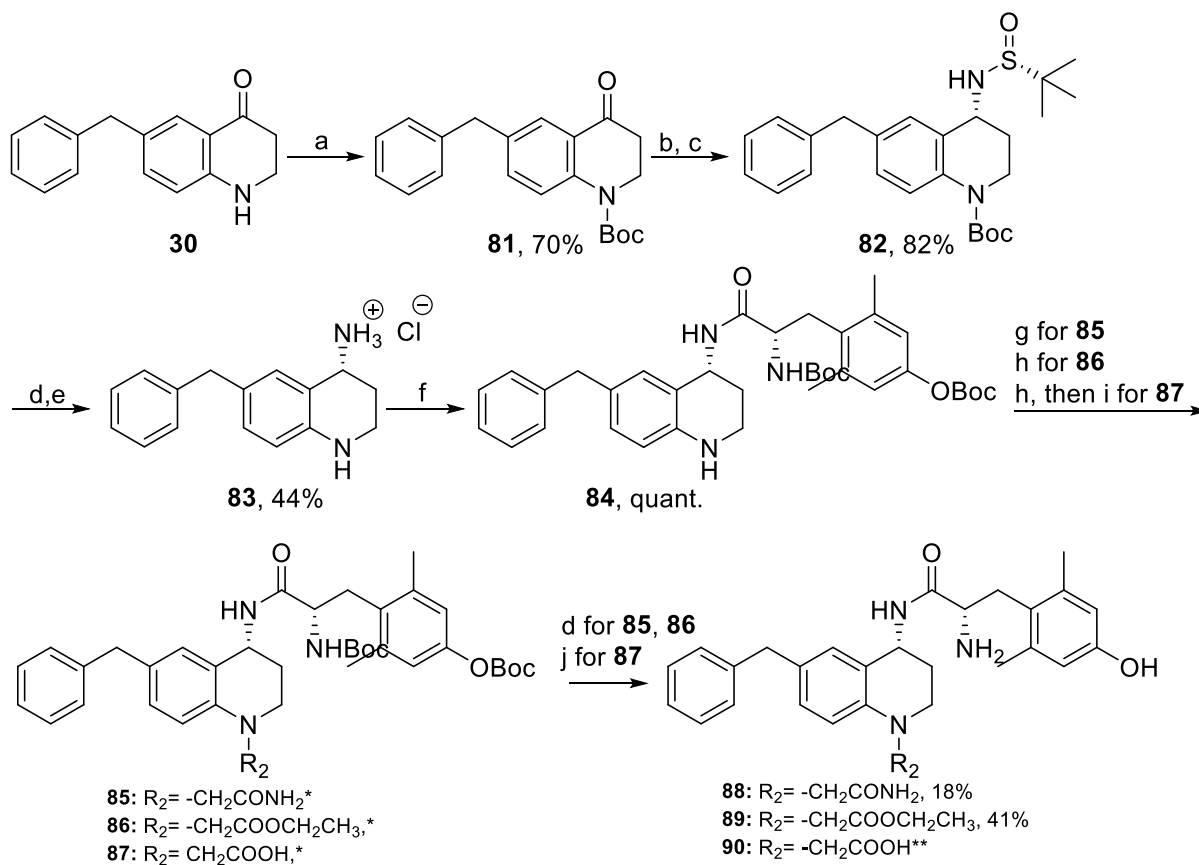
(a) Boc$_2$O, DMAP, DIPEA, DCM, 60°C (b) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (c) NaBH$_4$, THF, -50°C to RT, 3h, then MeOH, RT (d) 1:1 TFA:DCM (e) HCl, dioxane, RT (f) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (g) NaI, 2-chloroacetamide, then DIPEA (h) ethyl 2-bromoacetate, K$_2$CO$_3$, CH$_3$CN, 24 h (i) LiOH, EtOH, 60°C, 2.5 h (j) 3 N HCl, RT. *Yield not calculated. **yield not calculated because only a portion of the crude final product was purified

Scheme 3.2 Synthesis of additional *N*-substituted analogues containing the benzyl pendant

3.2.3 Synthesis of N-acylated analogues containing the 2-methylindanyl pendant

Like the benzyl *N*-acylated series, *N*-acylated peptidomimetics containing the 2-methylindanyl pendant, **97-99**, were prepared in four steps starting from the dihydroquinolinone intermediate **6** which was subjected to acylation using either an acid anhydride or acyl chloride to form intermediates **91-93**. Intermediates **91-93** were treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to yield imines *in situ*, which were reduced with NaBH$_4$ to form the desired *R*-stereochemistry of intermediates **94-96**.[32-34] The Ellman auxiliary was cleaved using concentrated HCl, forming primary amine salts, which were then coupled to diBoc-Dmt and subsequently deprotected to yield compounds **97-99**.

91: -COCH$_2$CH$_3$, 76%
92: -COCH$_2$CH$_2$CH$_3$, 38%
93: -COOCH$_3$, 13%

94: -COCH$_2$CH$_3$, 49%
95: -COCH$_2$CH$_2$CH$_3$*
96: -COOCH$_3$, 7%

97: -COCH$_2$CH$_3$, quant.
98: -COCH$_2$CH$_2$CH$_3$**
99: -COOCH$_3$,70%
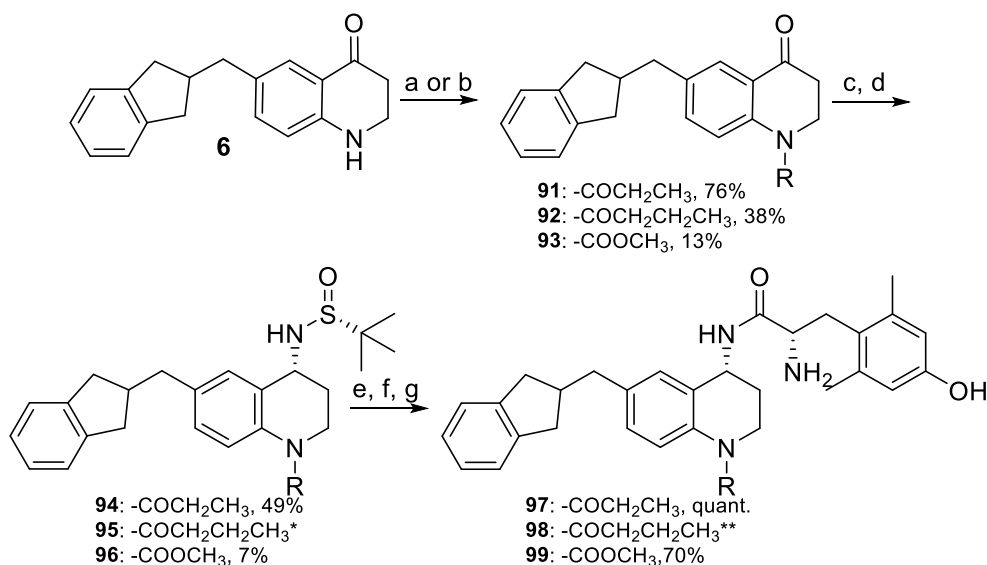
(a) neat acid anhydride, 100°C, 24 h (for **91** and **92**) (b) MeCOOCl, DCM, (for **93**) (c) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (d) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (e) HCl, dioxane, RT, 3 h (f) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (g) 1:1 TFA:DCM. *yield not determined for this intermediate. **yield not calculated because not all crude final product was purified.

Scheme 3.3 Synthesis of *N*-acylated analogues containing the 2-methylindanyl pendant

3.2.4 Synthesis of N-acylated analogues containing the 2-methylnaphthyl pendant

The *N*-acylated peptidomimetics containing the 2-methylnaphthyl pendant, **113-115**, were prepared starting with the acylation of *p*-methylaniline using 3-bromopropionyl chloride to yield **100**. Intermediate **100** was cyclized under basic conditions to form lactam **101**, and was then treated with TfOH to form intermediate **102**. The nitrogen of **102** was protected with a *tert*-butyloxycarbonyl (Boc) group forming **103**. Intermediate **103** was brominated using *N*-bromosuccinimide and benzoyl peroxide to yield **104** which was then subjected to Suzuki cross-coupling to incorporate the 2-methylnaphthyl moiety and yield **105** Intermediate **105** was treated with TFA to remove the Boc group forming **106**. Intermediate **106** was treated with propionic anhydride to yield **107**, butyric anhydride to yield **108**, or methylchloroformate to yield **109**. Intermediates **107-109** were treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to form a chiral imine *in situ* which was reduced with NaBH$_4$ to form the desired *R*-stereochemistry for intermediate **110-112**.[32-34] The Ellman auxillary was cleaved using concentrated HCl forming primary amines which were then coupled to diBoc-Dmt and deprotected to yield compound **113-115** (Scheme 3.4).
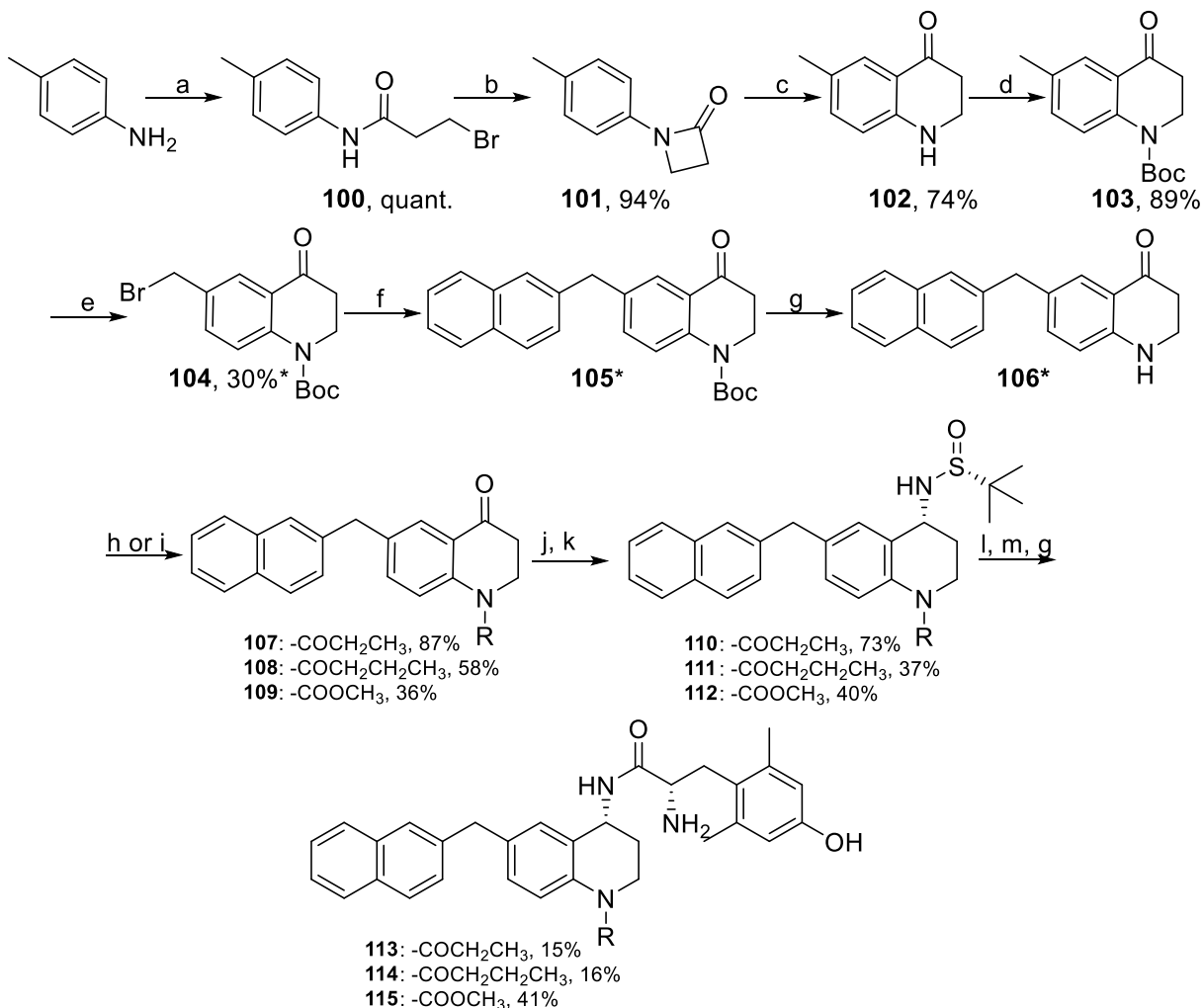
100, quant.   **101**, 94%   **102**, 74%   **103**, 89%

104, 30%*   **105***   **106***

107: -COCH$_2$CH$_3$, 87%
108: -COCH$_2$CH$_2$CH$_3$, 58%
109: -COOCH$_3$, 36%

110: -COCH$_2$CH$_3$, 73%
111: -COCH$_2$CH$_2$CH$_3$, 37%
112: -COOCH$_3$, 40%

113: -COCH$_2$CH$_3$, 15%
114: -COCH$_2$CH$_2$CH$_3$, 16%
115: -COOCH$_3$, 41%

(a) 3-bromopropionyl chloride, K$_2$CO$_3$, DCM, RT, 3 h (b) NaOtBu, DMF, RT, 3 h (c) TfOH, DCE, RT, 3 h (d) Boc$_2$O, DMAP, DIPEA, DCM, 60°C (e) NBS, benzoyl peroxide, CCl$_4$, 70°C, 6-8 h (f) R-B(OH)$_2$, Pd(dppf)Cl$_2$, K$_2$CO$_3$, 3:1 acetone:H$_2$O (g) 1:1 TFA:DCM (h) neat acid anhydride, reflux, 24 h (for **107** and **108**) (i) MeCOOCl, DCM, RT, 16 h (for **109**) (j) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (k) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (l) HCl, dioxane, RT, 3 h (m) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT. *not all of this intermediate was purified, so yield appears low or was not calculated.

Scheme 3.4 Synthesis of *N*-acylated analogues containing the 2-methylnaphthyl pendant

3.3 Results

Peptidomimetics **77-80**, **88-90**, **97-99**, and **113-115** were evaluated in *in vitro* binding and efficacy assays, as described in **8.2**. Select analogues were chosen for *in vivo* evaluation in the WWTW assay, as described in **8.3** (Figure 3.2). Additional analogues screened that displayed no *in vivo* activity at 10 mg /kg in the WWTW assay include the 2-methylindanyl compounds **98** and 99 and the 2-methylnapthyl compounds **113-115**. *In vivo* data for these compounds are not shown.

Table 3.1 Binding and Efficacy Data for Peptidomimetics with Benzyl Pendants

Cpd	R$_2$	Binding, K$_i$ (nM)[a,c]			EC$_{50}$ (nM)[b,c]			% stimulation [b,c]		
		MOR	DOR	KOR	MOR	DOR	KOR	MOR	DOR	KOR
1[f]	H	0.22 (0.02)	9.4 (0.8)	68 (2)	1.6 (0.3)	110 (6)	540 (72)	81 (2)	16 (2)	22 (2)
52[g]	(acetyl)	0.13 (0.02)	1.8 (0.1)	87 (11)	6.0 (1)	68 (2)	>1300	76 (4)	26 (3)	29 (5)
116[h]	(propanoyl)	0.12 (0.01)	0.76 (0.4)	28[d] (2)	5 (2)	41 (20)	>1300[e]	90 (7)	58 (6)	14[e]
117[h]	(butanoyl)	0.10 (0.03)	0.41[e]	100[e]	18 (10)	8.1[d] (0.9)	>1500[d]	53 (3)	44[d] (3)	20[d] (3)
77	(isobutyryl)	0.27 (0.1)	0.32 (0.2)	66 (20)	9.5 (3)	25 (20)	>1400	90 (6)	52 (2)	35 (10)
118[h]	(cyclopropanecarbonyl)	0.10 (0.03)	0.35 (0.01)	25 (5)	1.8 (0.3)	18 (9)	dns[d]	82 (4)	70 (10)	dns[d]
119[h]	(cyclobutanecarbonyl)	0.14 (0.09)	0.15 (0.07)	41 (20)	2.1 (0.20)	5.6 (3)	dns[d]	94 (5)	66 (10)	dns[d]
78	(methyl carbamate/carbonate)	0.19 (0.05)	0.51 (0.2)	29 (8)	0.78 (0.2)	14 (3)	280 (40)	95 (5)	40 (7)	29 (4)
79	(methoxyacetyl)	0.15 (0.04)	2.7 (0.7)	34 (4)	3.0 (0.5)	67 (20)	>1700	91 (1)	47 (8)	38 (4)
80	(benzoyl)	0.08 (0.03)	0.24 (0.09)	21 (10)	2.6 (0.6)	dns	430 (170)	74 (7)	dns	16 (4)
88	(β-alanyl amide)	0.23 (0.06)	2.0 (0.4)	4.3 (1)	1.54 (0.15)	560 (300)	380 (60)	99 (3)	29 (6)	49 (8)
89	(ethyl carbonate)	0.24 (0.10)	0.58 (0.20)	31[d] (20)	5.1 (2)	15 (3)	>2700[d]	79 (0.4)	34 (2)	31[d] (20)
90	(carboxymethyl)	4.4 (0.8)	67 (8)	280 (50)	78 (30)	dns	dns	87 (2)	dns	dns

[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 S.E.M. in parentheses for n=3 independent assays in duplicate, unless otherwise noted. [d]n=2 independent assays in duplicate. [e]n=1 independent assay in duplicate. dns: does not stimulate. [f]published in ref. 21. [g]published in ref 23. [h]Synthesized by Aaron Bender.

Table 3.2 Binding and Efficacy Data for Peptidomimetics with 2-methylindanyl Pendants
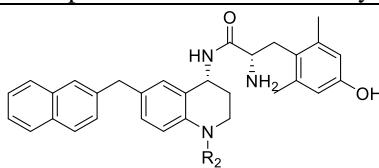

Cpd	R₂	Binding, K$_i$ (nM)[a, c]			EC$_{50}$ (nM)[b,c]			% stimulation [b, c]		
		MOR	**DOR**	**KOR**	**MOR**	**DOR**	**KOR**	**MOR**	**DOR**	**KOR**
9[f]	H	0.16 (0.04)	4.1 (1.6)	1.2 (0.4)	0.24 (0.03)	dns	dns	86 (1)	dns	38 (2)
50[g]		0.05 (0.00)	0.44 (0.07)	12 (4)	0.56 (0.1)	dns	610 (250)	84 (2)	dns	60 (10)
97		0.06 (0.01)	0.30 (0.1)	340[e]	2.8 (1.7)	dns[d]	390 (30)	61 (10)	dns[d]	27 (0.50)
98		0.19 (0.07)	0.40 (0.05)	22 (4)	4.1 (1.6)	dns[d]	340[d] (70)	63 (10)	dns[d]	16[d] (1)
99		0.10 (0.02)	0.32 (0.05)	7[d] (3)	0.39 (0.05)	dns[d]	170[d] (40)	94 (8)	dns[d]	26[d] (3)

[a]Binding affinities (K$_i$ (nM)) were obtained by competitive displacement of radiolabeled [³H]diprenorphine in membrane preparations. [b]Efficacy data were obtained using agonist induced stimulation of [³⁵S]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 S.E.M. in parentheses for n=3 independent assays in duplicate, unless otherwise noted. [d]n=2 independent assays in duplicate. [e]n=1 independent assay in duplicate. dns: does not stimulate. [f]published in ref. 21. [g]published in ref 23.

Table 3.3 Binding and Efficacy Data for Peptidomimetics with 2-methylnaphthyl Pendants

Cpd	R$_2$	Binding, K$_i$ (nM)[a, c]			EC$_{50}$ (nM)[b,c]			% stimulation [b, c]		
		MOR	DOR	KOR	MOR	DOR	KOR	MOR	DOR	KOR
56[e]	H	0.078 (0.007)	10 (2)	54 (7)	0.53 (0.08)	dns	dns	96 (3)	dns	dns
54[f]	(acetyl)	0.04 (0.01)	0.23 (0.02)	48 (20)	0.93 (0.2)	dns	dns[d]	87 (3)	dns	dns[d]
113	(propanoyl)	0.28 (0.05)	0.21 (0.1)	58 (10)	13 (2)	dns	>1400	75 (0.50)	dns	15 (3)
114	(butanoyl)	0.14 (0.07)	0.80 (0.1)	64 (30)	0.90 (0.3)	dns	dns	92 (7)	dns	dns
115	(methyl carbonate)	0.32 (0.08)	1.0 (0.6)	140[d] (70)	0.39 (0.2)	dns[d]	dns[d]	110 (5)	dns[d]	dns[d]

[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 S.E.M. in parentheses for n=3 independent assays in duplicate, unless otherwise noted. [d]n=2 independent assays in duplicate. dns: does not stimulate. [e]published in ref. 21. [f]published in ref 23
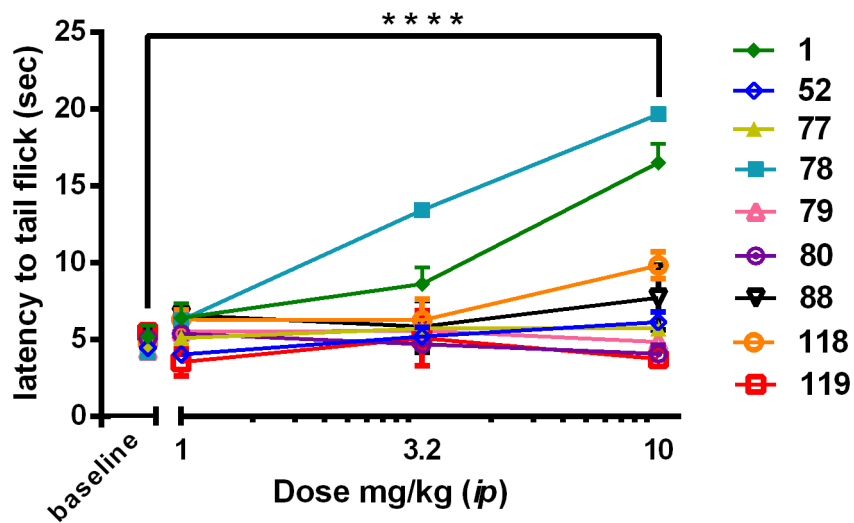
Figure 3.2 Cumulative antinociceptive dose response curves of select *N*-substituted analogues in the mouse warm water tail withdrawal (WWTW) assay following *ip* administration. n=3 for all analogues, plotted as average +/- S.E.M. ****, p < 0.0001 for **1** and **78** for the 10 mg/kg dose when compared to baseline.
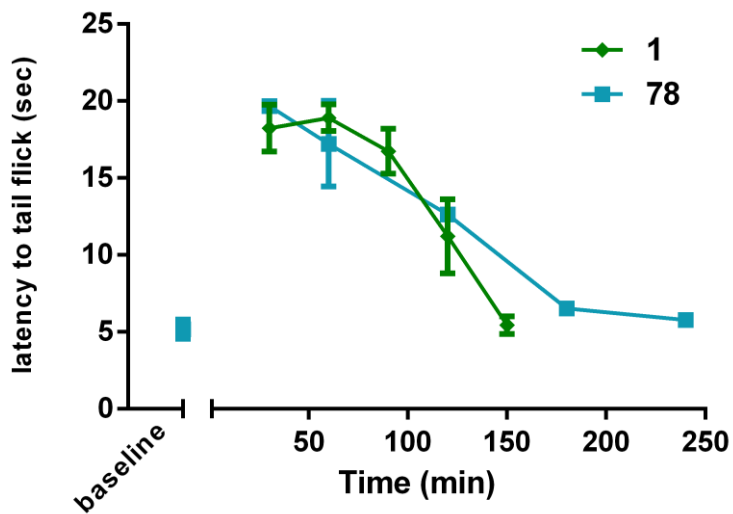

Figure 3.3 Time course of antinociception of **1** and **78** in the mouse WWTW assay following *ip* administration of 10 mg/kg. n=3, plotted as average ± S.E.M

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3.4 Discussion

All new compounds, excluding **90**, maintained subnanomolar binding affinity at MOR and exhibited an increased DOR binding affinity when compared to the unsubstituted parent compounds (**1**, **9**, **56**), presumably due to the carbonyl moiety incorporated into each of the *N*-substitutions. The only exception to this trend, **90**, contained a carboxylic acid moiety and had significantly decreased affinity across all three receptors, potentially due to electrostatic repulsion between the carboxylic acid moiety of the compound and a conserved Asp residue in TM3 (Asp[128] in DOR) in the three opioid receptors. Based on these initial *in vitro* results, it appears that a carbonyl-containing moiety was beneficial to maintaining higher binding affinity at DOR. Conversely, a negatively charged species was not well tolerated.

An additional trend seen in the benzyl series was that increasing the *N*-acyl chain length or overall bulk increases DOR stimulation with the exception of **80**, which contained a benzoyl moiety and produced no stimulation at DOR. As seen in Table 3.1, the unsubstituted compound **1** showed very weak stimulation at DOR (16%) while the *N*-acetyl analogue **52** increased stimulation at DOR to 26% and the *N*-propionyl (**116**) and *N*-butyryl (**117**) analogues further increased DOR stimulation to between 50-60%. Compounds **77**, **118**, and **119** contained branched or cyclic *N*-substitutions, and in the case of **118** (containing a cyclopropanecarbonyl moiety) and **119** (containing a cyclobutanecarbonyl moiety) DOR stimulation increased to 60% and 70%, respectively, giving both of these compounds a MOR agonist/DOR agonist *in vitro* profile. While this profile was not our initial focus, the importance of the MOR agonist/DOR agonist profile should be mentioned. Several reports have shown that coadministration a DOR agonist with a MOR agonist can increase both the potency and efficacy of the MOR agonist.[41-42] In fact, it has been shown that even subantinociceptive doses of a DOR agonist (in this case Leu-enkephalin) could potentiate the analgesic actions of morphine.[41] These findings imply ligands producing a mixed-efficacy MOR agonist/DOR agonist profile could allow for the effective management of pain with a decrease in side effects seen with the administration of only a MOR agonist.

Furthermore, in the benzyl series, compounds with longer chain lengths (**116**), increased bulk (**118**, **119**, **80**), or longer chains incorporating heteroatoms (**78**, **79**, **88**, **89**) displayed an increased affinity at KOR (K_i values ranging from 8 nM to 40 nM) when compared to **1** (K_i = 68 nM). In particular, **88**, containing an amide functionality, not only displayed increased affinity at

KOR (8 nM vs 68 nM for **1**), it also exhibited significant KOR stimulation (49%), when compared to the unsubstituted **1** (22%), suggesting the possibility that hydrogen bond donors in this area of the binding pocket might play a role in increasing affinity and efficacy at KOR. One potential interaction that could play a role in the increased affinity and stimulation at KOR is hydrogen bonding with His[54] near the N-terminus of KOR, a residue that is not conserved in MOR or DOR.

Unlike the benzyl series, increasing the *N*-acyl chain length does not increase DOR stimulation in the 2-methylindanyl series. In fact, none of the compounds in the 2-methylindanyl series produce agonist activity at DOR. However, all analogues produce agonism at both MOR and KOR, as seen in Table 3.2. As in the benzyl series, additional chain length increased affinity at KOR in the 2-methylindanyl series relative to **1**. For example, compounds **9** (Ki =1.2 nM) , **50** (Ki=12 nM), and **99** (Ki=7.3 nM) all have relatively high binding affinities at KOR relative to **1** (68 nM). As mentioned, all substitutions on the 2-methylindanyl scaffold maintained various degrees of efficacy at KOR with **50** producing the largest agonist effect at KOR with 60% stimulation. With these *in vitro* results, the 2-methylindanyl series could serve as a starting point for the design and synthesis of compounds producing a MOR agonist/KOR agonist profile or MOR antagonist/KOR agonist profile—a profile that has implications in the treatment of cocaine addiction.[43-46]

As the acyl chain length increases in the 2-methylnaphthyl series, the balanced-affinity MOR agonist/DOR antagonist profile seen with **54** remains essentially constant, while KOR affinity slightly decreases indicating that increased chain length helps provide MOR and DOR selectivity over KOR (Table 3.3). Additionally, all the compounds in the 2-methylnaphthyl series produce full agonism at MOR, all higher than the efficacy of morphine. Perhaps the differences in DOR efficacy between the benzyl and the 2-methylnaphthyl series imply that the pendant moiety could play an important role in orienting and anchoring the ligand in the DOR binding pocket in the inactive receptor conformation.

When looking at the *in vitro* data as a whole it appears that various *N*-acyl substitutions on the benzyl scaffold start to alter the MOR agonist/DOR antagonist profile to a MOR agonist/DOR agonist profile. Additionally, the 2-methylindanyl series does not enhance the desired MOR agonist/DOR antagonist profile, but could potentially serve as a starting point for the synthesis of a series of compounds that produce a mixed-efficacy MOR agonist/KOR

agonist profile or a MORantagonist/KORagonist profile, as long as the MOR efficacy could be removed. Lastly, the 2-methylnaphthyl series appears to be the only series that maintains and improves the desired MOR agonist/DOR antagonist profile through enhanced selectivity for MOR and DOR over KOR.

In view of the promising *in vitro* observations seen in the *N*-substituted series, 13 of the 17 novel analogues in this series were chosen for *in vivo* screening (compounds **116**, **117**, **90**, and **97** were not selected), but only two analogues emerged as having *in vivo* efficacy. Analogue **118** produced partial antinociception with an 11 sec latency to tail flick at the 10 mg/kg dosage in the WWTW assay after *ip* administration while **78** produced full antinoception at the same dosage.

Interestingly, while **118** (containing a cyclopropanecarbonyl moiety) produced partial antinociception in the WWTW assay, neither **77** (containing a isopropanecarbonyl moiety) nor **119** (containing a cyclobutanecarbonyl moiety) produced antinociception under the same conditions. The *in vivo* results for **118** are particularly encouraging given the implications of a mixed-efficacy MOR agonist/DOR agonist ligand in reducing the tolerance potential seen with selective MOR agonists.

Because **78** produced full antinociception at the 10 mg/kg dosage, it was submitted for evaluation in the *in vivo* WWTW time course assay. As can be seen in Figure 3.3, **78** has a similar duration of action to that of **1**, in that produces maximal antinociception for approximately 1 h. This result was interesting because it suggests that the methyl carboxylate moiety of **78**, despite blocking a potential site of metabolism, does not increase the duration of action. As the time course of **78** is so similar to **1**, this could potentially mean that **78** is in fact inactive *in vivo* but is quickly metabolized to **1** resulting in the observed *in vivo* efficacy and duration of action of 1 h, similar to that of **1**.

Interestingly, **115**, which had the most promising *in vitro* profile of the 2-methylnapthyl series, did not produce any stimulation at the 10 mg/kg dose in the WWTW assay following *ip* administration, despite having the same methyl carboxylate moiety as the fully efficacious **78**. This particular finding supports the hypothesis that the methyl carboxylate moiety could be metabolically labile and might be removed *in vivo* resulting in the formation of compound **56**, a compound with minimal activity at the 10 mg/kg dosage following *ip* administration.

CHAPTER 4

Probing the steric and electronic requirements and limitations on the THQ core and in the pendant region with methyl-, methoxy-, and hydroxyl-containing moieties

4.1 Introduction

The benzyl and 2-methylindanyl pendants, both containing numerous unsubstituted carbon atoms, offered a large amount of chemical space that was easily modified at one or multiple carbons for systematic SAR studies. Moreover, the 2-methylindanyl analogues served as probes for determining the spatial depth of the receptor. In this series of analogues, methyl, methoxy, and hydroxyl moieties were incorporated onto both the benzyl and 2-methylindanyl scaffolds in order to probe the area of the binding pocket where the pendant resides with the hopes of exploiting minor differences in the MOR, DOR, and KOR binding pockets that could help tailor binding and efficacy profiles (Figure 4.1, Panel B). Furthermore, a large portion of the *N*-substituted series of compounds described in Chapter 3 introduced lipophilic moieties that increased the cLogP and created solubility issues. An additional goal of this series was to improve solubility and lower cLogP to create more "druggable" compounds through incorporation of methoxy and hydroxyl moieties in specific locations on the THQ core, notably at carbon 7 (C7) and carbon 8 (C8), that did not affect binding affinity and efficacy (Figure 4.1, Panel A).

The *in vitro* data was acquired chiefly by Nicholas Griggs of the Traynor Lab at the University of Michigan (Table 4.1-4.3). In addition, Tyler Trask, Evan Schramm, Aaron Chadderdon and Chao Gao also of the Traynor Lab made significant contributions to collecting the *in vitro* pharmacology data (Table 4.1-4.3). Dr. Jessica Anand of the Jutkiewicz Lab at the University of Michigan is responsible for performing all of the *in vivo* assays (data not shown). The syntheses, *in vitro* data, and *in vivo* data for this series of analogues has not yet been published.
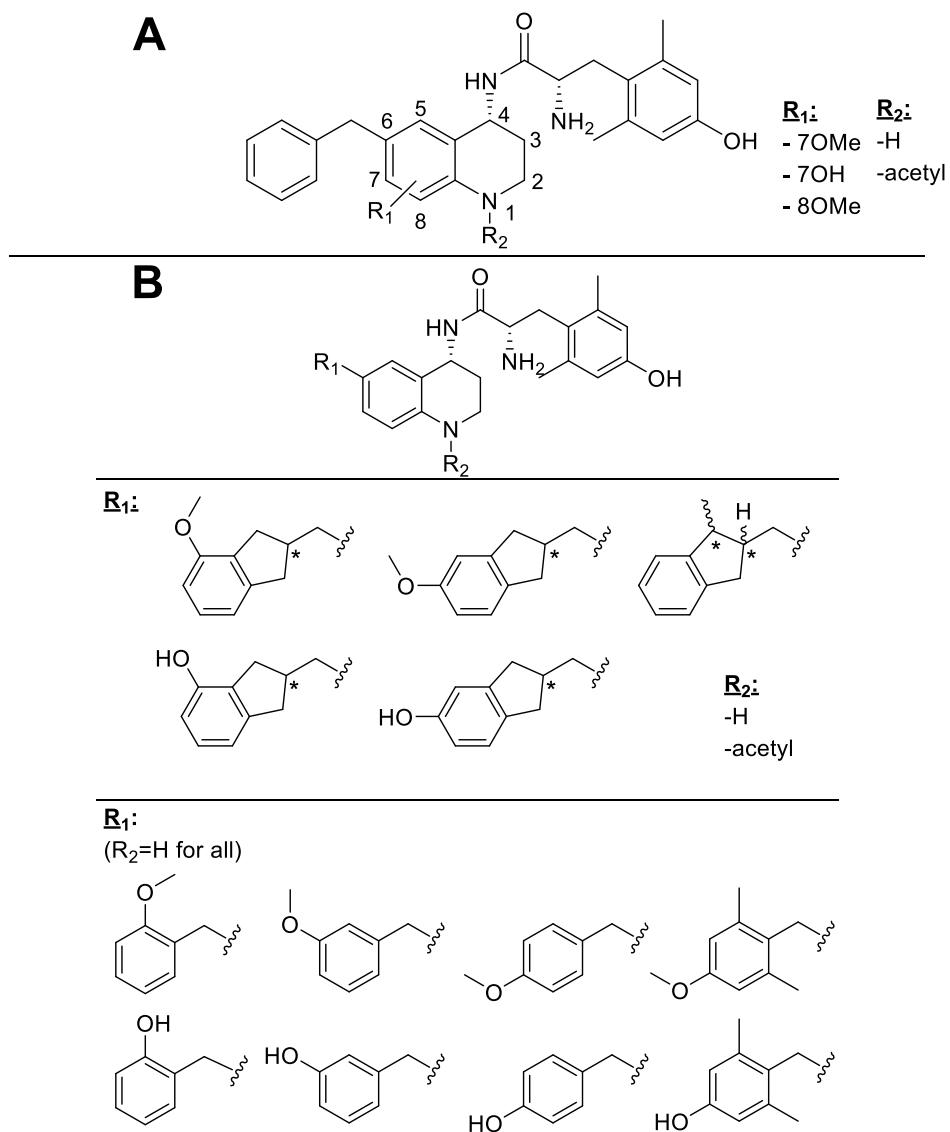
Figure 4.1 Methyl-, methoxy, and hydroxyl- modifications to peptidomimetics. **A.** Modifications to the THQ core and **B.** Modifications to the 2-methylindanyl and benzyl pendants.

4.2 Design and Synthesis

4.2.1 Synthesis of analogues with methoxy and hydroxyl moieties on the THQ core

Syntheses of analogues containing a methoxy moiety on the THQ were straight-forward starting from either 4-bromo-2-methoxyaniline or 4-bromo-3-methoxyaniline. Despite the fact that the methoxy moieties are on the 2- or 3- position of the starting material, throughout the synthesis the intermediates are referred to as "-7OMe" for the 3-methoxy starting material and "-8OMe" for the 2-methoxy starting material due to the numbering scheme on the final

compounds. The synthesis of analogues **134-137** began with acylation of the aniline starting material with 3-bromoproionyl chloride to form intermediates **120** and **121**, which were subsequently cyclized in the presence of base to form the lactam intermediate, which was then treated with TfOH to form the dihydroquinolinone intermediates **124** and **125**. Intermediate **124** was boc-protected forming **126,** while boc-protection of **125** was unsuccessful, most likely due to sterics. Instead, **125** was *N*-acetylated forming **127**. Intermediates **125-127** were subjected to Suzuki coupling to form **128-130**. Intermediates **128-130** were treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to yield imines *in situ*, which were reduced with NaBH$_4$ to form the desired *R*-stereochemistry of intermediates **131-133**. The Ellman auxiliary was cleaved using concentrated HCl, forming primary amine salts, which were then coupled to diBoc-Dmt and subsequently deprotected to yield compounds **134-136** (Scheme 4.1).

The synthesis of **137** deviated from the synthesis of its 7-methoxy analogue, **134**, after coupling to the amine formed during the cleavage of the Ellman auxillary to diBoc-Dmt. The identity of the diBoc-Dmt-coupled intermediate was confirmed by mass spectrometry, but was otherwise not extensively characterized and thus does not have a number assigned to its identity. This intermediate was treated with BBr$_3$ then quenched with MeOH to form **137** (Scheme 4.1).
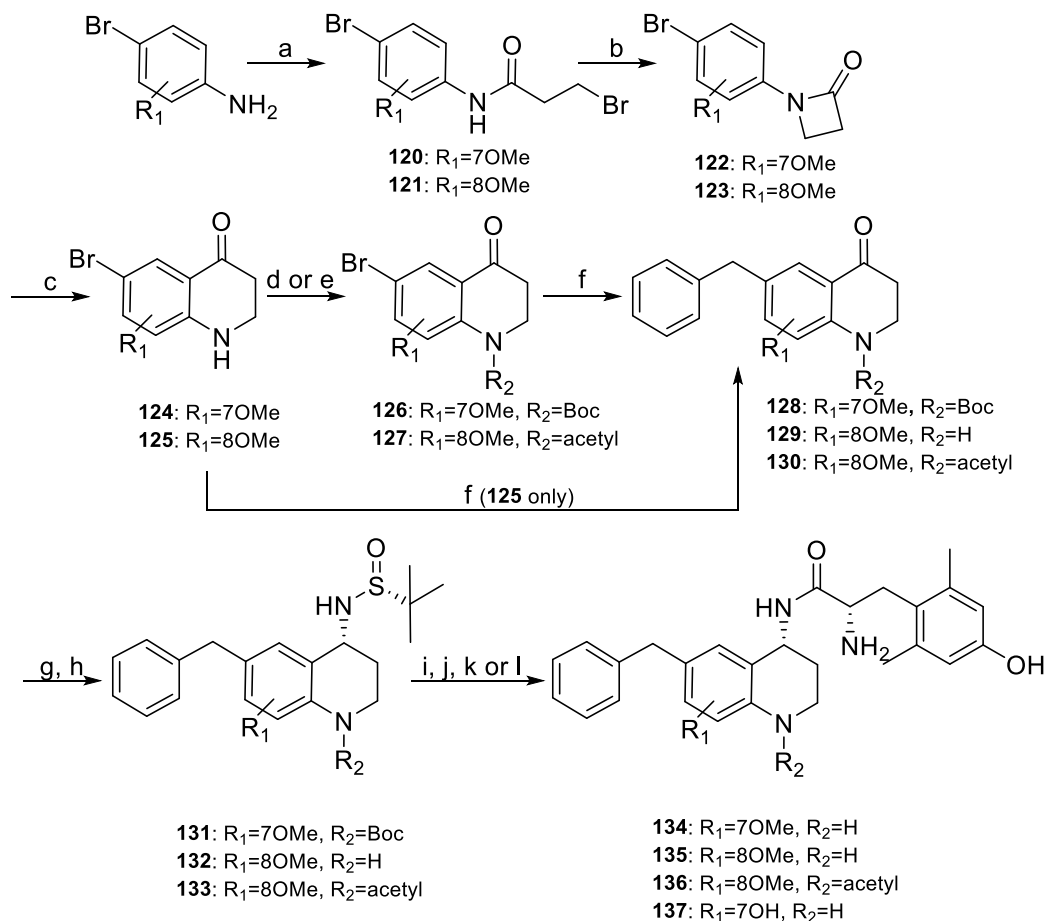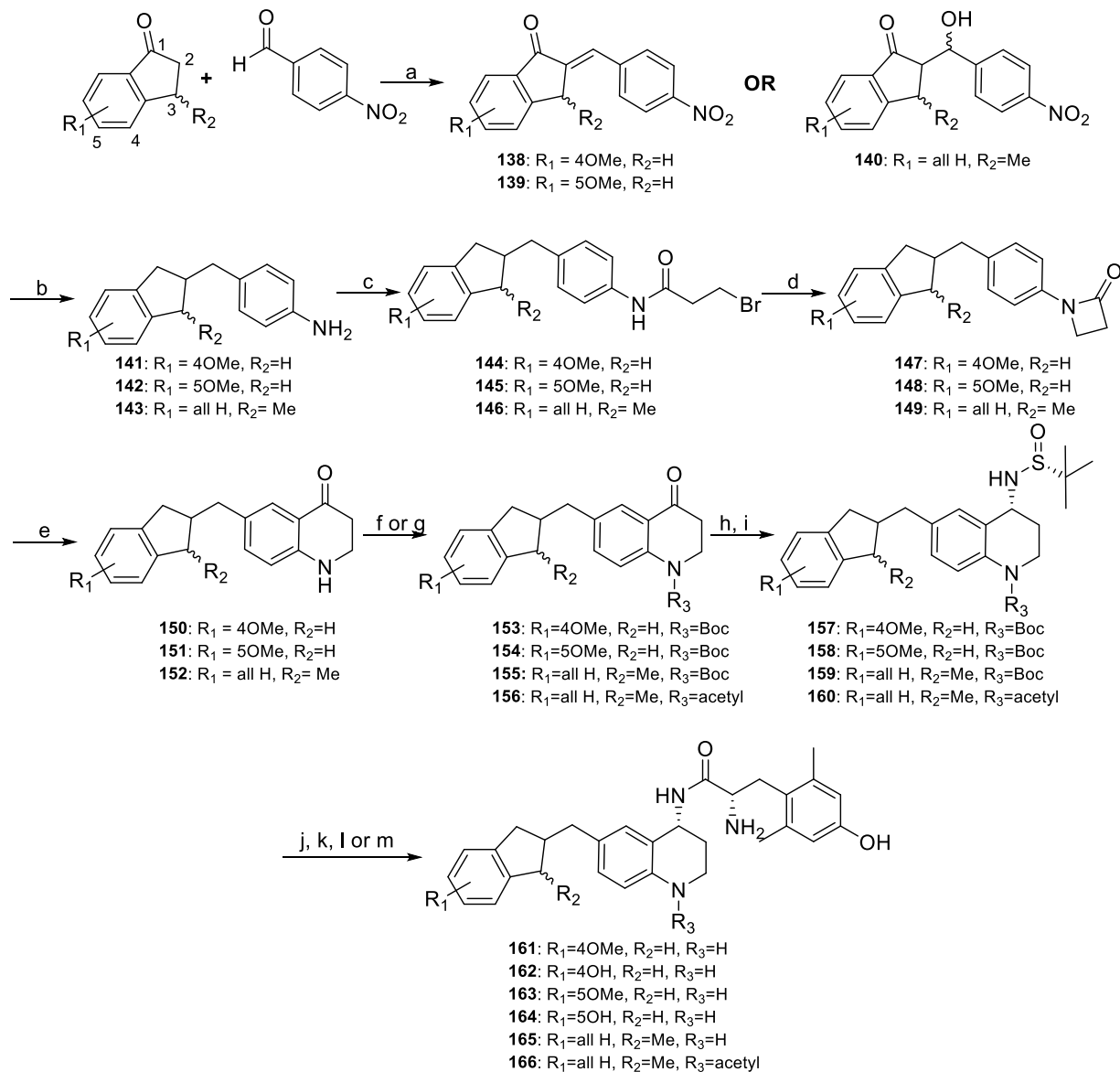
(a) 3-bromopropionyl chloride, K_2CO_3, DCM, RT, 3 h (b) NaO*t*Bu, DMF, RT, 3 h (c) TfOH, DCE, RT, 3 h (d) Boc_2O, DMAP, DIPEA, DCM, 60°C (e) neat Ac_2O, 100°C, 24 h (for **133**) (f) benzyl-Bpin, Pd(dppf)Cl$_2$, K_2CO_3, 3:1 acetone:H_2O, MW 100°C, 300 W (g) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (h) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (i) HCl, dioxane, RT, 3 h (j) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (k) 1:1 TFA:DCM (l) BBr$_3$, DCM, 2 h, then MeOH (for **137**). See Experimentals (**8.1**) for yields.

Scheme 4.1 Synthesis of analogues containing methoxy moieties on the THQ core

4.2.2 Synthesis of substituted 2-methylindanyl analogues

For the synthesis of the 2-methylindanyl analogues the pendant moiety is incorporated in the first step through an aldol condensation between a substituted 1-indanone and *p*-nitrobenzaldeyde to yield **138-140** which were hydrogenated to yield the anilines **141-143**. The amines in **141-143** were acylated with 3-bromopropionyl chloride to give **144-146**, cyclized to form lactams **147-149**, and then treated with TfOH to promote a Fries-Rearrangement and yield **150-152**. Intermediates **150-152** were boc-protected forming intermediates 153-155. Additionally, **152** was *N*-acetylated using Ac$_2$O to form **156**. Intermediates **153-156** were treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to yield imines *in situ*, which were reduced with NaBH$_4$ to form the desired *R*-stereochemistry of intermediates **157-160**. The Ellman auxiliary was cleaved using concentrated HCl, forming primary amine salts, which were then coupled to diBoc-Dmt and subsequently deprotected to yield compounds **161**, **163**, **164**, and **165**. Analogues **162** and **164** were synthesized by using BBr$_3$ (Scheme 4.2).
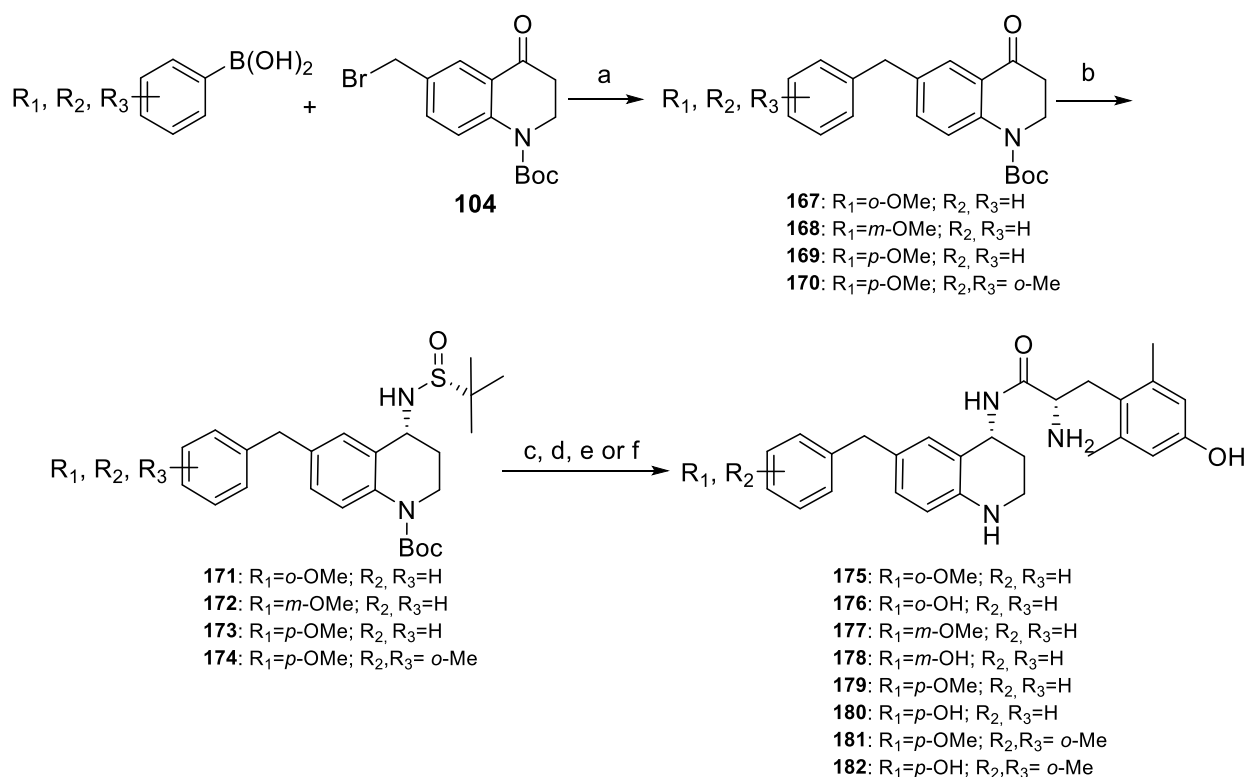
Scheme 4.2 Synthesis of substituted 2-methylindanyl compounds

(a) KOH, MeOH, RT, 1 h (b) H_2, Pd/C, 50 psi, 2-3 drops HCl, MeOH, RT, 24 h (c) 3-bromopropionyl chloride, K_2CO_3, DCM, RT, 3 h (d) NaOtBu, DMF, RT, 3 h (e) TfOH, DCE, RT, 3 h (f) Boc$_2$O, DMAP, DIPEA, DCM, 60°C (g) Ac$_2$O, reflux, 24 h (h) (R)-t-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (i) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (j) HCl, dioxane, RT, 3 h (k) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT, 6 h (l) 1:1 TFA:DCM, RT, 1 h (m) BBr$_3$, DCM, 2 h, then MeOH (for **162** and **164**). See Experimentals (**8.1**) for yields.

4.2.3 Synthesis of the substituted benzyl analogues

Synthesis of the methoxy- and hydroxyl- benzyl analogues began with a Suzuki coupling between **104** and the commercially available methoxybenzyl boronic acid to form **167-170**. Treatment of **167-170** with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ yielded imines *in situ*, which were then reduced with NaBH$_4$ to form **171-174** with the desired *R*-stereochemistry at the C4 position. The Ellman auxiliary of **171-174** was cleaved using concentrated HCl, forming the primary amine salts, which were then coupled to diBoc-Dmt and subsequently deprotected with either TFA to yield compounds **175**, **177**, **179**, and **181**, or with BBr$_3$ to yield **176**, **178**, **180**, and **182** (Scheme 4.3)

167: R$_1$=*o*-OMe; R$_2$, R$_3$=H
168: R$_1$=*m*-OMe; R$_2$, R$_3$=H
169: R$_1$=*p*-OMe; R$_2$, R$_3$=H
170: R$_1$=*p*-OMe; R$_2$,R$_3$= *o*-Me

171: R$_1$=*o*-OMe; R$_2$, R$_3$=H
172: R$_1$=*m*-OMe; R$_2$, R$_3$=H
173: R$_1$=*p*-OMe; R$_2$, R$_3$=H
174: R$_1$=*p*-OMe; R$_2$,R$_3$= *o*-Me

175: R$_1$=*o*-OMe; R$_2$, R$_3$=H
176: R$_1$=*o*-OH; R$_2$, R$_3$=H
177: R$_1$=*m*-OMe; R$_2$, R$_3$=H
178: R$_1$=*m*-OH; R$_2$, R$_3$=H
179: R$_1$=*p*-OMe; R$_2$, R$_3$=H
180: R$_1$=*p*-OH; R$_2$, R$_3$=H
181: R$_1$=*p*-OMe; R$_2$,R$_3$= *o*-Me
182: R$_1$=*p*-OH; R$_2$,R$_3$= *o*-Me

(a) R-B(OH)$_2$, Pd(dppf)Cl$_2$, K$_2$CO$_3$, 3:1 acetone:H$_2$O, MW 100°C, 300 W (b) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (c) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (c) HCl, dioxane, RT, 3 h (d) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (e) 1:1 TFA:DCM (for **175**, **177**, **179**, **181**) (f) BBr$_3$, DCM, 2 h, then MeOH (for **176, 178, 180, 182**). See Experimentals (**8.1**) for yields.

Scheme 4.3 Synthesis of the substituted benzyl analogues

4.3 Results

Peptidomimetics **134-136**, **161-166**, and **175-182** were evaluated in *in vitro* binding and efficacy assays, as previously described (Tables 4.1- 4.3). Analogues chosen for *in vivo* evaluation in the WWTW assay include **134**, **137**, **162**, and **165**. None of the analogues selected produced *in vivo* activity at 10 mg/kg; data for these compounds are not shown.
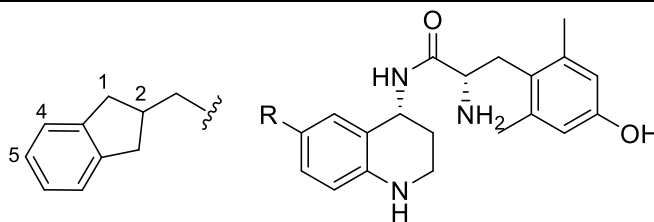
Table 4.1 Binding and Efficacy Data for Peptidomimetics with Methoxy and Hydroxyl Moieties on the THQ Core

R= OMe or OH

Cpd	R	Binding, K_i (nM)[a,c]			EC$_{50}$ (nM)[b,c]			% stimulation[b,c]		
		MOR	DOR	KOR	MOR	DOR	KOR	MOR	DOR	KOR
1[f]	H	0.22 (0.02)	9.4 (0.8)	68 (2)	1.6 (0.3)	110 (6)	540 (70)	81 (2)	16 (2)	22 (2)
134	7-OMe	0.26 (0.09)	2.8 (0.8)	8.5[e]	8.0 (3)	110[d] (20)	dns[d]	98 (3)	45[d] (10)	dns[d]
137	7-OH	0.33 (0.1)	2.7 (0.07)	35 (10)	9.9 (4)	680[d] (360)	dns[d]	95 (4)	16 (4)	dns[d]
135	8-OMe	0.24 (0.11)	3.1 (1.0)	30[d] (10)	2.5 (0.5)	63 (10)	dns[d]	84 (1)	51 (10)	dns[d]
136	8-OMe; *N*-acetyl	0.14 (0.01)	2.2 (1.2)	45 (17)	0.78 (0.20)	4.6 (2)	>1400	96 (10)	45 (4)	16 (6)

[a]Binding affinities (K_i (nM)) were obtained by competitive displacement of radiolabeled [³H]diprenorphine in membrane preparations. [b]Efficacy data were obtained using agonist induced stimulation of [³⁵S]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 S.E.M. in parentheses for n=3 independent assays in duplicate, unless otherwise noted. [d]n=2 independent assays in duplicate. dns: does not stimulate. [e]n=1 independent assay in duplicate. [f]published in ref. 21

Table 4.2 Binding and Efficacy Data for Peptidomimetics with Methoxy and Hydroxyl Moieties on the 2-Methylindanyl Pendant
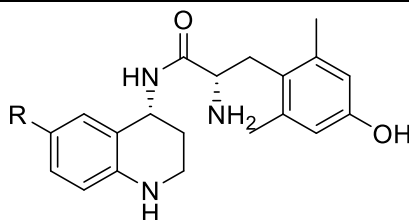

Cpd	R	Binding, K_i (nM)[a,c]			EC$_{50}$ (nM)[b,c]			% stimulation[b,c]		
		MOR	DOR	KOR	MOR	DOR	KOR	MOR	DOR	KOR
9[f]		0.16 (0.04)	4.1 (2)	1.2 (0.4)	0.24 (0.03)	dns	dns	86 (1)	dns	38 (2)
161		0.09 (0.0)	4.1 (2)	670[e]	1.4[e]	dns[d]	dns[d]	33[e]	dns[d]	dns[d]
162		0.18 (0.03)	6.0 (1)	16 (10)	5.0 (1)	dns[d]	26[d] (6)	69 (6)	dns[d]	94[d] (4)
163		0.26 (0.2)	6.2 (2)	830[e]	350[e]	dns[e]	nyt	11[e]	dns[e]	nyt
164		0.73[d] (0.0)	20[d] (4)	290[d] (200)	dns	dns[e]	nyt	dns	dns[e]	nyt
165		0.43 (0.2)	9.5 (3)	27 (19)	3.2 (1)	dns[d]	45[d] (20)	92 (8)	dns[d]	19[d] (0.2)
166		0.03 (0.1)	1.0 (0.37)	11 (8)	2.1 (2)	dns[e]	dns[d]	75 (9)	dns[e]	dns[d]

[a]Binding affinities (K_i (nM)) were obtained by competitive displacement of radiolabeled [3H]diprenorphine in membrane preparations. [b]Efficacy data were obtained using agonist induced stimulation of [35S]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 S.E.M. in parentheses for n=3 independent assays in duplicate, unless otherwise noted. [d]n=2 independent assays in duplicate. [e]n=1 independent assay in duplicate. dns: does not stimulate. nyt:not yet tested. [f]published in ref. 21.

Table 4.3 Binding and Efficacy Data for Peptidomimetics with Methoxy and Hydroxyl Moieties on the Benzyl Pendant

Cpd	R	Binding, K_i (nM)[a,c]			EC_{50} (nM)[b,c]			% stimulation[b,c]		
		MOR	DOR	KOR	MOR	DOR	KOR	MOR	DOR	KOR
1[f]	(benzyl)	0.22 (0.02)	9.4 (0.8)	68 (2)	1.6 (0.3)	110 (6)	540 (70)	81 (2)	16 (2)	22 (2)
175		0.34 (0.08)	6.5 (2)	56[d] (20)	9 (2)	>1000[e]	>1500[d]	91 (7)	18[e]	10[d] (1)
176		0.26 (0.04)	5.6 (2)	5.5[d] (2)	9.8 (4)	>1500[e]	280[d] (7)	89 (3)	23[e]	64[d] (2)
177		0.24 (0.10)	5.4 (1)	48[d] (20)	4.4 (0.6)	>2700[e]	dns[d]	99 (2)	35[e]	dns[d]
178		0.19 (0.02)	1.40 (0.17)	16[d] (4)	4.8 (0.4)	380[d] (200)	280[d] (60)	96 (5)	72[d] (6)	17[d] (2)
179		0.41 (0.14)	16[d] (0.4)	130[d] (50)	10[d] (3)	dns[e]	dns[e]	54[d] (4)	dns[e]	dns[e]
180		1.0[e]	170[e]	740[e]	dns[d]	dns[e]	dns[e]	dns[d]	dns[e]	dns[e]
181		1.6[d] (0.3)	38[e]	210[e]	dns[d]	dns[e]	dns[e]	dns[d]	dns[e]	dns[e]
182		1.5[d] (0.1)	90[e]	110[e]	dns[d]	dns[e]	dns[e]	dns[d]	dns[e]	dns[e]

[a]Binding affinities (K_i (nM)) were obtained by competitive displacement of radiolabeled [³H]diprenorphine in membrane preparations. [b]Efficacy data were obtained using agonist induced stimulation of [³⁵S]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 S.E.M. in parentheses for n=3 independent assays in duplicate, unless otherwise noted. [d]n=2 independent assays in duplicate. [e]n=1 independent assay in duplicate. dns: does not stimulate. [f]published in ref. 21.

4.4 Discussion

Of the three subsets of analogues, the methoxy and hydroxyl substitutions on the THQ core appeared to affect the affinity and efficacy the least across all three opioid receptors when compared to **1**. Even in going from the 7-methoxy (**134**) to 7-hydroxyl analogue (**137**), when a hydrogen bond donor was introduced, the binding and affinity data are very similar (Table 4.1). The only minor trend seen was the slight increase in DOR stimulation with the addition of the oxygenated substituent at both C7 and C8, with the methoxy-containing analogues **134-136** increasing stimulation more than the hydroxyl-containing analogue **137** (Table 4.1). As indicated in the previous chapter, the high DOR potency of **136** can be attributed to the *N*-acetyl substitution. Since substitutions in these positions did not greatly affect the binding affinity at MOR and DOR relative to **1**, substitutions at either C7 or C8 could serve as an ideal means to incorporate smaller R-groups with the intention of increasing bioavailability through blocking a site of metabolism or altering the hydrophilic and hydrophobic balance to help analogues penetrate the BBB.

In the 2-methylindanyl subset, none of the analogues **161-166** significantly altered MOR and DOR binding affinity relative to **9**, but most of the substituted 2-methylindanyl compounds significantly decreased affinity at KOR (Table 4.2), again relative to **9**. However, an even more striking effect seen with the substituted 2-methylindanyl series was the reduction or elimination of efficacy at MOR seen with most of the methoxy- and hydroxyl-containing analogues. When compared to **9**, **161** decreased efficacy at MOR 3-fold (from 86% to 33%) while **162** (the hydroxyl analogue of **161**) recovered most of the efficacy lost by **161** with 70% stimulation at MOR. Additionally, analogues **163** and **164** completely eliminate MOR efficacy, creating a high affinity antagonist profile at MOR.

The methoxy- and hydroxyl- substituted benzyl subset offers quite a bit of insight into the electronic limitations and requirements in the pendant binding region of the receptors. First and foremost, binding affinities at MOR and DOR for **175-178** remain unchained with the addition of a methoxy or hydroxyl moiety relative to **1** (Table 4.3). Binding affinity at KOR increased for both **176** with the *o*-OH (5.5 nM) and **178** with the *m*-OH (16.40 nM) relative to **1** (68 nM) and their corresponding methoxy analogues, **175** (56 nM) and **177** (48 nM), respectively. This observation implicates the importance of a hydrogen bond donor, rather than an acceptor, in this area of the binding pocket of KOR. Compounds **175** and **176** with ortho- substituents maintained

a similar low efficacy profile at DOR when compared to **1** (16%), while an increase in DOR stimulation was seen with **177** (35%) and **178** (72%), both with meta-substituents. Although **175-178** produced varying levels of agonist activity at DOR, these analogues had low potency at DOR as indicated by the high EC_{50} values. In addition, both **176** and **178** displayed an increase in agonist activity at KOR, compared to their methoxy counterparts, with **176** producing 64% stimulation at KOR, implicating the role of a hydrogen bond donor in KOR efficacy. Analogues **179-182** all contain a *p*-substituent, which appeared to be the primary factor in the noteworthy decrease in binding affinity across all three receptors relative to **1** (Table 4.3). Additionally, the incorporation of a *p*-substituent completely abolishes efficacy at MOR, DOR, and KOR, with the exception of **179** which maintains 54% stimulation at MOR. This observation with the *p*-methoxy and *p*-hydroxyl analogues aligns with the results from the 2-methylindanyl subset where a 4-methoxy moiety on the 2-methylindanyl pendant significantly decreases MOR efficacy while the 5-methoxy and 5-hydroxyl moieties completely eliminate MOR efficacy (Table 4.2). Another interesting observation is that both **162** and **176** display relatively high binding affinity and efficacy at KOR when compared to **1**, most likely due to the fact that the hydroxyl moiety on both of these analogues occupies the same area of the KOR receptor.

Overall, this SAR campaign showed that small modifications on the THQ core are tolerated indicating that substitutions at these locations (C7 and C8) could be used as a strategy to incorporate small moieties to subtly increase bioavailability or BBB penetration. Additionally, hydroxyl and methoxy substituents that extend deep into the pendant binding pocket (like the 5-substituted 2-methylindanyl and *p*-substituted benzyl series) are not well tolerated in that they either decrease binding affinity or efficacy at MOR or decrease both. Lastly, KOR affinity is increased with hydroxyl moieties for the *o*- and *m*- hydroxyl substituted analogues as well as the 4-substituted 2-methylindanyl analogue, while the *m*-hydroxyl significantly increases KOR efficacy.

CHAPTER 5

Effects of Stereochemistry on Binding Affinity and Efficacy

5.1 Introduction

It is understood that because nearly all of the opioid receptor ligands from the endogenous peptides to the small-molecule peptides to the morphine-like analogues incorporate specific stereocenters at multiple locations, that stereochemistry plays an important role on binding and efficacy. In fact, multiple reports have shown that switching from an L- to D- amino acid in an opioid peptide ligand can drastically alter the binding affinity profiles.[47-49] For this reason, incorporation of a stereocenter on the aliphatic carbons on the THQ and THN cores was pursued to probe the effects that stereochemistry has on the binding and efficacy of the peptiomimetic ligands (Figure 5.1).

Figure 5.1 Structures of the peptidomimetics containing various stereo-specific moieties

5.2 Design and Synthesis

First and foremost, it should be noted that when numbering a THQ core, the nitrogen atom is designated as atom one (N1) (Figure 5.1), Conversely, in the conventional numbering system for a THN core, the carbon atom taking place of N1 is not technically deemed carbon 1 (C1). However, for consistency and clarity, the substituted THN analogues discussed are described as having "C1"-substitutions (Figure 5.1).

The synthesis of **191** (with the 2R-methyl) was the only synthesis that was completed asymmetrically (Scheme 5.1) and was designed to probe a specific amino acid difference across MOR, DOR and KOR (Figure 5.2). The intention was to design a ligand with methyl at the C2 position that could favorably interact with Trp[284] of DOR and potentially with the aliphatic portion of Lys[303] in MOR, while either not interacting much with Glu[297] of KOR or interacting in such a way that further reduced binding affinity at KOR. The 2R-methyl was chosen instead of the *S*-methyl for this particular analogue because it was hypothesized that the downward-pointing *S*-methyl would be too far away from the specific residues that were being probed.

66
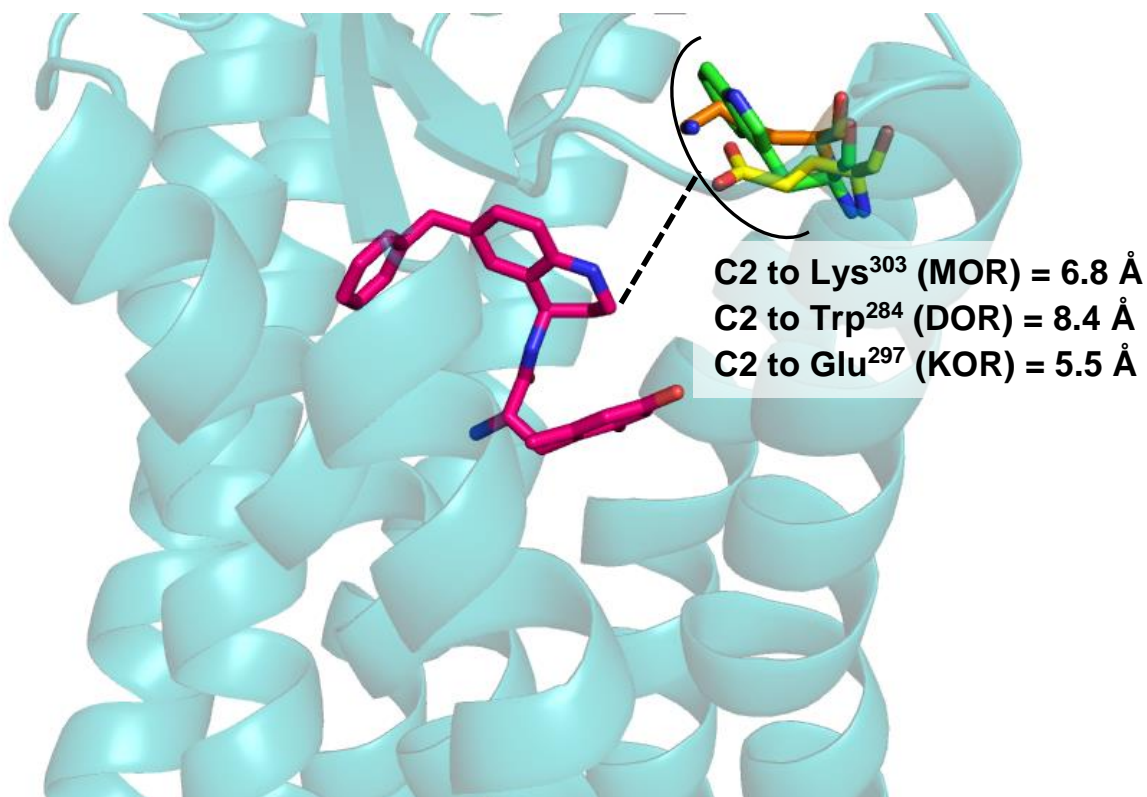
Figure 5.2 Compound **1** docked in MOR with an overlay of non-conserved residues among MOR, DOR, and KOR

The other analogues in this series were not designed to exploit specific amino acid residue differences among the three receptors. Instead, they were synthesized with the intention of probing whether the stereochemistry at these locations on the ligand produced any significant changes in the affinity and efficacy profiles across MOR, DOR, and KOR.

Although the syntheses of the remaining compounds in the series were not completed asymmetrically, diastereomers were separated at a late stage intermediate. Furthermore, the amine intermediate **199** (Scheme 5.2.2) in the synthesis of the 3(*R/S*)-methyl compounds, was crystallized to and submitted for X-ray crystallography to determine the stereochemistry of the methyl at C3 to be *R*. Lastly, the stereochemistry of the "C1"-methyl analogues remains unknown, however the final diastereomeric mixture was separable by HPLC.

5.2.1 Synthesis of the 2R-methyl THQ analogue

The synthesis of **191**, began with chemistry developed by the Davies group[50] the incorporation of a chiral auxiliary in the second step, which will set the *R*-stereochemistry for the 2*R*-methyl (Scheme 5.1). In the first step, *p*-methoxyphenol was deprotonated in the presence of base followed by the addition of the acid chloride to form **183**. Additionally, benzyne was formed *in situ* from the silylaryl triflate which then undergoes nucleophilic attack by an aryl amine to form **184**. Deprotonation of *N*-substituted aniline intermediate using n-Butyllithium led to the formation of the lithium amide which was added to compound **184** to form **185**. Saponification of **185** leads to the carboxylic acid intermediate which is immediately cyclized with polyphosphoric acid (PPA) to form **186**. Treatment of **186** with NBS selectively brominates in the 6 position to form **187**, which is then Boc protected forming **188**, and coupled to the benzyl boronic pinacol ester to form **189**. Treatment of **189** with (*R*)-*t*-butanesulfinamide and $Ti(OEt)_4$ yields an imine *in situ*, which is then reduced with $NaBH_4$ to form the desired *R*-stereochemistry at position 4 of intermediate **190**.[32-34] The Ellman auxiliary of **190** is cleaved using concentrated HCl, forming the primary amine salt, which is then coupled to diBoc-Dmt and subsequently deprotected to yield compound **191**, with *R*-stereochemistry at both C2 and C4.
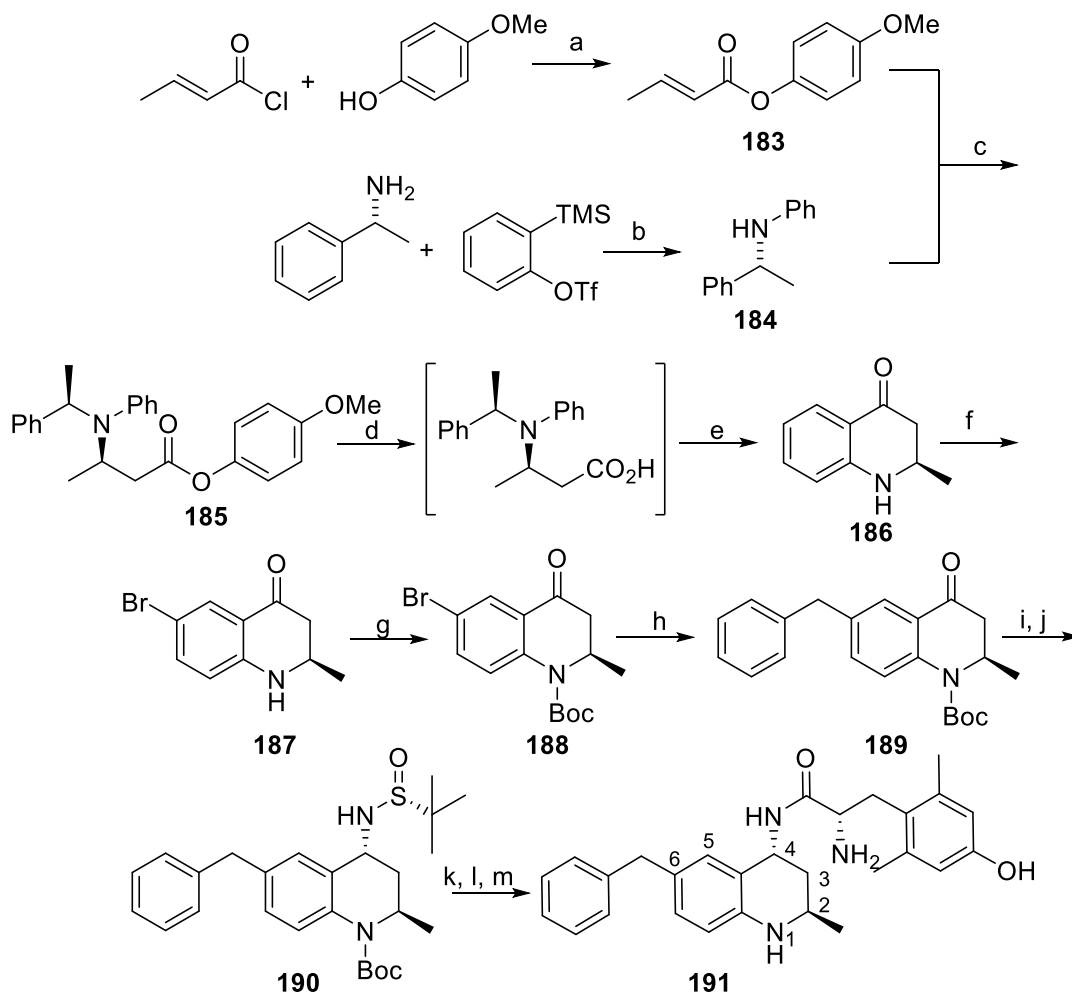
(a) Et$_3$N, DCM, RT, 16 h (b) CsF, CH$_3$CN, 60°C, 16 h (c) n-BuLi, THF, -78°C, 2.5 h (d) LiOH, 1:1 THF:H$_2$O (e) PPA, 100°C (f) NBS, DCM, 1.5 h, RT (g) Boc$_2$O, DMAP, DIPEA, DCM, 60°C (h) benzyl-Bpin, Pd(dppf)Cl$_2$, K$_2$CO$_3$, 3:1 acetone:H$_2$O, MW 100°C, 300 W (i) (R)-t-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (j) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (k) HCl, dioxane, RT, 3 h (l) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (m) 1:1 TFA:DCM. See Experimentals (**8.1**) for yields.

Scheme 5.1 Synthesis of the 2R-methyl, "C2-methyl" THQ analogue

5.2.2 Synthesis of the 3R- and 3S-methyl THQ analogues

The synthesis of **201** and **202** began with an S$_N$2 reaction between aniline and methyl (R)-3-bromo-2-methylpropanoate to form **192**, which was saponified and cyclized to form racemized **193**. Intermediate **193** was brominated, boc-protected, then coupled to benzyl boronic pinacol ester to form **196**. Treatment of **196** with (R)-t-butanesulfinamide and Ti(OEt)$_4$ yielded an imine *in situ*, which was then reduced with NaBH$_4$ to form the desired *R*-stereochemistry at the C4

position. The introduction of the chiral Ellman moiety produced a set of diastereomers which were separable via flash column chromatography, thus forming **197** and **198**. The Ellman auxiliary of **197** and **198** was cleaved using concentrated HCl, forming the primary amine salts **199** and **200**, which were then coupled to diBoc-Dmt and subsequently deprotected to yield compounds **201** and **202**.
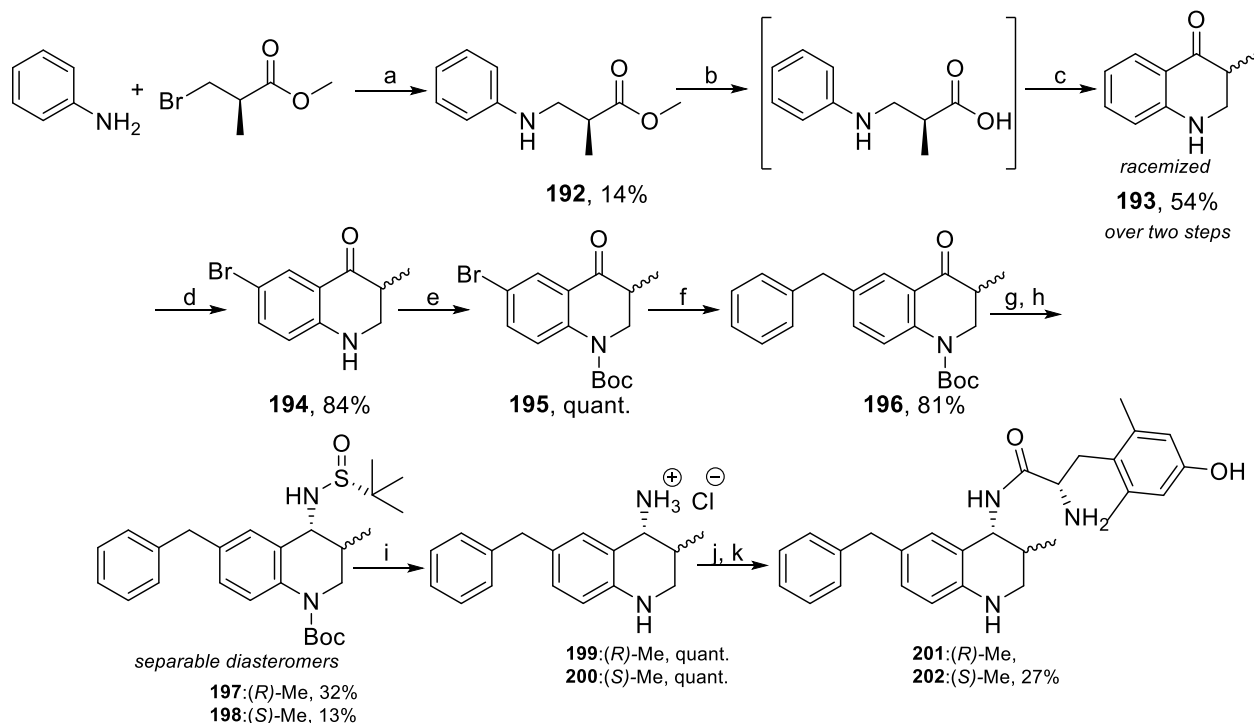
(a) K_2CO_3, DMF, 70°C, 12 h (b) LiOH, 1:1 THF:H_2O, 40°C, 2 h (c) PPA, 110°C, 3-4 h (d) NBS, DCM, 1.5 h, RT (e) Boc_2O, DMAP, DIPEA, DCM, 60°C (f) benzyl-Bpin, Pd(dppf)Cl_2, K_2CO_3, 3:1 acetone:H_2O, MW 100°C, 300 W (g) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (h) $NaBH_4$, THF, -50°C to RT, 3 h, then MeOH, RT (i) HCl, dioxane, RT, 3 h (j) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (k) 1:1 TFA:DCM. See Experimentals (**8.1**) for yields.

Scheme 5.2 Synthesis of the 3*R/S*-methyl THQ analogues

5.2.3 Synthesis of the "C1"-methyl THN analogues

The syntheses for the three "C1"-substituted analogues begins with a Friedel crafts acylation reaction between benzene and a racemic mixture of valerolactone **203**, which was then brominated forming **204**. Next, Suzuki coupling with the benzyl pinacol boronic ester yielded **205**, which was treated with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ to yield an imine *in situ*, which was reduced with $NaBH_4$ to form the desired *R*-stereochemistry of intermediates **206**. The introduction of a new chiral moiety produced a set of diastereomers for intermediate **206**.

However, these diastereomers were inseparable via flash column chromatography and also via semi-preparative HPLC; Thus, **206** was carried forward as a mixture of diastereomers. The Ellman auxiliary on **206** was cleaved using concentrated HCl, forming primary amine salts, which were then coupled to diBoc-Dmt and subsequently deprotected to yield compounds **207** and **208**. The previously inseparable diastereomeric mixture (diastereomers of **217**) was separable by semi-preparative HPLC at this final stage yielding **219** and **220**, however the stereochemistry remains unknown.
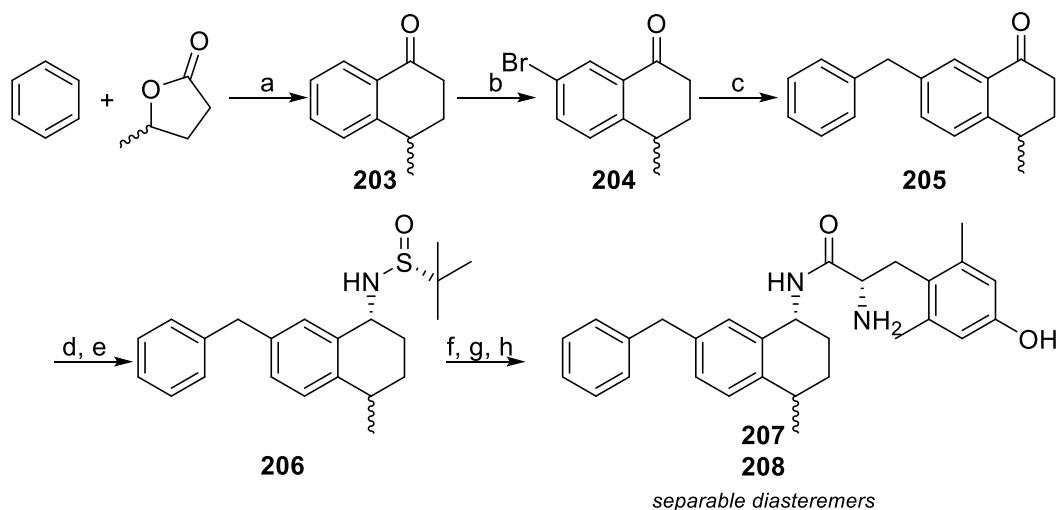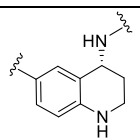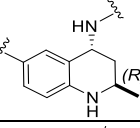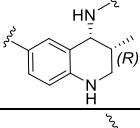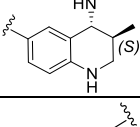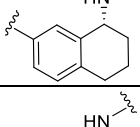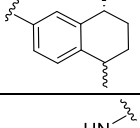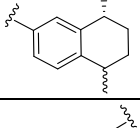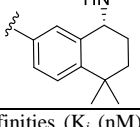
(a) benzene, valerolactone, reflux (b) NBS, H_2SO_4 (c) benzyl-Bpin, Pd(dppf)Cl$_2$, K$_2$CO$_3$, 3:1 acetone:H$_2$O, MW 100°C, 300 W (d) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (e) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (f) HCl, dioxane, RT, 3 h (g) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (h) 1:1 TFA:DCM. See Experimentals (**8.1**) for yields.

Scheme 5.3 Synthesis of "C1"-methyl THN analogues

5.3 Results

Peptidomimetics **191**, **201**, **202**, **207**, and **208** were evaluated in *in vitro* binding and efficacy assays, as described in **8.2**. Analogues chosen for *in vivo* evaluation in the WWTW assay, as described in **8.3**, include **201** and **208**. Neither analogue produced *in vivo* activity at 10 mg/kg.; data for these compounds are not shown.

Table 5.1 Binding and Efficacy Data for Peptidomimetics with Chiral Moieties

Cpd	Core	Binding, K_i (nM)[a,c]			EC_{50} (nM)[b,c]			% stimulation[b,c]		
		MOR	DOR	KOR	MOR	DOR	KOR	MOR	DOR	KOR
1[f]		0.16 (0.04)	4.1 (2)	1.2 (0.4)	0.24 (0.03)	dns	dns	86 (1)	dns	38 (2)
191		1.24 (0.50)	87[d] (60)	240[d] (20)	8.9 (4)	630 (90)	>4000	88 (2)	45 (8)	29 (10)
201		0.75 (0.03)	2.0 (0.2)	13 (5)	6.0 (1)	15 (8)	750 (280)	75 (13)	16 (3)	27 (4)
202		270[e]	390[e]	130[d] (20)	550[e]	dns[e]	dns[e]	44[e]	dns[e]	dns[e]
68		0.045 (0.03)	4.0 (1)	19 (7)	2.9 (0.6)	dns	Dns	64 (9)	dns	dns
207		0.08 (0.02)	5.9 (0.6)	nyt	16 (2)	dns	>1300[e]	72 (4)	dns	60[e]
208		0.32 (0.10)	16 (5)	nyt	dns[d]	110 (80)	>3100[e]	dns[d]	14 (4)	62[e]
209[g]		0.36 (0.08)	6.5 (0.7)	nyt	16 (5)	>1000	>1700[d]	75 (4)	16 (3)	75[d] (3)

[a]Binding affinities (K_i (nM)) were obtained by competitive displacement of radiolabeled [³H]diprenorphine in membrane preparations. [b]Efficacy data were obtained using agonist induced stimulation of [³⁵S]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 S.E.M. in parentheses for n=3 independent assays in duplicate, unless otherwise noted. [d]n=2 independent assays in duplicate. [e]n=1 independent assay in duplicate. dns: does not stimulate. nyt: not yet tested. [f]published in ref. 21.[g]Synthesized by Tony Nastase

5.4 Discussion

As can be seen by the data, stereochemistry at positions 1, 2, and 3 on the THQ or THN core appear to significantly affect the binding and efficacy of the peptidomimetics. As mentioned, it was reasoned that the upward-pointing *R*-methyl at the C2 (referred to as 2*R*-methyl from this point forward) position could favorably interact with Trp[284] of DOR and potentially with the aliphatic portion of Lys[303] in MOR, while either not interacting much with Glu[297] of KOR or interacting in such a way that KOR further reduce binding affinity at KOR. However, as the data suggests (Table 5.1), the 2*R*-methyl moiety (**191**) decreased affinity across all three receptors relative to **1**. This decrease in affinity could be due to a conformational change in the aliphatic portion of the THQ ring induced by the 2*R*-methyl that causes clashing between the ligand and the receptors. In other words, the 2*R*-methyl is essentially too close to the residues to form any favorable interactions and instead forces the ligand to shift within the receptors, thereby disrupting the binding system and decreasing affinity. While synthesis of the 2*S*-methyl analogue has not yet been completed, this analogue will help determine if small substitutions are tolerated at the C2 position, and if tolerated, which stereochemistry, if any, yields tighter binding.

When comparing compounds **201** (3*R*-methyl) and **202** (3*S*-methyl) with each other, **201** displays a significantly better binding affinity profile (Ki = 0.75 nM at MOR, 2.0 nM at DOR, 13 nM at KOR) than **202** (Ki = 270 nM at MOR, 390 nM at DOR, 130 nM at KOR). Additionally, **202** reduces MOR efficacy to 44%, whereas MOR efficacy for **201** remains high at 75%. The most reasonable explanation for these stark differences is steric clashing between the 3*S*-methyl and residues in MOR, DOR, and KOR. Figure 5.3 shows a representation of potential steric clashing that could occur between all three ORs and the C3 methyls of both **201** and **202**, where the spheres represent the spatial volume of the moieties that might sterically clash. As can be seen, the volume sphere of upward-pointing 3*S*-methyl of **202** overlaps more with residues in MOR, DOR, and KOR than the downward-pointing 3*R*-methyl of **201**, suggesting the higher probability of the 3*S*-methyl to clash with receptor residues thus resulting in weaker binding. Additionally, **201** and **1** have similar binding profiles at MOR and DOR, indicating that smaller substituents at the C3 position with the downward-pointing, *R*-stereochemistry can be accommodated in these receptors. Furthermore, compound **201** showed 10-fold lower binding

affinity than **1** at KOR, improving upon the high affinity MOR and DOR binding profile desired for MOR agonist/DOR antagonist ligands.
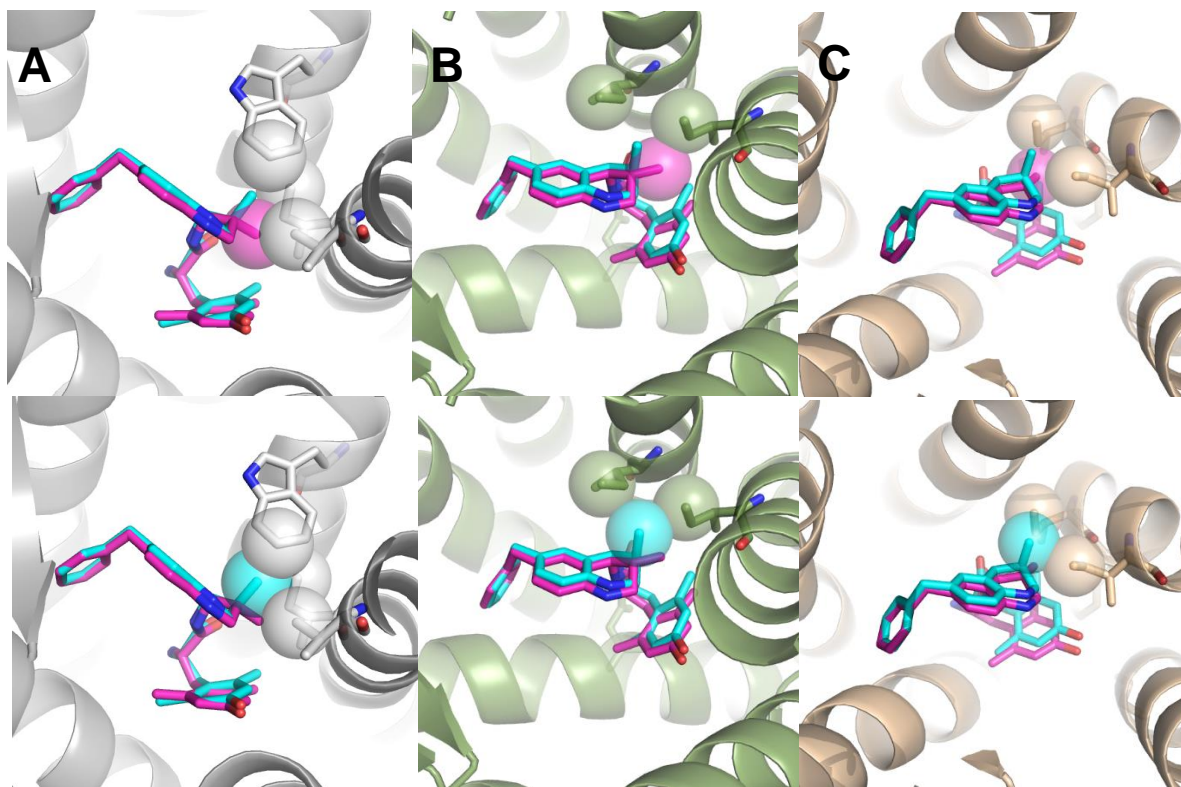

Figure 5.3 Overlay of **201** and **202** in MOR, DOR, and KOR. **A.** MOR (grey), **B.** DOR (green) **C.** KOR (tan). **201** is magenta and **202** is cyan in A-C.

Compounds **207-209** represent an interesting subset of analogues. The binding affinities for **207-209** at MOR and DOR are similar to each other and to **1**, indicating that a methyl or gem-dimethyl substituent at the "C1" position is tolerated in these binding pockets. The most remarkable difference seen was that **207** is a full agonist at MOR while **208** was an antagonist at MOR. Meanwhile, **209** with the gem-dimethyl moiety maintained MOR efficacy. These data have two implications (1) the stereochemistry at "C1" of the mono methyl compounds **207** and **208** plays a significant role in maintaining MOR efficacy, (2) the gem-dimethyl moiety must adjust the conformation of the ligand in the receptor in such a way the MOR efficacy can be maintained, despite the presence of both an "*R*-methyl" and an "*S*-methyl" component in the gem-dimethyl moiety. Computational modeling of the "C1"*S*-methyl (methyl group pointing downward), the "C1"*R*-methyl (methyl group pointing upward), and the gem-dimethyl compound was completed. To create the images in Figure 5.4, residues within a 5 Å radius of the

methyl moiety were first selected, then distances between the residues and the methyl moieties were measured. For both compounds, the distance between the methyl moiety and Lys[303] had the shortest measurement ranging between 2.2 Å for the "C1"R-methyl (Figure 5.4, Panel A) and 3.2 Å for the "C1"S-methyl (Figure 5.4, Panel B). As the modeling depicts, the S-methyl group appears to point down and inward, thereby potentially avoiding interaction with Lys[303] in MOR in both the active and inactive conformations as indicated by the lack of overlap of the spatial volume spheres. In contrast, the R-methyl group points upward and might interact with Lys[303] in MOR, helping to secure the receptor in the inactive conformation, aiding in the elimination of MOR efficacy. As for compound **209** with the gem-dimethyl moiety, the modeling does not provide enough insight into how or why this compound retains MOR efficacy, as it appears to interact with the Lys[303] residue (Figure 5.4 C). However, one potential hypothesis for the retained efficacy at MOR for **209** is that the potency of the MOR agonist activity of **207** is high enough to overcome the MOR antagonist activity of **208**. Specifically, the presence of the upward pointing methyl in the gem-dimethyl moiety is sufficient to produce agonist activity at MOR despite the presence of a moiety that produces MOR antagonist activity.
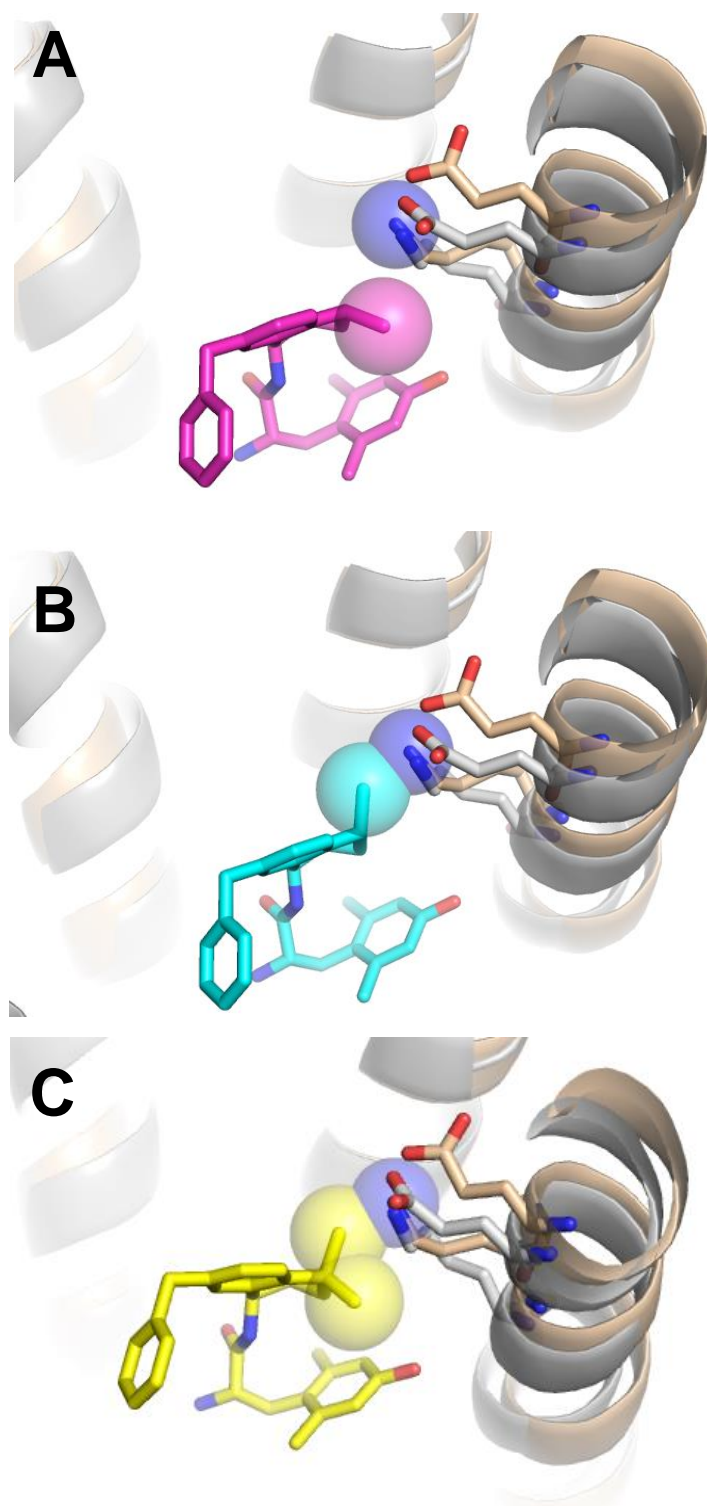
Figure 5.4 Overlay of MOR in the active (MORa) and inactive (MORi) confirmations with **207**, **208**, **209** docked. **A.** MORa (grey) and MORi, tan) with the "C1"*S*-methyl ligand (magenta), **B.** the "C1"*R*-methyl ligand (cyan, **B**), and **C. 220** (yellow). Spheres represent spatial volume of methyl moieties and the amine moiety of Lys[303] in MOR.

In conclusion, stereochemistry of methyl groups around the THQ and THN role play a significant role in binding affinity and efficacy at all three opioid receptors. Based on the *in vitro* data from this study and the computational modeling, it seems that "downward-pointing" stereochemistry appears to be tolerated more so than "upward-pointing" stereochemistry. However, to confirm this hypothesis the 2*S*-methyl analogue must be synthesized and the stereochemistry of the "C1" methyl analogues must be confirmed.

CHAPTER 6

Integrating fluorine to increase bioavailability

6.1 Introduction

Although fluorine is a small atom with a van der Waals radius of 1.47 Å, which is only marginally larger than that of hydrogen (1.2 Å), the high electronegativity (3.98 on the Pauling electronegativity scale) creates a highly polarized C-F bond.[51] When designing analogues, these particular properties of fluorine can be exploited in order to design analogues where a hydrogen atom is replaced by a fluorine without considerable consequences. In fact, incorporation of fluorine atoms is a common medicinal chemistry practice that often alters the physical properties of neighboring substituents such that an increase potency can be observed.[52] For example, in the case of a fluorine proximal to basic amine, the electronegativity of the fluorine can reduce the basicity of the amine ultimately resulting in better permeability and bioavailability.[53,54] Additionally, strategic introduction of fluorine atoms, especially on electron-rich aromatic rings, has been shown to block metabolic oxidation processes associated with labile hydrogen atoms.[51,54] The blocking of sites of metabolic oxidation could ultimately lead to a longer duration of action since the compound will not be metabolized and excreted as easily. In pursuit of more bioavailable molecules, a series of fluorine-containing analogues was synthesized (Figure 6.1). In each of these analogues, fluorine was introduced on either the pendant benzyl moiety or the aromatic portion of the THQ core. In particular, the 8-fluoro compounds were pursued because if shown to produce *in vivo* activity, the fluorinated THQ core could be easily modified during the synthesis to incorporate other pendants.

Figure 6.1 Fluorinated peptidomimetics

6.2 Design and Synthesis

6.2.1 Synthesis of fluorinated benzyl pendant analogues

Synthesis of the fluorinated pendant analogues began with a Suzuki coupling between **116** and the commercially available fluorinated boronic acids to form **222** and **223**. Treatment of **222** and **223** with (*R*)-*t*-butanesulfinamide and Ti(OEt)$_4$ yields imines *in situ*, which are then reduced with NaBH$_4$ to form **224** and **225** with the desired *R*-stereochemistry at the C4 position. The Ellman auxiliary of **224** and **225** was cleaved using concentrated HCl, forming the primary amine salts, which were then coupled to diBoc-Dmt and subsequently deprotected to yield compounds **226** and **227**.
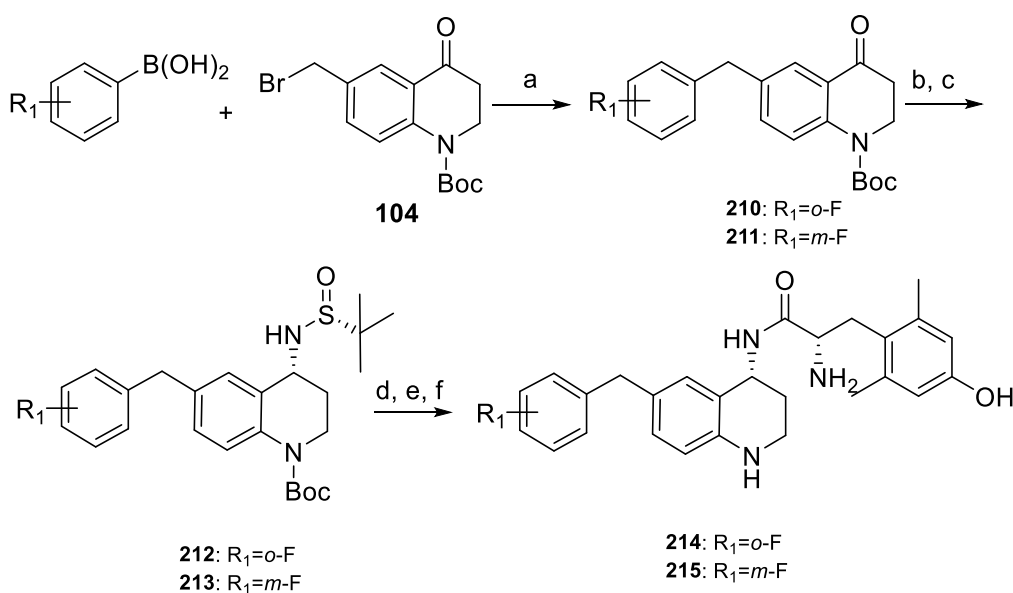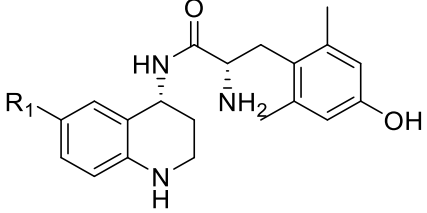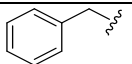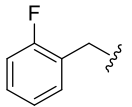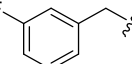

(a) R$_2$-Bpin, Pd(dppf)Cl$_2$, K$_2$CO$_3$, 3:1 acetone:H$_2$O (b) (*R*)-*t*-Butanesulfinamide, THF, Ti(OEt)$_4$, 0°C, then reflux at 75°C (c) NaBH$_4$, THF, -50°C to RT, 3 h, then MeOH, RT (d) HCl, dioxane, RT, 3 h (e) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT (f) 1:1 TFA:DCM. See Experimentals (**8.1**) for yields.

Scheme 6.1 Synthesis of fluorinated benzyl pendant analogues

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6.2.2 Synthesis of 8-fluoro THQ analogues

Synthesis of the 8-fluoro analogues began with with acylation of the aniline starting material with 3-bromoproionyl chloride to form intermediate **216**, which was subsequently cyclized in the presence of base to form the lactam intermediate **217**, which was then treated with TfOH to form the dihydroquinolinone intermediate **218**. Intermediate **218** was boc-protected forming **219**, then subjected to Suzuki coupling to form **220**. Intermediate **220** was treated with TFA to remove the boc group, then treated with Ac_2O to form **222**. Intermediates **220** and **222** were treated with (*R*)-*t*-butanesulfinamide and $Ti(OEt)_4$ to yield imines *in situ*, which were reduced with $NaBH_4$ to form the desired *R*-stereochemistry of intermediates **223** and **224**. The Ellman auxiliary was cleaved using concentrated HCl, forming primary amine salts, which were then coupled to diBoc-Dmt and subsequently deprotected to yield compounds **225** and **226** (Scheme 6.2).
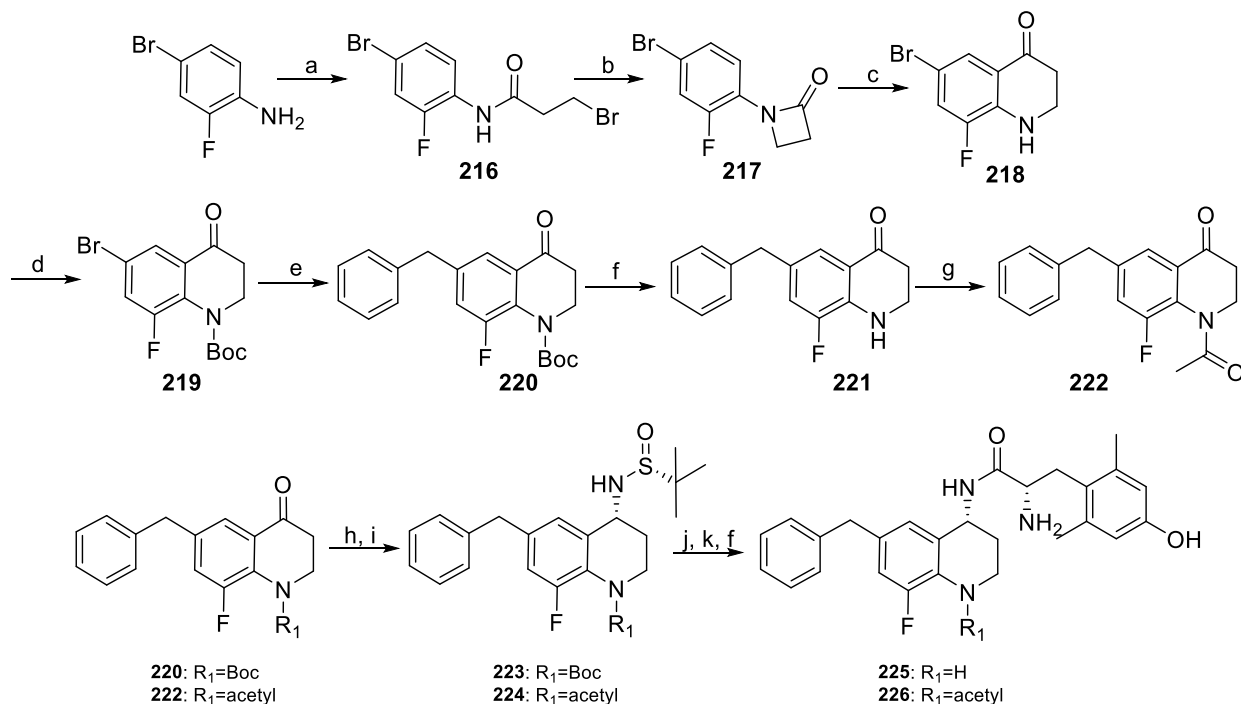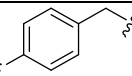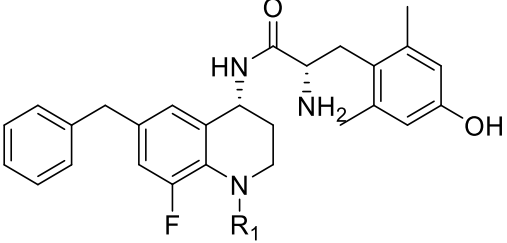
220: R₁=Boc
222: R₁=acetyl

223: R₁=Boc
**224**: R₁=acetyl

225: R₁=H
226: R₁=acetyl

(a) 3-bromopropionyl chloride, K_2CO_3, DCM, RT, 3 h (b) NaO*t*Bu, DMF, RT, 3 h (c) TfOH, DCE, RT, 3 h (d) Boc₂O, DMAP, DIPEA, DCM, 60°C (e) R₂-Bpin, Pd(dppf)Cl₂, K_2CO_3, 3:1 acetone:H_2O (f) 1:1 TFA:DCM (g) Ac₂O, reflux, 20 h (h) (*R*)-*t*-Butanesulfinamide, THF, $Ti(OEt)_4$, 0°C, then reflux at 75°C (i) $NaBH_4$, THF, -50°C to RT, 3 h, then MeOH, RT (j) HCl, dioxane, RT, 3 h (k) diBoc-Dmt, PyBOP, 6Cl-HOBt, DIPEA, DMF, RT. See Experimentals (**8.1**) for yields.

Scheme 6.2 Synthesis of 8-fluoro THQ analogues

6.3. Results

Peptidomimetics **214**, **215**, and **225-226** were evaluated in *in vitro* binding and efficacy assays, as previously described (Tables 4.1- 4.3). All analogues (**214, 215, and 225-227**) in this series were chosen for *in vivo* evaluation in the WWTW assay (Figure 6.2). Compounds **214, 215**, and **225** produced full antinociception at a 10 mg/kg dosage following *ip* administration.

Table 6.1 Binding and Efficacy Data for Peptidomimetics with Fluoro Substitutions

Cpd	R₁	Binding, Kᵢ (nM)[a,c]			EC₅₀ (nM)[b,c]			% stimulation[b,c]		
		MOR	DOR	KOR	MOR	DOR	KOR	MOR	DOR	KOR
1[f]		0.22 (0.02)	9.4 (0.8)	68 (2)	1.6 (0.3)	110 (6)	540 (70)	81 (2)	16 (2)	22 (2)
214		0.61 (0.3)	4.2[d] (2)	22 (8)	3.8[d] (0.60)	50 (20)	240[e]	75 (3)	33[d] (10)	22[e]
215		1.1 (0.5)	2.5[d] (1.2)	13 (5)	3.5[d] (0.8)	410[d] (150)	390[d] (30)	100[d] (2)	35[d] (1)	39[d] (2)
227[g]		Results pending								

Cpd	R₁	Binding, Kᵢ (nM)[a,c]			EC₅₀ (nM)[b,c]			% stimulation[b,c]		
		MOR	DOR	KOR	MOR	DOR	KOR	MOR	DOR	KOR
225	H	0.12[d] (0.01)	3.0[d] (0.5)	7.5[d] (1)	1.6 (0.20)	340[d] (200)	370[d] (8)	94 (3)	26[d] (2)	38[d] (0.2)
226		0.16[d] (0.02)	1.1[d] (0.4)	35[d] (2)	1.4 (0.2)	79[d] (10)	890[d] (70)	99 (3)	48[d] (6)	50[d] (1)

[a]Binding affinities (Kᵢ (nM)) were obtained by competitive displacement of radiolabeled [³H]diprenorphine in membrane preparations. [b]Efficacy data were obtained using agonist induced stimulation of [³⁵S]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 S.E.M. in parentheses for n=3 independent assays in duplicate, unless otherwise noted. [d]n=2 independent assays in duplicate. [e]n=1 independent assay in duplicate. dns: does not stimulate. [f]published in ref. 21. [g]Synthesized by Kate Kojiro.
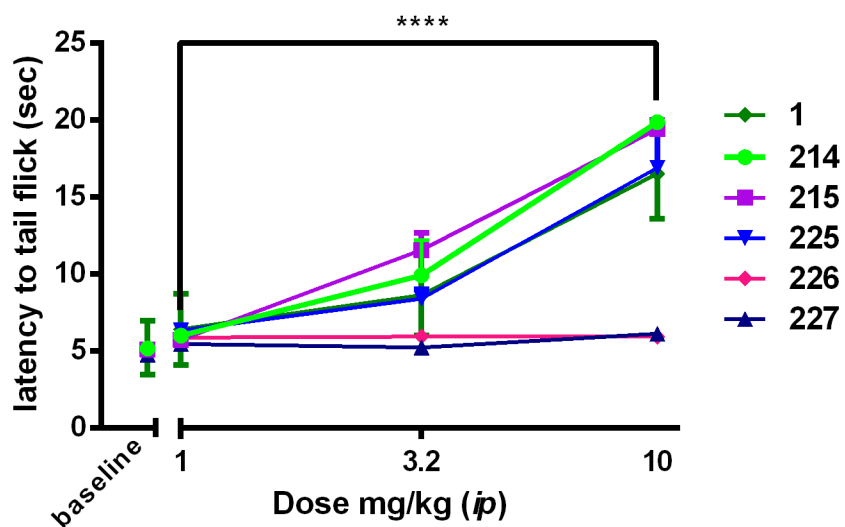
Figure 6.2 Cumulative antinociceptive dose response curves of select fluorinated analogues in the mouse WWTW assay following *ip* administration. n=3 for all analogues, plotted as average +/- S.E.M. ****, p < 0.0001 for **1**, **214**, **215**, and **225** for the 10 mg/kg dose when compared to baseline.

6.4 Discussion

As expected, the fluorinated analogues produced *in vitro* profiles similar to that of compound **1**. All analogues maintain subnanomolar binding affinity at MOR and nanomolar affinity at DOR. However, like **1** which produces 16% stimulation at DOR and 22% stimulation at KOR, all fluorinated analogues not only produce full agonism at MOR, but also varying degrees of partial agonism at DOR (26-48%) and KOR (22-50%). Preliminary *in vivo* results show that compounds with an *o*-fluoro and a *m*-fluoro produce full *in vivo* activity in the WWTW assay at the 10 mg/kg dose, whereas compound **227** with the *p*-fluoro is inactive *in vivo*. Moreover, **225** with an 8-fluoro moiety is active *in vivo*, but the *N*-acetylated version (**236**) is not. Unfortunately, the data does not indicate whether the incorporation of a fluorine atom increased the *in vivo* bioavailability because **1** was already shown to produce *in vivo* activity and the additional non-acetylated, fluorinated analogues **214**, **215**, and **225** also produced *in vivo* activity. Additionally, the *N*-acetylated version of **1** (compound **52**) produced no *in vivo* activity, and nor did **226** (the *N*-acetylated, 8-fluoro compound). Additional, *N*-acetylated analogues of **214**, **215**, and **227** (with the *o*-, *m*-, and *p*-fluoro benzyl pendants, respectively) could aid in understanding whether the addition of a fluorine atom could effectively alter the *in vivo* activity of a compound from inactive to active. Furthermore, subtle changes to the basicity of the nitrogen in the THQ core and how this basicity might play a role in bioavailability could be explored with an analogue incorporating a fluorine in the 7 position on the THQ core, especially when compared to the 8-fluoro analogue **225**. Lastly, time course studies are planned to determine if the addition of a fluorine atom in compounds **214**, **215**, and **225** increases the duration of action of the *in vivo* activity relative to **1**.

CHAPTER 7

Conclusions

7.1 Summary

When considering all the *in vitro* and *in vivo* data across the multiple series of peptidomimetics, a few general conclusions about the opioid receptor peptidomimetic pharmacophore can be made. First and foremost, *N*-acetylation of the THQ nitrogen results in an increase in DOR binding affinity, regardless of pendant moiety. This increase in affinity is likely due to an interaction between the carbonyl of the acetyl group and a tyrosine residue in one of the transmembrane helices of DOR. In contrast, DOR efficacy does appear to be somewhat dependent on the pendant moiety. For example, *N*-acetylated compounds with larger pendants (1- and 2-methylnaphtyhl and 1- and 2-methylindanyl moieties) do not produce any DOR stimulation *in vitro*, whereas *N*-acetylated compounds with smaller pendants (benzyl and methylcyclohexyl) produce partial DOR agonism *in vitro*. This implies that the pendants might play a role in orienting the ligand in the receptor such that DOR is locked in the inactive conformation with the larger pendants, resulting in loss of DOR stimulation. Furthermore, all *N*-acylated compounds bind to MOR and DOR with subnanomolar binding affinity, excluding the carboxylic acid-containing analogue, indicating that this area of the binding pocket across in both MOR and DOR is large and accommodating of several different moieties. Most *N*-acylated compounds with the benzyl pendant produce partial DOR stimulation, excluding the benzoyl analogue; however, *N*-acylated analogues with the 2-methylnaphthyl or 2-methylindanyl pendant do not produce any DOR stimulation regardless of chain length. This finding further supports the hypothesis that the larger pendants could help lock the peptidomimetic in the inactive conformation of DOR. KOR affinity and efficacy is more varied across the *N*-acylated series, especially with the analogues containing the benzyl pendant, implying that ligands exhibiting

KOR affinity and efficacy could be designed and optimized through SAR at this site of the peptidomimetic core.

Another observation is that smaller moieties, such as a methoxy and hydroxyl groups, on C7 or C8 of the THQ core do not considerably alter the binding and efficacy profiles at MOR, DOR, and KOR, relative to the parent peptidomimetic, **1**. In contrast, introduction of methoxy and hydroxyl groups onto the 2-methylindanyl and benzyl pendants significantly affects binding and efficacy profiles. Methoxy and hydroxyl moieties on the 2-methylindanyl pendant tend to significantly decrease or eliminate MOR efficacy, with the exception of compound **162**. Additionally, compounds with *o-* or *m-* methoxy or hydroxyl on the benzyl pendant still produced high MOR stimulation, but the *p*-methoxy and hydroxyl analogues eliminated all MOR efficacy, with the exception of analogue with the *p*-methoxy, **179**, which reduced MOR efficacy to 54% but did not completely eliminate it. Given the methoxy and hydroxyl data, it appears that *p*- methoxy and *p*-hydroxyl moieties on the benzyl pendant, or analogues containing a methoxy or hydroxyl in this same spatial area, are not tolerated and result in elimination of MOR efficacy.

While chiral moieties around the THQ and THN cores results in disparate binding affinities between the resulting diastereomers, chiral groups at the "C1", C2, and C3 positions are not necessary for binding and efficacy or for *in vivo* activity. However, *R*-stereochemistry at C4 is important and necessary for maintaining high affinity binding for the peptidomimetic series.

Addtionally, *in vitro* data for fluorinated peptidomimetics suggests that the integration of a fluorine atom into the peptidomimetic scaffold does not significantly alter the *in vitro* binding and efficacy profile, relative to **1**. Three of five fluorinated analogues are active *in vivo* which has promising implications. Pending the results of an additional time course assays, the fluorinated analogues could have a longer duration of action than **1** *in vivo* indicating that the fluorine atom could be reducing the basicity of the THQ amine or blocking a site of metabolism, or both.

Of all peptidomimetics synthesized, 39 were screened in the *in vivo* WWTW assay. Of those 39 analogues screened, five novel analogues were active *in vivo* (Table 7.1). All compounds active *in vivo*, excluding **54**, produce some degree of DOR agonism *in vitro*, and in the case of **237**, a relatively high affinity for KOR. Additionally, this compound set ranges in molecular weights from 430-522 with cLogP values from 3.7-4.5, implying that neither molecular weight nor cLogP are good predictors of *in vivo* activity with these peptidomimetic compounds.

Table 7.1 Summary of Data for Compounds that Produce *In Vivo* Activity

Cpd	Structure	MW	cLogP	*In Vitro* profile (Ki (nM), % stim)	*In Vivo* Profile
1		430	3.7	**MOR:** 0.22, 81% **DOR:** 9.4, 16% **KOR:** 68, 22%	Full antinociception 1 h
54		522	4.5	**MOR:** 0.04, 87% **DOR:** 0.23, dns **KOR:** 48, dns	Full antinociception >3 h no development of chronic tolerance
78		488	3.8	**MOR:** 0.19, 95% **DOR:** 0.51, 40% **KOR:** 29, 29%	Full antinociception
214		448	3.9	**MOR:** 0.61, 75% **DOR:** 4.2, 33% **KOR:** 22, 22%	Full antinociception
215		448	3.9	**MOR:** 1.1, 100% **DOR:** 2.5, 35% **KOR:** 13, 39%	Full antinociception
225		448	4.2	**MOR:** 0.12, 95% **DOR:** 3.0, 26% **KOR:** 7.5, 38%	Full antinociception
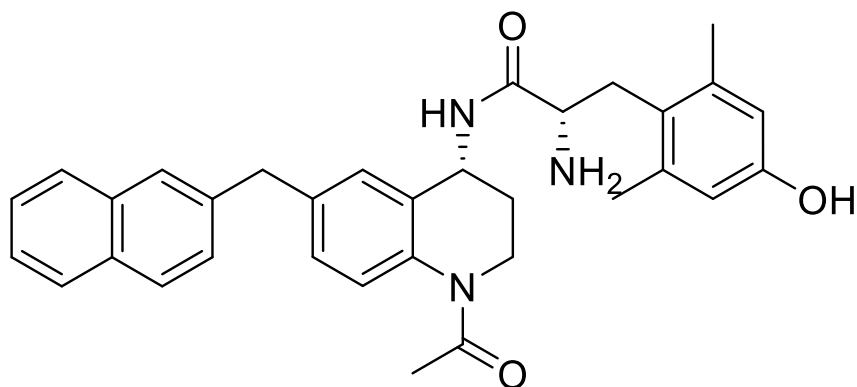
Figure 7.2 Structure of **54**

Finally, out of the set of active compounds, **54** has nearly balanced MOR and DOR affinities (K_i = 0.04 nM and 0.23 nM, respectively, resulting in a 6-fold preference for MOR over DOR), 200-fold selectivity for MOR and DOR over KOR, and superior *in vitro* MOR agonist/DOR antagonist profile as it is the only compound that does not produce any DOR stimulation and in fact acts as an antagonist at DOR when screened against DPDPE. Furthermore, **54** has an *in vivo* duration of action for over 3 h following *ip* administration of a 10 mg/kg dosage, which is similar duration of action to that of morphine at the same dosage. However, unlike morphine, **54** does not produce tolerance upon chronic administration. With this profile, **54** represents a promising lead candidate for the design of bioavailable mixed-efficacy MOR agonist/DOR antagonist ligands that provide the desired analgesic effects but with a reduced risk of producing tolerance and dependence.

7.2 Future directions

The *in vitro* and *in vivo* data for this complete set of peptidomimetics opens several avenues for future directions. First, synthesis of the 2*S*-methyl THQ analogue should be completed in addition to determining the stereochemistry of analogues **207** and **208** (Figure 7.1, Panel A). *In vitro* results from the 2*S*-methyl will elucidate which stereochemistry, if any, is preferred at the C2 position. Additionally, determining the stereochemistry of the "C1"-methyl compounds will provide additional insight into which stereochemistry results in MOR agonist activity. Based on the *in vitro* data and computational modeling of the incomplete chiral-methyl containing series of peptidomimetics, it could be reasoned, that all stereochemistry that results in a "downward-pointing" methyl group would be better tolerated in the receptors relative to the "upward-pointing" counterpart.

Results from the fluorinated compounds are interesting, but this set of compounds is also incomplete. Synthesis of the *N*-acetylated versions of **214**, **215**, and **227** (Figure 7.1, Panel B) should be completed in order to determine whether *in vivo* activity can be conferred from a peptidomimetic that is inactive *in vivo,* like **52**, to a compound that is active *in vivo*. Moreover, synthesis of the both the THQ and *N*-acetylated THQ analogues with a 7-fluoro could provide additional insight into the effects that fluorine has on basicity, metabolism, and overall bioavailability (Figure 7.1, Panel C).

In addition, *in vivo* studies to test for the development of dependence with chronic administration of **54** are planned. Also, time course assays to determine the duration of action for compounds **214**, **215**, and **225** are planned. If the results from these time course assays are promising, in that they increase the duration of action relative to **1**, then assays to determine whether tolerance and dependence develop after chronic administration will be completed. Furthermore, if **225** or either of the proposed 7-fluoro analogues (Figure 7.1, Panel C) produce antinociception for a longer duration of action than **1**, than additional analogues incorporating the 7- and 8-fluoro THQ core will be synthesized (Figure 7.1, Panel D).

Furthermore, because *in vivo* activity is still produced, via MOR agonism, by compounds that have varying degrees of affinity and efficacy at both DOR and KOR, this could indicate that the idea of synthesizing a MOR agonist/DOR antagonist ligand might not be the full picture in creating an opioid analgesic without of risk of tolerance and dependence. Recently, there have been two key observations that have pointed towards the relevance of biased agonism at

MOR.[56-58] In particular, one study showed that administration of morphine produced an increased maximal stimulation and duration of action with reduced side effects in β-arrestin knockout mice relative to wildtype mice.[59] Since this finding, Trevena, Inc. a company specializing in the synthesis of biased agonists for opioid receptors has synthesized a compound, **TRV130**, now in phase 2 clinical trials for the treatment of severe acute pain. **TRV130** was shown to be a potent analgesic in mice and rats while causing less gastrointestinal dysfunction and respiratory suppression than morphine at equipotent doses.[59] Given the findings from the knockout studies and the success of **TRV130**, it would be of interest to see if the peptidomimetic compounds produced biased agonism at both MOR and DOR, given that some of the peptidomimetics still produce stimulation at DOR.
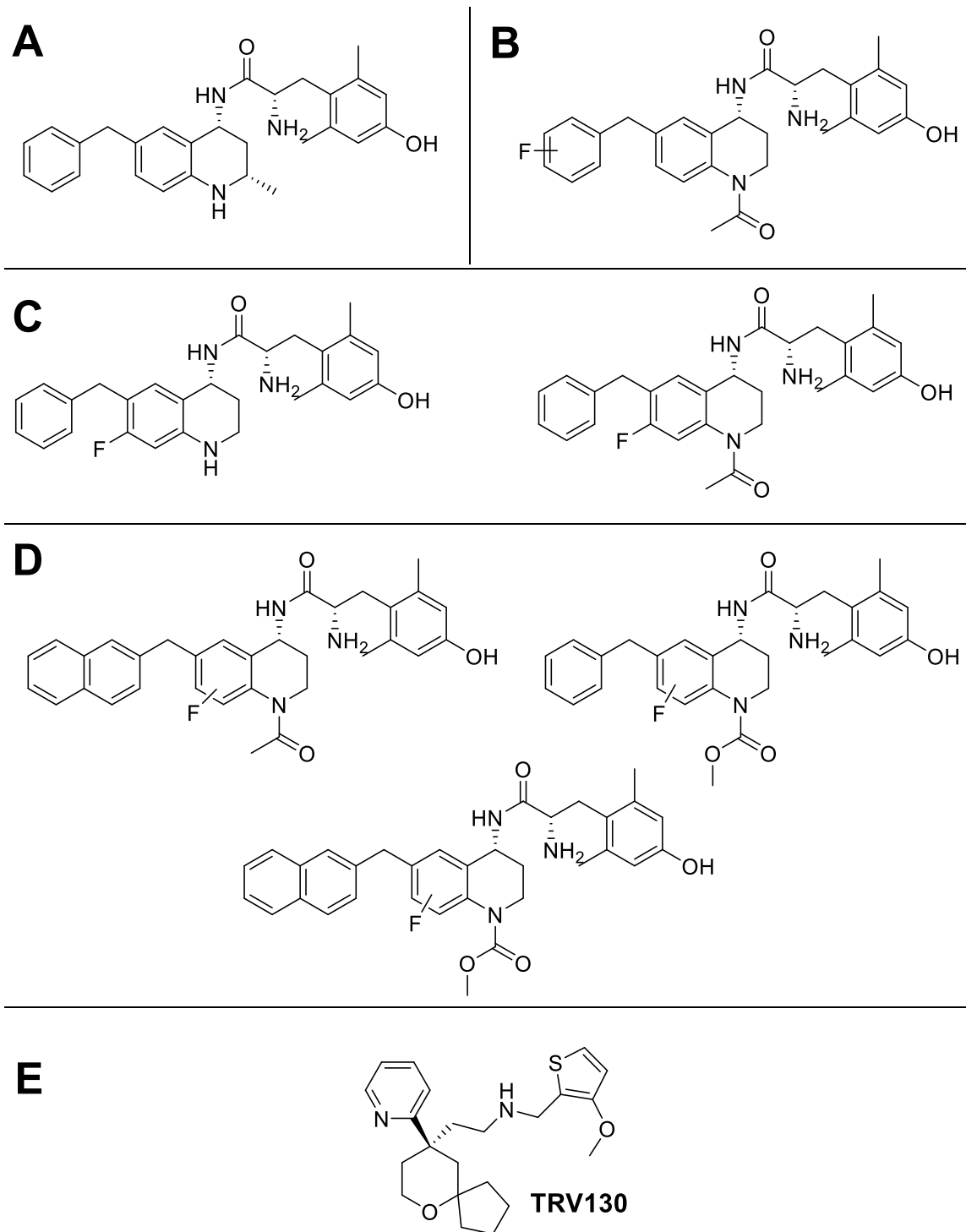
Figure 7.1 Additional proposed analogues and structure of **TRV130**

In conclusion, out of this peptidomimetic library compound **54** is a promising lead in the development of a MOR agonist/DOR antagonist ligand that produces analgesia, and thus far, with development of chronic tolerance in the mouse model. However, the disparate *in vivo* results for **54** and **55**, and the lack of predictability of *in vivo* activity for these peptidomimetics remains an intellectual challenge. While the ideal profile for an opioid analgesic with reduced risk of tolerance and dependence has many leads, that is, ligands with a MOR agonist/DOR antagonist, MOR agonist/DOR agonist, or a biased agonism at MOR are all promising, this peptidomimetic library serves as one more step made quest toward finding an opioid analgesic with reduced abuse liability.

CHAPTER 8

Experimentals

8.1 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% Pd/C as the catalyst. Flash column chromatography was carried out using P60 silica gel (230−400 mesh) either manually or with a Biotage Isolera. 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% solvent B (0.1% TFA in acetonitrile) in solvent A (0.1% TFA in water) to 50% solvent B in solvent A at a rate of either 0.5% or 1% 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% solvent B in solvent A to 45%, 70%, or 90% 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 synthesis of aldol adducts.[21] To a reaction vessel containing MeOH (375 mL) was added KOH. After dissolution, 1-indanone was added and allowed to dissolve. Next, p-nitrobenzaldehyde was added to the reaction mixture and allowed to stir for 1 h. Solvent was removed under reduced pressure and the residual solid was washed with cold H_2O (50 mL) and filtered to yield a homogeneous, tan powder as the pure product.

General Procedure B for synthesis p-substituted anilines.[21] To a hydrogenation vessel was added 10% Pd/C catalyst (1.5 g) followed by the slow addition of MeOH (120 mL). The aldol intermediate was dissolved in minimal MeOH and added to the vessel, followed by concentrated HCl (5.8 mL). The reaction vessel was placed on the hydrogenator under 50 psi of H_2 gas and allowed to shake for 24 h. The reaction mixture was then filtered through a pad of Celite, and solvent was removed under reduced pressure. The crude residue was extracted twice with DCM (150 mL) from 2 M NaOH (200 mL), and the combined organic layers were subsequently washed $2 \times$ NaHCO$_3$ (100 mL), $1 \times$ brine (100 mL), dried under MgSO$_4$, filtered, and concentrated. The crude residue was purified using silica gel chromatography to yield the pure product.

General procedure C for the synthesis of the 3-Bromo-N-propanamides.[21,30] To a flame-dried round bottom flask under Ar was added the aniline compound (1.0 eq) and K$_2$CO$_3$ (2.05 eq). The reaction vessel was placed back under vacuum and anhyd. DCE was added via syringe. The reaction solution stirred under vacuum for 5 min. After 5 min, the reaction vessel was then flooded with Ar and 3-bromopropionyl chloride (1.02 eq) was added via syringe. The reaction stirred under Ar at RT for 1 h and was monitored by TLC using a ninhydrin stain for disappearance of aniline compound. Once the reaction was complete, it was quenched with dI H_2O and the layers separated. The organic layer was washed with dI H_2O (1 x 50 mL) followed by brine (1 x 30 mL), then dried over MgSO$_4$, filtered, and concentrated under reduced pressure to yield the pure product.

General procedure D for the synthesis of phenylazetidin-2-ones. [21,30]To a round bottom flask already containing the dried, desiccated 3-bromo-N-propanamide (1.0 eq) was added NaOtBu (1.05 eq). The reaction vessel was placed under vacuum and anhyd. DMF was added via syringe. The solution stirred under vacuum for 5 min, and then was flooded with Ar. The reaction stirred

under Ar at RT for up to 3 h and was monitored by TLC. Once complete, the solvent was removed under reduced pressure and the resulting crude residue was re-suspended in DCM and dI H_2O, and the layers separated. The organic layer was washed once with dI H_2O (1 x 30 mL), then brine (1 x 30 mL), 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 E for the synthesis of 2,3-dihydroquinolin-4(1*H*)-ones.[21,30] To the round bottom flask already containing the dried, desiccated phenylazetidin-2-ones (1.0 eq) was added anhyd. DCE under vacuum. The reaction vessel stirred under vacuum for 5 min then was flooded with Ar. Next, triflic acid (TfOH) (3.0 eq) was added via syringe. The reaction 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 separated. The organic layer was washed once with dI H_2O (1 x 30 mL), then sat. $NaHCO_3$ (1 x 30 mL), then brine (1 x 30 mL), 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 F for diBoc-Dmt coupling to form final product. The amine intermediate and diBoc-Dmt (1.05 eq) and the coupling reagents PyBOP (1.0 eq), HOBt-Cl (1.0 eq), were dissolved in DMF (10-15 mL) followed by the addition of the and DIPEA (10.0 eq). The reaction mixture stirred for 18 h at room temperature. After concentration 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 while 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.

General procedure G for the synthesis of *tert*-butyl 4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylates. To a flame-dried round bottom flask under Ar was added the 2,3-dihydroquinolin-4(1*H*)-one (1.0 eq), Boc_2O (1.2-2.0 eq), and DMAP (0.1 eq). The reaction vessel was placed back under vacuum for 5 min, then anhyd. DCM was added via syringe and the solution stirred for 5 min under vacuum. The round bottom flask was flooded with Ar, and DIPEA (1.2-2.0 eq)

was added via syringe. The reaction vessel was equipped with a condenser and placed in oil bath at 60°C. The reaction 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 x 20 mL) and brine (1 x 20 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a crude yellow oil which was purified using silica gel chromatography to obtain the pure product.

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 eq) was added (*R*)-2-methylpropane-2-sulfinamide (2.0-3.0 eq), 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 allowed to stir under vacuum for ~5 min and then was flooded with Ar. The round bottom flask was placed in ice bath and allowed to equilibrate. Next, Ti(OEt)$_4$ (4.0-6.0 eq) was added slowly via syringe. Once addition was complete, the reaction vessel was taken out of ice bath and placed in oil bath at 70°C-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, reaction vessel was taken out of oil bath and cooled to ambient temperature. Meanwhile, an additional round bottom flask containing a stir bar was flame-dried under vacuum, then flooded with Ar, then NaBH$_4$ was added quickly, and then reaction vessel was placed back under vacuum for 5 min. Minimal anhyd. THF was added (~5 mL) and vessel allowed to stir under vacuum for ~ 5 min, then was flooded with Ar. The round bottom flask was placed in dry ice/xylenes bath and allowed to equilibrate. Contents from the round bottom flask containing the imine intermediate were transferred to round bottom flask containing NaBH$_4$ via cannula. Once contents completely added, the reaction was taken out of dry ice/xylenes bath and allowed to warm to room temperature. The reaction stirred at ambient temperature for 2-3 h. Once the reaction was complete, MeOH was added to quench. The solvent was removed under reduced pressure yielding a solid residue. The residue was re-suspended in DCM, solid remained 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 sulfinamide intermediate was added 15-20 mL dioxane followed by conc. HCl (6.0 eq). The reaction stirred at RT for up to 3 h. Solvent was removed under reduced pressure to yield slightly yellow, clear residue. The residue was re-suspended in Et$_2$O. *If a white solid precipitated (the HCl salt of the amine):* solid was removed via filtration as product without any further purification necessary. *If a white solid did not precipitate, but residue remains as film on flask*: residue washed with fresh Et$_2$O (3 x 5 mL) and dried without any further purification necessary.

General procedure J for Suzuki couplings using an aliphatic boronic acid. The aromatic bromide (1.0 eq), boronic acid (1.1-2.0 eq), K$_2$CO$_3$ (3.0 eq), Ag$_2$O (2.5 eq), and Pd(dppf)Cl$_2$ (0.1 eq), were added to a microwave tube and the tube was placed under vacuum for 15 min, then flooded with Ar. Roughly 1-2 mL of anhyd THF was added to tube via syringe, then tube was placed in 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, 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 which was purified using silica gel chromatography to obtain the pure product. Procedure adapted from ref. 35.

General Procedure K for the synthesis of 1-acetyl-2,3-dihydroquinolin-4(1*H*)-ones. To a flame-dried round bottom flask under Ar was added the 2,3-dihydroquinolin-4(1*H*)-one. The reaction vessel was placed back under vacuum for 5 min, then excess Ac$_2$O was added via syringe and the solution stirred for 5 min. The round bottom flask was flooded with Ar, equipped with a condenser, and placed in oil bath at 100°C. The reaction 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 which was purified using silica gel chromatograph to obtain the pure product.

General procedure L for Suzuki couplings using an aromatic boronic ester or an aromatic boronic acid. A solution of 3:1 acetone:dI H$_2$O was degassed for 1 h, then Ar was bubbled through solution for 1 h to ensure removal and displacement of ambient oxygen. *When all the reagents are solid*: aromatic bromide (1.0 eq), boronic ester (2.0 eq), K$_2$CO$_3$ (3.0 eq), and Pd(dppf)Cl$_2$ (0.1 eq), were added to a microwave tube and the tube was placed under vacuum for

15 min, then flooded with Ar. Roughly 1-2 mL of the 3:1 acetone:dI H_2O solution was added to tube via syringe, then tube was placed in 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 eq), K_2CO_3 (3.0 eq), and Pd(dppf)Cl_2 (0.1 eq), were added to a microwave tube and the tube was placed under vacuum for 15 min, then flooded with Ar. Roughly 1-2 mL of the 3:1 acetone:dI H_2O solution was added to tube via syringe, followed by addition of the boronic ester (2.0 eq) via syringe. The tube was placed in 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, 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 which was purified using silica gel chromatography to obtain the pure product. Procedure adapted from ref. 36.

General procedure M for the synthesis of *N*-acylated analogues using an acid chloride. To a flame-dried round bottom flask with stir bar under Ar atomosphere, was added 2,3-dihydroquinolin-4(1*H*)-one intermediate (1.0 eq). The reaction vessel was re-evacuated, then flooded with Ar. Anhydrous DCM was added via a syringe and the starting material dissolved. Next, the acid chloride (2.0 eq) was added via syringe. The reaction was monitored by TLC. Once reaction was complete, solvent was removed under reduced pressure. The crude mixture was purified using column chromatography to yield the pure product.

General Procedure N for the synthesis of *N*-acylated analogues using an acid anhydride. To a flame-dried round bottom flask under Ar was added the 2,3-dihydroquinolin-4(1*H*)-one. The reaction vessel was placed back under vacuum for 5 min, then excess acid anhydride (propionic or butyric) was added via syringe and the solution stirred for 5 min. The round bottom flask was flooded with Ar, equipped with a condenser, and placed in oil bath at 100°C. The reaction 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 which was purified using silica gel chromatograph to obtain the pure product.
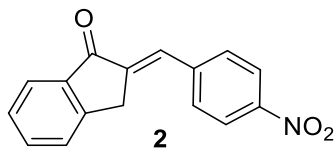
2-(4-Nitrobenzylidene)-2,3-dihydro-1*H*-inden-1-one (2). 2 was synthesized according to general procedure A starting from 1-indanone (3.00 g, 22.7 mmol, 1.0 eq) and *p*-nitrobenzaldehyde (4.12 g, 27.2 mmol, 1.2 eq) to yield the title compound **2** as a homogeneous, tan powder (5.57 g, 93%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.32 (d, *J* = 8.3, 2H), 7.94 (d, *J* = 7.7, 1H), 7.82 (d, *J* = 8.2, 2H), 7.73−7.63 (m, 2H), 7.59 (d, *J* = 7.5, 1H), 7.47 (t, *J* = 7.3, 1H), 4.10 (s, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 193.63, 149.28, 141.63, 138.43, 137.50, 135.26, 130.95, 130.81, 128.06, 126.24, 124.74, 124.08, 32.33.
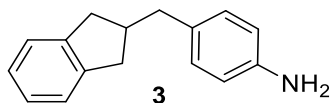
4-((2,3-Dihydro-1*H*-inden-2-yl)methyl)aniline (3). 3 was synthesized according to general procedure B starting from **2** (2.13 g, 8.04 mmol, 1.0 eq) to yield the title compound **3** as a brown solid (1.70 g, 95%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.16 (dd, *J* = 8.0, 4.5, 2H), 7.14−7.08 (m, 2H), 7.01 (d, *J* = 8.2, 2H), 6.67 (d, *J* = 8.2, 2H), 3.31 (s, 2H), 2.97 (dd, *J* = 13.7, 5.7, 2H), 2.75−2.60 (m, 5H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 143.91, 143.34, 131.97, 129.67, 126.04, 124.48, 115.51, 41.71, 40.73, 38.86.
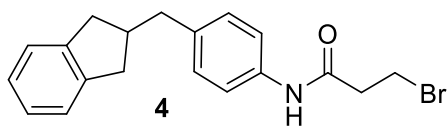
3-Bromo-*N*-(4-((2,3-dihydro-1*H*-inden-2-yl)methyl)phenyl)propanamide (4). 4 was synthesized according to general procedure C starting from **3** (686 mg, 3.07 mmol, 1.0 eq) to yield the title compound **4** as a fluffy, white solid (1.07 g, 98%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, *J* = 8.2, 2H), 7.20−7.06 (m, 6H), 3.71 (t, *J* = 6.5, 2H), 2.98−2.63 (m, 4H), 2.77−2.60 (m, 5H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.74, 143.10, 137.96, 135.21, 129.39, 126.11, 124.48, 120.13, 41.46, 40.93, 40.69, 38.81, 27.16.
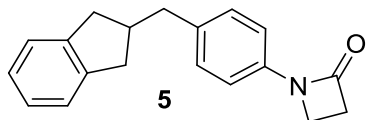
1-(4-((2,3-Dihydro-1*H*-inden-2-yl)methyl)phenyl)azetidin-2one (5). 5 was synthesized according to general procedure D starting from **4** (1.07 g, 3.00 mmol, 1.0 eq) to yield the title compound **5** as a light tan powder (811 mg, 98%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 (d, J = 8.3, 2H), 7.20−7.09 (m, 6H), 3.62 (t, J = 4.4, 2H), 3.11 (t, J = 4.4, 2H), 2.97 (dd, J = 14.6, 5.4, 2H), 2.78−2.61 (m, 5H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 164.26, 143.10, 137.03, 136.61, 129.47, 126.14, 124.49, 116.16, 41.56, 41.00, 38.82, 38.01, 36.07.
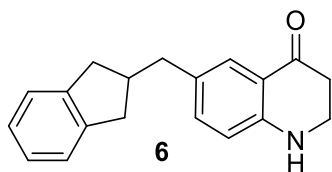
6-((2,3-Dihydro-1*H*-inden-2-yl)methyl)-2,3-dihydroquinolin4(1*H*)-one (6). 6 was synthesized according to general procedure E starting from **5** (811 mg, 2.93 mmol, 1.0 eq) to yield the title compound **6** as a viscous yellow oil (772 mg, 95%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70 (d, J = 1.9, 1H), 7.22− 7.08 (m, 5H), 6.63 (d, J = 8.3, 1H), 4.30 (br s, 1H), 3.57 (t, J = 6.9, 2H), 2.97 (dd, J = 14.2, 5.9, 2H), 2.78−2.60 (m, 7H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 193.84, 150.42, 143.12, 136.09, 131.00, 127.12, 126.06, 124.45, 119.30, 115.90, 42.47, 41.42, 40.42, 38.75, 38.22.
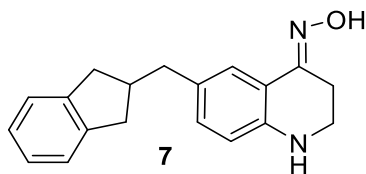
(*E/Z*)-6-((2,3-dihydro-1*H*-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1*H*)-one oxime (7). 7 was synthesized by suspending **6** (772 mg, 2.78 mmol, 1.0 eq) in 1:1 EtOH/H$_2$O followed by the addition of NH$_2$OH·HCl (147 mg, 3.05 mmol, 1.1 eq) and NaOAc·H$_2$O (463 mg, 3.05 mmol, 1.1 eq). The mixture stirred at reflux for 24 h, after which time solvents were condensed and redissolved in EA (30 mL). The organic layer was washed with brine (10 mL), dried with MgSO$_4$, filtered, concentrated under reduced pressure, and purified using silica gel

chromatography to yield the title compound **7** as a yellow solid (662 mg, 81%). ^{1}H NMR (400 MHz, CDCl$_3$) 7.63 (d, J = 1.8, 1H), 7.19 −7.05 (m, 5H), 6.60 (dd, J = 21.6, 8.3, 1H), 3.30 (t, J = 6.5, 2H), 2.93 (dt, J = 13.0, 7.6, 3H), 2.76−2.59 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 152.50, 145.41, 143.38, 131.51, 131.34, 129.41, 126.08, 124.52, 124.23, 115.78, 41.57, 40.78, 40.74, 38.86, 23.45.
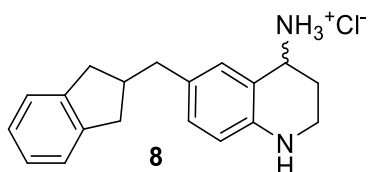
6-((2,3-Dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-amine (**8**). For the synthesis of **8**, 10% Pd/C (60 mg) was added to a hydrogenation vessel followed by the slow addition of MeOH (10 mL). **7** (662 mg, 2.26 mmol, 1.0 eq) was dissolved in minimal MeOH and added to the vessel, followed by the addition of glacial AcOH (0.4 mL). The reaction vessel was placed on the hydrogenator under 40 psi of H$_2$ gas and allowed to shake for 12 h. The reaction mixture was then filtered through a pad of Celite, and solvent was removed under reduced pressure. The crude residue was resuspended in 1 M HCl (30 mL) and extracted with 3 × EA (30 mL). The organic layer was washed with 3 × 2 M NaOH (30 mL), 1 × brine (30 mL), dried under MgSO$_4$, filtered, and concentrated to yield the title compound as a tan oil (120 mg, 75%), which was carried to the next reaction without further purification to yield the title compound **8** as a brown oil (527 mg, 84%). ^{1}H NMR (400 MHz, CDCl$_3$) 7.13 (ddd, J = 8.7, 7.0, 4.2, 5H), 7.05 (s, 1H), 6.87 (dd, J = 8.1, 1.8, 1H), 6.46 (t, J = 6.8, 1H), 4.00 (t, J = 4.8, 1H), 3.43−3.34 (m, 1H), 3.29 (dt, J = 11.0, 5.4, 1H), 3.02−2.94 (m, 3H), 2.77−2.59 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.04, 150.14, 143.38, 130.14, 129.11, 128.42, 125.98, 124.44, 114.50, 46.89, 41.70, 40.74, 38.88, 37.75, 31.65. ESI-MS 262.1 [M − NH3 + H] +. HPLC (gradient A): retention time = 31.39 min.

mixture of diastereomers
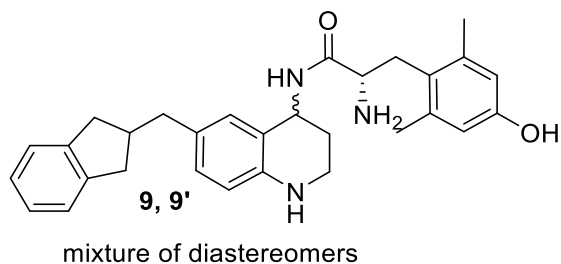
(2*S*)-1-((6-((2,3-dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)1-oxopropan-2-amide (9, 9'). **9** and **9'** were synthesized according to general procedure F from **8** to form a mixture of crude diastereomers which were isolated and purified by semipreparative HPLC and lyophilized to yield the diastereomers of the title compound, with **9** as a white powder of the early diastereomer and a **9'** as a tan powder of the late diastereomer. HPLC (gradient A): retention time = 31.09 min (early), 33.76 min (late). ESI-MS 492.2 [M + Na]$^+$ for both diastereomers. No ^{1}H or ^{13}C NMR data acquired.
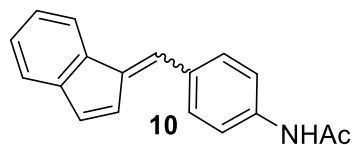
N-(4-((1*H*-inden-1-ylidene)methyl)phenyl)acetamide (10). 10** was synthesized according to published procedure[31] starting from commercially available 1-indene and 4-acetamidobenzaldehyde to yield title compound **10** (94 mg, 59%). NMR data matched previously reported literature values.[31]
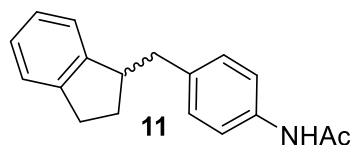
N-(4-((2,3-dihydro-1*H*-inden-1-yl)methyl)phenyl)acetamide (11).** [31] **11** was synthesized according to published procedure[31] using **10** to yield title compound **11** (80 mg, 84%). NMR data matched previously reported literature values.[31]
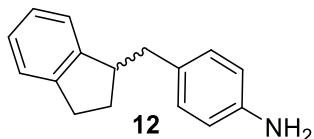
4-((2,3-Dihydro-1*H*-inden-1-yl)methyl)aniline (12). **12** was synthesized according to published procedure[31] using **11** to yield title compound **12** (36 mg, 54%). NMR data matched previously reported literature values.[31]
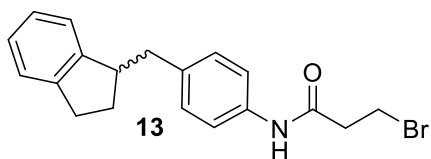
3-Bromo-*N*-(4-((2,3-dihydro-1*H*-inden-1-yl)methyl)phenyl)propanamide (13). **13** was synthesized following general procedure C using **12** (473 mg, 2.1 mmol, 1.0 eq), K_2CO_3 (600 mg, 4.3 mmol, 2.05 eq), and 3-bromopropionyl chloride (220 mL, 2.2 mmol, 1.02 eq) to yield title compound as an off-white 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.
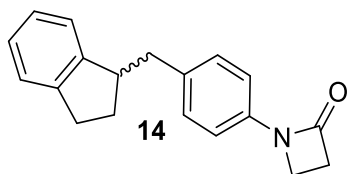
1-(4-((2,3-Dihydro-1*H*-inden-1-yl)methyl)phenyl)azetidin-2-one (14). 14 was synthesized following general procedure E using **13** (759 mg, 2.12 mmol, 1.0 eq), NaO*t*Bu (214 mg, 2.22 mmol, 1.05 eq) to yield the title compound as a light tan solid (512 mg, 87.4%) with no additional purification necessary. ^{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, 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.
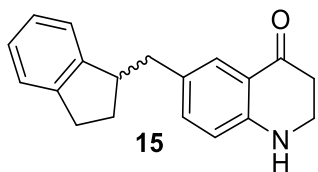
6-((2,3-Dihydro-1*H*-inden-1-yl)methyl)-2,3-dihydroquinolin-4(1*H*)-one **(15).** **15** was synthesized following general procedure E from **14** (512 mg, 1.85 mmol, 1.0 eq) to yield the title compound **15** as a yellow oil (459 mg, 89.6%) after purficiation via silica gel chromatography. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 (s, 1H), 7.19 (s, 1H), 7.11 (d, *J* = 11.8 Hz, 5H), 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 (dd, *J* = 14.6, 6.5 Hz, 5H), 2.80 – 2.74 (m, 1H), 2.70 – 2.64 (m, 2H), 2.63 – 2.50 (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 193.92, 150.52, 146.64, 143.97, 136.20, 130.20, 127.12, 126.34, 125.88, 124.39, 123.59, 119.01, 115.82, 46.27, 42.28, 40.17, 38.09, 31.54, 30.95.
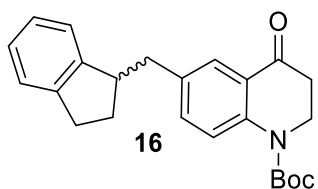
***Tert*-butyl-6-((2,3-dihydro-1*H*-inden-1-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-**

carboxylate (16). 16 was synthesized following general procedure G using **15** (214 mg, 0.77 mmol, 1.0 eq), Boc$_2$O (337 mg, 1.54 mmol, 2.0 eq), DMAP (9 mg, 0.077 mmol, 0.1 eq), DIPEA (0.268 mL, 1.54 mmol, 2.0 eq). The reaction stirred at reflux for 16 h. Once enough starting material was converted to product, the crude yellow oil was purified using silica gel chromatography (equil in 100% hex, run in 2:3 EA:hex) to yield the title compound **16** as a yellow oil (83 mg, 28.5%). Additionally, 122 mg of starting material **15** was recovered, this was not considered when calculating 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, 46.2, 44.3, 40.5, 39.0, 31.6, 31.0, 28.3.

17
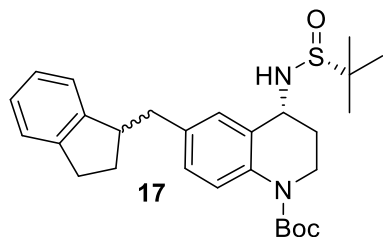
Tert-**butyl(4*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-((2,3-dihydro-1*H*-inden-1-yl)methyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (17). 17** was synthesized as a mixture of diastereomers following general procedure H using **16** (83 mg, 0.220 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (80 mg, 0.660 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.277 mL, 0.132 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into 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 eq) and stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography (equil in 100%, run in 2:3 EA:hex) to yield the title compound **17** as a clear, colorless oil of a mixture of diastereomers (27 mg, 25.7% from **16**). ^{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.
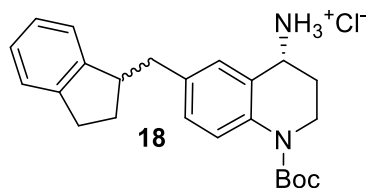
(4*R*)-1-(*tert*-butoxycarbonyl)-6-((2,3-dihydro-1*H*-inden-1-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride (18). 18 was synthesized as a mixture of diastereomers following general procedure I using **17** (27 mg 0.0559 mmol, 1.0 eq) and conc. HCl (8 μL, 0.336 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et₂O, and solid crashed out. Solid was filtered off and washed 3 x with fresh Et₂O and dried to yield title compound **18** as a white solid (10 mg, 43.5%). ^{1}H NMR (500 MHz, CD₃OD) 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, CD₃OD) δ 154.8, 147.7, 145.1, 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.
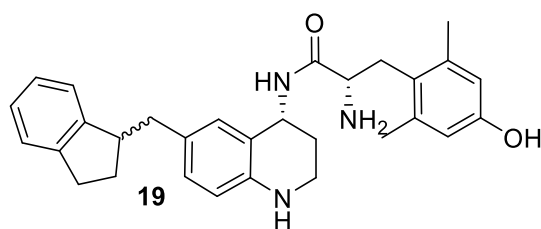
mixture of inseparable diastereomers

(*S*)-2-amino-*N*-((*R*)-6-(((*R/S*)-2,3-dihydro-1*H*-inden-1-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (19). 19 was synthesized following general procedure F starting from the (*R*) amine intermediate **18** (10 mg, 0.0241 mmol, 1.0 eq) as a mixture of enantiomers to yield crude product as a mixture of diastereomers which was purified by semipreparative HPLC then lyophilized to yield the title compound **19** as the TFA salt of a mixture of inseparable diastereomers (5 mg, 35.7%). ^{1}H NMR (500 MHz, CD₃OD) 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]$^{+}$.
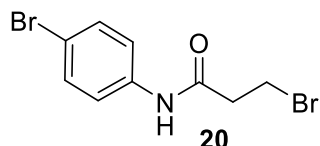
3-Bromo-*N*-(4-bromophenyl)propanamide (20). 20 was synthesized following general procedure C starting from commercially available *p*-nitrobenzaldehyde (2.0 g, 11.6 mmol, 1.0 eq), K$_2$CO$_3$ (3.29 g, 23.8 mmol, 2.05 eq), and 3-bromopropionyl chloride (1.20 mL, 11.9 mmol, 1.02 eq) to yield title compound **20** as an off-white solid (3.53 g, 98.9%) with no additional purification necessary after quench and work-up. ^{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.
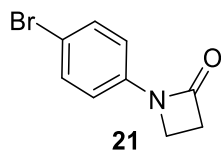
1-(4-Bromophenyl)azetidin-2-one (21). 21 was synthesized following general procedure D starting with **20** (3.53 g, 11.5 mmol, 1.0 eq) and NaO*t*Bu (1.16 g, 12.1 mmol, 1.05 eq). Following solvent removal and work-up, the crude product was chromatographed on silica gel (equil in 100% hex, run in 1:4 EA:hex) to yield title compound **21** 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 data acquired.
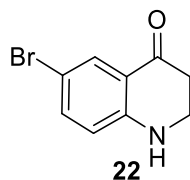
6-Bromo-2,3-dihydroquinolin-4(1*H*)-one (22). 22 was synthesized following general procedure

E starting with **21** (1.36 g, 6 mmol, 1.0 eq) and TfOH (1.60 mL, 18.0 mmol, 3.0 eq) to yield a crude yellow oil. Following work-up, the crude material was chromatographed on silica gel (equil in 100% hex, run in 2:3 EA:hex) to yield title compound **22** 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.

23 Boc
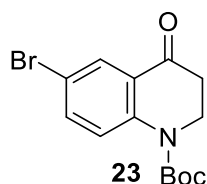
***Tert*-butyl 6-bromo-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (23). 23** was synthesized following general procedure G using **22** (300 mg, 1.33 mmol, 1.0 eq), Boc$_2$O (348 mg, 1.59 mmol, 1.2 eq), DMAP (16.2 mg, 0.13 mmol, 0.1 eq) and DIPEA (0.277 mL, 1.59 mmol, 1.2 eq). Following the quench and work-up, the crude product was chromatographed on silica gel (equil in 100% hex, run in 2:3 EA:hex) to yield the title compound **23** 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.

24 Boc
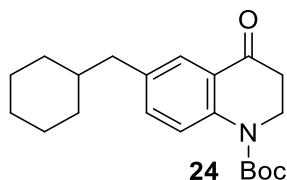
***Tert*-butyl 6-(cyclohexylmethyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (24). 24** was synthesized following general procedure J using **23** (100 mg, 0.31 mmol, 1.0 eq), (cyclohexylmethyl)boronic acid (87 mg, 0.61 mmol, 2.0 eq), K$_2$CO$_3$ (127 mg, 0.92 mmol, 3.0 eq), Ag$_2$O (178 mg, 0.77 mmol, 2.5 eq), and Pd(dppf)Cl$_2$ (22 mg, 0.031 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 80°C, 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 (equil in 100% pet. ether, run in 5:1 pet ether:Et₂O) to yield title compound **24** as clear, colorless oil (81 mg, 77.1%). ^{1}H NMR (500 MHz, CDCl₃) 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, CDCl₃) 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.

25 Boc
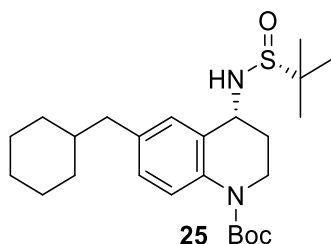
***Tert*-butyl(*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-(cyclohexylmethyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (25). 25** was synthesized following general procedure H using **24** (78 mg, 0.227 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (55 mg, 0.454 mmol, 2.0 eq), and Ti(OEt)₄ (0.191 mL, 0.909 mmol, 4.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 40 h), the reaction mixture was transferred to a round bottom flask containing NaBH₄ (34 mg, 0.909 mmol, 4.0 eq) and stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography (equil in 100% hex, run in 1:3 EA:hex) to yield the title compound **25** as a dark, yellow oil (102 mg, 23.5% from **24**). ^{1}H NMR (500 MHz, CDCl₃) 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, CDCl₃) 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.
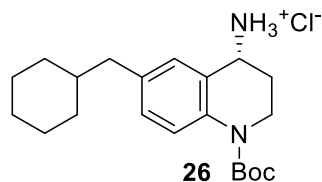
(*R*)-1-(*tert*-butoxycarbonyl)-6-(cyclohexylmethyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride (26). 26 was synthesized following general procedure I using **25** (22 mg, 0.0490 mmol, 1.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding the title compound **26** 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.
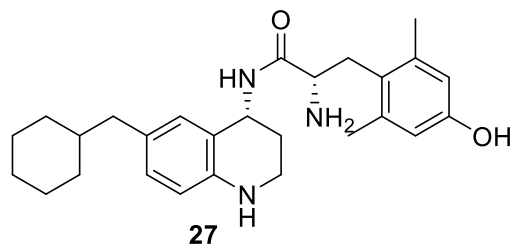
(*S*)-2-amino-*N*-((*R*)-6-(cyclohexylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (27). 27 was synthesized following general procedure F starting from the (*R*) amine intermediate **26** (10 mg, 0.0262 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC then lyophilized to yield the title compound **27** as a TFA salt (9 mg, 63.2%). ^{1}H NMR (500 MHz, CD$_3$OD) 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$_3$OD) 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
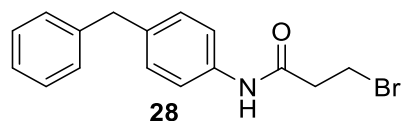
N-(4-benzylphenyl)-3-bromopropanamide (28). **28** was synthesized according to general procedure C using commercially available benzylaniline (2.15 g, 11.7 mmol, 1.0 eq) to yield title compound **28** as tan solid (2.63 g, 98.0%) with no additional purification necessary. ¹H NMR (500 MHz, CDCl₃) δ 7.43 (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). ¹³C NMR (126 MHz, CDCl₃) 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.
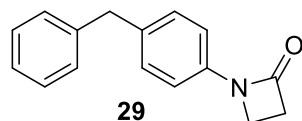
1-(4-Benzylphenyl)azetidin-2-one (29). **29** was synthesized following general procedure D using **28** (3.63 g, 1.1 mmol, 1.0 eq) and NaO*t*Bu (1.15 g, 1.2 mmol, 1.05 eq) in anhyd. DMF. Following aqueous washes, the title compound **29** was isolated as a tan solid (2.70 g, quant.) and was taken ahead to next step (formation of **30**) without purification, isolation, or characterization. No ¹H or ¹³C data acquired.
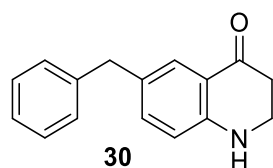
6-Benzyl-2,3-dihydroquinolin-4(1H)-one (30). **30** was synthesized following general procedure E using **29** (2.70 g, 1.1 mmol, 1.0 eq) and TfOH (3.0 mL, 3.4 mmol, 3.0 eq). Following column purification (equil in 100% hex, run in 2:3 EA:hex) title compound **30** was isolated as a yellow solid (1.91 g, 70.7%). ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 1.6, 1H), 7.69 (d, J = 1.6, 1H), 7.29 (dd, J = 8.6, 1.9, 1H), 7.26−7.19 (m, 2H), 7.18− 7.10 (m, 3H), 4.08 (t, J = 6.2, 2H), 3.90 (s, 2H), 2.68 (t, J = 6.3, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 194.23, 142.37, 140.39, 134.61, 128.80, 128.54, 127.14, 126.26, 124.78, 123.81, 44.26, 41.14, 38.97.

31
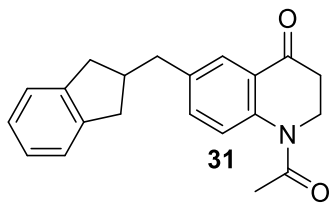
1-Acetyl-6-((2,3-dihydro-1*H*-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1*H*)-one (31). 31 was synthesized following general procedure K using **6** (55 mg, 0.24 mmol, 1.0 eq). The reaction stirred at reflux for 20 h. Once the reaction was complete, solvent was removed and the crude residue was purified using silica gel chromatography (equil in 100% hex, run in 2:3 EA:hex) to yield title compound **31** 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.

32
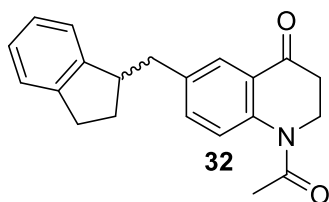
1-Acetyl-6-((2,3-dihydro-1*H*-inden-1-yl)methyl)-2,3-dihydroquinolin-4(1*H*)-one (32). 32 was synthesized following general procedure K using **15** (245 mg, 0.88 mmol, 1.0 eq). The reaction stirred at reflux for 16 h. Once the reaction was complete, the solvent was removed and the crude residue was purified using silica gel chromatography (equil in 100% hex, run in 2:3 EA:hex) to yield the title compound **32** 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.
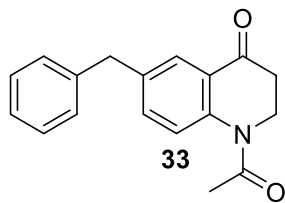
**1-Acetyl-6-benzyl-2,3-dihydroquinolin-4(1*H*)-one (33). 33** was synthesized following general procedure K using **30** (170 mg, 0.72 mmol, 1.0 eq). The reaction stirred at reflux for 16 h. Once the reaction was complete solvent was removed under reduced pressure and the crude product was chromatographed on silica gel (equil in 100% 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.
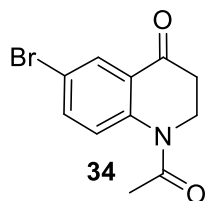
1-Acetyl-6-bromo-2,3-dihydroquinolin-4(1*H*)-one (34). 34 was synthesized following general procedure K starting with **22** (739 mg, 3.27 mmol, 1.0 eq) fo 16 h. Following removal of solvent, the resulting crude yellow oil was purified using silica gel chromatography (equil in 100%, run in 1:3 EA:hex) to yield title compound **33** 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.
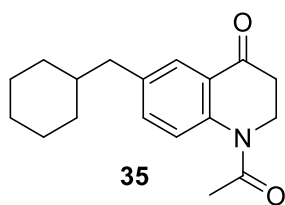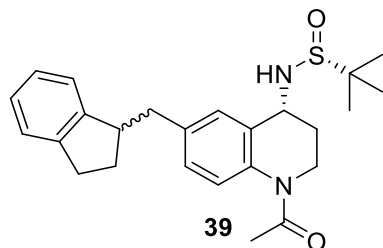

1-Acetyl-6-(cyclohexylmethyl)-2,3-dihydroquinolin-4(1*H*)-one (35). 35 was synthesized following general procedure J using **34** (100 mg, 0.37 mmol, 1.0 eq), (cyclohexylmethyl)boronic

acid (58 mg, 0.41 mmol, 1.1 eq), K_2CO_3 (155 mg, 1.12 mmol, 3.0 eq), Ag_2O (216 mg, 0.93 mmol, 2.5 eq), and $Pd(dppf)Cl_2$ (27 mg, 0.37 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 80°C, max power of 300 W for 60 min, with the "Powermax" option disabled. Once filtered through Celite, crude residue purified via silica gel chromatography (equil in 100% hex, run in 1:3 EA:hex) to yield title compound **35** as clear, colorless oil (30 mg, 28.3%). Additionally, 51 mg of **34** was recovered; this was not considered when calculating 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, 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.
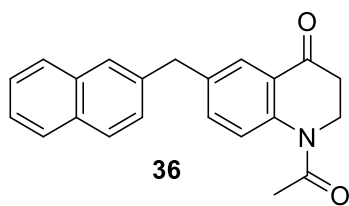
1-Acetyl-6-(naphthalen-2-ylmethyl)-2,3-dihydroquinolin-4(1H)-one (36). 36 was synthesized following general procedure L using **34** (50 mg, 0.19 mmol, 1.0 eq), 4,4,5,5-tetramethyl-2-(naphthalen-2-ylmethyl)-1,3,2-dioxaborolane (100 mg, 0.37 mmol, 2.0 eq), K_2CO_3 (78 mg, 0.56 mmol, 3.0 eq), and $Pd(dppf)Cl_2$ (14 mg, 0.019 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography (equil in 100% hex, run in 1:1 EA:hex) to yield title compound **36** (51 mg, 83.6%) as 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.
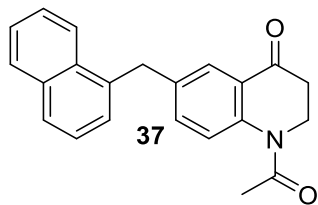
1-Acetyl-6-(naphthalen-1-ylmethyl)-2,3-dihydroquinolin-4(1*H*)-one (37). 37 was synthesized following general procedure L using **34** (50 mg, 0.19 mmol, 1.0 eq), 4,4,5,5-tetramethyl-2-(naphthalen-1-ylmethyl)-1,3,2-dioxaborolane (100 mg, 0.37 mmol, 2.0 eq), K_2CO_3 (78 mg, 0.56 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (14 mg, 0.019 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min with "Powermax" enabled. Once crude mixture was filtered through Celite, the residue was purified via silica gel chromatography (equil in 100% hex, run in 9:1 EA:hex) to yield title compound **37** as 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.
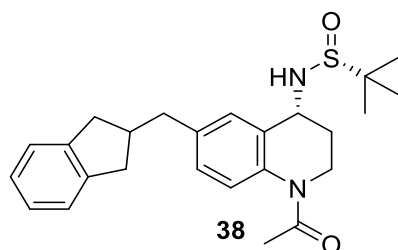
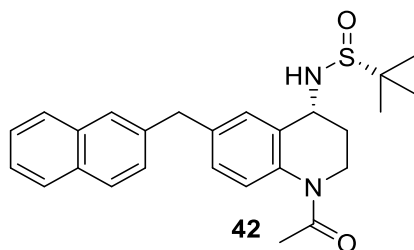**(*R*)-*N*-((*R*)-1-acetyl-6-((2,3-dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (38). 38** was synthesized following general procedure H using **31** (39 mg, 0.122 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (30 mg, 0.244 mmol, 2.0 eq), and Ti(OEt)$_4$ (0.102 mL, 0.488 mmol, 4.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into 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 eq) and stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography (equil in 100% hex, run in 9:1 EA:hex) to yield the title compound **38** as a clear, colorless oil (46 mg,

88.9% from **31**). 1H 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 data acquired.

39

(*R*)-*N*-((4*R*)-1-acetyl-6-((2,3-dihydro-1*H*-inden-1-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (39). 39 was synthesized as a mixture of diastereomers following general procedure H using **32** (176 mg, 0.551 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (200 mg, 1.65 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.693 mL, 3.31 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into 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 eq) and stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography (equil in and run in 100% EA) to yield the title compound **39** as a clear, colorless oil of a mixture of diastereomers (219 mg, 93.6% from **32**). ^{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, 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.
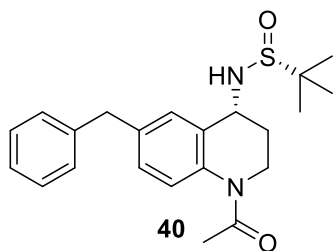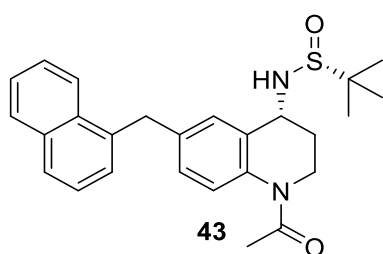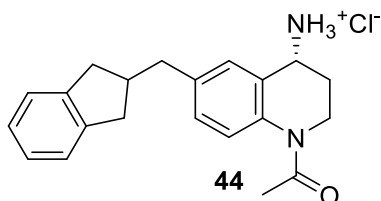
(*R*)-*N*-((*R*)-1-acetyl-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (40). 40 was synthesized following general procedure H using **33** (168 mg, 0.601 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (219 mg, 1.80 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.757 mL, 3.61 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into 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 eq) and stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography (4:1 EA:hex) to yield the title compound **40** as a clear, colorless oil (105 mg, 45.5% from **33**), that was taken ahead to the next step (formation of **46**) without further characterization. No ^{1}H or ^{13}C data acquired.
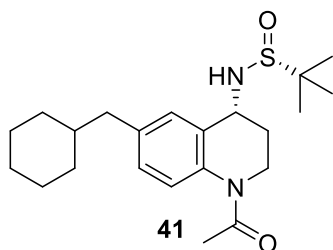
(*R*)-*N*-((*R*)-1-acetyl-6-(cyclohexylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (41). 41 was synthesized following general procedure H using **35** (56 mg, 0.196 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (48 mg, 0.392 mmol, 2.0 eq), and Ti(OEt)$_4$ (0.165 mL, 0.785 mmol, 4.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into 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 eq) and stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography (equil in 100% hex, run in 4:1 EA:hex) to yield the title compound **41** as a clear, yellow oil (20 mg,

26.1% from **35**) that was taken ahead to the next step (formation of **47**) without further characterization. No ^{1}H or ^{13}C data acquired.


42

(R)-N-((R)-1-acetyl-6-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (42). 42 was synthesized following general procedure H from **36** (51 mg, 0.155 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (56 mg, 0.464 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.195 mL, 0.929 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into 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 eq) and stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography (equil in 100% hex, run in 100% EA) to yield the title compound **42** as a clear, colorless oil (67 mg, quant. from **36**) which was taken ahead to the next step (formation of **48**) without further characterization. No ^{1}H or ^{13}C data acquired.

43

(R)-N-((R)-1-acetyl-6-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (43). 43 was synthesized following general procedure H using **37** (31 mg, 0.0941 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (34 mg, 0.282 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.118 mL, 0.565 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into 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 eq) and stirred at room temperature for 3 h before being quenched with MeOH. The resultant solid was removed, to yield the crude, clear, colorless title compound **43** (41 mg, quant), that was taken ahead to the next step (formation of **49**) without further purification, isolation, or characterization. No ^{1}H or ^{13}C data acquired.
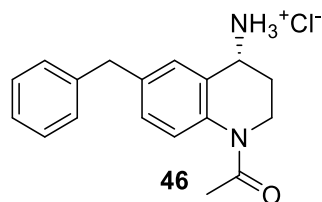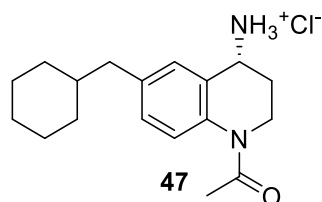

(R)-1-acetyl-6-((2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride (44). 44 was synthesized following general procedure I using **38** (46 mg 0.108 mmol, 1.0 eq) and conc. HCl (16 µL, 0.650 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and residue crashed out. Residue was gummy and sticky so it was washed 3 x with fresh Et$_2$O and dried to yield the title compound **44** as a tan solid (39 mg, quant.). Solid was taken ahead to next reaction (formation of **50**) without further isolation, purification, or characterization. No ^{1}H or ^{13}C data acquired.
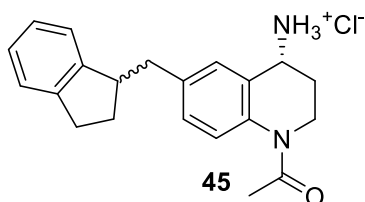
(4R)-1-acetyl-6-((2,3-dihydro-1H-inden-1-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride (45). 45 was synthesized as a mixture of diastereomers following general procedure I using **39** (219 mg 0.516 mmol, 1.0 eq) and conc. HCl (76 µL, 3.10 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. Solid was filtered off and washed 3 x with fresh Et$_2$O and dried to yield title compound **45** as a white solid (135 mg, 73.4%). ^{1}H NMR (500 MHz, CD$_3$OD) 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$_3$OD) 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.

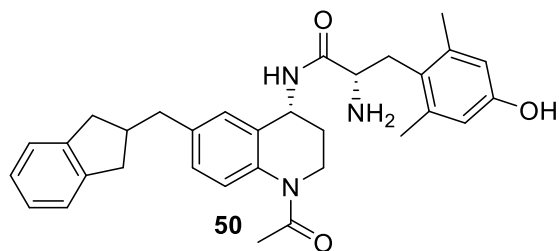**(*R*)-1-acetyl-6-benzyl-1,2,3,4-tetrahydroquinolin-4-aminium chloride (46). 46** was synthesized following general procedure I using **40** (105 mg 0.273 mmol, 1.0 eq) and conc. HCl (40 µL, 1.64 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. Solid was filtered off and washed 3 x with fresh Et$_2$O and dried to yield title compound **46** as a white solid (68 mg, 78.2%). ^{1}H NMR (500 MHz, CD$_3$OD) 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$_3$OD) 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-(cyclohexylmethyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride (47). 47 was synthesized following general procedure I using **41** (20 mg, 0.0512 mmol, 1.0 eq) and conc. HCl (7.5 µL, 0.31 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding the title compound **47** as an off-white solid (12 mg, 72.7%). ^{1}H NMR (500 MHz, CD$_3$OD) 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 data acquired.
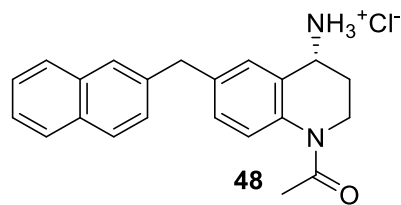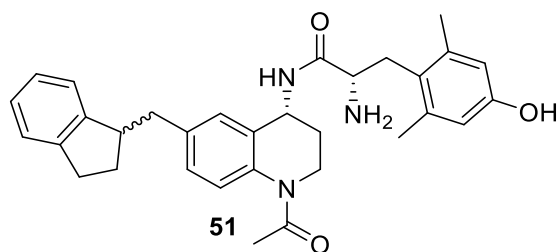
(*R*)-1-acetyl-6-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-aminium   chloride (48). 48 was synthesized following general procedure I using **42** (56 mg, 0.135 mmol, 1.0 eq). After removing solvent, residue was re-suspended in Et_2O, and solid did not crash out. Residue was washed 3 x with fresh Et_2O and dried to yield title compound **48** 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.
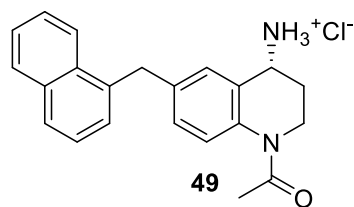
(*R*)-1-acetyl-6-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-aminium   chloride (49). 49 was synthesized following general procedure I using **43** (41 mg (from theoretical yield of **43**), 0.0943 mmol, 1.0 eq) and conc. HCl (14 μL, 0.566 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et_2O, and solid crashed out. Solid was filtered off and washed 3 x with fresh Et_2O and dried to yield title compound **49** 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.
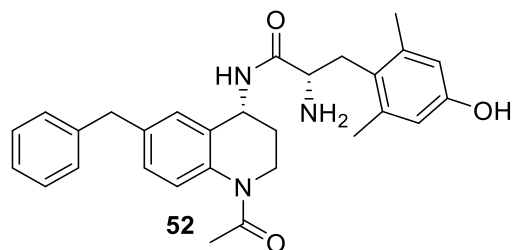
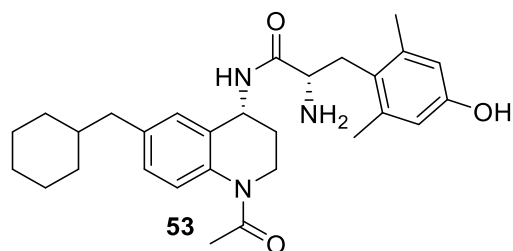**(S)-N-((R)-1-acetyl-6-((2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (50). 50** was synthesized following general procedure F starting from the (R) amine intermediate **44** (39 mg, 0.108 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC then lyophilized to yield the title compound **50** as a TFA salt (14 mg, 20.6%).^{1}H NMR (500 MHz, CD₃OD) 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 data 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 (51). 51 was synthesized following general procedure F starting from the (R) amine intermediate **35** (20 mg, 0.056 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC then lyophilized to yield the title compound **51** as the TFA salt of a mixture of diastereomers (8 mg, 22.9%). Starting material **45** was recovered, but not considered when calculating percent yield. ^{1}H NMR (500 MHz, CD₃OD) 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]$^+$**.**
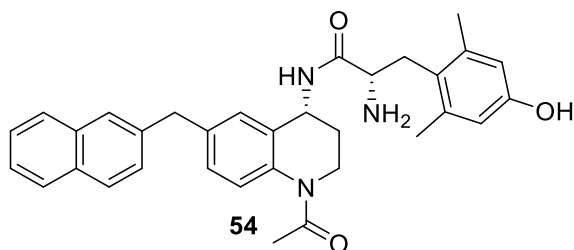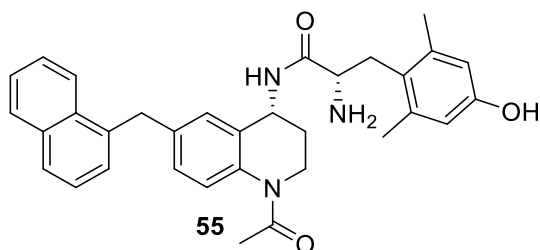

52

(*S*)-*N*-((*R*)-1-acetyl-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (52). 52 was synthesized following general procedure F starting from the (*R*) amine intermediate **46** (68 mg, 0.215 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC then lyophilized to yield the title compound **52** as a TFA salt (16 mg, 12.7%). Starting material **46** was recovered, but not considered when calculating percent yield. ^{1}H NMR (500 MHz, CD$_3$OD) 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]$^+$**.**

53

(*S*)-*N*-((*R*)-1-acetyl-6-(cyclohexylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (53). 53 was synthesized following general procedure F starting from the (*R*) amine intermediate **47** (12 mg, 0.0372 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC then lyophilized to yield the title compound **53** as a TFA salt (12 mg, 55.5%). ^{1}H NMR (500 MHz, CD$_3$OD) 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$_3$OD) 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]$^+$.


54

(*S*)-*N*-((*R*)-1-acetyl-6-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphe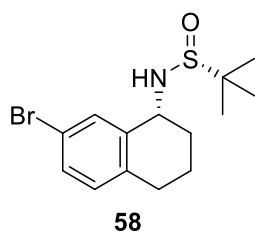nyl)propanamide (54). 54 was synthesized following general procedure F starting from the (*R*) amine intermediate **48** (56 mg, 0.153 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC then lyophilized to yield the title compound **54** as a TFA salt (17 mg, 30.4%). Starting material **48** was recovered, but not considered when calculating percent yield. ^{1}H NMR (500 MHz, CD$_3$OD) 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$_3$OD) 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]$^+$.

55

(*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 (55). 55 was synthesized following general

procedure F starting from the (*R*) amine intermediate **49** (22 mg, 0.060 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC then lyophilized to yield the title compound **55** as a TFA salt (4 mg, 12.9%). Starting material **49** was recovered, but not considered when calculating percent yield. ^{1}H NMR (500 MHz, CD$_3$OD) 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]$^+$.
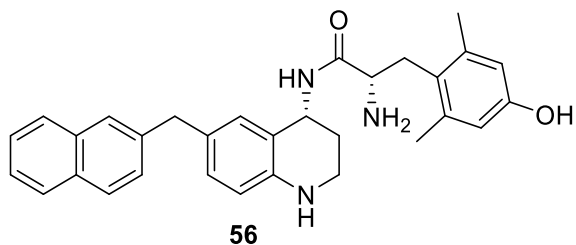
56

Synthesized by Larisa Yeomans. Synthesis and characterization can be found in Ref. 21

57

Synthesized by Larisa Yeomans. Synthesis and characterization can be found in Ref. 21

58
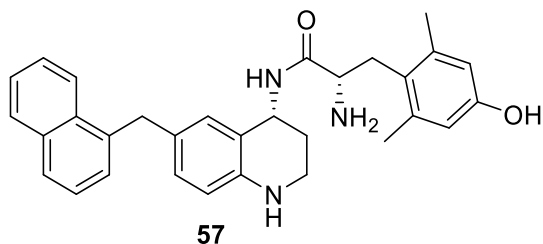
Synthesized by Larisa Yeomans. Synthesis and characterization herein and in Ref. 23

(*R*)-*N*-((*R*)-7-bromo-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methylpropane-2-sulfinamide (58). 58 was synthesized following general procedure H using commercially available 7-bromo-

3,4-dihydronaphthalen-1(2*H*)-one (1.0 g, 4.44 mmol, 1 eq), (*R*)-2-methylpropane-2-sulfinamide (1.08 g, 8.88 mmol, 2.0 eq), and Ti(OEt)$_4$ (3.73 mL, 17.8 mmol, 4 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into 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 eq) and 13 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography (1:9 EA:hex) to yield the title compound **58** as a clear, colorless oil (1.13 g, 77%). ^{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, 55.4, 52.5, 30.2, 28.4, 22.5, 18.0.

59
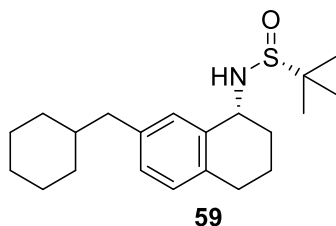
(*R*)-*N*-((*R*)-7-(cyclohexylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methylpropane-2-sulfinamide (59). 59 was synthesized following general procedure J using **58** (100 mg, 0.30 mmol, 1.0 eq), (cyclohexylmethyl)boronic acid (86 mg, 0.61 mmol, 2.0 eq), K$_2$CO$_3$ (126 mg, 0.91 mmol, 3.0 eq), Ag$_2$O (175 mg, 0.76 mmol, 2.5 eq), and Pd(dppf)Cl$_2$ (22 mg, 0.031 mmol, 0.1 eq). The reagents were placed in a microwave tube followed by 1.5 mL anhyd. THF and reacted in microwave with max temp of 80°C, max power of 300 W for 60 min, "Powermax" option disabled. Once the crude mixture was filtered through Celite, the residue purified via silica gel chromatography (equil in 100% hex, run in 2:3 EA:hex) to yield the title compound **59** as clear, colorless oil (105 mg, quant), which was taken to the next step (formation of **62**) without further characterization. No ^{1}H or ^{13}C data acquired.
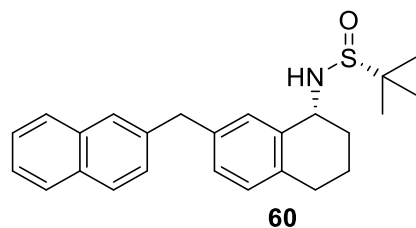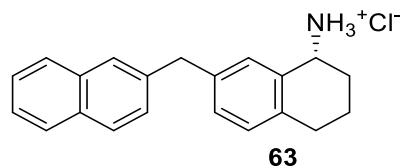
60

(*R*)-2-methyl-*N*-((*R*)-7-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propane-2-sulfinamide (60). 60 was synthesized following general procedure L using **58** (49 mg, 0.15 mmol, 1.0 eq), 4,4,5,5-tetramethyl-2-(naphthalen-2-ylmethyl)-1,3,2-dioxaborolane (80 mg, 3.0 mmol, 2.0 eq), K_2CO_3 (58 mg, 0.42 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (11 mg, 0.015 mmol, 0.1 eq). 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 microwave with max temp of 110°C, max power of 300 W for 60 min with "Powermax" enabled. Once crude mixture was filtered through Celite, the residue was purified via silica gel chromatography (equil in 100% hex, run in 1:1 EA:hex) to yield title compound **60** (32 mg, 55.2%) as a clear, colorless oil which was taken ahead to the next step (formation of **63**) without further characterization. No ^{1}H or ^{13}C data acquired.
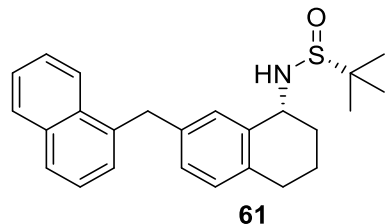
61

(*R*)-2-methyl-*N*-((*R*)-7-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propane-2-sulfinamide (61). 61 was synthesized following general procedure L using **58** (46 mg, 0.14 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(naphthalen-1-ylmethyl)-1,3,2-dioxaborolane (75 mg, 0.28 mmol, 2 eq), K_2CO_3 (58 mg, 0.42 mmol, 3 eq), and Pd(dppf)Cl$_2$ (10 mg, 0.014 mmol, 0.1 eq). The reagents were placed in a microwave tube followed by the previously degassed 3:1 acetone/water solvent system and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min with "Powermax" enabled. Once crude mixture was filtered through Celite, the residue was purified via silica gel chromatography (equil in 100% hex, run in 1:4 EA:hex) to yield title compound **61** (11 mg, 20.2%) as 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.
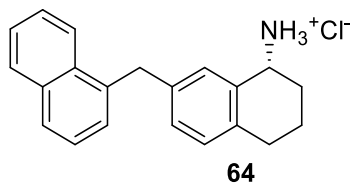

62
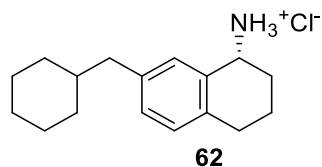
(**R**)-7-(cyclohexylmethyl)-1,2,3,4-tetrahydronaphthalen-1-aminium chloride (62). 62 was synthesized following general procedure I using **59** (100 mg, 0.29 mmol, 1.0 eq) and conc. HCl (42 μL, 1.7 mmol, 6.0 eq). After removing solvent, the residue was re-suspended in Et$_2$O and a white solid crashed out. The Et$_2$O was filtered off leaving a white, flaky precipitate which was washed with cold Et$_2$O, 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.


63

(**R**)-7-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-aminium chloride (63). 63 was synthesized following general procedure I using **60** (30 mg, 0.077 mmol, 1.0 eq) and conc. HCl (11 μL, 0.46 mmol, 6.0 eq). After removing solvent, the residue was re-suspended in Et$_2$O, and solid did not crash out. Residue was washed 3 x with fresh Et$_2$O then dried to yield the title compound **63** as off white, sticky solid (11 mg, 44.3%). ^{1}H NMR (500 MHz, CD$_3$OD) 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$_3$OD) 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.


64

(*R*)-7-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-aminium chloride (64). 64 was synthesized following general procedure I using **61** (11 mg, 0.028 mmol, 1.0 eq) and conc. HCl (4 µL, 0.17 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding the title compound **64** as a white solid (7 mg, 77.8%). ^{1}H NMR (400 MHz, CD$_3$OD) 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 data acquired.

65
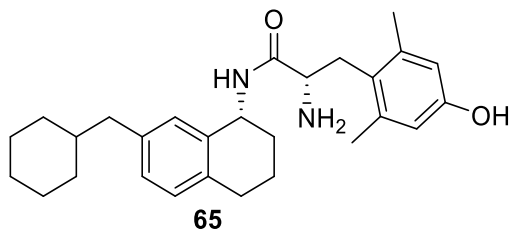
(*S*)-2-amino-*N*-((*R*)-7-(cyclohexylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (65). 65 was synthesized following general procedure F starting from the (*R*) amine intermediate **62** (20 mg, 0.0715 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **65** as a TFA salt (35 mg, 89.7%). ^{1}H NMR (500 MHz, CD$_3$OD) 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$_3$OD) 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]$^+$.
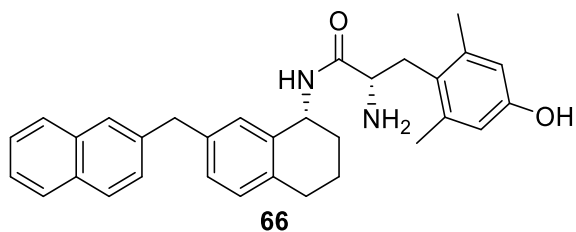

66

(*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-7-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide (66). 66 was synthesized following general procedure F starting from the (*R*) amine intermediate **63** (11 mg, 0.034 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **66** as a TFA salt (14 mg, 69.7%). ^{1}H NMR (500 MHz, CD$_3$OD) 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$_3$OD) 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]$^+$.
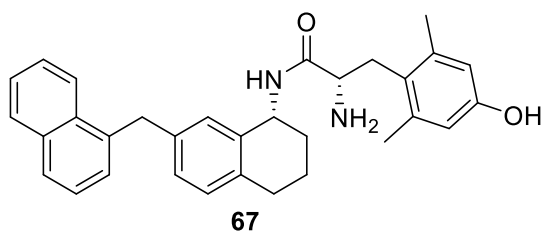

67

(*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-7-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide (67). 67 was synthesized following general procedure F starting from the (*R*) amine intermediate **64** (7 mg, 0.0216 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **67** as a TFA salt (11 mg, 85.9%). ^{1}H NMR (500 MHz, CD$_3$OD) 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$_3$OD) 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. ESI-MS 501.1 [M+Na]$^+$.

68
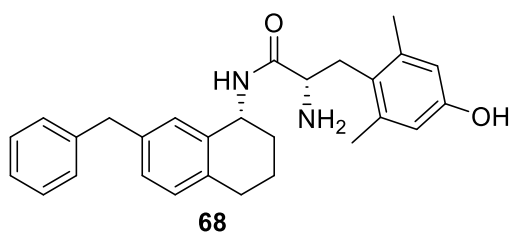
Synthesized by Larisa Yeomans. Synthesis and characterization can be found in Ref. 23
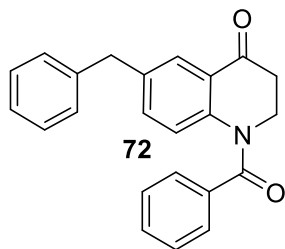

69
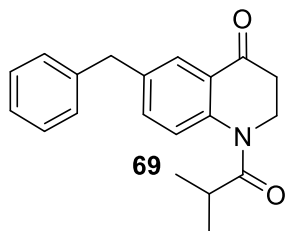
6-Benzyl-1-isobutyryl-2,3-dihydroquinolin-4(1*H*)-one (69). 69 was synthesized following general procedure M starting from the **30** (100 mg, 0.42 mmol, 1.0 eq), isobutyryl chloride (0.46 mL, 0.44 mmol, 2.0 eq) and Et$_3$N (0.062 mL, 0.44 mmol, 2.0 eq) to yield crude product which was purified to yield the title compound as a clear, colorless oil (105 mg, 80.8%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (d, *J* = 2.0 Hz, 1H), 7.37 – 7.25 (m, 4H), 7.25 – 7.17 (m, 3H), 4.21 (t, *J* = 6.3 Hz, 2H), 3.99 (s, 2H), 3.14 (hept, *J* = 6.7 Hz, 1H), 2.75 (t, *J* = 6.2 Hz, 2H), 1.18 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.33, 176.97, 142.29, 140.05, 138.84, 134.59, 128.90, 128.87, 128.68, 127.64, 126.46, 126.15, 124.22, 43.90, 41.25, 39.79, 31.13, 19.88.
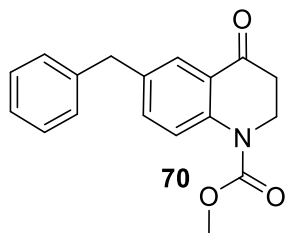
Methyl 6-benzyl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (70). 70 was synthesized following general procedure M starting from the **30** (150 mg, 0.63 mmol, 1.0 eq) and methyl chloroformate (0.100 mL, 1.26 mmol, 2.0 eq) yield crude product which was purified to yield the title compound as a clear, colorless oil (111 mg, 59.4%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.86 (d, J = 2.1 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.34 (dd, J = 8.6, 2.2 Hz, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.23 – 7.16 (m, 3H), 4.18 (t, J = 6.3 Hz, 2H), 3.97 (s, 2H), 3.84 (s, 3H), 2.76 (t, J = 6.3 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.79, 154.23, 141.74, 140.24, 137.32, 134.79, 128.74, 128.51, 127.13, 126.25, 124.79, 123.58, 53.30, 44.40, 41.09, 38.81.
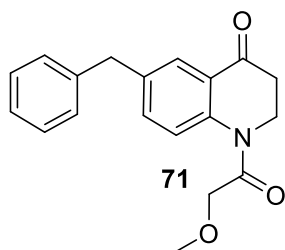
6-Benzyl-1-(2-methoxyacetyl)-2,3-dihydroquinolin-4(1*H*)-one (71). 71 was synthesized following general procedure M starting from the **30** (150 mg, 0.63 mmol, 1.0 eq) and 2-methoxyacetyl chloride (0.116 mL, 1.26 mmol, 2.0 eq) yield crude product which was purified to yield the title compound as a white solid (176 mg, 89.8%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (d, J = 2.2 Hz, 1H), 7.37 (dd, J = 8.4, 2.2 Hz, 1H), 7.28 (t, J = 7.6 Hz, 2H), 7.23 – 7.15 (m, 3H), 4.26 (s, 2H), 4.17 (t, J = 6.3 Hz, 2H), 3.98 (s, 2H), 3.45 (s, 3H), 2.78 (t, J = 6.2 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.62, 168.07, 141.25, 139.91, 139.02, 134.72, 128.77, 128.58, 128.55, 127.56, 126.37, 125.78, 123.66, 76.74, 71.84, 59.24, 43.95, 41.17, 39.41.

1-Benzoyl-6-benzyl-2,3-dihydroquinolin-4(1H)-one (72). **72** was synthesized following general procedure M starting from the **30** (100 mg, 0.42 mmol, 1.0 eq) and benzoyl chloride (100 mL, 0.84 mmol, 2.0 eq) to yield crude product which was purified to yield the title compound as a clear, slightly yellow oil (139 mg, 96.5%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, J = 2.1 Hz, 1H), 7.42 – 7.34 (m, 3H), 7.31 – 7.25 (m, 2H), 7.22 – 7.17 (m, 2H), 7.14 – 7.10 (m, 1H), 7.08 – 7.04 (m, 2H), 7.01 (dd, J = 8.5, 2.2 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.21 (t, J = 6.3 Hz, 2H), 3.85 (s, 2H), 2.77 (t, J = 6.3 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.73, 170.04, 142.60, 139.99, 138.06, 135.06, 134.31, 130.99, 128.78, 128.58, 128.47, 128.39, 127.38, 126.36, 124.82, 124.63, 45.30, 41.10, 39.50.
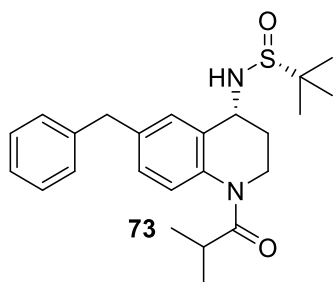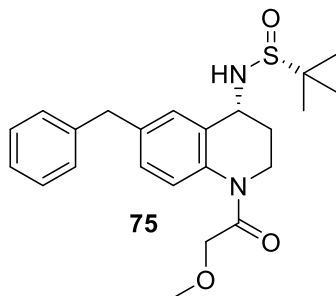

(R)-N-((R)-6-benzyl-1-isobutyryl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (73). 73 was synthesized following general procedure H using **69** (105 mg, .34 mmol, 1.0 eq), (R)-2-methylpropane-2-sulfinamide (124 mg, 1.02 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.430 mL, 2.05 mmol, 6.0 eq) to form the (R)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (77 mg, 2.05 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (70 mg, 50%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 – 7.26 (m, 3H), 7.24 – 7.19 (m, 3H), 7.10 (dd, J = 8.2, 2.2 Hz, 1H), 4.53 (q, J = 3.9 Hz, 1H), 3.96 (s, 2H), 3.94 – 3.89 (m, 1H),

3.75 – 3.67 (m, 1H), 3.30 (bs, 1H), 3.12 (p, J = 6.9 Hz, 1H), 2.24 – 2.15 (m, 1H), 2.08 – 1.98 (m, 1H), 1.23 – 1.16 (s, 9H), 1.13 (dd, J = 9.0, 6.7 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 177.35, 140.53, 138.70, 136.67, 128.92, 128.67, 128.58, 128.54, 126.28, 124.60, 55.76, 51.04, 41.37, 40.00, 31.09, 30.96, 22.55, 20.03, 20.01.
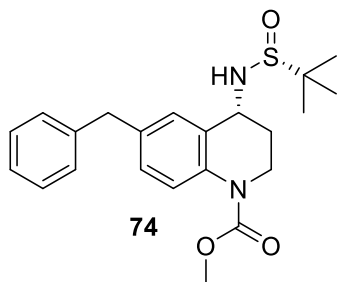

Methyl(R)-6-benzyl-4-(((R)-tert-butylsulfinyl)amino)-3,4-dihydroquinoline-1(2H)-carboxylate (74). 74 was synthesized following general procedure H using **70** (111 mg, 0.376 mmol, 1.0 eq), (R)-2-methylpropane-2-sulfinamide (137 mg, 1.13 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.473 mL, 2.26 mmol, 6.0 eq) to form the (R)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (85 mg, 2.26 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (124 mg, 82.1%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.73 (d, J = 8.7 Hz, 1H), 7.27 (t, J = 7.8 Hz, 2H), 7.23 – 7.16 (m, 4H), 7.11 – 7.06 (m, 1H), 4.54 (q, J = 3.6 Hz, 1H), 4.01 (dt, J = 13.0, 4.6 Hz, 1H), 3.93 (s, 2H), 3.78 (d, J = 1.0 Hz, 3H), 3.64 (ddd, J = 12.9, 11.1, 3.8 Hz, 1H), 3.26 (d, J = 2.7 Hz, 1H), 2.24 – 2.14 (m, 1H), 2.03 – 1.94 (m, 1H), 1.20 (d, J = 1.0 Hz, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.94, 140.75, 137.11, 136.11, 129.11, 128.79, 128.77, 128.57, 128.44, 126.09, 126.08, 123.68, 55.59, 52.94, 50.24, 41.15, 40.23, 29.43, 22.51.

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(*R*)-*N*-((*R*)-6-benzyl-1-(2-methoxyacetyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-
methylpropane-2-sulfinamide (75). **75** was synthesized following general procedure H using
71 (176 mg, 0.60 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (207 mg, 1.71 mmol, 3.0
eq), and Ti(OEt)$_4$ (0.716 mL, 3.41 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine
intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h),
the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (129
mg, 3.41 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution
was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid
was removed, crude residue was purified using silica gel chromatography to yield the title
compound as a clear, colorless oil (148 mg, 62.7%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30 – 7.24
(m, 3H), 7.18 (d, *J* = 7.6 Hz, 3H), 7.09 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.52 (q, *J* = 4.3 Hz, 1H), 4.17
(s, 2H), 3.93 (s, 2H), 3.79 (d, *J* = 40.2 Hz, 11H), 3.44 (d, *J* = 3.6 Hz, 1H), 3.39 (s, 3H), 2.20 (dq,
J = 14.5, 4.9 Hz, 1H), 2.04 (qd, *J* = 9.2, 8.7, 5.0 Hz, 1H), 1.20 (s, 35H), 1.17 (s, 10H). ^{13}C NMR
(126 MHz, CDCl$_3$) δ 168.45, 140.40, 135.69, 128.97, 128.82, 128.68, 128.50, 128.46, 128.21,
126.20, 126.14, 123.95,71.69, 59.16, 55.72, 55.22, 50.80, 41.38, 41.29, 39.90, 30.47, 29.60,
22.52, 22.21, 22.07.

76
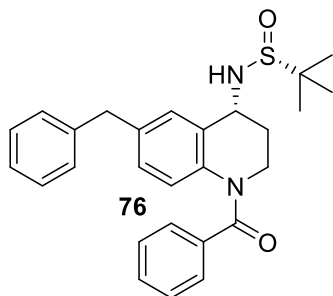
(*R*)-*N*-((*R*)-1-benzoyl-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-
sulfinamide (76). **76** was synthesized following general procedure H using **72** (139 mg, 0.41

mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (148 mg, 1.22 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.512 mL, 2.44 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (92 mg, 2.44 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as an off-white solid (127 mg, 69.8%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (td, *J* = 8.0, 1.4 Hz, 3H), 7.27 – 7.15 (m, 5H), 7.14 – 7.09 (m, 1H), 7.09 – 7.04 (m, 2H), 6.78 (t, *J* = 9.0 Hz, 2H), 4.54 (q, *J* = 3.9 Hz, 1H), 3.93 (dt, *J* = 12.5, 5.1 Hz, 1H), 3.82 (s, 2H), 3.78 – 3.68 (m, 1H), 3.32 (d, *J* = 3.1 Hz, 1H), 2.20 (dq, *J* = 14.0, 4.7 Hz, 1H), 2.02 (ddt, *J* = 14.5, 9.9, 5.0 Hz, 1H), 1.13 (d, *J* = 1.5 Hz, 11H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 170.22, 140.50, 138.06, 136.69, 135.96, 130.33, 129.87, 128.79, 128.68, 128.46, 128.34, 128.32, 128.23, 126.15, 125.31, 60.32, 55.72, 50.61, 41.47, 41.19, 30.24, 22.53, 20.99, 14.15.
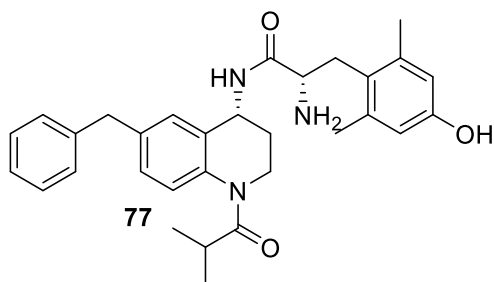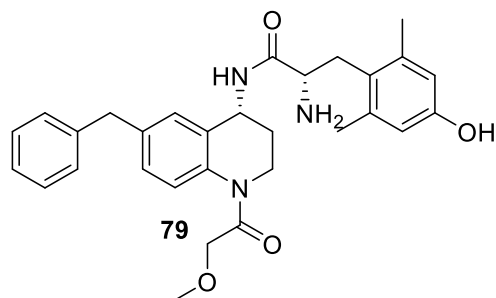

(*S*)-2-amino-*N*-((*R*)-6-benzyl-1-isobutyryl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (77). 77 was synthesized following general procedure I using **73** (70 mg, 0.17 mmol, 1.0 eq) and conc. HCl (0.1 mL, 1.0 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (58 mg). Then by following general procedure F with newly formed (*R*) amine intermediate (58 mg, 0.17 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound as a TFA salt (42 mg, 40.7 % from **73**). Note that not all crude product was purified. δ ^{1}H NMR (500 MHz, CD$_3$OD) δ 8.18 (d, *J* = 8.2 Hz, 0H), 7.19 (dt, *J* = 35.4, 7.7 Hz, 6H), 7.04 (d, *J* = 8.3 Hz, 3H), 6.51 (s, 2H), 3.92 (d, *J*

= 14.2 Hz, 3H), 3.26 (t, J = 12.6 Hz, 1H), 3.12 (ddt, J = 41.3, 13.4, 5.3 Hz, 4H), 2.27 (s, 7H), 1.86 (dq, J = 12.6, 6.2 Hz, 1H), 1.37 (dd, J = 12.8, 6.4 Hz, 1H), 1.12 (d, J = 6.6 Hz, 5H), 1.05 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 179.32, 169.29, 162.72, 157.37, 142.26, 140.05, 137.53, 129.77, 129.45, 129.20, 127.13, 125.65, 123.29, 116.40, 53.46, 46.89, 42.12, 32.38, 31.92, 31.83, 20.44, 20.17, 19.90. HPLC (gradient A): retention time 37.8. ESI-MS 500.3 [M+H]$^+$ and 522.3 [M+Na]$^+$.
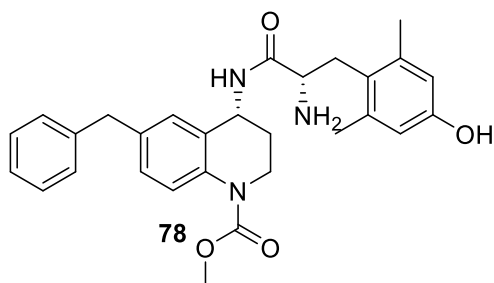
Methyl (*R*)-4-((*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamido)-6-benzyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (78). 78 was synthesized following general procedure I using **74** (124 mg, 0.31 mmol, 1.0 eq) and conc. HCl (5 µL, 1.86 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (79 mg). Then by following general procedure F with newly formed (*R*) amine intermediate (40 mg, 0.12 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **78** as a TFA salt (50 mg, 69.5% from **74**). ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.65 (d, *J* = 8.6 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.17 – 7.12 (m, 3H), 7.07 (d, *J* = 2.2 Hz, 1H), 7.03 (dd, *J* = 8.8, 1.9 Hz, 1H), 6.50 (s, 2H), 4.97 (t, *J* = 5.2 Hz, 1H), 3.87 (s, 2H), 3.86 – 3.81 (m, 1H), 3.75 (d, *J* = 1.4 Hz, 4H), 3.25 (ddd, *J* = 13.1, 11.5, 1.4 Hz, 1H), 3.16 (tdd, *J* = 6.7, 3.8, 1.4 Hz, 12H), 3.05 – 2.94 (m, 2H), 2.27 (d, *J* = 1.4 Hz, 7H), 1.90 – 1.82 (m, 12H), 1.77 (tt, *J* = 9.7, 4.8 Hz, 1H), 1.54 – 1.45 (m, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 36.6. ESI-MS 488.3 [M+H]$^+$ and 510.3 [M+Na]$^+$.

(S)-2-amino-N-((R)-6-benzyl-1-(2-methoxyacetyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (79). 79 was synthesized following general procedure I using **75** (148 mg, 0.36 mmol, 1.0 eq) and conc. HCl (5 µL, 2.14 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (106 mg). Then by following general procedure F with newly formed (R) amine intermediate (55 mg, 0.159 mmol) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound as a TFA salt (**79**). No yield was determined because only a fraction of crude product was purified. ¹H NMR (400 MHz, CD$_3$OD) δ 7.23 (t, *J* = 7.8 Hz, 2H), 7.14 (dd, *J* = 9.3, 2.6 Hz, 4H), 7.07 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.51 (s, 2H), 4.96 (t, *J* = 5.7 Hz, 1H), 4.25 (dd, *J* = 14.6, 1.1 Hz, 1H), 4.14 (d, *J* = 14.5 Hz, 1H), 3.90 (s, 2H), 3.84 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.40 (s, 3H), 3.25 (t, *J* = 12.6 Hz, 1H), 3.15 (tdd, *J* = 6.7, 3.7, 1.2 Hz, 7H), 3.02 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.27 (s, 6H), 1.88 – 1.81 (m, 8H), 1.48 (s, 1H). No ¹³C data acquired. HPLC (gradient A): retention time 32.5. ESI-MS 502.3 [M+H]⁺ and 524.3 [M+Na]⁺.
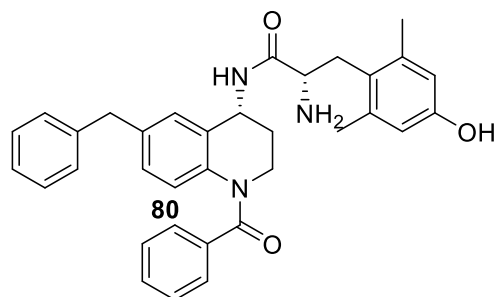

(S)-2-amino-N-((R)-1-benzoyl-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (80). 80 was synthesized following general procedure I using **76** (182 mg, 0.41 mmol, 1.0 eq) and conc. HCl (6 µL, 2.45 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh

Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (154 mg). Then by following general procedure F with newly formed (*R*) amine intermediate (77 mg, 0.20 mmol) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **80** as a TFA salt. No yield was determined because only a fraction of crude product was purified ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.47 – 7.42 (m, 1H), 7.37 (d, *J* = 6.8 Hz, 4H), 7.25 – 7.20 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.87 – 6.76 (m, 2H), 6.49 (s, 2H), 5.04 (t, *J* = 6.0 Hz, 1H), 3.92 – 3.81 (m, 4H), 3.25 (d, *J* = 12.3 Hz, 1H), 3.06 (dd, *J* = 13.8, 5.1 Hz, 1H), 2.28 (s, 6H), 1.94 (t, *J* = 10.4 Hz, 1H), 1.48 (dd, *J* = 13.0, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 172.42, 169.14, 157.49, 142.26, 140.04, 139.67, 137.75, 137.19, 131.74, 130.37, 129.71, 129.50, 129.45, 129.39, 128.99, 127.15, 126.27, 123.18, 116.45, 53.53, 49.00, 46.85, 42.06, 31.98, 31.42, 20.44.

81
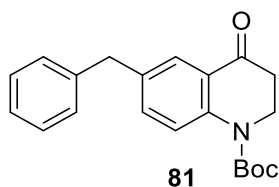
***Tert*-butyl 6-benzyl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (81). 81** was synthesized following general procedure G using **30** (1.1 g, 4.63 mmol, 1.0 eq), Boc$_2$O (1.52 g, 6.95 mmol, 1.5 eq), DMAP (57 mg, 0.463 mmol, 0.1 eq) and DIPEA (1.21 mL, 6.95 mmol, 1.5 eq). Following the quench and work-up, the crude product was chromatographed on silica gel (equil in 100% hex, run in 2:3 EA:hex) to yield pure product as a white solid (1.1 g, 70.2%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.76 (t, *J* = 2.0 Hz, 1H), 7.60 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.27 – 7.17 (m, 3H), 7.15 – 7.07 (m, 3H), 4.08 – 4.02 (m, 2H), 3.88 (s, 2H), 2.66 (td, *J* = 6.5, 6.0, 1.7 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.22, 152.71, 142.35, 140.37, 136.84, 134.60, 128.78, 128.53, 127.11, 126.24, 124.76, 123.80, 82.04, 44.23, 41.12, 38.95, 28.25. HPLC (gradient A): retention time 39.9. ESI-MS 534.3 [M+H]$^+$ and 556.2 [M+Na]$^+$.


82
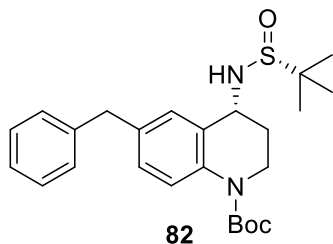
***Tert*-butyl(*R*)-6-benzyl-4-(((*R*)-*tert*-butylsulfinyl)amino)-3,4-dihydroquinoline-1(2*H*)-carboxylate (82). 82** was synthesized following general procedure H using **81** (1.1g, 4.8 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (175 mg, 1.44 mmol, 3.0 eq), and Ti(OEt)₄ (0.604 mL, 2.88 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH₄ (109 mg, 2.44 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (175 mg, 82.2%). ¹H NMR (500 MHz, CDCl₃) δ 7.69 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.20 - 7.15 (qd, *J* = 6.5, 5.4, 1.6 Hz, 4H), 7.06 (dd, *J* = 8.5, 2.3 Hz, 1H), 4.52 (q, *J* = 3.4 Hz, 1H), 3.97 – 3.87 (m, 3H), 3.57 (tdd, *J* = 12.9, 4.2, 1.7 Hz, 1H), 3.32 (bs, 1H), 2.20 – 2.13 (m, 1H), 1.99 – 1.90 (m, 1H), 1.50 (s, 9H), 1.19 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 153.43, 140.77, 136.51, 136.42, 128.88, 128.71, 128.55, 128.47, 128.34, 125.97, 123.89, 80.97, 55.52, 50.36, 41.08, 40.00, 29.41, 28.22, 22.48.


83
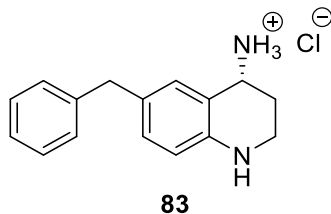
(*R*)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-aminium chloride (83). 83 was synthesized by first treating **82** (400 mg, 0.904 mml, 1.0 eq) with excess 1:1 TFA: DCM. After 1 h, solvent was removed under reduced pressure. Next, following general procedure I, the Ellman auxillary was cleaved using conc. HCl (0.133 mL, 5.43 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et₂O, and solid crashed out. After washing the solid 3 x with fresh Et₂O, the remaining Et₂O was decanted off, yielding the title compound as tan solid (110 mg, 44.4% from **82**). ¹H NMR (500 MHz, CD₃OD) δ 7.68 (d, J = 1.8 Hz, 1H), 7.44 (dd, J = 8.3, 1.8 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.31 – 7.24 (m, 4H), 7.22 – 7.17 (m, 1H), 4.77 (t, J = 6.0 Hz, 1H), 4.06 (s,

2H), 3.73 (ddd, J = 12.4, 9.0, 3.1 Hz, 1H), 3.65 (ddd, J = 13.0, 7.8, 3.3 Hz, 1H), 2.61 (dddd, J = 14.8, 9.0, 5.7, 3.3 Hz, 1H), 2.38 (dddd, J = 14.8, 7.8, 6.4, 3.1 Hz, 1H). No ^{13}C NMR data acquired.


84
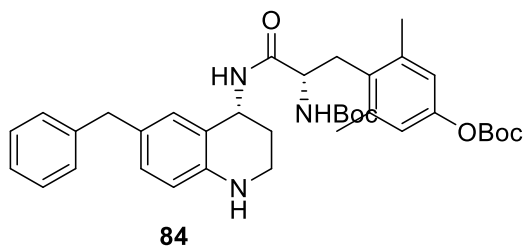
***Tert*-butyl((*S*)-1-(((*R*)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)-3-(4-((*tert*-butoxycarbonyl)oxy)-2,6-dimethylphenyl)-1-oxopropan-2-yl)carbamate (84). 84** was synthesized following a modified version of general procedure F using **83** (110 mg, 0.40 mmol, 1.0 eq). After coupling to diBoc-Dmt, residue was not deprotected with TFA. Instead, the crude residue was purified by semipreparative HPLC and lyophilized to yield the title compound **84** (287 mg, quant). HPLC (gradient A): retention time = 57.0. ESI-MS 630.3 [M+H]$^+$ and ESI-MS 652.3 [M+Na]$^+$. No ^{1}H or ^{13}C NMR data acquired.


85
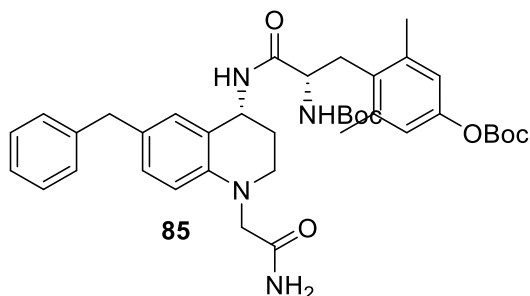
***Tert*-butyl((*S*)-1-(((*R*)-1-(2-amino-2-oxoethyl)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)-3-(4-((*tert*-butoxycarbonyl)oxy)-2,6-dimethylphenyl)-1-oxopropan-2-yl)carbamate (85).** To form **85** from **84**, first acetone was degassed for 30 min, then flooded with Ar for an additional 30 min. To a flame-dried round bottom flask equipped with a stir bar with Ar atmosphere was added sodium iodide (25 mg, 0.16 mmol, 2.0 eq) and 2-chloroacetamide (15 mg, 0.16 mmol, 2.0 eq), which was then placed back under vacuum. Next, 10 mL of degassed acetone was added to the reaction vessel via cannula, reaction stirred for 10 min. Meanwhile, to another flame-dried round bottom flask equipped with a stirbar was added **84**, degassed acetone, followed by DIPEA (0.021 mL, 0.12 mmol, 1.5 eq) and the solution stirred for

10 min. Next, the contents of the round bottom flask containing the sodium iodide and 2-chloroacetamide was transferred to the flask containing **84** via cannula. The reaction stirred stirred at room temp for 24 h. The next day, the solvent was removed under reduced pressure to yield the crude product (13 mg) that was taken ahead to next step (formation of **88**) without further purification, isolation or characterization. HPLC (gradient A): retention time = 60.5. ESI-MS 687.3 [M+H]$^+$ and ESI-MS 709.3 [M+Na]$^+$. No ^{1}H or ^{13}C NMR data acquired.
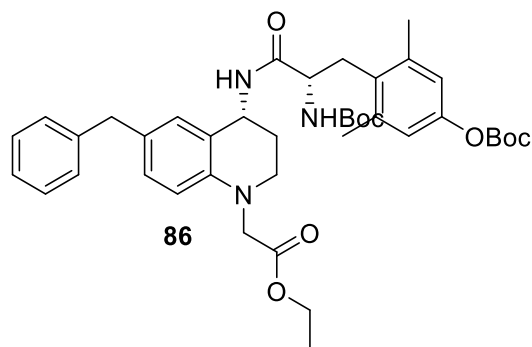
Ethyl2-((*R*)-6-benzyl-4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((*tert*-butoxycarbonyl)oxy)-2,6-dimethylphenyl)propanamido)-3,4-dihydroquinolin-1(2*H*)-yl)acetate (86). To synthesize **86**, **84** (214 mg, 0.34 mmol, 1.0 eq) and K$_2$CO$_3$ (94 mg, 0.68 mmol, 2.0 eq) were placed in a round bottom flask and the atmosphere was evacuated then the reaction vessel was flooded with Ar. Anhydrous CH$_3$CN was added via syringe and the solution stirred for 15 min. Next, bromo ethylacetate (0.377 mL, 3.4 mmol, 10 eq) was added to the reaction vessel, which was equipped with a condenser and placed in an 80˚C oil bath. After 6 h, no reaction was taking place (reaction was monitored by TLC). Reaction vessel was taken off heat and stirred overnight at RT. After 24 h, the solvent was removed under reduced pressure and crude residue was resuspended in DCM and dI H$_2$O and the layers separated. The organic layer was washed with 5% citric acid solution (1 x 20 mL) and then with brine (1 x 20 mL), dried over MgSO$_4$ to yield the crude residue of **86**. HPLC (gradient A): retention time = 72.4. ESI-MS 716.3 [M+H]$^+$ and ESI-MS 738.3 [M+Na]$^+$. The residue was carried forward (to synthesize **87** and **89**) without further purification, isolation or characterization. No ^{1}H or ^{13}C NMR data acquired.
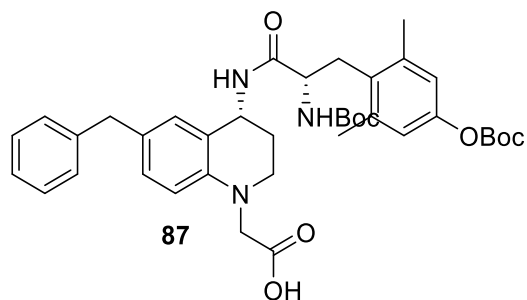
2-((*R*)-6-benzyl-4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((*tert*-butoxycarbonyl)oxy)-2,6-dimethylphenyl)propanamido)-3,4-dihydroquinolin-1(2*H*)-yl)acetic acid (87). 87 was synthesized by treating crude **86** (107 mg, 0.15 mmol, 1.0 eq) with LiOH (excess) in EtOH at 60˚C for 2.5 h. Reaction was monitored for loss of starting material by analytical HPLC ((gradient A): starting material retention time = 72.4). Once starting material was consumed, solvent was removed under reduced pressure. HPLC (gradient A): retention time = 49.9. The residue was carried forward (**90**) without further purification, isolation or characterization. No ^{1}H or ^{13}C NMR data acquired.
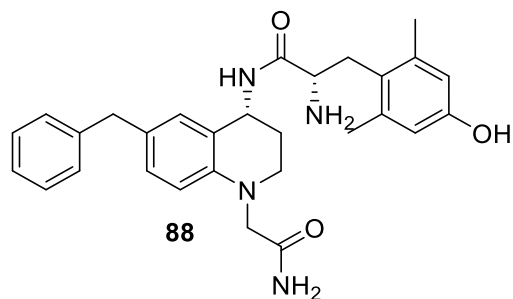

(*S*)-2-amino-*N*-((*R*)-1-(2-amino-2-oxoethyl)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (88). 88 was synthesized from 84 by boc-deprotection using 1:1 TFA:DCM. After removal of solvent under reduced pressure, the crude product was purified by semipreparative HPLC and lyophilized to yield the title compound **88** (2 mg, 18%). HPLC (gradient A): retention time = 29.8. ESI-MS 509.3 [M+H]$^+$. ^{1}H NMR (500 MHz, CD$_3$OD) δ 8.33 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 2H), 7.14 – 7.07 (m, 3H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.86 (s, 1H), 6.46 (s, 2H), 6.38 (d, *J* = 8.5 Hz, 1H), 3.91 (d, *J* = 17.8 Hz, 1H), 3.80 (dd, *J* = 11.8, 5.1 Hz, 1H), 3.76 (s, 2H), 3.66 – 3.59 (m, 1H), 3.25 (t, *J* = 12.4 Hz, 1H), 3.00 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.86 (d, *J* = 12.1 Hz, 1H), 2.38 (t, *J* = 12.1 Hz, 1H), 1.81 (t, *J* = 13.1 Hz, 1H), 1.52 (d, *J* = 13.4 Hz, 1H), 1.29 (s, 1H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 175.88, 157.43, 144.84, 140.04, 131.51, 131.21, 130.86, 129.63, 129.29, 126.85, 123.21, 121.80, 116.48,

112.92, 66.62, 55.53, 53.45, 49.00, 47.37, 47.27, 46.62, 41.77, 31.89, 28.93, 20.46. HPLC (gradient A): retention time 29.8. ESI-MS 487.3.3 [M+H]+ and 509.3 [M+Na]+.
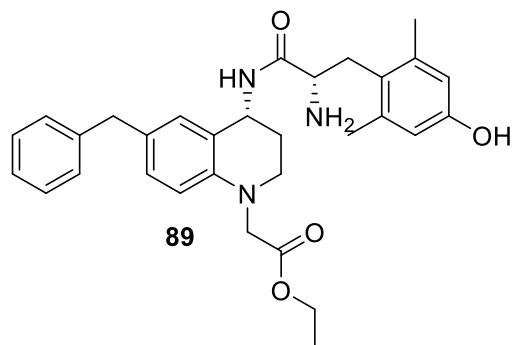

Ethyl 2-((R)-4-((S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamido)-6-benzyl-3,4-dihydroquinolin-1(2H)-yl)acetate (89). 89 was synthesized by treating crude **86** with 3 N HCl to remove the remaining boc-groups and yield the crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **89** (44 mg, 41.1%).^{1}H NMR (500 MHz, CD3OD) δ 8.17 (d, J = 7.6 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.14 – 7.07 (m, 3H), 6.92 – 6.85 (m, 2H), 6.43 (s, 2H), 6.39 (d, J = 8.4 Hz, 1H), 4.87 (s, 6H), 4.24 (s, 0H), 4.23 – 4.15 (m, 2H), 3.81 (q, J = 5.3 Hz, 1H), 3.76 (d, J = 8.6 Hz, 2H), 3.31 (s, 2H), 3.25 (dd, J = 13.5, 11.8 Hz, 1H), 3.00 (dd, J = 13.6, 5.0 Hz, 1H), 2.85 (dt, J = 11.8, 4.1 Hz, 1H), 2.42 (td, J = 12.3, 3.2 Hz, 1H), 2.27 (s, 6H), 1.75 (tt, J = 12.8, 4.1 Hz, 1H), 1.57 (dq, J = 13.3, 3.5 Hz, 1H), 1.29 (td, J = 7.1, 1.0 Hz, 3H). 13C NMR (126 MHz, CD3OD) δ 173.03, 168.05, 157.42, 144.44, 143.28, 140.00, 131.60, 131.03, 130.84, 129.64, 129.29, 126.84, 123.20, 121.53, 116.47, 112.40, 62.35, 53.49, 53.20, 49.51, 49.34, 49.17, 49.00, 48.83, 48.66, 48.49, 47.56, 46.18, 41.75, 31.87, 28.78, 20.48, 14.51. HPLC (gradient A): retention time = 41.7. ESI-MS 516.3 [M+H]+ and 538.3 [M+Na]+.
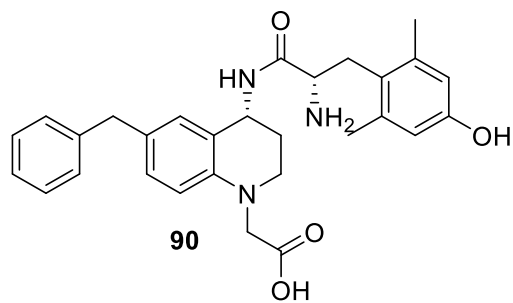

2-((R)-4-((S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamido)-6-benzyl-3,4-

dihydroquinolin-1(2*H*)-yl)acetic acid (90). 90 was formed by treating the crude residue of 87 with 1:1 TFA:DCM to form crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **90**. No yield was determined because only a fraction of crude product was purified. HPLC (gradient A): retention time = 26.4. ESI-MS 488.3 [M+H]$^+$ and 510.3 [M+Na]$^+$. No ^{1}H or ^{13}C NMR data acquired. Instead, formation of final product verified by mass spectrometry.


91
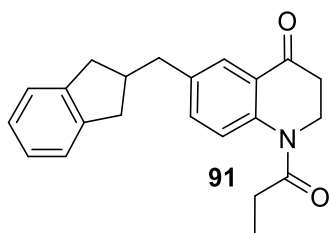
6-((2,3-Dihydro-1*H*-inden-2-yl)methyl)-1-propionyl-2,3-dihydroquinolin-4(1*H*)-one (91). 91 was synthesized according to general procedure N using **6** (155 mg, 0.56 mmol, 1.0 eq) and excess propionic anhydride. Once complete, excess anhydride was removed and the crude residue was purified using silica gel chromatography to yield the title compound **91** as a clear, colorless oil (136 mg, 76.1%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.86 (s, 1H), 7.42 (s, 1H), 7.39 (s, 1H), 7.16 (q, *J* = 4.1 Hz, 2H), 7.12 (q, *J* = 4.5 Hz, 2H), 4.23 (t, *J* = 6.3 Hz, 2H), 3.00 (dd, *J* = 15.3, 6.7 Hz, 2H), 2.85 - 2.74 (m, 5H), 2.69 – 2.57 (m, 4H), 1.23 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.25, 172.94, 142.73, 141.93, 138.80, 134.59, 127.42, 126.15, 125.92, 124.42, 124.12, 43.81, 41.07, 40.65, 39.53, 38.71, 27.88, 9.79.


92
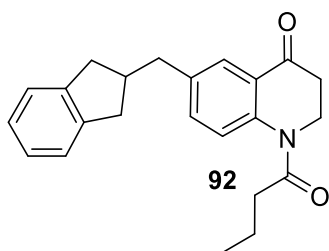
1-Butyryl-6-((2,3-dihydro-1*H*-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1*H*)-one (92). 92 was synthesized according to general procedure N using **6** (320 mg, 1.2 mmol, 1.0 eq) and excess butyric anhydride. Once complete, excess anhydride was removed and the crude residue was purified using silica gel chromatography to yield the title compound **92** as a clear, colorless

oil (152 mg, 37.9%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 (s, 1H), 7.40 (s, 1H), 7.18 – 7.14 (m, 2H), 7.13 -7.08 (m, 2H), 4.22 (t, J = 6.4 Hz, 2H), 2.99 (dd, J = 15.4, 6.8 Hz, 2H), 2.82 – 2.71 (m, 5H), 2.66 (dd, J = 15.4, 6.5 Hz, 2H), 2.57 (t, J = 7.5 Hz, 2H), 1.75 (h, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 4H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.25, 172.14, 142.68, 141.85, 138.74, 134.55, 127.34, 126.09, 125.83, 124.36, 124.12, 43.80, 41.00, 40.58, 39.55, 38.64, 36.32, 18.99, 13.70.
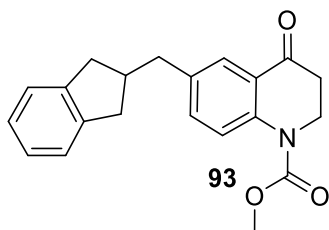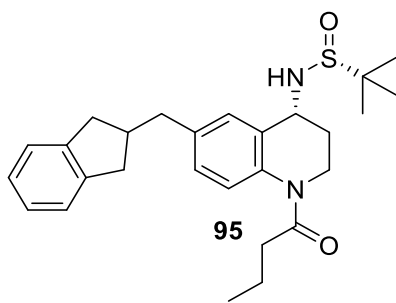

Methyl6-((2,3-dihydro-1H-inden-2-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (93). 93 was synthesized using a modified general procedure N using **6** (250 mg, 0.90 mmol, 1.0 eq), ethyl methyl dicarbonate (0.150 mL, 1.4 mmol, 1.5 eq), DMAP (11 mg, 0.09 mmol, 0.1 eq), and DIPEA (235 mL, 1.4 mmol, 1.5 eq). The reaction stirred overnight, once complete, solvent was removed and the crude residue was purified using silica gel chromatography to yield the title compound **93** as a clear, colorless oil (38 mg, 12.6%). Starting material was recovered, but not included in final yield calculation. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 (d, J = 2.2 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.38 (dd, J = 8.6, 2.3 Hz, 1H), 7.19 – 7.15 (m, 2H), 7.15 – 7.10 (m, 2H), 4.21 (t, J = 6.3 Hz, 2H), 3.86 (s, 3H), 2.99 (dd, J = 15.5, 6.3 Hz, 2H), 2.81 – 2.77 (m, 5H), 2.66 (dd, J = 15.2, 6.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.02, 154.35, 142.90, 141.65, 137.58, 134.94, 127.11, 126.17, 124.79, 124.48, 123.42, 109.98, 53.39, 44.50, 41.19, 40.64, 38.92, 38.77.
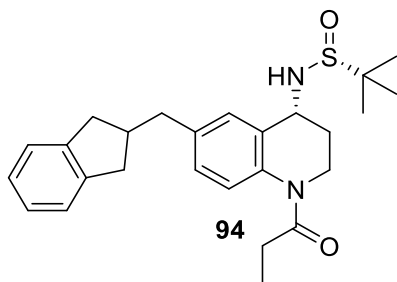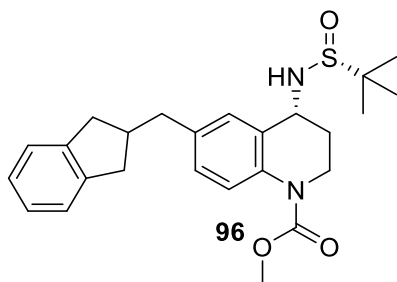

(R)-N-((R)-6-((2,3-dihydro-1H-inden-2-yl)methyl)-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (94). 94 was synthesized according to general procedure

H using **91** (136 mg, 0.41 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (148 mg, 1.22 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.51 mL, 2.4 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (93 mg, 2.4 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **94** as a clear, colorless oil (87 mg, 48.6%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29 – 7.27 (bs, 1H), 7.19 – 7.15 (m, 2H), 7.15 – 7.10 (m, 3H), 4.56 (q, *J* = 4.2 Hz, 1H), 3.93 (dt, *J* = 12.7, 5.4 Hz, 1H), 3.76 (ddd, *J* = 12.7, 9.5, 5.1 Hz, 1H), 3.32 (d, *J* = 3.5 Hz, 1H), 3.04 – 2.95 (m, 2H), 2.81 – 2.71 (m, 3H), 2.67 (dd, *J* = 15.1, 5.5 Hz, 2H), 2.53 (qt, *J* = 7.2, 1.2 Hz, 2H), 2.27 - 2.16 (m, 1H), 2.12 – 2.01 (m, 1H), 1.22 (d, *J* = 1.2 Hz, 9H), 1.18 (td, *J* = 7.4, 1.2 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 173.44, 142.96, 142.94, 138.73, 136.41, 128.67, 128.61, 126.10, 124.59, 124.43, 124.42, 55.69, 50.97, 41.23, 40.80, 39.92, 38.82, 38.78, 30.73, 28.07, 22.53, 9.96.
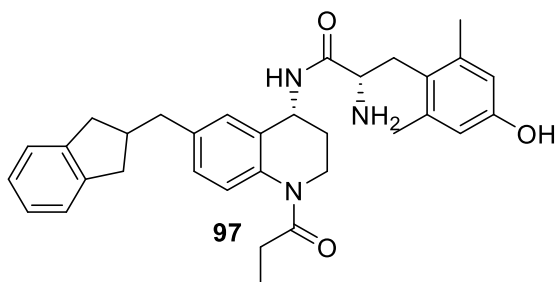

(*R*)-*N*-((*R*)-1-butyryl-6-((2,3-dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (95). 95 was synthesized according to general procedure H using **92** (152 mg, 0.44 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (159 mg, 1.3 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.55 mL, 2.6 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (99 mg, 2.6 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (198 mg, quant). No ^{1}H or ^{13}C NMR spectrum acquired.

Instead, product taken ahead to next reaction (formation of **98**) without any further isolation, purification, or characterization.


Methyl(*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-((2,3-dihydro-1*H*-inden-2-yl)methyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (96). 96 was synthesized according to general procedure H using **93** (94 mg, 0.28 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (102 mg, 0.84 mmol, 3.0 eq), and Ti(OEt)$_4$ (1.06 mL, 1.7 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (191 mg, 1.7 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (8 mg, 6.5%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 – 7.72 (m, 1H), 7.22 (bs, 1H), 7.17 (s, 2H), 7.14 – 7.08 (m, 3H), 4.58 (bs, 1H), 4.05 (dd, *J* = 11.4, 5.9 Hz, 1H), 3.81 (d, *J* = 1.9 Hz, 3H), 3.69 – 3.59 (m, 1H), 3.28 (s, 1H), 2.99 (d, *J* = 14.9 Hz, 2H), 2.74 (s, 3H), 2.70 – 2.61 (m, 2H), 2.24 – 2.14 (m, 1H), 2.02 (t, *J* = 12.7 Hz, 1H), 1.22 (d, *J* = 1.8 Hz, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 175.35, 155.02, 143.08, 143.06, 137.41, 136.00, 129.23, 128.93, 128.42, 126.11, 124.48, 124.45, 123.49, 55.63, 53.02, 50.32, 41.36, 40.67, 40.25, 38.86, 38.84, 22.57.
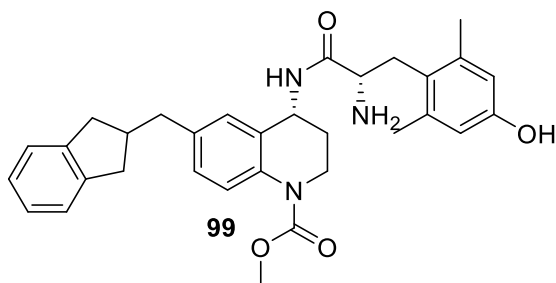
(*S*)-2-amino-*N*-((*R*)-6-((2,3-dihydro-1*H*-inden-2-yl)methyl)-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (97). 97 was synthesized following general procedure I using **94** (87 mg, 0.20 mmol, 1.0 eq) and conc. HCl (0.029 mL, 1.2 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (60 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (18 mg, 0.16 mmol) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound as a TFA salt (31 mg, quant.).^{1}H NMR (500 MHz, CD$_3$OD) δ 7.43 (s, 1H), 7.16 – 7.03 (m, 6H), 6.51 (s, 2H), 4.96 (t, *J* = 6.3 Hz, 1H), 3.87 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.81 (s, 1H), 3.30 – 3.22 (m, 1H), 3.19 (s, 1H), 3.04 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.98 – 2.85 (m, 2H), 2.77 - 2.68 (m, 3H), 2.66 – 2.59 (m, 2H), 2.59 – 2.42 (m, 2H), 2.28 (s, 6H), 1.88 (ddt, *J* = 13.4, 8.0, 5.3 Hz, 1H), 1.49 – 1.37 (m, 1H), 1.18 – 1.08 (t, 3H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 175.80, 169.18, 157.46, 144.09, 144.05, 140.07, 137.41, 129.16, 127.21, 125.64, 125.37, 125.35, 123.25, 116.44, 53.49, 47.02, 42.76, 41.85, 39.88, 39.66, 31.97, 31.47, 28.91, 20.43, 10.12. HPLC (gradient A): retention time 40.6. ESI-MS 526.1 [M+H]$^+$ and 548.1 [M+Na]$^+$.
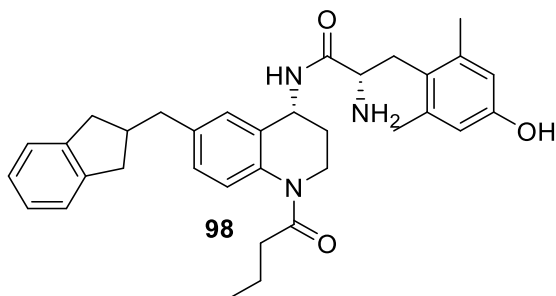

(*S*)-2-amino-*N*-((*R*)-1-butyryl-6-((2,3-dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (98). 98 was synthesized following general procedure I using **95** (198 mg, 0.44 mmol, 1.0 eq) and conc. HCl (0.064 mL, 2.6 mmol, 6.0 eq). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (168 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (168 mg, 0.44 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **98** as a TFA salt (9 mg). No percent yield done because not all crude

material was purified. ¹H NMR (500 MHz, CD₃OD) δ 7.12 (t, J = 5.4 Hz, 7H), 7.07 (dt, J = 5.6, 2.7 Hz, 2H), 6.51 (s, 2H), 4.95 (s, 1H), 3.92 – 3.78 (m, 2H), 3.18 (bs, 2H), 3.05 (dd, J = 13.5, 5.1 Hz, 1H), 2.99 – 2.86 (m, 2H), 2.73 (d, J = 14.5 Hz, 3H), 2.66 – 2.57 (m, 2H), 2.49 (q, J = 7.1 Hz, 2H), 2.28 (s, 6H), 1.88 (dq, J = 12.9, 6.5, 6.0 Hz, 1H), 1.65 (q, J = 7.7 Hz, 2H), 1.41 (s, 1H), 0.95 (t, J = 7.7 Hz, 3H). ¹³C NMR (126 MHz, CD₃OD) δ 174.96, 169.19, 157.46, 144.09, 144.05, 140.06, 137.40, 129.13, 127.21, 125.68, 125.37, 125.36, 123.25, 116.45, 53.50, 46.97, 42.74, 41.86, 39.88, 39.66, 37.53, 31.97, 31.63, 27.61, 20.44, 20.07, 14.11. HPLC (gradient A): retention time 44.8. ESI-MS 540.3 [M+H]⁺ and 562.3 [M+Na]⁺.


Methyl(*R*)-4-((*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamido)-6-((2,3-dihydro-1*H*-inden-2-yl)methyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (99). 99 was synthesized following general procedure I using **96** (8 mg, 0.018 mmol, 1.0 eq) and conc. HCl (1 drop). After removing solvent, residue was re-suspended in Et₂O, and solid crashed out. After washing the solid 3 x with fresh Et₂O, the remaining Et₂O was decanted off, yielding a white solid amine hydrochloride salt (6 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (6 mg, 0.0.16 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **99** as a TFA salt (7 mg, 70%). ¹H NMR (500 MHz, CD₃OD) δ 7.66 (d, J = 8.5 Hz, 1H), 7.16 – 7.01 (m, 5H), 6.50 (s, 2H), 5.00 (t, J = 5.2 Hz, 1H), 3.85 (dd, J = 11.6, 5.0 Hz, 1H), 3.77 (s, 4H), 3.26 (dd, J = 13.6, 11.6 Hz, 1H), 3.08 – 3.00 (m, 2H), 2.92 (ddd, J = 28.1, 14.9, 5.9 Hz, 2H), 2.74 – 2.57 (m, 5H), 2.27 (s, 6H), 1.80 (ddt, J = 14.4, 9.6, 4.7 Hz, 1H), 1.52 – 1.44 (m, 1H). ¹³C NMR (126 MHz, CD₃OD) δ 168.93, 157.49, 156.63, 144.13, 144.08, 140.00, 138.40, 137.28, 130.17, 129.42, 128.67, 127.20, 125.38, 125.35, 124.47, 123.20, 116.44, 53.54, 53.44, 46.97, 42.82,

42.39, 41.71, 39.91, 39.64, 31.95, 30.47, 20.45. HPLC (gradient A): retention time 42.9. ESI-MS 528.3 [M+H]+ and 550.3 [M+Na]+.
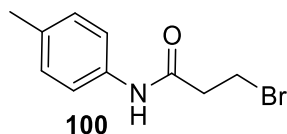
3-Bromo-*N*-(*p*-tolyl)propanamide (100). 100 was synthesized according to general procedure C starting from the commercially available starting material *p*-toluidine (2.0 g, 18.7 mmol, 1.0 eq), K$_2$CO$_3$ (5.29 g, 38.3 mmol, 2.05 eq) and bromopropionyl chloride (3.05 mL, 19.0 mmol, 1.02 eq) to yield the title compound as an off-white solid (4.52 g, quant.) %) with no additional purification necessary. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33 – 7.28 (m, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.84 (t, *J* = 6.6 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 167.85, 134.78, 134.37, 129.49, 120.21, 40.58, 27.17, 20.86.
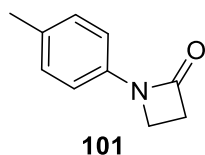

1-(*P*-tolyl)azetidin-2-one (101). 101 was synthesized according to general procedure D starting from **100** (4.5 g, 19 mmol, 1.0 eq) and NaO*t*Bu (1.9 g, 20 mmol, 1.05 eq) to yield the crude product which was purified using silica gel chromatography to yield title compound as an off-white solid (2.8 g, 93.7%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 3.60 (m, 2H), 3.12 – 3.06 (m, 2H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 164.22, 136.12, 133.36, 129.56, 116.03, 37.95, 35.97, 20.87.
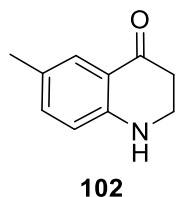

6-Methyl-2,3-dihydroquinolin-4(1*H*)-one (102). 102 was synthesized according to general procedure E starting from **101** (2.8 g, 18 mmol, 1.0 eq) and TfOH (4.6 mL, 58 mmol, 3.0 eq) to yield the crude product which was then purified using silica gel chromatography to yield title

compound as yellow solid (2.1 g, 73.8%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, J = 2.1 Hz, 1H), 7.13 (dd, J = 8.3, 2.1 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 3.58 – 3.52 (m, 2H), 2.68 (dd, J = 7.5, 6.4 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.85, 149.95, 136.34, 127.41, 127.12, 119.34, 115.92, 42.55, 38.22, 20.24.


103
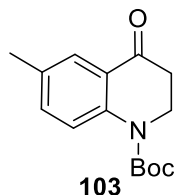
***Tert*-butyl 6-methyl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (103). 103** was synthesized according to general procedure G starting from **102** (1.0 g, 6.2 mmol, 1.0 eq), Boc$_2$O (2.0 g, 9.3 mmol, 1.5 eq), DMAP (76 mg, 0.62 mmol, 0.1 eq) and DIPEA (1.6 mL, 9.3 mmol, 1.5 eq). Following the quench and work-up, the crude product was chromatographed on silica gel (equil in 100% hex, run in 2:3 EA:hex) to yield pure product as a white solid (1.4 g, 89.1%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 (d, J = 2.2 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.30 (dd, J = 8.6, 2.3 Hz, 1H), 4.13 (q, J = 6.3, 4.8 Hz, 2H), 2.74 (t, J = 6.3 Hz, 2H), 2.33 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.44, 152.79, 141.79, 134.88, 133.56, 127.11, 124.68, 123.60, 81.95, 44.29, 39.03, 28.29, 20.60.


104
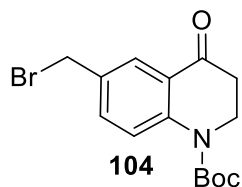
***Tert*-butyl 6-(bromomethyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (104). 104** was synthesized by placing **103** (1.44 g, 5.5 mmol, 1.0 eq), *N*-bromosuccinimide (1.0 g, 5.6 mmol, 1.02 eq) and benzoyl peroxide (40 mg, 0.165 mmol, 0.03 eq) into a round bottom flask which was then placed under vaccum for 15 min. Meanwhile, in a separate round bottom flask CCl$_4$ was degassed for 30 min, then flooded with Ar for 30 min. Then, CCl$_4$ was transferred to reaction vessel containing the starting material and reagents via cannula. The reaction vessel was then placed in an oil bath at 70°C where it stirred for 4 h. The reaction was monitored by TLC. Once complete, solid was filtered off and the mother liquor was concentrated under reduced

pressure then purified using silica gel chromatography to yield the title compound as a white solid (565 mg, 30%). Note that purification was difficult because starting material and product had similar Rf values, thus there is additional impure product not calculated in the yield. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (d, J = 9.1 Hz, 1H), 7.78 (t, J = 9.0 Hz, 1H), 7.51 (t, J = 9.1 Hz, 1H), 4.46 (d, J = 9.3 Hz, 2H), 4.19 – 4.07 (m, 2H), 2.75 (dt, J = 11.9, 6.5 Hz, 2H), 1.55 (d, J = 9.4 Hz, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.50, 152.49, 144.02, 134.53, 133.22, 127.58, 124.68, 124.12, 82.47, 44.18, 38.72, 32.32, 28.23.


105
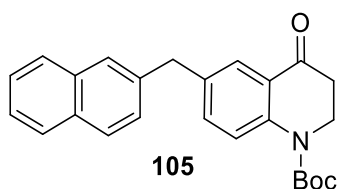
Tert-butyl 6-(naphthalen-2-ylmethyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (105).
105 was synthesized following general procedure L starting from **104**. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 (d, J = 2.2 Hz, 1H), 7.81 – 7.73 (m, 3H), 7.69 (d, J = 8.7 Hz, 1H), 7.63 (s, 1H), 7.49 – 7.40 (m, 2H), 7.35 (dt, J = 8.6, 1.8 Hz, 1H), 7.30 (dt, J = 8.4, 1.5 Hz, 1H), 4.16 – 4.10 (m, 4H), 2.78 – 2.71 (m, 2H), 1.54 (d, J = 1.3 Hz, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.26, 152.75, 142.47, 137.89, 136.72, 134.71, 133.58, 132.13, 128.24, 127.61, 127.54, 127.35, 127.31, 127.25, 127.08, 126.78, 126.05, 125.46, 124.82, 123.87, 82.12, 77.25, 77.20, 77.00, 76.75, 44.28, 41.33, 38.99, 28.29.


106
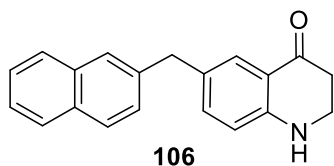
6-(Naphthalen-2-ylmethyl)-2,3-dihydroquinolin-4(1H)-one (106). 106 was synthesized by deprotected 105 with a 1:1 mixture of TFA:DCM. After stirring at RT for 1 h, solvent was removed under reduced pressure to yield the title compound **106** as a yellow solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84 – 7.72 (m, 2H), 7.68 (s, 0H), 7.62 (s, 1H), 7.49 – 7.38 (m, 1H), 7.33 – 7.24 (m, 1H), 7.16 (ddd, J = 8.3, 4.8, 1.9 Hz, 1H), 6.65 (ddd, J = 15.4, 8.3, 2.4 Hz, 1H), 4.03 (s, 1H), 3.59 – 3.53 (m, 2H), 2.77 – 2.66 (m, 2H), 2.25 (s, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.66,

138.64, 136.34, 136.11, 133.56, 132.05, 130.95, 128.11, 127.58, 127.51, 127.40, 127.36, 127.20, 126.87, 125.95, 125.31, 119.67, 119.42, 116.41, 116.22, 77.00, 42.57, 42.41, 41.14, 38.08.
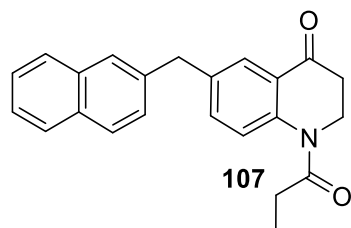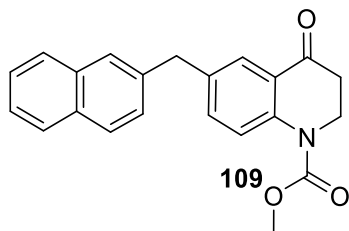

6-(Naphthalen-2-ylmethyl)-1-propionyl-2,3-dihydroquinolin-4(1*H*)-one (107). **107** was synthesized according to general procedure N using **106** (150 mg, 0.52 mmol, 1.0 eq) and excess propionic anhydride. Once complete, excess anhydride was removed and the crude residue was purified using silica gel chromatography to yield the title compound **107** as a clear, pale orange oil (156 mg, 87.2%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.91 (s, 1H), 7.81 – 7.73 (m, 3H), 7.63 (s, 1H), 7.47 – 7.32 (m, 4H), 7.28 (dd, *J* = 8.4, 1.9 Hz, 1H), 4.22 – 4.15 (m, 2H), 4.12 (s, 2H), 2.74 (td, *J* = 6.3, 1.9 Hz, 2H), 2.61 – 2.52 (m, 2H), 1.21 (t, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.08, 172.83, 142.08, 141.47, 138.43, 137.45, 134.74, 134.52, 133.42, 132.01, 128.23, 127.51, 127.49, 127.41, 127.17, 127.03, 126.03, 125.92, 125.45, 124.30, 123.97, 43.69, 41.27, 39.43, 27.80, 9.71.
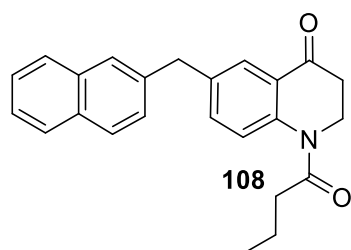

1-Butyryl-6-(naphthalen-2-ylmethyl)-2,3-dihydroquinolin-4(1*H*)-one (108). **108** was synthesized according to general procedure N using **106** (155 mg, 0.54 mmol, 1.0 eq) and excess butyric anhydride. Once complete, excess anhydride was removed and the crude residue was purified using silica gel chromatography to yield the title compound **108** as a clear, slightly dark red oil (112 mg, 58.0%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94 (s, 1H), 7.85 – 7.76 (m, 3H), 7.66

(s, 1H), 7.51 – 7.39 (m, 4H), 7.32 (d, J = 8.5 Hz, 1H), 4.20 (t, J = 6.3 Hz, 2H), 4.15 (s, 2H), 2.76 (t, J = 5.9 Hz, 2H), 2.60 – 2.49 (m, 2H), 1.75 (h, J = 7.7 Hz, 2H), 0.97 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.00, 171.99, 142.10, 138.38, 137.42, 134.69, 134.47, 133.42, 132.01, 128.21, 127.49, 127.47, 127.39, 127.16, 127.02, 126.00, 125.90, 125.42, 124.32, 124.00, 43.71, 41.25, 39.50, 36.28, 18.94, 13.66.
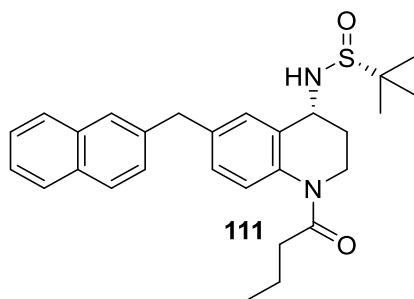

Methyl 6-(naphthalen-2-ylmethyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (109).
109 was synthesized according to general procedure N using **106** (150 mg, 0.52 mmol, 1.0 eq) and methylchloroformate (0.200 mL, 2.3 mmol, 2.3 eq). The reaction stirred overnight, once complete, solvent was removed and the crude residue was purified using silica gel chromatography to yield the title compound **109** as a clear oil (65 mg, 36.1%). Starting material was recovered, but not included in final yield calculation. Additionally, not all product was purified as the Rf values for the starting material and product were similar and separation was difficult. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92 (d, J = 2.2 Hz, 1H), 7.82 – 7.74 (m, 3H), 7.72 (d, J = 8.6 Hz, 1H), 7.64 (s, 1H), 7.48 – 7.41 (m, 2H), 7.38 (dd, J = 8.6, 2.3 Hz, 1H), 7.30 (dd, J = 8.4, 1.8 Hz, 1H), 4.18 (t, J = 6.3 Hz, 2H), 4.13 (s, 2H), 3.84 (s, 3H), 2.77 (t, J = 6.3 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.81, 154.23, 141.81, 137.73, 137.18, 134.88, 133.49, 132.05, 128.21, 127.55, 127.47, 127.26, 127.23, 127.03, 126.01, 125.42, 124.81, 123.63, 53.32, 44.39, 41.26, 38.81.
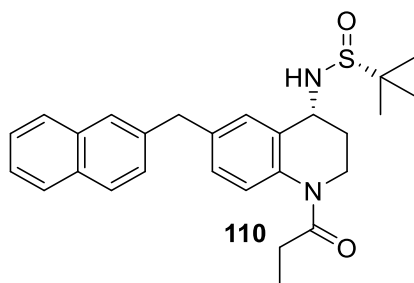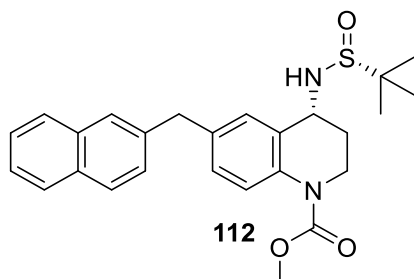

(*R*)-2-methyl-*N*-((*R*)-6-(naphthalen-2-ylmethyl)-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)propane-2-sulfinamide (110). 110 was synthesized according to general procedure H using

107 (156 mg, 0.45 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (165 mg, 1.36 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.57 mL, 2.7 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (103 mg, 2.7 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **110** as a clear, colorless oil (148 mg, 72.5%). No ^{1}H or ^{13}C NMR data acquired. Instead, product taken ahead to next reaction (formation of **113**) without any further isolation, purification, or characterization.


111

(*R*)-*N*-((*R*)-1-butyryl-6-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (111). 111 was synthesized according to general procedure H using **108** (112 mg, 0.31 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (114 mg, 0.94 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.39 mL, 1.9 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (71 mg, 1.9 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (54 mg, 37.2^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (q, *J* = 7.7 Hz, 3H), 7.66 (s, 1H), 7.44 (pd, *J* = 7.1, 3.4 Hz, 2H), 7.33 (dd, *J* = 6.4, 2.1 Hz, 2H), 7.14 (dt, *J* = 8.2, 2.0 Hz, 1H), 4.52 (t, *J* = 4.4 Hz, 1H), 4.11 (s, 2H), 3.89 (dt, *J* = 12.2, 5.5 Hz, 1H), 3.74 (ddd, *J* = 13.6, 9.8, 6.2 Hz, 1H), 3.32 (d, *J* = 3.3 Hz, 1H), 2.52 – 2.39 (m, 2H), 2.20 (dh, *J* = 15.3, 7.4, 5.6 Hz, 1H), 2.04 (dq, *J* = 12.7, 4.6, 3.9 Hz, 1H), 1.74 – 1.61 (m, 2H), 1.17 (d, *J* = 1.9

Hz, 9H), 0.91 (t, J = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 187.72, 172.68, 138.03, 136.64, 133.57, 132.10, 128.79, 128.72, 128.57, 128.21, 127.58, 127.52, 127.46, 127.10, 126.03, 125.43, 124.85, 124.60, 55.73, 50.96, 41.52, 39.95, 36.69, 30.68, 22.51, 19.14, 13.88.


**Methyl(*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-(naphthalen-2-ylmethyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (112). 112** was synthesized according to general procedure H using **109** (65 mg, 0.19 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (68 mg, 0.57 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.24 mL, 1.1 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (43 mg, 1.1 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (34 mg, 40.0%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 – 7.71 (m, 4H), 7.64 (d, J = 5.2 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.34 – 7.26 (m, 2H), 7.13 (ddd, J = 8.5, 6.0, 2.2 Hz, 1H), 4.55 (h, J = 3.7 Hz, 1H), 4.09 (s, 2H), 4.05 – 3.96 (m, 1H), 3.78 (s, 3H), 3.69 – 3.59 (m, 1H), 3.33 (q, J = 2.7 Hz, 1H), 2.18 (ddt, J = 12.8, 10.4, 4.3 Hz, 1H), 2.06 – 1.93 (m, 1H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.94, 138.25, 136.95, 136.16, 133.53, 132.02, 129.23, 128.84, 128.65, 128.08, 127.52, 127.48, 127.43, 126.96, 125.92, 125.30, 123.70, 55.60, 52.95, 50.35, 41.33, 40.28, 29.49, 22.49.
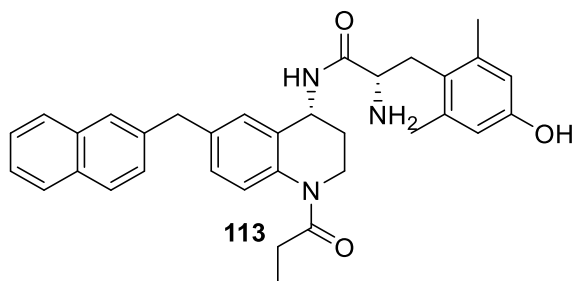
(*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(naphthalen-2-ylmethyl)-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (113). 113 was synthesized following general procedure I using **110** (148 mg, 0.33 mmol, 1.0 eq) and conc. HCl (6 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (126 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (60 mg, 0.16 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **113** as a TFA salt (15 mg, 14.7 %). Note that not all crude product was purified. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.76 (ddd, *J* = 21.9, 8.2, 3.1 Hz, 3H), 7.60 (d, *J* = 3.2 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.28 (dt, *J* = 8.6, 2.2 Hz, 1H), 7.19 (d, *J* = 3.5 Hz, 1H), 7.15 – 7.09 (m, 1H), 6.51 (d, *J* = 3.4 Hz, 2H), 4.93 (p, *J* = 5.2 Hz, 1H), 4.08 (d, *J* = 3.4 Hz, 2H), 3.86 (dt, *J* = 11.2, 4.3 Hz, 1H), 3.78 (s, 1H), 3.24 (td, *J* = 12.6, 11.2, 3.5 Hz, 1H), 3.15 (s, 1H), 3.03 (dt, *J* = 13.9, 4.5 Hz, 1H), 2.58 – 2.41 (m, 2H), 2.26 (d, *J* = 3.6 Hz, 6H), 1.85 (dtd, *J* = 13.5, 8.7, 4.7 Hz, 1H), 1.45 (s, 1H), 1.11 (td, *J* = 7.1, 3.2 Hz, 3H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 175.85, 169.20, 157.47, 140.07, 139.86, 137.62, 135.07, 133.59, 129.47, 129.07, 128.58, 128.46, 128.38, 127.87, 127.09, 126.46, 125.87, 123.24, 116.45, 53.49, 47.11, 42.27, 31.95, 31.29, 28.92, 20.42, 10.06. HPLC (gradient A): retention time 41.3. ESI-MS 536.3 [M+H]$^+$ and 558.3 [M+Na]$^+$.
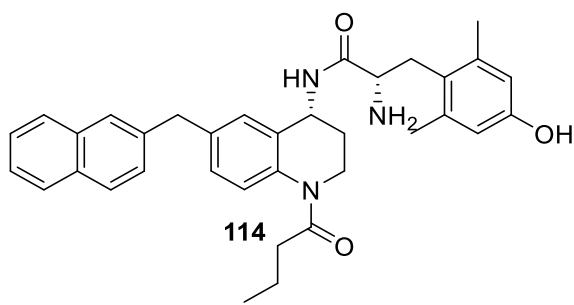
(*S*)-2-amino-*N*-((*R*)-1-butyryl-6-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (114). 114 was synthesized following general procedure I using **112** (34 mg, 0.076 mmol, 1.0 eq) and conc. HCl (3 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (46 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (46 mg, 0.12 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **114** as a TFA salt (12 mg, 15.6%). Note that not all crude product was purified. No ^{1}H or ^{13}C data acquired. Instead, final product was verified only via mass spectrometry. HPLC (gradient A): retention time 44.0. ESI-MS 550.3 [M+H]$^+$ and 572.3 [M+Na]$^+$.
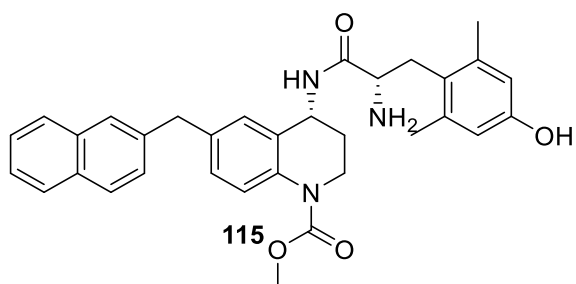

Methyl (*R*)-4-((*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamido)-6-(naphthalen-2-ylmethyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (115). 115 was synthesized following general procedure I using **112** (34 mg, 0.076 mmol, 1.0 eq) and conc. HCl (3 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (19 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (19 mg, 0.0.16 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **115** as a TFA salt (13 mg, 40.6%). Note that not all crude product was purified. ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.73 (dd, *J* = 8.3, 2.9 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.59 (s, 1H), 7.42 (dt, *J* = 8.9, 6.2 Hz, 2H), 7.27 (dt, *J* = 8.4, 1.7 Hz, 1H), 7.12 (s, 1H), 7.09 (dt, *J* = 8.6, 1.8 Hz, 1H), 6.50 (s, 2H), 4.96 (t, *J* = 5.1 Hz, 1H), 4.04 (s, 2H), 3.87 − 3.80 (m, 1H), 3.75 (d, *J* = 1.5 Hz, 4H), 3.28 − 3.19 (m, 1H), 3.00 (dt, *J* = 12.6, 8.3 Hz, 2H), 2.26 (d, *J* = 1.5 Hz, 7H), 1.78 (ddt,

J = 14.7, 9.9, 4.7 Hz, 1H), 1.50 (ddd, *J* = 13.4, 8.6, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 168.96, 157.48, 156.61, 139.99, 138.03, 137.48, 135.07, 133.57, 130.31, 129.72, 129.02, 128.78, 128.57, 128.46, 128.39, 127.80, 127.05, 126.41, 124.63, 123.19, 116.43, 111.40, 53.54, 53.41, 47.06, 42.32, 42.14, 31.92, 30.30, 20.44. HPLC (gradient A): retention time 42.7. ESI-MS 538.3 [M+H]$^+$ and 560.3 [M+Na]$^+$.
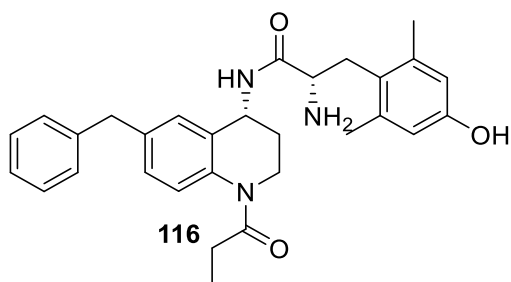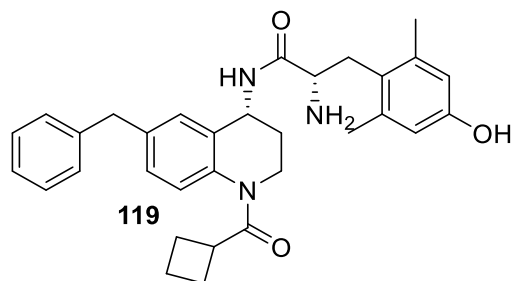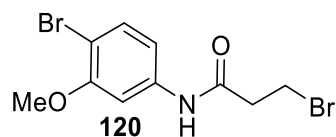

Synthesized by Dr. Aaron M. Bender.
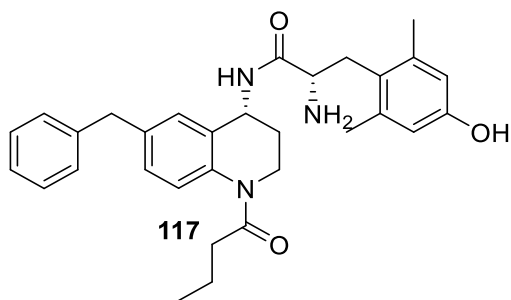
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Synthesized by Dr. Aaron M. Bender.

119

Synthesized by Dr. Aaron M. Bender.

120
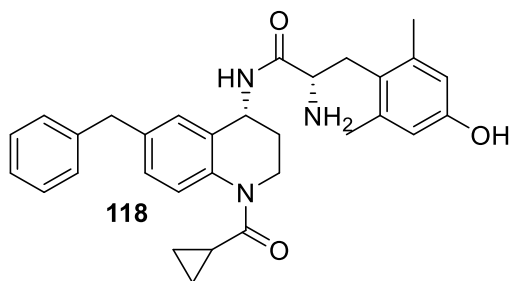
3-Bromo-*N*-(4-bromo-3-methoxyphenyl)propanamide (120). 120 was synthesized according to general procedure C starting from the commercially available starting material 4-bromo-3-methoxyaniline (1.0 g, 5.0 mmol, 1.0 eq), K_2CO_3 (1.40 g, 10.1 mmol, 2.05 eq) and bromopropionyl chloride (0.810 mL, 5.1 mmol, 1.02 eq) to yield the crude product which was pure following work-up to yield title compound **120** as a pinkish grey solid (1.67 g, quant.).^{1}H NMR (500 MHz, CDCl$_3$) δ 7.54 (dt, *J* = 5.0, 2.2 Hz, 1H), 7.44 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.75 (dt, *J* = 8.5, 1.9 Hz, 1H), 3.90 (s, 3H), 3.71 (t, *J* = 6.6 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 167.89, 156.21, 137.93, 133.06, 112.49, 106.47, 104.28, 56.27, 40.74, 26.69.


121
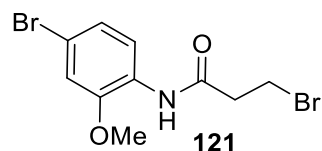
3-Bromo-*N*-(4-bromo-2-methoxyphenyl)propanamide (121). 121 was synthesized according to general procedure C starting from the commercially available starting material 4-bromo-2-methoxyaniline (0.50 g, 2.47 mmol, 1.0 eq), K_2CO_3 (0.701 g, 5.1 mmol, 2.05 eq) and bromopropionyl chloride (0.404 mL, 2.5 mmol, 1.02 eq) to yield the title compound as an off-white solid (834 mg g, quant.) with no additional purification necessary. ^{1}H NMR (500 MHz, CDCl$_3$ δ 8.32 – 8.24 (m, 1H), 7.75 (s, 1H), 7.10 (ddd, *J* = 8.7, 2.2, 1.1 Hz, 1H), 7.00 (q, *J* = 1.7 Hz, 1H), 3.89 (t, *J* = 1.5 Hz, 3H), 3.70 (tt, *J* = 6.9, 1.5 Hz, 2H), 3.00 – 2.93 (m, 2H). ^{13}C NMR

(126 MHz, CDCl$_3$) δ 167.62, 143.55, 133.03, 123.99, 120.90, 116.27, 113.54, 56.04, 40.90, 26.74.
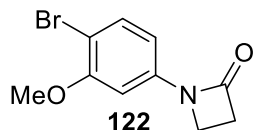
1-(4-Bromo-3-methoxyphenyl)azetidin-2-one (122). **122** was synthesized according to general procedure D using **120** (1.70 g, 5.0 mmol, 1.0 eq) and NaOtBu (510 mg, 5.3 mmol, 1.05 eq) to yield the crude product which was then purified using silica gel chromatography to yield the title compound (**122**) as an off-white solid (1.14 g, 88.7%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44 (dd, J = 8.5, 2.6 Hz, 1H), 7.23 (t, J = 2.3 Hz, 1H), 6.57 (dt, J = 8.6, 2.2 Hz, 1H), 3.90 (s, 3H), 3.62 (dd, J = 5.7, 3.3 Hz, 2H), 3.13 (dd, J = 5.8, 3.1 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 164.50, 156.35, 138.92, 133.28, 108.33, 105.74, 101.12, 56.29, 38.35, 36.29.
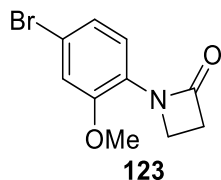

1-(4-Bromo-3-methoxyphenyl)azetidin-2-one (123). **123** was synthesized according to general procedure D using **120** (860 mg, 2.6 mmol, 1.0 eq) and NaOtBu (257 mg, 2.7 mmol, 1.05 eq) to yield the crude product which was then purified using silica gel chromatography to yield the title compound (**123**) as a mauve, waxy solid (631 mg, 94.5%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 (dd, J = 8.6, 2.1 Hz, 1H), 7.04 (dt, J = 8.6, 2.3 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 3.91 (t, J = 4.5 Hz, 2H), 3.81 (d, J = 2.4 Hz, 3H), 3.09 (t, J = 4.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 166.08, 150.53, 126.53, 123.92, 122.65, 117.14, 115.20, 55.86, 43.14, 38.01.
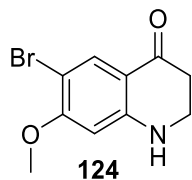
6-Bromo-7-methoxy-2,3-dihydroquinolin-4(1*H*)-one (124). 124 was synthesized according to general procedure E using **122** (1.14 g, 4.5 mmol, 1.0 eq) and TfOH (1.2 mL, 13.4 mmol, 3.0 eq) to yield the crude product which was then purified using silica gel chromatography to yield the title compound (**124**) as an off-white solid (0.48 g, 59.7%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.01 (s, 1H), 6.11 (s, 1H), 3.87 (s, 3H), 3.57 (t, 2H), 2.65 (t, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 191.06, 160.83, 152.58, 132.45, 114.48, 109.99, 101.96, 97.59, 56.32, 42.31, 37.28.
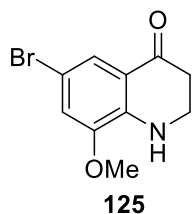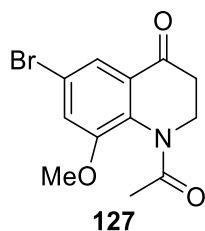

6-Bromo-8-methoxy-2,3-dihydroquinolin-4(1*H*)-one (125). 125 was synthesized according to general procedure E using **123** (631 mg, 2.5 mmol, 1.0 eq) and TfOH (0.654 mL, 7.4 mmol, 3.0 eq) to yield the crude product which was then purified using silica gel chromatography to yield the title compound (**125**) as an off-white solid (0.48 g, 59.7%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.59 (t, *J* = 2.2 Hz, 1H), 6.90 (t, *J* = 2.2 Hz, 1H), 3.86 (d, *J* = 1.9 Hz, 3H), 3.62 – 3.55 (m, 2H), 2.69 (td, *J* = 7.0, 2.1 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 192.19, 147.82, 142.20, 121.14, 119.64, 116.61, 108.76, 56.06, 41.84, 37.69.
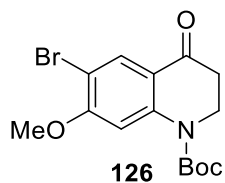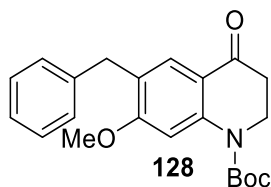

***Tert*-butyl 6-bromo-7-methoxy-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (126). 126** was synthesized according to general procedure G using **124** (0.48 g, 1.9 mmol, 1.0 eq) to yield the crude product which was then purified using silica gel chromatography to yield the title compound (**126**) as a viscous yellow oil (0.567 g, 85.1%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (s,

1H), 7.33 (s, 1H), 4.01 (t, 2H), 3.82 (s, 3H), 2.56 (t, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 191.27, 159.31, 151.96, 144.78, 131.41, 118.86, 106.76, 105.83, 82.13, 56.14, 44.25, 37.74, 27.96.


127

1-Acetyl-6-bromo-8-methoxy-2,3-dihydroquinolin-4(1H)-one (127). 127 was synthesized according to general procedure K using **125** (0.165 mg, 0.64 mmol, 1.0 eq) and excess Ac$_2$O. Once the reaction was complete, the solvent was removed under reduced pressure and the crude residue was purified using silica gel chromatography to yield the title compound (127) as a slightly yellow oil (152 mg, 79.2%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.63 (d, J = 2.2 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 4.90 (s, 1H), 3.84 (s, 4H), 3.37 (s, 1H), 2.80 (s, 1H), 2.62 (d, J = 18.2 Hz, 1H), 2.02 (s, 4H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.43, 170.71, 153.18, 133.23, 129.03, 122.05, 120.15, 120.10, 56.31, 44.10, 39.88, 21.93.

128

***Tert*-butyl 6-benzyl-7-methoxy-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (128). 128** was synthesized following general procedure L using **126** (142 mg, 0.40 mmol, 1.0 eq), benzyl-Bpin (0.130 mL, 0.60 mmol, 2.0 eq), K$_2$CO$_3$ (165 mg, 1.2 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (29 mg, 0.04 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography (equil in 100% hex, run in 1:1 EA:hex) to yield title compound (146 mg, 98.9%) as yellow, clear oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (s, 1H), 7.35 (s, 1H), 7.27 – 7.22 (m, 2H), 7.22 – 7.18 (m, 2H), 7.18 – 7.12 (m, 1H), 4.11 (t, 2H), 3.91 (s,

2H), 3.86 (s, 3H), 2.67 (t, 2H), 1.57 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 192.72, 161.68, 152.46, 144.49, 140.05, 128.79, 128.52, 128.05, 126.02, 125.71, 117.94, 104.75, 81.83, 55.47, 44.54, 38.26, 35.25, 28.14.
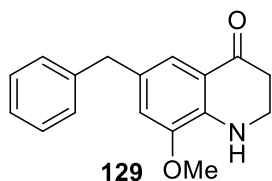

6-Benzyl-8-methoxy-2,3-dihydroquinolin-4(1*H*)-one (129). 129 was synthesized following general procedure L using **125** (50 mg, 0.20 mmol, 1.0 eq), benzyl-Bpin (0.65 mL, 0.30 mmol, 2.0 eq), K$_2$CO$_3$ (81 mg, 0.59 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (14 mg, 0.02 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography (equil in 100% hex, run in 1:1 EA:hex) to yield title compound (20 mg, 38.5%) as clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 (s, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.21 – 7.16 (m, 3H), 6.66 (s, 1H), 3.89 (s, 2H), 3.80 (d, *J* = 1.1 Hz, 3H), 3.57 (t, *J* = 6.7 Hz, 2H), 2.70 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.68, 147.27, 141.88, 141.18, 129.29, 128.63, 128.39, 126.00, 118.79, 118.26, 114.64, 55.65, 42.13, 41.49, 38.01.
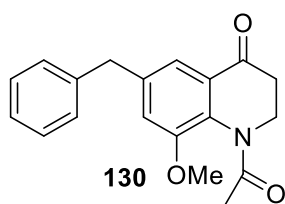
1-Acetyl-6-benzyl-8-methoxy-2,3-dihydroquinolin-4(1*H*)-one (130). 130 was synthesized following general procedure L using **127** (152 mg, 0.51 mmol, 1.0 eq), benzyl-Bpin (0.167 mL, 0.77 mmol, 2.0 eq), K$_2$CO$_3$ (211 mg, 1.53 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (37 mg, 0.05 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography to yield title compound (112 mg, 70.9%) as clear, colorless oil. ^{1}H

NMR (500 MHz, CDCl$_3$) δ δ 7.37 (s, 1H), 7.26 – 7.20 (m, 2H), 7.17 – 7.09 (m, 3H), 6.89 (s, 1H), 4.93 (s, 1H), 3.92 (s, 2H), 3.76 (s, 3H), 3.32 (t, J = 12.1 Hz, 1H), 2.78 (t, J = 15.6 Hz, 1H), 2.57 (d, J = 18.4 Hz, 1H), 1.99 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 195.01, 171.07, 152.37, 140.47, 139.75, 132.19, 128.76, 128.64, 128.19, 126.48, 119.25, 117.67, 55.86, 44.00, 41.72, 39.97, 21.90.

131 Boc
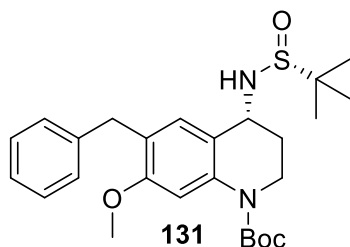
***Tert*-butyl (*R*)-6-benzyl-4-(((*R*)-*tert*-butylsulfinyl)amino)-7-methoxy-3,4-dihydroquinoline-1(2*H*)-carboxylate (131). 131** was synthesized according to general procedure H using **128** (200 mg, 0.54 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (198 mg, 1.63 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.685 mL, 3.27 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (124 mg, 3.27 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (64 mg, 24.9%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44 (s, 1H), 7.31 – 7.18 (m, 5H), 7.06 (s, 1H), 4.52 – 4.44 (m, 1H), 3.98 (dt, J = 12.9, 4.3 Hz, 1H), 3.95 – 3.84 (m, 2H), 3.84 – 3.78 (s, 3H), 3.55 (qd, J = 12.4, 10.9, 3.7 Hz, 1H), 3.21 (s, 1H), 2.17 (dq, J = 14.1, 3.8 Hz, 1H), 1.95 (dddt, J = 29.9, 15.2, 11.7, 3.6 Hz, 1H), 1.53 (s, 9H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.70, 153.40, 140.88, 137.74, 130.25, 128.71, 128.17, 125.72, 125.55, 120.22, 106.18, 81.07, 55.46, 49.66, 39.96, 35.29, 29.33, 28.36, 22.52.

132 OMe
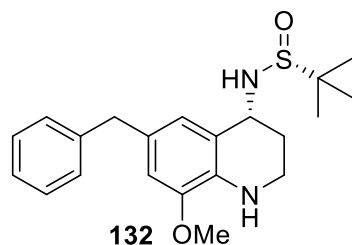
(R)-N-((R)-6-benzyl-8-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (132). 132 was synthesized according to general procedure H using **130** (112 mg, 0.36 mmol, 1.0 eq), (R)-2-methylpropane-2-sulfinamide (132 mg, 1.1 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.455 mL, 2.2 mmol, 6.0 eq) to form the (R)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (82 mg, 2.2 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (56 mg, 37.8%). No ^{1}H or ^{13}C data taken. Product was moved on to next step.
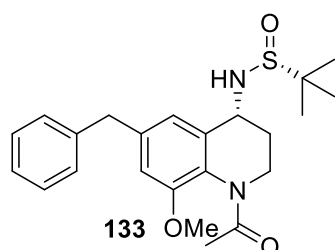
133 OMe

(R)-N-((R)-1-acetyl-6-benzyl-8-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (133). 133 was synthesized according to general procedure H using **129** (106 mg, 0.40 mmol, 1.0 eq), (R)-2-methylpropane-2-sulfinamide (144 mg, 1.19 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.500 mL, 2.4 mmol, 6.0 eq) to form the (R)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (90 mg, 2.4 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the still impure

title compound. No ^{1}H or ^{13}C NMR spectrum acquired. Intermediate taken ahead to the next step (formation of **136**) without any additional isolation, purification, or characterization.
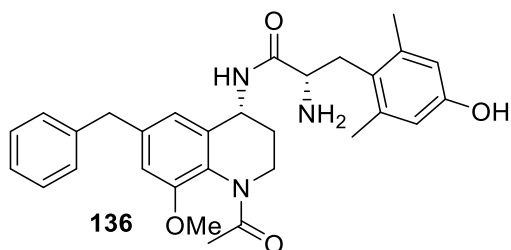

134
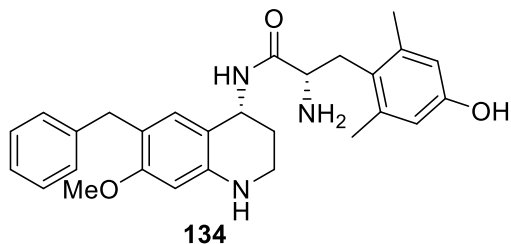
(*S*)-2-amino-*N*-((*R*)-6-benzyl-7-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (134). 134 was synthesized following general procedure I using **131** (56 mg, 0.14 mmol, 1.0 eq) and conc. HCl (4 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (41 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (41 mg, 0.16 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **134** as a TFA salt. Note that not all crude product was purified, therefore no yield was calculated. ^{1}H NMR (500 MHz, CD$_3$OD) δ 8.15 (d, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.09 (d, *J* = 7.4 Hz, 3H), 6.89 (s, 1H), 6.48 (s, 2H), 6.35 (s, 1H), 5.05 (s, 2H), 3.89 – 3.73 (m, 3H), 3.71 (s, 3H), 3.24 (dd, *J* = 13.6, 11.6 Hz, 1H), 3.10 – 2.96 (m, 2H), 2.55 (td, *J* = 12.0, 2.5 Hz, 1H), 2.27 (s, 6H), 1.83 – 1.73 (m, 1H), 1.55 (tt, *J* = 10.0, 8.2, 3.2 Hz, 1H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 168.56, 168.47, 162.31, 157.39, 142.68, 140.79, 140.03, 133.12, 129.51, 129.10, 126.67, 124.61, 123.29, 116.41, 115.88, 101.01, 55.88, 53.32, 49.00, 45.55, 45.46, 38.66, 36.34, 31.88, 28.78, 20.46. HPLC (gradient A): retention time 27.8. ESI-MS 482.3 [M+Na]$^+$.
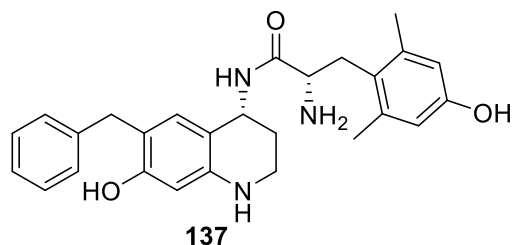

135
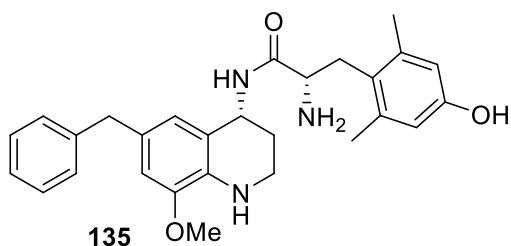
(*S*)-2-amino-*N*-((*R*)-6-benzyl-8-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-

dimethylphenyl)propanamide (135). 135 was synthesized following general procedure I using **132** (56 mg, 0.14 mmol, 1.0 eq) and conc. HCl (4 drops). After removing solvent, residue was re-suspended in Et₂O, and solid crashed out. After washing the solid 3 x with fresh Et₂O, the remaining Et₂O was decanted off, yielding a white solid amine hydrochloride salt (41 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (41 mg, 0.14 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **135** as a TFA salt. Note that not all crude product was purified, therefore no yield was calculated. No ¹H or ¹³C data was collected. Instead, product formation was verified via mass spectrometry. HPLC (gradient A): retention time 25.5. ESI-MS 482.3 [M+Na]⁺.

**(*S*)-*N*-((*R*)-1-acetyl-6-benzyl-8-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (136). 136** was synthesized following general procedure I using **133** (150 mg, 0.36 mmol, 1.0 eq) and conc. HCl (4 drops). After removing solvent, residue was re-suspended in Et₂O, and solid crashed out. After washing the solid 3 x with fresh Et₂O, the remaining Et₂O was decanted off, yielding a white solid amine hydrochloride salt (126 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (126 mg, 0.36 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **136** as a TFA salt. Note that not all crude product was purified, therefore no yield was calculated. No ¹H or ¹³C data was collected. Instead, product formation was verified via mass spectrometry. HPLC (gradient A): retention time: no data collected. ESI-MS 502.2 [M+H]⁺ and 424.2 [M+Na]⁺.

137

(*S*)-2-amino-*N*-((*R*)-6-benzyl-7-hydroxy-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (137). 137 was synthesized following general procedure I using **131** (150 mg, 0.36 mmol, 1.0 eq) and conc. HCl (4 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (126 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (126 mg, 0.36 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **136** as a TFA salt. Note that not all crude product was purified, therefore no yield was calculated. ^{1}H NMR (500 MHz, CDCl$_3$) δ ^{1} 8.11 (d, *J* = 7.6 Hz, 1H), 7.23 – 7.05 (m, 5H), 6.85 (s, 1H), 6.47 (s, 2H), 6.27 (s, 1H), 3.89 – 3.73 (m, 3H), 3.23 (dd, *J* = 13.6, 11.7 Hz, 1H), 3.08 – 2.94 (m, 2H), 2.52 (t, *J* = 11.8 Hz, 1H), 2.26 (d, *J* = 1.5 Hz, 6H), 1.77 (d, *J* = 12.3 Hz, 1H), 1.53 (d, *J* = 13.7 Hz, 1H). No ^{13}C data was collected. HPLC (gradient A): retention time 22.0. ESI-MS 468.3 [M+Na]$^+$.

138
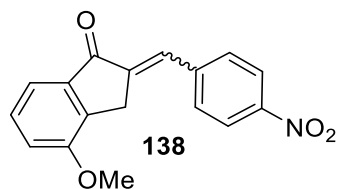
4-Methoxy-2-(4-nitrobenzylidene)-2,3-dihydro-1*H*-inden-1-one (138). 138 was synthesized according to general procedure A starting from commercially available 4-methoxy-2,3-dihydro-1*H*-inden-1-one (0.500 g, 3.1 mmol, 1.0 eq) and *p*-Nitrobenzaldehyde (0.559 g, 3.7 mmol, 1.2 eq) to yield a mustard yellow powder (0.881 g, 96.8%) No ^{1}H ^{13}C data was collected. Product was taken on to the next step (formation of **141**) without additional isolation, purification, or characterization.
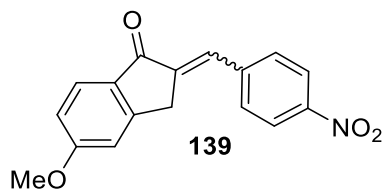
5-Methoxy-2-(4-nitrobenzylidene)-2,3-dihydro-1*H*-inden-1-one (139). 139 was synthesized according to general procedure A starting from commercially available 5-methoxy-2,3-dihydro-1*H*-inden-1-one (0.500 g, 3.1 mmol, 1.0 eq) and *p*-Nitrobenzaldehyde (0.559 g, 3.7 mmol, 1.2 eq) to yield a mustard yellow powder (0.809 g, 88.9%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.34 – 8.28 (m, 2H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.76 (m, 2H), 7.62 (t, *J* = 2.3 Hz, 1H), 7.04 – 6.96 (m, 2H), 4.06 – 4.02 (m, 2H), 3.93 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 191.91, 165.71, 152.25, 141.87, 139.09, 130.96, 130.79, 129.61, 126.58, 124.06, 115.69, 109.98, 109.73, 77.00, 55.78, 32.42.
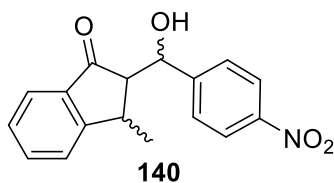
2-(Hydroxy(4-nitrophenyl)methyl)-3-methyl-2,3-dihydro-1*H*-inden-1-one (140). 140 was synthesized according to general procedure A starting from commercially available 3-methyl-2,3-dihydro-1*H*-inden-1-one (0.500 g, 3.4 mmol, 1.0 eq) and *p*-Nitrobenzaldehyde (0.620 g, 4.1 mmol, 1.2 eq) to yield the title compound (**140**) as a tan powder (844 mg, 82.7%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.29 – 8.22 (m, 3H), 7.82 – 7.77 (m, 1H), 7.66 (dt, *J* = 8.7, 2.1 Hz, 5H), 7.44 (td, *J* = 12.6, 12.2, 6.7 Hz, 3H), 5.73 (d, *J* = 4.7 Hz, 1H), 5.14 (d, *J* = 1.9 Hz, 1H), 4.97 (d, *J* = 9.7 Hz, 1H), 4.46 (d, *J* = 7.3 Hz, 0H), 3.49 (s, 1H), 3.47 – 3.40 (m, 1H), 2.97 (p, *J* = 6.6 Hz, 1H), 2.61 (dd, *J* = 4.7, 2.6 Hz, 1H), 2.57 – 2.47 (m, 2H), 2.17 (d, *J* = 1.9 Hz, 5H), 1.58 – 1.51 (m, 3H), 1.44 – 1.35 (m, 1H), 1.25 (s, 1H), 1.00 – 0.91 (m, 3H), 0.88 (dd, *J* = 7.1, 1.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 208.33, 159.02, 158.35, 136.08, 135.55, 128.11, 127.88, 127.69, 126.38, 125.14, 125.09, 124.04, 123.85, 123.74, 123.69, 77.26, 77.00, 76.75, 74.82, 71.13, 62.96, 61.34, 36.14, 33.18, 30.93, 29.74, 20.17, 19.50.
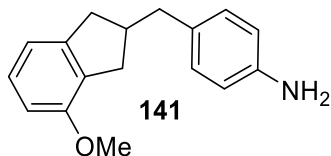
4-((4-Methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)aniline (141). 141 was synthesized according to general procedure B starting from **138** (0.881 g, 2.98 mmol, 1.0 eq) to yield a light orange solid (698 mg, 92.3 %). ^{1}H NMR (400 MHz, CDCl3) δ 7.11 (td, *J* = 7.8, 3.5 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.80 (dd, *J* = 7.4, 3.6 Hz, 1H), 6.65 (td, *J* = 8.6, 2.6 Hz, 3H), 4.12 (qd, *J* = 7.1, 3.5 Hz, 1H), 3.84 – 3.78 (m, 3H), 3.02 – 2.93 (m, 2H), 2.76 – 2.62 (m, 4H), 2.58 (ddd, *J* = 16.2, 6.4, 4.1 Hz, 1H), 2.05 (d, *J* = 3.3 Hz, 1H), 1.30 – 1.22 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.00, 145.32, 144.23, 144.21, 131.53, 130.79, 129.87, 129.64, 127.48, 127.48, 116.97, 116.96, 115.28, 115.19, 107.75, 60.38, 55.13, 41.31, 40.88, 39.10, 35.34, 21.04, 14.19.
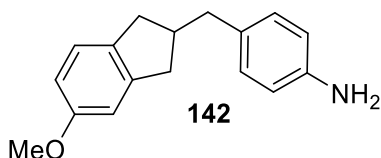
4-((5-Methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)aniline (142). 142 was synthesized according to general procedure B starting from **139** (809 mg, 0.27 mmol, 1.0 eq) to yield a light orange solid (365 mg, 52.6 %). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.02 (q, *J* = 7.7 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 2H), 6.77 – 6.68 (m, 1H), 6.66 (d, *J* = 9.7 Hz, 1H), 6.58 (dt, *J* = 8.6, 4.5 Hz, 2H), 3.72 (d, *J* = 5.4 Hz, 3H), 3.58 – 3.41 (m, 2H), 2.88 (tt, *J* = 13.8, 6.5 Hz, 2H), 2.60 (dtq, *J* = 29.1, 22.1, 7.2 Hz, 5H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.42, 144.75, 144.23, 135.23, 131.31, 129.49, 124.78, 115.07, 111.71, 110.01, 55.24, 42.11, 40.63, 39.02, 37.87.
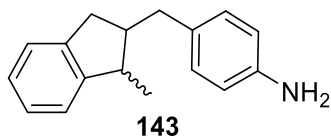
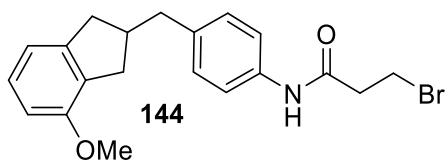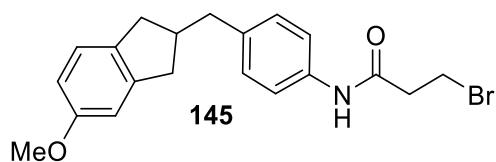**4-((1-Methyl-2,3-dihydro-1*H*-inden-2-yl)methyl)aniline (143). 143** was synthesized according to general procedure B starting from **140** (844 mg, 0.28 mmol, 1.0 eq) to yield a a crude residue that was taken ahead to the next step without further purification (674 mg, quant.). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 – 7.36 (m, 7H), 7.20 – 7.03 (m, 8H), 3.49 (s, 13H), 3.19 (d, *J* = 15.4 Hz,

1H), 2.99 (q, *J* = 5.6 Hz, 1H), 2.89 – 2.79 (m, 2H), 2.65 (t, *J* = 11.0 Hz, 1H), 2.54 (dd, *J* = 15.3, 8.0 Hz, 1H), 2.20 (d, *J* = 14.5 Hz, 2H), 1.41 (d, *J* = 6.9 Hz, 0H), 1.38 (s, 0H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.02 (dd, *J* = 14.9, 6.7 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 147.64, 142.66, 141.96, 140.73, 130.39, 129.04, 128.74, 126.41, 126.35, 126.32, 126.27, 124.44, 124.40, 124.28, 124.18, 123.60, 123.43, 123.36, 123.28, 123.16, 87.21, 84.87, 77.25, 77.21, 77.00, 76.74, 56.14, 55.00, 53.93, 50.75, 50.24, 44.85, 43.35, 42.83, 41.12, 39.83, 37.64, 35.28, 34.72, 34.01, 20.64, 19.46, 19.42, 18.46.

3-Bromo-*N*-(4-((4-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)phenyl)propanamide (144). **144** was synthesized according to general procedure C starting from **141** (698mg, 2.76 mmol, 1.0 eq) to yield the title compound as white, waxy solid (997 mg, 93.2%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.22 (s, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 3.80 (d, *J* = 1.7 Hz, 3H), 3.72 (t, *J* = 6.8 Hz, 2H), 3.01 – 2.91 (m, 5H), 2.75 (s, 3H), 2.62 (ddd, *J* = 40.6, 14.7, 5.0 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 179.90, 167.70, 156.01, 155.80, 145.07, 137.98, 135.21, 130.57, 129.42, 127.60, 120.12, 116.96, 107.83, 55.15, 41.14, 41.05, 40.72, 39.12, 35.33, 27.14.

3-Bromo-*N*-(4-((5-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)phenyl)propanamide (145). **145** was synthesized according to general procedure C starting from **142** (365 mg, 1.4 mmol, 1.0 eq) to yield the title compound as a tan solid (554 mg, 99%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 4.6 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 2.3 Hz, 1H), 6.70 – 6.66 (m, 1H), 3.77 (d, *J* = 1.3 Hz, 3H), 3.72 (t, *J* = 6.4 Hz, 2H), 2.97 – 2.86 (m, 5H), 2.73 (s, 3H), 2.60 (ddd, *J* = 21.4, 14.8, 5.2 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 167.76, 158.58, 144.61, 137.97, 135.24, 135.08, 129.38, 124.91, 120.14, 111.90,

110.10, 55.40, 41.93, 40.98, 40.68, 39.09, 37.95, 27.14.

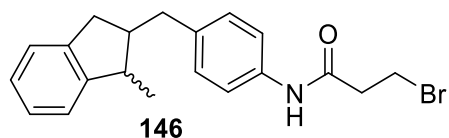**3-Bromo-*N*-(4-((1-methyl-2,3-dihydro-1*H*-inden-2-yl)methyl)phenyl)propanamide (146).** **146** was synthesized according to general procedure C starting from **143** (773 mg, 2.8 mmol, 1.0 eq) to yield the title compound as a tan solid (1.06 g, quant.). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 – 7.51 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.16 (dd, *J* = 21.5, 10.6 Hz, 7H), 3.72 (q, *J* = 6.3 Hz, 3H), 3.57 (td, *J* = 6.7, 3.3 Hz, 2H), 3.10 (td, *J* = 6.6, 1.6 Hz, 1H), 3.01 – 2.90 (m, 5H), 2.91 – 2.82 (m, 2H), 2.61 (ddd, *J* = 33.3, 14.9, 9.2 Hz, 2H), 2.24 – 2.16 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.76, 167.99, 147.97, 142.35, 137.91, 135.23, 129.45, 128.34, 128.16, 126.54, 126.27, 126.23, 124.44, 124.26, 123.37, 123.18, 120.25, 119.98, 67.00, 56.28, 54.80, 50.50, 44.81, 44.28, 43.04, 40.64, 39.74, 38.57, 37.73, 37.33, 36.09, 27.19, 25.29, 24.01, 19.45, 18.46.

1-(4-((4-Methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)phenyl)azetidin-2-one (147). 147 was synthesized according to general procedure D starting from **144** (997 mg, 2.57 mmol, 1.0 eq) to yield the title compound brown oil (789 mg, quant.). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 (s, 1H), 7.31 – 7.27 (m, 2H), 7.20 – 7.16 (m, 2H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 3.80 (d, *J* = 1.3 Hz, 4H), 3.61 (dh, *J* = 4.6, 2.6 Hz, 2H), 3.10 (tt, *J* = 4.6, 2.2 Hz, 2H), 2.98 (d, *J* = 6.4 Hz, 1H), 2.95 (t, *J* = 1.8 Hz, 6H), 2.88 (q, *J* = 1.2 Hz, 4H), 2.74 (d, *J* = 3.3 Hz, 3H), 2.65 (dd, *J* = 15.5, 5.6 Hz, 1H), 2.60 – 2.53 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 164.22, 162.45, 155.93, 144.97, 136.97, 136.49, 130.47, 129.42, 129.23, 127.55, 127.52, 119.93, 116.89, 116.08, 107.76, 55.07, 41.10, 41.07, 41.02, 39.03, 37.95, 36.41, 35.98, 35.22, 31.36.

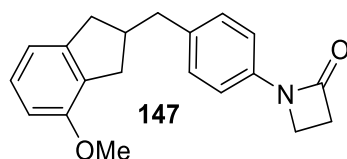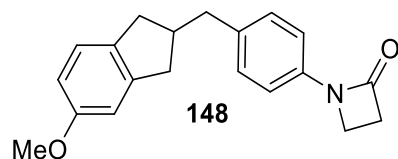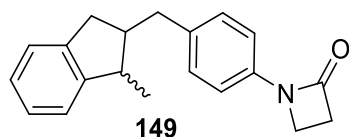**1-(4-((5-Methoxy-2,3-dihydro-1 *H* -inden-2-yl)methyl)phenyl)azetidin-2-one (148). 148** was synthesized according to general procedure D starting from **145** (544 mg, 1.43 mmol, 1.0 eq) to yield the title compound as a solid (439 mg, quant.). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (s, 0H), 7.33 – 7.27 (m, 2H), 7.20 – 7.14 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.76 – 6.72 (m, 1H), 6.71 – 6.65 (m, 1H), 3.77 (d, *J* = 1.1 Hz, 3H), 3.62 (td, *J* = 4.5, 1.2 Hz, 2H), 3.11 (td, *J* = 4.5, 1.1 Hz, 2H), 2.95 (d, *J* = 1.2 Hz, 1H), 2.95 – 2.86 (m, 4H), 2.73 (d, *J* = 2.7 Hz, 4H), 2.60 (ddd, *J* = 20.9, 15.1, 5.7 Hz, 3H) ^{13}C NMR (126 MHz, CDCl$_3$) δ 164.25, 158.57, 144.57, 137.02, 136.55, 135.04, 129.43, 124.88, 116.11, 111.87, 110.09, 55.37, 42.00, 40.99, 39.05, 37.98, 37.91, 36.03.
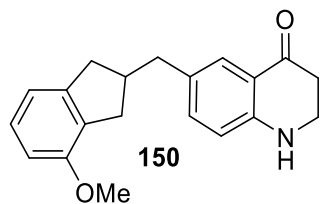

1-(4-((1-Methyl-2,3-dihydro-1H-inden-2-yl)methyl)phenyl)azetidin-2-one (149). 149 was synthesized according to general procedure D starting from **146** (1.06 g, 2.85 mmol, 1.0 eq) to yield the title compound as a solid (185 mg, 22.3%). δ ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29 (d, *J* = 8.2 Hz, 2H), 7.20 – 7.09 (m, 6H), 3.58 (t, *J* = 4.4 Hz, 2H), 3.07 (t, *J* = 4.4 Hz, 2H), 2.95 (dd, *J* = 13.5, 5.5 Hz, 1H), 2.89 – 2.82 (m, 2H), 2.60 (ddd, *J* = 34.2, 14.6, 9.1 Hz, 2H), 2.20 (pd, *J* = 8.5, 5.5 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 164.21, 147.88, 142.23, 136.83, 136.48, 129.44, 126.18, 126.15, 124.15, 123.08, 116.06, 50.49, 44.69, 39.70, 37.92, 37.65, 35.95, 18.38.

6-((4-Methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1*H*)-one (150). 150 was synthesized according to general procedure E starting from **147** (789 mg, 2.57 mmol,

1.0 eq) to yield that title compound (205 mg, 25.9%) ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 (t, J = 1.8 Hz, 1H), 7.16 (dt, J = 8.5, 1.8 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.66 – 6.58 (m, 2H), 3.79 (d, J = 1.4 Hz, 3H), 3.57 – 3.48 (m, 2H), 3.01 – 2.92 (m, 2H), 2.76 – 2.60 (m, 7H), 2.55 (dd, J = 16.0, 6.5 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.89, 155.92, 150.47, 145.04, 136.10, 130.87, 130.53, 127.51, 127.05, 119.18, 116.92, 115.91, 107.76, 55.06, 42.39, 40.95, 40.57, 39.02, 38.17, 35.20.
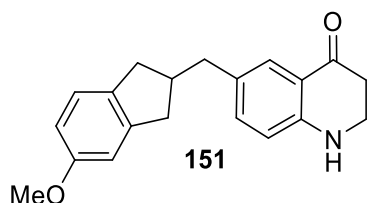
6-((5-Methoxy-2,3-dihydro-1H-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1H)-one   (151).
151 was synthesized according to general procedure E starting from **148** (514 mg, 1.67 mmol) to yield the title compound as a viscous yellow oil (172 mg, 33.4%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 (d, J = 2.1 Hz, 1H), 7.16 (dd, J = 8.3, 2.1 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.74 – 6.72 (m, 1H), 6.67 (dd, J = 8.2, 2.5 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 3.77 (s, 3H), 3.57 (t, J = 6.9 Hz, 2H), 2.92 (td, J = 15.9, 6.9 Hz, 2H), 2.74 – 2.65 (m, 6H), 2.60 (ddd, J = 22.3, 15.1, 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.86, 158.57, 150.43, 144.66, 136.12, 135.14, 131.06, 127.15, 124.90, 119.33, 115.91, 111.90, 110.09, 55.40, 42.51, 41.92, 40.48, 39.04, 38.24, 37.90.
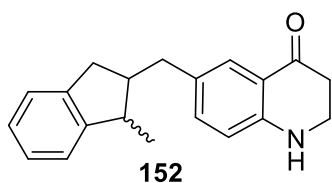

6-((1-Methyl-2,3-dihydro-1H-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1H)-one (152). 152
was synthesized according to general procedure E starting from **149** (185 mg, 0.64 mmol) to yield the title compound as a viscous yellow oil (87 mg, 47%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70 (d, J = 2.3 Hz, 1H), 7.21 – 7.07 (m, 5H), 6.63 (dd, J = 8.3, 2.0 Hz, 1H), 3.56 (td, J = 7.0, 2.2 Hz, 2H), 2.94 – 2.82 (m, 3H), 2.69 (td, J = 7.1, 6.4, 2.0 Hz, 2H), 2.57 (ddq, J = 13.7, 9.4, 2.9 Hz, 2H), 2.17 (dddt, J = 14.4, 7.5, 5.2, 2.1 Hz, 1H), 1.28 (dd, J = 6.8, 2.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.93, 150.46, 147.99, 142.38, 136.19, 130.80, 127.14, 126.18, 126.16, 126.13,

124.21, 123.12, 119.23, 115.92, 50.48, 44.63, 42.43, 39.09, 38.18, 37.62, 18.37.
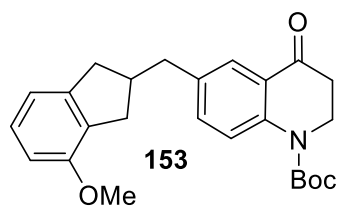
Tert-butyl 6-((4-methoxy-2,3-dihydro-1_H_-inden-2-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2_H_)-carboxylate (153). 153 was synthesized following general procedure G using **150** (118 mg, 0.384 mmol, 1.0 eq), Boc$_2$O (101 mg, 0.46 mmol, 2.0 eq), DMAP (5 mg, 0.038 mmol, 0.1 eq), DIPEA (0.08 mL, 0.46 mmol, 2.0 eq). The reaction stirred at reflux for 16 h. Once enough starting material was converted to product, the crude yellow oil was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (83 mg, 53.2%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84 (d, _J_ = 2.3 Hz, 1H), 7.71 (d, _J_ = 8.6 Hz, 1H), 7.36 (dd, _J_ = 8.3, 2.1 Hz, 1H), 7.11 (t, _J_ = 7.8 Hz, 1H), 6.79 (d, _J_ = 7.4 Hz, 1H), 6.65 (d, _J_ = 8.1 Hz, 1H), 4.15 (t, _J_ = 6.3 Hz, 2H), 3.80 (s, 3H), 2.99 (dt, _J_ = 16.0, 6.4 Hz, 2H), 2.81 – 2.72 (m, 5H), 2.71 – 2.62 (m, 1H), 2.61 – 2.52 (m, 1H), 1.57 (d, _J_ = 1.4 Hz, 9H), 1.53 (d, _J_ = 4.3 Hz, 1H), 1.47 (d, _J_ = 1.2 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.22, 155.91, 152.71, 144.80, 142.14, 137.02, 134.62, 130.34, 127.57, 126.96, 124.67, 123.56, 116.87, 107.77, 81.92, 80.87, 55.02, 44.24, 40.75, 40.71, 39.04, 38.95, 35.20, 28.23, 27.81.
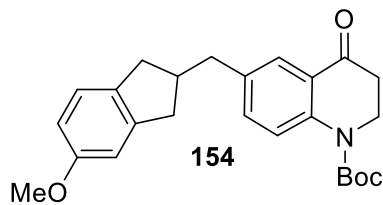
Tert-butyl 6-((5-methoxy-2,3-dihydro-1_H_-inden-2-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2_H_)-carboxylate (154). 154 was synthesized following general procedure G using **151** (100 mg, 0.325 mmol, 1.0 eq), Boc$_2$O (85 mg, 0.39 mmol, 2.0 eq), DMAP (4 mg, 0.033 mmol, 0.1 eq), DIPEA (0.068 mL, 0.39 mmol, 2.0 eq). The reaction stirred at reflux for 16 h. Once enough starting material was converted to product, the crude yellow oil was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (47 mg, 35.3%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (s, 1H), 7.71 (d, _J_ = 8.4 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.05 (d, _J_ = 8.1 Hz, 1H), 6.73 (s, 1H), 6.68 (d, _J_ = 7.9 Hz, 1H), 4.15 (t, _J_ = 6.3 Hz, 2H), 3.76 (s, 3H), 2.93 (ddd, _J_

= 18.8, 10.9, 4.1 Hz, 2H), 2.75 (d, *J* = 6.9 Hz, 6H), 2.60 (ddd, *J* = 20.8, 14.5, 4.4 Hz, 3H), 1.56 (s, 11H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.28, 158.58, 152.74, 144.39, 142.18, 137.04, 134.86, 134.64, 126.95, 124.86, 124.68, 123.58, 111.94, 110.05, 81.98, 77.26, 77.00, 76.75, 55.33, 44.27, 41.64, 40.63, 39.01, 38.97, 37.88, 28.26, 27.84.
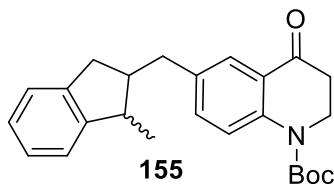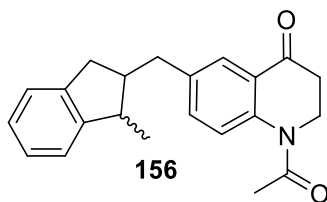

155

***Tert*-butyl 6-((1-methyl-2,3-dihydro-1*H*-inden-2-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (155). 155** was synthesized following general procedure G using **152** (87 mg, 0.3 mmol, 1.0 eq), Boc$_2$O (78 mg, 0.36 mmol, 2.0 eq), DMAP (4 mg, 0.03 mmol, 0.1 eq), DIPEA (0.062 mL, 0.36 mmol, 2.0 eq). The reaction stirred at reflux for 16 h. Once enough starting material was converted to product, the crude yellow oil was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (51 mg, 43.6%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84 (d, *J* = 2.4 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.19 – 7.09 (m, 6H), 4.15 (t, *J* = 6.4 Hz, 2H), 3.01 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.88 (ddd, *J* = 11.9, 7.7, 4.4 Hz, 2H), 2.76 (t, *J* = 6.2 Hz, 3H), 2.67 (dd, *J* = 13.6, 9.5 Hz, 1H), 2.59 (dd, *J* = 15.6, 9.0 Hz, 1H), 2.23 (pd, *J* = 8.6, 5.3 Hz, 1H), 1.56 (s, 18H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.36, 152.74, 147.79, 142.20, 142.16, 136.95, 134.74, 127.04, 126.27, 126.24, 124.69, 124.22, 123.60, 123.14, 82.00, 50.22, 44.74, 44.27, 39.34, 38.98, 37.59, 29.66, 28.27, 27.85, 18.37.

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1-Acetyl-6-((1-methyl-2,3-dihydro-1*H*-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1*H*)-one (156) 156 was synthesized following general procedure K using **152** (46 mg, 0.158 mmol, 1.0 eq). Once the reaction was completed, the crude product was purified using silica gel chromatography to yield the title comound **156** (49 mg, 92.5%) as a clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (s, 1H), 7.44 – 7.39 (m, 1H), 7.20 – 7.07 (m, 5H), 4.30 – 4.19

(m, 3H), 3.04 (dd, J = 13.7, 5.1 Hz, 1H), 2.90 (ddd, J = 13.0, 8.0, 4.4 Hz, 2H), 2.80 (t, J = 6.3 Hz, 3H), 2.71 (dd, J = 13.5, 9.6 Hz, 1H), 2.60 (dd, J = 15.6, 9.1 Hz, 1H), 2.35 (s, 4H), 2.25 (pd, J = 8.6, 3.7 Hz, 1H), 1.31 (dd, J = 7.1, 2.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.23, 169.32, 147.70, 142.03, 138.97, 134.81, 134.65, 127.62, 126.38, 126.36, 126.32, 125.94, 124.51, 124.27, 124.09, 123.53, 123.21, 77.29, 77.23, 77.03, 76.99, 76.78, 50.18, 44.78, 44.69, 41.82, 39.54, 39.48, 37.61, 36.18, 35.32, 23.13, 18.43, 15.29.

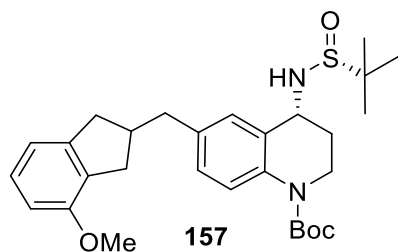***Tert*-butyl (4*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-((4-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (157).** **157** was synthesized following general procedure H using **153** (83 mg, 0.20 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (74 mg, 0.61 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.325 mL, 1.22 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (46 mg, 1.22 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as an off-white solid (43 mg, 41.3%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.71 (d, J = 8.5 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.11 (t, J = 7.9 Hz, 2H), 6.79 (d, J = 7.5 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 4.57 (q, J = 3.1 Hz, 1H), 4.52 (s, 1H), 4.03 – 3.94 (m, 1H), 3.80 (d, J = 2.7 Hz, 3H), 3.62 – 3.52 (m, 1H), 3.04 – 2.91 (m, 2H), 2.74 (s, 3H), 2.70 – 2.62 (m, 1H), 2.61 – 2.52 (m, 1H), 2.19 (dt, J = 13.0, 3.9 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.53 (s, 10H), 1.44 (s, 3H), 1.22 (s, 11H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.95, 153.56, 145.04, 136.90, 136.34, 130.54, 129.01, 128.68, 128.66, 128.37, 127.54, 123.79, 116.93, 107.77, 81.07, 77.26, 77.21, 77.00, 76.75, 55.59, 55.10, 55.08, 50.35, 40.91, 40.87, 40.83, 40.03, 40.01, 39.15, 35.29, 35.27, 29.55, 28.33, 24.16, 22.59.

158

MeO
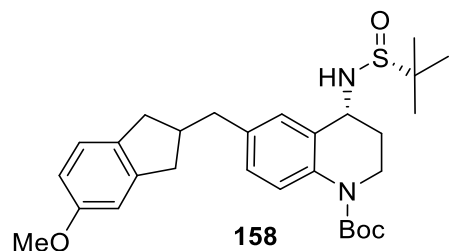
***Tert*-butyl (4*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-((5-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (158). 158** was synthesized following general procedure H using **154** (139 mg, 0.41 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (47 mg, 0.12 mmol, 3.0 eq), and Ti(OEt)₄ (0.145 mL, 0.69 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH₄ (26 mg, 0.69 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as clear, colorless oil (25 mg, 44.0%). ¹H NMR (500 MHz, CDCl₃) δ 7.73 (d, *J* = 8.5 Hz, 1H), 7.19 (s, 1H), 7.07 (dd, *J* = 19.0, 8.3 Hz, 2H), 6.73 (s, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 4.62 – 4.49 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 0H), 3.99 (dt, *J* = 13.5, 4.5 Hz, 1H), 3.77 (s, 3H), 3.63 – 3.52 (m, 1H), 3.30 (s, 1H), 3.00 – 2.86 (m, 2H), 2.72 (s, 3H), 2.67 – 2.52 (m, 2H), 2.18 (dt, *J* = 13.5, 4.2 Hz, 1H), 2.00 (ddd, *J* = 20.6, 11.7, 4.1 Hz, 2H), 1.53 (s, 9H), 1.22 (s, 11H). ¹³C NMR (126 MHz, CDCl₃) δ 158.54, 153.54, 144.58, 144.56, 136.88, 136.35, 135.07, 135.04, 129.01, 128.65, 128.38, 124.85, 124.84, 123.74, 111.88, 111.86, 110.06, 81.05, 77.25, 77.00, 76.79, 76.75, 55.58, 55.35, 50.44, 41.81, 40.68, 40.06, 39.11, 39.09, 37.97, 37.95, 29.65, 28.32, 24.16, 22.57.


159   **Boc**
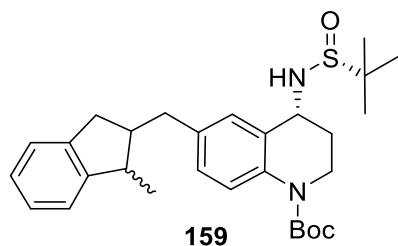
***Tert*-butyl (4*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-((1-methyl-2,3-dihydro-1*H*-inden-2-yl)methyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (159). 159** was synthesized following

general procedure H using **155** (51 mg, 0.13 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (47 mg, 0.39 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.164 mL, 0.78 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (30 mg, 0.69 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as clear, colorless oil (19 mg, 29.2%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.74 (d, *J* = 8.5 Hz, 1H), 7.12 (t, *J* = 11.3 Hz, 5H), 4.60 – 4.50 (m, 1H), 4.00 (dq, *J* = 13.3, 4.4 Hz, 1H), 3.61 – 3.50 (m, 1H), 3.31 (s, 1H), 3.00 – 2.83 (m, 3H), 2.69 – 2.53 (m, 2H), 2.20 (dp, *J* = 12.7, 4.3 Hz, 2H), 2.02 – 1.92 (m, 1H), 1.53 (s, 9H), 1.43 (d, *J* = 1.9 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.22 (dd, *J* = 4.8, 2.1 Hz, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.55, 153.53, 147.94, 142.37, 142.32, 136.70, 136.38, 136.35, 129.13, 128.78, 128.70, 128.33, 128.31, 126.20, 126.17, 124.22, 124.20, 123.79, 123.75, 123.14, 123.12, 81.06, 77.25, 77.00, 76.74, 55.60, 55.59, 50.37, 50.33, 50.31, 50.27, 44.71, 44.69, 39.98, 39.95, 39.31, 39.29, 37.68, 37.66, 29.47, 28.33, 24.16, 22.57, 18.41, 18.35.

160
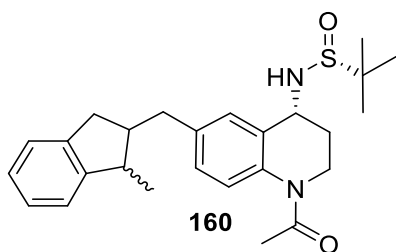
(*R*)-*N*-((4*R*)-1-acetyl-6-((1-methyl-2,3-dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (160). 160 was synthesized following general procedure H using **156** (49 mg, 0.15 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (53 mg, 0.44 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.185 mL, 0.88 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (33 mg, 0.88 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica

gel chromatography to yield the title compound which was still impure with residual Ellman reagent, but was taken ahead to next step. No yield calculated. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26 – 7.18 (m, 2H), 7.11 – 7.00 (m, 5H), 4.50 (d, *J* = 4.7 Hz, 1H), 3.34 (s, 1H), 2.92 (dt, *J* = 13.7, 4.5 Hz, 1H), 2.88 – 2.77 (m, 2H), 2.62 (ddd, *J* = 13.6, 9.3, 4.0 Hz, 1H), 2.54 (dd, *J* = 15.6, 9.0 Hz, 1H), 2.22 – 2.11 (m, 5H), 2.05 – 1.98 (m, 1H), 1.23 (dd, *J* = 6.8, 1.3 Hz, 3H), 0.85 – 0.78 (m, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 169.90, 147.80, 142.19, 142.15, 128.86, 128.75, 128.68, 126.23, 124.61, 124.55, 124.20, 124.18, 123.14, 123.12, 77.00, 66.73, 55.71, 50.24, 50.19, 44.68, 44.66, 39.47, 39.44, 38.66, 37.65, 37.63, 33.93, 30.55, 30.33, 29.63, 28.84, 24.41, 24.18, 23.71, 23.34, 22.89, 22.55, 21.94, 18.40, 18.36, 13.98, 10.92.
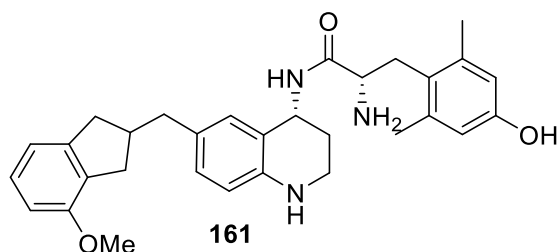
(2*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((4*R*)-6-((4-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (161). 161 was synthesized following general procedure I using **157** (43 mg, 0.084 mmol, 1.0 eq) and conc. HCl (3 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (15 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (25 mg, 0.073 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **161** as a TFA salt (35 mg, 79.5%). ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.18 – 7.11 (m, 2H), 7.06 (td, *J* = 7.8, 4.9 Hz, 1H), 6.95 (dd, *J* = 8.2, 4.7 Hz, 1H), 6.76 – 6.71 (m, 1H), 6.67 (dd, *J* = 8.3, 4.9 Hz, 1H), 6.50 (d, *J* = 4.9 Hz, 2H), 5.07 (q, *J* = 5.0 Hz, 1H), 3.90 (dt, *J* = 11.1, 5.2 Hz, 1H), 3.76 (d, *J* = 4.8 Hz, 3H), 3.31 (s, 2H), 3.28 – 3.18 (m, 2H), 3.06 (dt, *J* = 13.6, 5.1 Hz, 1H), 2.90 (dddd, *J* = 32.8, 17.5, 11.7, 5.8 Hz, 2H), 2.82 – 2.74 (m, 1H), 2.64 (s, 0H), 2.59 (dt, *J* = 15.3, 5.5 Hz, 1H), 2.48 (dt, *J* = 15.9, 5.2 Hz, 1H), 2.28 (d, *J* = 4.9 Hz, 6H), 1.99 – 1.87 (m, 1H), 1.59 (dq, *J* = 11.6, 5.8, 5.2 Hz, 1H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 168.95, 157.37, 145.84, 145.80, 140.07, 134.95, 131.89, 131.86, 131.25, 131.20, 130.89, 130.85, 128.80, 127.63, 123.34, 121.21, 117.85, 117.83, 116.41,

108.96, 108.94, 55.52, 53.39, 49.51, 49.45, 49.34, 49.27, 49.17, 49.00, 48.83, 48.72, 48.66, 48.49, 45.19, 45.17, 42.33, 42.25, 41.91, 41.89, 40.15, 39.87, 39.59, 39.56, 36.24, 35.96, 31.82, 28.10, 20.44. HPLC (gradient A): retention time 31.7. ESI-MS 522.1 [M+Na]+.

162
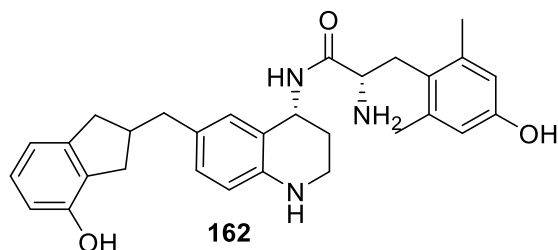
(2S)-2-amino-N-((4R)-6-((4-hydroxy-2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (162). To a round bottom flask already containing **161** (25 mg, 0.043 mmol, 1.0 eq) was added anhyd DCM and then reaction vessel was placed under vacuum for 10 min, then flooded with Ar. A 1M BBr3 solution in DCM (0.2 mL, 0.172 mmol, 4.0 eq) was slowly added to the reaction vessel. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x. The crude mixture was purified using semipreparative HPLC to yield title compound **162** (15 mg, 62.5%) as a white fluffy powder. Additional starting material, **161**, was recoverd but not included in final yield calculation. ^{1}H NMR (500 MHz, CD3OD) δ 8.18 – 8.14 (m, 0H), 7.05 – 6.98 (m, 2H), 6.94 – 6.88 (m, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 7.3 Hz, 1H), 6.52 (dd, *J* = 7.9, 2.7 Hz, 1H), 6.49 (d, *J* = 1.9 Hz, 2H), 5.01 (q, *J* = 4.2 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.28 – 3.21 (m, 1H), 3.15 – 3.07 (m, 1H), 3.02 (ddd, *J* = 13.8, 5.4, 1.9 Hz, 1H), 2.95 – 2.78 (m, 2H), 2.62 (dq, *J* = 27.1, 16.4, 13.4 Hz, 5H), 2.52 – 2.44 (m, 1H), 1.82 (d, *J* = 12.8 Hz, 1H), 1.61 – 1.50 (m, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 25.9. ESI-MS 508.1 [M+Na]+.
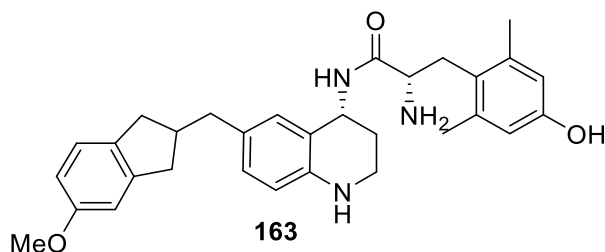

163

(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((4R)-6-((5-methoxy-2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (163). 163 was synthesized following general procedure I using **158** (26 mg, 0.057 mmol, 1.0 eq) and conc. HCl (3 drops). After removing solvent, residue was re-suspended in Et₂O, and solid crashed out. After washing the solid 3 x with fresh Et₂O, the remaining Et₂O was decanted off, yielding a white solid amine hydrochloride salt (15 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (15 mg, 0.044 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **163** as a TFA salt (19 mg, 70.4%). No ^{1}H or ^{13}C data acquired. Instead, product formation was verified using mass spectrometry. HPLC (gradient A): retention time 30.1. ESI-MS 500.1 [M+H]$^+$ and 522.1 [M+Na]$^+$.

164
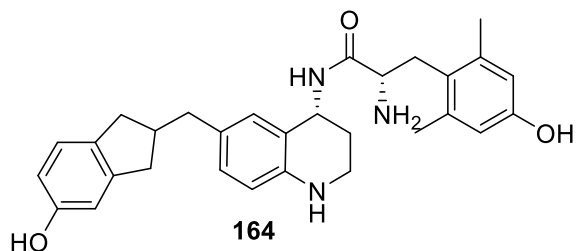
(2S)-2-amino-N-((4R)-6-((5-hydroxy-2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (164). To a round bottom flask already containing **163** (13 mg, 0.024 mmol, 1.0 eq) was added anhyd DCM and then reaction vessel was placed under vacuum for 10 min, then flooded with Ar. A 1M BBr₃ solution in DCM (0.125 mL, 0.090 mmol, 4.0 eq) was slowly added to the reaction vessel. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x. The crude mixture was purified using semipreparative HPLC to yield title compound **164** (1.3 mg, 10%) as a white fluffy powder. Title compound was 80% pure, an additional 15% was the methoxy starting material (**163**), and the entity of remaining 5% impurity was undetermined. Title compound formation was verified by mass spectrometry. No ^{1}H or ^{13}C data acquired. Instead, product formation was verified using mass spectrometry. HPLC (gradient A): retention time 31.7. ESI-MS 508.1 [M+Na]$^+$. Retention times of impurities are 24.8 (starting

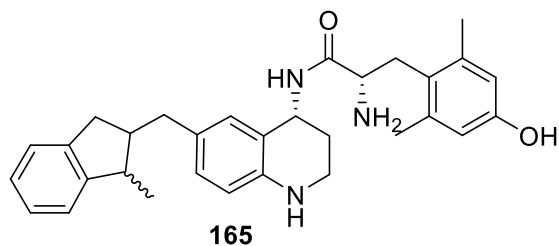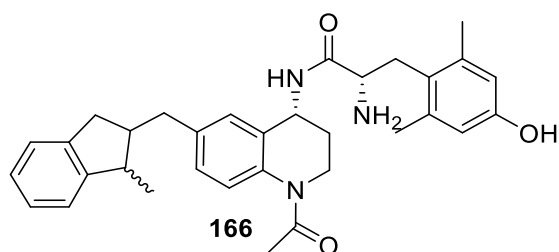material **163**) and 28.1 (unknown impurity).

165

(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((4R)-6-((1-methyl-2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (165). 165 was synthesized following general procedure I using **159** (19 mg, 0.038 mmol, 1.0 eq) and conc. HCl (3 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (13 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (15 mg, 0.040 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **165** as a TFA salt (24 mg, quant.) of two sets of inseparable diastereomers. Title compound formation was verified by mass spectrometry as title compound was synthesized as a mixture of two sets of diastereomers. No ^{1}H or ^{13}C data acquired. HPLC (gradient A): retention time 34.0. ESI-MS 506.1 [M+Na]$^+$.

166

(2S)-*N*-((4R)-1-acetyl-6-((1-methyl-2,3-dihydro-1H-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (166). 166 was synthesized following general procedure I using **160** (64 mg, 0.15 mmol, 1.0 eq) and conc. HCl (3 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (30 mg). The synthesis was completed by

following general procedure F with newly formed (*R*) amine intermediate (30 mg, 0.081 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **166** as a TFA salt of two sets of inseparable diastereomers. No yield calculated because only a portion of the crude product was purified. Title compound formation was verified by mass spectrometry as title compound was synthesized as a mixture of two sets of diastereomers. No ^{1}H or ^{13}C data acquired. HPLC (gradient A): retention time 41.8. ESI-MS 526.1 [M+H]$^+$ and 548.1 [M+H]$^+$.
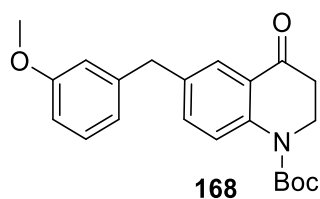

167 Boc
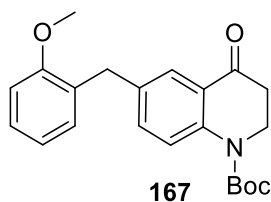
***Tert*-butyl 6-(2-methoxybenzyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (167). 167** was synthesized following general procedure L using **104** (150 mg, 0.44 mmol, 1.0 eq), (2-methoxyphenyl)boronic acid (0.134 mg, 0.88 mmol, 2.0 eq), K$_2$CO$_3$ (183 mg, 1.3 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (32 mg, 0.04 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography to yield title compound (105 mg, 64.8%) as clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.76 (d, *J* = 2.2 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.26 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.79 – 6.72 (m, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.85 (s, 2H), 3.70 (s, 3H), 2.63 (t, *J* = 6.3 Hz, 2H), 1.45 (d, *J* = 1.3 Hz, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.19, 157.11, 152.67, 141.97, 136.78, 134.63, 130.12, 128.78, 127.55, 127.06, 124.60, 123.45, 120.40, 110.32, 81.82, 55.15, 44.15, 38.90, 35.13, 28.17.

168 Boc

***Tert*-butyl 6-(3-methoxybenzyl)-4-oxo-3,4-dihydroquinoline-1(2 *H*)-carboxylate (167). 167**

was synthesized following general procedure L using **104** (150 mg, 0.44 mmol, 1.0 eq), (e-methoxyphenyl)boronic acid (0.134 mg, 0.88 mmol, 2.0 eq), K_2CO_3 (183 mg, 1.3 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (32 mg, 0.04 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography to yield title compound (72 mg, 44.4%) as clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84 (q, *J* = 5.9, 4.4 Hz, 1H), 7.68 (dt, *J* = 9.6, 4.8 Hz, 1H), 7.32 (dt, *J* = 8.5, 2.8 Hz, 1H), 7.20 (tq, *J* = 9.8, 6.3, 4.8 Hz, 1H), 6.82 – 6.65 (m, 3H), 4.18 – 4.06 (m, 2H), 3.92 (t, *J* = 5.3 Hz, 2H), 3.82 – 3.69 (m, 3H), 2.80 – 2.67 (m, 2H), 1.61 – 1.45 (m, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.20, 159.68, 152.68, 142.35, 141.92, 136.63, 134.56, 129.47, 127.08, 124.72, 123.78, 121.18, 114.63, 111.43, 82.02, 55.08, 44.20, 41.09, 38.92, 28.23.
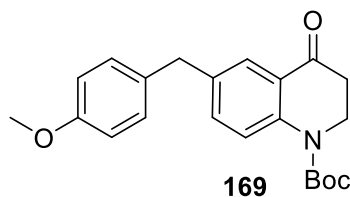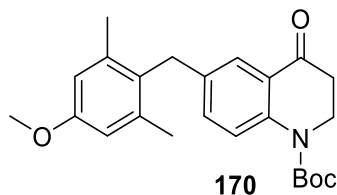

169

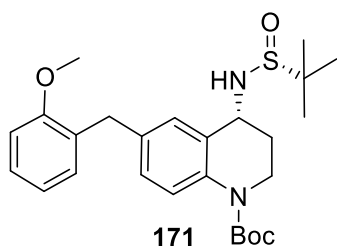***Tert*-butyl 6-(4-methoxybenzyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (167). 167** was synthesized following general procedure L using **104** (150 mg, 0.44 mmol, 1.0 eq), (4-methoxyphenyl)boronic acid (0.134 mg, 0.88 mmol, 2.0 eq), K_2CO_3 (183 mg, 1.3 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (32 mg, 0.04 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography to yield title compound (110 mg, 67.9%) as clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.73 (d, *J* = 2.2 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.21 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 2H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 2H), 3.67 (s, 3H), 2.65 (t, *J* = 6.3 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.23, 157.97, 152.66, 142.20, 137.27, 134.45, 132.41, 129.67, 126.88, 124.67, 123.72, 115.90, 114.62, 113.88, 81.97, 55.12, 44.16, 40.14, 38.88, 28.18.

170 Boc

Tert-butyl6-(4-methoxy-2,6-dimethylbenzyl)-4-oxo-3,4-dihydroquinoline-1(2_H_)-carboxylate (170). 170 was synthesized following general procedure L using **104** (115 mg, 0.34 mmol, 1.0 eq), (2,2-dimethyl-4-methoxyphenyl)boronic acid (0.122 mg, 0.68 mmol, 2.0 eq), K_2CO_3 (140 mg, 1.0 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (25 mg, 0.034 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography to yield title compound (108mg, 62.1%) as clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.10 (dd, J = 8.7, 2.1 Hz, 1H), 6.63 (s, 2H), 4.12 (t, J = 6.3 Hz, 2H), 3.96 (s, 2H), 3.79 (s, 3H), 2.73 (t, J = 6.3 Hz, 2H), 2.21 (s, 6H), 1.54 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.20, 157.70, 152.70, 141.97, 139.04, 138.17, 136.00, 133.29, 128.23, 126.14, 124.69, 123.62, 122.32, 113.48, 111.54, 81.91, 54.96, 44.16, 38.93, 33.52, 28.19, 20.45.

171 Boc

Tert-butyl (_R_)-4-(((_R_)-_tert_-butylsulfinyl)amino)-6-(2-methoxybenzyl)-3,4-dihydroquinoline-1(2_H_)-carboxylate (171). 171 was synthesized following general procedure H using **167** (105 mg, 0.28 mmol, 1.0 eq), (_R_)-2-methylpropane-2-sulfinamide (104 mg, 0.86 mmol, 3.0 eq), and Ti(OEt)4 (0.359 mL, 1.71 mmol, 6.0 eq) to form the (_R_)-tert-butanesulfinyl imine intermediate in situ. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH4 (65 mg, 1.71 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound

as clear, colorless oil (60 mg, 44.4%). 1H NMR (500 MHz, CDCl$_3$) δ 7.66 (d, J = 8.5 Hz, 1H), 7.22 – 7.14 (m, 2H), 7.13 – 7.05 (m, 2H), 6.90 – 6.81 (m, 2H), 4.52 (bs, 1H), 3.99 – 3.87 (m, 3H), 3.82 (s, 3H), 3.61 – 3.50 (m, 1H), 3.30 (s, 1H), 2.24 – 2.12 (m, 1H), 1.99 – 1.90 (m, 1H), 1.50 (s, 9H), 1.20 (s, 9H). 13C NMR (126 MHz, CDCl$_3$) δ 157.19, 153.57, 136.54, 136.24, 130.21, 129.35, 128.98, 128.68, 128.34, 127.43, 123.79, 120.43, 110.35, 80.99, 55.59, 55.27, 50.25, 39.95, 35.09, 29.33, 28.31, 22.57.
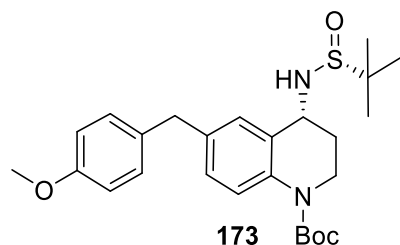

172
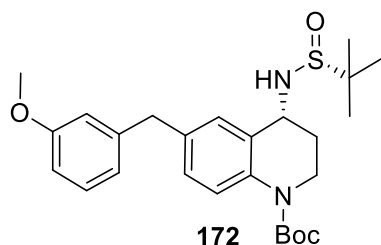
***Tert*-butyl (*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-(3-methoxybenzyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (172). 172** was synthesized following general procedure H using **168** (72 mg, 0.2 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (71 mg, 0.59 mmol, 3.0 eq), and Ti(OEt)4 (0.246 mL, 1.18 mmol, 6.0 eq) to form the (*R*)-tert-butanesulfinyl imine intermediate in situ. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH4 (44 mg, 1.18 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as clear, colorless oil (44 mg, 47.3%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.68 (d, *J* = 8.4 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.07 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.75 – 6.70 (m, 2H), 4.52 (q, *J* = 3.5 Hz, 1H), 3.94 (dt, *J* = 12.9, 4.5 Hz, 1H), 3.88 (s, 2H), 3.77 (s, 3H), 3.61 – 3.53 (m, 1H), 3.33 (s, 1H), 2.18 (dq, *J* = 14.1, 4.0 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.50 (s, 9H), 1.20 (s, 9H).^{13}C NMR (126 MHz, CDCl$_3$) δ 159.63, 153.50, 142.41, 136.50, 136.37, 129.37, 128.93, 128.54, 128.53, 123.96, 121.23, 114.61, 111.33, 81.05, 55.62, 55.07, 50.41, 41.16, 40.01, 29.41, 28.28, 22.53.

173 Boc

***Tert*-butyl (*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-(4-methoxybenzyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (173). 173** was synthesized following general procedure H using **169** (110 mg, 0.3 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (109 mg, 0.9 mmol, 3.0 eq), and Ti(OEt)4 (0.377 mL, 1.80 mmol, 6.0 eq) to form the (*R*)-tert-butanesulfinyl imine intermediate in situ. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH4 (68 mg, 1.8 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as clear, colorless oil (136 mg, 96.5%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.66 (d, *J* = 8.5 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.10 – 7.06 (m, 2H), 7.03 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.81 – 6.76 (m, 2H), 4.50 (q, *J* = 3.6 Hz, 1H), 3.91 (dt, *J* = 12.9, 4.6 Hz, 1H), 3.83 (s, 2H), 3.74 (s, 3H), 3.62 – 3.51 (m, 1H), 3.39 (bs, 1H), 2.16 (dq, *J* = 13.7, 4.3 Hz, 1H), 1.95 – 1.89 (m, 1H), 1.48 (s, 9H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 157.78, 153.40, 136.93, 136.25, 132.88, 129.74, 129.61, 128.70, 128.46, 128.30, 123.83, 113.75, 113.72, 80.90, 55.54, 55.04, 50.38, 40.11, 39.96, 29.34, 28.16, 22.43.


174 Boc
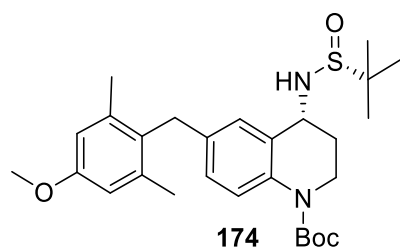
***Tert*-butyl (*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-(4-methoxy-2,6-dimethylbenzyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (174). 174** was synthesized following general procedure H using **170** (108 mg, 0.27 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (100 mg, 0.82 mmol, 3.0 eq), and Ti(OEt)4 (0.343 mL, 1.6 mmol, 6.0 eq) to form the (*R*)-tert-butanesulfinyl

imine intermediate in situ. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH₄ (62 mg, 1.6 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as clear, colorless oil (92 mg, 67.1%). ^{1}H NMR (500 MHz, CDCl₃) δ 7.61 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 2.1 Hz, 1H), 6.82 (dd, J = 8.6, 2.1 Hz, 1H), 6.61 (s, 2H), 4.49 (q, J = 3.4 Hz, 1H), 3.97 – 3.85 (m, 3H), 3.78 (s, 3H), 3.63 – 3.53 (m, 1H), 3.33 (s, 1H), 2.20 (s, 6H), 1.99 – 1.90 (m, 1H), 1.49 (s, 9H), 1.19 (s, 9H). ^{13}C NMR (126 MHz, CDCl₃) δ 157.60, 153.54, 138.20, 136.07, 135.62, 128.76, 128.61, 127.84, 127.32, 123.87, 113.43, 80.96, 55.61, 55.00, 50.36, 40.05, 33.53, 29.35, 28.27, 22.52, 20.50.
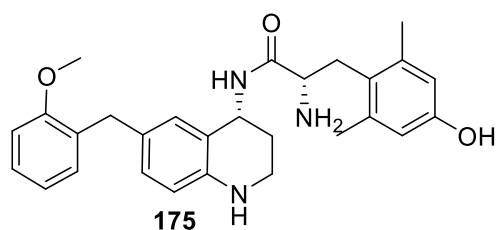
(*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(2-methoxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (175). 175 was synthesized following general procedure I using **171** (60 mg, 0.13 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et₂O, and solid crashed out. After washing the solid 3 x with fresh Et₂O, the remaining Et₂O was decanted off, yielding a white solid amine hydrochloride salt (51 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (51 mg, 0.13 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **175** as a TFA salt. ^{1}H NMR (500 MHz, CD₃OD) δ 7.14 (ddd, J = 9.2, 7.5, 1.8 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.88 (ddd, J = 8.0, 6.0, 1.5 Hz, 2H), 6.80 (td, J = 7.5, 1.1 Hz, 1H), 6.57 (d, J = 8.3 Hz, 1H), 6.48 (s, 2H), 4.92 (t, J = 4.4 Hz, 1H), 3.85 (dd, J = 11.5, 5.0 Hz, 1H), 3.81 – 3.72 (m, 5H), 3.25 (dd, J = 13.7, 11.5 Hz, 1H), 3.01 (dt, J = 13.4, 5.1 Hz, 2H), 2.52 (td, J = 11.7, 2.7 Hz, 1H), 2.27 (s, 6H), 1.80 – 1.69 (m, 1H), 1.54 (dd, J = 12.8, 5.9 Hz, 1H). HPLC (gradient A): retention time 26.5. ESI-MS 482.2 [M+Na]⁺.

176
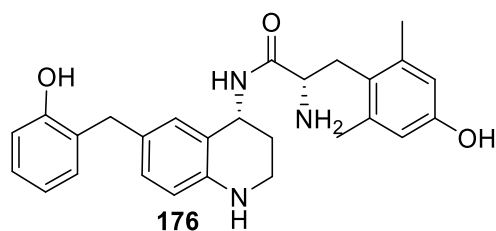
(S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(2-hydroxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (176). 176 was synthesized following general procedure I using **171** (60 mg, 0.13 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (38 mg). The synthesis was completed by following a modified version general procedure F with newly formed (R) amine intermediate (38 mg, 0.13 mmol, 1.0 eq). After coupling to diBoc-Dmt, instead of using TFA:DCM to deprotect, .a 1M solution of BBr$_3$ in DCM (0.316 mL, 5.0 eq) was slowly added to the reaction vessel to remove the boc groups and cleave the methyl ether. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **176** as a TFA salt. ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.12 (d, J = 2.4 Hz, 1H), 7.07 (dd, J = 8.1, 2.4 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.96 – 6.92 (m, 1H), 6.81 (dd, J = 8.3, 2.9 Hz, 1H), 6.76 – 6.67 (m, 2H), 6.49 (d, J = 2.7 Hz, 2H), 4.99 (q, J = 4.3 Hz, 1H), 3.85 (tdd, J = 14.7, 11.5, 4.3 Hz, 3H), 3.25 (ddd, J = 14.4, 11.5, 3.0 Hz, 1H), 3.07 – 3.00 (m, 1H), 2.70 – 2.60 (m, 1H), 2.27 (d, J = 2.9 Hz, 6H), 1.87 (ddt, J = 14.3, 10.6, 4.0 Hz, 1H), 1.59 (dd, J = 12.8, 6.2 Hz, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 21.3. ESI-MS 468.2 [M+Na]$^+$.
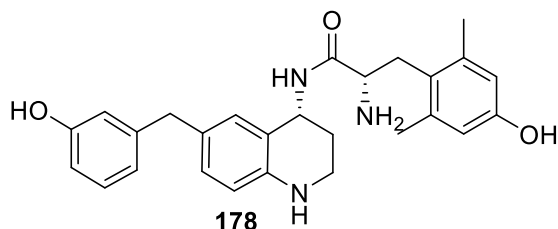

177
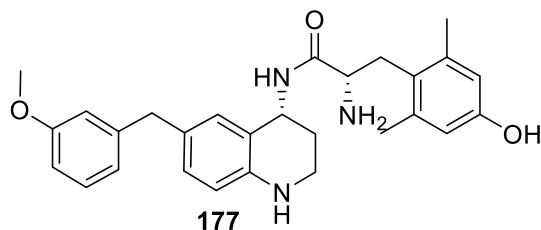
(*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(3-methoxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (177). 177 was synthesized following general procedure I using **172** (44 mg, 0.093 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (38 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (38 mg, 0.13 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **177** as a TFA salt. ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.90 (dd, *J* = 9.0, 1.1 Hz, 0H), 7.76 (d, *J* = 1.4 Hz, 0H), 7.43 (dt, *J* = 8.8, 1.6 Hz, 0H), 7.15 – 7.09 (m, 1H), 6.95 (s, 1H), 6.91 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.70 (t, *J* = 6.5 Hz, 2H), 6.65 (d, *J* = 2.3 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.48 (s, 2H), 4.96 – 4.91 (m, 1H), 3.85 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.77 (s, 2H), 3.72 (d, *J* = 1.1 Hz, 3H), 3.28 – 3.21 (m, 1H), 3.02 (ddd, *J* = 18.3, 14.0, 4.8 Hz, 2H), 2.55 (td, *J* = 11.9, 2.4 Hz, 1H), 2.27 (s, 7H), 1.80 – 1.70 (m, 1H), 1.57 – 1.48 (m, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 25.6. ESI-MS 482.2 [M+Na]$^{+}$.
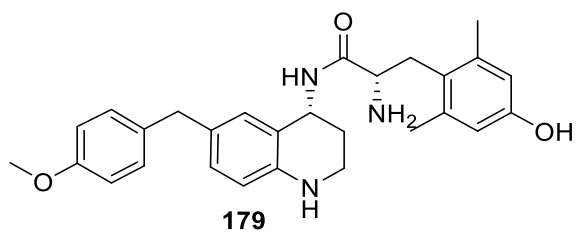

178

(*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(3-hydroxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (178). 178 was synthesized following general procedure I using **172** (44 mg, 0.093 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (38 mg). The synthesis was completed by following a modified version general procedure F with newly formed (*R*) amine intermediate (38 mg, 0.13 mmol, 1.0 eq). After coupling to diBoc-Dmt, instead of using TFA:DCM to deprotect, a 1M solution of BBr$_3$ in DCM (0.132 mL, 5.0 eq) was slowly added to the reaction vessel to remove the boc groups and cleave the methyl ether. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced

pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **178** as a TFA salt. ^{1}H NMR (500 MHz, CD₃OD) δ 7.03 (td, *J* = 7.8, 1.3 Hz, 1H), 7.00 (s, 1H), 6.97 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.69 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.62 – 6.55 (m, 2H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.48 (s, 2H), 4.99 – 4.93 (m, 1H), 3.91 – 3.83 (m, 1H), 3.75 (s, 2H), 3.29 – 3.22 (m, 1H), 3.08 (dt, *J* = 12.2, 4.2 Hz, 1H), 3.02 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.59 (t, *J* = 11.3 Hz, 1H), 2.30 – 2.24 (m, 6H), 1.83 – 1.74 (m, 1H), 1.54 (dd, *J* = 11.5, 4.8 Hz, 1H). No ¹³C data acquired. HPLC (gradient A): retention time 20.5. ESI-MS 468.2 [M+Na]⁺.
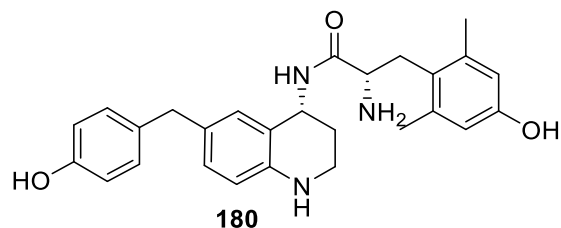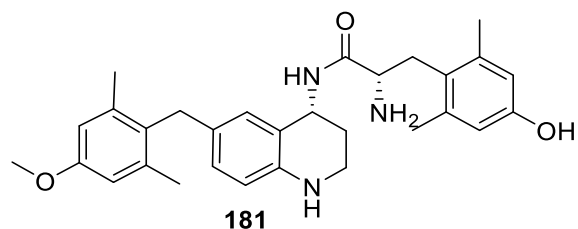

179

(*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(4-methoxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (179). 179 was synthesized following general procedure I using **173** (136 mg, 0.29 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et₂O, and solid crashed out. After washing the solid 3 x with fresh Et₂O, the remaining Et₂O was decanted off, yielding a white solid amine hydrochloride salt (117 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (117 mg, 0.13 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **179** as a TFA salt. ^{1}H NMR (500 MHz, CD₃OD) δ 7.09 (d, *J* = 2.0 Hz, 1H), 7.05 – 7.01 (m, 3H), 6.86 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.80 – 6.76 (m, 2H), 6.49 (s, 2H), 5.00 (t, *J* = 4.8 Hz, 1H), 3.89 (ddd, *J* = 11.6, 5.2, 1.2 Hz, 1H), 3.80 (s, 2H), 3.73 (d, *J* = 1.3 Hz, 3H), 3.29 – 3.22 (m, 1H), 3.16 (dt, *J* = 12.8, 4.4 Hz, 1H), 3.05 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.72 – 2.65 (m, 1H), 2.27 (s, 6H), 1.87 (ddt, *J* = 14.7, 10.5, 4.0 Hz, 1H), 1.63 – 1.54 (m, 1H). No ¹³C data acquired. HPLC (gradient A): retention time 24.7. ESI-MS 482.2 [M+Na]⁺.
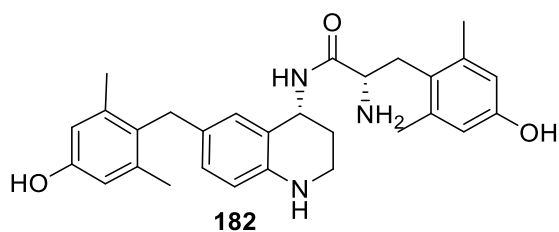
180

(*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(4-hydroxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (180). 180 was synthesized following general procedure I using **173** (136 mg, 0.029 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (38 mg). The synthesis was completed by following a modified version general procedure F with newly formed (*R*) amine intermediate (117 mg, 0.13 mmol, 1.0 eq). After coupling to diBoc-Dmt, instead of using TFA:DCM to deprotect, a 1M solution of BBr$_3$ in DCM (0.375 mL, 5.0 eq) was slowly added to the reaction vessel to remove the boc groups and cleave the methyl ether. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **180** as a TFA salt. ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.05 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 2H), 6.49 (s, 2H), 4.99 (t, *J* = 4.7 Hz, 1H), 3.88 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.76 (s, 2H), 3.26 (t, *J* = 12.7 Hz, 1H), 3.14 (dt, *J* = 12.7, 4.2 Hz, 1H), 3.03 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.69 − 2.61 (m, 1H), 2.27 (s, 6H), 1.85 (tt, *J* = 11.0, 4.2 Hz, 1H), 1.56 (d, *J* = 14.9 Hz, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 18.9. ESI-MS 468.2 [M+Na]$^+$.


181

(*S*)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(4-methoxy-2,6-dimethylbenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (181). 181 was synthesized following general procedure I using **174** (92 mg, 0.184 mmol, 1.0 eq) and conc. HCl (5 drops). After removing

solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (80 mg). The synthesis was completed by following general procedure F with newly formed (R) amine intermediate (80 mg, 0.19 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **181** (30 mg, 53.6%) as a TFA salt. ^{1}H NMR (500 MHz, CD$_3$OD) δ 6.97 (d, J = 1.9 Hz, 1H), 6.70 (s, 1H), 6.67 (d, J = 1.9 Hz, 1H), 6.60 (s, 2H), 6.49 (s, 2H), 4.94 (t, J = 4.6 Hz, 1H), 3.89 (d, J = 6.6 Hz, 3H), 3.74 (s, 3H), 3.25 (dd, J = 13.7, 11.5 Hz, 1H), 3.10 (ddd, J = 12.4, 5.4, 3.7 Hz, 1H), 3.03 (dd, J = 13.7, 5.3 Hz, 1H), 2.65 – 2.57 (m, 1H), 2.28 (s, 6H), 2.13 (s, 6H), 1.82 (ddt, J = 14.9, 11.1, 4.0 Hz, 1H), 1.59 (dtd, J = 13.8, 4.9, 2.7 Hz, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 29.4. ESI-MS 510.3 [M+Na]$^+$.

182

(**S**)**-2-amino-N-((R)-6-(4-hydroxy-2,6-dimethylbenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (182). 182** was synthesized following general procedure I using **174** (92 mg, 0.184 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (80 mg). The synthesis was completed by following a modified version general procedure F with newly formed (R) amine intermediate (80 mg, 0.13 mmol, 1.0 eq). After coupling to diBoc-Dmt, instead of using TFA:DCM to deprotect, a 1M solution of BBr$_3$ in DCM (0.463 mL, 5.0 eq) was slowly added to the reaction vessel to remove the boc groups and cleave the methyl ether. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **182** (15 mg, 27.8%) as a TFA salt. ^{1}H NMR (500 MHz, CD$_3$OD) δ 6.95 (d, J = 1.6 Hz, 1H), 6.68 (d, J = 2.3 Hz, 2H), 6.50 –

6.48 (m, 4H), 4.94 (t, J = 4.6 Hz, 1H), 3.89 (dd, J = 11.5, 5.2 Hz, 1H), 3.85 (s, 2H), 3.26 (dd, J = 13.7, 11.5 Hz, 1H), 3.09 (dt, J = 12.4, 4.3 Hz, 1H), 3.03 (dd, J = 13.7, 5.2 Hz, 1H), 2.58 (td, J = 11.8, 2.6 Hz, 1H), 2.28 (s, 6H), 2.09 (s, 6H), 1.81 (ddt, J = 15.1, 11.2, 4.0 Hz, 1H), 1.59 (dtd, J = 13.6, 5.1, 2.9 Hz, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 22.6. ESI-MS 496.2 [M+Na]$^+$.


183
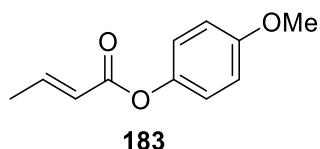
4-Methoxyphenyl (*E*)-but-2-enoate (183). To a flame-dried round bottom flask with a stir bar was added anhydrous DCM via syringe. Next, 4-methoxyphenol (1 g, 8.1 mmol, 1.5 eq) was added to the round bottom flask, followed by crotonyl chloride (0.515 mL, 5.4 mmol, 1.0 eq), and Et$_3$N (1.5 mL, 10.1 mmol, 2.0 eq). Reaction stirred at RT for 16 h. After reaction completed, organic layer was washed with 1 M HCl (1 x 75 mL), then with diluted 2M NaOH (1 x 75 mL), and finally with brine (1 x 75 mL), then organic layer was dried over MgSO$_4$, concentrated, the purified using column chromatography to yield the title compound (**183**) as a clear, colorless oil, 1.03 g, quant.). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22 – 7.11 (m, 1H), 7.05 – 7.00 (m, 2H), 6.92 – 6.86 (m, 2H), 6.07 – 6.00 (m, 1H), 3.79 (s, 3H), 1.95 (dd, J = 6.9, 1.6 Hz, 3H). No ^{13}C data acquired.

184
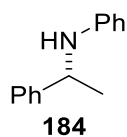
(*R*)-*N*-(1-phenylethyl)aniline (184). To synthesize **184** CsF was first added to a round bottom flask equipped with a stir bar, then flame-dried under vacuum. Acetonitrile was added to the reaction vessel followed by the addition of (*R*)-1-phenylethan-1-amine, then the aryl TMS-triflate. Reaction vessel was placed in an oil bath at 60C and stirred for 36 h. Once complete, reaction quenched with brine, then layers separated. Crude organic residue was purified using silica gel column chromatography to yield title compound as a solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 – 7.27 (m, 4H), 7.27 – 7.18 (m, 1H), 7.09 (dd, J = 8.9, 3.6 Hz, 2H), 6.64 (t, J = 6.3 Hz, 1H), 6.52 (d, J = 6.7 Hz, 2H), 4.53 – 4.44 (m, 1H), 4.23 (s, 1H), 1.52 (dd, J = 5.9, 4.0 Hz,

3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 147.05, 145.04, 129.07, 128.61, 126.86, 125.84, 117.35, 113.40, 53.58, 24.96.

185
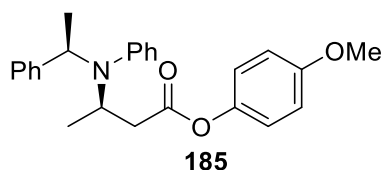
4-Methoxyphenyl (*R*)-3-(phenyl((*R*)-1-phenylethyl)amino)butanoate (185). 185 was synthesized by lithium conjugate addition using **183** and **184**. To begin, *n*-BuLi was added to a flame-dried reaction vessel in Ar atomosphere at -78˚C that contained amine **184.** After 15 min, **183** was added to the reaction vessel via cannula. The reactions stirred at -78˚C for 2.5 h under Ar. Once complete, the reaction was quenched with NH$_4$Cl solution (3 x 25). Crude residue was purified using column chromatography to yield the title compound as a white solid (187 mg, 50.6%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.34 (m, 3H), 7.34 – 7.27 (m, 3H), 7.25 – 7.17 (m, 3H), 7.12 – 7.05 (m, 1H), 6.98 – 6.83 (m, 6H), 6.79 – 6.71 (m, 1H), 6.67 – 6.60 (m, 1H), 6.53 – 6.47 (m, 1H), 4.75 (q, *J* = 6.7 Hz, 1H), 4.48 (d, *J* = 6.7 Hz, 1H), 4.21 (td, *J* = 8.5, 5.4 Hz, 1H), 3.81 – 3.76 (m, 3H), 3.75 (s, 1H), 2.83 (ddd, *J* = 15.1, 5.2, 2.3 Hz, 1H), 2.53 (ddd, *J* = 15.2, 8.6, 2.2 Hz, 1H), 1.53 – 1.47 (m, 5H), 1.30 – 1.26 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.02, 157.13, 147.21, 146.21, 145.17, 144.45, 144.02, 129.05, 128.58, 128.40, 128.33, 127.06, 126.81, 126.66, 125.78, 122.44, 122.15, 120.73, 117.16, 115.96, 114.72, 114.34, 113.22, 56.62, 55.71, 55.54, 53.40, 50.59, 40.01, 25.01, 20.28, 18.58.

186
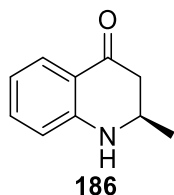
(*R*)-2-methyl-2,3-dihydroquinolin-4(1*H*)-one (186). LiOH was added to a solution of **185** in 1:1 THF: H$_2$O. The resultant mixture was heated at 50˚C for 3 h. The mixture then cooled to room temp and was acidifed with 1 M HCl, then extracted with EtOAc. The combined organic extracts were heated at 100˚C for 16 h with PPA to form the dihydroquinolinone. Once completed, the reaction was cooled to room temp and basified with 10% aqueous NaOH. The

crude product was purified using silica gel chromatography to yield the title compound (14 mg, 24.7 %) ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83 (dd, J = 7.9, 1.7 Hz, 1H), 7.34 – 7.24 (m, 1H), 6.73 (t, J = 7.5 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 4.37 – 4.25 (m, 1H), 3.78 (dqd, J = 12.9, 6.4, 3.5 Hz, 1H), 2.64 (dd, J = 16.2, 3.6 Hz, 1H), 2.47 (dd, J = 16.1, 13.0 Hz, 1H), 1.33 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 194.07, 151.55, 135.17, 127.47, 118.87, 117.96, 115.68, 49.10, 45.75, 21.35.

187
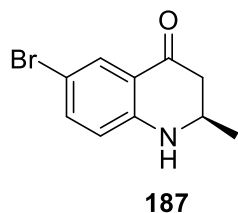
(R)-6-bromo-2-methyl-2,3-dihydroquinolin-4(1H)-one (187). NBS (134 mg, 0.75 mmol, 1.0 eq) was added to a solution of **186** (121 mg, 0.75 mmol, 1.0 eq) in anhydrous DCM. The mixture stirred at room temperature for 1.5 h. Once complete, reaction was quenched with NaHCO$_3$, and the layers separated. The organic layer was washed with brine, dried over MgSO$_4$, filtered, then concentrated under reduced pressure to yield the crude product which was purified via silica gel chromatography to yield the title compound (132 mg, 73.3%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (d, J = 2.4 Hz, 1H), 7.36 (dd, J = 8.7, 2.4 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 3.77 (dqd, J = 12.8, 6.3, 3.6 Hz, 1H), 2.64 (dd, J = 16.2, 3.6 Hz, 1H), 2.45 (dd, J = 16.2, 13.0 Hz, 1H), 1.34 (d, J = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 192.66, 150.14, 137.68, 129.88, 120.09, 117.54, 110.25, 49.01, 45.27, 21.20.

188
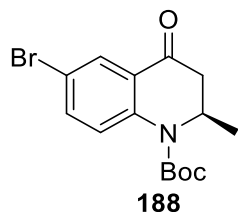
***Tert*-butyl (R)-6-bromo-2-methyl-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (188). 188** was synthesized following general procedure G using **187** (132 mg, 0.55 mmol, 1.0 eq), Boc$_2$O (156 mg, 0.72 mmol, 1.3 eq), DMAP (7 mg, 0.007 mmol, 0.1 eq), DIPEA (0.124 mL, 0.72 mmol, 1.3 eq). The reaction stirred at reflux for 16 h. Once enough starting material was converted to product, the crude yellow oil was purified using silica gel chromatography (equil in

100% hex, run in 2:3 EA:hex) to yield the title compound as a yellow oil (43 mg, 23%). Starting material was also recovered, this was not considered when calculating the yield. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (t, J = 3.0 Hz, 1H), 7.84 – 7.69 (m, 2H), 7.58 (dd, J = 9.0, 2.5 Hz, 0H), 7.50 (d, J = 8.1 Hz, 1H), 7.39 – 7.31 (m, 2H), 6.78 (d, J = 3.7 Hz, 1H), 5.86 (d, J = 6.5 Hz, 1H), 5.20 (p, J = 6.7 Hz, 1H), 3.02 (dd, J = 17.3, 5.6 Hz, 0H), 2.61 (s, 2H), 2.06 (s, 1H), 1.97 (s, 1H), 1.56 (s, 6H), 1.55 (s, 8H), 1.52 (s, 9H), 1.36 (s, 2H), 1.24 – 1.20 (m, 1H), 1.14 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 186.29, 170.22, 155.85, 152.31, 150.92, 141.67, 140.52, 137.95, 137.06, 136.89, 134.24, 130.92, 129.41, 126.20, 126.16, 126.14, 124.79, 124.00, 121.03, 121.00, 120.89, 118.11, 116.43, 106.45, 83.98, 81.85, 49.56, 48.56, 44.12, 28.69, 28.29, 28.21, 27.63, 20.33, 18.87, 17.68.


189   Boc
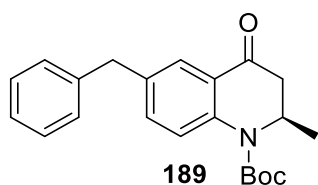
Ter*t*-butyl (*R*)-6-benzyl-2-methyl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (189). 189 was synthesized following general procedure L using **188** (43 mg, 0.13 mmol, 1.0 eq), benzyl-Bpin (0.055 mL, 0.25 mmol, 2.0 eq), K$_2$CO$_3$ (52 mg, 0.38 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (9 mg, 0.003 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography (equil in 100% hex, run in 1:1 EA:hex) to yield title compound (35 mg, 79.5%) as a clear colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (d, J = 2.2 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.34 – 7.25 (m, 4H), 7.20 (t, J = 7.9 Hz, 3H), 5.07 (p, J = 6.4 Hz, 1H), 3.96 (s, 2H), 3.01 (dd, J = 17.4, 5.9 Hz, 1H), 2.53 (d, J = 17.5 Hz, 1H), 2.41 (d, J = 11.1 Hz, 0H), 1.54 (s, 9H), 1.21 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 193.79, 152.76, 140.39, 139.73, 136.37, 134.92, 128.83, 128.53, 126.59, 126.24, 124.51, 124.01, 81.98, 49.50, 44.40, 41.08, 28.29, 17.77.

190
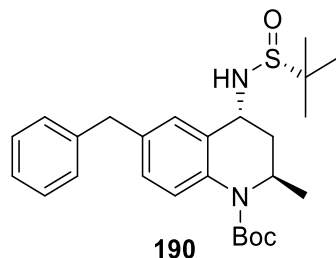
Tert-butyl(2R,4R)-6-benzyl-4-(((R)-tert-butylsulfinyl)amino)-2-methyl-3,4-dihydroquinoline-1(2H)-carboxylate (190). 190 was synthesized according to general procedure H using **189** (35 mg, 0.095 mmol, 1.0 eq), (R)-2-methylpropane-2-sulfinamide (24 mg, 0.20 mmol, 2.0 eq), and Ti(OEt)$_4$ (0.84 mL, 0.40 mmol, 4.0 eq) to form the (R)-tert-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (30 mg, 0.40 mmol, 4.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as a clear, colorless oil (12 mg, 26.4 %). ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.33 (s, 0H), 7.65 (d, *J* = 5.9 Hz, 0H), 7.49 (t, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 3H), 7.19 (d, *J* = 7.1 Hz, 3H), 7.16 – 7.05 (m, 2H), 6.27 (q, *J* = 5.7 Hz, 0H), 4.61 (p, *J* = 6.5, 5.9 Hz, 1H), 4.46 (dq, *J* = 15.3, 7.7 Hz, 1H), 4.35 (td, *J* = 11.3, 3.8 Hz, 1H), 3.98 (s, 2H), 3.96 – 3.91 (m, 2H), 2.68 (ddd, *J* = 12.4, 8.0, 4.1 Hz, 1H), 2.40 (d, *J* = 10.5 Hz, 1H), 2.30 (dt, *J* = 13.6, 6.7 Hz, 0H), 2.13 (s, 1H), 2.05 (s, 0H), 1.96 (dt, *J* = 12.6, 5.9 Hz, 0H), 1.53 (s, 3H), 1.51 (s, 11H), 1.48 (s, 1H), 1.35 (s, 8H), 1.26 (s, 2H), 1.18 (d, *J* = 6.1 Hz, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 153.54, 153.48, 153.44, 140.70, 140.65, 137.25, 136.97, 134.71, 133.95, 133.76, 129.79, 129.09, 128.96, 128.55, 128.50, 128.48, 127.67, 127.49, 126.19, 126.16, 126.12, 125.62, 122.35, 99.66, 81.10, 80.90, 60.28, 59.93, 51.64, 51.46, 50.44, 48.88, 48.72, 47.60, 44.18, 41.49, 41.26, 38.87, 29.68, 28.34, 24.30, 24.18, 22.67, 21.62, 21.21, 19.43, 17.41.

191
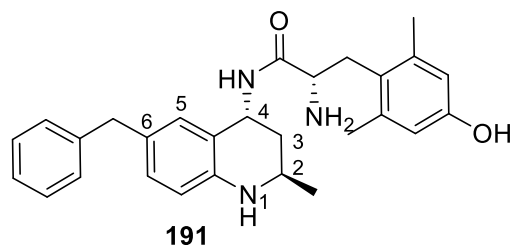
(*S*)-2-amino-*N*-((2*R*,4*R*)-6-benzyl-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (191). 191 was synthesized following general procedure I using **190** (12 mg, 0.03 mmol, 1.0 eq) and conc. HCl (4 drops). After removing solvent, residue was re-suspended in Et_2O, and solid crashed out. After washing the solid 3 x with fresh Et_2O, the remaining Et_2O was decanted off, yielding a white solid amine hydrochloride salt (11 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (11 mg, 0.03 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **191** as a TFA salt. No ^{1}H or ^{13}C data acquired. Product confirmed by mass spectrometry. HPLC (gradient A): retention time 28.8. ESI-MS 466.2 [M+Na][+].

192
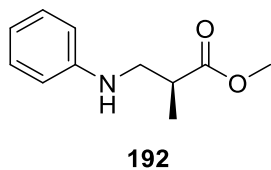
Methyl (*S*)-2-methyl-3-(phenylamino)propanoate (192). Methyl (*R*)-3-bromo-2-methylpropanoate (1.0 mL, 7.86 mmol, 1.0 eq) was added to a flask containing aniline (717 mL, 7.86 mmol, 1.0 eq) and K_2CO_3 (2.2 g, 15 mmol, 2.0 eq) in DMF. The resulting mixture stirred at 80C overnight. The next day, the solvent was removed under reduced pressure and the resulting residue was resuspended in DCM and diH2O. The organic layer was washed with bring (2 x 25 mL), dried over $MgSO_4$, and concentrated toyield the title compound (212 mg, 13.9 %). No ^{1}H or ^{13}C data acquired. Instead, intermediate taken ahead to next step (formation of **193**) without any further isolation, purification or characterization. No ^{1}H or ^{13}C data acquired.

racemized
193
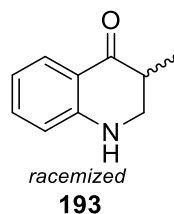
3-Methyl-2,3-dihydroquinolin-4(1H)-one (193). 193 was added to a solution of LiOH (131 mg, 5.5 mmol, 5.0 eq) 1:1 THF:H_2O and a few drops of MeOH. Solution stirred at 50C for 3 h. The reactin was monitored by TLC, and once saponification was finished, solution was acidified with 1 M HCl and the organic layer was concentrated under reduced pressure. Then PPA was added to the reaction flask and the solution stirred at 100C for 16 h. Reaction was monitored by TLC. Once the reaction was complete, reaction vessel was taken out of the oil bath and allowed to cool for 10 min, then ice water was poured into the reaction vessel, followed by DCM. The layers separated. The organic layer was washed with brine (1x25) then concentrated under reduced pressure to yield a crude residue which was then purified using silica gel chromatography to yield the pure title compound as a yellow oil (0.177, quant). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84 (dq, J = 7.3, 1.9 Hz, 1H), 7.27 (tdd, J = 7.3, 3.8, 1.7 Hz, 1H), 6.71 (qd, J = 6.6, 2.6 Hz, 1H), 6.65 (dd, J = 8.6, 3.7 Hz, 1H), 4.52 (s, 1H), 3.53 (ddd, J = 11.2, 6.7, 4.3 Hz, 1H), 3.30 – 3.19 (m, 1H), 2.74 – 2.61 (m, 1H), 1.23 – 1.16 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 196.45, 151.68, 134.76, 127.79, 118.58, 117.71, 115.58, 48.62, 41.01, 12.51.

194
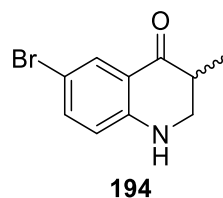
6-Bromo-3-methyl-2,3-dihydroquinolin-4(1H)-one (194). NBS (95 mg, 0.53 mmol, 1.0 eq) was added to a solution of **193** (86 mg, 0.53 mmol, 1.0 eq) in anhydrous DCM. The mixture stirred at room temperature for 1.5 h. Once complete, reaction was quenched with NaHCO$_3$, and the layers separated. The organic layer was washed with brine, dried over MgSO$_4$, filtered, then concentrated under reduced pressure to yield the crude product which was purified via silica gel chromatography to yield the title compound as a yellow oil (108 mg, 84.4%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 (d, J = 2.4 Hz, 1H), 7.25 (dd, J = 8.7, 2.4 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H),

4.54 (s, 1H), 3.47 (dd, *J* = 11.9, 5.4 Hz, 1H), 3.18 (t, *J* = 11.7 Hz, 1H), 2.66 – 2.54 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 195.17, 150.34, 139.25, 137.54, 137.28, 130.06, 129.73, 127.30, 119.68, 117.90, 117.50, 109.87, 77.00, 48.32, 48.02, 47.79, 40.66, 40.33, 40.07, 29.63, 12.42, 12.32, 0.97.

195
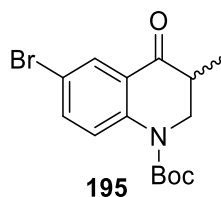
***Tert*-butyl 6-bromo-3-methyl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (195). 195** was synthesized following general procedure G using **187** (108 mg, 0.45 mmol, 1.0 eq), Boc$_2$O (147 mg, 0.67 mmol, 1.f eq), DMAP (5 mg, 0.05 mmol, 0.1 eq), DIPEA (0.118 mL, 0.67 mmol, 1.f eq). The reaction stirred at reflux for 16 h. Once enough starting material was converted to product, the crude yellow oil was purified using silica gel chromatography (equil in 100% hex, run in 2:3 EA:hex) to yield the title compound as a yellow oil (153 mg, quant.) ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.00 (q, *J* = 2.0 Hz, 1H), 7.63 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.47 (ddd, *J* = 11.2, 5.6, 2.7 Hz, 1H), 4.30 (s, 0H), 4.23 (ddd, *J* = 13.4, 4.5, 2.1 Hz, 1H), 4.14 (dtdd, *J* = 10.9, 7.8, 5.9, 1.9 Hz, 0H), 3.63 – 3.54 (m, 1H), 2.67 (dqdd, *J* = 9.0, 6.9, 5.7, 4.4, 1.8 Hz, 1H), 1.47 (d, *J* = 2.1 Hz, 8H), 1.15 (dd, *J* = 7.1, 2.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 195.52, 167.62, 152.58, 142.87, 136.28, 130.07, 125.19, 116.89, 82.44, 77.00, 68.03, 50.07, 42.13, 28.16, 12.52, 0.95.

196
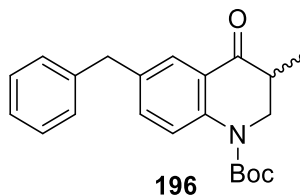
***Tert*-butyl (*R*)-6-benzyl-2-methyl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (196). 196** was synthesized following general procedure L using **195** (153 mg, 0.45 mmol, 1.0 eq), benzyl-Bpin (0.147 mL, 0.675 mmol, 2.0 eq), K$_2$CO$_3$ (186 mg, 1.35 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (33 mg, 0.045 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was

purified via silica gel chromatography (equil in 100% hex, run in 1:1 EA:hex) to yield title compound (35 mg, 79.5%) as a clear colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, J = 2.0 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.25 – 7.17 (m, 4H), 7.12 (dt, J = 12.4, 4.4 Hz, 3H), 4.22 (ddd, J = 13.4, 4.5, 1.6 Hz, 1H), 4.18 – 4.12 (m, 1H), 3.88 (s, 2H), 3.59 (ddd, J = 13.2, 9.8, 1.7 Hz, 1H), 2.66 (dtt, J = 10.0, 7.4, 5.7 Hz, 1H), 1.47 (s, 9H), 1.15 (dd, J = 7.1, 1.6 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 197.08, 167.71, 153.02, 142.25, 140.44, 136.75, 134.44, 128.81, 128.54, 127.41, 126.24, 124.03, 123.60, 82.00, 77.00, 50.29, 42.44, 41.14, 28.27, 12.74.

197
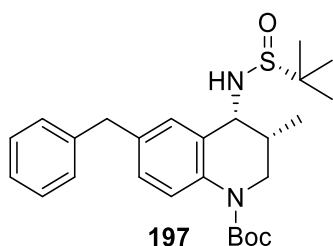
***Tert*-butyl(3*R*,4*R*)-6-benzyl-4-(((*R*)-*tert*-butylsulfinyl)amino)-3-methyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (197). 197** and **198** were synthesized according to general procedure H using **196** (35 mg, 0.095 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (24 mg, 0.20 mmol, 2.0 eq), and Ti(OEt)$_4$ (0.84 mL, 0.40 mmol, 4.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (30 mg, 0.40 mmol, 4.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **(197)** and the diastereomer (**198,** see below) as a clear, colorless oils yield for **197** was 53 mg, 31.9 % of overall yield. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.71 (d, J = 8.5 Hz, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.22 – 7.15 (m, 2H), 7.03 (dd, J = 8.7, 2.2 Hz, 1H), 4.41 (t, J = 4.6 Hz, 1H), 3.92 (s, 2H), 3.82 (dd, J = 12.9, 4.1 Hz, 1H), 3.37 – 3.29 (m, 1H), 3.17 (d, J = 5.3 Hz, 1H), 2.14 – 2.05 (m, 1H), 1.52 (d, J = 1.5 Hz, 9H), 1.23 (d, J = 1.4 Hz, 9H), 1.06 (dd, J = 6.8, 1.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.66, 141.09, 136.56, 135.66, 129.70, 129.19, 128.84, 128.43, 128.39, 125.96, 123.37, 81.17, 56.51, 56.33, 46.77, 41.20, 34.01, 28.32, 22.88, 22.84, 14.60.

198
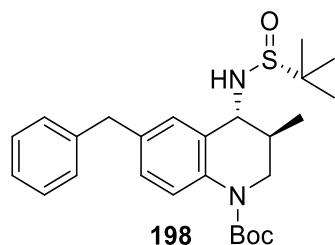
***Tert*-butyl(3*S*,4*R*)-6-benzyl-4-(((*R*)-*tert*-butylsulfinyl)amino)-3-methyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (198).** See synthesis of **197** for details. Yield for **198** was 27 mg, 15.7%. ¹H NMR (500 MHz, CDCl₃) δ 7.67 (d, *J* = 8.5 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.21 – 7.16 (m, 3H), 7.12 – 7.06 (m, 2H), 4.39 (dd, *J* = 7.3, 4.0 Hz, 1H), 3.93 (s, 2H), 3.70 (ddd, *J* = 12.8, 8.5, 1.7 Hz, 1H), 3.57 (ddd, *J* = 12.8, 4.8, 1.5 Hz, 1H), 3.45 – 3.41 (m, 1H), 2.35 – 2.27 (m, 1H), 1.50 (d, *J* = 1.6 Hz, 9H), 1.14 (d, *J* = 1.7 Hz, 9H), 1.07 (dd, *J* = 6.9, 1.6 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 153.77, 140.86, 135.88, 135.53, 128.95, 128.69, 128.45, 128.41, 126.04, 123.67, 80.96, 57.51, 56.14, 47.98, 41.17, 33.48, 28.32, 28.30, 22.66, 22.64, 22.61, 22.48, 13.60.

199
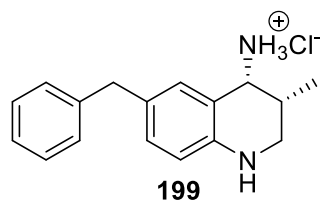
(3*R*,4*R*)-6-benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-4-aminium chloride (199). Synthesis of **199** was achieved by treating **197** with HCl in dioxane to cleave the Ellman auxillary and to remove the Boc-protecting group. X-ray crystal structure of this compound showed that the C3-methyl has *R*-stereochemistry. ¹H NMR (500 MHz, CD₃OD) δ 7.50 (d, *J* = 1.9 Hz, 1H), 7.42 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.31 – 7.16 (m, 5H), 4.69 (d, *J* = 4.6 Hz, 1H), 4.05 (s, 2H), 3.60 (s, 2H), 3.52 – 3.45 (m, 3H), 2.73 – 2.61 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.20 – 1.14 (m, 3H). ¹³C NMR (126 MHz, CD₃OD) δ 141.54, 139.77, 132.69, 131.68, 131.26, 129.97, 129.71, 127.53, 126.12, 123.63, 111.41, 66.90, 64.31, 50.64, 49.00, 44.25, 42.12, 29.81, 21.47, 15.44, 13.22.

200
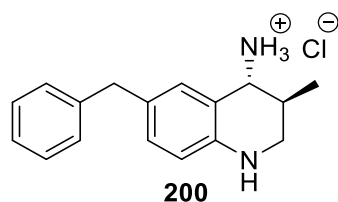
(3*S*,4*R*)-6-benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-4-aminium chloride (200) Synthesis

of **200** was achieved by treating **198** with HCl in dioxane to cleave the Ellman auxillary and to remove the Boc-protecting group. ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.58 – 7.53 (m, 1H), 7.48 – 7.42 (m, 2H), 7.26 (ddt, J = 33.3, 14.3, 9.3 Hz, 10H), 4.71 (d, J = 4.7 Hz, 1H), 4.06 (s, 2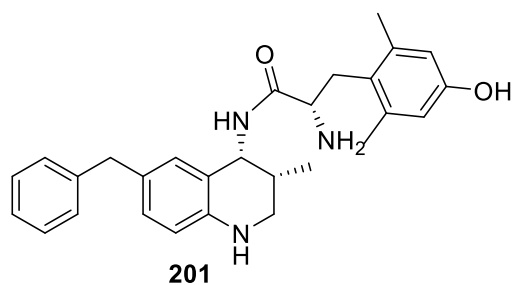H), 3.60 (s, 4H), 3.52 (dd, J = 13.0, 9.8 Hz, 1H), 2.77 – 2.65 (m, 2H), 1.25 (d, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 144.34, 141.45, 132.70, 131.77, 130.75, 130.47, 129.98, 129.72, 127.54, 126.73, 124.08, 122.45, 64.30, 50.48, 49.00, 44.26, 42.12, 29.73, 13.21.

201

(*S*)-2-amino-*N*-((3*R*,4*R*)-6-benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (201). 201 was synthesized following general procedure F starting from the (*R*) amine intermediate **199** (25 mg, 0.076 mmol) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound as a TFA salt (20 mg, 41.6%). ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.24 – 7.19 (m, 2H), 7.17 – 7.13 (m, 2H), 7.10 (td, J = 7.2, 1.5 Hz, 1H), 6.84 (dt, J = 8.3, 1.7 Hz, 1H), 6.62 (dd, J = 8.3, 1.4 Hz, 1H), 6.52 (s, 2H), 6.50 (d, J = 1.8 Hz, 1H), 4.99 (d, J = 4.5 Hz, 1H), 3.96 (ddd, J = 10.9, 5.0, 1.5 Hz, 1H), 3.82 (q, J = 15.1 Hz, 2H), 3.28 – 3.19 (m, 2H), 3.03 – 2.91 (m, 2H), 2.27 (d, J = 1.4 Hz, 8H), 0.97 (dd, J = 7.0, 1.4 Hz, 3H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 169.65, 157.42, 143.14, 140.17, 130.44, 130.36, 129.94, 129.29, 126.87, 123.08, 118.02, 116.67, 53.81, 51.12, 49.51, 49.34, 49.17, 49.00, 48.83, 48.66, 48.49, 45.48, 41.85, 32.18, 31.95, 20.48, 13.67. HPLC (gradient A): retention time 27.6. ESI-MS 466.2 [M+Na]$^+$.

202
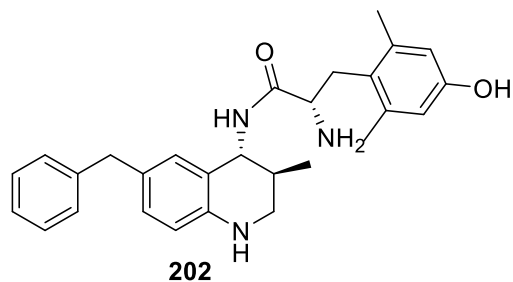
(*S*)-2-amino-*N*-((3*S*,4*R*)-6-benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (202). **202** was synthesized following general procedure F starting from the (*R*) amine intermediate **198** (22 mg, 0.076 mmol) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound as a TFA salt (12 mg, 27.3%). No ^{1}H or ^{13}C data acquired. HPLC (gradient A): retention time 29.3. ESI-MS 466.2 [M+Na]$^+$.

**203**
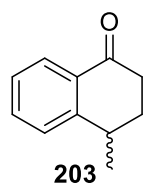
4-Methyl-3,4-dihydronaphthalen-1(2*H*)-one (203). Two round bottom flasks were flame-dried under vaccum, then flooded with Ar. Valerolactone (1.0 g, 10 mmol, 1.0 eq) was added to one round bottom flask via syringe followed by benzene (excess). AlCl$_3$ (4.0 g, 30 mmol, 3 eq) was added to the other flask and then that flask was flooded with Ar, then 40 mL anhydrous benzene was added. The reaction vessel stirred at RT for 5 min and was then placed in an oil bath at 95C. Contents of flask containing the valerolactone were transferred to the flask containing AlCl$_3$ via cannula. Reaction vessel was equipped with a condenser and stirred for 4.5 h. Once complete, reaction cooled to room temp then quenched with 2 M HCl and dI H$_2$O. Organic layer was washed with dI H$_2$O (1 x 25 mL), then brine (1 x 25 mL), then dried over MgSO4 and concentrated to yield a crude orange oil that was purified to yield the title compound as a clear, yellow oil (1.60 g, quant.) ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.03 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.31 (dt, *J* = 15.3, 7.6 Hz, 3H), 7.22 – 7.12 (m, 1H), 3.10 (td, *J* = 7.3, 4.7 Hz, 1H), 2.80 (ddd, *J* = 17.6, 8.9, 4.6 Hz, 1H), 2.61 (ddd, *J* = 17.4, 8.6, 4.7 Hz, 1H), 2.25 (ddt, *J* = 13.5, 9.0, 3.9 Hz, 2H), 1.91 (dtd, *J* = 12.8, 7.9, 3.3 Hz, 2H), 1.40 (d, *J* = 6.9 Hz, 4H), 1.28 (d, *J* = 7.1 Hz, 1H). No ^{13}C data acquired.

204
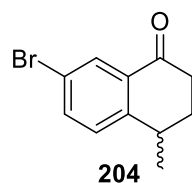
7-Bromo-4-methyl-3,4-dihydronaphthalen-1(2*H*)-one (204). To a reaction vessel already containing **203** (1.60 g, 10 mmol, 1.0eq) was added conc. H_2SO_4 and reaction vessel was heated in an oil bath at 60˚C. Next, NBS (2.13 g, 11.2 mmol, 1.2 eq) was added in four portions. The reaction stirred for 90 min and was monitored by TLC. Once complete, reaction taken off heat and quenched with dIH_2O, layers separated. The organic layer was washed with brine (1 x 50 mL) and dIH_2O (1 x 50 mL), then dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to yield the crude product which was this purified via silica gel chromatography to yield the pure title compound **204** (168 mg, 27.9%) as an orange oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2.2 Hz, 1H), 8.03 (dt, *J* = 7.9, 1.6 Hz, 0H), 7.61 (dt, *J* = 8.3, 2.0 Hz, 1H), 7.52 (tt, *J* = 7.6, 1.7 Hz, 0H), 7.36 – 7.30 (m, 1H), 7.22 (dd, *J* = 8.3, 1.8 Hz, 1H), 3.11 (dd, *J* = 13.1, 6.7 Hz, 1H), 3.08 – 3.01 (m, 1H), 2.79 (dddd, *J* = 17.5, 8.6, 4.6, 2.0 Hz, 2H), 2.60 (dddd, *J* = 17.1, 9.3, 4.7, 2.2 Hz, 2H), 2.25 (dtt, *J* = 13.6, 6.5, 3.5 Hz, 2H), 1.90 (dddt, *J* = 17.8, 8.9, 7.0, 3.2 Hz, 2H), 1.62 (d, *J* = 7.0 Hz, 1H), 1.43 – 1.40 (m, 2H), 1.38 (d, *J* = 1.9 Hz, 2H). No ^{13}C data acquired.

205
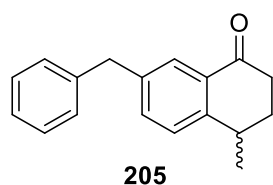
7-benzyl-4-methyl-3,4-dihydronaphthalen-1(2*H*)-one (205). 205 was synthesized following general procedure L using **204** (58 mg, 0.24 mmol, 1.0 eq), (2,2-dimethyl-4-methoxyphenyl)boronic acid (0.106 mg, 0.49 mmol, 2.0 eq), K_2CO_3 (101 mg, 0.73 mmol, 3.0 eq), and $Pd(dppf)Cl_2$ (18 mg, 0.024 mmol, 0.1 eq). The contents were placed microwave tube and reacted in microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography to yield title compound (57

mg, 93.4%) as clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$)
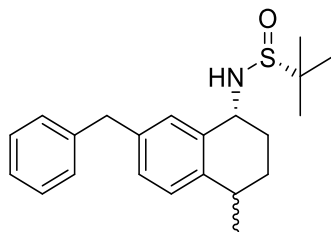
206

(R)-N-((1R)-7-benzyl-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methylpropane-2-sulfinamide (206). 206 was synthesized according to general procedure H using **205** (170 mg, 0.68 mmol, 1.0 eq), (R)-2-methylpropane-2-sulfinamide (248 mg, 2.05 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.858 mL, 4.1 mmol, 6.0 eq) to form the (R)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (154 mg, 4.1 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **206** as a clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$)
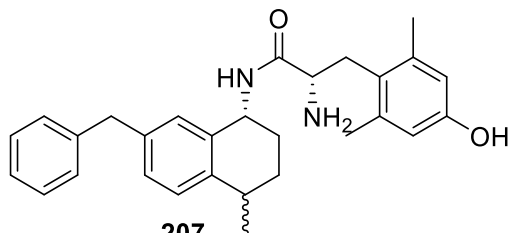
207

(2S)-2-amino-N-((1R)-7-benzyl-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (207). 207 was synthesized following general procedure I using **206** (55 mg, 0.16 mmol, 1.0 eq) and conc. HCl (4 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (22 mg) as a mixture of diastereomers. The synthesis was completed by following general procedure F with newly formed (R) amine intermediate (22 mg, 0.076 mmol, 1.0 eq) to yield crude product as a mixture of diastereomers which were separated and purified by semipreparative HPLC then

lyophilized to yield the title compound **207** (and **208**, see below) as a TFA salt. ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.99 (dd, J = 32.1, 8.3 Hz, 1H), 7.21 (t, J = 7.6 Hz, 2H), 7.12 (q, J = 6.9 Hz, 4H), 7.05 (d, J = 8.2 Hz, 1H), 6.96 (t, J = 6.3 Hz, 1H), 6.49 (d, J = 3.9 Hz, 2H), 4.90 (d, J = 16.9 Hz, 4H), 3.89 (dd, J = 15.9, 11.4 Hz, 2H), 3.26 (t, J = 12.6 Hz, 1H), 3.03 (dt, J = 13.4, 3.9 Hz, 1H), 2.71 (dh, J = 27.7, 7.6, 6.8 Hz, 1H), 2.27 (s, 7H), 1.78 (tt, J = 11.2, 5.6 Hz, 0H), 1.70 – 1.54 (m, 1H), 1.49 (qd, J = 11.6, 10.0, 4.8 Hz, 1H), 1.31 (dt, J = 10.3, 6.3 Hz, 1H), 1.17 (t, J = 7.4 Hz, 3H), 1.10 – 0.99 (m, 1H). ^{13}C NMR (126 MHz, CD$_3$OD) δ 168.90, 168.81, 168.78, 168.69, 157.32, 157.27, 142.70, 142.68, 141.49, 141.47, 140.21, 140.18, 139.93, 139.91, 136.26, 136.22, 136.04, 130.38, 130.34, 129.73, 129.67, 129.43, 129.39, 129.33, 129.05, 126.95, 123.25, 116.47, 116.45, 53.54, 53.49, 49.51, 49.42, 49.34, 49.17, 49.05, 49.00, 48.95, 48.83, 48.66, 48.49, 42.29, 42.27, 33.21, 32.83, 31.97, 28.86, 28.23, 28.03, 27.10, 23.10, 22.44, 20.48. HPLC (gradient A): retention time 43.0. ESI-MS 443.2 [M+H]$^{+}$ and 465.2 [M+Na]$^{+}$.
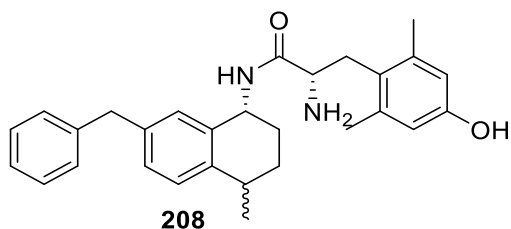
208

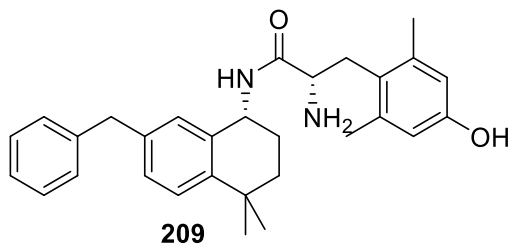**(2S)-2-amino-N-((1R)-7-benzyl-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (208)**. See synthesis of **207**. No ^{1}H or ^{13}C data acquired. HPLC (gradient A): retention time 44.5. ESI-MS 443.2 [M+H]$^{+}$ and 465.2 [M+Na]$^{+}$.

209

209 was synthesized by Tony Nastase.

210 Boc
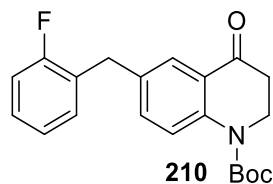
***Tert*-butyl 6-(2-fluorobenzyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (210). 210** was synthesized following general procedure L using **104** (100 mg, 0.29 mmol, 1.0 eq), *o*-fluoroboronic acid (82 mg, 0.59 mmol, 2.0 eq), K_2CO_3 (120 mg, 0.89 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (22 mg, 0.030 mmol, 0.1 eq). The crude product which was purified using silica gel chromatography to yield the title compound **210** as a slightly yellow oil (95 mg, 91.3%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84 (d, *J* = 2.2 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.34 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.21 – 7.11 (m, 2H), 7.07 – 6.98 (m, 2H), 4.12 (t, *J* = 6.3 Hz, 2H), 3.96 (s, 2H), 2.73 (t, *J* = 6.5 Hz, 2H), 1.54 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.03, 161.73, 159.78, 152.63, 142.38, 135.50, 134.41, 130.84, 130.81, 128.13, 128.06, 127.32, 127.20, 126.95, 124.71, 124.09, 124.06, 123.78, 115.38, 115.21, 81.98, 44.14, 38.85, 34.01, 33.98, 28.17.

211 Boc
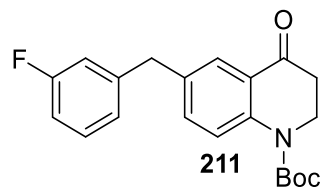
***Tert*-butyl 6-(3-fluorobenzyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (211). 211** was synthesized following general procedure L using **104** (100 mg, 0.29 mmol, 1.0 eq), *m*-fluoroboronic acid (82 mg, 0.59 mmol, 2.0 eq), K_2CO_3 (120 mg, 0.89 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (22 mg, 0.030 mmol, 0.1 eq). The crude product which was purified using silica gel chromatography to yield the title compound **211** as a slightly yellow oil (87 mg, 83.7%) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 (bs, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.30 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.27 – 7.19 (m, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.90 – 6.83 (m, 2H), 4.13 (t, *J* = 6.2, 2H), 3.94 (s, 2H), 2.75 (t, *J* = 6.2 Hz, 2H), 1.55 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.11, 163.84, 161.89, 152.65, 142.89, 142.84, 142.53, 135.91, 134.51, 129.94, 129.87, 127.13, 124.76, 124.40, 124.38, 123.88, 115.69, 115.52, 113.22, 113.06, 82.09, 44.20, 40.72, 38.88, 28.21.

212
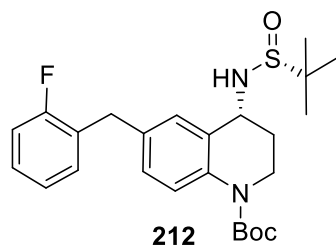
***Tert*-butyl (*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-(2-fluorobenzyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (212). 212** was synthesized according to general procedure H using **210** (95 mg, 0.27 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (97 mg, 0.80 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.336 mL, 1.6 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (61 mg, 1.6 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **212** (81 mg, 65.9%) as an oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.62 (d, *J* = 8.6 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 7.09 (td, *J* = 7.6, 2.3 Hz, 2H), 7.02 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.99 – 6.91 (m, 2H), 4.59 (d, *J* = 9.8 Hz, 0H), 4.45 (d, *J* = 3.2 Hz, 1H), 3.89 – 3.82 (m, 3H), 3.50 (tdd, *J* = 11.1, 3.9, 1.4 Hz, 1H), 3.28 – 3.24 (m, 1H), 2.16 – 2.09 (m, 1H), 1.97 (d, *J* = 2.0 Hz, 0H), 1.94 (d, *J* = 2.9 Hz, 0H), 1.92 – 1.84 (m, 1H), 1.43 (d, *J* = 1.7 Hz, 10H), 1.36 (d, *J* = 2.5 Hz, 2H), 1.13 (d, *J* = 1.7 Hz, 10H). 128.62, 128.47, 127.97, 127.91, 127.84, 127.72, 124.06, 124.03, 115.37, 115.20, 81.09, 55.63, 50.32, 40.03, 34.08, 34.06, 29.35, 28.28, 24.14, 22.54.

213
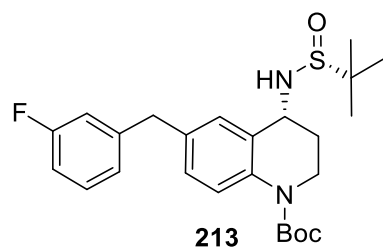
***Ter*t-butyl (*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-(3-fluorobenzyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (213). 213** was synthesized according to general procedure H using **211** (87 mg, 0.25 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (89 mg, 0.73 mmol, 3.0 eq), and Ti(OEt)$_4$ (0.308 mL, 1.5 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction

mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (56 mg, 1.5 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **213** (80 mg, 700.8%) as an oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.64 (dd, J = 8.5, 1.9 Hz, 1H), 7.22 – 7.10 (m, 2H), 6.98 (dd, J = 8.6, 2.1 Hz, 1H), 6.93 – 6.87 (m, 1H), 6.80 (ddd, J = 10.9, 8.4, 1.9 Hz, 2H), 4.62 (s, 1H), 4.46 (dd, J = 4.5, 2.5 Hz, 1H), 3.88 (ddt, J = 12.5, 6.3, 3.0 Hz, 1H), 3.83 (d, J = 1.9 Hz, 2H), 3.51 (dddd, J = 12.9, 11.1, 3.9, 1.8 Hz, 1H), 3.26 (d, J = 2.6 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.90 (ddd, J = 14.3, 9.6, 5.0 Hz, 1H), 1.44 (d, J = 2.0 Hz, 12H), 1.36 (d, J = 2.4 Hz, 3H), 1.13 (d, J = 2.0 Hz, 11H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 163.84, 161.89, 153.49, 143.45, 143.39, 136.73, 135.69, 129.84, 129.77, 129.05, 128.67, 128.55, 124.44, 124.42, 124.04, 115.70, 115.53, 113.04, 112.87, 81.14, 77.00, 55.65, 50.46, 40.80, 40.79, 40.08, 29.48, 28.28, 24.14, 22.53.

214
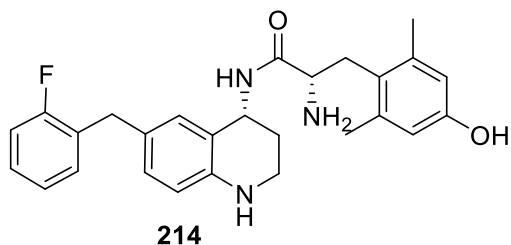
(S)-2-amino-N-((R)-6-(2-fluorobenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (214). **214** was synthesized following general procedure I using **212** (81 mg, 0.18 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (69 mg). The synthesis was completed by following general procedure F with newly formed (R) amine intermediate (69 mg, 0.17 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **214** (51 mg, 51.5%) as a TFA salt. ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.23 – 7.13 (m, 3H), 7.08 – 6.98 (m, 3H), 6.89 (d, J = 8.3 Hz, 1H), 6.49 (s, 2H), 5.01 (t, J = 4.7 Hz, 2H), 3.95 – 3.85 (m, 3H), 3.26 (dd, J = 13.6, 11.6 Hz, 1H), 3.17 (ddd, J = 12.5, 5.7, 3.4 Hz, 1H), 3.05 (dd, J = 13.7, 5.2 Hz, 1H), 2.68 (ddd, J = 13.0, 11.1, 2.5 Hz, 1H), 2.27 (s, 6H), 1.88 (tt, J = 11.0, 4.1 Hz, 1H), 1.59 (dtd, J = 13.5, 5.3, 2.6 Hz, 1H). 13C NMR (126 MHz, CD3OD) δ 168.88, 163.16, 161.22, 157.36, 140.07, 138.01, 135.83,

132.13, 132.10, 131.85, 130.69, 129.39, 129.32, 129.04, 128.91, 127.16, 125.35, 125.32, 123.33, 121.11, 116.42, 116.24, 116.06, 111.39, 53.35, 45.30, 39.26, 34.87, 34.85, 31.83, 28.02, 20.44. HPLC (gradient A): retention time 25.7. ESI-MS 448.2 [M+H]$^+$ and 470.2 [M+Na]$^+$.
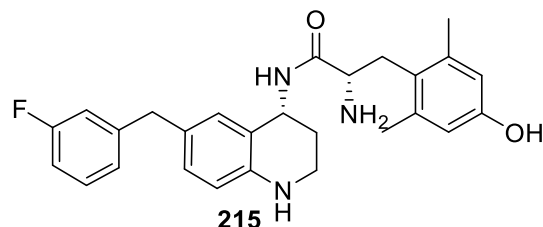

(*S*)-2-amino-*N*-((*R*)-6-(3-fluorobenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (215). 215 was synthesized following general procedure I using **213** (80 mg, 0.17 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et$_2$O, and solid crashed out. After washing the solid 3 x with fresh Et$_2$O, the remaining Et$_2$O was decanted off, yielding a white solid amine hydrochloride salt (68 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (68 mg, 0.173 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **215** (21 mg, 21.6%) as a TFA salt. ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.23 (td, *J* = 7.9, 6.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.87 (td, *J* = 8.6, 2.6 Hz, 1H), 6.83 (dt, *J* = 10.1, 2.0 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.49 (s, 2H), 4.98 (t, *J* = 4.9 Hz, 1H), 3.88 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.84 (s, 2H), 3.26 (dd, *J* = 13.6, 11.6 Hz, 1H), 3.13 – 3.06 (m, 1H), 3.03 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.63 (td, *J* = 12.2, 11.7, 2.6 Hz, 1H), 2.27 (s, 6H), 1.81 (ddt, *J* = 14.6, 11.0, 4.0 Hz, 1H), 1.55 (dtd, *J* = 13.4, 5.1, 2.8 Hz, 1H). HPLC (gradient A): retention time 26.5. ESI-MS 470.2 [M+Na]$^+$.
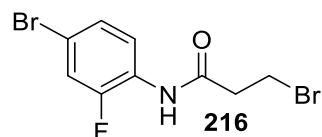
3-Bromo-*N*-(4-bromo-2-fluorophenyl)propanamide (216). was synthesized according to general procedure C starting from the commercially available starting material 4-bromo-2-fluoroaniline (1.0 g, 5.26 mmol, 1.0 eq), K$_2$CO$_3$ (1.49 g, 10.8 mmol, 2.05 eq) and bromopropionyl chloride (0.860 mL, 5.37 mmol, 1.02 eq) to yield the title compound as an a white, fluffy, shiny solid (1.71 g, quant.) with no additional purification necessary. ^{1}H NMR (400

MHz, CDCl$_3$) δ 8.18 (t, J = 8.5 Hz, 1H), 7.33 (s, 1H), 7.24 – 7.18 (m, 3H), 3.63 (t, J = 6.5 Hz, 2H), 2.93 (t, J = 6.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 167.85, 152.96, 127.83, 127.80, 125.13, 122.80, 118.55, 118.37, 116.22, 77.25, 77.00, 40.63, 26.36.
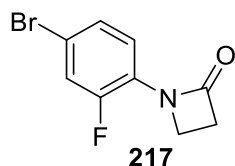
1-(4-Bromo-2-fluorophenyl)azetidin-2-one (217). 217 was synthesized according to general procedure D starting from **216** (1.71 g, 5.26 mmol, 1.0 eq) and NaO*t*Bu (530 mg, 5.52 mmol, 1.05 eq) to yield the crude product which was purified using silica gel chromatography to yield title compound as solid (1.0 g, 78.1%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (t, J = 8.6 Hz, 1H), 7.25 – 7.15 (m, 2H), 3.87 (q, J = 4.4 Hz, 2H), 3.15 (t, J = 4.6 Hz, 2H). 13C NMR (126 MHz, CDCl$_3$) δ 165.40, 152.52, 150.53, 127.71, 127.68, 125.66, 125.58, 122.06, 122.03, 119.69, 119.51, 115.66, 115.59, 42.07, 42.01, 38.39, 38.38.
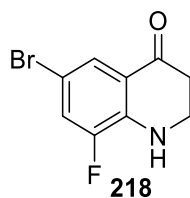
6-Bromo-8-fluoro-2,3-dihydroquinolin-4(1*H*)-one (218). 218 was synthesized according to general procedure E starting from **217** (1.0 g, 4.1 mmol, 1.0 eq) and using TfOH (1.09 mL, 12.3 mmol, 3.0 eq) to yield the crude product which was purified using silica gel chromatography to yield the title compound as a yellow solid (508 mg, 50.8%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.93 (d, J = 4.9 Hz, 1H), 7.84 (d, J = 1.8 Hz, 1H), 7.72 (ddd, J = 6.5, 4.6, 2.7 Hz, 1H), 7.54 (ddd, J = 9.6, 3.6, 2.0 Hz, 1H), 7.42 (dt, J = 4.7, 1.9 Hz, 1H), 7.21 (ddt, J = 10.2, 4.8, 2.8 Hz, 1H), 7.15 – 7.11 (m, 1H), 6.65 (t, J = 8.7 Hz, 1H), 3.67 (t, J = 6.3 Hz, 2H), 3.61 (t, J = 7.0 Hz, 2H), 3.08 (dq, J = 6.3, 3.1 Hz, 2H), 2.70 (q, J = 5.5, 3.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 191.24, 168.91, 151.21, 127.54, 125.29, 124.39, 122.55, 122.37, 119.92, 119.57, 118.58, 118.40, 118.16, 114.53, 113.11, 41.67, 38.98, 37.55, 34.28.
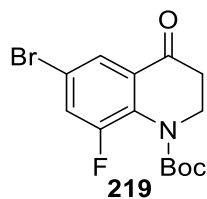
Tert-butyl 6-bromo-8-fluoro-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (219). 219 was synthesized according to general procedure G starting from **218** (510 mg, 2.1 mmol, 1.0 eq), Boc$_2$O (680 mg, 3.1 mmol, 1.5 eq), DMAP (25 mg, 0.2 mmol, 0.1 eq) and DIPEA (0.54 mL, 3.1 mmol, 1.5 eq). Following the quench and work-up, the crude product was chromatographed on silica gel (equil in 100% hex, run in 2:3 EA:hex) to yield pure product as a white solid (370 mg, 51.5%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 – 7.83 (m, 1H), 7.43 (dd, J = 9.7, 2.3 Hz, 1H), 4.12 (bs, 2H), 2.80 (t, J = 6.2 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 192.15, 156.34, 156.32, 154.29, 152.20, 132.06, 131.97, 128.46, 125.57, 125.54, 124.58, 124.38, 118.10, 118.03, 82.69, 44.68, 39.17, 27.88.
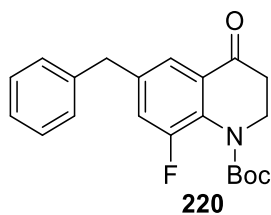
Tert-butyl 6-benzyl-8-fluoro-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (220). 220 was synthesized following general procedure L using **219** (369 mg, 1.1 mmol, 1.0 eq), benzyl boronic pinnacol ester (350 mL, 1.6 mmol, 2.0 eq), K$_2$CO$_3$ (445 mg, 3.2 mmol, 3.0 eq), and Pd(dppf)Cl$_2$ (78 mg, 0.10 mmol, 0.1 eq). The crude product which was purified using silica gel chromatography to yield the title compound **220** as a brown oil (273 mg, 71.7%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.64 (d, J = 1.9 Hz, 1H), 7.31 (t, J = 7.4 Hz, 2H), 7.28 – 7.21 (m, 1H), 7.18 (d, J = 7.7 Hz, 2H), 7.10 (dd, J = 11.2, 1.9 Hz, 1H), 4.11 (s, 3H), 3.97 (s, 2H), 2.78 (t, J = 6.2 Hz, 2H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.62, 193.60, 156.25, 154.24, 152.58, 139.64, 139.59, 139.47, 128.86, 128.81, 128.76, 128.74, 128.71, 128.68, 128.47, 128.38, 127.63, 126.55, 122.40, 122.37, 121.89, 121.72, 82.12, 77.00, 44.78, 41.15, 39.35, 27.90.

221
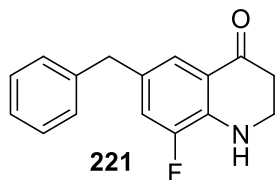
6-Benzyl-8-fluoro-2,3-dihydroquinolin-4(1*H*)-one (221). **221** was synthesized was synthesized by first treating **221** (130 mg, 0.37 mmol, 1.0 eq) with 1:1 TFA:DCM for 1 h. Once complete, solvent was removed under reduced pressure to yield a crude yellow residue which was taken ahead to the next step (formation of **222**) without any additional isolation, purification, or characterization. No ^{1}H or ^{13}C data acquired.

222
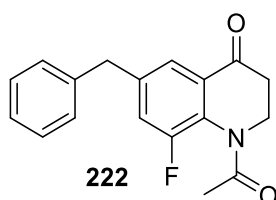
1-Acetyl-6-benzyl-8-fluoro-2,3-dihydroquinolin-4(1*H*)-one (222). **222** The crude residue from **221** was treated with Ac$_2$O following general procedure K. The reaction stirred at reflux for 20 h. Once the reaction was complete, solvent was removed and the crude residue was purified using silica gel chromatography to yield title compound **222** as a clear oil (78 mg, 71.5% over two steps). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.60 (d, *J* = 2.1 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.17 (dd, *J* = 8.1, 6.5 Hz, 2H), 7.14 – 7.07 (m, 2H), 3.92 (s, 2H), 2.83 – 2.63 (m, 4H), 2.11 (s, 3H). No ^{13}C data acquired.

223
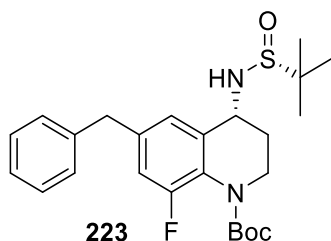
***Tert*-butyl (*R*)-6-benzyl-4-(((*R*)-*tert*-butylsulfinyl)amino)-8-fluoro-3,4-dihydroquinoline-1(2*H*)-carboxylate (223).** **223** was synthesized following general procedure H using **221** (140 mg, 0.39 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (143 mg, 1.18 mmol, 3.0 eq), and Ti(OEt)4 (0.496 mL, 2.36 mmol, 6.0 eq) to form the (*R*)-tert-butanesulfinyl imine intermediate in situ. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction

mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (89 mg, 2.36 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as clear, colorless oil (65 mg, 35.9%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.28 (td, J = 7.7, 2.6 Hz, 2H), 7.23 – 7.15 (m, 3H), 7.01 (d, J = 3.0 Hz, 1H), 6.83 (dt, J = 11.4, 2.5 Hz, 1H), 4.52 (p, J = 3.7 Hz, 1H), 3.91 (s, 2H), 3.85 – 3.72 (bs, 1H), 3.63 (bs, 1H), 3.28 (s, 1H), 2.21 (bs, 1H), 1.95 (bs, 1H), 1.44 (d, J = 2.8 Hz, 9H), 1.19 (d, J = 2.7 Hz, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.63, 154.63, 153.42, 139.94, 139.46, 139.40, 133.20, 128.83, 128.55, 126.33, 125.14, 125.04, 123.36, 123.33, 116.12, 115.95, 81.12, 60.28, 55.66, 50.55, 41.20, 40.37, 30.47, 27.94, 22.51, 22.43, 14.12.
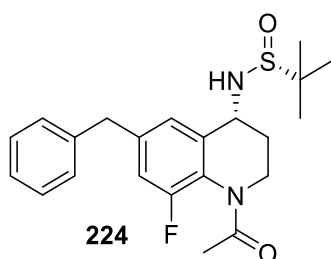
(R)-N-((R)-1-acetyl-6-benzyl-8-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide (224). 224 was synthesized following general procedure H using **222** (78 mg, 0.26mmol, 1.0 eq), (R)-2-methylpropane-2-sulfinamide (95 mg, 0.79 mmol, 3.0 eq), and Ti(OEt)4 (0.330 mL, 1.57 mmol, 6.0 eq) to form the (R)-tert-butanesulfinyl imine intermediate in situ. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing NaBH$_4$ (60 mg, 1.57 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **224** as clear, colorless oil (56 mg, 52.8%). No ^{1}H or ^{13}C data acquired. Instead, intermediate was taken ahead to the next step (formation of **226**) without further purification, isolation, or characterization.

225
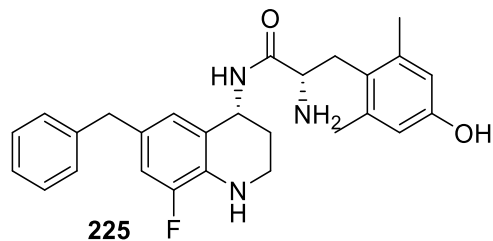
(*S*)-2-amino-N-((*R*)-6-benzyl-8-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (225). **225** was synthesized following general I using **223** (65 mg, 0.14 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et₂O, and solid crashed out. After washing the solid 3 x with fresh Et₂O, the remaining Et₂O was decanted off, yielding a white solid amine hydrochloride salt (55 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (55 mg, 0.140 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **225** (24 mg, 30.4%) as a TFA salt. ^{1}H NMR (500 MHz, CD₃OD) δ 7.25 – 7.19 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 6.70 (s, 1H), 6.63 (d, *J* = 12.1 Hz, 1H), 6.48 (s, 2H), 4.93 (s, 1H), 3.84 (dd, *J* = 11.6, 4.7 Hz, 1H), 3.75 (s, 2H), 3.25 (t, *J* = 12.6 Hz, 1H), 3.01 (q, *J* = 11.7, 9.8 Hz, 2H), 2.46 (t, *J* = 11.7 Hz, 1H), 2.31 – 2.23 (m, 7H), 1.68 (t, *J* = 12.6 Hz, 1H), 1.50 (d, *J* = 13.4 Hz, 1H). HPLC (gradient A): retention time 35.3. ESI-MS 470.2 [M+Na]$^+$.
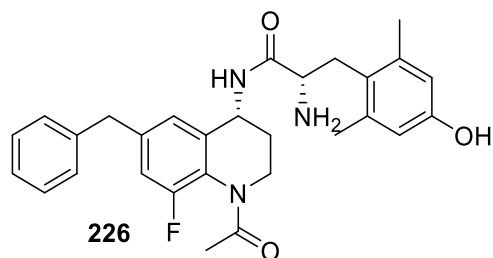
226

(*S*)-N-((*R*)-1-acetyl-6-benzyl-8-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (226). **226** was synthesized following general procedure I using **224** (56 mg, 0.14 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et₂O, and solid crashed out. After washing the solid 3 x with fresh Et₂O, the remaining Et₂O was decanted off, yielding a white solid amine hydrochloride salt (47 mg). The synthesis was completed by following general procedure F with newly formed (*R*) amine intermediate (47 mg, 0.140 mmol, 1.0 eq) to yield crude product which

was purified by semipreparative HPLC and lyophilized to yield the title compound **226** (30 mg, 35.3%) as a TFA salt. ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.26 (dd, J = 8.6, 6.6 Hz, 2H), 7.18 (dd, J = 8.2, 6.6 Hz, 3H), 7.04 (s, 1H), 6.89 (d, J = 11.4 Hz, 1H), 6.52 (s, 2H), 3.96 – 3.87 (m, 2H), 3.26 (dd, J = 13.7, 11.5 Hz, 1H), 3.12 – 3.02 (m, 1H), 2.28 (s, 6H), 2.07 (bs, 3H), 1.95 – 1.83 (m, 1H), 1.50 – 1.31 (m, 1H). HPLC (gradient A): retention time 33.8. ESI-MS 490.2 [M+H]$^+$ 512.2 and [M+Na]$^+$.
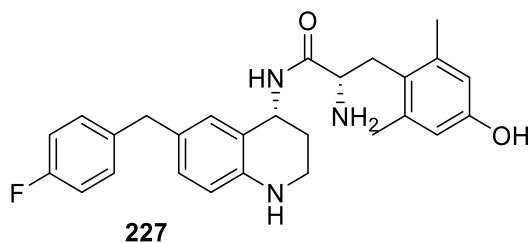
227   Synthesized by Dr. Kate Kojiro and Dr. Yafei Jin

8.2 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 three times with ice cold phosphate buffered saline (0.9% NaCl, 0.61 mM Na$_2$HPO$_4$, 0.38 mM KH$_2$PO$_4$, 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, Inc., Bartlesville, OK, U.S.) 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, U.S.) using bovine serum albumin as the standard.

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Radioligand Binding Assays. Radiolabeled compounds were purchased from Perkin-Elmer (Waltham, MA, U.S.). 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, U.S.) and washed five times 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 (Perkin-Elmer, Waltham, MA, U.S.). 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 Inc., La Jolla, CA).

Stimulation of [^{35}S]GTPγS Binding. Agonist stimulation of [^{35}S]guanosine 5′-O-[γ-thio]triphosphate ([^{35}5S]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 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 [$_D$-Ala^2,N-MePhe^4,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 times 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.

8.3 In Vivo Pharmacology.

Animals. Adult male C57BL/6 mice weighing between 20 and 30 g at 8−16 weeks old purchased from Harlan (Indianapolis, IN). 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 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] To determine 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 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 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 analogue (10 mg/kg, *ip*). To confirm that **54** produces antinociception via the opioid receptors, the cumulative dose response was repeated 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 **54**, and the ED_{50} for the mice receiving 1 mg/kg naltrexone is 15.07 +/-1.03 mg/kg **54**, suggesting that the antinociception **54** produces is MOR-mediated.

8.4 Computational Modeling

Three-dimensional models of opioid receptors in inactive conformation were produced as previously described[60] using X-ray structures of the mouse MOR (PDB ID: 4dkl)[61], the human

DOR (PDB ID: 4n6h)[62] and the human KOR (PDB ID: 4djh)[63] as structural templates. The recently obtained crystal structure of mouse MOR in the active conformation (PDB ID: 5c1m)[61] 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), KOR (residues 45-57) were modeled using the structure of MOR N-terminus in the active conformation with a few adjustment to satisfy formation of Zn-binding centers involving D216 (H54-D216) and H319 (H57-H319), which were previously suggested for MOR.[64] 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[65,66] were selected and minimized with CHARMm implemented in QUANTA (Adopted-Basis Newton Raphson method, 100 steps, $\varepsilon=10$). 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.

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