Synthesis and Evaluation of Mixed Efficacy Mu Opioid Receptor (MOR), Delta Opioid Receptor (DOR) Peptidomimetic Ligands

by

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TABLE OF CONTENTS

Acknowledgements ..... **ii**

List of Figures ..... **vi**

List of Schemes ..... **viii**

List of Tables ..... **x**

List of Abbreviations ..... **xi**

Chapter 1 ..... **1**
- **Mixed Efficacy Opioid Ligands** **1**
  - 1.1 Introduction 1
  - 1.2 The Role of DOR in the Development of Dependence and Tolerance 2
  - 1.3 The Development of MOR Agonist/DOR Antagonist Peptides 4
  - 1.4 The Development of MOR Agonist/DOR Antagonist Small Molecules 12
  - 1.5 MOR Agonist/DOR Antagonists for the Treatment of IBS-d 15

Chapter 2 ..... **18**
- **Synthesis of THQ Peptidomimetics Modified at the 6 Position** **18**
  - 2.1 Introduction 18
  - 2.2 Modifications to the 6-Position of the THQ Scaffold 20
  - 2.3 Acetylation of the THQ Nitrogen and In Vivo Data for Selected Analogues 32
  - 2.4 Experimental Procedures (Analogues **1** – **106**) 37

Chapter 3 ..... **87**
- **Further Modifications to the THQ Peptidomimetics** **87**
  - 3.1 Introduction 87
  - 3.2 Modifications to the Di-Benzylic Position 88
  - 3.3 Modifications to the THQ Core 94
  - 3.4 Preliminary Amide Bond Substitutions 102
  - 3.5 In Vivo Data for Selected Analogues 104
  - 3.6 Experimental Procedures (Analogues **107** – **232**) 106

Chapter 4 ..... **154**
- **Synthesis of 2',6'-dimethyl-L-tyrosine Derivatives and Incorporation into Opioid Peptidomimetics** **154**
  - 4.1 Introduction 154
  - 4.2 Synthesis of 2',6'-dimethyl-L-tyrosine Analogues via Negishi Coupling 155
  - 4.3 In Vivo Studies on Analogue 251 161
  - 4.4 Experimental Procedures (Analogues **233** – **257**) 163

Chapter 5 ..... **176**
4-Substituted Piperidines and Piperazines as Mixed Efficacy MOR/DOR Ligands **176**
5.1 Introduction 176
5.2 Synthesis and Evaluation of 4-Substituted Piperidine and Piperazine Opioid Ligands 177
5.3 Experimental Procedures (Analogues **259** – **286**) 183
Chapter 6 ..... **195**
Conclusions and Future Directions **195**

References **200**

List of Figures

Figure 1. Chemical Structures of Morphine, Codeine, Fentanyl and Methadone 1

Figure 2. Chemical Structure of Naltrindole.....3

Figure 3. Chemical Structures of the Endomorphins.....5

Figure 4. Chemical Structures of TIPP[Ψ] and DIPP-NH_2[Ψ].....6

Figure 5. Chemical Structures of DPDPE and the Enkephalins 8

Figure 6. Chemical Structures of JOM-6, JOM-13 and KSK103.....9

Figure 7. Chemical Structure of MMP-2200 11

Figure 8. Chemical Structure of SoRI 9409.....13

Figure 9. Chemical Structures of MDAN-21, CYM51010 and UMB425.....14

Figure 10. Chemical Structures of 1c, 4a and Eluxadoline.....17

Figure 11. Chemical Structure of Lead THQ Peptidomimetic 1 (1E) 18

Figure 12. (A) Comparison of 1 Docked in the MOR Active/DOR Active Sites (B) Comparison of DOR Active/DOR Inactive Sites 19

Figure 13. Crystal Structure of 6-benzyl-1-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride.....28

Figure 14. Docking of Analogue 80 in the MOR Active Site.....31

Figure 15. Overlay of Analogue 82 in the MOR, DOR and KOR Active Sites 34

Figure 16. Cumulative Antinociceptive Dose-Response Curves for Analogues 69, 75, 81, 82, 86, 102, 103 and 105 in the Mouse WWTW Assay After ip Administration (n = 3-6) ..36

Figure 17. Time Courses of Antinociceptive Response For Analogues **86** and **102** in the Mouse WWTW Assay After ip Administration of a 10 mg/kg Dose.....37

Figure 18. Metabolic Hotspots of Compound 1 in Mouse Liver Microsomes 87

Figure 19. Cumulative Antinociceptive Dose-Response Curves for Analogues 116E, 143, 188, 202, 203, 214, and 217 in the Mouse WWTW Assay After ip Administration (n = 3-6) 105

Figure 20. Time Course of Antinociceptive Response For Analogue 214 in the Mouse WWTW Assay After ip Administration of a 10 mg/kg Dose.....106

Figure 21. Cumulative Antinociceptive Dose-Response Curve for Analogue 251 in the Mouse WWTW Assay After ip Administration (n = 3) 162

Figure 22. Time Course of Antinociceptive Response For Analogue **251** in the Mouse WWTW Assay After ip Administration of a 10 mg/kg Dose.....162

Figure 23. Chemical Structure of Compound 258 176

List of Schemes

Scheme 1. Synthesis of Analogues 12 and 13 21

Scheme 2. Asymmetric Synthesis of Compound 1 23

Scheme 3. Synthesis of Analogues 68-89 26

Scheme 4. Synthesis of Intermediates 28, 29, and 35 27

Scheme 5. Synthesis of Intermediate 100 27

Scheme 6. Synthesis of Intermediate 101 27

Scheme 7. Synthesis of Analogues 102-106 33

Scheme 8. Synthesis of Analogues 115 and 116 89

Scheme 9. Synthesis of Analogues 138-143 90

Scheme 10. Synthesis of Intermediates 144 and 146 91

Scheme 11. Synthesis of Analogues 157 and 158 91

Scheme 12. Synthesis of Analogues 169-174 92

Scheme 13. Synthesis of Analogues 183 and 184 95

Scheme 14. Synthesis of Analogue 188 96

Scheme 15. Synthesis of Analogues 199-203 97

Scheme 16. Synthesis of Analogue 210 99

Scheme 17. Synthesis of Analogue 214 99

Scheme 18. Synthesis of Analogue 217 100

Scheme 19. Synthesis of Analogues 223 and 224 100

Scheme 20. Synthesis of Analogue 228 101

Scheme 21. Synthesis of Analogues 231 and 232 103

Scheme 22. Synthesis of Boc-2',6'-dimethyl-L-tyrosine 156

Scheme 23. Synthesis of Analogues 246-251 158

Scheme 24. Synthesis of Intermediate 252 158

Scheme 25. Synthesis of Intermediate 253 159

Scheme 26. Synthesis of Analogue 254 159

Scheme 27. Synthesis of Analogue 257 160

Scheme 28. Synthesis of Analogue 261 177

Scheme 29. Synthesis of Analogues 262-265 178

Scheme 30. Synthesis of Analogues 268 and 269 179

Scheme 31. Synthesis of Analogues 276 and 277 179

Scheme 32. Synthesis of Analogue 281 180

Scheme 33. Synthesis of Analogue 285 180

Scheme 34. Synthesis of Analogue 286 181

List of Tables

Table 1. Opioid Receptor Binding Affinities and Efficacies for Analogues 1E, 1L, 12E, 13E, 13L.....22

Table 2. Opioid Receptor Binding Affinities and Efficacies for Analogues 68-89.....28

Table 3. Opioid Receptor Binding Affinities and Efficacies for Analogues 102-106.....33

Table 4. Opioid Receptor Binding Affinities and Efficacies for Analogues Modified at the di-benzylic Position.....92

Table 5. Opioid Receptor Binding Affinities and Efficacies for Analogues Substituted at the THQ Nitrogen.....97

Table 6. Opioid Receptor Binding Affinities and Efficacies for Analogues Featuring Replacements to the THQ Nitrogen.....101

Table 7. Opioid Receptor Binding Affinities and Efficacies for Both Diastereomers of Analogues 231 and 232.....104

Table 8. Opioid Receptor Binding Affinities and Efficacies for Analogues 246-251, 254 and 257.....161

Table 9. Opioid Receptor Binding Affinities and Efficacies for Analogues 261-265, 268, 269, 276, 277, 281, 285, 286.....182

List of Abbreviations

$(Ac)_2O$, Acetic Anhydride; $(Boc)_2O$, *tert*-Butyloxycarbonyl Anhydride; AcOH, Acetic Acid; Boc-Dmt, Boc-protected 2'6'-dimethyl-L-tyrosine; CBS, Corey-Bakshi-Shibata; CNS, Central Nervous System; DAMGO, [D-Ala^2, N-MePhe^4, Gly-ol]-enkephalin; DCE, Dichloroethane; DCM, Dichloromethane; DIAD, Diisopropyl Azodicarboxylate; DIBAL-H, Diisobutylaluminium Hydride; DIPEA, Diisopropylethylamine; DMAP, Dimethylaminopyridine; DMF, N,N-Dimethylformamide; DPDPE, [D-Pen^2,D-Pen^5]enkephalin; EC_{50}, Half Maximal Effective Concentration; Et_3N, Triethylamine; EtOAc, Ethyl Acetate; EtOH, Ethanol; GTPγS, guanosine 5'-O-[gamma-thio]triphosphate; HATU, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate; HBTU, 3-[Bis(dimethylamino)methyliumyl]-3H-benzotriazol-1-oxide hexafluorophosphate; Hex, Hexanes; HOBt-Cl, 6-Chloro-1-hydroxibenzotriazol; K_i, Dissociation Constant; LAH, Lithium Aluminum Hydride; MeCN, Acetonitrile; MeOH, Methanol; MIDA, N-methyliminodiacetyl; MsCl, Mesyl Chloride; *n*-BuLi, *n*-Butyllithium; NaOtBu, Sodium *tert*-Butoxide; NBS, *N*-bromosuccinimide; PCC, Pyridinium Chlorochromate; $Pd(dppf)Cl_2$, [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II); Pd/C, Palladium on Carbon; $Pd_2(dba)_3$, Tris(dibenzylideneacetone)dipalladium(0); PyBOP, benzotriazol-1-yl-oxytripyrrolidinophosphonium Hexafluorophosphate; RP-HPLC, Reverse Phase High Performance Liquid Chromatography; SEM, Standard Error of the Mean; SPhos, 2-

Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; TfOH, Triflic Acid; THF, Tetrahydrofuran; $Ti(OEt)_4$, Titanium Ethoxide; $Ti(OiPr)_4$, Titanium Isopropoxide; U69593, *N*-methyl-2-phenyl-*N*-[(5*R*,7*S*,8*S*)-7-(pyrrolidin-1-yl)-1-oxaspiro[4.5]dec-8-yl]acetamide; WWTW, Warm Water Tail Withdrawal; TFA, Trifluoroacetic Acid

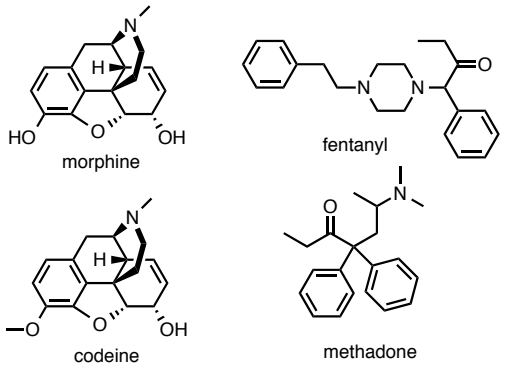
CHAPTER 1

MIXED EFFICACY OPIOID LIGANDS

1.1 Introduction

For thousands of years, alkaloids extracted from the opium-containing poppy plant have been used as analgesics.[1] Even today, these naturally occurring opioids such as morphine and codeine (Figure 1) are considered the standard of care for the treatment of moderate to severe pain. Synthetic opioids, such as fentanyl and methadone (Figure 1) have also found widespread use as potent analgesics, and other classes of natural opioids have also been extracted from a number of non-poppy sources.[2–4]

Figure 1. Chemical Structures of Morphine, Codeine, Fentanyl and Methadone



Although opioid analgesics are certainly effective in the clinic, the prolonged usage of opioids is complicated by the development of serious side effects. These side effects include constipation, respiratory depression, and the development of dependence

and tolerance.[5] There is thus a great unmet need to develop an efficacious opioid analgesic devoid of these negative side effects.

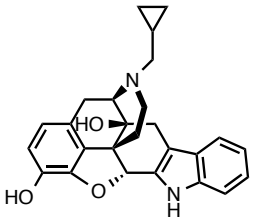
Opioids exert their pharmacological effects through binding to one or more of the G protein-coupled opioid receptors, the μ opioid receptor (MOR)[6], the δ opioid receptor (DOR)[7] and the κ opioid receptor (KOR).[8] In general, clinically used opioid analgesics such as morphine evoke both the desired and undesired effects through activation of MOR. Activation of both DOR and KOR has also been shown to produce a mild analgesic effect, although the effectiveness of DOR and KOR-stimulating ligands is hampered by the possibility of convulsions and dysphoria, respectively.[9] Numerous reports have indicated that the undesired MOR-related side effects may be ameliorated by concomitant ligand interaction with DOR.[10] It has been shown that the co-administration of DOR-selective agonists[11] or antagonists[12] with a MOR agonist can attenuate the dependence and tolerance typically associated with the latter. The work presented here details the synthesis and evaluation of MOR agonist/DOR antagonist ligands for the purpose of developing effective opioid analgesics devoid of the aforementioned side effects.

1.2 The Role of DOR in the Development of Dependence and Tolerance

The role of DOR in the modulation of the biological effects of MOR has long been the subject of intense interest.[13] It has been shown that DORs exist on the same neurons as MORs,[14] and there is additional biological evidence for functionally distinct MOR/DOR heteromers.[15,16] It has also been demonstrated that the density of DOR binding sites in mice is increased following chronic treatment with the MOR agonist

morphine, further demonstrating an interaction between MOR and DOR.[17] In light of these studies, much work has been done on examining the biological effects of a DOR ligand on MOR-mediated processes. The therapeutic potential for the co-administration of a DOR antagonist with morphine was demonstrated in 1991. In this study, mice were given a subcutaneous (sc) dose of morphine for a period of 3 days. Compared to control mice that were given a placebo, morphine-receiving mice displayed an approximately 19-fold increase in morphine ED_{50} after this time. Mice receiving naltrindole[18] (a potent and selective DOR antagonist, Figure 2) along with morphine displayed a smaller (roughly 2-fold) increase in the ED_{50} for morphine, highlighting the effectiveness of the co-administration of a DOR antagonist in decreasing the development of chronic tolerance to a selective MOR agonist.

Figure 2. Chemical Structure of Naltrindole



naltrindole

Additionally, acute tolerance to morphine was completely eliminated in mice that were given naltrindole.[12] The effects of naltrindole on morphine-induced tolerance and dependence have also been studied in rats. In one study, rats were pretreated with saline (control) or naltrindole, and given morphine for a period of 24 hours. Withdrawal was precipitated with the opioid antagonist naloxone, and all withdrawal symptoms were significantly reduced in the naltrindole-treated rats.[19]

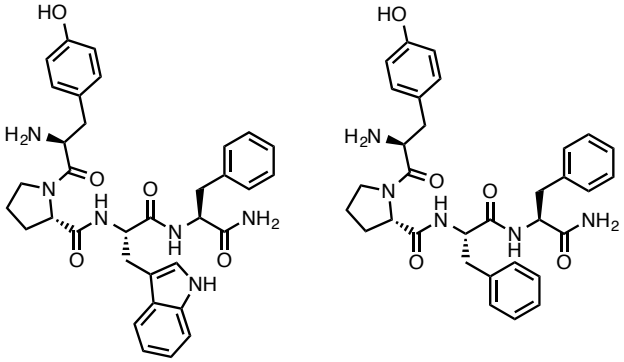
In another study, morphine was shown to maintain its analgesic properties in DOR-1 knockout mice, and in contrast to wild-type mice, these animals did not demonstrate tolerance following the daily sc administration of morphine.[20] In an alternative approach, intracerebroventricular (icv) administration of a DOR-1 antisense or a mismatch control oligodeoxynucleotide showed no effect on baseline morphine analgesia compared to untreated or saline (control) mice. The development of tolerance to morphine was blocked in the antisense-receiving mice but not mismatch oligodeoxynucleotide or saline-treated mice. The same result was also shown for the development of dependence.[21] These results lend further support to the involvement of DOR in the modulation of dependence and tolerance of MOR-selective ligands.

1.3 The Development of MOR Agonist/DOR Antagonist Peptides

The recognition that the simultaneous modulation of multiple targets may generate a more desirable drug profile has challenged the long prevailing, intuitive bias toward selectively targeted drugs as the optimal approach for the discovery and development of new therapeutics.[22] As discussed, this concept is exemplified in the field of opioid analgesics by the observation that co-administration of a MOR agonist with a DOR antagonist retains MOR-mediated analgesia but displays reduced development of tolerance and dependence.[12,19] For pharmacokinetic simplicity it is preferable to incorporate all desired activities into a single compound, and the development of bi-functional opioid ligands has thus become a topic of increasing interest. The mounting evidence for the value of MOR agonist/DOR antagonist ligands has led to the development of a number of peptides featuring this bi-functional pharmacological profile.

Linear Peptides: A number of short, linear mixed efficacy MOR/DOR peptides have been developed.[23] Among these are peptide sequences based on endomorphin 1 (Tyr-Pro-Trp-Phe-NH_2) and endomorphin 2 (Tyr-Pro-Phe-Phe-NH_2), endogenous tetrapeptides with high selectivity for MOR (Figure 3).[24] The endomorphins have been shown to produce an analgesic effect comparable to morphine, but without many of the negative side effects associated with the drug.[25] Extensive modifications have therefore been performed on this sequence for the purpose of elucidating their pharmacological characteristics and improving biological activity.

Figure 3. Chemical Structures of the Endomorphins

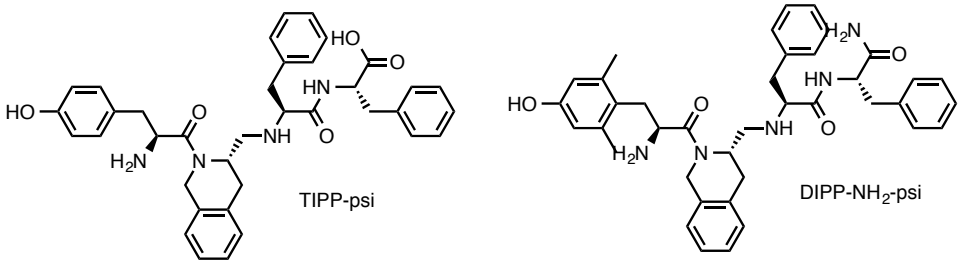


Li and colleagues have demonstrated that alkylated phenylalanine (Phe) residues in the third position of endomorphin 2 can confer a mixed MOR agonist/DOR antagonist profile to the scaffold, which is interesting given that the endomorphins typically lack any type of interaction with the DOR. The MOR agonist/DOR antagonist peptides discussed feature the sequences Dmt-Pro-Dmp-Phe-NH_2 and Dmt-Pro-Tmp-Phe-NH_2, where Dmp is 2',6'-dimethylphenylalanine, Tmp is 2',4',6'-trimethylphenylalanine, and Dmt is 2',6'-dimethyltyrosine.[26] Other endomorphin-derived linear peptides have since been

developed, namely Dmt-Pro-Tmp-Tmp-NH_2 and Dmt-Pro-1-Nal-NH_2 (where 1-Nal is 1-naphthylalanine), which display potent mixed MOR agonism/DOR antagonism and are also devoid of β-arrestin2 recruitment activity.[27] Opioids that are selective for the G protein signaling pathway over the β-arrestin signaling pathway have also shown promise for the development of analgesics devoid of dependence and tolerance.[28,29]

Schiller and colleagues have shown that the highly selective DOR antagonist peptide H-Tyr-TicΨ[CH_2-NH]-Phe-Phe-OH (**TIPP[Ψ]**, Figure 4) was more effective than naltrindole in the attenuation of morphine-induced dependence and tolerance in rats.[30] Further modifications on the TIPP[Ψ] peptide sequence, namely the replacement of tyrosine with 2',6'-dimethyltyrosine to confer agonist properties at MOR, and the replacement of the C-terminal acid with an amide, led to the peptide H-Dmt-TicΨ[CH_2-NH]-Phe-Phe-NH_2 (**DIPP-NH_2[Ψ]**, Figure 4).

Figure 4. Chemical Structures of TIPP[Ψ] and DIPP-NH_2[Ψ]



DIPP-NH_2[Ψ] showed binding affinities in the subnanomolar range for both MOR and DOR, and represents the first example of a balanced MOR agonist/DOR antagonist peptide with high potency at MOR. After icv administration in rats, DIPP-NH_2[Ψ] also demonstrated a potent analgesic effect in the warm water tail withdrawal (WWTW) assay. DIPP-NH_2[Ψ] also displayed less acute tolerance than morphine and no physical

dependence after chronic administration at high doses. Despite these advances, DIPP-NH_2[Ψ] has not been shown to be active after peripheral administration.[31] Efforts toward the development of a bioavailable MOR agonist/DOR antagonist ligand therefore remain ongoing.

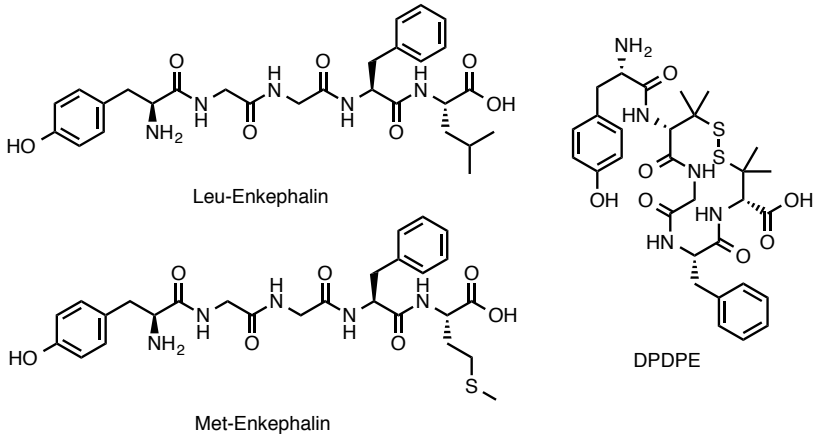
The Balboni group has also disclosed a number of linear peptide and peptidomimetic structures that build upon the DOR-antagonist pharmacophore dipeptide structure Dmt-Tic, where Tic is 1,2,3,4- tetrahydroisoquinoline-3-carboxylic acid. In 1999, Balboni and colleagues found that the addition of hydrophobic moieties to the C-terminal end of Dmt-Tic peptides could give compounds that displayed MOR agonism in vitro, while preserving DOR antagonism. Namely, the peptide N,N-$(Me)_2$Dmt-Tic-NH-1-adamantane showed good binding affinities for both MOR and DOR (with some selectivity for DOR) and a MOR agonist/DOR antagonist selectivity profile. The compound was not evaluated in an animal model.[32]

In a later study, it was found that by adding a third aromatic center to Dmt-Tic peptides and by varying the length of the spacer between the Dmt-Tic pharmacophore and the new aromatic center, peptides with different mixed properties could be obtained. In short, it was observed that the peptide H-Dmt-Tic-Gly-NH-Ph had nearly equivalent potent MOR and DOR agonist properties, while H-Dmt-Tic-Gly-NH-CH_2-Ph (the only difference being elongation by a methylene group) maintained MOR agonism, but became a DOR antagonist.[33] Further substitution of H-Dmt-Tic-Gly-NH-CH_2-Ph with an Aba-Gly scaffold (an expanded ring mimetic used to circumvent dioxopiperazine formation in small peptides) in place of Tic-Gly afforded the peptide H-Dmt-Aba-Gly-NH-CH_2-Ph, which loses some DOR binding affinity but maintains good MOR affinity

and efficacy.[34] Conversely, it was found that the replacement of Gly in this sequence with aspartic acid could confer DOR selectivity by lowering MOR affinity.[35] Balboni and colleagues have examined a number of other substituted aromatic moieties after the spacer unit of these Dmt-Tic peptides. The lead MOR agonist/DOR antagonist peptidomimetic H-Dmt-Tic-Gly-NH-CH_2-Ph was modified by the addition of aromatic rings with different electronic characteristics, with certain new analogues (para-chloro) maintaining the MOR agonist/DOR antagonist profile of the parent compound.[36]

Cyclic Peptides: [Leu^5]-enkephalin (Tyr-Gly-Gly-Phe-Leu-OH) and [Met^5]-enkephalin (Tyr-Gly-Gly-Phe-Met-OH) (Figure 5) are endogenous pentapeptides selective for DOR.[37] Chemical modifications on these structures have been extensively studied, one such ligand being the cyclic, bis-penicillamine pentapeptide **DPDPE** [D-Pen^2, D-Pen^5]enkephalin (Figure 5), which is a remarkably potent and selective DOR agonist (penicillamine is β,β-dimethyl-D-cysteine).[38] Removal of a glycine residue from DPDPE to contract the pentapeptide into a cyclic tetrapeptide resulted in a compound with improved DOR binding affinity and comparable selectivity to DPDPE.

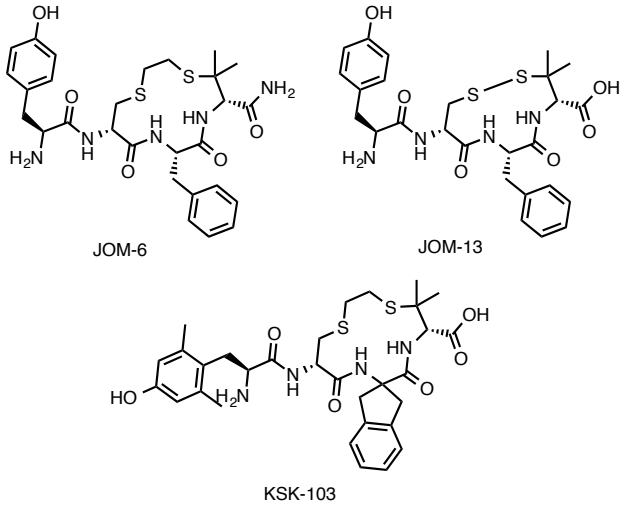
Figure 5. Chemical Structures of DPDPE and the Enkephalins



This cyclic tetrapeptide Tyr-c(SS)[DCys-Phe-DPen]OH (**JOM-13**, Figure 6) where DPen is D-penicillamine and c(SS) denotes cyclization through the side-chain sulfurs of DCys and DPen via a disulfide bridge, served as the starting point for a number of modifications aimed at conferring a MOR agonist/DOR antagonist profile.

More recently, our group has described the development of MOR agonist/DOR antagonist opioid cyclic pentapeptides that are cyclized either through a disulfide or dithioether bridge. These pentapeptides display decreased DOR efficacy compared with DPDPE and JOM-13 due to steric interactions with the DOR active pocket resulting from the replacement of Phe^3 and Phe^4 residues with bulkier 1-naphthylalanine (1-Nal) or 2-naphthylalanine (2-Nal) residues.[39,40] Through similar types of modifications to JOM-13 and the MOR selective tetrapeptide Tyr-c(SCH_2CH_2S)[DCys-Phe-DPen]NH_2 (**JOM-6**, Figure 6),[41] follow up studies have described a number of cyclic tetrapeptides, in particular Dmt-c(SCH_2CH_2S)[DCys-Aci-DPen]OH (**KSK-103**, Figure 6), which binds with equal affinity to MOR and DOR but acts as a MOR agonist with improved potency as compared to morphine.

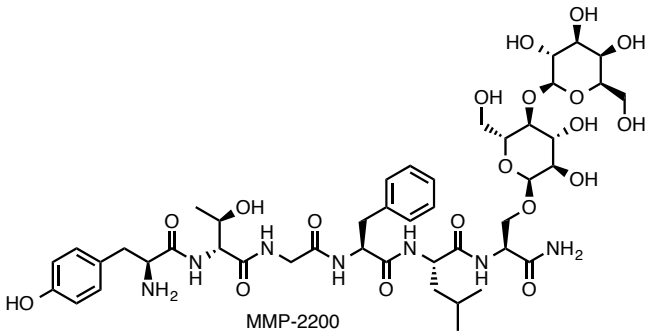
Figure 6. Chemical Structures of JOM-6, JOM-13 and KSK103



KSK-103 also behaved as a DOR antagonist in cellular assays measuring both G protein stimulation and adenylyl cyclase inhibition.[42] KSK-103 features a C-terminal acid in place of the C-terminal amide of JOM-6, as well as substituting for Phe^3 the bulky and conformational-constrained 2-aminoindane-2-carboxylic acid (Aci) residue. Like DIPP-NH_2[Ψ], a serious flaw with KSK103 and other MOR agonist/DOR antagonist peptides is poor bioavailability.

Glycosylated Bifunctional MOR/DOR Peptides: It is known that the incorporation of a glycosylated amino acid residue into opioid peptides can result in compounds that improve CNS bioavailability.[43] Although the initial hypothesis was that such analogues were crossing the BBB by acting as a substrate for the Glut-1 transporter, this was determined to be incorrect, and the mechanism by which these glycoside opioid ligands reach the brain still requires further study.[44] It was also found that the optimal placement of the glycoside was near the C-terminal end of the peptide.[44] Polt and colleagues have described a MOR agonist/DOR agonist glycopeptide featuring the sequence Tyr-D-Thr-Gly-Phe-Leu-Ser-(O-β-D-lactose)-$CONH_2$ (**MMP-2200**, Figure 7). MMP-2200 showed dose-dependent antinociception in the WWTW assay after several different routes of administration (highlighting its ability to cross the BBB), and showed less chronic tolerance and dependence compared to morphine.[45]

Figure 7. Chemical Structure of MMP-2200



The C-terminal glycosylation strategy was also implemented for KSK103. It was found that the addition of a C-terminal serine carboxylic acid residue to KSK103 resulted in a compound with an analogous in vitro profile (balanced binding affinities for MOR and DOR with selectivity over KOR, and partial agonist activity at MOR without stimulation of DOR or KOR). The addition of a C-terminal serine carboxamide was also comparable. Glycosylation of this C-terminal carboxamide compound with β-D-glucose led to an analogue with a very similar in vitro profile to KSK103. This glycosylated KSK103 analogue, **VRP26**, was found to produce dose-dependent analgesia in the WWTW assay after ip administration (80% maximal effect at 10 mg/kg). At 32 mg/kg, the compound was found to display a maximal antinociceptive effect between 30 and 60 minutes after administration, with a total duration of action of around 150 minutes (approximately half of morphine). Additionally, the compound displayed no acute tolerance at 10 mg/kg, in contrast to the acute tolerance observed for fentanyl.[46] Furthermore, after continuous infusion for a 7-day period, VRP26 shows no chronic tolerance or dependence (J. Anand, personal communication). While these results are

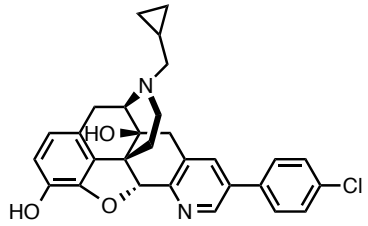
very promising, the compound's short duration of action and complicated synthesis remain barriers for clinical development.

1.4 The Development of MOR Agonist/DOR Antagonist Small Molecules

Despite the ease of synthesis and excellent target selectivity that can often be achieved by peptide ligands, peptides often make for poor drugs, especially in the realm of CNS research. Peptides often have very high molecular weight and polarity, making the crossing of the BBB problematic.[47] Additionally, peptides are typically subject to extensive hydrolysis by peptidases. These common drawbacks for peptide ligands are exemplified in the opioid field, as peptidic opioid drugs such as the endomorphins[48] and DIPP-NH_2[Ψ][31] must be administered through an icv route in order to achieve the desired analgesic effect. While approaches such as glycosylation and increased hydrophobicity through ring closing metathesis cyclization techniques[49] can often overcome the CNS bioavailability problems of peptides, the design of small molecule (or peptidomimetic) opioid ligands that maintain the key binding moieties of the endogenous and synthetic opioid peptides represents an important alternative strategy.

Many small molecule opioid MOR agonist/DOR antagonists have been derived from the naturally occurring alkaloids found in opium, namely morphine, codeine and thebaine. **SoRI 9409** (Figure 8), a small molecule derived from naltrexone, displayed partial agonist activity in the WWTW assay (icv administration), and full agonist activity in the acetic assay writhing assay after ip administration. The compound was not active in the WWTW assay after ip administration.

Figure 8. Chemical Structure of SoRI 9409



SoRI-9409

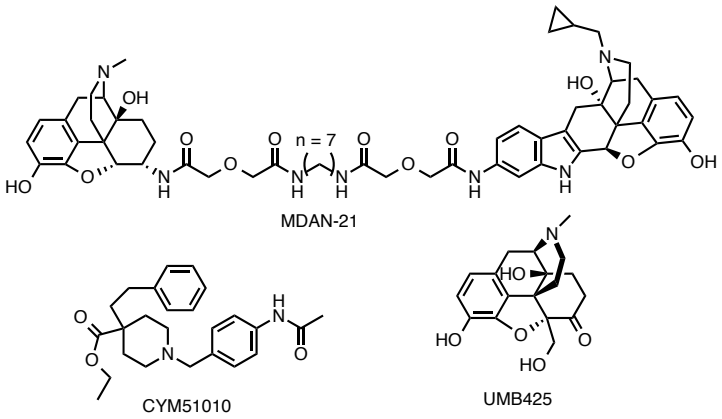
Additionally, the compound produced very little tolerance after repeated ip administrations in the acetic acid writhing test.[50] Although SoRI 9409 displayed potent antagonist activity at DOR and agonist activity at MOR in the mouse vas deferens and guinea pig ileum assays respectively, the compound did not display MOR agonist activity in functional assays with MOR-expressing cells. The incorporation of alkoxy and arylalkoxy moieties at the 14 position of the morphinan-6-one scaffold, while maintaining the N-methylcyclopropyl group common in opioid antagonists, led to a new analogue which was not only shown to act as a MOR agonist/DOR antagonist in functional assays, it also displayed diminished chronic tolerance as compared to morphine. Unfortunately, the compound was only given through an icv route.[51]

A number of bioavailable MOR agonist/DOR antagonist compounds have been developed. The MOR/DOR bivalent ligands developed by Portoghese and colleagues have been demonstrated to be effective analgesics (**MDAN-21** is 50-fold more potent than morphine after intravenous administration, Figure 9) with a dependence and tolerance profile that is modulated by the length of the spacer between the MOR agonist and DOR antagonist pharmacophores. This finding further supports the notion that physical interaction between MOR and DOR modulates MOR-mediated tolerance and

dependence.[52] Portoghese has also used this bivalent ligand approach to target a number of other purported MOR-containing heteromers for the treatment of pain, namely a MOR-CB_1 heteromer[53] and a MOR-mGluR5 heteromer.[54]

Recently the MOR/DOR heteromer-biased agonist **CYM51010** (Figure 9) was also shown to display reduced antinociceptive tolerance as compared to morphine after sc administration.[55] Additionally, **UMB425** (Figure 9), a small-molecule MOR agonist/DOR antagonist derived from thebaine, was reported to display analgesia after sc administration with reduced tolerance compared with morphine.[56]

Figure 9. Chemical Structures of MDAN-21, CYM51010 and UMB425



Several other small molecule classes of MOR agonist/DOR antagonist peptidomimetics have also been developed, including a series of compounds where 2',6'-dimethyltyrosine is linked to a pyrazinone ring platform.[57] Additionally, the Mosberg group has used the pharmacophore of the previously reported MOR agonist/DOR antagonist peptide series to design a series of opioid peptidomimetics that retain the key binding features of the peptides, but feature a smaller and more drug-like tetrahydroquinoline (THQ) core (see Chapter 2).[58,59]

Although the compounds shown in Figure 9 are promising as MOR agonist/DOR antagonist leads for the purpose of developing safer opioids, the THQ compounds offer several advantages. The THQ scaffold is highly amenable to substitutions, and is thus a synthetically versatile and novel scaffold for SAR studies as compared to the morphinan scaffold of MDAN-21 or UMB425. Additionally, MDAN-21 and CYM51010 both target a purported MOR/DOR heteromer, a relatively unexplored biological target that requires further validation before such compounds can be useful clinically. In the case of UMB425, the compound is a drug-like small molecule that binds to MOR and DOR separately, but is very selective for MOR over DOR in competitive binding assays. The THQ compounds discussed in Chapter 2 are much more potent than UMB425 in these assays, particularly at DOR. In the WWTW assay, UMB425 requires a dose of 20 mg/kg to sustain a maximal effect (10 s cutoff time),[56] roughly double the dosage required for the THQ lead compounds in vivo (20 s cutoff time).[60,61]

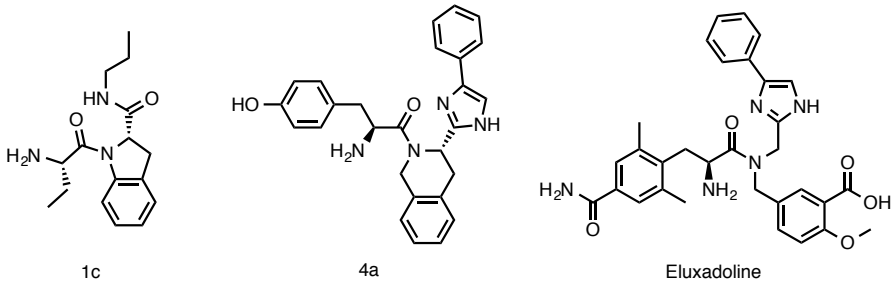
1.5 MOR Agonist/DOR Antagonists for the Treatment of IBS-d

In addition to MOR agonist/DOR antagonist small molecules that cross the BBB, non CNS-penetrating ligands of this type are also of interest. Opioids have long been known to block gastrointestinal motility, and compounds such as loperamide[62] have found widespread use for their ability to treat related disorders such as irritable bowel syndrome (IBS). Recently, Johnson & Johnson has developed a series of opioid ligands featuring an imidazole scaffold. These compounds were based on a cholecystokinin (CCK)-related dipeptide scaffold. The CCK dipeptide **1c** (Figure 10) was known to be unstable though spontaneous cyclization to a diketopiperazine, and the imidazole moiety

was installed as a bioisostere for the unstable amide peptide bond. One of the imidazoles developed, (**4a**, Figure 10), was found to be devoid of antinociceptive activity when administered sc in a mouse model (but showed activity icv), despite binding to MOR (55 nM) and DOR, with good selectivity for DOR (0.9 nM). In vitro, **4a** also displayed potent agonism at DOR. It was also found that **4a** reduced gastrointestinal motility in mice, which could be quantified in a dose dependent manner, as well as reversed by the opioid antagonist naloxone, showing that the effect was mediated through interaction with the opioid receptors.[63]

For the purpose of synthetic accessibility, the authors continued their SAR study by breaking a bond in the tetrahydroisoquinoline (Tic) core of **4a** and synthesizing a number of acyclic analogues. Additionally, the N-terminal tyrosine moiety of **4a** was replaced with Dmt, for the purpose of improving potency at the opioid receptors. A number of other synthetic substitutions, such as the insertion of 4'-(aminocarbonyl)-2',6'-dimethyl-Phe (Cpa) as a bioisostere for Dmt[64] led to the discovery of compound **5l**, which displayed a potent MOR agonist/DOR antagonist profile in vitro.[65] This compound, known as MuDelta and **Eluxadoline** (Figure 10), has found success in a Phase II Proof of Concept clinical trial in 800 patients suffering from diarrhea-predominant irritable bowel syndrome (IBS-d). Recently, the compound was approved by the FDA for treatment of IBS-d.[66,67] Although some of the THQ compounds developed by the Mosberg group show potent antinociception after peripheral administration, many of the analogues discussed in subsequent chapters are conversely inactive after being administered ip. Like Eluxadoline, such analogues may also found use for the treatment of IBS-d and similar disorders.

Figure 10. Chemical Structures of 1c, 4a and Eluxadoline[a]



1c 4a Eluxadoline

[a.] Compounds 1c and 4a from reference 63

All of the peptides and small molecules discussed here lend support to the idea that compounds featuring a mixed MOR/DOR efficacy profile are beneficial for the development of safer opioid analgesics, as well as compounds that are clinically useful for the treatment of IBS-d. In Chapter 2, the development of this MOR agonist/DOR antagonist profile in peptidomimetic compounds featuring a tetrahydroquinoline (THQ) core will be discussed.

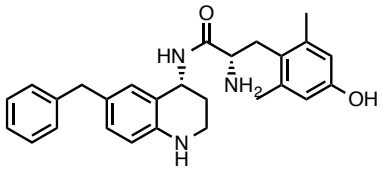
CHAPTER 2

SYNTHESIS OF THQ PEPTIDOMIMETICS MODIFIED AT THE 6 POSITION[a]

2.1 Introduction

Peptidomimetic **1**, which was initially synthesized as a mixture of diastereomers at the 4 position, was designed to incorporate the key opioid pharmacophore elements of the parent tetrapeptide Tyr-c(SS)[D-Cys-Phe-D-Pen]OH (JOM-13) and related cyclic tetrapeptides, namely a tyramine moiety and a second aromatic group, attached to a tetrahydroquinoline (THQ) scaffold. This design strategy proved to be successful, as the higher affinity 4*R* diastereomer of **1** (Figure 11) displayed high binding affinity to MOR, DOR, and KOR.[59,68]

Figure 11. Chemical Structure of Lead THQ Peptidomimetic **1 (1E)**



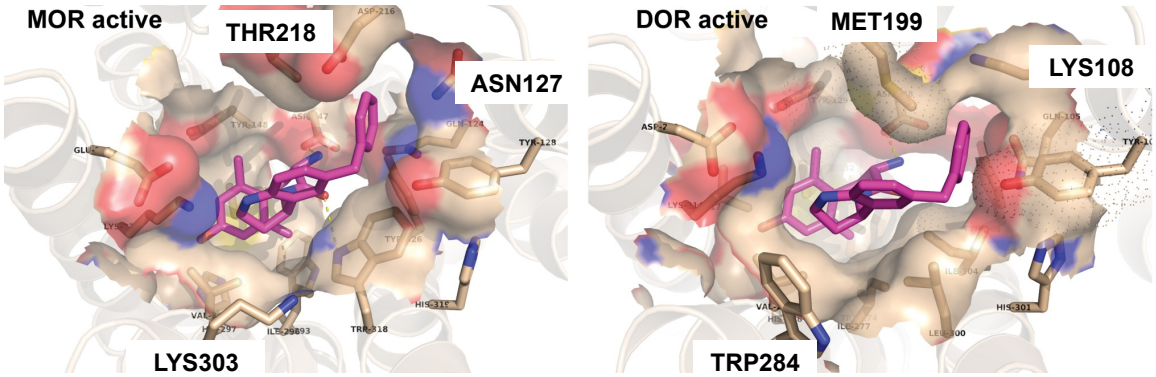
The observation that Aic and other bulky aromatic replacements for Phe in cyclic peptides confer a MOR agonist/DOR antagonist profile suggested that **1** might be a promising starting point for the development of related peptidomimetics with similar profiles but with improved bioavailability compared to the peptides. The binding pocket

[a]See references 59 and 60. In vitro assays were performed by Nicholas Griggs. In vivo work was done by Jessica Anand and Emily Jutkiewicz. Computational modeling was done by Irina Pogozheva. Compound 12 was synthesized by Michael Agius. Compounds 83, 84, 103 and 104 were synthesized by Dylan Kahl.

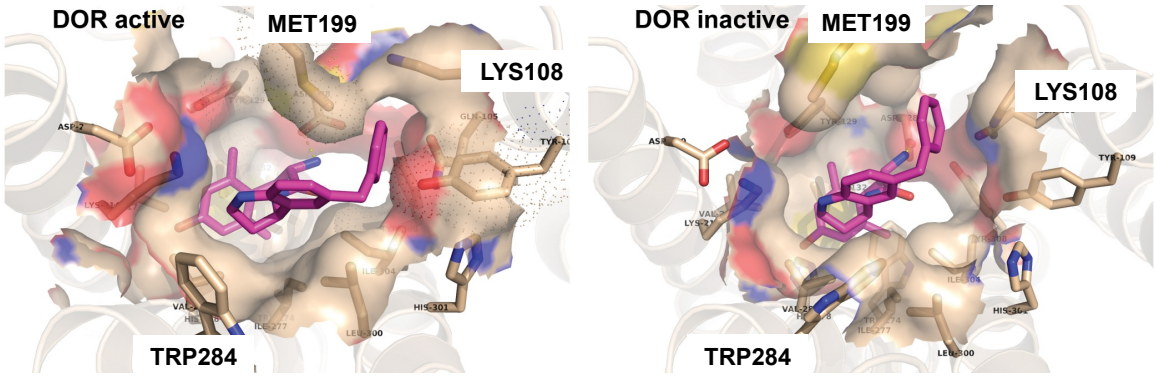
in the region of the Phe[3] side chain of the 6-benzyl substituent of the THQ scaffold of **1** includes Asn[125], Thr[218], and Lys[303] in MOR and the corresponding, bulkier Lys[108], Met[199], and Trp[254] in DOR. The inactive state of both receptors can accommodate benzyl and even bulkier substituents; however, these bulkier substituents clash with the larger residues of DOR in the more compact binding pocket found in the *active* state of the receptor, reducing efficacy at this receptor (Figure 12). **1** was also found to be fully efficacious in the mouse WWTW assay after ip administration, with a total duration of action shorter than morphine.[59]

Figure 12. (A) Comparison of **1** Docked in the MOR Active/DOR Active Sites (B) Comparison of DOR Active/DOR Inactive Sites

A.



B.



The initial SAR study done on compound **1** was focused on several additional hydrophobic, aromatic substitutions at the 6 position, including 1-methylnaphthyl, 2-methylnaphthyl, 2-methylindanyl, and ethylphenyl. As expected, modifications featuring a more extended pendant (2-methylnaphthyl, 2-methylindanyl, ethylphenyl) were compatible with the larger DOR inactive binding pocket but not the smaller DOR active pocket, explaining the observed low efficacy at DOR. While these compounds displayed the desired MOR agonist/DOR antagonist efficacy profile, their binding profile was not optimal. The MOR affinity for all four compounds was at least an order of magnitude higher than the DOR affinity, and the 2-methylnaphthyl compound showed an over 2 orders of magnitude preference for MOR. Ligands with more balanced binding affinities at MOR and DOR would provide a better starting point for further development of this type of mixed-efficacy opioid ligand.[31,69] Additionally, although it was shown that an extended hydrophobic pendant translates to low DOR efficacy, changes in the electronic characteristics and polarity of the pendant were left unexplored.

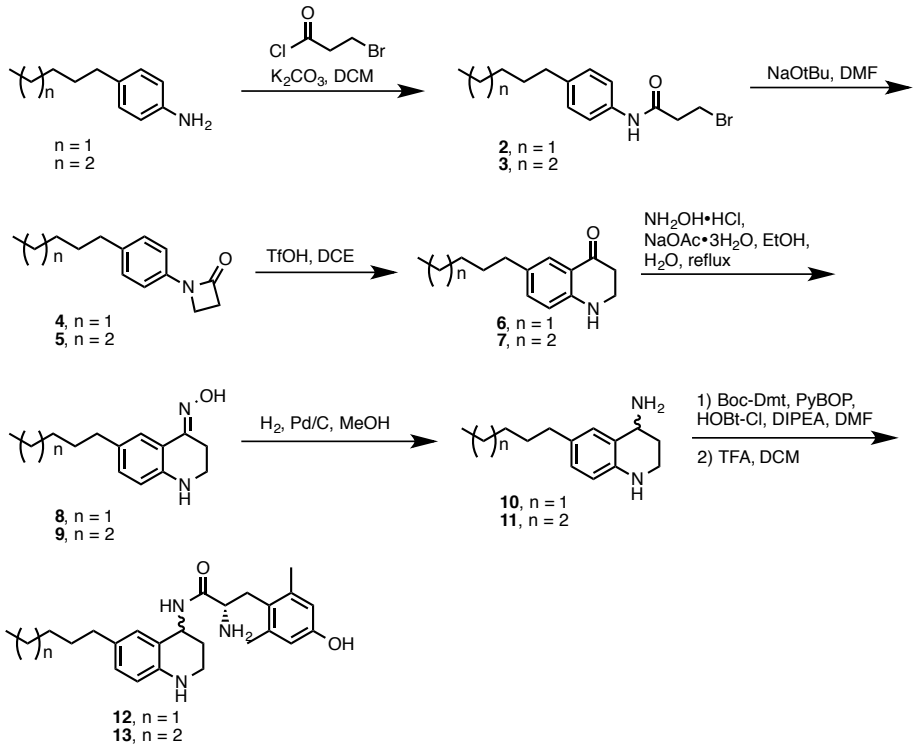
RESULTS AND DISCUSSION

2.2 Modifications to the 6-Position of the Tetrahydroquinoline Scaffold

The original modifications to the 6-position of the THQ scaffold consisted of 2-methylnaphthyl, 1-methylnaphthyl, 2-methylindanyl and ethylphenyl.[59] To begin the expanded SAR at the 6-position, linear pentyl and hexyl chains were first examined. The length of these alkyl chains was chosen as to be approximately the same as the previous aromatic substitutions, and so would reach into the binding pocket at a similar distance. As shown in Scheme 1, the synthesis of these analogues began with commercially

available para-substituted anilines, which were acylated with 3-bromopropionyl chloride, and then cyclized with NaOtBu to form the β-lactam. The β-lactam was cyclized under Friedel-Crafts conditions to give the THQ core.[70,71] After oxime formation, and subsequent hydrogenation to give the racemic primary amines, the scaffold could be coupled to Boc-protected 2',6'-dimethyl-L-tyrosine (di-Boc-protection on NH_2 and OH) under standard conditions, and deprotected with trifluoroacetic acid (TFA) in DCM. Diastereomers could then by separated on RP-HPLC and lyophilized to give powders suitable for in vitro testing.

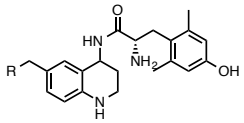
Scheme 1. Synthesis of Analogues **12** and **13**



As shown in Table 1, the early eluting diastereomer on RP-HPLC of **12** and **13** (**12E** and **13E**) have binding affinities at MOR and DOR that are comparable to **1**, although analogues **12E** and **13E** have improved binding affinity at KOR. The late

eluting diastereomer of **13** (**13L**) was found to have binding affinities of several orders of magnitude lower than **13E**, and so efficacies were not determined for this compound, and the late eluting diastereomer of **12** was not isolated. Although the MOR potency of **13E** is comparable to lead compound **1E**, the maximal percent stimulation of **13E** is less. **12E** was also inferior to **1E** for MOR potency and efficacy. Because linear alkyl chain substitutions did not improve upon our lead compound **1E**, substitutions of this type at the 6-position were not explored further.

Table 1. Opioid Receptor Binding Affinities and Efficacies for Analogues **1E**, **1L**, **12E**, **13E**, **13L**[a]



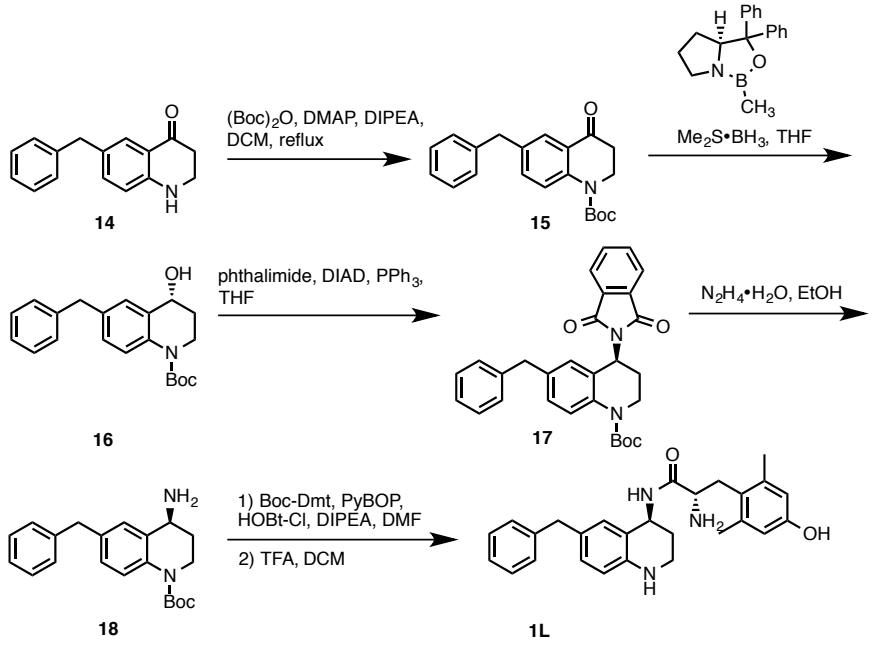
		MOR			DOR			KOR		
	R	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
1E		0.22 ± 0.02	1.6 ± 0.3	81 ± 2	9.4 ± 0.8	110 ± 6	16 ± 2	68 ± 2	540 ± 72	22 ± 2
1L		2.6 ± 0.3	-	-	56 ± 5	-	-	220 ± 48	-	-
12E		0.22 ± 0.09	12 ± 6	20 ± 7	8.8 ± 3	dns	dns	22 ± 10	540 ± 150	24 ± 1
13E		0.13 ± 0.02	2.4 ± 0.08	36 ± 5	5.9 ± 0.8	dns	dns	15 ± 6	770 ± 30	35 ± 1
13L		300 ± 70	-	-	1200 ± 400	-	-	3900*	-	-

[a] Binding affinities (K_i) were obtained by competitive displacement of [^{3}H]diprenorphine in membrane preparations expressing either MOR, DOR, or KOR. All values are mean ± standard error of the mean (SEM) of three separate assays performed in duplicate. Efficacy data were obtained using agonist-induced stimulation of [^{35}S]GTPγS binding in membrane preparations expressing either MOR, DOR, or KOR. Potencies are represented as EC_{50} (nM) and efficacies as percent maximal stimulation relative to the standard agonist DAMGO (MOR), DPDPE (DOR), or U69,593 (KOR) at 10 μM. All values are expressed as the mean ± SEM of three separate assays performed in duplicate. dns: does not stimulate. Dashed line indicates assay was not performed. * n = 1.

In order to determine the absolute stereochemistry at the 4 position of compound **1**, an asymmetric synthesis was completed (Scheme 2). Ketone **14** was first Boc protected on the THQ nitrogen to give ketone **15**, which was reduced with the (*S*)-methyl-CBS

catalyst[72] to give chiral, 4*R* alcohol **16** in 80% ee as determined by chiral HPLC, similar to previous reports for analogous scaffolds.[72,73] The secondary chiral alcohol was then converted to an amine, with complete inversion of stereochemistry via a Mitsunobu reaction,[74] yielding chiral, 4*S* amine **18** to which Boc protected 2',6'-dimethyl-L-tyrosine was coupled. After deprotection of this unequivocal 4*S* diastereomer, HPLC revealed a 9:1 ratio of late eluting to early eluting diastereomer of **1**, confirming that the late eluting diastereomer is 4*S* and the (higher affinity) early eluting diastereomer is 4*R* (**1** or **1E**).

Scheme 2. Asymmetric Synthesis of Compound **1**



Additional analogues featuring modifications at the 6-position were also synthesized via an asymmetric synthesis to give the 4*R* diastereomers, but through a different route (Scheme 3). Similar to the analogues in Scheme 1, *p*-toluidine was first acylated with 3-bromopropionyl chloride, and cyclized to give the corresponding para-

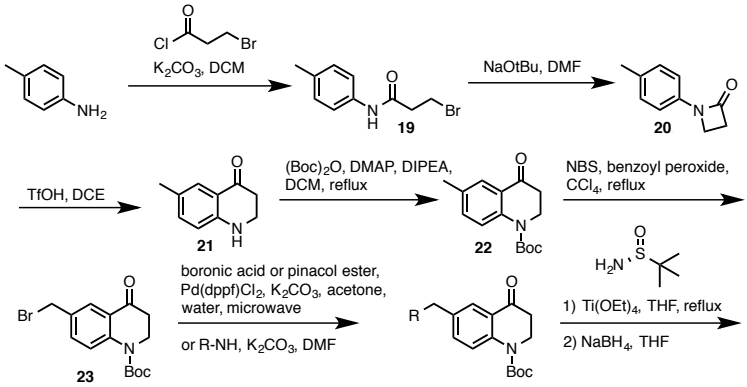
methyl β-lactam. The β-lactam was cyclized under Friedel-Crafts conditions to give the THQ core.[70,71] After TfOH-mediated cyclization, the THQ core was Boc-protected to give ketone **22**, which was then brominated on the aryl methyl group as previously described.[75] Benzyl bromide intermediate **23** can then be used as a useful later-stage intermediate for rapid diversification at the 6-position, either through Suzuki coupling or S_N2 substitution. All substitutions on benzyl bromide intermediate **23** were straightforward, with some notable exceptions. In the case of 2-benzofuranyl intermediate **31**, it is necessary to perform the Suzuki coupling with 2-benzofuranyl boronic acid MIDA ester, as the unprotected boronic acid is known to be unstable.[76] The synthesis of intermediate **45** was accomplished through first reducing 3-azaspiro[5.5]undecane-2,4-dione to secondary amine **101** as previously described (Scheme 6)[77] followed by S_N2 substitution of intermediate **23** to give **45**.

Additionally, the first steps in the synthesis of morpholinyl intermediate **28**, 1,2,4-triazolyl intermediate **29** and diphenylmethyl intermediate **35** were synthesized via an alternative route. **28** and **29** were synthesized starting from the appropriate commercially available para-substituted aniline (Scheme 4). **35** was synthesized as shown in Scheme 5, through a TfOH-catalyzed addition of benzene to 4-nitrobenzaldehyde,[78] followed by reduction of nitro compound **99** to give aniline **100**. This intermediate was then carried forward in a similar manner as shown in Scheme 4 to give **35**.

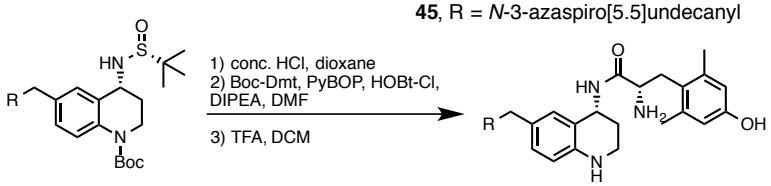
Ketones **24-45** were converted to the corresponding imines with (*R*)-(+)-2-methyl-2-propanesulfinamide and $Ti(OEt)_4$ and could then be reduced asymmetrically with $NaBH_4$ in situ to give tert-butanesulfinyl-protected amines **46-67** as single diastereomers as previously described for analogous scaffolds (Scheme 3).[79,80]

Deprotection with concentrated HCl gave the corresponding primary, enantiomerically pure (*R*)-amines as HCl salts. The stereochemistry of the HCl salts was verified by X-ray crystallography of 6-benzyl-1-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride, which was prepared by an identical synthetic route (Figure 13). Boc-protected 2',6'-dimethyl-L-tyrosine could then be coupled to the chiral HCl salt, and subsequent deprotection with TFA in DCM afforded final analogues **68-89**, which were assayed for binding and efficacy at all three opioid receptor types (Table 2).[60] The TFA content of analogue **103** (Chapter 2.3) was determined by ^{19}F-NMR as previously described,[81] and was found to be approximately 2.5 molecules of TFA per molecule of compound.

Scheme 3. Synthesis of Analogues **68-89**



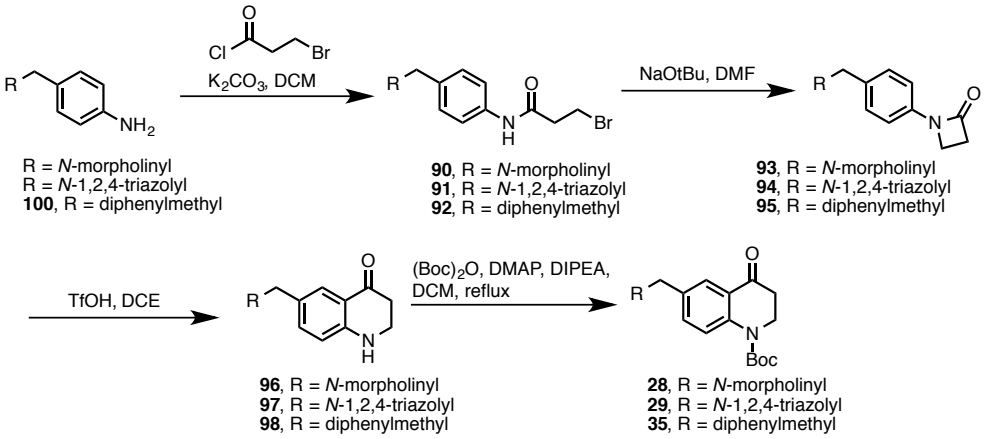
24, R = 3-pyridinyl
25, R = *N*-piperidinyl
26, R = *N*-azepanyl
27, R = *N*-piperazinyl-*N*-Boc
28, R = *N*-morpholino
29, R = 1,2,4-triazolyl
30, R = 3-furanyl
31, R = 2-benzofuranyl
32, R = 3,4-(methylenedioxy)phenyl
33, R = 6-(1,4-benzodioxane)
34, R = 2,6-dichlorophenyl
35, R = diphenylmethyl
36, R = 6-quinolinyl
37, R = 3-quinolinyl
38, R = *N*-1,2,3,4-THIQ
39, R = *N*-1,2,3,4-THIQ(7-fluoro)
40, R = *N*-1,2,3,4-THIQ(8-trifluoromethyl)
41, R = *N*-1,2,3,4-THIQ(7-methyl)
42, R = *N*-isoindolinyl
43, R = *N*-(4aR,8as)-DHIQ
44, R = *N*-*trans*-DHQ
45, R = *N*-3-azaspiro[5.5]undecanyl



46, R = 3-pyridinyl
47, R = *N*-piperidinyl
48, R = *N*-azepanyl
49, R = *N*-piperazinyl-*N*-Boc
50, R = *N*-morpholino
51, R = 1,2,4-triazolyl
52, R = 3-furanyl
53, R = 2-benzofuranyl
54, R = 3,4-(methylenedioxy)phenyl
55, R = 6-(1,4-benzodioxane)
56, R = 2,6-dichlorophenyl
57, R = diphenylmethyl
58, R = 6-quinolinyl
59, R = 3-quinolinyl
60, R = *N*-1,2,3,4-THIQ
61, R = *N*-1,2,3,4-THIQ(7-fluoro)
62, R = *N*-1,2,3,4-THIQ(8-trifluoromethyl)
63, R = *N*-1,2,3,4-THIQ(7-methyl)
64, R = *N*-isoindolinyl
65, R = *N*-(4aR,8as)-DHIQ
66, R = *N*-*trans*-DHQ
67, R = *N*-3-azaspiro[5.5]undecanyl

68, R = 3-pyridinyl
69, R = *N*-piperidinyl
70, R = *N*-azepanyl
71, R = *N*-piperazinyl
72, R = *N*-morpholino
73, R = 1,2,4-triazolyl
74, R = 3-furanyl
75, R = 2-benzofuranyl
76, R = 3,4-(methylenedioxy)phenyl
77, R = 6-(1,4-benzodioxane)
78, R = 2,6-dichlorophenyl
79, R = diphenylmethyl
80, R = 6-quinolinyl
81, R = 3-quinolinyl
82, R = *N*-1,2,3,4-THIQ
83, R = *N*-1,2,3,4-THIQ(7-fluoro)
84, R = *N*-1,2,3,4-THIQ(8-trifluoromethyl)
85, R = *N*-1,2,3,4-THIQ(7-methyl)
86, R = *N*-isoindolinyl
87, R = *N*-(4aR,8as)-DHIQ
88, R = *N*-*trans*-DHQ
89, R = *N*-3-azaspiro[5.5]undecanyl

Scheme 4. Synthesis of Intermediates **28, 29,** and **35**



R = *N*-morpholinyl
R = *N*-1,2,4-triazolyl
100, R = diphenylmethyl

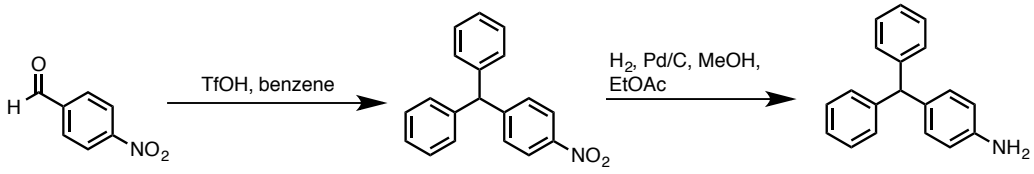
90, R = *N*-morpholinyl
91, R = *N*-1,2,4-triazolyl
92, R = diphenylmethyl

93, R = *N*-morpholinyl
94, R = *N*-1,2,4-triazolyl
95, R = diphenylmethyl

96, R = *N*-morpholinyl
97, R = *N*-1,2,4-triazolyl
98, R = diphenylmethyl

28, R = *N*-morpholinyl
29, R = *N*-1,2,4-triazolyl
35, R = diphenylmethyl

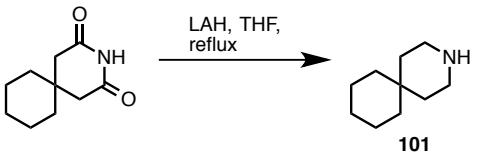
Scheme 5. Synthesis of Intermediate **100**



99

100

Scheme 6. Synthesis of Intermediate **101**



101

Figure 13. Crystal Structure of 6-benzyl-1-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride

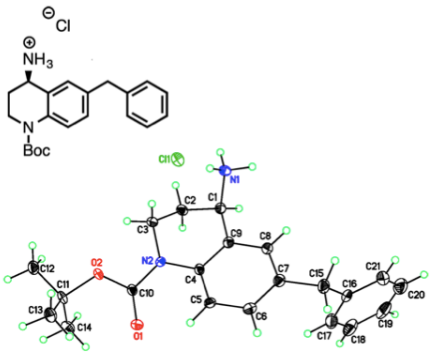
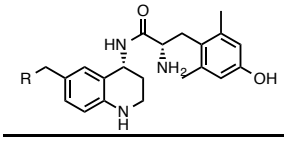


Table 2. Opioid Receptor Binding Affinities and Efficacies for Analogues **68-89**[a]



		MOR			DOR			KOR		
	R	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
1		0.22 ± 0.02	1.6 ± 0.3	81 ± 2	9.4 ± 0.8	110 ± 6	16 ± 2	68 ± 2	540 ± 72	22 ± 2
68		0.66 ± 0.08	93 ± 20	37 ± 7	17 ± 4	dns	dns	66 ± 8	dns	dns
69		0.3 ± 0.1	9 ± 1	73 ± 8	120 ± 29	dns	dns	29 ±9	dns	dns
70		0.15 ± 0.02	25 ± 11	52 ± 2	61 ± 9	dns	dns	3.6 ± 0.7	dns	dns
71		17 ± 7	dns	dns	1560 ± 290	-	-	12 ± 2**	-	-
72		0.6 ± 0.1	60 ± 2	82 ± 2	140 ± 67	dns	dns	170 ± 32	dns	dns
73		3.1 ± 0.6	dns	dns	50 ± 14	dns	dns	450 ± 14	dns	dns
74		0.8 ± 0.2	72 ± 24	18 ± 2	18 ± 6	dns	dns	20 ± 3	>1000	>40
75		0.11 ± 0.03	1.1 ± 0.5	98 ± 1	4.8 ± 2	dns	dns	41 ± 20	dns	dns
76		0.12 ± 0.01	14 ± 3	36 ± 3	4.3 ± 0.8	dns	dns	21 ± 2	dns	dns
77		0.35 ± 0.1	7.3 ± 2	88 ± 8	5.5 ± 0.8	dns	dns	116 ± 70	dns	dns
78		0.08 ± 0.01	2.7 ± 0.7	46 ± 5	4.6 ± 0.06**	dns	dns	4.9 ± 0.7	dns*	dns*

		MOR			DOR			KOR		
	R	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
79		0.2 ± 0.02	13 ± 9	25 ± 0.3	2.3 ± 0.4	dns	dns	6.9 ± 3	dns*	dns*
80		2.1 ± 0.6	23 ± 13	34 ± 6	23 ± 5	dns	dns	120 ± 21	dns	dns
81		0.1 ± 0.02	2.2 ± 0.9	84 ± 6	1.5 ± 0.2	dns	dns	16 ± 4	dns	dns
82		0.03 ± 0.01	0.4 ± 0.1	105 ± 6	3.1 ± 0.2	dns	dns	2.2 ± 0.4	90 ± 65	25 ± 4
83		0.17 ± 0.02	1.9 ± 1	111 ± 7	16.7 ± 2.5	dns	dns	9.6 ± 0.4	dns	dns
84		0.17 ± 0.03	16.3 ± 8	49 ± 11	13.6 ± 1.3	dns*	dns*	50 ± 20	dns*	dns*
85		0.17 ± 0.06	0.35 ± 0.1	111 ± 5	23.3 ± 2.5	dns	dns	11.9 ± 6.1	dns	dns
86		0.15 ± 0.08	3 ± 1	96 ± 4	15 ± 5	dns	dns	2 ± 1	15 ± 9	14 ± 2
87		0.15 ± 0.01	2 ± 0.5	56 ± 2	4.8 ± 0.9	dns	dns	37 ± 8	600 ± 400	14 ± 1
88		0.18 ± 0.03	1.9 ± 0.7	31 ± 8	9.5 ± 1.2	dns	dns	7 ± 1	dns	dns
89		0.22 ± 0.1	dns	dns	40 ± 20	dns	dns	2.4 ± 1	92 ± 15	72 ± 4

[a.] dns = does not stimulate. See Table 1 for further in vitro details. * = n of 1, ** = n of 2

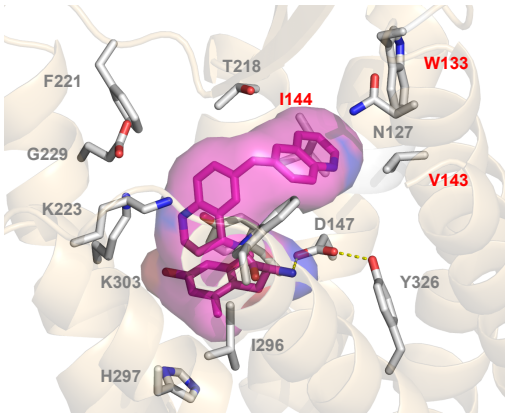
The phenyl pendant of the lead compound (**1**, Figure 11) was first replaced with a 3-pyridine (**68**, Table 2). Not only was a slight loss in binding affinity at both MOR and DOR observed, but also a significant loss in MOR efficacy and potency (Table 2). Although **68** adopts a similar conformation in the MOR active site to the lead compound, this loss in MOR potency can be attributed to loss of hydrophobic contacts in this region of the receptor binding pocket (see Figure 14). Although this analogue did not improve upon the MOR agonist/DOR antagonist profile of the previous compounds, the drastic consequences that a simple change in pendant electronics had on both binding and efficacy was intriguing. Compared to **68** and the lead compound, replacement with piperidine in analogue **69** widened the binding affinity preference for MOR over DOR

even further, although this compound behaved as a moderately potent, full agonist at MOR, improving upon the MOR efficacy profile of **68**. Expansion of the piperidine ring in **69** to azepane (**70**) resulted in improved binding at DOR and KOR. In contrast, morpholine analogue **72** displayed diminished binding affinities at DOR and KOR, and also decreased potency at MOR as compared to **69**. N-piperazinyl analogue **71** displayed a marked loss in binding affinity and efficacy at MOR. Smaller aromatic systems, including a 1,2,4-triazole substitution (**73**) and a 3-furan (**74**) were also examined. While the overall binding profile of **74** was comparable to the previous substitutions, **73** displayed a marked loss in binding affinity for MOR and KOR, and displayed no efficacy at MOR. Although **73** showed no efficacy at any of the three receptors, pan-opioid receptor antagonists are currently being developed,[82] and may be of clinical value for the treatment of drug dependence.

In the initial series[59] the 2-methylnaphthyl modification resulted in the highest MOR efficacy, but the MOR/DOR binding balance favored MOR by over 2 orders of magnitude. To see if changes in electronics to the naphthyl system could improve DOR binding while maintaining low DOR efficacy, 6-quinoline analogue **80** was synthesized. Interestingly, the binding affinity of 6-quinoline analogue **80** at all three receptors was considerably lower than the previous bicyclic analogues. This finding suggests that both an extended pendant and pendant electronic characteristics are important for maintaining binding for this series at DOR. Using previously published models of interactions of opioid ligands with the active states of the three receptors,[40,42] **80** was docked into the MOR active binding pocket. The quinoline nitrogen of **80** was found to extend much

deeper into the hydrophobic pocket of the MOR active pocket, disrupting important contacts with hydrophobic residues W133, V143, and I144 as shown in Figure 14.

Figure 14. Docking of Analogue **80** in the MOR Active Site[a]



[a.] Key hydrophobic residues are highlighted in red (W133, I144, V143).

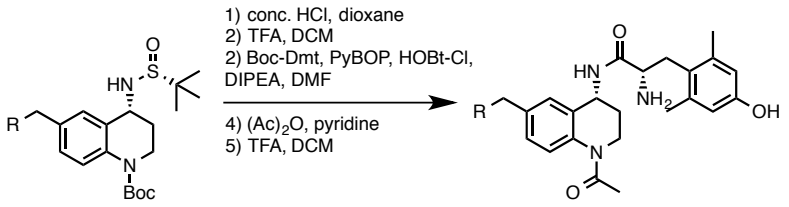
These initial data suggested that superior MOR efficacy (and low DOR efficacy) might result from a fused ring pendant in which the six-membered, non-heteroatom containing aromatic moiety is located in the most distal position from the THQ core. To test this hypothesis, analogues **75-77**, **81**, **82**, **86** and **87** were synthesized. **81** showed high efficacy at MOR, and improved DOR binding approximately tenfold as compared to the lead compound **1** and **80**. **82** and **86** both behaved as potent, full MOR agonists that improved upon the efficacy of the original lead **1**, with no efficacy at DOR. Several additional substitutions were made on the tetrahydroisoquinoline (THIQ) pendant of compound **82** (**83-85**), and small modifications (methyl and fluoro) at the 7 position were found to be well tolerated. On the other hand, MOR efficacy is reduced in the case of 3,4-

(methylenedioxy)phenyl analogue **76**. This is again consistent with the observation that distal electronegative substitutions can adversely affect MOR efficacy. Reduction of the aromatic ring of **82** to give decahydroisoquinoline analogue **87** maintained a comparable, if slightly inferior in vitro profile as compared to **82**. Interestingly, the azaspiro analogue **89** displayed good binding affinity for MOR and KOR, and features a MOR antagonist/KOR agonist profile that is unique to this series.[60]

2.3 Acetylation of the THQ Nitrogen and In Vivo Data for Selected Analogues

While **82** and **86** showed potent stimulation at MOR (while exhibiting no efficacy at DOR), binding affinities of each of these analogues at DOR left room for improvement. It was reasoned that the THQ aniline was synthetically accessible and amenable to substitutions, and would be the next logical site for diversification. Preliminary studies in related analogues suggested that N-acetylation at the THQ core improved DOR affinity without increasing DOR efficacy,[61] so we likewise explored the effect of an acetyl substituent here, giving final analogues **102-106**. These analogues were synthesized as shown in Scheme 7. Boc deprotection of the THQ nitrogen was performed prior to coupling to Boc-L-Dmt. After the amide coupling, the acetyl group was introduced by stirring the crude material in excess pyridine/acetic anhydride (1:1) overnight, followed by a second Boc deprotection and RP-HPLC purification. Binding and efficacy data for these analogues is shown in Table 3.

Scheme 7. Synthesis of Analogues **102-106**

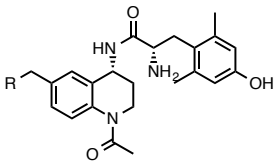


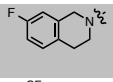
60, R = *N*-1,2,3,4-THIQ
61, R = *N*-1,2,3,4-THIQ(7-fluoro)
62, R = *N*-1,2,3,4-THIQ(8-trifluoromethyl)
64, R = *N*-isoindolinyl
65, R = *N*-(4aR,8aS)-DHIQ

102, R = *N*-1,2,3,4-THIQ
103, R = *N*-1,2,3,4-THIQ(7-fluoro)
104, R = *N*-1,2,3,4-THIQ(8-trifluoromethyl)
105, R = *N*-isoindolinyl
106, R = *N*-(4aR,8aS)-DHIQ

This modification not only improved DOR binding relative to the un-acetylated counterpart compounds (**82-84, 86, 87**) but additionally, **102** showed similarly high affinity for MOR and DOR, and interestingly for KOR as well.

Table 3. Opioid Receptor Binding Affinities and Efficacies for Analogues **102-106**[a]

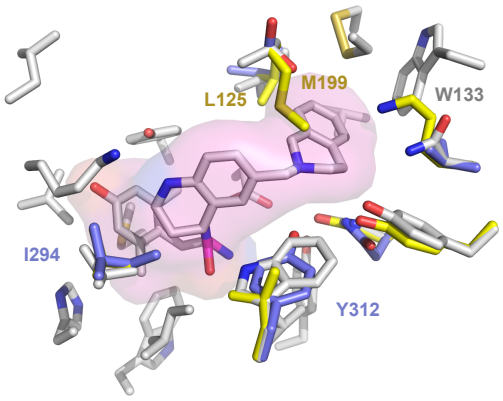


		MOR			DOR			KOR		
	R	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
102		0.19 ± 0.1	6 ± 2	91 ± 8	0.89 ± 0.2	dns	dns	0.78 ± 0.1	160 ± 36	46 ± 5
103		0.05 ± 0.01	0.54 ± 0.3	103 ± 1	0.77 ± 0.2	dns	dns	16 ± 8	234 ± 70**	34 ± 8**
104		0.16 ± 0.01	1.3 ± 0.4	55 ± 3	3.1 ± 0.9	dns	dns	59 ± 12	dns	dns
105		0.32 ± 0.09	0.9 ± 0.4	118 ± 5	2.6 ± 0.2	dns	dns	7 ± 3	400 ± 130	32 ± 1
106		0.8 ± 0.2	40 ± 20	72 ± 3	2 ± 1	dns	dns	15 ± 6	>2000	>20

[a] dns = does not stimulate. See Table 1 for further in vitro details, ** = n of 2.

An overlay of **82** docked into the active site of all three receptors is shown in Figure 15. The compound fits nicely into the MOR active site, but clashes with M199 and L125 in the DOR active site. It is interesting to note that **82** and **102**, both featuring the THIQ pendant at the 6-position, behave as partial KOR agonists (as does azaspiro analogue **89**). As shown in Figure 15, **82** fits in the KOR active site, but clashes slightly with I294 (and thus displays lower efficacy as compared to MOR). Additionally, the THIQ nitrogen of **82** is positioned to make a polar contact with Y312, a residue unique to the KOR binding pocket at this position, which may account for the high affinity of **82** and **102** for KOR. The MOR/KOR mixed efficacy profile has shown promise as a treatment for drug dependence, specifically cocaine addiction[83,84] and additional SAR on MOR/KOR agonist peptides has recently been reported.[85] Further substitutions on the THIQ pendant will have to be explored to fully optimize this profile, particularly for the purpose of improved potency at KOR.

Figure 15. Overlay of Analogue **82** in the MOR, DOR and KOR Active Sites[a]



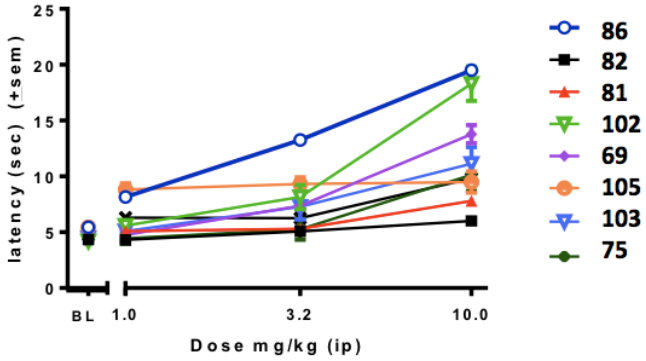
[a.] Grey, yellow and purple residues correspond to MOR, DOR and KOR respectively.

On the basis of their favorable in vitro profiles, compounds **82**, **86**, **102**, and **105** were initially chosen for in vivo studies. Effects of **82**, **86**, **102**, and **105** were compared with the lead compound **1** by two-way ANOVA with Tukey's multiple comparisons post hoc test. There was a significant interaction ($F(12,76)=8.7$, $p< 0.0001$) as well as significant main effects of dose ($F(3,76)=82.7$, $p<0.0001$) and compound ($F(4,76)=24.6$, $p<0.0001$). In the mouse warm water tail withdrawal (WWTW) assay (Figure 16), the benzyl pendant lead compound **1** and compounds **86** and **102** were fully efficacious and produced dose-dependent increases in latency to tail flick, with 3.2 ($p < 0.05$) and 10 mg/kg ($p < 0.001$) significantly increasing latency times as compared with baseline. **102** was not statistically different from the lead compound **1**, but **86** produced slightly higher tail flick latencies at 3.2 ($p < 0.001$) and 10 ($p < 0.05$) mg/kg as compared with the lead compound. It is interesting to note that **82**, which lacks only the N-acetyl group of **102**, and **105**, which is the N-acetylated counterpart to **86**, did not significantly increase tail flick latency above baseline levels up to a dose of 10 mg/kg. Compounds **69, 75, 81, 103** and **105** were also tested in the WWTW assay, and were found to be less efficacious than **1**, **86** and **102** (Figure 16). Compounds **77**, **82**, **83** and **87** exhibited no significant antinociceptive activity at 10 mg/kg in the mouse WWTW assay.

To determine the duration of action of compounds **86** and **102**, tail withdrawal latencies were measured at intervals following the administration of the 10 mg/kg dose (Figure 17). Compounds **86** and **102** showed a full antinociceptive response for 200 minutes before returning to baseline. Compared with the lead compound **1** (Figure 11), these compounds both displayed a much longer duration of action after ip injection.

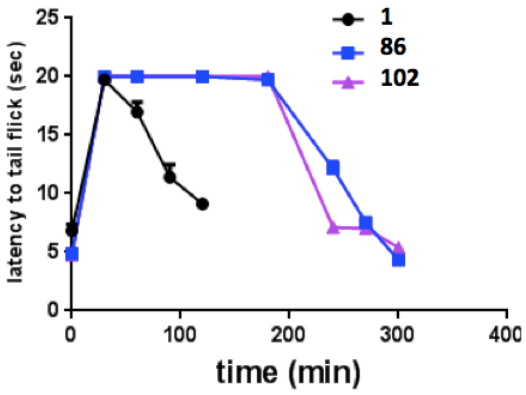
From the 6-position SAR discussed in this chapter, as well as preliminary THQ N-acetylation of several analogues, a number of trends emerge. Firstly, placement of electron rich heteroatoms on the pendant is crucial for maintaining MOR potency. Furthermore, attachment of the pendant at a basic, tertiary nitrogen resulted in a number of analogues which showed superior binding affinity and potency at MOR, with improved binding affinity at KOR. In particular, N-acetylated, THIQ analogue **102** showed equal, subnanomolar binding affinity for MOR, DOR and KOR, with a low nanomolar EC_{50} at MOR and no stimulation at DOR. **102**, in addition to isoindoline analogue **86**, were also shown to produce dose dependent antinociception in the WWTW assay, with both compounds having a total duration of action comparable to morphine, an improvement on lead peptidomimetic **1**. These peptidomimetics are therefore promising leads for dependence and tolerance studies.

Figure 16. Cumulative Antinociceptive Dose-Response Curves for Analogues **69, 75, 81, 82, 86, 102, 103** and **105** in the Mouse WWTW Assay After ip Administration (n = 3-6)[a]



[a.] Data are plotted as mean ± SEM.

Figure 17. Time Courses of Antinociceptive Response For Analogues **86** and **102** in the Mouse WWTW Assay After ip Administration of a 10 mg/kg Dose



2.4 Experimental Procedures

2.4.1 Chemistry

All reagents and solvents were obtained from commercial sources and used without additional purification. Reactions were carried out in anhydrous solvents under an inert atmosphere unless otherwise specified. Suzuki couplings were performed on a Discover S-class (CEM) microwave in a closed vessel with maximum power input of 300 W. Hydrogenations were performed on a Parr hydrogenator apparatus from Parr Instrument Company, model 3916EA, at the pressures specified. Flash column chromatography was carried out using P60 silica gel (230−400 mesh). Purification of final compounds was performed using a Waters semipreparative HPLC with a Vydac protein and peptide C18 reverse phase column, using a linear gradient of 10% solvent B (0.1% TFA in acetonitrile) in solvent A (0.1% TFA in water) to 60% solvent B in solvent A at a rate of 1% per minute. UV absorbance was monitored 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% solvent B in solvent A in 45 min, measuring UV absorbance at 230 nm. Purities of the final compounds used for testing were ≥95% as determined by HPLC and NMR. ^{1}H-NMR and ^{13}C-NMR data were obtained on either a 400 or 500 MHz Varian instrument. In chloroform-d, shifts are referenced to TMS. If TMS peak was not visible in ^{13}C-NMR spectra, shifts were referenced to the solvent peak (δ 77.16). Samples in CD_3OD are unreferenced. Mass spec analysis was performed using an Agilent 6130 LC−MS mass spectrometer in positive mode.

(1E/1L) 2-Amino-N-((S)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide. Compound **18** (0.12 g, 0.358 mmol) was dissolved in DMF (5 mL) followed by the addition of the coupling reagents PyBOP (0.19 mg, 0.36 mmol), HOBt-Cl (0.070 g, 0.36 mmol), and DIPEA (624 μL, 3.58 mmol). Boc-L-Dmt (0.15 g, 0.36 mmol) was dissolved in DMF (5 mL) and added to the reaction mixture via syringe, which was stirred for 18 h at r.t. After concentration under reduced pressure the product was re-suspended in EtOAc (30 mL) and washed with a solution of 5% citric acid in H_2O (30 mL). The aqueous layer was then extracted with EtOAc (10 mL), and the combined organic extracts were washed with brine (1 × 10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was dissolved in a 1:1 mixture of DCM and TFA (10 mL) and stirred for 3 h. The mixture was concentrated and purified by semipreparative RP-HPLC to yield the title compound in a 9:1 ratio of diastereomers. (**1E**): (MS)EI: 452.2 [M + Na], Retention Time: 25.50 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.17 (d, J = 7.9, 1H), 7.16 – 7.09 (m, 2H), 7.07 – 7.00 (m, 4H), 6.96

(dd, J = 8.3, 2.0, 1H), 6.77 (d, J = 8.3, 1H), 6.39 (s, 2H), 4.91 (t, J = 4.8, 1H), 3.83 – 3.75 (m, 3H), 3.16 (dd, J = 13.6, 11.5, 1H), 3.11 – 3.03 (m, 1H), 2.95 (dd, J = 13.7, 5.2, 1H), 2.66 – 2.54 (m, 1H), 2.17 (s, 6H), 1.84 – 1.72 (m, 1H), 1.53 – 1.43 (m, 1H). (**1L**): (MS)EI: 452.2 [M + Na], Retention Time: 28.85 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.19 – 7.11 (m, 2H), 7.10 – 7.01 (m, 3H), 6.82 (dd, J = 8.3, 1.9, 1H), 6.70 (d, J = 8.3, 1H), 6.46 (s, 3H), 4.72 (t, J = 5.1, 1H), 3.87 – 3.67 (m, 3H), 3.28 – 3.12 (m, 3H), 2.90 (dd, J = 13.8, 4.7, 1H), 2.20 (s, 6H), 2.06 – 1.97 (m, 2H).

(2) 3-bromo-N-(4-pentylphenyl)propanamide

To 4-pentylaniline (1.00 g, 6.13 mmol) and K_2CO_3 (1.69 g, 12.3 mmol) in DCM (15 mL) was added 3-bromopropionyl chloride (0.64 mL, 6.44 mmol) dropwise via syringe. The resulting cloudy mixture was stirred at r.t. overnight under an inert atmosophere, after which time the reaction was quenched with H_2O (15 mL) and diluted with DCM (10 mL). The aqueous layer was extracted with DCM (3 x 15 mL), and combined organic extracts were dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure to give a light brown solid (1.74 g, 96%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.4, 2H), 7.17 (br s, 1H), 7.13 (d, J = 8.3, 2H), 3.71 (t, J = 6.6, 2H), 2.92 (t, J = 6.6, 2H), 2.59 – 2.52 (m, 2H), 1.63 – 1.56 (m, 2H), 1.33 – 1.25 (m, 4H), 0.87 (t, J = 6.9, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.65, 139.52, 134.89, 128.91, 120.04, 40.68, 35.31, 31.16, 27.16, 22.51, 14.02.

(3) 3-bromo-N-(4-hexylphenyl)propanamide

Followed procedure for compound **2** with 4-hexylaniline (4.27 g, 24.1 mmol), K_2CO_3 (6.66 g, 48.2 mmol) and 3-bromopropionyl chloride (2.55 mL, 25.3 mmol) in DCM (70 mL), stirring for 2 h to give product as a white solid (7.16 g, 95%). ^{1}H-NMR (400 MHz,

$CDCl_3$) δ 7.40 (d, *J* = 8.0, 2H), 7.29 (br s, 1H), 7.13 (d, *J* = 8.0, 2H), 3.70 (t, *J* = 6.5, 2H), 2.92 (t, *J* = 6.6, 2H), 2.56 (t, *J* = 7.7, 2H), 1.58 (p, *J* = 7.3, 2H), 1.36 – 1.23 (m, 6H), 0.91 – 0.84 (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.93, 139.69, 135.09, 129.05, 120.30, 40.82, 35.52, 31.85, 31.59, 29.04, 27.32, 22.75, 14.23.

(4) 1-(4-pentylphenyl)azetidin-2-one

To a solution of NaOtBu (0.59 g, 6.13 mmol) in dry DMF (15 mL) was added compound **2** (1.74 g, 5.85 mmol) in DMF (20 mL) dropwise via syringe, under an inert atmosphere. The solution was stirred at r.t. overnight, after which time DMF was removed under reduced pressure. The crude residue was re-suspended in EtOAc (30 mL) and H_2O (30 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), and combined organic extracts were washed with brine, and dried with $MgSO_4$. Solvents were filtered and removed, and crude residue was purified by column chromatography (4:1 hex/EtOAc) to give product as a white solid (1.21 g, 96%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.4, 2H), 7.12 (d, J = 8.4, 2H), 3.57 (t, J = 5.9, 2.9, 2H), 3.06 (t, J = 4.4, 2H), 2.54 (t, 2H), 1.61 – 1.52 (m, 2H), 1.35 – 1.24 (m, 4H), 0.87 (t, J = 6.9, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.22, 138.56, 136.285, 128.96, 116.04, 37.96, 35.99, 35.35, 31.38, 31.24, 22.51, 14.03.

(5) 1-(4-hexylphenyl)azetidin-2-one

Followed procedure for compound **4** with compound **3** (7.16 g, 22.9 mmol), and NaOtBu (2.31 g, 24.1 mmol) in DMF (150 mL) to give product as a white solid (1.55 g, 29%). ^{1}H-NMR (400 MHz, CDCl3) δ 7.27 (d, *J* = 9.0, 2H), 7.13 (d, *J* = 8.2, 2H), 3.60 (t, *J* = 4.5, 2H), 3.09 (t, *J* = 4.5, 2H), 2.56 (t, *J* = 7.7, 2H), 1.56 (p, J = 7.5, 2H), 1.38 – 1.18 (m,

6H), 0.97 – 0.78 (m, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 164.36, 138.74, 136.48, 129.13, 116.23, 38.14, 36.18, 35.56, 31.86, 31.67, 29.03, 22.76, 14.23.

(6) 6-pentyl-2,3-dihydroquinolin-4(1H)-one

To compound **4** (0.86 g, 3.96 mmol) in DCE (40 mL) was added TfOH (1.05 mL, 11.8 mmol) carefully via syringe. The solution was allowed to stir at r.t. overnight, after which time the reaction was quenched with the addition of K_2CO_3 (4 g), and stirred for 40 min. $MgSO_4$ was added to the reaction mixture, and solids were removed via filtration. Solvents were removed under reduced pressure, and crude residue was purified by column chromatography (4:1 hex/EtOAc) to give product as a yellow oil (0.70 g, 82%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.09 (d, J = 8.4, 1H), 6.59 (d, J = 8.3, 1H), 4.59 (br s, 1H), 3.52 – 3.45 (t, 2H), 2.62 (t, J = 7.2, 2.4, 2H), 2.48 – 2.39 (t, 2H), 1.56 – 1.45 (m, 2H), 1.30 – 1.20 (m, 4H), 0.87 – 0.79 (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.18, 150.55, 135.86, 132.24, 126.32, 118.98, 116.00, 42.39, 38.22, 34.78, 31.34, 31.12, 22.50, 14.03.

(7) 6-hexyl-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **6** with compound **5** (1.54 g, 6.65 mmol) and TfOH (1.76 mL, 19.9 mmol) in DCE (75 mL), stirring at r.t. overnight to give product as a yellow solid (1.43 g, 93%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.14 (d, J = 8.3, 1H), 6.61 (d, J = 8.4, 1H), 4.28 (brs, 1H), 3.55 (t, J = 7.0, 2H), 2.68 (t, J = 6.9, 2H), 2.49 (t, J = 7.7, 2H), 1.66 – 1.47 (m, 2H), 1.37 – 1.19 (m, 6H), 0.86 (t, J = 6.3, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.18, 150.53, 136.02, 132.85, 126.81, 119.56, 116.09, 42.80, 38.53, 35.11, 31.96, 31.68, 29.12, 22.85, 14.34.

(8) (E)-6-pentyl-2,3-dihydroquinolin-4(1H)-one oxime

To compound **6** (0.86 g, 3.96 mmol) in 1:1 EtOH/H_2O (30 mL) was added NH_2OH•HCl (0.82 g, 11.9 mmol) and NaOAc•$3H_2O$ (0.97 g, 11.9 mmol). The solution was stirred at reflux overnight, after which time EtOH was removed under reduced pressure. EtOAc was added, and the aqueous layer was extracted with EtOAc (2 x 15 mL). Combined organic layers were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure. Crude residue was purified by column chromatography (2:1 hex/EtOAc) to give product as a light yellow solid (0.64 g, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 6.96 (dd, J = 8.2, 1.9, 1H), 6.55 (d, J = 8.2, 1H), 3.30 (t J = 6.5, 2H), 2.91 (t, J = 6.8, 2.2, 2H), 2.52 – 2.44 (m, 2H), 1.61 -1.51 (t, 2H), 1.35 – 1.24 (m, 4H), 0.87 (t, J = 6.9, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 152.60, 145.00, 133.16, 130.89, 123.66, 116.64, 115.77, 40.76, 35.12, 31.45, 31.31, 23.52, 22.53, 14.02.

(9) (E)-6-hexyl-2,3-dihydroquinolin-4(1H)-one oxime

Followed procedure for compound **8** with compound **7** (1.40 g, 6.06 mmol), NH_2OH•HCl (0.51 g, 7.27 mmol) and NaOAc•$3H_2O$ (0.60 g, 7.27 mmol) in 1:1 EtOH/H_2O (90 mL), stirring at reflux for 40 h, to give product as a yellow solid (0.92 g, 62%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 2.0, 1H), 6.97 (dd, *J* = 8.2, 2.0, 1H), 6.55 (d, *J* = 8.2, 1H), 3.30 (t, *J* = 6.5, 2H), 2.93 (t, *J* = 6.5, 2H), 2.48 (t, *J* = 7.6, 2H), 1.56 (p, J = 7.8, 2H), 1.37 – 1.22 (m, 6H), 0.90 – 0.80 (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 152.66, 145.28, 133.27, 131.07, 123.79, 116.75, 115.93, 40.93, 35.32, 31.90, 31.75, 29.10, 23.81, 22.76, 14.26.

(10) 6-pentyl-1,2,3,4-tetrahydroquinolin-4-amine

10% Pd/C (~0.2 g) was added to a hydrogenation vessel, followed by compound **8** (0.64 g, 2.75 mmol) in MeOH (20 mL). Glacial AcOH (1 mL) was then added. The mixture

was allowed to shake under 40 psi H_2 at r.t. overnight, after which time the reaction mixture was filtered through a pad of celite, washed with MeOH, and concentrated under reduced pressure. 2M NaOH (20 mL) and DCM (20 mL) were added to the crude residue, and the aqueous layer was washed with DCM (2 x 15 mL). Combined organic extracts were dried with $MgSO_4$, and solvents were filtered and removed under reduced pressure. Crude residue was purified by column chromatography (9:1 DCM/MeOH) to give product as a yellow oil (0.42 g, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 1.6, 1H), 6.84 (dd, J = 8.1, 1.9, 1H), 6.43 (d, J = 8.1, 1H), 3.96 (t, J = 4.9, 1H), 3.38 – 3.29 (m, 1H), 3.29 – 3.21 (m, 1H), 2.51 – 2.43 (t, 2H), 2.04 – 1.97 (m, 1H), 1.79 (ddd, J = 13.9, 8.7, 5.4, 1H), 1.56 (dt, J = 15.2, 7.5, 2H), 1.35 – 1.27 (m, 4H), 0.88 (t, J = 6.9, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 141.94, 131.71, 128.57, 127.86, 125.46, 114.47, 46.89, 37.79, 35.13, 31.86, 31.60, 22.58, 14.07.

(11) 6-hexyl-1,2,3,4-tetrahydroquinolin-4-amine

Followed procedure for compound **10** with compound **9** (0.59 g, 2.38 mmol), shaking at r.t. under 40 psi H_2 overnight to give product as a white solid (0.32 g, 57%). ^{1}H-NMR (400 MHz, CD_3OD) δ 6.97 (d, J = 1.6, 1H), 6.79 (dd, J = 8.2, 1.9, 1H), 6.46 (d, J = 8.1, 1H), 3.91 (t, J = 4.8, 1H), 3.32 – 3.11 (m, 2H), 2.46 (t, J = 7.6, 2H), 2.00 – 1.91 (m, 1H), 1.85 – 1.73 (m, 1H), 1.56 – 1.51 (m, 2H), 1.30 (s, 6H), 0.87 (t, J = 7.4, 3H); ^{13}C-NMR (101 MHz, CD_3OD) δ 142.48, 131.11, 128.30, 127.91, 123.27, 114.80, 46.50, 37.04, 34.97, 31.77, 31.67, 30.13, 28.83, 22.45, 13.38.

(12E) (2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-(6-pentyl-1,2,3,4-tetrahydroquinolin-4-yl)propanamide

To compound **10** (0.094 g, 0. 43 mmol), PyBOP (0.22 g, 0.43 mmol), HOBt-Cl (0.073 g, 0.43 mmol) and Boc-L-Dmt (0.18 g, 0.43 mmol) was added DMF (10 mL) and DIPEA (0.75 mL, 4.31 mmol) via syringe. The mixture was allowed to stir overnight under an inert atmosphere, after which time DMF was removed under reduced pressure. The crude residue was re-suspended in EtOAc and 5% citric acid. The organic layer was washed with 5% citric acid (2 x 20 mL) and brine (1 x 15 mL). The organic layer was dried with $MgSO_4$, and solvents were filtered and removed under reduced pressure. A solution of 1:1 DCM/TFA was added (10 mL) and was allowed to stir for 1 h. DCM/TFA were removed under reduced pressure, and crude residue was purified by RP-HPLC and lyophilized to give a white powder. (MS)EI: 410.3 [M+H], Retention Time: 27.80 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.03 (m, J = 24.6, 9.0, 2H), 6.86 (d, J = 8.0, 1H), 6.47 (s, 2H), 5.02 (d, J = 4.2, 1H), 3.88 (dd, J = 11.5, 5.1, 1H), 3.23 (d, J = 11.9, 1H), 3.20 – 3.12 (m, 1H), 3.04 (dd, J = 13.6, 5.0, 1H), 2.69 (dd, J = 22.9, 12.0, 1H), 2.50 (t, J = 7.7, 2H), 2.26 (s, 6H), 1.94 – 1.80 (m, 1H), 1.58 – 1.48 (m, 3H), 1.29 (m, J = 12.5, 6.4, 4H), 0.87 (t, J = 6.9, 3H).

(13E/13L) (2S)-2-amino-N-(6-hexyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

To compound **11** (0.086 g, 0.37 mmol) in DMF (5 mL) was added PyBOP (0.19 g, 0.37 mmol) and HOBt-Cl (0.063 g, 0.37 mmol), and placed under an inert atmosphere. DIPEA (0.65 mL, 3.71 mmol) was then added via syringe, followed by Boc-L-Dmt (0.17 g, 0.41 mmol) in DMF (3 mL). The solution was allowed to stir at r.t. for 24 h, after which time DMF was removed under reduced pressure. Crude residue was re-dissolved in EtOAc. 5% citric acid was added, and extracted with EtOAc. Combined organic extracts were

washed with brine and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure. A solution of 1:1 DCM/TFA was added (10 mL) and was allowed to stir for 1 h. DCM/TFA were removed under reduced pressure, and crude residue was purified by RP-HPLC to give the early and late diastereomers, and lyophilized to give a white powder. (**13E**): (MS)EI: 446.3 (M+Na), Retention Time: 32.30 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 6.97 (d, J = 8.2, 2H), 6.70 (d, J = 7.9, 1H), 6.47 (s, 2H), 4.97 (t, J = 4.6, 1H), 3.85 (dd, J = 11.6, 5.1, 1H), 3.26 – 3.18 (m, 1H), 3.12 – 3.05 (m, 1H), 3.01 (dd, J = 13.7, 5.1, 1H), 2.60 (t, J = 10.5, 1H), 2.46 (t, J = 7.6, 1H), 2.26 (s, 6H), 1.87 – 1.75 (m, 1H), 1.57 – 1.44 (m, 2H), 1.27 (s, 6H), 0.87 (t, J = 6.7, 3H); ^{13}C-NMR (400 MHz, CD_3OD) δ 167.50, 155.97, 138.59, 129.68, 128.75, 121.84, 117.75, 114.96, 51.93, 44.30, 37.57, 34.78, 31.47, 31.45, 30.44, 28.67, 27.26, 22.26, 19.02, 12.97. (**13L**): (MS)EI: 446.3 (M+Na), Retention Time: 35.03 min.

(14) 6-benzyl-2,3-dihydroquinolin-4(1H)-one

Compound **176** (3.90 g, 16.4 mmol) was dissolved in DCE (100 mL), and placed under an inert atmosphere. TfOH (4.36 mL, 49.3 mmol) was added via syringe. The resulting dark orange solution was stirred at r.t. for 18 h, after which time it was quenched with the addition of K_2CO_3 (15 g) and H_2O (0.8 mL), and was allowed to stir for 1 h. The reaction mixture was filtered through a plug of $MgSO_4$, and solvents were removed under reduced pressure to give product as a yellow oil (3.26 g, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 1.5, 1H), 7.29 – 7.23 (m, 2H), 7.20 – 7.14 (m, 3H), 7.11 (dd, J = 8.4, 2.2, 1H), 6.59 (d, J = 8.4, 1H), 4.31 (br s, 1H), 3.86 (s, 2H), 3.54 (t, J = 7.0, 2H), 2.68 (t, J = 6.8, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.72, 150.54, 141.19, 136.03, 130.74, 128.70, 128.44, 127.24, 126.02, 119.23, 116.18, 42.39, 40.93, 38.15.

(15) tert-butyl 6-benzyl-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

To compound **14** (2.57 g, 10.8 mmol) in DCM (70 mL), was added $(Boc)_2O$ (3.06 g, 14.1 mmol), DMAP (0.13 g, 1.08 mmol), and DIPEA (2.45 mL, 14.1 mmol). The mixture was stirred at reflux for 35 h, after which time it was quenched with 1M HCl (50 mL). The aqueous layer was extracted with DCM, and combined organic extracts were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica gel (1:2 EtOAc/hex) to yield product as a white solid (2.79 g, 77%). ^{1}H-NMR (400 MHz, $CDCl_3$) 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), 1.53 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.23, 152.74, 142.37, 140.39, 136.85, 134.61, 128.80, 128.54, 127.14, 126.26, 124.78, 123.81, 82.07, 44.26, 41.14, 38.97, 28.27.

(16) tert-butyl (R)-6-benzyl-4-hydroxy-3,4-dihydroquinoline-1(2H)-carboxylate

Compound **15** (2.69 g, 7.97 mmol) in THF (30 mL) was stirred at r.t. with 4 Å molecular sieves (1.0 g) for 1 h. This solution was transferred to the (S)-(−)-2-methyl-CBS-oxazaborolidine catalyst via cannula, and the reaction vessel was cooled to −20 °C. $BH_3 \cdot Me_2S$ (3.99 mL, 7.97 mmol) was then added via syringe over a period of 10 min. The mixture was stirred at −20 °C for 6 h. After the addition of MeOH (7 mL) the mixture was allowed to reach r.t. The mixture was partitioned between 1 M HCl (10 mL) and Et_2O (30 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated, and the residue was chromatographed on silica gel (1:2 EtOAc/hex) to yield the title compound as a colorless oil (2.19 g, 81%, 80% ee). ^{1}H-NMR (400 MHz,

$CDCl_3$) δ 7.72 (d, J = 8.5, 1H), 7.30−7.14 (m, 6H), 7.08 (dd, J = 8.16, 1.6, 1H), 4.53 (t, J = 4.8, 1H), 3.92 (s, 2H), 3.53 (ddd, J = 13.1, 9.5, 3.8, 1H), 3.40 (s, 1H), 1.98−1.90 (m, 1H), 1.89−1.79 (m, 1H), 1.56 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.73, 141.15, 136.11, 135.71, 131.04, 128.92, 128.49, 128.25, 126.10, 123.57, 81.08, 65.47, 41.33, 40.74, 32.13, 28.43. Enantioselectivity determined by HPLC (Chiracel OD-RH column, 45% acetonitrile/water, 230 nm, 25 °C): t_{major} = 21.3 min, t_{minor} = 25.2 min.

(17) (S)-tert-Butyl 6-Benzyl-4-(1,3-dioxoisoindolin-2-yl)-3,4-dihy- droquinoline-1(2H)-carboxylate. Compound **16** (2.12 g, 6.27 mmol) was dissolved in THF (25 mL) and added via syringe to a mixture of phthalimide (1.38 g, 9.40 mmol) and PPh_3 (2.47 g, 9.40 mmol). The reaction mixture was allowed to stir for 10 min and then cooled to 0 °C. Once cooled, a solution of DIAD (2.48 mL, 12.5 mmol) in THF (10 mL) was added to the reaction mixture over a period of 30 min. The mixture was allowed to reach room temperature and was then stirred for 24 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in Et_2O (30 mL). A solution of 2M NaOH (15 mL) was added, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure, and the residue was chromatographed on silica gel (2:3 EtOAc/hexane) to yield the title compound as a colorless oil (1.00 g, 35%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79− 7.77 (m, 2H), 7.72−7.60 (m, 3H), 7.27−7.08 (m, 2H), 7.08−6.95 (m, 4H), 6.73 (s, 1H), 5.49 (t, J = 7.8, 1H), 4.16 (dt, J = 10.0, 4.4, 1H), 3.79 (s, 2H), 3.70 (ddd, J = 13.1, 9.8, 3.5, 1H), 2.56−2.44 (m, 1H), 2.26−2.16 (m, 1H), 1.54 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.75, 153.57, 140.72, 137.40, 136.31, 134.14,

131.80, 128.78, 128.27, 127.87, 126.79, 126.40, 125.93, 124.50, 123.36, 80.98, 46.48, 43.20, 41.01, 28.51, 28.40.

(18) (S)-tert-Butyl 4-Amino-6-benzyl-3,4-dihydroquinoline-1(2H)- carboxylate. Compound **17** (0.93 g, 1.99 mmol) was dissolved in absolute EtOH (20 mL) followed by the addition of hydrazine monohydrate (460 μL, 5.97 mmol). The reaction mixture was stirred at room temperature for 48 h, during which time a white precipitate formed. The mixture was filtered, and the precipitate was washed with EtOH (20 mL) and the filtrate concentrated under reduced pressure. The residue was partitioned between EtOAc (20 mL) and H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). Combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure, and the residue was chromatographed on silica gel (1:9 MeOH/DCM) to yield the title compound as a colorless oil (0.24 g, 60%, 78−80% ee). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.5, 1H), 7.31−7.22 (m, 2H), 7.21−7.12 (m, 4H), 7.01 (dd, J = 8.5, 1.7, 1H), 3.92 (s, 2H), 3.90 (t, J = 5.8, 1H), 3.86−3.79 (m, 1H), 3.71−3.63 (m, 1H), 2.14−2.02 (m, 1H), 1.77−1.65 (m, 1H), 1.51 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.73, 141.13, 136.11, 135.56, 133.26, 128.87, 128.42, 127.44, 127.16, 126.02, 123.79, 80.89, 47.71, 41.57, 41.34, 33.21, 28.38. Enantioselectivity determined by HPLC (Chiracel OD- RH column, 34% acetonitrile/water, 1.0 mL/min, 230 nm, 25 °C): tmajor = 4.79 min, tminor = 8.87 min.

(21) 6-methyl-2,3-dihydroquinolin-4(1H)-one

p-toluidine (1.09 g, 10.2 mmol) and K_2CO_3 (2.8 g, 20.4 mmol) were added to a dry round bottomed flask, which was placed under an inert atmosphere. DCM (30 mL) was then added via syringe. After dissolution of p-toluidine, 3-bromopropionyl chloride (1.08 mL,

10.7 mmol) was added dropwise via syringe. The resulting cloudy mixture was stirred at r.t. for 1 h, after which time the reaction mixture was transferred to a separatory funnel and washed with sat. $NaHCO_3$ (3x) and brine. Combined organic layers were dried with $MgSO_4$. Solvents were filtered and removed to give a white solid which was dried under vacuum and used without further purification. The white solid was dissolved in DMF (20 mL) and added via syringe to NaOtBu (0.89 g, 9.2 mmol) in DMF (20 mL). The mixture was stirred at r.t. under an inert atmosphere for 3 h, after which time DMF was removed under reduced pressure. EtOAc (20 mL) and H_2O (20 mL) were added, and the aqueous layer was extracted with EtOAc (3x). Combined organic layers were dried with $MgSO_4$. Solvents were filtered and removed to give a pale orange solid. The solid was immediately dissolved in DCE (50 mL). TfOH (2.33 mL, 26.4 mmol) was then added carefully via syringe. The orange mixture was stirred at r.t. for 2 h, after which time the mixture was quenched with the addition of H_2O (40 mL), followed by slow addition of K_2CO_3 until the solution became a bright yellow color. Aqueous layer was extracted with DCM (3x) and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure, and the crude residue was purified by column chromatography (3:2 hex/EtOAc) to give pure product as a yellow solid (1.06 g, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.09 (dd, J = 8.4, 2.2, 1H), 6.62 (d, J = 8.3, 1H), 4.82 (br s, 1H), 3.50 (t, J = 7.0, 2H), 2.64 (t, J = 7.0, 2H), 2.20 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.05, 150.38, 136.30, 126.60, 126.57, 118.68, 115.95, 42.16, 38.01, 20.06.

(22) tert-butyl 6-methyl-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate. Compound **21** (1.06 g, 6.56 mmol) was dissolved in DCM (30 mL). DIPEA (2.3 mL, 13.1 mmol) was then added via syringe, followed by $(Boc)_2O$ (2.9 g, 13.1 mmol) and DMAP (0.08 g,

0.66 mmol). The yellow mixture was refluxed at 60°C for 16 h, after which time it was quenched with 1 M HCl (20 mL). The aqueous layer was extracted with DCM (3x). Combined organic extracts were dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure, and crude residue was purified by column chromatography (2:1 hex/EtOAc) to give product as a white solid (1.4 g, 83%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.65 (d, J = 8.5, 1H), 7.30 (d, J = 8.6, 1H), 4.12 (t, J = 6.3, 2H), 2.73 (t, J = 6.3, 2H), 2.32 (s, 3H), 1.55 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.15, 152.67, 141.74, 134.74, 133.37, 127.01, 124.61, 123.55, 81.78, 44.23, 38.93, 28.21, 20.51.

(23) tert-butyl 6-(bromomethyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Compound **22** (0.54 g, 2.05 mmol), NBS (0.37 g, 2.09 mmol) and benzoyl peroxide (25 mg) were added to a dry round bottomed flask and placed under an inert atmosphere. CCl_4 (25 mL, degassed) was then added via syringe. The mixture was refluxed at 70°C under an infrared lamp for 3 h, after which time solids were removed by filtration, and solvent was removed under reduced pressure. The resulting crude residue was purified by column chromatography (10:1 petroleum ether/EtOAc) to give product as a white solid (0.27 g, 39%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 2.3, 1H), 7.80 (d, J = 8.7, 1H), 7.53 (dd, J = 8.7, 2.4, 1H), 4.48 (s, 2H), 4.15 (t, J = 6.4, 2H), 2.77 (t, J = 6.4, 2H), 1.56 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.66, 152.68, 144.20, 134.70, 133.40, 127.75, 124.87, 124.30, 82.64, 44.36, 38.90, 32.49, 28.40.

(24) tert-butyl 4-oxo-6-(pyridin-3-ylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Compound **23** (0.082 g, 0.24 mmol), 3-pyridinylboronic acid (0.044 g, 0.26 mmol), K_2CO_3 (0.10 g, 0.72 mmol) and $Pd(dppf)Cl_2$ (0.018 g, 0.024 mmol) were added to a

microwave vessel and placed under an inert atmosphere. 3:1 acetone/H_2O (degassed and saturated with Argon gas) was then added via syringe. The mixture was placed in a microwave reactor, and stirred at 100°C for 30 min, after which time solvents were removed under reduced pressure. The crude residue was purified by column chromatography (100% EtOAc) to give product as a colorless oil (0.064 g, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 1.5, 1H), 8.47 (dd, J = 4.8, 1.6, 1H), 7.83 (d, J = 1.8, 1H), 7.72 (d, J = 8.6, 1H), 7.46 (dt, J = 7.9, 2.0, 1H), 7.30 (dd, J = 8.6, 2.3, 1H), 7.21 (ddd, J = 7.8, 4.8, 0.9, 1H), 4.14 (t, J = 6.4, 2H), 3.96 (s, 2H), 2.75 (t, J = 6.4, 2H), 1.55 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.18, 152.79, 150.18, 147.99, 142.84, 136.35, 135.93, 135.56, 134.55, 127.23, 124.98, 124.21, 123.60, 82.33, 44.37, 39.04, 38.37, 28.39.

(25) tert-butyl 4-oxo-6-(piperidin-1-ylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

To a stirring solution of **23** (0.087 g, 0.26 mmol) and K_2CO_3 (0.042 g, 0.31 mmol) in DMF (10 mL) was added piperidine (0.030 mL, 0.31 mmol) dropwise via syringe. The mixture was allowed to stir under an inert atmosphere for 16 h, after which time DMF was removed under reduced pressure. The crude reside was re-dissolved in EtOAc, and 2M NaOH was added. The aqueous layer was extracted with EtOAc (3x) and combined organic extracts were dried with $MgSO_4$. Solvents were filtered and removed to give a yellow oil which was isolated without further purification (0.080 g, 91% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 2.1, 1H), 7.72 (d, J = 8.6, 1H), 7.51 (dd, J = 8.6, 2.2, 1H), 4.15 (t, J = 6.5, 2H), 3.45 (s, 2H), 2.76 (t, J = 6.5, 2H), 2.37 (br s, 4H), 1.60 – 1.52 (m, 12H), 1.45 – 1.38 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.41, 152.87, 143.13,

135.08, 134.40, 127.76, 124.55, 123.61, 82.20, 62.87, 54.43, 44.42, 39.11, 28.41, 25.97, 24.39.

(26) tert-butyl 6-(azepan-1-ylmethyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **25** with **23** (0.100 g, 0.29 mmol) and azepane (0.040 mL, 0.35 mmol) to give product as a slightly yellow oil (0.101 g, 96%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 2.2, 1H), 7.73 (d, J = 8.6, 1H), 7.57 (dd, J = 8.6, 2.2, 1H), 4.15 (t, J = 6.4, 2H), 3.64 (s, 2H), 2.76 (t, J = 6.4, 2H), 2.66 – 2.61 (m, 4H), 1.69 – 1.58 (m, 8H), 1.56 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.37, 152.86, 143.12, 135.37, 134.79, 127.32, 124.58, 123.67, 82.18, 61.72, 55.48, 44.41, 39.09, 28.39, 28.02, 27.07.

(27) tert-butyl 6-((4-(tert-butoxycarbonyl)piperazin-1-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **25** with **23** (0.095 g, 0.28 mmol) and N-Boc piperazine (0.062 g, 0.34 mmol) to give product as a white solid (0.090 g, 73%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 2.1, 1H), 7.72 (d, J = 8.6, 1H), 7.48 (d, J = 8.0, 1H), 4.12 (t, J = 6.3, 2H), 3.47 (s, 2H), 3.39 (t, J = 5.0, 4H), 2.73 (t, J = 6.3, 2H), 2.36 (t, J = 4.9, 4H), 1.52 (s, 9H), 1.42 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.08, 154.66, 152.67, 143.29, 134.77, 133.44, 127.60, 124.52, 123.63, 82.15, 79.56, 61.93, 52.67, 44.27, 43.48, 38.91, 28.38, 28.26.

(28) tert-butyl 6-(morpholinomethyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **15** with **96** (0.07 g, 0.272 mmol) to give product as a colorless oil (0.056 g, 60%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 2.2, 1H), 7.74 (d,

J = 8.6, 1H), 7.51 (dd, J = 8.7, 2.2, 1H), 4.13 (t, J = 6.3, 2H), 3.69 (t, J = 4.6, 4H), 3.48 (s, 2H), 2.74 (t, J = 6.4, 2H), 2.44 (t, J = 4.4, 4H), 1.54 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.13, 152.69, 143.32, 134.87, 133.15, 127.71, 124.53, 123.65, 82.18, 66.80, 62.32, 53.39, 44.29, 38.93, 28.27.

(29) tert-butyl 6-((1H-1,2,4-triazol-1-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **15** with **97** (0.10 g, 0.438 mmol) to give product as a colorless oil (0.11 g, 76%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.97 (s, 1H), 7.93 (d, J = 2.2, 1H), 7.82 (d, J = 8.7, 1H), 7.41 (dd, J = 8.7, 2.3, 1H), 5.33 (s, 2H), 4.16 (t, J = 6.0, 2H), 2.77 (t, J = 6.4, 2H), 1.55 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.62, 152.57, 152.41, 144.44, 143.13, 133.54, 130.14, 126.98, 124.91, 124.49, 82.66, 52.77, 44.26, 38.82, 28.32.

(30) tert-butyl 6-(furan-3-ylmethyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **24** with **23** (0.094 g, 0.28 mmol) and 3-furanylboronic acid (0.046 g, 0.41 mmol) to give product as a colorless oil (0.07 g, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 2.3, 1H), 7.70 (d, J = 8.6, 1H), 7.38 – 7.31 (m, 2H), 7.22 (s, 1H), 6.22 (s, 1H), 4.14 (t, J = 6.3, 2H), 3.75 (s, 2H), 2.75 (t, J = 6.3, 2H), 1.55 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.35, 152.86, 143.33, 142.56, 139.69, 136.20, 134.41, 126.96, 124.90, 123.93, 123.74, 111.18, 82.21, 44.39, 39.09, 30.50, 28.40.

(31) tert-butyl 6-(benzofuran-2-ylmethyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **24** with **23** (0.11 g, 0.33 mmol) and 2-benzofuranyl boronic acid MIDA ester (0.13 g, 0.49 mmol) to give product as a colorless oil (0.088 g,

72%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 2.3, 1H), 7.75 (d, J = 8.9, 1H), 7.50 – 7.42 (m, 2H), 7.39 (d, J = 7.7, 1H), 7.24 – 7.13 (m, 2H), 6.41 (s, 1H), 4.14 (t, J = 6.2, 2H), 4.08 (s, 2H), 2.76 (t, J = 6.2, 2H), 1.56 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.06, 156.92, 154.98, 152.72, 142.93, 134.55, 132.95, 128.68, 127.37, 124.89, 123.99, 123.56, 122.59, 120.49, 110.91, 103.56, 82.20, 44.27, 38.93, 34.19, 28.30.

(32) tert-butyl 6-(benzo[d][1,3]dioxol-5-ylmethyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **24** with **23** (0.13 g, 0.37 mmol) and 3,4-(methylenedioxy)phenylboronic acid (0.091 g, 0.55 mmol) to give product as a colorless oil (0.12 g, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 2.3, 1H), 7.68 (d, J = 8.6, 1H), 7.30 (dd, J = 8.6, 2.2, 1H), 6.72 (d, J = 7.7, 1H), 6.64 (d, J = 8.1, 2H), 5.90 (s, 2H), 4.13 (t, J = 6.3, 2H), 3.86 (s, 2H), 2.74 (t, J = 6.3, 2H), 1.55 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.32, 152.81, 147.84, 146.09, 142.47, 137.10, 134.59, 134.30, 127.11, 124.86, 123.97, 121.79, 109.30, 108.31, 100.94, 82.16, 44.34, 40.86, 39.06, 28.37.

(33) tert-butyl 6-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **24** with **23** (0.11 g, 0.31 mmol) and (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)boronic acid (0.084 g, 0.47 mmol) to give product as a colorless oil (0.078 g, 63%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 2.2, 1H), 7.67 (d, J = 8.6, 1H), 7.30 (dd, J = 8.6, 2.3, 1H), 6.76 (d, J = 8.0, 1H), 6.67 – 6.62 (m, 2H), 4.21 (s, 4H), 4.13 (t, J = 6.3, 2H), 3.84 (s, 2H), 2.74 (t, J = 6.3, 2H), 1.54 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.34, 152.86, 143.53, 142.45, 142.12, 137.18, 134.68, 133.86,

127.16, 124.90, 123.93, 121.81, 117.60, 117.34, 82.16, 64.47, 64.39, 44.38, 40.50, 39.10, 28.40.

(34) tert-butyl 6-(2,6-dichlorobenzyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **24** with **23** (0.11 g, 0.34 mmol) and 2,6-dichlorophenylboronic acid (0.096 g, 0.50 mmol) to give product as a colorless oil (0.12 g, 86%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 2.3, 1H), 7.67 (d, J = 8.7, 1H), 7.32 (d, J = 8.2, 2H), 7.27 (t, J = 8.2, 1H), 7.13 (dd, J = 8.6, 7.7, 1H), 4.30 (s, 2H), 4.12 (t, J = 8.0, 2H), 2.73 (t, J = 8.0, 2H), 1.54 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.16, 152.82, 142.54, 136.06, 136.05, 134.08, 133.92, 128.51, 126.93, 126.91, 124.80, 123.78, 82.15, 44.31, 39.06, 35.92, 28.37.

(35) tert-butyl 6-benzhydryl-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **15** with **98** (0.22 g, 0.70 mmol) to give product as a colorless oil (0.11 g, 37%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 2.2, 1H), 7.71 (d, J = 8.7, 1H), 7.31 – 7.24 (m, 5H), 7.24 – 7.18 (m, 2H), 7.10 (d, J = 7.2, 4H), 5.53 (s, 1H), 4.13 (t, J = 6.2, 2H), 2.73 (t, J = 6.2, 2H), 1.54 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.10, 152.75, 143.15, 142.50, 139.64, 135.03, 129.29, 128.44, 127.79, 126.52, 124.66, 123.57, 82.17, 56.17, 44.25, 38.97, 28.30.

(36) tert-butyl 4-oxo-6-(quinolin-6-ylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **24** with **23** (0.093 g, 0.27 mmol), and 6-quinolineboronic pinacol ester (0.105 g, 0.41 mmol) to give product as a colorless oil (0.105 g, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.86 (dd, J = 4.3, 1.7, 1H), 8.08 (d, J = 8.3, 1H), 8.02 (d, J = 8.6, 1H), 7.89 (d, J = 2.2, 1H), 7.73 (d, J = 8.6, 1H), 7.59 (s, 1H),

7.54 (dd, J = 8.7, 2.0, 1H), 7.40 – 7.33 (m, 2H), 4.17 – 4.12 (m, 4H), 2.76 (t, J = 6.4, 2H), 1.54 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.29, 152.78, 150.04, 147.26, 142.69, 138.92, 136.18, 135.78, 134.76, 131.07, 129.75, 128.39, 127.40, 126.92, 124.93, 124.04, 121.31, 82.25, 44.33, 41.15, 39.02, 28.35.

(37) tert-butyl 4-oxo-6-(quinolin-3-ylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **24** with **23** (0.093 g, 0.27 mmol) and 3-quinolineboronic acid (0.071 g, 0.41 mmol) to give product as a colorless oil (0.094 g, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.80 (d, J = 2.2, 1H), 8.08 (d, J = 8.5, 1H), 7.89 (s, 2H), 7.77 – 7.71 (m, 2H), 7.67 (ddd, J = 8.5, 6.9, 1.4, 1H), 7.52 (td, J = 7.4, 6.8, 1.1, 1H), 7.36 (dd, J = 8.6, 2.3, 1H), 4.18 – 4.11 (m, 4H), 2.76 (t, J = 6.0, 2H), 1.55 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.21, 152.77, 151.81, 146.89, 142.87, 135.41, 135.09, 134.63, 133.28, 129.14, 128.13, 127.56, 127.41, 127.37, 126.92, 125.01, 124.23, 82.34, 44.33, 39.02, 38.55, 28.37.

(38) tert-butyl 6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **25** with **23** (0.15 g, 0.44 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.066 mL, 0.53 mmol) to give product as a slightly yellow oil (0.16 g, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 2.1, 1H), 7.75 (d, J = 8.6, 1H), 7.59 (dd, J = 8.6, 2.2, 1H), 7.13 – 7.05 (m, 3H), 6.99 – 6.92 (m, 1H), 4.16 (t, J = 6.3, 2H), 3.66 (s, 2H), 3.62 (s, 2H), 2.89 (t, J = 5.5, 2H), 2.79 – 2.70 (m, 4H), 1.56 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.32, 152.86, 143.33, 134.82, 134.38, 134.30, 128.78,

127.63, 127.57, 126.65, 126.21, 125.68, 124.65, 123.83, 82.26, 61.92, 56.11, 50.69, 44.43, 39.09, 29.24, 28.41.

(39) tert-butyl 6-((7-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **25** with **23** (0.15 g, 0.44 mmol) and 7-fluoro-1,2,3,4-tetrahydroisoquinoline (0.10 g, 0.53 mmol) to give product as a yellow oil (0.21 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H), 2.77 (m, 4H), 2.90 (br. s, 2H), 3.92 (br. s, 2H), 3.94 (br. s, 2H), 4.09-4.19 (m, 2H), 6.82 (m, 1H), 6.99 (m, 1H), 7.13 (m, 2H), 7.52 (br. s, 1H), 7.92 (m, 1H).

(40) tert-butyl 4-oxo-6-((8-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **25** with **23** and 8-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline to give product as a yellow oil (61%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H), 2.71 (br. s, 2H), 2.78 (t, J = 5.6 Hz, 2H), 2.93 (br. s, 2H), 3.71 (br. s, 2H), 3.85 (br. s, 2H), 4.17 (t, J = 7.2 Hz, 2H), 7.23 (d, J = 7.6 Hz,1H), 7.27 (d, J = 3.2 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.61 (br. s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.95 (s, 1H).

(41) tert-butyl 6-((7-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **25** with **23** (0.11 g, 0.34 mmol) and 6-methyl-1,2,3,4-tetrahydroisoquinoline HCl salt (0.074 g, 0.40 mmol) to give product as a slightly yellow oil (0.092 g, 68%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 2.1, 1H), 7.74 (d, J = 8.6, 1H), 7.59 (dd, J = 8.6, 2.2, 1H), 7.00 – 6.91 (m, 2H), 6.78 (s, 1H), 4.16 (t, J = 6.5, 2H), 3.65 (s, 2H), 3.57 (s, 2H), 2.84 (t, J = 5.9, 2H), 2.76 (t, J = 6.5, 2H), 2.72 (t, J = 5.9, 2H),

2.26 (s, 3H), 1.56 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.33, 152.87, 143.30, 135.11, 134.88, 134.64, 134.41, 131.28, 128.64, 127.58, 127.16, 127.07, 124.64, 123.81, 82.25, 61.89, 56.08, 50.88, 44.43, 39.10, 28.81, 28.41, 21.08.

(42) tert-butyl 6-(isoindolin-2-ylmethyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **25** with **23** (0.12 g, 0.36 mmol) and isoindoline (0.051 mL, 0.43 mmol) to give product as a slightly brown oil (0.10 g, 77%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 2.2, 1H), 7.76 (d, J = 8.6, 1H), 7.61 (dd, J = 8.6, 2.2, 1H), 7.17 (s, 4H), 4.16 (t, J = 6.4, 2H), 3.92 (s, 4H), 3.89 (s, 2H), 2.77 (t, J = 6.4, 2H), 1.56 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.34, 152.83, 143.30, 140.10, 134.98, 134.69, 127.17, 126.80, 124.70, 123.96, 122.40, 82.26, 59.36, 58.96, 44.39, 39.07, 28.39.

(43) tert-butyl 6-(((4aR,8aS)-octahydroisoquinolin-2(1H)-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **25** with **23** (0.11 g, 0.34 mmol) and (4aR, 8aS)-decahydroisoquinoline (0.056 g, 0.40 mmol) to give product as a colorless oil (0.11 g, 82%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 2.1, 1H), 7.71 (d, J = 8.6, 1H), 7.49 (dd, J = 8.6, 2.2, 1H), 4.13 (t, J = 6.5, 2H), 3.44 (s, 2H), 2.87 – 2.81 (m, 1H), 2.74 (t, J = 6.5, 2H), 2.68 (ddd, J = 10.9, 3.7, 1.7, 1H), 1.97 – 1.91 (m, 1H), 1.71 – 1.64 (m, 2H), 1.62 – 1.14 (m, 17H), 1.01 – 0.79 (m, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.40, 152.86, 143.11, 135.04, 134.53, 127.70, 124.54, 123.60, 82.18, 62.57, 60.42, 54.42, 44.41, 41.89, 41.87, 39.10, 33.07, 33.04, 30.74, 28.40, 26.59, 26.17.

(44) tert-butyl 6-(((4aR,8aS)-octahydroquinolin-1(2H)-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **25** with **23** (0.11 g, 0.32 mmol) and trans-decahydroquinoline (0.053 g, 0.38 mmol) to give product as a white solid (0.081 g, 64%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 2.2, 1H), 7.74 (d, J = 8.6, 1H), 7.50 (dd, J = 8.6, 2.2, 1H), 4.20 – 4.10 (m, 2H), 4.06 (d, J = 13.7, 1H), 3.32 (d, J = 13.7, 1H), 2.88 – 2.81 (m, 1H), 2.79 – 2.72 (m, 2H), 2.28 – 2.21 (m, 1H), 2.00 (td, J = 12.0, 3.4, 1H), 1.86 – 1.79 (m, 2H), 1.67 – 1.48 (m, 13H), 1.40 – 1.17 (m, 5H), 1.06 – 0.91 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.33, 152.84, 143.12, 135.22, 134.20, 127.91, 124.52, 123.57, 82.24, 66.78, 55.89, 53.59, 44.40, 41.77, 39.07, 33.31, 32.48, 30.48, 28.40, 25.98, 25.83, 25.19.

(45) tert-butyl 6-((3-azaspiro[5.5]undecan-3-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **25** with **23** (0.091 g, 0.27 mmol) and **101** (0.061 g, 0.32 mmol) to give product as a colorless oil (0.038 g, 34%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 2.0, 1H), 7.71 (d, J = 8.5, 1H), 7.50 (dd, J = 8.6, 2.2, 1H), 4.14 (t, J = 6.3, 2H), 3.47 (s, 2H), 2.75 (t, J = 6.2, 2H), 2.35 (t, J = 5.6, 4H), 1.55 (s, 9H), 1.44 (t, J = 5.6, 4H), 1.40 – 1.28 (m, 10H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.29, 152.76, 142.98, 134.94, 134.49, 127.64, 124.44, 123.49, 82.07, 62.56, 49.21, 44.30, 38.99, 36.57, 36.21, 30.71, 28.30, 26.86, 21.48.

(46) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(pyridin-3-ylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Compound **24** (0.064 g, 0.19 mmol) was dissolved in THF (17 mL) and placed under an inert atmosphere. (R)-(+)-2-methyl-2-propanesulfinamide (0.069 g, 0.58 mmol) was then added, and allowed to dissolve. The mixture was cooled to 0°C, and $Ti(OEt)_4$ (0.30 mL,

1.13 mmol) was added dropwise via syringe. The mixture was warmed to r.t., and then allowed to reflux at 75°C for 20 h, after which time the mixture was cooled to r.t. under an inert atmosphere, and immediately added via syringe to a stirring solution of $NaBH_4$ (0.043 g, 1.13 mmol) in THF (3 mL, cooled with a bath of xylenes/dry ice). The resulting yellow mixture was warmed back to r.t. and stirred for 1.5 h, after which time the reaction was quenched with the slow addition of MeOH. Solids were removed by filtration, and the resulting crude material was purified directly by column chromatography (100% EtOAc) to give product as a colorless oil (0.035 g, 42%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.48 – 8.42 (m, 2H), 7.81 – 7.71 (m, 2H), 7.42 (dd, J = 8.0, 5.9, 1H), 7.24 (d, J = 2.2, 1H), 7.02 (dd, J = 8.6, 2.2, 1H), 4.53 (q, J = 4.1, 1H), 3.97 (s, 2H), 3.94 (t, J = 4.7, 1H), 3.60 (ddd, J = 13.0, 10.8, 3.9, 1H), 3.27 (d, J = 3.4, 1H), 2.20 – 2.11 (m, 1H), 2.06 – 1.93 (m, 1H), 1.52 (s, 9H), 1.22 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.57, 147.63, 145.44, 139.50, 139.26, 137.66, 133.16, 129.42, 129.39, 128.64, 125.18, 124.64, 81.58, 55.89, 51.10, 40.46, 38.17, 30.02, 28.45, 22.72.

(47) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(piperidin-1-ylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **46** with **25** (0.080 g, 0.23 mmol) to give crude product as a colorless oil (0.011 g, 11%) which was filtered through a plug of silica and used without further purification.

(48) tert-butyl (R)-6-(azepan-1-ylmethyl)-4-(((R)-tert-butylsulfinyl)amino)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **46** with **26** (0.103 g, 0.29 mmol) to give product as a colorless oil (0.027 g, 24% yield). ^{1}H-NMR (500 MHz, CD_3OD) δ 7.83 (d, J = 8.6, 1H),

7.44 (d, J = 2.1, 1H), 7.33 (dd, J = 8.6, 2.2, 1H), 4.58 (q, J = 3.9, 1H), 4.02 (dt, J = 13.0, 4.6, 1H), 3.86 (s, 2H), 3.58 (ddd, J = 13.0, 11.0, 3.7, 1H), 3.31 (d, J = 3.0, 1H), 3.13 – 2.87 (m, 4H), 2.18 (dq, J = 14.0, 4.2, 1H), 2.06 – 1.98 (m, 1H), 1.94 – 1.80 (m, 1H), 1.63 – 1.46 (m, 16H), 1.22 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.35, 138.94, 133.39, 132.49, 127.86, 127.12, 123.01, 81.51, 66.55, 60.55, 59.82, 55.69, 50.41, 40.23, 29.49, 29.21, 28.31, 22.58.

(49) tert-butyl (R)-6-((4-(tert-butoxycarbonyl)piperazin-1-yl)methyl)-4-(((R)-tert-butylsulfinyl)amino)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **27** (0.090 g, 0.20 mmol) to give product as a colorless oil (0.021 g, 19%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.6, 1H), 7.40 (d, J = 2.2, 1H), 7.24 (dd, J = 8.6, 2.2, 1H), 4.58 (q, J = 4.1, 1H), 4.06 – 3.94 (m, 3H), 3.88 – 3.66 (m, 4H), 3.61 (ddd, J = 13.6, 10.8, 3.7, 1H), 3.29 (d, J = 3.3, 1H), 2.88 – 2.78 (m, 2H), 2.71 – 2.59 (m, 2H), 2.18 (dq, J = 13.5, 4.4, 1H), 2.06 – 1.99 (m, 1H), 1.53 (s, 9H), 1.43 (s, 9H), 1.22 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 154.25, 153.35, 139.34, 133.71, 132.72, 128.35, 124.82, 123.34, 81.70, 80.30, 68.52, 55.76, 55.44, 55.22, 50.78, 40.42, 29.67, 28.32, 28.30, 22.58.

(50) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(morpholinomethyl)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **28** (0.056 g, 0.16 mmol) to give product as a colorless oil (0.013 g, 18%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.6, 1H), 7.41 (d, J = 2.0, 1H), 7.25 (dd, J = 6.8, 2.0, 1H), 4.58 (q, J = 3.8, 1H), 4.41 – 4.26 (m, 2H), 4.04 – 3.93 (m, 3H), 3.74 – 3.55 (m, 3H), 3.29 (d, J = 3.2, 1H), 2.93 – 2.74 (m, 4H), 2.20 (dq, J = 13.5, 4.3, 1H), 2.09 – 1.96 (m, 1H), 1.54 (s, 9H), 1.22 (s, 9H); ^{13}C-NMR (101 MHz,

$CDCl_3$) δ 153.48, 139.46, 133.87, 133.01, 128.53, 124.94, 123.58, 81.85, 69.09, 62.22, 55.92, 55.66, 55.48, 50.94, 50.92, 40.53, 29.78, 28.45, 22.74.

(51) tert-butyl (R)-6-((1H-1,2,4-triazol-1-yl)methyl)-4-(((R)-tert-butylsulfinyl)amino)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **46** with **29** (0.11 g, 0.34 mmol) to give product as a colorless oil (0.094 g, 65%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.02 (s, 1H), 7.92 – 7.83 (m, 1H), 7.52 (d, J = 2.2, 1H), 7.25 – 7.15 (m, 1H), 5.28 (s, 2H), 4.54 (q, J = 4.5, 1H), 4.02 – 3.90 (m, 1H), 3.70 – 3.56 (m, 1H), 3.43 (d, J = 4.3, 1H), 2.18 – 1.94 (m, 2H), 1.53 (s, 9H), 1.22 (s, 9H).

(52) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(furan-3-ylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **46** with **30** (0.070 g, 0.21 mmol) to give product as a colorless oil (0.051 g, 55%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.5, 1H), 7.34 (t, J = 1.7, 1H), 7.25 – 7.18 (m, 2H), 7.10 (dd, J = 8.6, 2.2, 1H), 6.24 (dd, J = 1.8, 0.9, 1H), 4.54 (q, J = 3.6, 1H), 3.96 (dt, J = 12.9, 4.5, 1H), 3.71 (s, 2H), 3.58 (ddd, J = 12.9, 11.2, 3.8, 1H), 3.26 (d, J = 3.3, 1H), 2.19 (dq, J = 13.9, 4.0, 1H), 2.02 – 1.91 (m, 1H), 1.51 (s, 9H), 1.21 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.68, 143.16, 139.63, 136.71, 135.97, 128.86, 128.70, 128.41, 124.11, 111.31, 111.28, 81.26, 55.76, 50.58, 40.18, 30.48, 29.63, 28.46, 22.71.

(53) tert-butyl (R)-6-(benzofuran-2-ylmethyl)-4-(((R)-tert-butylsulfinyl)amino)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **31** (0.088 g, 0.23 mmol) to give product as a colorless oil (0.078 g, 70%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.5, 1H), 7.46 (d,

J = 7.8, 1H), 7.38 (d, J = 8.2, 1H), 7.30 (s, 1H), 7.22 – 7.12 (m, 3H), 6.41 (s, 1H), 4.55 (q, J = 3.7, 1H), 4.04 (s, 2H), 3.95 (dt, J = 13.1, 5.0, 1H), 3.64 – 3.50 (m, 1H), 3.30 (s, 1H), 2.22 – 2.15 (m, 1H), 2.02 – 1.92 (m, 1H), 1.51 (s, 9H), 1.19 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 157.38, 154.93, 153.53, 137.16, 132.62, 129.10, 128.78, 128.75, 128.61, 124.16, 123.39, 122.49, 120.42, 110.88, 103.34, 81.22, 55.66, 50.44, 40.12, 34.19, 29.50, 28.33, 22.58.

(54) tert-butyl (R)-6-(benzo[d][1,3]dioxol-5-ylmethyl)-4-(((R)-tert-butylsulfinyl)amino)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **46** with **32** (0.12 g, 0.30 mmol) to give product as a colorless oil (0.071 g, 48%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.5, 1H), 7.15 (d, J = 2.1, 1H), 7.05 (dd, J = 8.5, 2.1, 1H), 6.72 (d, J = 8.5, 1H), 6.65 (d, J = 7.1, 2H), 5.90 (s, 2H), 4.53 (q, J = 3.5, 1H), 3.94 (dt, J = 12.9, 4.5, 1H), 3.82 (s, 2H), 3.57 (td, J = 12.1, 3.9, 1H), 3.26 (d, J = 2.3, 1H), 2.19 (dq, J = 12.9, 4.1, 1H), 2.03 – 1.90 (m, 1H), 1.51 (s, 9H), 1.20 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.67, 147.80, 146.00, 136.89, 136.68, 134.85, 128.99, 128.77, 128.62, 124.18, 124.13, 121.80, 109.48, 109.41, 108.29, 100.92, 81.24, 55.75, 50.52, 40.95, 40.16, 29.53, 28.46, 22.72.

(55) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **33** (0.078 g, 0.20 mmol) to give product as a colorless oil (0.060 g, 61%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.5, 1H), 7.15 (d, J = 2.1, 1H), 7.06 (dd, J = 8.6, 2.2, 1H), 6.76 (d, J = 8.1, 1H), 6.68 – 6.63 (m, 2H), 4.52 (q, J = 3.6, 1H), 4.22 (s, 4H), 3.94 (dt, J = 12.9, 4.5, 1H), 3.80 (s, 2H), 3.57 (ddd, J = 12.9, 11.3, 3.9, 1H), 3.29 (d, J = 1.1, 1H), 2.20 (dq, J = 14.0, 4.0, 1H), 2.00 – 1.89 (m,

1H), 1.51 (s, 9H), 1.20 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.68, 143.48, 142.01, 136.92, 136.63, 134.36, 128.99, 128.73, 128.69, 124.15, 121.85, 117.62, 117.25, 81.20, 64.47, 64.41, 55.76, 50.48, 40.54, 40.15, 29.50, 28.46, 22.73.

(56) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(2,6-dichlorobenzyl)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **34** (0.12 g, 0.28 mmol) to give product as a colorless oil (0.032 g, 22%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.6, 1H), 7.32 (d, J = 8.0, 2H), 7.18 – 7.10 (m, 2H), 7.08 (dd, J = 8.6, 2.2, 1H), 4.52 (q, J = 3.4, 1H), 4.27 (s, 2H), 3.93 (dt, J = 12.9, 4.5, 1H), 3.55 (ddd, J = 12.8, 11.3, 3.9, 1H), 3.26 (br s, 1H), 2.20 (dq, J = 14.2, 4.1, 1H), 2.02 – 1.88 (m, 1H), 1.50 (s, 9H), 1.20 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.67, 136.83, 136.54, 136.09, 133.56, 128.74, 128.67, 128.52, 128.35, 128.17, 124.10, 81.23, 55.73, 50.18, 40.11, 35.94, 29.28, 28.46, 22.72.

(57) tert-butyl (R)-6-benzhydryl-4-(((R)-tert-butylsulfinyl)amino)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **35** (0.11 g, 0.26 mmol) to give product as a colorless oil (0.063 g, 47%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.6, 1H), 7.30 – 7.24 (m, 4H), 7.23 – 7.17 (m, 2H), 7.14 – 7.07 (m, 5H), 7.01 (dd, J = 8.7, 2.2, 1H), 5.48 (s, 1H), 4.48 (q, J = 3.4, 1H), 3.94 (dt, J = 12.8, 4.5, 1H), 3.58 (ddd, J = 12.9, 11.3, 4.0, 1H), 3.21 (d, J = 2.8, 1H), 2.21 (dq, J = 14.0, 4.0, 1H), 2.02 – 1.89 (m, 1H), 1.51 (s, 9H), 1.16 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.70, 143.83, 143.76, 139.37, 136.86, 129.58, 129.47, 129.44, 129.26, 128.63, 128.46, 128.45, 126.48, 123.86, 81.30, 56.30, 55.76, 50.20, 40.18, 29.24, 28.48, 24.33, 22.70.

(58) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(quinolin-6-ylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **46** with **36** (0.099 g, 0.26 mmol) to give crude product as a colorless oil (0.016 g, 14%) which was filtered through a plug of silica and used without further purification.

(59) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(quinolin-3-ylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **46** with **37** (0.093 g, 0.24 mmol) to give crude product as a colorless oil (0.020 g, 17%) which was filtered through a plug of silica and used without further purification.

(60) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **46** with **38** (0.16 g, 0.41 mmol) to give product as a colorless oil (0.094 g, 46%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, J = 12.8, 8.6, 1H), 7.43 (dd, J = 4.6, 2.1, 1H), 7.25 – 7.14 (m, 4H), 7.06 – 6.96 (m, 1H), 4.56 (dd, J = 9.1, 3.7, 1H), 4.06 – 3.84 (m, 5H), 3.63 – 3.52 (m, 1H), 3.38 (d, J = 2.8, 1H), 3.30 – 3.19 (m, 2H), 3.14 – 2.93 (m, 2H), 2.27 – 2.15 (m, 1H), 2.03 – 1.94 (m, 1H), 1.52 (s, 9H), 1.21 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.45, 139.20, 133.80, 133.61, 132.51, 132.28, 131.26, 131.23, 130.75, 130.71, 128.71, 128.60, 128.26, 128.15, 127.37, 127.30, 126.83, 126.81, 125.99, 123.21, 81.65, 81.61, 63.78, 62.84, 58.10, 57.37, 55.83, 55.82, 54.93, 54.30, 50.47, 50.28, 40.36, 40.27, 29.35, 29.31, 28.41, 25.01, 24.83, 22.71.

(61) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-((7-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **39** to give product as a white solid (40%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.51 (s, 9H), 1.96-2.19 (m, 2H), 2.85-3.03 (m, 2H), 3.20 (m, 2H), 3.90-4.04 (m, 4H), 4.56 (q, J = 4 Hz, 2H), 6.72 (qd, J = 8, 4 Hz, 1H), 6.91 (m, 1H), 7.10 (td, J = 4, 4 Hz, 1H), 7.16 (qd, J = 16, 4 Hz, 1H), 7.45 (s, 1H), 7.82 (t, J = 8 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 22.54, 22.63, 28.29, 40.29, 40.37, 54.12, 54.56, 55.76, 63.83, 64.68, 81.59, 114.47, 123.30, 125.54, 126.87, 128.32, 130.08, 132.43, 132.56, 133.63, 139.21, 153.37, 162.52.

(62) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-((8-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **40** (0.12 g, 0.26 mmol) to give product as a white solid (22%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.51 (s, 9H), 1.98-2.22 (m, 2H), 2.94-3.08 (m, 2H), 3.18-3.33 (m, 2H), 3.95-4.04 (m, 2H), 4.07-4.17 (m, 2H), 4.18-4.55 (dd, J = 116, 16 Hz, 2H), 7.28 (m, 1H), 7.30-7.35 (m, 2H), 7.40 (s, 1H), 7.52 (d, J = 12 Hz, 1H), 7.83 (dd, J = 4, 4 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 22.52, 22.61, 28.26, 39.08, 40.28, 52.79, 55.74, 55.79, 65.42, 65.43, 81.58, 121.08, 123.40, 125.19, 125.22, 126.77, 128.32, 128.37, 129.17, 132.48, 133.22, 133.32, 139.22, 158.34.

(63) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-((7-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **41** (0.092 g, 0.23 mmol) to give product as a colorless oil (0.032 g, 28%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, J = 10.4, 8.5, 1H), 7.44 (s, 1H), 7.19 (ddd, J = 34.1, 8.6, 2.1, 1H), 7.09 – 7.00 (m, 2H), 6.83 (d, J = 19.9, 1H), 4.60 – 4.53 (m, 1H), 4.04 – 3.84 (m, 5H), 3.63 – 3.53 (m, 1H), 3.37 (d, J = 2.7, 1H), 3.30 – 2.88 (m, 4H), 2.31 (s, 3H), 2.26 – 2.15 (m, 1H), 2.04 – 1.93 (m, 1H), 1.52 (s, 9H),

1.22 (d, J = 3.3, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.49, 139.21, 136.50, 136.49, 133.88, 133.69, 132.52, 132.30, 130.56, 130.54, 128.61, 128.51, 128.31, 128.26, 128.24, 128.14, 128.11, 127.27, 127.26, 126.14, 123.21, 81.67, 81.64, 63.62, 62.72, 58.26, 57.48, 55.85, 55.14, 54.51, 50.46, 50.29, 40.39, 40.29, 29.37, 29.33, 28.44, 24.66, 24.48, 22.75, 21.19, 21.16.

(64) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(isoindolin-2-ylmethyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **46** with **42** (0.10 g, 0.28 mmol) to give product as a colorless oil (0.062 g, 47%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5, 1H), 7.40 (d, J = 2.1, 1H), 7.25 – 7.12 (m, 5H), 4.52 (q, J = 4.0, 1H), 4.47 – 4.29 (m, 4H), 4.09 (s, 2H), 3.94 (dt, J = 12.9, 4.7, 1H), 3.58 (ddd, J = 12.8, 10.8, 3.8, 1H), 3.28 (d, J = 3.2, 1H), 2.16 (dq, J = 13.4, 4.3, 1H), 2.00 – 1.93 (m, 1H), 1.52 (s, 9H), 1.22 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.43, 139.13, 136.98, 136.90, 133.10, 132.16, 128.40, 127.92, 127.88, 127.10, 123.41, 122.69, 122.60, 81.65, 65.17, 64.78, 64.48, 55.86, 50.74, 40.42, 29.57, 28.40, 22.71.

(65) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(((4aR,8aS)-octahydroisoquinolin-2(1H)-yl)methyl)-3,4-dihydroquinoline-1(2H)-carboxylate)

Followed procedure for compound **46** with **43** (0.11 g, 0.27 mmol) to give product as a colorless oil (0.020 g, 7%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.6, 3.4, 1H), 7.35 (dd, J = 5.9, 2.1, 1H), 7.30 – 7.22 (m, 1H), 4.58 (br s, 1H), 4.05 – 3.88 (m, 3H), 3.58 (ddd, J = 12.9, 11.1, 3.7, 1H), 3.28 (d, J = 2.8, 1H), 2.98 – 2.88 (m, 1H), 2.80 – 2.69 (m, 1H), 2.61 – 2.51 (m, 1H), 2.25 – 1.01 (m, 31H), 0.82 – 0.68 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.55, 139.15, 133.77, 133.11, 128.13, 125.91, 123.29, 81.75, 70.03,

62.69, 57.28, 55.86, 50.51, 41.17, 40.40, 36.56, 32.20, 30.64, 29.60, 28.51, 28.46, 26.39, 25.76, 22.72.

(66) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(((4aR,8aS)-octahydroquinolin-1(2H)-yl)methyl)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **44** (0.17 g, 0.42 mmol) to give product as a colorless oil (0.029 g, 14%) which was filtered through a plug of silica and used without further purification.

(67) tert-butyl (R)-6-((3-azaspiro[5.5]undecan-3-yl)methyl)-4-(((R)-tert-butylsulfinyl)amino)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **45** (0.038 g, 0.092 mmol) to give product as a colorless oil (0.031 g, 65%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.6, 1H), 7.39 (d, J = 2.1, 1H), 7.31 (dd, J = 8.6, 2.1, 1H), 4.57 (q, J = 3.7, 1H), 4.00 (dt, J = 13.0, 4.6, 1H), 3.89 (s, 2H), 3.56 (ddd, J = 13.1, 11.2, 3.7, 1H), 3.30 (d, J = 2.7, 1H), 2.91 – 2.77 (m, 2H), 2.77 – 2.64 (m, 2H), 2.20 (dq, J = 14.0, 4.1, 1H), 2.03 – 1.85 (m, 1H), 1.52 (s, 9H), 1.44 – 1.23 (m, 14H), 1.20 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.37, 138.91, 133.41, 132.71, 127.77, 126.29, 123.02, 81.50, 55.66, 52.87, 52.23, 50.20, 40.12, 31.12, 30.08, 29.20, 28.31, 26.54, 22.61, 22.13, 21.41.

(68) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(pyridin-3-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide)

Compound **46** (0.035 g, 0.079 mmol) was dissolved in 1,4-dioxane (7 mL). Conc. HCl (0.039 mL, 0.47 mmol) was then added dropwise via syringe. The mixture was stirred at r.t. for 1 h, after which time 1,4-dioxane was removed under reduced pressure, and Et_2O was added to the reaction vessel, precipitating the HCl salt as a white solid, which was

subsequently washed with Et_2O (3x). This solid was dried under vacuum and used without further purification. The HCl salt (0.022 g, 0.08 mmol) was dissolved in DMF (10 mL). DIPEA (0.14 mL, 0.80 mmol, 10 eq) was then added dropwise via syringe, followed by PyBOP (0.042 g, 0.08 mmol, 1 eq) and HOBt-Cl (0.014 g, 0.08 mmol, 1 eq). Boc-L-2',6'-dimethyltyrosine (0.033 g, 0.08 mmol, 1 eq) was dissolved in DMF (2 mL) and added to the reaction mixture dropwise via syringe. The yellow solution was stirred at r.t. under an inert atmosphere for 5 h, after which time DMF was removed under reduced pressure. The crude residue was redissolved in 1:1 DCM/TFA (10 mL) and stirred at r.t. for 1 h. DCM/TFA were then removed under reduced pressure. The crude residue was then purified by semi-prep RP-HPLC and lyophilized to give product as a white solid. (MS)EI: 431.2 (M+H), Retention Time: 13.77 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.65 (d, J = 5.6, 1H), 8.61 (s, 1H), 8.34 (d, J = 8.0, 1H), 8.14 (d, J = 7.8, 1H), 7.92 (t, J = 6.8, 1H), 6.98 (s, 1H), 6.90 (d, J = 8.2, 1H), 6.56 (d, J = 8.2, 1H), 6.47 (s, 2H), 4.96 – 4.91 (m, 1H), 4.02 (s, 2H), 3.88 (dd, J = 11.6, 4.8, 1H), 3.28 – 3.19 (m, 1H), 3.02 (dd, J = 13.5, 4.5, 2H), 2.55 (t, J = 11.6, 1H), 2.27 (s, 6H), 1.76 – 1.63 (m, 1H), 1.56 – 1.44 (m, 1H).

(69) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide)

Followed procedure for compound **68** with **47** (0.008 g, 0.021 mmol) to give product as a white solid. (MS)EI: 459.3 (M+Na), Retention Time: 17.91 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.10 (d, J = 8.0, 1H), 7.05 (d, J = 2.1, 1H), 7.03 (dd, J = 8.3, 2.2, 1H), 6.52 (d, J = 8.3, 1H), 6.49 (s, 2H), 4.95 – 4.91 (m, 1H), 4.07 – 3.98 (m, 2H), 3.88 (dd, J = 11.7, 4.9, 1H), 3.38 (d, J = 12.5, 2H), 3.28 (dd, J = 13.6, 11.7, 1H), 3.03 (dd, J = 13.4, 5.2, 2H),

2.83 (t, J = 12.5, 2H), 2.55 (td, J = 12.2, 3.1, 1H), 2.29 (s, 6H), 1.93 – 1.77 (m, 3H), 1.76 – 1.60 (m, 3H), 1.55 – 1.42 (m, 2H).

(70) (S)-2-amino-N-((R)-6-(azepan-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide)

Followed procedure for compound **68** with **48** (0.027 g, 0.058 mmol) to give product as a white solid. (MS)EI: 473.3 (M+Na), Retention Time: 19.54 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.10 (d, J = 7.9, 1H), 7.05 (s, 1H), 7.03 (d, J = 1.9, 1H), 6.52 (d, J = 8.1, 1H), 6.48 (s, 2H), 4.94 – 4.90 (m, 1H), 4.12 – 4.03 (m, 2H), 3.87 (dd, J = 11.7, 4.9, 1H), 3.41 – 3.34 (m, 2H), 3.27 (dd, J = 13.6, 11.7, 1H), 3.11 – 2.99 (m, 4H), 2.56 – 2.49 (m, 1H), 2.28 (s, 6H), 1.96 – 1.60 (m, 9H), 1.54 – 1.47 (m, 1H).

(71) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(piperazin-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide

Followed procedure for compound **68** with **49** (0.021 g, 0.038 mmol) to give product as a white solid. (MS)EI: 460.3 (M+Na), Retention Time: 14.44 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.06 (d, J = 8.0, 1H), 7.08 (d, J = 2.1, 1H), 7.01 (dd, J = 8.3, 2.1, 1H), 6.51 (d, J = 8.3, 1H), 6.48 (s, 2H), 4.95 – 4.90 (m, 1H), 3.99 (q, J = 12.9, 2H), 3.87 (dd, J = 11.6, 4.8, 1H), 3.46 – 3.40 (m, 4H), 3.34 – 3.32 (m, 1H), 3.26 – 3.22 (m, 4H), 3.03 (td, J = 13.3, 12.2, 5.1, 2H), 2.63 – 2.56 (m, 1H), 2.28 (s, 6H), 1.68 – 1.61 (m, 1H), 1.53 – 1.46 (m, 1H).

(72) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(morpholinomethyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide)

Followed procedure for compound **68** with **50** (0.13 g, 0.029 mmol) to give product as a white solid. (MS)EI: 461.3 (M+Na), Retention Time: 15.53 min. ^{1}H-NMR (500 MHz,

CD_3OD) δ 8.07 (d, J = 7.8, 1H), 7.07 (d, J = 1.7, 1H), 7.03 (dd, J = 8.4, 1.9, 1H), 6.51 (d, J = 8.3, 1H), 6.48 (s, 2H), 4.92 (t, J = 4.2, 1H), 4.15 – 4.05 (m, 2H), 4.01 (d, J = 12.5, 2H), 3.87 (dd, J = 11.6, 4.8, 1H), 3.69 (t, J = 12.5, 2H), 3.28 – 3.22 (m, 3H), 3.11 – 2.99 (m, 4H), 2.60 – 2.51 (m, 1H), 2.28 (s, 6H), 1.69 – 1.58 (m, 1H) 1.54 – 1.46 (m, 1H).

(73) (S)-N-((R)-6-((1H-1,2,4-triazol-1-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide)

Followed procedure for compound **68** with **51** (0.094 g, 0.22 mmol) to give product as a white solid. (MS)EI: 443.2 (M+Na), Retention Time: 15.29 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.46 (s, 1H), 8.11 (d, J = 7.9, 1H), 7.99 (s, 1H), 7.04 (d, J = 2.1, 1H), 6.99 (dd, J = 8.3, 2.1, 1H), 6.52 (d, J = 8.3, 1H), 6.47 (s, 2H), 5.24 – 5.13 (m, 2H), 4.95 – 4.89 (m, 1H), 3.85 (dd, J = 11.6, 4.9, 1H), 3.25 (dd, J = 13.6, 11.6, 1H), 3.05 – 2.96 (m, 2H), 2.58 – 2.47 (m, 1H), 2.27 (s, 6H), 1.73 – 1.61 (m, 1H), 1.55 – 1.46 (m, 1H).

(74) (S)-2-amino-N-((R)-6-(furan-3-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide)

Followed procedure for compound **68** with **52** (0.051 g, 0.12 mmol) to give product as a white solid. (MS)EI: 420.2 (M+H), Retention Time: 20.22 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.21 (d, J = 7.9, 1H), 7.36 (t, J = 1.7, 1H), 7.21 (dd, J = 1.6, 0.9, 1H), 7.06 – 7.00 (m, 2H), 6.76 (d, J = 8.3, 1H), 6.48 (s, 2H), 6.18 (dd, J = 1.9, 0.9, 1H), 5.01 – 4.95 (m, 1H), 3.86 (dd, J = 11.5, 5.1, 1H), 3.64 (s, 2H), 3.25 (dd, J = 13.6, 11.6, 1H), 3.15 – 3.07 (m, 1H), 3.02 (dd, J = 13.6, 5.1, 1H), 2.63 (td, J = 12.0, 2.8, 1H), 2.27 (s, 6H), 1.88 – 1.77 (m, 1H), 1.60 – 1.51 (m, 1H).

(75) (S)-2-amino-N-((R)-6-(benzofuran-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **53** (0.078 g, 0.16 mmol) to give product as a white solid. (MS)EI: 492.2 (M+Na), Retention Time: 30.25 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.13 (d, J = 8.0, 1H), 7.44 (d, J = 6.6, 1H), 7.31 (d, J = 7.9, 1H), 7.20 – 7.10 (m, 2H), 7.00 (s, 1H), 6.98 (d, J = 2.1, 1H), 6.57 (d, J = 8.1, 1H), 6.48 (s, 2H), 6.34 (s, 1H), 4.97 – 4.93 (m, 1H), 3.98 – 3.87 (m, 2H), 3.85 (dd, J = 11.5, 5.0, 1H), 3.25 (dd, J = 13.6, 11.6, 1H), 3.04 – 2.96 (m, 2H), 2.52 (td, J = 11.7, 2.5, 1H), 2.27 (s, 6H), 1.77 – 1.69 (m, 1H), 1.56 – 1.49 (m, 1H).

(76) (S)-2-amino-N-((R)-6-(benzo[d][1,3]dioxol-5-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide)

Followed procedure for compound **68** with **54** (0.071 g, 0.15 mmol) to give product as a white solid. (MS)EI: 474.2 (M+H), Retention Time: 24.70 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 8.1, 1H), 7.01 – 6.88 (m, 2H), 6.67 (d, J = 7.9, 2H), 6.62 – 2.55 (m, 2H), 6.48 (s, 2H), 5.85 (s, 2H), 4.99 – 4.92 (m, 1H), 3.86 (dd, J = 11.5, 5.1, 1H), 3.73 (s, 2H), 3.25 (dd, J = 13.6, 11.6, 1H), 3.12 – 2.97 (m, 2H), 2.64 – 2.52 (m, 1H), 2.27 (s, 6H), 1.83 – 1.72 (m, 1H), 1.58 – 1.49 (m, 1H).

(77) (S)-2-amino-N-((R)-6-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **55** (0.060 g, 0.12 mmol) to give product as a white solid. (MS)EI: 488.3 (M+H), Retention Time: 24.49 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 6.96 (d, J = 2.0, 1H), 6.93 (dd, J = 8.2, 2.0, 1H), 6.67 (dd, J = 8.1, 6.8, 2H), 6.58 – 6.54 (m, 2H), 6.48 (s, 2H), 4.96 (t, J = 4.6, 1H), 4.17 (s, 4H), 3.86 (dd, J = 11.5, 5.1, 1H), 3.69 (s, 2H), 3.25 (dd, J = 13.6, 11.5, 1H), 3.07 (dt, J = 12.4, 4.5, 1H), 3.02 (dd,

J = 13.6, 5.1, 1H), 2.58 (td, J = 11.7. 2.7, 1H), 2.27 (s, 6H), 1.83 – 1.74 (m, 1H), 1.58 – 1.50 (m, 1H).

(78) (S)-2-amino-N-((R)-6-(2,6-dichlorobenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **56** (0.032 g, 0.63 mmol) to give product as a white solid. (MS)EI: 520.2 (M+Na), Retention Time: 30.67 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.20 (d, J = 7.6, 1H), 7.37 (d, J = 8.0, 2H), 7.21 (dd, J = 8.5, 7.5, 1H), 7.01 – 6.93 (m, 1H), 6.77 – 6.72 (m, 1H), 6.54 (d, J = 8.3, 1H), 6.47 (s, 2H), 4.93 – 4.89 (m, 1H), 4.22 – 4.11 (m, 2H), 3.86 (dd, J = 11.5, 5.1, 1H), 3.25 (dd, J = 13.6, 11.5, 1H), 3.00 (dd, J = 13.4, 5.1, 2H), 2.52 – 2.40 (m, 1H), 2.27 (s, 6H), 1.78 – 1.66 (m, 1H), 1.58 – 1.49 (m, 1H).

(79) (S)-2-amino-N-((R)-6-benzhydryl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **57** (0.063 g, 0.12 mmol) to give product as a white solid. (MS)EI: 528.2 (M+Na), Retention Time: 35.41 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 7.9, 1H), 7.28 – 6.98 (m, 10H), 6.89 (d, J = 1.8, 1H), 6.76 (dd, J = 8.4, 1.9, 1H), 6.57 (d, J = 8.4, 1H), 6.47 (s, 2H), 5.38 (s, 1H), 4.89 – 4.86 (m, 1H), 3.82 (dd, J = 11.5, 5.1, 1H), 3.23 (dd, J = 13.5, 11.7, 1H), 3.05 – 2.92 (m, 2H), 2.46 (td, J = 12.0, 2.4, 1H), 2.26 (s, 6H), 1.78 – 1.66 (m, 1H), 1.58 – 1.47 (m, 1H).

(80) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(quinolin-6-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide)

Followed procedure for compound **68** with **58** (0.017 g, 0.04 mmol) to give product as an oily yellow solid. (MS)EI: 481.3 (M+H), Retention Time: 16.70 min. ^{1}H-NMR (500

MHz, CD_3OD) δ 8.95 (d, J = 4.4, 1H), 8.68 (d, J = 8.3, 1H), 8.01 (d, J = 8.7, 1H), 7.86 (s, 1H), 7.79 (d, J = 8.9, 2H), 6.95 (d, J = 2.0, 1H), 6.88 (dd, J = 8.6, 1.9, 1H), 6.49 (t, J = 4.2, 1H), 6.48 (s, 2H), 4.92 – 4.90 (m, 1H), 4.04 (s, 2H), 3.85 (dd, J = 11.8, 5.2, 1H), 3.25 (dd, J = 13.7, 11.6, 1H), 2.99 (td, J = 13.5, 4.7, 2H), 2.52 – 2.44 (m, 1H), 2.27 (s, 6H), 1.73 – 1.64 (m, 1H), 1.54 – 1.47 (m, 1H).

(81) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(quinolin-3-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide)

Followed procedure for compound **68** with **59** (0.020 g, 0.04 mmol) to give product as a pale yellow solid. (MS)EI: 481.3 (M+H), Retention Time: 18.69 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.92 (d, J = 2.0, 1H), 8.67 (s, 1H), 8.19 – 8.10 (m, 3H), 8.01 (ddd, J = 8.4, 6.9, 1.4, 1H), 7.85 (ddd, J = 8.1, 6.9, 1.1, 1H), 7.03 (d, J = 2.0, 1H), 6.96 (dd, J = 8.3, 2.1, 1H), 6.58 (d, J = 8.3, 1H), 6.47 (s, 2H), 4.97 – 4.92 (m, 1H), 4.14 (s, 2H), 3.87 (dd, J = 11.6, 5.0, 1H), 3.25 (dd, J = 13.6, 11.6, 1H), 3.01 (dd, J = 13.3, 4.8, 2H), 2.54 (t, J = 10.7, 1H), 2.27 (s, 6H), 1.75 – 1.64 (m, 1H), 1.56 – 1.44 (m, 1H).

(82) (S)-2-amino-N-((R)-6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide)

Followed procedure for compound **68** with **60** (0.040 g, 0.08 mmol) to give product as a white solid. (MS)EI: 507.3 (M+Na), Retention Time: 22.15 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.08 (d, J = 7.9, 1H), 7.33 – 7.21 (m, 3H), 7.18 – 7.05 (m, 3H), 6.54 (d, J = 8.5, 1H), 6.48 (s, 2H), 4.98 – 4.90 (m, 1H), 4.38 – 4.16 (m, 5H), 3.87 (dd, J = 11.6, 4.9, 1H), 3.78 – 3.65 (m, 1H), 3.28 – 3.21 (m, 1H), 3.21 – 3.10 (m, 2H), 3.09 – 2.98 (m, 2H), 2.55 (t, J = 11.6, 1H), 2.28 (s, 6H), 1.70 – 1.60 (m, 1H), 1.58 – 1.46 (m, 1H).

(83) (S)-2-amino-N-((R)-6-((7-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **61** to give product as a white solid. (MS)EI: 525.3 (M+Na), Retention Time: 23.6 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 1.43-1.59 (m, 2H), 2.19 (s, 6H), 2.46 (m, 2H), 2.91-2.97 (m, 2H), 3.17 (m, 2H), 3.23 (m, 2H), 3.77 (dd, J = 5.2, 4 Hz, 2H), 4.16 (d, J = 10.4 Hz, 2H), 4.24 (m, 1H), 4.86 (m, 1H), 6.39 (s, 2H), 6.45 (d, J = 6.8 Hz, 1H), 6.86 (m, 1H), 6.94-7.02 (m, 3H), 7.17 (dd, J = 4.4, 2.4 Hz, 1H), 7.70 (m, 1H), 7.99 (d, J = 6.4 Hz, 1H), 8.62 (m, 1H).

(84) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-((8-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide

Followed procedure for compound **68** with **62** (0.025 g, 0.044 mmol) to give product as a white solid. (MS)EI: 575.3 (M+Na), Retention Time: 27.7 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 1.41-1.59 (m, 2H), 2.18 (s, 6H), 2.44 (m, 2H), 2.92 (m, 2H), 3.15 (m, 2H), 3.23 (m, 2H), 3.77 (dd, J = 5.6, 4 Hz, 2H), 4.18-4.24 (m, 2H), 4.40 (m, 1H), 4.84 (m, 1H), 6.39 (s, 2H), 6.45 (d, J = 6.8 Hz, 1H), 6.98 (d, J = 1.2 Hz, 1H), 7.03 (s, 1H), 7.39-7.57 (dd, J = 42.8, 6.4 Hz, 2H), 7.44 (t, J = 6 Hz, 1H), 7.80 (m, 1H), 7.99 (d, J = 6.4 Hz, 1H), 8.28 (m, 1H), 8.68 (s, 1H).

(85) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-((7-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide

Followed procedure for compound **68** with **63** (0.032 g, 0.063 mmol) to give product as a white solid. (MS)EI: 521.3 (M+Na), Retention Time: 25.70 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.14 – 7.05 (m, 4H), 6.96 (s, 1H), 6.55 (d, J = 8.3, 1H), 6.49 (s, 2H), 4.98 –

4.91 (m, 1H), 4.34 – 4.15 (m, 5H), 3.87 (dd, J = 11.7, 4.9, 1H), 3.75 – 3.65 (m, 1H), 3.29 – 3.22 (m, 1H), 3.14 – 2.99 (m, 4H), 2.56 (t, J = 11.6, 1H), 2.30 (s, 3H), 2.28 (s, 6H), 1.70 – 1.63 (m, 1H), 1.56 – 1.48 (m, 1H).

(86) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(isoindolin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide)

Followed procedure for compound **68** with **64** (0.062 g, 0.13 mmol) to give product as a white solid. (MS)EI: 493.3 (M+Na), Retention Time: 20.69 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 8.1, 1H), 7.38 (s, 4H), 7.12 (d, J = 2.1, 1H), 7.09 (dd, J = 8.3, 2.1, 1H), 6.54 (d, J = 8.3, 1H), 6.48 (s, 2H), 4.98 – 4.89 (m, 1H), 4.68 – 4.51 (m, 4H), 4.42 – 4.28 (m, 2H), 3.88 (dd, J = 11.7, 4.8, 1H), 3.25 (dd, J = 12.0, 4.0, 1H), 3.09 – 2.97 (m, 2H), 2.57 (td, J = 12.1, 11.5, 3.1, 1H), 2.28 (s, 6H), 1.72 – 1.59 (m, 1H), 1.57 – 1.45 (m, 1H).

(87) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(((4aR,8aS)-octahydroisoquinolin-2(1H)-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide)

Followed procedure for compound **68** with **65** (0.028 g, 0.056 mmol) to give product as a white solid. (MS)EI: 491.3 (M+H), Retention Time: 25.96 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.09 (d, J = 7.9, 1H), 7.05 (s, 1H), 7.02 (dd, J = 8.5, 1.7, 1H), 6.52 (d, J = 8.4, 1H), 6.48 (s, 2H), 4.95 – 4.90 (m, 1H), 4.09 – 3.95 (m, 2H), 3.87 (dd, J = 11.7, 4.9, 1H), 3.43 – 3.36 (m, 1H), 3.30 – 3.18 (m, 2H), 3.06 – 2.99 (m, 2H), 2.92 – 2.82 (m, 1H), 2.61 – 2.50 (m, 2H), 2.28 (s, 6H), 1.86 – 0.95 (m, 14H).

(88) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(((4aR,8aS)-octahydroquinolin-1(2H)-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide

Followed procedure for compound **68** with **66** (0.029 g, 0.058 mmol) to give product as a white solid. (MS)EI: 513.3 (M+Na), Retention Time: 24.07 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.05 – 6.97 (m, 2H), 6.53 (dd, J = 8.0, 2.5, 1H), 6.49 (s, 2H), 4.96 – 4.91 (m, 1H), 4.52 – 4.43 (m, 1H), 3.87 (dd, J = 11.5, 4.7, 1H), 3.80 – 3.71 (m, 1H), 3.28 – 3.21 (m, 2H), 3.06 – 2.99 (m, 2H), 2.83 – 2.68 (m, 2H), 2.60 – 2.48 (m, 2H), 2.28 (s, 6H), 2.02 – 1.10 (m, 14H).

(89) (S)-N-((R)-6-((3-azaspiro[5.5]undecan-3-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **67** (0.031 g, 0.060 mmol) to give product as a white solid. (MS)EI: 505.4 (M+H), Retention Time: 28.68 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.09 (d, J = 7.9, 1H), 7.05 (d, J = 2.1, 1H), 7.02 (dd, J = 8.4, 2.1, 1H), 6.51 (d, J = 8.3, 1H), 6.48 (s, 2H), 4.96 – 4.91 (m, 1H), 4.11 – 3.96 (m, 2H), 3.87 (dd, J = 11.7, 4.9, 1H), 3.28 – 3.16 (m, 3H), 3.07 – 2.95 (m, 4H), 2.59 – 2.50 (m, 1H), 2.28 (s, 6H), 1.86 (d, J = 14.6, 2H), 1.70 – 1.23 (m, 14H).

(90) 3-bromo-N-(4-(morpholinomethyl)phenyl)propanamide

To a stirring solution of 4-(morpholinomethyl)aniline (0.44 g, 2.26 mmol) and K_2CO_3 (0.63 g, 4.53 mmol) in DCM (20 mL) was added 3-bromopropionyl chloride (0.24 mL, 2.38 mmol) dropwise via syringe. The resulting cloudy solution was stirred at r.t. for 2 h, after which time the reaction mixture was transferred to a separatory funnel, and washed with sat. $NaHCO_3$ (3x) and brine. The organic layer was dried with $MgSO_4$, and solvents were filtered and removed under reduced pressure to give product as a white solid (0.68 g, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.52 (d, J = 8.4, 2H), 7.27 (d, J = 8.4, 2H), 3.72 (t, J = 4.8, 2H), 3.70 – 3.63 (m, 6H), 3.50 (s, 2H), 2.95 (t, J = 6.6, 2H), 2.47

(t, J = 4.8, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.52, 137.04, 129.94, 120.15, 66.65, 62.63, 53.29, 40.26, 27.43.

(91) N-(4-((1H-1,2,4-triazol-1-yl)methyl)phenyl)-3-bromopropanamide)

Followed procedure for compound **90** with 4-((1H-1,2,4-triazol-1-yl)methyl)aniline (0.51 g, 2.92 mmol) to give product as a pale, spongy solid (0.79 g, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.98 (s, 1H), 7.88 (s, 1H), 7.53 (d, J = 8.4, 2H), 7.22 (d, J = 8.4, 2H), 5.30 (s, 2H), 3.70 (t, J = 6.5, 2H), 2.94 (t, J = 6.5, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.29, 152.19, 143.11, 138.12, 130.57, 129.03, 120.59, 53.30, 40.65, 27.17.

(92) N-(4-benzhydrylphenyl)-3-bromopropanamide

Followed procedure for compound **90** with compound **100** (0.53 g, 2.0 mmol) to give product as a white solid (0.64 g, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.5, 2H), 7.33 – 7.05 (m, 12H), 5.51 (s, 1H), 3.69 (t, J = 6.5, 2H), 2.91 (t, J = 6.5, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.99, 143.83, 140.55, 135.71, 130.15, 129.50, 128.47, 126.49, 120.16, 56.37, 40.78, 27.27.

(93) 1-(4-(morpholinomethyl)phenyl)azetidin-2-one)

To a dry round bottomed flask was added NaOtBu (0.21 g, 2.17 mmol) and placed under an inert atmosphere. DMF (30 mL) was then added via syringe. Compound **90** (0.68 g, 2.06 mmol) was dissolved in DMF (20 mL) and added to the dissolved NaOtBu via cannula. The reaction was stirred under an inert atmosphere for 5 h, after which time DMF was removed under reduced pressure. The crude residue was redissolved in EtOAc (20 mL) and H_2O (20 mL) was added. The aqueous layer was extracted with EtOAc (3x). Combined organic layers were washed with brine, and dried with $MgSO_4$. Solvents were

filtered and removed, and the resulting yellow oil was used immediately without further purification.

(94) 1-(4-((1H-1,2,4-triazol-1-yl)methyl)phenyl)azetidin-2-one)

Followed procedure for compound **93** with **91** (0.79 g, 2.56 mmol) to give product as a pale orange solid (0.38 g, 65%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.96 (s, 1H), 7.36 (d, J = 8.5, 2H), 7.26 (d, J = 8.5, 2H), 5.30 (s, 2H), 3.63 (t, J = 4.5, 2H), 3.13 (t, J = 4.5, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.61, 152.30, 143.01, 138.86, 129.82, 129.24, 116.72, 53.29, 38.22, 36.39.

(95) 1-(4-benzhydrylphenyl)azetidin-2-one

Followed procedure for compound **93** with **92** (0.64 g, 1.6 mmol) to give product as a white solid (0.23 g, 45%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 6H), 7.22 – 7.16 (m, 2H), 7.11 – 7.04 (m, 6H), 5.50 (s, 1H), 3.52 (t, J = 4.5, 2H), 3.03 (t, J = 4.5, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.36, 143.81, 139.52, 136.88, 130.14, 129.38, 128.39, 126.41, 116.13, 56.32, 38.04, 36.14.

(96) 6-(morpholinomethyl)-2,3-dihydroquinolin-4(1H)-one

Compound **93** (0.51 g, 2.06 mmol) was dissolved in DCE (30 mL). TfOH (0.55 mL, 6.18 mmol) was then added carefully via syringe. The resulting bright red solution was stirred at r.t. for 3 h, after which time H_2O (20 mL) was added. The reaction mixture was transferred to a separatory funnel, and sat. $NaHCO_3$ was added. The aqueous layer was extracted with DCM (3x). Combined organic layers were dried with $MgSO_4$, and solvents were filtered and removed under reduced pressure to give product as a yellow oil (0.13 g, 26%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 2.1, 1H), 7.32 (dd, J = 8.4, 2.1, 1H), 6.66 (d, J = 8.4, 1H), 3.72 – 3.66 (m, 4H), 3.56 (td, J = 7.5, 7.1, 1.9, 2H), 3.38 (s, 2H),

2.68 (t, J = 7.0, 2H), 2.44 – 2.39 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.01, 151.60, 136.56, 129.84, 119.97, 118.72, 116.15, 66.97, 62.62, 53.41, 42.49, 38.11.

(97) 6-((1H-1,2,4-triazol-1-yl)methyl)-2,3-dihydroquinolin-4(1H)-one)

Followed procedure for compound **96** with **94** (0.38 g, 1.67 mmol) to give product as a yellow oil that solidified upon standing after purification by column chromatography (12:1 DCM/MeOH, 1% Et_3N), (0.10 g, 26%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.94 (s, 1H), 7.81 (d, J = 2.0, 1H), 7.23 (dd, J = 8.5, 2.2, 1H), 6.69 (d, J = 8.5, 1H), 5.21 (s, 2H), 4.80 (br s, 1H), 3.58 (td, J = 7.8, 7.4, 2.0, 2H), 2.69 (t, J = 6.8, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.24, 152.21, 152.17, 142.84, 135.11, 127.78, 123.62, 118.96, 116.88, 53.16, 41.99, 37.83.

(98) 6-benzhydryl-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **96** with **95** (0.23 g, 0.73 mmol) to give product as a yellow oil (0.24 g, 100%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 2.0, 1H), 7.27 – 7.21 (m, 4H), 7.20 – 7.14 (m, 2H), 7.09 (d, J = 7.3, 4H), 7.05 (dd, J = 8.5, 2.2, 1H), 6.55 (d, J = 8.5, 1H), 5.41 (s, 1H), 4.44 (br s, 1H), 3.45 (t, J = 6.5, 2H), 2.61 (t, J = 7.2, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.84, 150.82, 143.82, 136.42, 133.50, 129.30, 128.39, 127.77, 126.36, 119.00, 116.16, 56.02, 42.46, 38.15.

(99) ((4-nitrophenyl)methylene)dibenzene

4-nitrobenzaldehyde (0.36 g, 2.4 mmol) was dissolved in anhydrous benzene (30 mL). TfOH (6 mL) was then added via syringe. The resulting bright red solution was stirred at 50 °C under an inert atmosphere for 45 min, after which time it was poured slowly and carefully into cold water. The aqueous layer was extracted with DCM (3x). Combined organic extracts were washed with brine and dried with $MgSO_4$. Solvents were filtered

and removed under reduced pressure to give product as a yellow solid (0.64 g, 93%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.11 – 8.07 (m, 2H), 7.32 – 7.20 (m, 8H), 7.08 (d, J = 7.3, 4H), 5.62 (s, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 151.65, 146.53, 142.35, 130.29, 129.35, 128.72, 126.98, 123.58, 56.65.

(100) 4-benzhydrylaniline

To 10% Pd/C in a hydrogenation vessel was added compound **99** (0.64 g, 2.2 mmol) dissolved in 1:1 MeOH/EtOAc (30 mL). The mixture was shaken under 40 psi H_2 for 1 h at r.t, after which time the mixture was filtered through a plug of Celite, and solvents were removed under reduced pressure. The residue was re-dissolved in DCM, and 2M NaOH was added. The aqueous layer was extracted with DCM (3x). Combined organic extracts were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure to give product as an orange solid (0.53 g, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J = 7.6, 4H), 7.14 (t, J = 6.9, 2H), 7.09 (d, J = 7.6, 4H), 6.85 (d, J = 8.3, 2H), 6.51 (d, J = 8.2, 2H), 5.41 (s, 1H), 3.43 (br s, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.67, 144.54, 133.92, 130.24, 129.41, 128.24, 126.13, 115.03, 56.03.

(101) 3-azaspiro[5.5]undecane

To a stirring solution of LAH (0.60 g, 15.9 mmol) in THF (20 mL) was added 3-azaspiro[5.5]undecane-2,4-dione (0.29 g, 1.6 mmol) dropwise. The solution was heated to 70 °C and stirred at reflux for 26 h, after which time it was cooled to 0 °C and quenched with H_2O (0.4 mL), 2M NaOH (0.4 mL) and H_2O (2 mL) sequentially. The resulting slurry was diluted with DCM and filtered. The organic layer was washed with brine. Solvents were filtered and removed under reduced pressure to give product as a

yellow oil (0.16 g, 65%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.82 (t, J = 5.8, 4H), 1.43 (t, J = 5.8, 4H), 1.39 – 1.24 (m, 10H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 41.16, 36.50, 35.93, 30.97, 26.64, 21.22.

(102) (S)-N-((R)-1-acetyl-6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide)

Followed procedure for compound **68** with the following modification: before coupling to Boc-Dmt, the HCl salt was stirred in 1:1 TFA/DCM (10 mL) for 30 minutes. TFA/DCM were removed under reduced pressure, and residue was dried under vacuum. After coupling to Boc-Dmt, DMF was removed under reduced pressure and the crude residue was passed through a plug of silica (1:1 hex/EtOAc). Solvents were removed under reduced pressure and residue was dried under vacuum. The residue was then stirred in excess 1:1 acetic anhydride/pyridine overnight under an inert atmosphere, after which time solvents were removed under reduced pressure and then stirred with 1:1 TFA/DCM (10 mL) to give a white solid after HPLC purification. (MS)EI: 527.3 (M+H), Retention Time: 22.35 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.76 (s, 1H), 7.45 (s, 1H), 7.41 (dd, J = 8.5, 2.1, 1H), 7.34 – 7.22 (m, 3H), 7.14 (d, J = 7.7, 1H), 6.52 (s, 2H), 4.98 (t, J = 6.0, 1H), 4.43 (s, 2H), 4.36 (s, 2H), 3.87 (dd, J = 11.7, 4.9, 1H), 3.83 – 3.74 (m, 1H), 3.28 – 3.11 (m, 4H), 3.05 (dd, J = 13.7, 4.9, 1H), 2.28 (s, 6H), 2.26 (s, 3H), 1.95 – 1.79 (m, 1H), 1.61 – 1.44 (m, 1H).

(103) (S)-N-((R)-1-acetyl-6-((7-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with the following modification: before coupling to Boc-Dmt, the HCl salt was stirred in 1:1 TFA/DCM (10 mL) for 30 minutes. TFA/DCM were removed under reduced pressure, and residue was dried under vacuum. After coupling to Boc-Dmt, DMF was removed under reduced pressure and the crude residue was passed through a plug of silica (1:1 hex/EtOAc). Solvents were removed under reduced pressure and residue was dried under vacuum. The residue was then stirred in excess 1:1 acetic anhydride/pyridine overnight under an inert atmosphere, after which time solvents were removed under reduced pressure and then stirred with 1:1 TFA/DCM (10 mL) to give a white solid after HPLC purification. (MS)EI: 545.3 (M+H), Retention Time: 22.8 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 1.38-1.81 (m, 2H), 2.16 (s, 3 H), 2.19 (s, 6 H), 2.94-3.81 (qd, J = 312.8, 4.8 Hz, 2H), 3.10 (m, 2H), 3.16 (m, 2H), 3.70-3.73 (m, 1H), 4.27 (s, 2H), 4.34 (s, 2H), 4.88 (m, 1H), 6.42 (s, 2H), 6.85 (dd, J = 6.8, 2.4 Hz, 1H), 6.96 (td, J = 6, 2.4 Hz, 1H), 7.17 (dd, J = 5.2, 3.2 Hz, 1H), 7.31 (dd, J = 6.4, 2 Hz, 1H), 7.36 (s, 1H).

(104) (S)-N-((R)-1-acetyl-6-((8-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with the following modification: before coupling to Boc-Dmt, the HCl salt was stirred in 1:1 TFA/DCM (10 mL) for 30 minutes. TFA/DCM were removed under reduced pressure, and residue was dried under vacuum. After coupling to Boc-Dmt, DMF was removed under reduced pressure and the crude residue was passed through a plug of silica (1:1 hex/EtOAc). Solvents were removed under reduced pressure and residue was dried under vacuum. The residue was then stirred

in excess 1:1 acetic anhydride/pyridine overnight under an inert atmosphere, after which time solvents were removed under reduced pressure and then stirred with 1:1 TFA/DCM (10 mL) to give a white solid after HPLC purification. (MS)EI: 595.3 (M+H), Retention Time: 26.5 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 1.46-1.90 (m, 2H), 2.25 (s, 3 H), 2.28 (s, 6 H), 3.03-3.89 (qd, J = 289.2, 4.8 Hz, 2H), 3.24-3.30 (m, 4H), 3.60 (br. s, 2H), 3.80-3.85 (m, 1H), 4.48 (m, 1H), 4.56 (s, 2H), 4.97 (m, 1H), 6.51 (s, 2H), 7.42 (d, J = 6.4 Hz, 1H), 7.48-7.55 (m, 3H), 7.66 (d, J = 6.8 Hz, 1H), 7.74 (m, 1H), 8.24 (d, J = 8 Hz, 1H).

(105) (S)-N-((R)-1-acetyl-6-(isoindolin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide)

Followed procedure for compound **68** with the following modification: before coupling to Boc-Dmt, the HCl salt was stirred in 1:1 TFA/DCM (10 mL) for 30 minutes. TFA/DCM were removed under reduced pressure, and residue was dried under vacuum. After coupling to Boc-Dmt, DMF was removed under reduced pressure and the crude residue was passed through a plug of silica (1:1 hex/EtOAc). Solvents were removed under reduced pressure and residue was dried under vacuum. The residue was then stirred in excess 1:1 acetic anhydride/pyridine overnight under an inert atmosphere, after which time solvents were removed under reduced pressure and then stirred with 1:1 TFA/DCM (10 mL) to give a white solid after HPLC purification. (MS)EI: 513.3 (M+H), Retention Time: 20.87 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.75 (br s, 1H), 7.49 – 7.34 (m, 6H), 6.52 (s, 2H), 4.99 (t, J = 6.1, 1H), 4.69 – 4.59 (m, 4H), 4.58 – 4.49 (m, 2H), 3.89 (dd, J = 11.7, 4.8, 1H), 3.86 – 3.75 (m, 1H), 3.29 – 3.19 (m, 2H), 3.06 (dd, J = 13.7, 4.8, 1H), 2.29 (s, 6H), 2.26 (s, 3H), 1.94 – 1.83 (m, 1H), 1.55 – 1.46 (m, 1H).

(106) (S)-N-((R)-1-acetyl-6-(((4aR,8aS)-octahydroisoquinolin-2(1H)-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide)

Followed procedure for compound **68** with the following modification: before coupling to Boc-Dmt, the HCl salt was stirred in 1:1 TFA/DCM (10 mL) for 30 minutes. TFA/DCM were removed under reduced pressure, and residue was dried under vacuum. After coupling to Boc-Dmt, DMF was removed under reduced pressure and the crude residue was passed through a plug of silica (1:1 hex/EtOAc). Solvents were removed under reduced pressure and residue was dried under vacuum. The residue was then stirred in excess 1:1 acetic anhydride/pyridine overnight under an inert atmosphere, after which time solvents were removed under reduced pressure and then stirred with 1:1 TFA/DCM (10 mL) to give a white solid after HPLC purification. (MS)EI: 533.3 (M+H), Retention Time: 25.60 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.75 (br s, 1H), 7.35 (d, J = 7.3, 2H), 6.52 (s, 2H), 4.98 (t, J = 5.8, 1H), 4.27 – 4.13 (m, 2H), 3.87 (dd, J = 11.7, 4.8, 1H), 3.83 – 3.74 (m, 1H), 3.48 – 3.39 (m, 1H), 3.36 – 3.32 (m, 1H), 3.29 – 3.22 (m, 1H), 3.22 – 3.13 (m, 1H), 3.05 (dd, J = 13.6, 4.8, 1H), 3.01 – 2.90 (m, 1H), 2.66 (t, J = 12.0, 1H), 2.28 (s, 6H), 2.25 (s, 3H), 1.92 – 0.95 (m, 14H).

2.4.2 In Vitro Assays

Binding affinity (K_i) was measured by the competitive displacement of [^{3}H]-diprenorphine (a non-selective opioid antagonist) in C6 cells stably expressing MOR or DOR, or Chinese Hamster Ovary (CHO) cells stably expressing KOR. In vitro potencies (EC_{50}) and efficacies (as maximal % stimulation) were obtained by agonist-stimulated [^{35}S]-GTPγS binding in the same cell types using previously described protocols.[42,86]

2.4.3 Animals and Antinociception

Adult male C57BL/6 mice, purchased from Harlan Laboratories (IN, USA) and weighing between 20-30g at 8-16 weeks old, were used for the described experiments. 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 12h light/dark cycle (with lights on at 0700). Each mouse was used only once and experiments were conducted between 9 am and 5 pm. 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.

All compounds were dissolved in sterile saline and administered by intraperitoneal injection in a volume of 10 mL/kg of body weight. Antinociceptive effects were evaluated in the warm water tail withdrawal (WWTW) assay. Tail withdrawal latencies were determined by briefly placing a mouse into a plastic, cylindrical restrainer and putting 2-3 cm of the tail tip into a water bath maintained at 50°C. The latency to tail withdrawal or rapidly flicking the tail back and forth was recorded with a maximum cutoff time of 20 sec. If the mouse did not remove its tail by the cutoff time, the experimenter removed its tail from the water to prevent tissue damage.

Acute antinociceptive effects were determined using a cumulative dosing procedure. Each animal received an injection of saline ip and then 30 min later, baseline withdrawal latencies (3-6 sec) were recorded. Following baseline determinations, increasing cumulative doses of the test compound were given ip at 30 min intervals. Thirty min after each injection, the tail withdrawal latency was measured as described above.

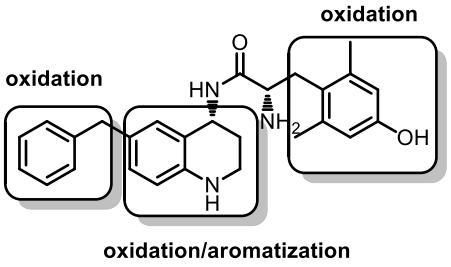
CHAPTER 3

FURTHER MODIFICATIONS TO THE THQ PEPTIDOMIMETICS[b]

3.1 Introduction

In order to better understand the metabolism of the THQ peptidomimetics in order to develop compounds with a longer total duration of action in vivo, compound **1** was incubated in mouse liver microsomes, and the resulting metabolites were analyzed via LC/MS/MS. The compound was found to have a half-life of < 5 minutes in this assay, and several major phase 1 metabolic hotspots were identified, as shown in Figure 18.

Figure 18. Metabolic Hotspots of Compound **1** in Mouse Liver Microsomes



The three major areas of the compound found to be the most subject to oxidation were the benzyl pendant, the THQ core, and the aromatic portion of the 2'6'-dimethyl-L-tyrosine moiety. This information was used to guide further SAR on the THQ scaffold, namely the replacement of the proposed metabolically labile positions with substitutions

[b] In vitro assays were performed by Nicholas Griggs and Mary Clark. In vivo work was done by Jessica Anand. Compound 199 was synthesized by Aubrie Harland. Compounds 138, 139, 141 and 142 were synthesized by Jeff Zwicker.

known to block or slow phase 1 metabolism. It was thought that compounds with a longer half-life in mouse liver microsomes would lead to analogues with a longer duration of action in vivo. Modifications were thus made (1) on the di-benzylic position between the pendant and the THQ core, and (2) to the THQ core itself to discourage aromatization. Although none of the compounds subsequently tested in mouse liver microsomes were found to improve upon the metabolic half-life of compound **1** (the half-life of all compounds tested was found to be < 5 minutes), the modifications made to these three areas led to a number of analogues with interesting in vitro profiles. Changes to areas of this scaffold other than the aromatic pendant group (discussed in Chapter 2) have proven invaluable as a means by which to toggle selectivity between the different opioid receptor types.

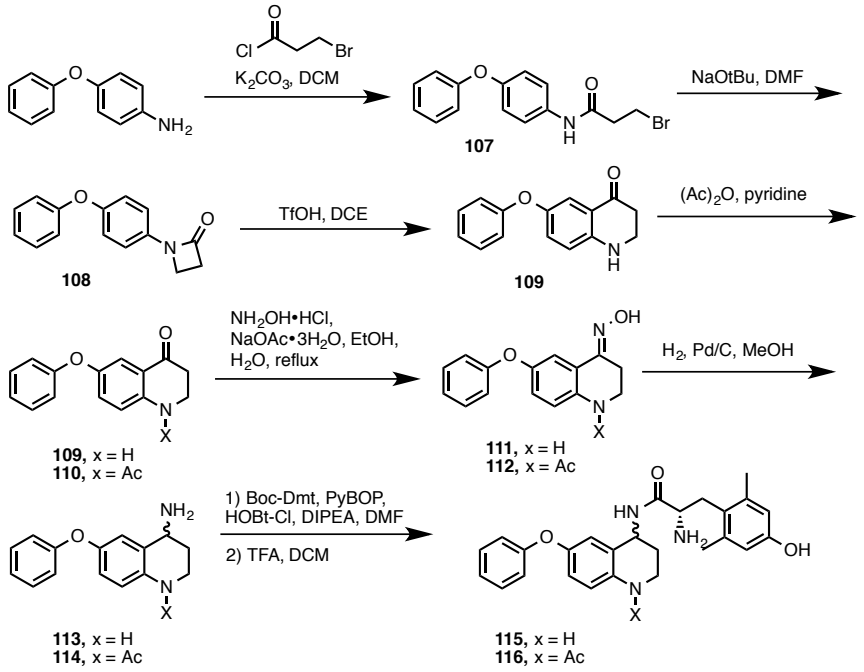
RESULTS AND DISCUSSION

3.2 Modifications to the Di-Benzylic Position

Carbon atoms adjacent to an aromatic system are known to be particularly susceptible to phase 1 metabolic oxidation,[87] and it was hypothesized based on LC/MS/MS analysis that the THQ analogues submitted for stability testing in mouse liver microsomes were likely getting hydroxylated at the di-benzylic position adjacent to the pendant (Chapter 2). This position was therefore initially replaced with oxygen, resulting in a diaryl ether system. An oxygen substitution at this position would certainly block any type of oxidation, and diaryl ether compounds are known to be particularly resistant to metabolic degradation.[88]

The first two analogues in this series, **115** and **116**, were synthesized as shown in Scheme 8. Commercially available 4-phenoxyaniline was acylated with 3-bromopropionyl chloride to give **107**, which was then cyclized as the β-lactam and rearranged under Friedel-Crafts conditions to give ketone intermediate **109**.

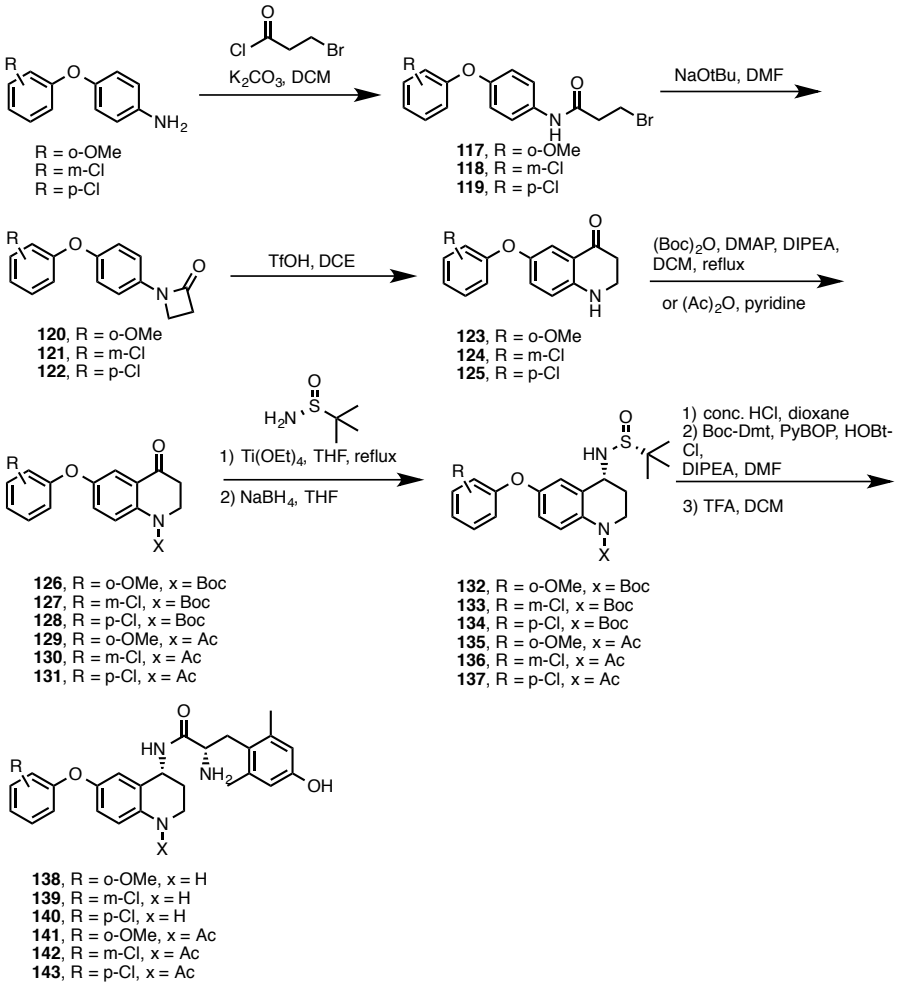
Scheme 8. Synthesis of Analogues **115** and **116**



Ketone **109** was then carried forward without modification, and with first introducing an acetyl group (**110**). Since it was found that substituting the THQ nitrogen with an acyl group often increased binding affinity at DOR (Chapter 2), a similar modification in this series was attempted. Oxime formation on both intermediates and subsequent hydrogenation gave racemic amine intermediates **113** and **114**, to which Boc-protected 2',6'-dimethyl-L-tyrosine could be coupled and deprotected with TFA to give **115** and **116** as two different diastereomers which could be separated by RP-HPLC to give four total analogues (**115E**, **115L**, **116E**, and **116L**).

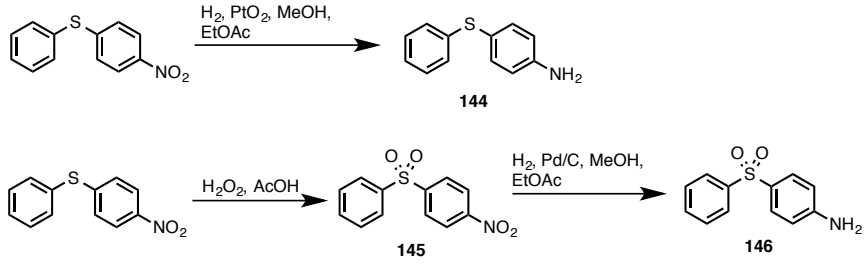
Given that the early eluting diastereomer for both of these compounds (**115E** and **116E**) showed a much better in vitro profile than the late eluting diastereomer as shown in Table 4 (like the straight chain alkyl analogues discussed in Chapter 2), the remainder of the analogues in this series were synthesized asymmetrically to give the presumed *R* stereochemistry at position 4, similar to the chemistry shown in Scheme 3 (Chapter 2). The synthesis of these analogues was carried forward starting from commercially available substituted 4-phenoxyanilines, as shown in Scheme 9.

Scheme 9. Synthesis of Analogues **138-143**

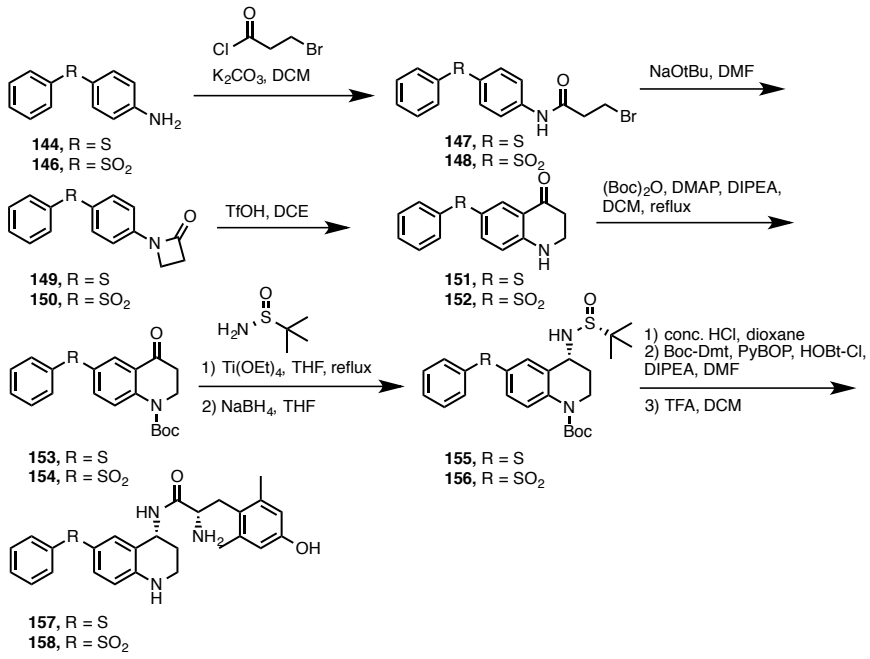


In addition to oxygen, the di-benzylic position was also replaced with a thioether and a sulfonyl moiety (Scheme 11), both starting from commercially available (4-nitrophenyl)(phenyl)sulfane (Scheme 10) to give analogues **157** and **158**.

Scheme 10. Synthesis of Intermediates **144** and **146**



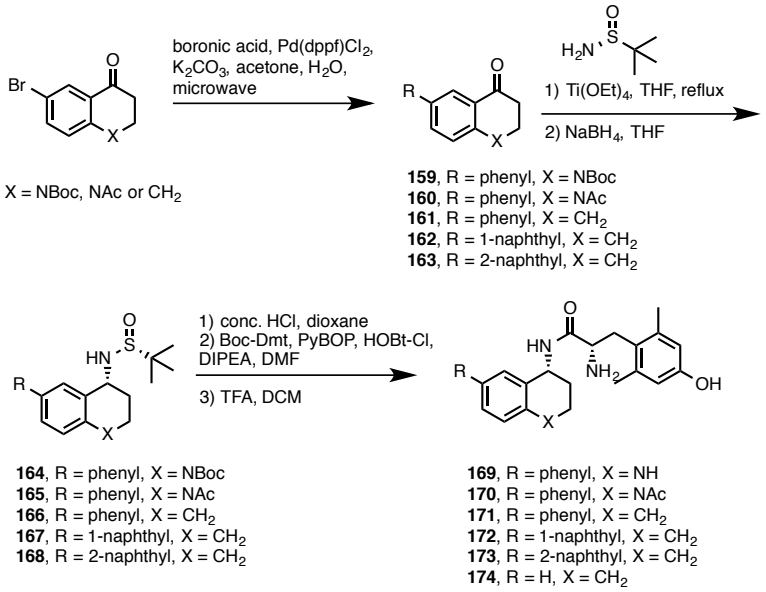
Scheme 11. Synthesis of Analogues **157** and **158**



Lastly, the di-benzylic position was removed entirely, and a series of less flexible analogues in which an aromatic moiety was fused directly to a THQ or

tetrahydronaphthalene (THN) core were synthesized (**169-173**, Scheme 12), as well as a THN analogue without any substitution at the 6 position (**174**).

Scheme 12. Synthesis of Analogues **169-174**[a]



X = NBoc, NAc or CH_2

159, R = phenyl, X = NBoc
160, R = phenyl, X = NAc
161, R = phenyl, X = CH_2
162, R = 1-naphthyl, X = CH_2
163, R = 2-naphthyl, X = CH_2

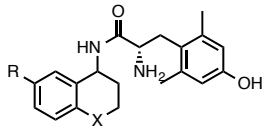
164, R = phenyl, X = NBoc
165, R = phenyl, X = NAc
166, R = phenyl, X = CH_2
167, R = 1-naphthyl, X = CH_2
168, R = 2-naphthyl, X = CH_2

169, R = phenyl, X = NH
170, R = phenyl, X = NAc
171, R = phenyl, X = CH_2
172, R = 1-naphthyl, X = CH_2
173, R = 2-naphthyl, X = CH_2
174, R = H, X = CH_2

a. See ref. 61 for synthesis of N-Boc and N-Ac starting materials.

Binding affinity and efficacy data for analogues modified at the benzylic position is summarized in Table 4.

Table 4. Opioid Receptor Binding Affinities and Efficacies for Analogues Modified at the di-benzylic Position[a]



			MOR			DOR			KOR		
	R	**X**	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
1E		NH	0.22 ± 0.02	1.6 ± 0.3	81 ± 2	9.4 ± 0.8	110 ± 6	16 ± 2	68 ± 2	540 ± 72	22 ± 2
115E		NH	0.42 ± 0.04	15 ± 5	68 ± 2	14 ± 7	dns	dns	65 ± 10**	957*	24*
115L		NH	41 ± 6	-	-	277 ± 50**	2000*	20*	-	-	-
116E		NAc	0.09 ± 0.02	6.5 ± 3	77 ± 3	4.2 ± 1.3	222*	16*	33 ± 0.1**	1084*	37*

			MOR			DOR			KOR		
	R	**X**	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
116L		NAc	6.3 ± 1.4	600 ± 300	60 ± 2	93 ± 20**	204*	16*	787*	-	-
138		NH	0.36 ± 0.04	33 ± 14	41 ± 6	10 ± 0.7**	dns*	dns*	-	-	-
139		NH	0.08 ± 0.01	9.1 ± 2	46 ± 19	2.59*	-	-	-	-	-
140		NH	0.1 ± 0.03	9.7 ± 1.3	53 ± 4	12.1 ± 3.5	dns	dns	24.8*	-	-
141		NAc	0.27 ± 0.05	32.3 ± 14	42 ± 12	2.7*	-	-	-	-	-
142		NAc	0.05 ± 0.01	8.1 ± 4.8	72 ± 2	5.0 ± 0.3	dns	dns	21.02*	791.2*	55*
143		NAc	0.1 ± 0.03	7 ± 1.5	61 ± 7	3.1 ± 0.7	dns	dns	45 ± 7**	1819*	47*
157		NH	0.45 ± 0.1	4.7 ± 1.4	52 ± 6	5.1 ± 0.5	dns*	dns*	11 ± 6	1120*	22*
158		NH	3.01 ± 1.9	32 ± 20	64 ± 9	2.9 ± 0.4	dns*	dns*	26 ± 7	1307*	38*
169		NH	1.1 ± 0.4	19 ± 3	31 ± 5	13.4 ± 4.3	dns	dns	54 ± 4	930 ± 220	57 ± 3
170		NAc	0.88 ± 0.4	5.6 ± 0.4	51 ± 8	1.3 ± 0.4	92 ± 9	47 ± 6	35.8 ± 17	291 ± 33	69 ± 5
171		CH_2	0.57 ± 0.3	9.5 ± 3	29 ± 2	4.0 ± 1.3	181 ± 28	21 ± 11	21 ± 4**	321 ± 180**	46 ± 2**
172		CH_2	5.4 ± 3	dns	dns	46 ± 30	dns	dns	131 ± 42**	dns	dns
173		CH_2	0.24 ± 0.1	dns	dns	6.03 ± 2	dns	dns	316 ± 0.91**	dns	dns
174	H	CH_2	25.7 ± 11	dns	dns	640 ± 220**	dns	dns	2060 ± 580	dns*	dns*

[a.] dns = does not stimulate. See Table 1 for further in vitro details. * = n of 1, ** = n of 2. Dashed line indicates assay was not performed. Structure above table does not distinguish if compound was synthesized asymmetrically to give the 4R stereochemistry, or as a mixture. See individual schemes for specific stereochemistry information.

The in vitro data for the diastereomeric pairs of diarylether analogues **115** and **116** show a trend that is consistent with the analogous carbon analogues discussed in Chapter 2. In both cases, the early eluting (and presumably *R*) diastereomer shows better binding affinity at both MOR and DOR, and N-acetylated compound **116E** exhibits improved

DOR binding affinity as compared to **115E**. Preliminary aryl substitutions on the diarylether pendant (**138-143**) are fairly well tolerated in terms of maintaining binding affinity at MOR and DOR, although MOR potency and efficacy is somewhat reduced in the case of ortho-methoxy substituted compounds **138** and **141**. Thioether analogue **157** displays improved MOR binding affinity as compared to sulfone analogue **158**, although both compounds exhibit low nanomolar potency and moderately high MOR stimulation.

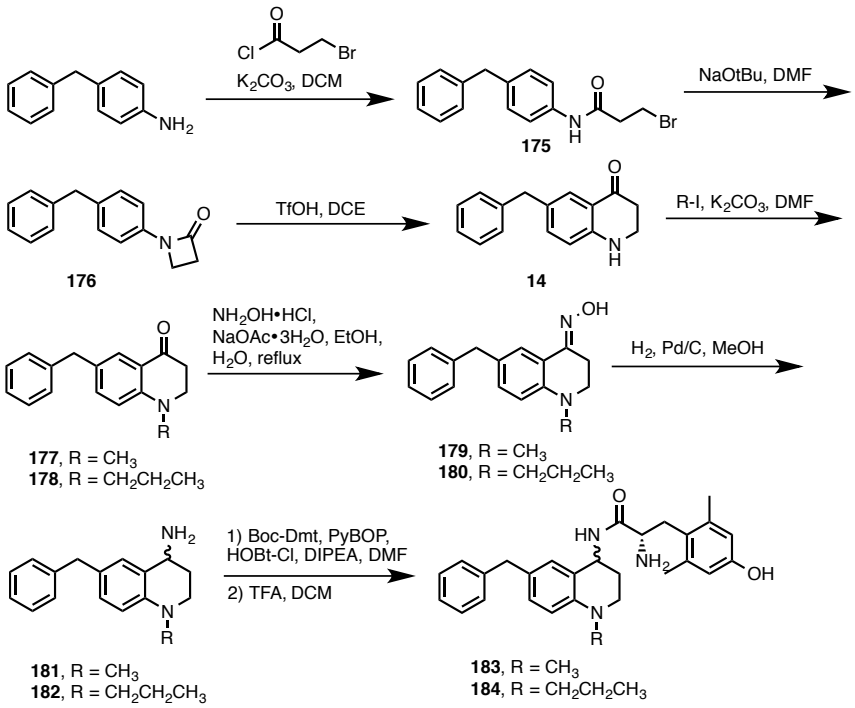
Analogues **169-173**, in which the aryl pendant is fused directly to the core of the molecule, display a broad range of binding affinities for MOR. N-acetylated analogue **170** displays superior MOR stimulation (and DOR binding affinity) compared to the other analogues in this series. Additionally, 1-naphthyl analogue **172** shows a marked loss in MOR and DOR binding affinity as compared to 2-naphthyl analogue **173**. Neither **172** or **173** showed any stimulation at MOR or DOR, presumably due to steric clash between residues in the active site and the rigid, bulkier naphthyl group (as compared to the phenyl analogues). Compound **174**, in which the 6-position pendant is removed entirely, leads to a loss of binding affinity and efficacy at MOR.

3.3 Modifications to the THQ Core

Given the observation that an acetyl substitution on the THQ nitrogen (Chapter 2) improves binding affinity at DOR, it was decided that a number of additional modifications should be made to this position. As shown in Scheme 13, commercially available 4-benzylaniline was acylated with 3-bromopropionyl chloride, and cyclized to the corresponding β-lactam with NaOtBu, and cyclized again to give substituted tetrahydroquinoline **14**. Preliminary modifications to **14** at the THQ nitrogen were short

alkyl chains, namely a methyl and a 1-propyl substitution (introduced by heating with base and the appropriate alkyl iodide) to give ketone intermediates **177** and **178**. These intermediates were carried forward as described previously in Scheme 8 to give final analogues **183** and **184** (Scheme 13). Additionally, ketone **14** was first reduced to give substituted tetrahydroquinoline **185**, which was cyclized with N,N-dimethylacrylamide and trifluoromethanesulfonic anhydride to give tricyclic intermediate **186**[89] which was carried forward asymmetrically as previously described in Scheme 12 to give tricyclic analogue **188** (Scheme 14). Despite the superior MOR efficacy afforded by these analogues (Table 5), N-alkyl analogues of this nature were found to oxidize rapidly when left at room temperature, and further alkyl substitutions of this type were not explored.

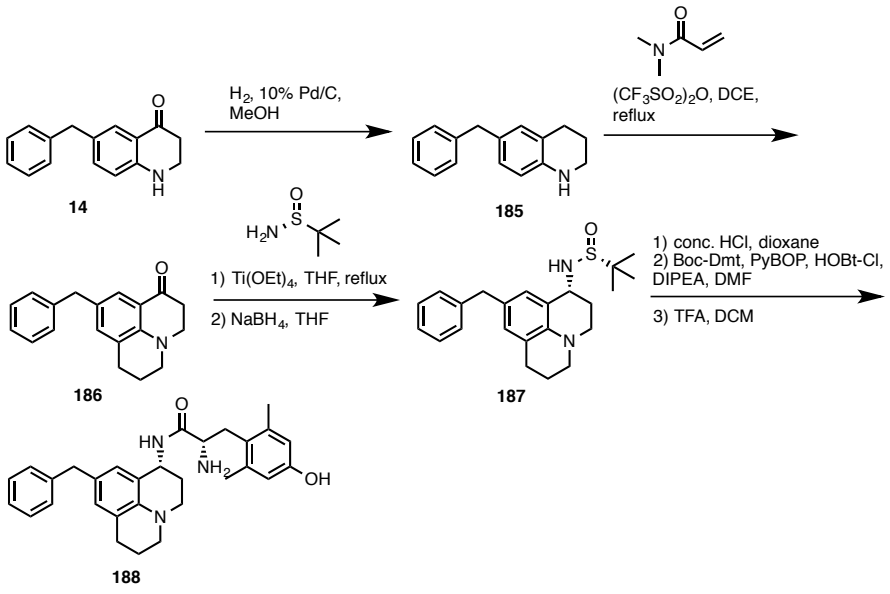
Scheme 13. Synthesis of Analogues **183** and **184**



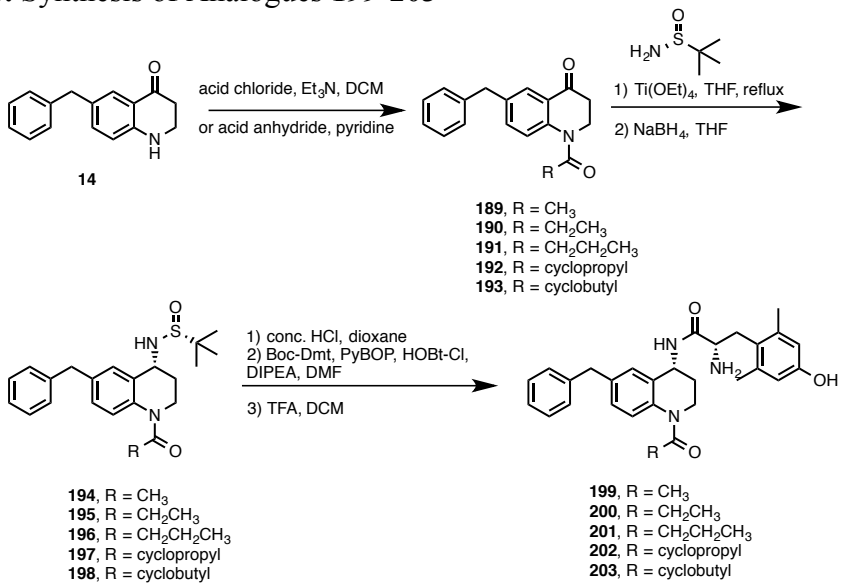
The hypothesis that an N-acyl substitution on the THQ nitrogen should be resistant to oxidative aromatization led to the synthesis of a number of other acyl chains

of varying length at this position. Starting again from ketone intermediate **14**, these substitutions were introduced by stirring with the appropriate acid chloride and Et_3N, or with the appropriate acid anhydride and pyridine to give N-acyl intermediates **189-193** (Scheme 15). From the resulting N-acyl intermediates were then prepared the corresponding tert-butanesulfinamides as previously discussed, which were then cleaved with concentrated HCl, coupled to Boc-Dmt and deprotected to give final intermediates **199-203** (Scheme 15).

Scheme 14. Synthesis of Analogue **188**



Scheme 15. Synthesis of Analogues **199-203**



14

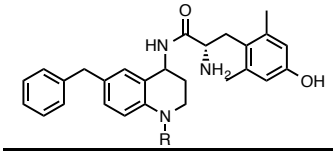
189, R = CH_3
190, R = CH_2CH_3
191, R = $CH_2CH_2CH_3$
192, R = cyclopropyl
193, R = cyclobutyl

194, R = CH_3
195, R = CH_2CH_3
196, R = $CH_2CH_2CH_3$
197, R = cyclopropyl
198, R = cyclobutyl

199, R = CH_3
200, R = CH_2CH_3
201, R = $CH_2CH_2CH_3$
202, R = cyclopropyl
203, R = cyclobutyl

The in vitro data for MOR, DOR and KOR for analogues with substitutions on the THQ nitrogen are summarized in Table 5.

Table 5. Opioid Receptor Binding Affinities and Efficacies for Analogues Substituted at the THQ Nitrogen[a]



		MOR			DOR			KOR		
	R	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
1E	H	0.22 ± 0.02	1.6 ± 0.3	81 ± 2	9.4 ± 0.8	110 ± 6	16 ± 2	68 ± 2	540 ± 72	22 ± 2
183E	Me	0.56 ± 0.2	4 ± 0.9	102 ± 5	7.3 ± 4	dns	dns	27.8 ± 0.7	2200 ± 1000	44 ± 8
183L	Me	71 ± 18	214 ± 40	72 ± 4	138 ± 30	dns	dns	632 ± 80	dns	dns
184E	1-Pro	0.34 ± 0.2	16 ± 8	83 ± 3	1.7 ± 0.6	2300 ± 1000	39 ± 5	72 ± 20	5000 ± 1000	38 ± 3
188	Scheme 14	0.39 ± 0.1	1.1 ± 0.5	95 ± 4	2.3 ± 0.8	570 ± 300**	50 ± 14**	6.6 ± 3	1002*	78*
199		0.13 ± 0.2	6 ± 1	76 ± 4	1.7 ± 0.6	68 ± 2	26 ± 3	87 ± 11	1340 ± 93	29 ± 5

		MOR			DOR			KOR		
	R	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
200		0.12 ± 0.01	5.1 ± 2	90 ± 7	0.76 ± 0.4	41 ± 17	58 ± 6	27 ± 2**	1339*	14*
201		0.1 ± 0.03	18 ± 15	53 ± 3	0.41*	8.1 ± 0.9**	44 ± 3**	99.6*	1530 ± 200**	21 ± 3**
202		0.1 ± 0.03	1.8 ± 0.3	82 ± 4	0.35 ± 0.01	17.8 ± 8.5	70 ± 12	25 ± 5	dns	dns
203		0.14 ± 0.09	2.1 ± 0.2	94 ± 5	0.15 ± 0.07	5.6 ± 3	66 ± 10	41 ± 20	dns	dns

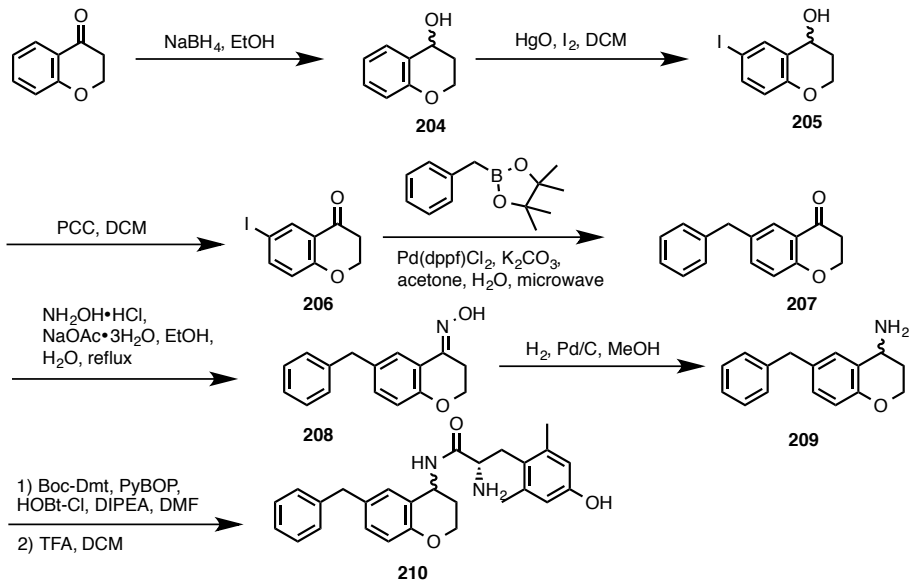
[a.] dns = does not stimulate. See Table 1 for further in vitro details. * = n of 1, ** = n of 2. Structure above table does not distinguish if compound was synthesized asymmetrically to give the 4R stereochemistry, or as a mixture. See individual schemes for specific stereochemistry information.

The early eluting diastereomer of methyl and propyl substituted analogues (**183** and **184** respectively) both display subnanomolar binding affinity for MOR and low nanomolar binding affinity for DOR, and both compounds are fully efficacious at MOR. Analogue **188**, in which the propyl substituent is tied into the adjacent aromatic ring, displays a similar overall profile, but with improved binding affinity for KOR. In the case of N-acylated analogues **199-203**, a longer and more bulky aliphatic group on the acyl chain corresponds to improved DOR binding affinity, and several of the analogues in this series, particularly cyclopropyl analogue **202** and cyclobutyl analogue **203**, display high efficacy at DOR.

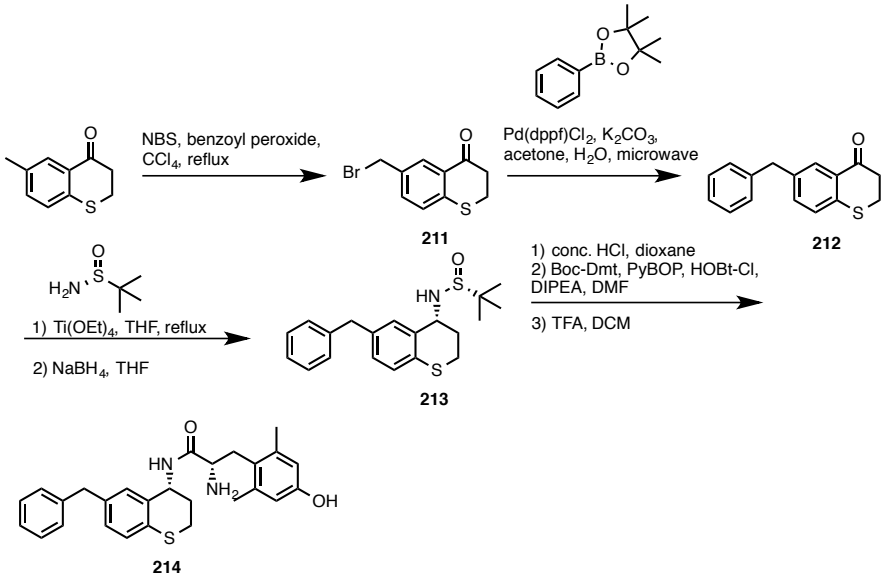
In addition to alkylation and acetylation of the THQ aniline, a number of other modifications to the THQ core were explored. Replacement at this position with an oxygen gave chroman analogue **210** (Scheme 16). This synthesis was accomplished through a Suzuki coupling between benzylboronic acid pinacol ester and iodo intermediate **206**, which was synthesized as previously described from commercially

available chroman-4-one.[90] Replacement with sulfur gave corresponding thiochroman analogue **214** (Scheme 17).

Scheme 16. Synthesis of Analogue **210**

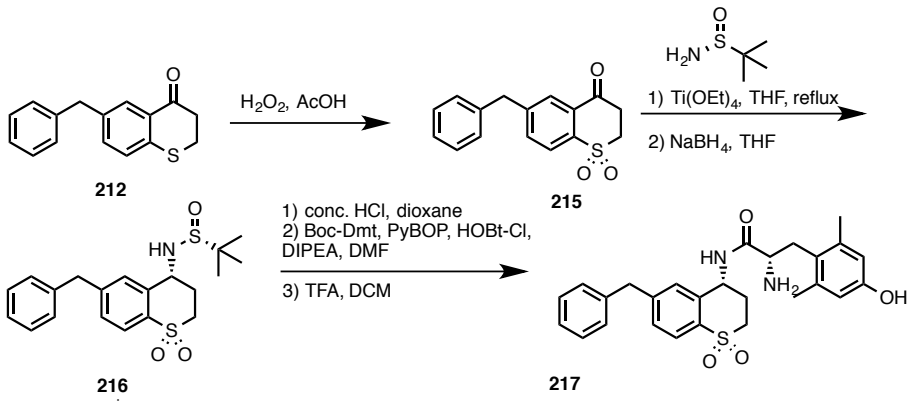


Scheme 17. Synthesis of Analogue **214**



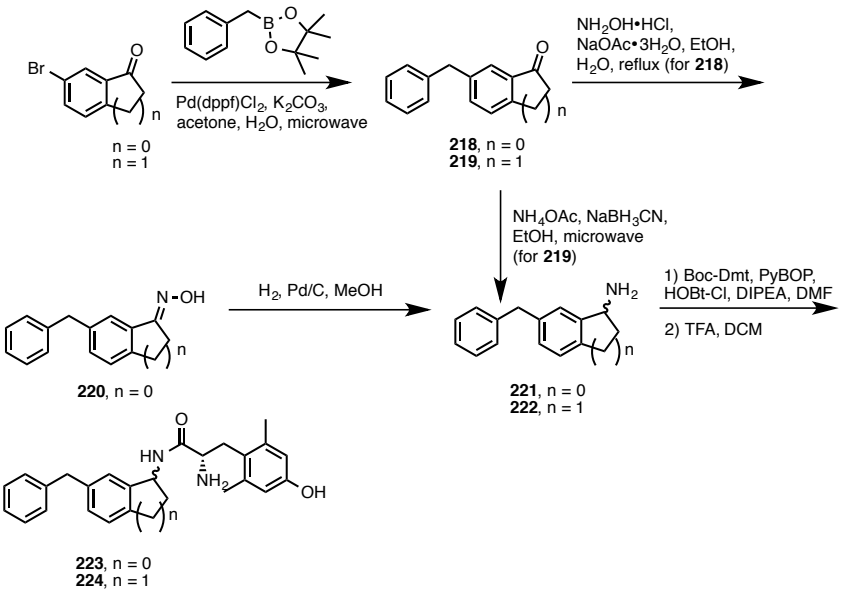
Oxidation of thiochroman intermediate **212** gave sulfone analogue **217** (Scheme 18).

Scheme 18. Synthesis of Analogue **217**



In order to explore changes to the flexibility and orientation of the fused 6-membered ring THQ core, analogues **223** and **224** (Scheme 19) were synthesized. In the case of analogue **224**, the THQ core was replaced with a 5-6 fused indanyl core. **224** was tested as a racemic mixture, as the resulting diastereomers proved inseparable by RP-HPLC. In the case of analogue **223**, the THQ core is replaced with an open phenethyl core, and the resulting diastereomers were separated by RP-HPLC and tested individually.

Scheme 19. Synthesis of Analogues **223** and **224**



Lastly, the THQ core was widened by one methylene to give benzo[b]azepine derivative **228** (Scheme 20). The results of these further modifications are summarized in Table 6.

Scheme 20. Synthesis of Analogue **228**

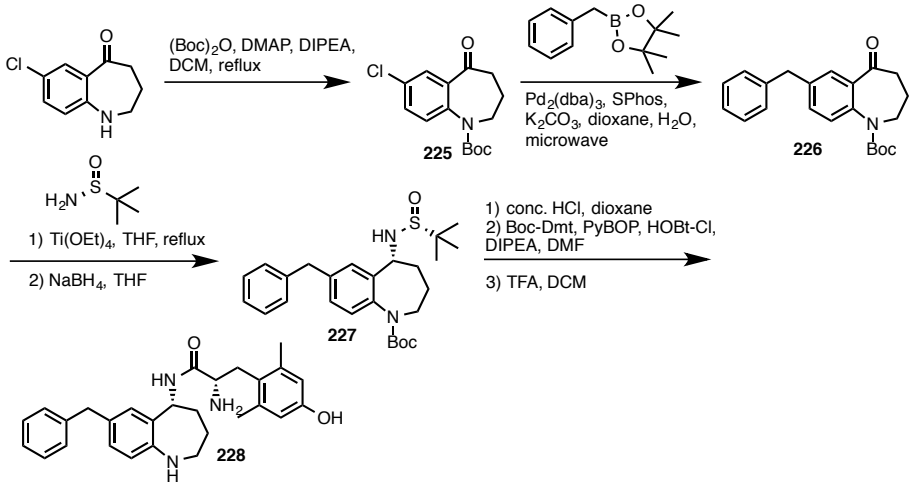
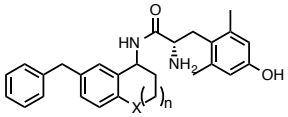


Table 6. Opioid Receptor Binding Affinities and Efficacies for Analogues Featuring Replacements to the THQ Nitrogen[a]



			MOR			DOR			KOR		
	X	n	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
1E	NH	1	0.22 ± 0.02	1.6 ± 0.3	81 ± 2	9.4 ± 0.8	110 ± 6	16 ± 2	68 ± 2	540 ± 72	22 ± 2
210E	O	1	0.046 ± 0.03	4.9 ± 2	70 ± 6	8.7 ± 1.6	dns	dns	58 ± 14	662 ± 150	28 ± 7
210L	O	1	6.1 ± 2	dns	dns	260 ± 60**	dns	dns	354 ± 40	dns	dns
214	S	1	0.15 ± 0.04	1.9 ± 0.5	80 ± 8	4.8 ± 1	dns	dns	48 ± 23	dns	dns
217	SO_2	1	0.06 ± 0.01	0.72 ± 0.1	94 ± 3	1.9 ± 1	100 ± 60	44 ± 4	27 ± 6	720 ± 320	36 ± 2
223E	H	0	11.2 ± 6	201 ± 130	45 ± 13	75 ± 10**	dns	dns	516 ± 150**	dns*	dns*
223L	H	0	0.62 ± 0.1	55 ± 6	42 ± 10	62 ± 12	1500 ± 700	12 ± 9	203 ± 13**	dns	dns
224	Scheme 19		0.55 ± 0.09	18 ± 8	43 ± 9	30 ± 10**	dns	dns	143 ± 45**	dns	dns
228	NH	2	0.41 ± 0.2	72 ± 23	73 ± 4	23 ± 2**	dns	dns	40 ± 20**	dns*	dns*

[a.] dns = does not stimulate. See Table 1 for further in vitro details. * = n of 1, ** = n of 2. Structure above table does not distinguish if compound was synthesized asymmetrically to give the 4R stereochemistry, or as a mixture. See individual schemes for specific stereochemistry information.

The early eluting diastereomer (presumably 4*R*) of chroman analogue **210** shows subnanomolar binding affinity and is fully efficacious at MOR. The same is true for thiochroman analogue **214** and sulfone analogue **217**. **217** in particular displays superior potency at MOR, as well as the best DOR binding affinity in this series. This is consistent with the earlier observation that extensions at this position of the core ring result in improved binding affinity at DOR, and can often increase potency and simulation as well. Interestingly, the late-eluting diastereomer of phenethyl analogue **223** displays a better in vitro profile at MOR than the early eluting diastereomer, although both show a comparable maximal stimulation at this receptor. **223**, **224** and **228** are all less potent at MOR than parent THQ compound **1**, suggesting that these changes to the THQ ring's size and flexibility profile are less than optimal.

3.4 Preliminary Amide Bond Substitutions

Preliminary alkyl substitutions were also made to the amide bond between the THQ core and 2',6'-dimethyl-L-tyrosine. Initially, a methyl substitution was examined, creating a tertiary amide bond that was hypothesized to be more resistant to metabolic degradation (**231**, Scheme 21). Like the other analogues described herein, **231** was not found to improve upon the metabolic half-life of **1** ($t_{1/2}$ < 5 min). Although the methyl substitution was found to not improve metabolic stability, analogue **232**, in which the amide bond was substituted with a cyclopropyl group (known to be highly resistant to metabolic de-alkylation[91,92]) was also synthesized.

231 and **232** were synthesized as shown in Scheme 21. In the case of **231**, ketone intermediate **14** was subject to reductive amination conditions in the presence of $Ti(OiPr)_4$, CH_3NH_2•HCl, Et_3N and $NaBH_4$ as a reducing agent.[93] In the case of analogue **232**, the reductive amination was performed with cyclopropylamine and $NaBH_3CN$ as the reducing agent under microwave conditions.[94] Both intermediates were then coupled to Boc-2',6'-dimethyl-L-tyrosine, deprotected, and purified by RP-HPLC to give two diastereomers that were tested separately (Table 7).

Scheme 21. Synthesis of Analogues **231** and **232**

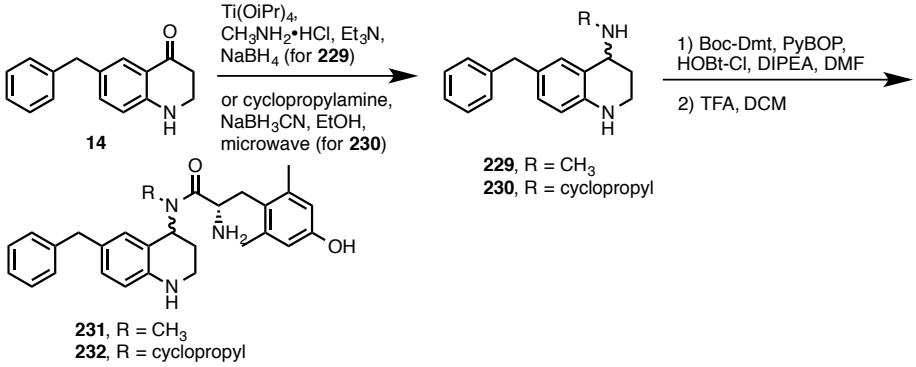
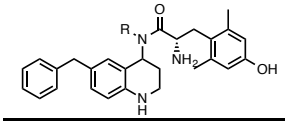


Table 7. Opioid Receptor Binding Affinities and Efficacies for Both Diastereomers of Analogues **231** and **232**[a]



		MOR			DOR			KOR		
	R	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
1E	H	0.22 ± 0.02	1.6 ± 0.3	81 ± 2	9.4 ± 0.8	110 ± 6	16 ± 2	68 ± 2	540 ± 72	22 ± 2
231E	Me	9 ± 0.3	3 ± 0.3	81 ± 5	16 ± 4	410 ± 140	13 ± 6	116 ± 30	dns	dns
231L	Me	0.8 ± 0.04	0.46 ± 0.1	66 ± 4	8.5 ± 0.2	dns	dns	4.1 ± 0.4	dns	dns
232E		26 ± 10	131 ± 20	16 ± 4	23 ± 11**	150 ± 40	20 ± 3	60 ± 30	dns	dns
232L		11 ± 6	28 ± 4	40 ± 11	53 ± 20	dns	dns	29 ± 7**	dns	dns

[a.] dns = does not stimulate. See Table 1 for further in vitro details. ** = n of 2. All analogues in this series were synthesized as a mixture of diastereomers.

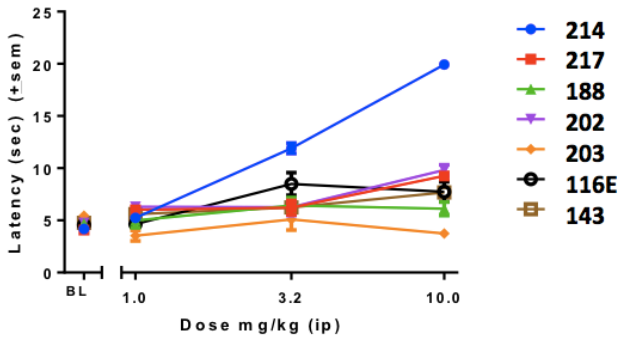
Unlike previous analogues, the early eluting diastereomer of **231** (**231E**) displays weaker binding at all three opioid receptors than the late eluting diasteromer (**231L**). Presumably, the late eluting analogue in this case has the 4*R* stereochemistry, although the superior MOR maximal stimulation of **231E** leaves this stereochemical assignment a bit ambiguous. Both diastereomers of cyclopropyl-substituted analogue **232** displayed low efficacy at MOR, and consequently bulkier substitutions on the amide bond were not explored.

3.5 In Vivo Data for Selected Analogues

On the basis of their favorable in vitro profiles, compounds **116E, 143, 188, 202, 203, 214**, and **217** were chosen for in vivo studies. In the mouse warm water tail withdrawal (WWTW) assay (Figure 19), thiochroman analogue **214** was fully efficacious, and produced dose-dependent increases in latency to tail flick. All other

analogues (including N-methyl amide analogue **231L**) produced either weak or insignificant antinociception at 10 mg/kg.

Figure 19. Cumulative Antinociceptive Dose-Response Curves for Analogues **116E, 143, 188, 202, 203, 214,** and **217** in the Mouse WWTW Assay After ip Administration (n = 3-6)[a]



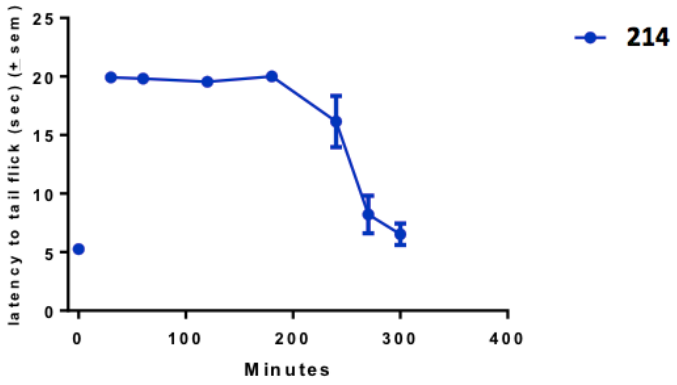
[a.] Data are plotted as mean ± SEM.

To determine the duration of action of compound **214**, tail withdrawal latencies were measured at intervals following the administration of a 10 mg/kg dose (Figure 20). Compound **214** showed a full antinociceptive response for just over 200 minutes before returning to baseline. Compared with the lead compound **1** (Figure 11), this compound displayed a much longer duration of action after ip injection (comparable to compounds **86** and **102**, see Figure 17, Chapter 2).

Although compound **214** was the only analogue in this series that displayed potent, dose-dependent antinociception at a dose of up to 10 mg/kg, the SAR discussed here on the THQ core revealed a number of important trends. Substitution on the THQ nitrogen with short alkyl or acyl substitutions was generally well tolerated in terms of preserving the desired MOR agonist/DOR antagonist profile, and such substitutions generally increased binding affinity at DOR. Longer and bulkier acyl chains at this

position resulted in improved DOR potency and efficacy relative to DPDPE, and heteroatom replacements of the THQ aniline preserved sub-nanomolar binding affinities and good potencies at MOR. Conversely, entire replacement of the THQ core through ring expansion or contraction resulted in analogues that did not improve upon the unaltered THQ core. Furthermore, removal of flexibility in the 6-position pendant resulted in analogues with diminished potency and efficacy at MOR.

Figure 20. Time Course of Antinociceptive Response For Analogue **214** in the Mouse WWTW Assay After ip Administration of a 10 mg/kg Dose



3.6 Experimental Procedures

3.6.1 Chemistry

For further general chemistry, *in vitro* and *in vivo* experimental detail, see section 2.4.

(107) 3-bromo-N-(4-phenoxyphenyl)propanamide

To a dry flask was added 4-phenoxyaniline (5.03 g, 27.2 mmol) and K_2CO_3 (7.50 g, 54.3 mmol), and placed under an inert atmosphere. DCM (70 mL) was then added via syringe, and 4-phenoxyaniline was allowed to dissolve. 3-bromopropionyl chloride (2.88 g, 28.5 mmol) was then added dropwise, and the resulting cloudy mixture was stirred at r.t. for 2

h. The reaction was quenched with the addition of H_2O, and transferred to a separatory funnel. The organic layer was washed with H_2O (2x) and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure to give product as a beige solid (7.72 g, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.51 – 7.42 (m, 2H), 7.32 (t, J = 7.9, 2H), 7.08 (t, J = 7.4, 1H), 7.01 – 6.92 (m, 4H), 3.70 (t, J = 6.5, 2H), 2.93 (t, J = 6.5, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.19, 157.47, 153.99, 132.90, 129.93, 123.32, 122.21, 119.65, 118.64, 40.60, 27.32.

(108) 1-(4-phenoxyphenyl)azetidin-2-one

NaOtBu (2.43 g, 25.3 mmol) was added to a dry flask and placed under an inert atmosphere. DMF (80 mL) was then added via syringe. **107** (7.71 g, 24.1 mmol) was dissolved in DMF (30 mL) and added dropwise. The mixture was allowed to stir at r.t. for 2.5 h, after which time DMF was removed under reduced pressure. Crude residue was redissolved in EtOAc. H_2O was added, and the aqueous layer was extracted with EtOAc. Combined organic layers were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure, and crude residue was purified by column chromatography to give product as a tan solid (1.24 g, 22%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 4H), 7.06 (t, J = 7.4, 1H), 7.01 – 6.91 (m, 4H), 3.57 (t, J = 4.4, 2H), 3.07 (t, J = 4.4, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.09, 157.57, 152.80, 134.42, 129.69, 122.97, 119.96, 118.13, 117.41, 38.13, 36.15.

(109) 6-phenoxy-2,3-dihydroquinolin-4(1H)-one

Compound **108** (1.24 g, 5.2 mmol) was dissolved in DCE (70 mL). TfOH (1.38 mL, 15.5 mmol) was then added via syringe. The mixture was stirred at r.t. for 16 h, after which time it was quenched with the addition of K_2CO_3 (7 g) and H_2O (0.5 mL) and allowed to

stir for 1 h. The mixture was then filtered through a plug of $MgSO_4$ with DCM. Solvents were removed under reduced pressure to give product as a yellow solid (1.39 g, 100%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 2.9, 1H), 7.28 – 7.21 (m, 2H), 7.06 – 6.97 (m, 2H), 6.94 – 6.88 (m, 2H), 6.67 (d, J = 8.8, 1H), 4.80 (br s, 1H), 3.48 (t, J = 7.0, 2H), 2.63 (t, 7.2, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.47, 158.08, 149.15, 147.86, 129.58, 128.29, 122.49, 119.23, 117.59, 117.40, 116.98, 42.18, 37.83.

(110) 1-acetyl-6-phenoxy-2,3-dihydroquinolin-4(1H)-one

Compound **109** (0.35 g, 1.47 mmol) was dissolved in pyridine (4 mL) under an inert atmosphere. $(Ac)_2O$ (5 mL) was then added dropwise via syringe. The mixture was stirred at r.t. for 16 h, after which time the mixture was poured onto H_2O. Aqueous layer was extracted with DCM (3x). Combined organic extracts were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure to give product as a yellow solid (0.38 g, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 2.9, 1H), 7.52 – 7.40 (m, 1H), 7.36 (t, J = 7.8, 2H), 7.22 (dd, J = 8.9, 3.0, 1H), 7.15 (t, J = 7.4, 1H), 7.01 (d, J = 8.0, 2H), 4.21 (t, J = 6.1, 2H), 2.77 (t, J = 6.2, 2H), 2.34 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.36, 169.23, 156.22, 154.92, 139.07, 130.01, 127.23, 125.91, 124.50, 124.09, 119.22, 115.90, 44.19, 39.33, 23.07.

(111) (E)-6-phenoxy-2,3-dihydroquinolin-4(1H)-one oxime

Compound **109** (0.38 g, 1.6 mmol) was dissolved in 1:1 EtOH/H_2O (30 mL). NH_2OH•HCl (0.30 g, 4.7 mmol) and NaOAc•$3H_2O$ (0.64 g, 4.7 mmol) were then added. The mixture was heated to 90 °C and stirred for 22 h, after which time EtOH was removed under reduced pressure. EtOAc was added, and the aqueous layer was extracted with EtOAc. Combined organic extracts were washed with brine, and dried with $MgSO_4$.

Solvents were filtered and removed under reduced pressure to give product (0.29 g, 97%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.91 (s, 1H), 7.36 – 7.30 (m, 2H), 7.26 (d, J = 2.8, 1H), 7.05 (t, J = 7.4, 1H), 6.92 (d, J = 7.9, 2H), 6.85 (dd, J = 8.8, 2.8, 1H), 6.71 (d, J = 8.7, 1H), 5.99 (s, 1H), 3.14 (td, J = 6.5, 1.9, 2H), 2.66 (t, J = 6.5, 2H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 158.57, 149.96, 147.37, 144.74, 130.26, 122.83, 122.34, 117.80, 117.53, 117.31, 113.87, 40.02, 23.44.

(112) (E)-1-(4-(hydroxyimino)-6-phenoxy-3,4-dihydroquinolin-1(2H)-yl)ethan-1-one

Followed procedure for compound **111** with **110** (0.38 g, 1.4 mmol) to give product as a brown solid after purification by column chromatography (1:1 hex/EtOAc) (0.30 g, 75%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.51 (d, J = 2.8, 1H), 7.32 (t, J = 7.8, 2H), 7.10 (t, J = 7.4, 1H), 7.05 – 6.95 (m, 3H), 3.94 (br s, 2H), 2.89 (t, J = 6.3, 2H), 2.22 (br s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 169.95, 156.66, 155.25, 151.42, 135.29, 129.87, 127.59, 125.71, 123.71, 119.93, 119.05, 114.16, 40.68, 25.96, 22.53.

(113) 6-phenoxy-1,2,3,4-tetrahydroquinolin-4-amine

Compound **111** was dissolved in MeOH, and added to 10% Pd/C in a hydrogenation vessel. AcOH (3 drops) was then added. The mixture was shaken on the hydrogenation apparatus for 18 h at 35 psi, after which time the mixture was filtered through Celite, and MeOH was removed under reduced pressure. 1M HCl was added, and the organic layer was discarded. Aqueous layer was basified with solid NaOH (pH 14), and was extracted with DCM (3x). Combined organic extracts were dried with $MgSO_4$, and solvents were filtered and removed. Crude residue was purified by column chromatography (9:1 DCM/MeOH) to give product as a colorless oil (0.10 g, 30%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.8, 2H), 7.00 – 6.94 (m, 2H), 6.89 (d, *J* = 8.1, 2H), 6.73 (dd, *J* =

8.8, 2.6, 1H), 6.45 (d, *J* = 8.6, 1H), 4.02 (t, *J* = 4.8, 1H), 3.36 (td, *J* = 11.0, 10.5, 3.4, 1H), 3.28 – 3.17 (m, 1H), 2.06 – 1.95 (m, 1H), 1.95 – 1.85 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.04, 147.15, 141.09, 129.58, 123.81, 122.01, 120.96, 120.90, 117.09, 115.74, 46.95, 37.59, 29.87.

(114) 1-(4-amino-6-phenoxy-3,4-dihydroquinolin-1(2H)-yl)ethan-1-one

Followed procedure for **113** with **112** (0.30 g, 1.03 mmol) to give product as a colorless oil (0.092 g, 32%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.8, 2H), 7.15 – 7.08 (m, 2H), 7.02 (d, *J* = 7.9, 2H), 6.88 (dd, 1H), 3.89 (br s, 1H), 3.62 (br s, 1H), 2.30 – 2.14 (m, 4H), 1.59 (br s, 2H).

(115) (2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-(6-phenoxy-1,2,3,4-tetrahydroquinolin-4-yl)propanamide

Compound **113** (0.042 g, 0.18 mmol) was dissolved in DMF (6 mL), and placed under an inert atmosphere. DIPEA (0.030 mL, 1.75 mmol) was added dropwise via syringe, followed by PyBOP (0.091 g, 0.18 mmol) and HOBt-Cl (0.030 g, 0.18 mmol). Boc-L-Dmt (0.072 g, 0.18 mmol) was dissolved in DMF (3 mL) and added dropwise via syringe. The mixture was stirred at r.t. for 5 h, after which time DMF was removed under reduced pressure. Crude residue was redissolved in EtOAc. 5% citric acid solution was added, and the aqueous layer was extracted with EtOAc. Combined organic extracts were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure, and crude residue was redissolved in 1:1 DCM/TFA solution (10 mL) and stirred for 1.5 h. Solvents were removed under reduced pressure, and residue was purified by semipreparative RP-HPLC and lyophilized to give product as a white solid. (**115E**): MS(EI): 432.2 (M+H), Retention Time: 24.37 min. ^{1}H-NMR (400 MHz,

CD_3OD) δ (d, J = 8.0, 1H), 7.29 – 7.22 (m, 2H), 7.02 – 6.97 (m, 1H), 6.87 – 6.80 (m, 3H), 6.73 (dd, J = 8.7, 2.7, 1H), 6.65 (d, J = 8.7, 1H), 6.49 (s, 2H), 4.98 – 4.93 (m, 1H), 3.84 (dd, J = 11.6, 5.0, 1H), 3.25 (dd, J = 13.6, 11.6, 1H), 3.12 – 3.04 (m, 1H), 3.01 (dd, J = 13.7, 5.0, 1H), 2.63 (td, J = 12.1, 11.4, 2.8, 1H), 2.28 (s, 6H), 1.82 – 1.72 (m, 1H), 1.57 – 1.48 (m, 1H). (**115L**): MS(EI): 432.2 (M+H), Retention Time: 27.33 min.

(116) (2S)-N-(1-acetyl-6-phenoxy-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for **115** with **114** (0.044 g, 0.16 mmol) to give product as a white solid. (**116E**): MS(EI): 474.2 (M+H), Retention Time: 31.01 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 8.1, 1H), 7.36 – 7.29 (m, 2H), 7.09 (t, *J* = 7.4, 1H), 7.01 (s, 1H), 6.95 – 6.91 (m, 2H), 6.83 (dd, *J* = 8.9, 2.8, 1H), 6.52 (s, 2H), 4.99 – 4.91 (m, 1H), 3.84 (dd, *J* = 11.5, 5.0, 1H), 3.25 (dd, *J* = 13.7, 11.5, 1H), 3.04 (dd, *J* = 13.7, 5.0, 1H), 2.28 (s, 6H), 2.21 (s, 3H), 1.95 – 1.84 (m, 1H), 1.44 (br s, 1H). (**116L**): MS(EI): 474.2 (M+H), Retention Time: 32.80 min.

(117) 3-bromo-N-(4-(2-methoxyphenoxy)phenyl)propanamide

Followed procedure for **107** with 4-(2-methoxyphenoxy)aniline (0.70 g, 3.25 mmol) to give product as a pale solid (100%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.12 (brs, 1H), 7.42 (d, J = 8.6, 2H), 7.12 (t, J = 7.0, 1H), 6.99 (d, J = 7.8, 1H), 6.81 – 6.96 (m, 4H), 3.81 (s, 3H), 3.65 (t, J = 5.7, 2H), 2.89 (t, J = 5.9, 2H).

(118) 3-bromo-N-(4-(3-chlorophenoxy)phenyl)propanamide

Followed procedure for **107** with 4-(3-chlorophenoxy)aniline (0.69 g, 3.13 mmol) to give product as a purple solid (100%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.40 (br s, 1H), 7.24 (t, J = 8.1, 1H), 7.06 (d, J = 7.8, 1H), 7.01 (m, 2H), 6.96 (s, 1H), 6.87 (d, J =

8.3, 1H), 3.73 (t, J = 6.6, 2H), 3.02 – 2.92 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 167.95, 158.45, 152.87, 135.05, 133.44, 130.48, 123.14, 121.98, 120.12, 118.42, 116.34, 40.58, 27.05.

(119) 3-bromo-N-(4-(4-chlorophenoxy)phenyl)propanamide

Followed procedure for **107** with 4-(4-chlorophenoxy)aniline (0.69 g, 3.13 mmol) to give product as a pale solid (1.05 g, 95%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.9, 2H), 7.27 (d, *J* = 9.5, 2H), 6.98 (d, *J* = 8.9, 2H), 6.91 (d, *J* = 8.9, 1H), 3.72 (t, *J* = 6.5, 2H), 2.95 (t, *J* = 6.5, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.98, 156.25, 153.58, 133.27, 129.86, 128.30, 122.07, 119.81, 40.74, 27.24.

(120) 1-(4-(2-methoxyphenoxy)phenyl)azetidin-2-one

Followed procedure for **108** with **117** (1.0 g, 0.35 mmol) to give product as a orange solid which was not characterized and used without further purification.

(121) 1-(4-(3-chlorophenoxy)phenyl)azetidin-2-one

Followed procedure for **108** with **118** (1.05 g, 2.96 mmol) to give product as a dark purple solid (82%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.37 (d, J = 8.8, 2H), 7.23 (t, J = 8.1, 1H), 7.07 – 6.97 (m, 3H), 6.92 (s, 1H), 6.87 – 6.81 (m, 1H), 3.64 (t, J = 4.4, 2H), 3.13 (t, J = 4.4, 2H).

(122) 1-(4-(4-chlorophenoxy)phenyl)azetidin-2-one

Followed procedure for **108** with **119** (1.05 g, 2.96 mmol) to give product as a light orange solid (0.71 g, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8, 2H), 7.25 (d, *J* = 8.8, 2H), 6.98 (d, *J* = 8.8, 2H), 6.88 (d, *J* = 8.8, 2H), 3.61 (t, *J* = 4.4, 2H), 3.11 (t, *J* = 4.4, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.28, 156.39, 152.53, 134.81, 129.73, 127.98, 120.14, 119.41, 117.61, 38.28, 36.28.

(123) 6-(2-methoxyphenoxy)-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **109** with **120** (0.80 g, 2.97 mmol) to give product as a yellow oil (20-65%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 2.9, 1H), 7.11 – 7.04 (m, 2H), 6.97 (d, J = 7.8, 1H), 6.86 (d, J = 3.9, 2H), 6.66 (d, J = 8.8, 1H), 3.90 – 3.77 (m, 3H), 3.54 (t, J = 7.1, 2H), 2.66 (t, J = 7.1, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.27, 150.81, 149.45, 148.43, 146.15, 127.09, 124.10, 121.06, 119.65, 119.48, 117.29, 115.27, 112.72, 55.98, 42.55, 38.06.

(124) 6-(3-chlorophenoxy)-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **109** with **121** (0.80 g, 2.9 mmol) to give product as a yellow oil (33-65%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 2.9, 1H), 7.19 (t, J = 8.1, 1H), 7.05 (dd, J = 8.6, 2.7, 1H), 7.00 (d, J = 7.8, 1H), 6.88 (s, 1H), 6.82 (d, J = 8.3, 1H), 6.71 (d, J = 8.8, 1H), 4.50 (brs, 1H), 3.58 (t, J = 6.4, 2H), 2.78 – 2.57 (m, 2H).

(125) 6-(4-chlorophenoxy)-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **109** with **122** (0.71 g, 2.6 mmol) to give product as a yellow oil (0.28 g, 39%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.9, 1H), 7.26 – 7.19 (m, 2H), 7.04 (dd, *J* = 8.8, 2.9, 1H), 6.88 – 6.82 (m, 2H), 6.70 (d, *J* = 8.8, 1H), 4.58 (br s, 1H), 3.56 (t, *J* = 6.8, 2H), 2.68 (t, *J* = 7.2, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.27, 156.90, 149.19, 147.93, 129.64, 128.20, 127.53, 119.62, 118.84, 117.69, 117.33, 42.43, 37.97.

(126) tert-butyl 6-(2-methoxyphenoxy)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **15** with **123** (0.080 g, 0.30 mmol) to give product as a yellow oil (>90%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 9.3, 1H), 7.40 (d, J = 2.9,

1H), 7.19 – 7.10 (m, 2H), 7.02 – 6.95 (m, 2H), 6.94 – 6.87 (m, 1H), 4.12 (t, J = 6.4, 2H), 3.84 – 3.77 (m, 3H), 2.71 (t, J = 6.4, 2H), 1.53 (s, 9H).

(127) tert-butyl 6-(3-chlorophenoxy)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **15** with **124** (0.12 g, 0.45 mmol) to give product as a yellow oil (>90%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.8, 1H), 7.58 (d, J = 2.9, 1H), 7.26 – 7.23 (m, 1H), 7.20 (dd, J = 9.3, 2.9, 1H), 7.09 (d, J = 7.8, 1H), 6.97 (s, 1H), 6.91 – 6.85 (m, 2H), 4.17 (t, J = 6.4, 2H), 2.77 (t, J = 6.1, 2H), 1.56 (s, 9H).

(128) tert-butyl 6-(4-chlorophenoxy)-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **15** with **125** (0.12 g, 0.45 mmol) to give product as a colorless oil after purification by column chromatography (4:1 hex/EtOAc) (0.10 g, 62%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 9.1, 1H), 7.54 (d, J = 2.8, 1H), 7.29 (d, J = 8.9, 2H), 7.19 (dd, J = 9.1, 2.9, 1H), 6.93 (d, J = 8.9, 2H), 4.15 (t, J = 6.3, 2H), 2.76 (t, J = 6.3, 2H), 1.56 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.58, 155.61, 153.12, 152.84, 140.11, 129.99, 128.77, 126.20, 125.81, 125.18, 120.15, 116.05, 82.40, 44.43, 38.99, 28.41.

(129) 1-acetyl-6-(2-methoxyphenoxy)-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **110** with **126** (0.080 g, 0.30 mmol) to give product as a light yellow oil (>90%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 1H), 7.24 – 7.12 (m, 3H), 7.02 (d, J = 8.8, 2H), 6.99 – 6.92 (m, 1H), 4.21 (br s, 1H), 3.86 – 3.77 (m, 2H), 2.76 (t, J = 5.9, 2H), 2.32 (s, 3H).

(130) 1-acetyl-6-(3-chlorophenoxy)-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **110** with **127** (0.12 g, 0.45 mmol) to give product as a light yellow oil that solidified upon standing (>90%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.59

(d, J = 2.9, 1H), 7.31 – 7.28 (m, 1H), 7.24 (dd, J = 8.8, 2.9, 1H), 7.13 (d, J = 8.3, 1H), 7.00 (s, 1H), 6.94 – 6.88 (m, 1H), 4.28 – 4.19 (m, 2H), 2.81 (t, J = 6.1, 2H), 2.36 (s, 3H).

(131) 1-acetyl-6-(4-chlorophenoxy)-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **110** with **128** (0.13 g, 0.47 mmol) to give product as a colorless oil after purification by column chromatography (3:1 hex/EtOAc to 1:1 hex/EtOAc) (0.068 g, 47%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 3.1, 1H), 7.51 (br s, 1H), 7.35 – 7.29 (m, 2H), 7.22 (dd, *J* = 8.9, 3.0, 1H), 6.99 – 6.93 (m, 2H), 4.22 (t, *J* = 5.9, 2H), 2.79 (t, *J* = 6.2, 2H), 2.35 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.17, 169.15, 154.94, 154.57, 139.41, 130.02, 129.18, 127.27, 126.02, 124.55, 120.45, 116.02, 44.11, 39.33, 23.09.

(132) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(2-methoxyphenoxy)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **126** (0.050 g, 0.14 mmol) to give product as a yellow oil (23%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 9.0, 1H), 7.16 – 7.06 (m, 1H), 6.99 (d, J = 8.2, 1H), 6.96 – 6.79 (m, 4H), 3.92 (dt, J = 12.9, 4.5, 1H), 3.84 (s, 3H), 3.64 – 3.50 (m, 1H), 2.25 – 2.16 (m, 1H), 2.02 – 1.90 (m, 1H), 1.50 (s, 9H), 1.18 (s, 9H).

(133) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(3-chlorophenoxy)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **127** (0.15 g, 0.41 mmol) to give product as a light yellow oil (78%).

(134) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(4-chlorophenoxy)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **128** (0.10 g, 0.27 mmol) to give product as a colorless oil (0.094 g, 72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 9.0, 1H), 7.26 (d, *J* = 8.7, 2H), 7.03 (s, 1H), 6.91 (d, *J* = 8.7, 3H), 4.51 (s, 1H), 4.01 – 3.88 (m, 1H), 3.71 – 3.53 (m, 1H), 3.29 (s, 1H), 2.26 – 2.12 (m, 1H), 2.09 – 1.93 (m, 1H), 1.52 (s, 9H), 1.21 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 156.18, 153.69, 152.46, 134.40, 130.61, 129.79, 128.19, 125.72, 119.71, 119.06, 118.97, 81.40, 55.86, 50.65, 40.37, 29.73, 28.45, 22.70.

(135) (R)-N-((R)-1-acetyl-6-(2-methoxyphenoxy)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **129** (0.35 g, 1.12 mmol) to give product as a light yellow oil which was carried forward without additional purification.

(136) (R)-N-((R)-1-acetyl-6-(3-chlorophenoxy)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **130** (0.1 g, 0.32 mmol) to give product as a light yellow oil (80%).

(137) (R)-N-((R)-1-acetyl-6-(4-chlorophenoxy)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **131** (0.068 g, 0.22 mmol) to give product as a colorless oil (0.070 g, 77%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.10 (d, J = 2.7, 1H), 6.97 – 6.89 (m, 3H), 4.50 (q, J = 4.6, 1H), 3.90 (dt, J = 11.9, 5.7, 1H), 3.79 (ddd, J = 13.2, 8.8, 5.6, 1H), 3.37 (d, J = 4.0, 1H), 2.31 – 2.20 (m, 4H), 2.17 – 2.05 (m, 1H), 1.20 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 169.96, 155.57, 134.12, 129.96, 129.52, 128.79, 126.42, 120.31, 118.38, 56.01, 51.27, 40.64, 30.78, 24.33, 22.69.

(138) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(2-methoxyphenoxy)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide

Followed procedure for compound **68** with **132** (0.015 g, 0.032 mmol) to give product as a white solid. MS(EI): 484.2 (M+Na), Retention Time: 21.39 min. 1H-NMR (500 MHz, CD3OD) δ 8.30 (d, J = 7.9, 1H), 7.16 – 7.10 (m, 1H), 7.08 (d, J = 8.1, 1H), 6.94 – 6.84 (m, 4H), 6.66 (dd, J = 8.6, 2.5, 1H), 6.50 (s, 2H), 5.01 (t, J = 5.3, 1H), 3.87 (dd, J = 11.5, 5.1, 1H), 3.75 (s, 3H), 3.28 – 3.19 (m, 2H), 3.04 (dd, J = 13.7, 5.1, 1H), 2.76 (t, J = 11.3, 1H), 2.28 (s, 6H), 1.94 – 1.85 (m, 1H), 1.62 – 1.54 (m, 1H).

(139) (S)-2-amino-N-((R)-6-(3-chlorophenoxy)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **133** (0.06 g, 0.13 mmol) to give product as a white solid. Retention Time: 28.86 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.29 (d, J = 7.8, 1H), 7.27 (t, J = 8.1, 1H), 7.05 (d, J = 7.8, 1H), 6.95 (s, 1H), 6.92 – 6.80 (m, 4H), 6.50 (s, 2H), 5.03 (d, J = 5.9, 1H), 3.87 (dd, J = 11.3, 4.9, 1H), 3.29 – 3.15 (m, 2H), 3.04 (dd, J = 13.7, 4.9, 1H), 2.77 (t, J = 10.8, 1H), 2.28 (s, 6H), 1.91 – 1.81 (m, 1H), 1.60 – 1.51 (m, 1H).

(140) (S)-2-amino-N-((R)-6-(4-chlorophenoxy)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **134** (0.094 g, 0.20 mmol) to give product as a white solid. MS(EI): 488.2 (M+Na), Retention Time: 29.81 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.12 (d, *J* = 7.9, 1H), 7.28 – 7.20 (m, 2H), 6.85 – 6.76 (m, 3H), 6.72 (dd, *J* = 8.7, 2.7, 1H), 6.59 (d, *J* = 8.7, 1H), 6.49 (s, 2H), 5.01 – 4.90 (m, 1H), 3.83 (dd, *J* = 11.6,

5.0, 1H), 3.24 (dd, *J* = 13.4, 11.7, 1H), 3.09 – 2.95 (m, 2H), 2.67 – 2.53 (m, 1H), 2.27 (s, 6H), 1.79 – 1.66 (m, 1H), 1.58 – 1.44 (m, 1H).

(141) (S)-N-((R)-1-acetyl-6-(2-methoxyphenoxy)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **135** (0.5 g, 1.20 mmol) to give product as a white solid. Retention Time: 30.19 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.21 (d, J = 8.2, 1H), 7.19 – 7.14 (m, 1H), 7.10 (d, J = 8.1, 1H), 6.98 – 6.90 (m, 2H), 6.57 (dd, J = 8.5, 2.8, 1H), 6.52 (s, 2H), 4.92 (br s, 1H), 3.86 (dd, J = 11.5, 4.9, 1H), 3.75 (s, 3H), 3.25 (t, J = 12.6, 1H), 3.04 (dd, J = 13.7, 5.0, 1H), 2.28 (s, 6H), 2.17 (s, 3H), 1.93 – 1.84 (m, 1H), 1.43 (br s, 1H).

(142) (S)-N-((R)-1-acetyl-6-(3-chlorophenoxy)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **136** (0.17 g, 0.41 mmol) to give product as a white solid. MS(EI): 530.2 (M+Na), Retention Time: 35.33 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.20 (d, J = 8.2, 1H), 7.30 (t, J = 8.1, 1H), 7.08 (dd, J = 8.1, 1.9, 1H), 7.03 (s, 1H), 6.94 – 6.82 (m, 3H), 6.52 (s, 2H), 5.00 – 4.92 (m, 1H), 3.85 (dd, J = 11.6, 5.0, 1H), 3.25 (dd, J = 13.7, 11.6, 1H), 3.05 (dd, J = 13.7, 5.0, 1H), 2.27 (s, 6H), 2.22 (s, 3H), 1.95 – 1.89 (m, 1H), 1.44 (br s, 1H).

(143) (S)-N-((R)-1-acetyl-6-(4-chlorophenoxy)-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **137** (0.070 g, 0.17 mmol) to give product as a white solid. MS(EI): 508.2 (M+H), Retention Time: 35.52. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.16 (d, *J* = 7.9, 1H), 7.48 (br s, 1H), 7.33 – 7.29 (m, 2H), 7.03 – 6.98 (m, 1H), 6.94 –

6.89 (m, 2H), 6.86 (dd, *J* = 8.9, 2.8, 1H), 6.51 (s, 2H), 4.99 – 4.91 (m, 1H), 3.83 (dd, *J* = 11.5, 5.1, 1H), 3.24 (dd, *J* = 13.5, 11.6, 1H), 3.03 (dd, *J* = 13.7, 5.0, 1H), 2.27 (s, 6H), 2.21 (s, 3H), 1.96 – 1.81 (m, 1H), 1.38 (br s, 1H).

(144) 4-(phenylthio)aniline

(4-nitrophenyl)(phenyl)sulfane (0.36 g, 1.54 mmol) was dissolved in 1:1 MeOH/EtOAc and added to a hydrogenation vessel. PtO_2 was added, and the mixture was shaken on the hydrogenation apparatus for 30 min at 8 psi, after which time the mixture was filtered through a plug of Celite with DCM. Solvents were removed under reduced pressure to give product as a light brown solid (0.29 g, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5, 2H), 7.27 – 7.18 (m, 2H), 7.18 – 7.09 (m, 3H), 6.71 (d, J = 8.5, 2H), 4.20 (br s, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 146.18, 139.41, 135.94, 128.84, 127.49, 125.36, 121.23, 116.20.

(145) 1-nitro-4-(phenylsulfonyl)benzene

(4-nitrophenyl)(phenyl)sulfane (0.31 g, 1.33 mmol) was dissolved in glacial acetic acid (10 mL) and 30% H_2O_2 solution (3 mL) was added. The mixture was heated to 80 °C and stirred for 3 h, after which time the mixture was diluted with H_2O, and extracted with DCM. Combined organic extracts were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure to give product as a white solid (0.34 g, 97%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 8.8, 2H), 8.12 (d, J = 8.7, 2H), 7.96 (d, J = 8.0, 2H), 7.62 (t, J = 7.5, 1H), 7.54 (t, J = 7.7, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 150.33, 147.31, 139.97, 134.14, 129.70, 128.98, 128.01, 124.53.

(146) 4-(phenylsulfonyl)aniline

Compound **145** (0.34 g, 1.3 mmol) was dissolved in 1:1 MeOH/EtOAc, and added to a hydrogenation vessel. 10% Pd/C was then added, and the mixture was shaken on the hydrogenation apparatus for 30 min at 20 psi, after which time the mixture was filtered through a plug of Celite with DCM. Solvents were removed under reduced pressure to give product as a white solid (0.28 g, 93%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.86 (m, 2H), 7.68 (d, J = 8.7, 2H), 7.52 – 7.42 (m, 3H), 6.64 (d, J = 8.7, 2H), 4.25 (br s, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 151.19, 142.92, 132.50, 132.32, 129.83, 129.07, 127.01, 114.16.

(147) 3-bromo-N-(4-(phenylthio)phenyl)propanamide

Followed procedure for compound **107** with **144** (0.35 g, 1.75 mmol) to give product as a white solid (0.54 g, 92%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.49 (d, J = 8.5, 2H), 7.34 (d, J = 8.6, 2H), 7.28 (d, J = 4.3, 3H), 7.24 – 7.18 (m, 1H), 3.69 (t, J = 6.5, 2H), 2.94 (t, J = 6.5, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 168.11, 136.79, 136.45, 132.75, 130.79, 130.12, 129.16, 126.75, 120.87, 40.59, 26.96.

(148) 3-bromo-N-(4-(phenylsulfonyl)phenyl)propanamide

Followed procedure for compound **107** with **146** (0.29 g, 1.24 mmol) to give product as a white solid (0.45 g, 99%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0, 2H), 7.88 (d, J = 8.6, 2H), 7.68 (d, J = 8.5, 2H), 7.58 – 7.54 (m, 1H), 7.52 – 7.47 (m, 2H), 3.68 (t, J = 6.4, 2H), 2.97 (t, J = 6.5, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 168.34, 141.88, 141.64, 136.53, 133.17, 129.31, 129.03, 127.44, 119.81, 40.60, 26.50.

(149) 1-(4-(phenylthio)phenyl)azetidin-2-one

Followed procedure for compound **108** with **147** (0.54 g, 1.61 mmol) to give product as a colorless oil that solidified upon standing (0.17 g, 42%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ

7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 7.29 – 7.21 (m, 4H), 7.21 – 7.15 (m, 1H), 3.59 (t, J = 4.5, 2H), 3.10 (t, J = 4.5, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.47, 138.03, 137.02, 133.62, 133.41, 129.52, 129.15, 126.53, 116.99, 38.15, 36.31.

(150) 1-(4-(phenylsulfonyl)phenyl)azetidin-2-one

Followed procedure for compound **108** with **148** (0.43 g, 1.16 mmol) to give product as a white solid (0.13 g, 38%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.87 (t, J = 8.5, 4H), 7.54 – 7.50 (m, 1H), 7.49 – 7.42 (m, 2H), 7.40 (d, J = 8.6, 2H), 3.64 (t, J = 4.7, 2H), 3.13 (t, J = 4.7, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 164.94, 142.20, 141.84, 135.70, 133.08, 129.28, 129.21, 127.34, 116.36, 38.43, 36.62.

(151) 6-(phenylthio)-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **109** with **149** (0.17 g, 0.67 mmol) to give product as a yellow oil (0.13 g, 75%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 2.2, 1H), 7.37 (dd, J = 8.5, 2.2, 1H), 7.22 (t, J = 7.6, 2H), 7.17 (d, J = 6.8, 2H), 7.13 (t, J = 7.2, 1H), 6.68 (d, J = 8.5, 1H), 4.87 (br s, 1H), 3.60 (t, J = 7.0, 2H), 2.71 (t, J = 7.0, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 192.73, 151.53, 140.66, 138.25, 133.61, 128.94, 128.27, 125.87, 121.71, 119.81, 117.26, 41.94, 37.67.

(152) 6-(phenylsulfonyl)-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **109** with **150** (0.13 g, 0.45 mmol) to give product as a yellow solid (0.052 g, 41%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 2.2, 1H), 7.88 (d, J = 8.2, 2H), 7.72 (dd, J = 8.8, 2.3, 1H), 7.54 – 7.49 (m, 1H), 7.49 – 7.43 (m, 2H), 6.71 (d, J = 8.8, 1H), 5.29 (br s, 1H), 3.60 (t, J = 7.1, 2H), 2.68 (t, J = 7.0, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 191.93, 154.47, 142.24, 133.13, 132.83, 129.48, 129.22, 128.91, 127.20, 118.02, 116.51, 41.10, 37.07.

(153) tert-butyl 4-oxo-6-(phenylthio)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **126** with **151** (0.13 g, 0.51 mmol) to give product as a colorless oil (0.088 g, 49%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 2.3, 1H), 7.75 (d, J = 8.8, 1H), 7.45 (dd, J = 8.8, 2.4, 1H), 7.34 – 7.26 (m, 4H), 7.26 – 7.21 (m, 1H), 4.14 (t, J = 6.4, 2H), 2.75 (t, J = 6.3, 2H), 1.55 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 193.27, 152.54, 143.21, 136.73, 135.43, 131.10, 130.83, 130.03, 129.27, 127.21, 125.28, 124.50, 82.47, 44.20, 38.79, 28.26.

(154) tert-butyl 4-oxo-6-(phenylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **126** with **152** (0.052 g, 0.18 mmol) to give product as a colorless oil (0.031 g, 44%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.55 – 8.53 (m, 1H), 8.01 (s, 2H), 7.95 (d, J = 7.6, 2H), 7.59 – 7.54 (m, 1H), 7.53 – 7.47 (m, 2H), 4.16 (t, J = 6.5, 2H), 2.78 (t, J = 6.5, 2H), 1.55 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 192.04, 152.15, 147.77, 141.32, 136.64, 133.29, 132.18, 129.36, 127.78, 127.67, 124.55, 124.18, 83.44, 44.15, 38.37, 28.17.

(155) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(phenylthio)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **153** (0.088 g, 0.25 mmol) to give product as a colorless oil (0.061 g, 54%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.8, 1H), 7.36 (d, J = 2.2, 1H), 7.31 – 7.22 (m, 5H), 7.22 – 7.16 (m, 1H), 4.49 (q, J = 3.5, 1H), 3.94 (dt, J = 12.8, 4.6, 1H), 3.59 (ddd, J = 12.7, 11.2, 3.9, 1H), 3.26 (s, 1H), 2.22 (dq, J = 13.8, 4.2, 1H), 2.01 – 1.91 (m, 1H), 1.51 (s, 9H), 1.18 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.38, 137.94, 136.37, 132.00, 131.81, 130.27, 129.60, 129.52, 129.10, 126.76, 124.65, 81.47, 55.71, 50.07, 40.16, 29.02, 28.30, 22.57.

(156) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-(phenylsulfonyl)-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **154** (0.031 g, 0.080 mmol) to give product as a colorless oil (0.023 g, 59%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.9, 1H), 7.96 – 7.93 (m, 2H), 7.90 (d, J = 2.3, 1H), 7.82 (dd, J = 8.9, 2.3, 1H), 7.57 – 7.53 (m, 1H), 7.52 – 7.47 (m, 2H), 4.56 (q, J = 3.8, 1H), 3.90 (dt, J = 12.9, 4.8, 1H), 3.65 (ddd, J = 12.9, 11.0, 4.4, 1H), 3.36 (d, J = 2.8, 1H), 2.29 (dq, J = 13.8, 4.5, 1H), 2.01 – 1.92 (m, 1H), 1.51 (s, 9H), 1.21 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.14, 142.94, 141.74, 135.46, 133.04, 129.41, 129.26, 128.28, 127.64, 124.07, 82.32, 55.98, 50.33, 40.62, 28.51, 28.20, 22.59.

(157) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(phenylthio)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide

Followed procedure for compound **68** with **155** (0.061 g, 0.13 mmol) to give product as a white solid. MS(EI): 448.2 (M+H), Retention Time: 33.90 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.13 (d, J = 8.1, 1H), 7.18 (d, J = 2.1, 1H), 7.16 (t, J = 7.7, 2H), 7.09 – 7.02 (m, 2H), 7.00 (dd, J = 8.3, 1.2, 2H), 6.51 (d, J = 8.4, 1H), 6.48 (s, 2H), 4.97 – 4.90 (m, 1H), 3.84 (dd, J = 11.6, 5.0, 1H), 3.24 (dd, J = 13.6, 11.6, 1H), 3.08 – 2.96 (m, 2H), 2.53 (td, J = 12.0, 3.0, 1H), 2.27 (s, 6H), 1.72 – 1.62 (m, 1H), 1.54 – 1.45 (m, 1H).

(158) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-(phenylsulfonyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide

Followed procedure for compound **68** with **156** (0.023 g, 0.047 mmol) to give product as a white solid. MS(EI): 480.2 (M+H), Retention Time: 28.37 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.19 (d, J = 7.9, 1H), 7.83 – 7.80 (m, 2H), 7.58 – 7.54 (m, 1H), 7.53 – 7.48

(m, 3H), 7.43 (dd, J = 8.7, 2.3, 1H), 6.52 (d, J = 8.8, 1H), 6.47 (s, 2H), 4.95 (t, J = 4.0, 1H), 3.85 (dd, J = 11.6, 5.0, 1H), 3.26 (dd, J = 13.6, 11.7, 1H), 3.07 – 2.99 (m, 2H), 2.45 (td, J = 12.8, 12.3, 3.3, 1H), 2.27 (s, 6H), 1.66 – 1.57 (m, 1H), 1.54 – 1.47 (m, 1H).

(159) tert-butyl 4-oxo-6-phenyl-3,4-dihydroquinoline-1(2H)-carboxylate

To a 10 mL microwave flask equipped with a stir bar was added tert-butyl 6-bromo-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (0.051 g, 0.16 mmol), phenylboronic acid pinacol ester (0.048 g, 0.24 mmol), K_2CO_3 (0.065 g, 0.47 mmol) and $Pd(dppf)Cl_2$ (0.012 g, 0.016 mmol) and placed under an inert atmosphere. 3:1 acetone/H_2O (degassed and saturated with Ar gas) was then added via syringe. The mixture was stirred under microwave irradiation for 30 min at 100 °C, after which time solvents were removed under reduced pressure, and crude residue was purified by column chromatography (8:1 hex/EtOAc) to give product as a white solid (0.041 g, 82%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, J = 2.4, 1.0, 1H), 7.86 (d, J = 8.4, 1H), 7.75 (ddd, J = 8.7, 2.4, 1.1, 1H), 7.63 – 7.58 (m, 2H), 7.47 – 7.40 (m, 2H), 7.38 – 7.31 (m, 1H), 4.19 (t, J = 5.8, 2H), 2.81 (t, J = 5.8, 2H), 1.58 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.12, 152.72, 143.25, 139.40, 136.63, 132.42, 128.86, 127.56, 126.78, 125.41, 124.99, 124.07, 82.31, 44.29, 38.98, 28.31.

(160) 1-acetyl-6-phenyl-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **159** with 1-acetyl-6-bromo-2,3-dihydroquinolin-4(1H)-one to give product as a colorless oil (0.092 100%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 2.3, 1H), 7.79 (dd, J = 8.5, 2.3, 1H), 7.64 – 7.56 (m, 2H), 7.54 (br s, 1H), 7.49 – 7.42 (m, 2H), 7.42 – 7.35 (m, 1H), 4.27 (t, J = 6.2, 2H), 2.84 (t, J = 6.2, 2H), 2.39 (s,

3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 193.94, 169.36, 142.90, 138.99, 138.40, 132.56, 128.89, 127.88, 126.73, 126.15, 125.80, 124.51, 43.92, 39.50, 23.16.

(161) 7-phenyl-3,4-dihydronaphthalen-1(2H)-one

Followed procedure for compound **159** with 7-bromo-3,4-dihydronaphthalen-1(2H)-one (0.13 g, 0.56 mmol) stirring at 110 °C to give product as a white solid (0.10 g, 82%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.1, 1H), 7.69 (dd, *J* = 7.9, 2.1, 1H), 7.63 – 7.56 (m, 2H), 7.42 (t, *J* = 7.6, 2H), 7.37 – 7.27 (m, 2H), 2.97 (t, *J* = 6.1, 2H), 2.67 (t, *J* = 6.4, 2H), 2.14 (p, *J* = 6.3, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 198.41, 143.47, 140.03, 139.65, 132.92, 131.96, 129.44, 128.90, 127.62, 127.01, 125.49, 39.28, 29.47, 23.33.

(162) 6',7'-dihydro-[1,2'-binaphthalen]-8'(5'H)-one

Followed procedure for compound **159** with 7-bromo-3,4-dihydronaphthalen-1(2H)-one (0.12 g, 0.55 mmol) and 1-naphthylboronic acid (0.14 g, 0.82 mmol) stirring at 110 °C to give product as a colorless oil (0.14 g, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 1.7, 1H), 7.90 – 7.80 (m, 3H), 7.57 (dd, *J* = 7.7, 2.1, 1H), 7.51 – 7.35 (m, 4H), 7.32 (d, *J* = 7.9, 1H), 2.99 (t, *J* = 6.1, 2H), 2.69 (t, *J* = 6.4, 2H), 2.15 (p, *J* = 6.4, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 198.67, 143.58, 139.28, 139.06, 135.15, 133.83, 132.58, 131.44, 128.89, 128.51, 128.42, 128.02, 127.10, 126.28, 125.90, 125.67, 125.43, 39.29, 29.53, 23.34.

(163) 6,7-dihydro-[2,2'-binaphthalen]-8(5H)-one

Followed procedure for compound **159** with 7-bromo-3,4-dihydronaphthalen-1(2H)-one (0.14 g, 0.62 mmol) and 2-naphthylboronic acid (0.16 g, 0.93 mmol) stirring at 110 °C to give product as a white solid (0.14 g, 83%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 1.4, 1H), 8.09 (s, 1H), 7.94 – 7.87 (m, 2H), 7.87 – 7.82 (m, 1H), 7.77 (dd, *J* = 8.5, 1.6,

2H), 7.57 – 7.47 (m, 2H), 7.35 (d, *J* = 8.0, 1H), 2.99 (t, *J* = 6.1, 2H), 2.72 (t, *J* = 6.5, 2H), 2.22 – 2.12 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 198.68, 143.58, 139.43, 137.20, 133.64, 132.90, 132.73, 132.17, 129.52, 128.59, 128.26, 127.66, 126.40, 126.13, 125.72, 125.67, 125.17, 39.25, 29.42, 23.28.

(164) tert-butyl (R)-4-(((R)-tert-butylsulfinyl)amino)-6-phenyl-3,4-dihydroquinoline-1(2H)-carboxylate

Followed procedure for compound **46** with **159** (0.041 g, 0.13 mmol) to give product as a colorless oil (0.043 g, 80%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6, 1H), 7.61 (s, 1H), 7.58 (d, J = 8.3, 2H), 7.51 (dd, J = 8.8, 1.8, 1H), 7.42 (t, J = 7.7, 2H), 7.35 – 7.28 (m, 1H), 4.65 (q, J = 3.6, 1H), 4.01 (dt, J = 13.0, 4.5, 1H), 3.63 (td, J = 12.0, 11.4, 3.9, 1H), 3.36 (d, J = 2.7, 1H), 2.24 (dq, J = 14.0, 3.7, 1H), 2.06 – 1.98 (m, 1H), 1.54 (s, 9H), 1.23 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.54, 139.92, 137.68, 136.38, 128.91, 128.82, 127.26, 127.18, 126.73, 126.68, 124.22, 81.36, 55.70, 50.75, 40.20, 29.43, 28.35, 22.62.

(165) (R)-N-((R)-1-acetyl-6-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **160** (0.090 g, 0.34 mmol) to give product as a colorless oil (0.098 g, 78%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.60 (d, J = 8.3, 2H), 7.54 (d, J = 8.4, 1H), 7.44 (t, J = 7.6, 2H), 7.38 – 7.31 (m, 1H), 4.63 (q, J = 4.7, 1H), 3.98 – 3.92 (m, 1H), 3.85 – 3.77 (m, 1H), 3.64 (d, J = 4.0, 1H), 2.34 – 2.22 (m, 4H), 2.16 – 2.07 (m, 1H), 1.23 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 170.03, 139.63, 138.16, 137.62, 131.77, 128.91, 127.49, 126.99, 126.77, 126.60, 125.01, 55.86, 51.51, 40.71, 30.68, 23.45, 22.62.

(166) (R)-2-methyl-N-((R)-7-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)propane-2-sulfinamide

Followed procedure for compound **46** with **161** (0.10 g, 0.46 mmol) to give product as a colorless oil (0.015 g, 10%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.60 (d, *J* = 7.5, 2H), 7.49 – 7.39 (m, 3H), 7.32 (t, *J* = 7.4, 1H), 7.19 (d, *J* = 8.0, 1H), 4.65 (q, *J* = 3.9, 1H), 3.28 (d, *J* = 3.8, 1H), 2.91 – 2.71 (m, 2H), 2.13 – 2.02 (m, 1H), 2.02 – 1.86 (m, 2H), 1.86 – 1.75 (m, 1H), 1.22 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 140.58, 139.61, 137.42, 136.97, 129.93, 128.93, 128.29, 127.35, 127.08, 126.44, 55.63, 52.92, 30.51, 28.97, 22.81, 18.19.

(167) (R)-2-methyl-N-((R)-5',6',7',8'-tetrahydro-[1,2'-binaphthalen]-8'-yl)propane-2-sulfinamide

Followed procedure for compound **46** with **162** (0.14 g, 0.50 mmol) to give product as a colorless oil (0.12 g, 61%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (t, *J* = 9.0, 2H), 7.83 (d, *J* = 8.3, 1H), 7.55 (s, 1H), 7.53 – 7.44 (m, 2H), 7.43 – 7.33 (m, 3H), 7.23 (d, *J* = 7.9, 1H), 4.66 (q, *J* = 3.7, 1H), 3.29 (d, *J* = 3.0, 1H), 2.98 – 2.74 (m, 2H), 2.19 – 2.07 (m, 1H), 2.02 – 1.89 (m, 2H), 1.87 – 1.77 (m, 1H), 1.19 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 139.63, 139.11, 136.94, 136.89, 133.89, 131.58, 131.01, 129.57, 129.26, 128.39, 127.71, 127.08, 126.05, 125.96, 125.78, 125.51, 55.49, 52.32, 30.23, 29.03, 22.72, 18.05.

(168) (R)-2-methyl-N-((R)-5,6,7,8-tetrahydro-[2,2'-binaphthalen]-8-yl)propane-2-sulfinamide

Followed procedure for compound **46** with **163** (0.14 g, 0.51 mmol) to give product as a colorless oil (0.11 g, 55%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 1.9, 1H), 7.89 (d, *J* = 8.3, 2H), 7.86 – 7.79 (m, 2H), 7.75 (dd, *J* = 8.6, 1.8, 1H), 7.58 (dd, *J* = 8.0, 2.0, 1H),

7.46 (pd, *J* = 6.9, 1.6, 2H), 7.21 (d, *J* = 8.0, 1H), 4.68 (q, *J* = 3.9, 1H), 3.31 (d, *J* = 3.4, 1H), 2.93 – 2.70 (m, 2H), 2.15 – 2.05 (m, 1H), 2.04 – 1.85 (m, 2H), 1.84 – 1.73 (m, 1H), 1.22 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 139.34, 137.80, 137.43, 137.07, 133.73, 132.67, 130.01, 128.56, 128.40, 128.32, 127.67, 126.63, 126.30, 125.93, 125.52, 125.45, 55.56, 52.70, 30.30, 28.92, 22.74, 18.03.

(169) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-6-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)propanamide

Followed procedure for compound **68** with **164** (0.043 g, 0.10 mmol) to give product as a white solid. MS(EI): 416.2 (M+H), Retention Time: 26.73 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.18 (d, J = 7.9, 1H), 7.47 (d, J = 7.4, 2H), 7.37 – 7.27 (m, 4H), 7.21 (t, J = 7.4, 1H), 6.66 (dd, J = 8.0, 1.4, 1H), 6.49 (s, 2H), 5.07 – 4.99 (m, 1H), 3.87 (dd, J = 11.7, 5.0, 1H), 3.25 (dd, J = 12.5, 10.5, 1H), 3.09 – 2.97 (m, 2H), 2.60 – 2.52 (m, 1H), 2.28 (s, 6H), 1.83 – 1.74 (m, 1H), 1.59 – 1.52 (m, 1H).

(170) (S)-N-((R)-1-acetyl-6-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **165** (0.078 g, 0.27 mmol) to give product as a white solid. MS(EI): 458.2 (M+H), Retention Time: 31.11 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.22 (d, J = 8.1, 1H), 7.57 (d, J = 8.4, 2H), 7.53 – 7.47 (m, 2H), 7.41 (t, J = 7.3, 2H), 7.32 (t, J = 6.7, 1H), 6.52 (s, 2H), 5.08 (t, J = 5.9, 1H), 3.90 – 3.79 (m, 2H), 3.26 (dd, J = 12.5, 11, 1H), 3.22 – 3.14 (m, 1H), 3.04 (dd, J = 13.6, 5.0, 1H), 2.28 (s, 6H), 2.25 (s, 3H), 1.97 – 1.88 (m, 1H), 1.53 – 1.44 (m, 1H).

(171) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-7-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide

Followed procedure for compound **68** with **166** (0.014 g, 0.040 mmol) to give product as a white solid. MS(EI): 415.2 (M+H), Retention Time: 38.96 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.10 (d, *J* = 8.4, 1H), 7.57 – 7.50 (m, 2H), 7.45 – 7.35 (m, 4H), 7.33 – 7.26 (m, 1H), 7.12 (d, *J* = 8.0, 1H), 6.50 (s, 2H), 5.13 – 5.02 (m, 1H), 3.84 (dd, *J* = 11.5, 4.9, 1H), 3.29 – 3.20 (m, 1H), 3.01 (dd, *J* = 13.6, 4.9, 1H), 2.74 – 2.64 (m, 2H), 2.28 (s, 6H), 1.78 – 1.66 (m, 1H), 1.66 – 1.55 (m, 1H), 1.53 – 1.41 (m, 1H), 1.38 – 1.24 (m, 1H).

(172) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-5',6',7',8'-tetrahydro-[1,2'-binaphthalen]-8'-yl)propanamide

Followed procedure for compound **68** with **167** (0.12 g, 0.31 mmol) to give product as a white solid. MS(EI): 465.3 (M+H), Retention Time: 44.74 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.11 (d, *J* = 8.5, 1H), 7.90 (d, *J* = 8.1, 1H), 7.85 (d, *J* = 8.3, 1H), 7.77 (d, *J* = 8.5, 1H), 7.52 – 7.44 (m, 2H), 7.42 – 7.36 (m, 1H), 7.34 – 7.27 (m, 2H), 7.25 (dd, *J* = 7.8, 1.8, 1H), 7.19 (d, *J* = 7.9, 1H), 6.51 (s, 2H), 5.15 – 5.06 (m, 1H), 3.79 (dd, *J* = 11.5, 5.0, 1H), 3.23 (dd, *J* = 13.5, 11.7, 1H), 2.98 (dd, *J* = 13.7, 5.0, 1H), 2.81 – 2.69 (m, 2H), 2.27 (s, 6H), 1.84 – 1.60 (m, 2H), 1.54 – 1.33 (m, 2H).

(173) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-5,6,7,8-tetrahydro-[2,2'-binaphthalen]-8-yl)propanamide

Followed procedure for compound **68** with **168** (0.11 g, 0.28 mmol) to give product as a white solid. MS(EI): 487.2 (M+Na), Retention Time: 45.02 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.01 (s, 1H), 7.93 – 7.83 (m, 3H), 7.71 (dd, *J* = 8.6, 1.6, 1H), 7.55 (d, *J* = 8.3, 2H), 7.52 – 7.43 (m, 2H), 7.18 (d, *J* = 7.9, 1H), 6.50 (s, 2H), 5.12 (t, *J* = 4.8, 1H), 3.85 (dd, *J* = 11.6, 4.9, 1H), 3.29 – 3.22 (m, 1H), 3.01 (dd, *J* = 13.6, 4.9, 1H), 2.78 – 2.66 (m,

2H), 2.29 (s, 6H), 1.79 – 1.70 (m, 1H), 1.68 – 1.58 (m, 1H), 1.56 – 1.45 (m, 1H), 1.39 – 1.24 (m, 1H).

(174) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide

Followed procedure for compound **115** with (R)-1,2,3,4-tetrahydronaphthalen-1-amine (0.040 g, 0.27 mmol) to give product as a white solid. MS(EI): 339.2 (M+H), Retention Time: 27.94 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.08 (d, J = 8.5, 1H), 7.16 (dd, *J* = 7.2, 1.9, 1H), 7.08 (td, *J* = 6.9, 1.8, 2H), 7.00 (dd, *J* = 7.0, 1.9, 1H), 6.47 (s, 2H), 4.97 (dt, *J* = 8.4, 5.5, 1H), 3.82 (dd, *J* = 11.6, 4.9, 1H), 3.24 (dd, *J* = 13.6, 11.6, 1H), 3.00 (dd, *J* = 13.6, 4.9, 1H), 2.64 (t, *J* = 5.9, 2H), 2.26 (s, 6H), 1.71 – 1.51 (m, 2H), 1.45 – 1.28 (m, 2H).

(175) N-(4-benzylphenyl)-3-bromopropanamide

To a dry flask was added 4-benzylaniline (5.31 g, 29.0 mmol) and K_2CO_3 (8.02 g, 58.0 mmol), and placed under an inert atmosphere. DCM (85 mL) was added, and 4-benzylaniline was allowed to dissolve. 3-bromopropionyl chloride (3.06 mL, 30.4 mmol) was then added dropwise via syringe. The resulting cloudy white mixture was stirred at r.t. for 2 h, after which time the reaction was quenched with H_2O (10 mL), and washed with H_2O (2x). Organic layer was dried with $MgSO_4$. Solvents were filtered and removed to give product as a tan solid (8.63 g, 98%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4, 2H), 7.32 – 7.25 (m, 2H), 7.21 – 7.10 (m, 5H), 3.93 (s, 2H), 3.68 (t, *J* = 6.6, 2H), 2.90 (t, *J* = 6.6, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.00, 141.12, 137.81, 135.57, 129.66, 129.00, 128.63, 126.27, 120.41, 41.76, 40.81, 27.14.

(176) 1-(4-benzylphenyl)azetidin-2-one

To a dry flask was added NaOtBu (2.86 g, 96.1 mmol), and placed under an inert atmosphere. DMF (75 mL) was then added via syringe. After dissolution of solids, **175** was dissolved in DMF (125 mL) and added dropwise via syringe. The mixture was allowed to stir at r.t. for 3 h, after which time DMF was removed under reduced pressure, and crude residue was redissolved in EtOAc. H2O was added, and the aqueous layer was extracted with EtOAc. Combined organic extracts were washed with H2O and brine, and dried with MgSO4. Solvents were filtered and removed under reduced pressure, and crude residue was purified by column chromatography (1:1 hex/EtOAc) to give product as a white solid (3.93 g, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 4H), 7.22 – 7.12 (m, 5H), 3.94 (s, 2H), 3.60 (t, J = 4.5, 2H), 3.09 (t, J = 4.5, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.42, 141.23, 136.90, 136.84, 129.76, 128.94, 128.63, 126.26, 116.43, 41.53, 38.16, 36.23.

(177) 6-benzyl-1-methyl-2,3-dihydroquinolin-4(1H)-one

To a dry flask was added compound **14** (0.74 g, 3.1 mmol) and K_2CO_3 (0.86 g, 6.2 mmol). DMF (15 mL) was then added via syringe. CH_3I (0.40 mL, 6.2 mmol) was then added via syringe. The resulting mixture was stirred at 100 °C for 18 h, after which time the reaction was diluted with the addition of EtOAc (50 mL) and H_2O (50 mL). The aqueous layer was extracted with EtOAc, and combined organic extracts were washed with brine, and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure, and the crude residue was purified by column chromatography (3:2 hex/EtOAc) to give product as a yellow oil (0.46 g, 59%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.7, 1H), 7.31 – 7.14 (m, 6H), 6.65 (d, J = 8.7, 1H), 3.88 (s, 2H), 3.41 (t, J = 7.0, 2H), 2.93 (s, 3H), 2.71 (t, J = 7.0, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.89, 151.43,

141.28, 136.31, 129.88, 128.74, 128.48, 127.80, 126.05, 119.74, 113.75, 51.51, 40.81, 39.42, 38.37.

(178) 6-benzyl-1-propyl-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **177** with **14** (0.17 g, 0.74 mmol) and 1-iodopropane (0.72 mL, 7.3 mmol), with heating at 110 °C to give product as a yellow oil (0.12 g, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 2.2, 1H), 7.28 – 7.45 (m, 2H), 7.20 – 7.14 (m, 4H), 6.64 (d, *J* = 8.7, 1H), 3.86 (s, 2H), 3.47 (t, *J* = 6.8, 2H), 3.27 (t, *J* = 7.6, 2H), 2.66 (t, *J* = 7.2, 2H), 1.69 – 1.56 (m, 2H), 0.98 (t, *J* = 7.6, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 193.73, 150.14, 141.36, 136.25, 128.74, 128.45, 127.98, 126.01, 119.30, 113.35, 53.31, 49.18, 40.77, 38.00, 19.58, 11.52.

(179) (E)-6-benzyl-1-methyl-2,3-dihydroquinolin-4(1H)-one oxime

Followed procedure for compound **111** with **177** (0.13 g, 0.50 mmol) to give product as a yellow oil (0.41 g, 85%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.29 – 7.21 (m, 2H), 7.21 – 7.11 (m, 3H), 7.04 (d, *J* = 8.5, 1H), 6.62 (d, *J* = 8.5, 1H), 3.87 (s, 2H), 3.13 (t, *J* = 6.5, 2H), 2.95 (t, *J* = 6.6, 2H), 2.84 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 152.86, 147.35, 141.70, 131.58, 130.60, 128.92, 128.52, 126.00, 124.51, 117.76, 113.29, 49.94, 41.18, 39.80, 24.20.

(180) (E)-6-benzyl-1-propyl-2,3-dihydroquinolin-4(1H)-one oxime

Followed procedure for compound **111** with **178** (0.12 g, 0.43 mmol) to give product as a yellow oil (0.084 g, 66%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.0, 1H), 7.29 – 7.21 (m, 2H), 7.21 – 7.12 (m, 3H), 7.00 (dd, *J* = 8.6, 2.1, 1H), 6.60 (d, *J* = 8.6, 1H), 3.85 (s, 2H), 3.26 – 3.15 (m, 4H), 2.91 (t, *J* = 6.6, 2H), 1.65 – 1.52 (m, 2H), 0.93 (t, *J* = 7.6,

3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.11, 145.79, 141.79, 131.57, 129.42, 128.92, 128.50, 125.95, 124.81, 116.94, 112.95, 53.49, 47.53, 41.11, 23.63, 19.28, 11.68.

(181) 6-benzyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-amine

Followed procedure for compound **113** with **179** (0.19 g, 0.70 mmol) shaking under H_2 at 50 psi to give product as a colorless oil which was taken forward without further purification or characterization.

(182) 6-benzyl-1-propyl-1,2,3,4-tetrahydroquinolin-4-amine

Followed procedure for compound **113** with **180** (0.084 g, 0.29 mmol) to give product as a colorless oil (0.072 g, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 7.02 (d, *J* = 1.8, 1H), 6.92 (dd, *J* = 8.4, 2.0, 1H), 6.53 (d, *J* = 8.4, 1H), 3.91 (t, *J* = 4.7, 1H), 3.87 (s, 2H), 3.37 (ddd, *J* = 14.8, 8.0, 3.6, 1H), 3.29 – 3.14 (m, 3H), 2.06 – 1.94 (m, 1H), 1.86 – 1.74 (m, 1H), 1.66 – 1.57 (m, 2H), 0.93 (t, *J* = 7.2, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 142.82, 142.11, 129.05, 128.81, 128.59, 128.31, 127.83, 126.14, 125.73, 110.96, 53.31, 47.48, 44.73, 40.97, 31.19, 19.52, 11.57.

(183) (2S)-2-amino-N-(6-benzyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **115** with **181** (0.083 g, 0.33 mmol) to give product as a white solid. (**183E**): MS(EI): 466.2 (M+Na), Retention Time: 33.31 min. (**183L**): MS(EI): 466.2 (M+Na), Retention Time: 34.85 min.

(184) (2S)-2-amino-N-(6-benzyl-1-propyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **115** with **180** (0.069 g, 0.25 mmol) to give product as white solid. (**184E**): 472.3 (M+H), Retention Time: 41.75 min.

(185) 6-benzyl-1,2,3,4-tetrahydroquinoline

Compound **14** was added to a hydrogenation vessel, and dissolved in MeOH. 10% Pd/C was added, followed by conc. HCl (6 drops). The mixture was allowed to shake on the hydrogenator at 45 psi for 3 h, after which time the mixture was filtered through a plug of Celite with MeOH. MeOH was removed under reduced pressure, and crude residue was redissolved in DCM. H_2O was added, and the aqueous layer was extracted with DCM. Combined organic extracts were dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure to give product as a light brown oil (0.21 g, 79%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.24 (t, J = 7.6, 2H), 7.19 – 7.10 (m, 3H), 6.76 (d, J = 7.4, 2H), 6.36 (d, J = 8.1, 1H), 3.80 (s, 2H), 3.49 (br s, 1H), 3.20 (t, J = 5.5, 2H), 2.67 (t, J = 6.4, 2H), 1.91 – 1.82 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 143.03, 142.23, 130.00, 129.62, 128.86, 128.37, 127.26, 125.79, 121.58, 114.44, 42.11, 41.21, 27.01, 22.34.

(186) 9-benzyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-1-one

To a stirring solution of N,N-dimethylacrylamide (0.12 mL, 1.18 mmol) in DCE (10 mL) at 0 °C was added trifluoromethylsulfonic anhydride (0.20 mL, 1.18 mmol) in DCE (5 mL) dropwise. **185** (0.21 g, 0.95 mmol) in DCE (5 mL) was then added dropwise, resulting in a bright orange solution. The mixture was warmed to r.t. and then refluxed at 85 °C for 3 h, after which time the mixture was cooled and poured into a stirring mixture of diethyl ether and aqueous K_2CO_3. The aqueous layer was extracted with diethyl ether. Combined organic extracts were dried with $MgSO_4$, and allowed to sit overnight. Solvents were filtered and removed, and crude residue was purified by column chromatography (hex/EtOAc) to give product as a yellow oil (0.11 g, 42%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.29 – 7.22 (m, 2H), 7.17 (d, J = 7.4, 3H), 6.93 (s, 1H),

3.81 (s, 2H), 3.33 (t, J = 7.0, 2H), 3.16 (t, J = 5.5, 2H), 2.71 – 2.66 (m, 4H), 2.06 – 1.96 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.05, 148.39, 141.48, 135.72, 129.54, 128.83, 128.54, 126.08, 125.62, 124.35, 119.14, 50.29, 50.23, 41.05, 38.14, 26.69, 21.73.

(187) (R)-N-((R)-9-benzyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-1-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **186** (0.11 g, 0.40 mmol) to give product as a slightly yellow oil (0.021 g, 14%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.25 (t, J = 7.5, 2H), 7.20 – 7.13 (m, 3H), 6.93 (d, J = 2.1, 1H), 6.69 (d, J = 2.1, 1H), 4.49 (q, J = 2.8, 1H), 3.84 – 3.73 (m, 2H), 3.21 (td, J = 11.7, 2.9, 1H), 3.17 – 3.07 (m, 3H), 2.96 (dt, J = 11.7, 3.9, 1H), 2.78 – 2.63 (m, 2H), 2.06 (dq, J = 13.7, 3.3, 1H), 2.02 – 1.88 (m, 3H), 1.20 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 142.03, 141.50, 129.58, 129.08, 128.89, 128.49, 128.45, 125.92, 122.46, 120.72, 55.40, 50.05, 49.94, 44.51, 41.10, 28.24, 27.69, 22.80, 21.99.

(188) (S)-2-amino-N-((R)-9-benzyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-1-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **187** (0.021 g, 0.055 mmol) to give product as a white solid. MS(EI): 470.3 (M+H), Retention Time: 37.09 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.99 (d, J = 7.8, 1H), 7.20 (t, J = 7.5, 2H), 7.14 – 7.07 (m, 3H), 6.67 (d, J = 2.1, 1H), 6.62 (d, J = 1.8, 1H), 6.48 (s, 2H), 4.85 – 4.82 (m, 1H) 3.83 (dd, J = 11.5, 5.0, 1H), 3.70 (s, 2H), 3.24 (dd, J = 13.6, 11.6, 1H), 3.10 – 3.02 (m, 1H), 3.03 – 2.92 (m, 2H), 2.76 (dt, J = 11.9, 4.2, 1H), 2.67 – 2.60 (m, 2H), 2.36 – 2.28 (m, 1H), 2.28 (s, 6H), 1.98 – 1.82 (m, 2H), 1.82 – 1.70 (m, 1H), 1.56 – 1.47 (m, 1H).

(190) 6-benzyl-1-propionyl-2,3-dihydroquinolin-4(1H)-one

Compound **14** (0.11 g, 0.47 mmol) was dissolved in propionic anhydride (10 mL) and heated to 90 °C for 14 h under an inert atmosphere. The reaction mixture was cooled and transferred to a separatory funnel, and EtOAc and sat. $NaHCO_3$ were added. The aqueous layer was extracted with EtOAc. Combined organic extracts were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure, and crude residue was purified by column chromatography (2:1 hex/EtOAc) to give product as a colorless oil (0.12 g, 85%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 0.9, 1H), 7.39 (br s, 1H), 7.35 (dd, *J* = 8.2, 2.2, 1H), 7.29 (t, *J* = 7.4, 2H), 7.23 – 7.16 (m, 3H), 4.20 (t, *J* = 6.2, 2H), 3.98 (s, 2H), 2.75 (t, *J* = 6.2, 2H), 2.58 (q, *J* = 7.4, 2H), 1.20 (t, *J* = 7.4, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.27, 173.03, 142.21, 140.13, 138.78, 134.63, 128.90, 128.71, 127.62, 126.49, 126.11, 124.44, 43.88, 41.29, 39.62, 27.98, 9.91.

(191) 6-benzyl-1-butyryl-2,3-dihydroquinolin-4(1H)-one

Compound **14** (0.18 g, 0.78 mmol) was dissolved in pyridine (4 mL) and placed under an inert atmosphere. Butyric anhydride (5 mL) was added via syringe. The mixture was stirred at r.t. for 24 h, after which time it was quenched with the addition of H_2O. DCM was added, and the aqueous layer was extracted with DCM. Combined organic extracts were washed with 2 M NaOH, and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure, and the crude residue was purified by column chromatography (3:2 hex/EtOAc) to give product as an oil (0.029 g, 12%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 (t, *J* = 1.3, 1H), 7.39 – 7.34 (m, 2H), 7.33 – 7.25 (m, 2H), 7.25 – 7.16 (m, 3H), 4.21 (t, *J* = 6.2, 2H), 3.99 (s, 2H), 2.76 (t, *J* = 6.2, 2H), 2.54 (t, *J* = 8.0, 2H), 1.79 – 1.66 (m, 2H), 0.95 (t, *J* = 7.4, 3H), ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.37, 172.35,

142.31, 140.18, 138.87, 134.71, 128.99, 128.80, 127.77, 126.58, 126.18, 124.55, 43.97, 41.38, 39.82, 36.57, 19.25, 13.94.

(192) 6-benzyl-1-(cyclopropanecarbonyl)-2,3-dihydroquinolin-4(1H)-one

Compound **14** (0.15 g, 0.65 mmol) was dissolved in DCM (10 mL), and Et_3N (0.18 mL, 1.29 mmol) was added dropwise. The solution was stirred for 5 min at r.t., after which time cyclopropanecarbonyl chloride (0.12 mL, 1.29 mmol) was added dropwise via syringe. The reaction was stirred for 3 h, after which time sat. $NaHCO_3$ was added. Aqueous layer was extracted with DCM. Combined organic extracts were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure, and crude residue was purified by column chromatography (3:2 hex/EtOAc) to give product as a colorless oil (0.15 g, 78%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.2, 1H), 7.46 (d, *J* = 8.3, 1H), 7.35 (dd, *J* = 8.4, 2.2, 1H), 7.31 – 7.26 (m, 2H), 7.22 – 7.17 (m, 3H), 4.26 (t, *J* = 6.3, 2H), 3.98 (s, 2H), 2.76 (t, *J* = 6.3, 2H), 2.06 – 1.96 (m, 1H), 1.21 – 1.15 (m, 2H), 0.91 – 0.82 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.41, 173.00, 142.45, 140.13, 138.53, 134.49, 128.89, 128.71, 127.74, 126.49, 125.85, 124.09, 43.53, 41.28, 39.70, 13.74, 9.77.

(193) 6-benzyl-1-(cyclobutanecarbonyl)-2,3-dihydroquinolin-4(1H)-one

Followed procedure for compound **192** with **14** (0.15 g, 0.62 mmol) and cyclobutanecarbonyl chloride (0.14 mL, 1.25 mmol) to give product as a white solid (0.20 g, 99%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 1.3, 1H), 7.48 – 7.37 (br s, 1H), 7.35 (dd, J = 8.2, 2.2, 1H), 7.29 (t, J = 7.5, 2H), 7.24 – 7.13 (m, 3H), 4.12 (t, J = 6.2, 2H), 3.98 (s, 2H), 3.52 (p, J = 8.4, 1H), 2.72 (t, J = 6.2, 2H), 2.43 (dq, J = 11.8, 9.2, 2H), 2.13 (q, J = 9.9, 2H), 2.02 – 1.88 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.09, 174.02,

142.14, 140.14, 138.52, 134.63, 128.85, 128.64, 127.49, 126.41, 125.75, 123.84, 43.78, 41.24, 39.57, 37.95, 25.72, 17.83.

(195) (R)-N-((R)-6-benzyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **190** (0.12 g, 0.40 mmol) to give product as a colorless oil (0.12 g, 78%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 3H), 7.23 – 7.17 (m, 3H), 7.10 (dd, *J* = 8.3, 2.1, 1H), 4.52 (q, *J* = 4.2, 1H), 3.95 (s, 2H), 3.88 (dt, *J* = 12.9, 5.4, 1H), 3.80 – 3.69 (m, 1H), 3.31 (d, *J* = 3.3, 1H), 2.53 – 2.46 (m, 2H), 2.22 (dq, *J* = 13.9, 5.0, 1H), 2.06 – 1.98 (m, 1H), 1.19 (s, 9H), 1.15 (t, *J* = 7.4, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 173.52, 140.60, 138.63, 136.66, 128.94, 128.68, 128.61, 128.59, 126.30, 124.89, 55.78, 50.98, 41.41, 39.99, 30.62, 28.12, 22.61, 10.04.

(196) (R)-N-((R)-6-benzyl-1-butyryl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **191** (0.029 g, 0.094 mmol) to give product as a colorless oil (0.010 g, 26%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 7.10 (dd, *J* = 8.3, 2.1, 1H), 4.53 (t, *J* = 4.6, 1H), 3.95 (s, 2H), 3.94 – 3.85 (m, 1H), 3.80 – 3.68 (m, 1H), 3.34 (br s, 1H), 2.51 – 2.41 (m, 2H), 2.27 – 2.15 (m, 1H), 2.08 – 1.97 (m, 1H), 1.74 – 1.63 (m, 2H), 1.20 (s, 9H), 0.92 (t, *J* = 7.4, 3H).

(197) (R)-N-((R)-6-benzyl-1-(cyclopropanecarbonyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **192** (0.16 g, 0.51 mmol) to give product as a colorless oil (0.12 g, 55%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.2, 1H), 7.32 – 7.26 (m, 3H), 7.23 – 7.18 (m, 3H), 7.09 (dd, *J* = 8.3, 2.0, 1H), 4.55 (q, *J* = 4.3, 1H), 4.01

– 3.93 (m, 3H), 3.75 (ddd, *J* = 12.9, 9.3, 5.6, 1H), 3.33 (d, *J* = 3.6, 1H), 2.23 (dq, *J* = 14.9, 5.1, 1H), 2.10 – 1.89 (m, 3H), 1.20 (s, 9H), 1.14 – 1.08 (m, 2H), 0.78 (dd, J = 7.9, 2.5, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.36, 140.65, 138.53, 136.83, 131.83, 128.98, 128.71, 128.58, 128.51, 126.36, 124.97, 55.85, 51.18, 41.47, 39.85, 30.74, 22.61, 13.65, 9.28.

(198) (R)-N-((R)-6-benzyl-1-(cyclobutanecarbonyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **193** (0.20 g, 0.62 mmol) to give product as a colorless oil (0.16 g, 60%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.23 – 7.17 (m, 2H), 7.09 (dd, J = 8.3, 2.1, 1H), 4.51 (q, J = 4.3, 1H), 3.95 (s, 2H), 3.86 – 3.77 (m, 1H), 3.74 – 3.63 (m, 1H), 3.50 – 3.39 (m, 2H), 2.44 – 2.30 (m 2H), 2.19 (dq, J = 14.3, 4.9, 1H), 2.12 – 1.97 (m, 3H), 1.97 – 1.82 (m, 2H), 1.21 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 174.44, 140.63, 138.39, 136.58, 128.89, 128.73, 128.56, 128.50, 126.23, 124.20, 55.77, 50.96, 41.37, 39.90, 38.22, 30.72, 25.80, 22.60, 17.84.

(200) (S)-2-amino-N-((R)-6-benzyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **195** (0.12 g, 0.31 mmol) to give product as a white solid. MS(EI): 486.3 (M+H), Retention Time: 35.59 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.15 (d, *J* = 8.2, 1H), 7.42 (br s, 1H), 7.27 – 7.19 (m, 2H), 7.18 – 7.11 (m, 4H), 7.05 (dd, *J* = 8.4, 2.1, 1H), 6.51 (s, 2H), 4.96 – 4.91 (m, 1H), 3.91 (s, 2H), 3.86 (dd, *J* = 11.5, 5.0, 1H), 3.78 (br s, 1H), 3.26 (dd, *J* = 13.6, 11.5, 1H), 3.18 – 3.10 (m, 1H), 3.03 (dd, *J* = 13.7, 5.1, 1H), 2.58 – 2.39 (m, 2H), 2.27 (s, 6H), 1.90 – 1.80 (m, 1H), 1.48 – 1.39 (m, 1H), 1.11 (t, *J* = 7.4, 3H).

(201) (S)-2-amino-N-((R)-6-benzyl-1-butyryl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **196** (0.010 g, 0.024 mmol) to give product as a white solid. MS(EI): 500.3 (M+H), Retention Time: 38.47 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.39 (br s, 1H), 7.27 – 7.20 (m, 2H), 7.18 – 7.11 (m, 4H), 7.06 (dd, *J* = 8.4, 2.1, 1H), 6.50 (s, 2H), 4.93 (t, *J* = 6.5, 1H), 3.91 (s, 2H), 3.88 – 3.75 (m, 2H), 3.25 (dd, *J* = 13.6, 11.5, 1H), 3.15 – 3.11 (m, 1H), 3.02 (dd, *J* = 13.7, 5.1, 1H), 2.54 – 2.39 (m, 2H), 2.27 (s, 6H), 1.91 – 1.81 (m, 1H), 1.69 – 1.58 (m, 2H), 1.44 – 1.40 (m, 1H), 0.93 (t, *J* = 7.2, 3H).

(202) (S)-2-amino-N-((R)-6-benzyl-1-(cyclopropanecarbonyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **197** (0.12 g, 0.28 mmol) to give product as a white solid. MS(EI): 498.3 (M+H), Retention Time: 37.47 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.39 (d, J = 8.3, 1H), 7.26 – 7.20 (m, 2H), 7.19 – 7.12 (m, 4H), 7.07 (dd, J = 8.4, 2.1, 1H), 6.50 (s, 2H), 4.96 (t, J = 6.3, 1H), 3.92 (s, 2H), 3.91 – 3.80 (m, 2H), 3.29 – 3.20 (m, 2H), 3.07 – 2.99 (m, 1H), 2.28 (s, 6H), 1.98 – 1.92 (m, 1H), 1.89 – 1.81 (m, 1H), 1.47 – 1.38 (m, 1H), 1.07 – 1.01 (m, 1H), 0.99 – 0.92 (m, 1H), 0.91 – 0.79 (m, 2H).

(203) (S)-2-amino-N-((R)-6-benzyl-1-(cyclobutanecarbonyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **198** (0.16 g, 0.37 mmol) to give product as a white solid. MS(EI): 512.3 (M+H), Retention Time: 39.62 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.39 (br s, 1H), 7.26 – 7.21 (m, 2H), 7.18 – 7.11 (m, 4H), 7.05 (dd, J = 8.3, 2.1, 1H), 6.50 (s, 2H), 4.98 – 4.89 (m, 1H), 3.91 (s, 2H), 3.85 (dd, J = 11.5, 5.1, 1H), 3.68

(br s, 1H), 3.50 (p, J = 8.5, 1H), 3.25 (dd, J = 13.6, 11.6, 1H), 3.12 – 3.01 (m, 2H), 2.35 – 1.94 (m, 11H), 1.89 – 1.77 (m, 2H), 1.43 – 1.32 (m, 1H).

(204) chroman-4-ol

4-chromanone (0.52 g, 3.5 mmol) was dissolved in absolute EtOH (15 mL). $NaBH_4$ (0.27 g, 7.0 mmol) was then added. The reaction was stirred at r.t. for 20 min, after which time it was quenched with sat. NH_4Cl (10 mL), and stirred vigorously for 5 min. EtOH was removed under reduced pressure, and the aqueous layer was extracted with EtOAc. Combined organic extracts were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure to give product as a colorless oil (0.51 g, 97%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 7.6, 1.7, 1H), 7.17 – 7.11 (m, 1H), 6.85 (td, *J* = 7.4, 1.2, 1H), 6.78 (dd, *J* = 8.2, 1.2, 1H), 4.58 (t, *J* = 4.2, 1H), 4.16 – 4.09 (m, 2H), 3.19 (s, 1H), 2.01 – 1.92 (m, 1H), 1.88 – 1.80 (m, 1H).

(205) 6-iodochroman-4-ol

Compound **204** (0.51 g, 3.4 mmol) was dissolved in anhydrous DCM (15 mL). HgO (0.74 g, 3.4 mmol) and I_2 (0.87 g, 3.4 mmol) were then added. The resulting dark purple mixture was stirred at r.t. for 16 h, after which time solids were removed by filtration, and were rinsed with DCM. Filtrate was washed with H_2O, and dried with $MgSO_4$. Solvents were filtered and removed, and crude residue was purified by column chromatography (5:1 hex/EtOAc to 2:1 hex/EtOAc) to give product as a white solid (0.70 g, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.2, 1H), 7.43 (dd, *J* = 8.7, 2.2, 1H), 6.58 (d, *J* = 8.7, 1H), 4.65 (t, *J* = 4.3, 1H), 4.27 – 4.14 (m, 2H), 2.48 (s, 1H), 2.11 – 1.98 (m, 1H), 1.98 – 1.87 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 154.50, 138.36, 138.23, 126.93, 119.53, 82.33, 62.82, 62.22, 30.57.

(206) 6-iodochroman-4-one

To a dry flask was added finely ground 4Å molecular sieves (1.5 g). Compound **205** (0.70 g, 2.5 mmol) was dissolved in anhydrous DCM (15 mL) and added to the flask, which was placed under an inert atmosphere. PCC (0.54 g, 2.5 mmol) was added portionwise. The resulting black mixture was stirred at r.t. for 18 h, after which time solids were removed via filtration through Florisil. The filtrate was transferred to a separatory funnel, and H_2O was added. Aqueous layer was extracted with DCM (3x). Combined organic extracts were dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure to give product as white crystals (0.63 g, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 2.3, 1H), 7.72 (dd, *J* = 8.7, 2.3, 1H), 6.76 (d, *J* = 8.7, 1H), 4.53 (t, *J* = 6.4, 2H), 2.80 (t, *J* = 6.4, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 190.30, 161.31, 144.13, 135.62, 122.98, 120.30, 83.74, 67.01, 37.26.

(207) 6-benzylchroman-4-one

Compound **206** (0.082 g, 0.30 mmol) was dissolved in 3:1 acetone/H_2O (degassed and saturated with Ar gas). This mixture was then transferred to a 10 mL microwave vessel containing K_2CO_3 (0.12 g, 0.90 mmol) via cannula. $Pd(dppf)Cl_2$ (0.022 g, 0.030 mmol) was then added, and the flask was flushed with Ar gas. Benzylboronic acid pinacol ester (0.13 g, 0.60 mmol) was then added via syringe. The mixture was stirred under microwave irradiation for 1 h at 110 °C, after which time solvents were removed under reduced pressure, and crude residue was purified by column chromatography (4:1 hex/EtOAc) to give a colorless oil (0.040 g, 56%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 2.3, 1H), 7.32 – 7.24 (m, 3H), 7.23 – 7.14 (m, 3H), 6.89 (d, *J* = 8.5, 1H), 4.51 (t, *J* = 6.4, 2H), 3.92 (s, 2H), 2.79 (t, *J* = 6.4, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 192.13,

160.54, 140.82, 136.93, 134.46, 128.91, 128.72, 126.90, 126.40, 121.18, 118.22, 67.15, 41.14, 37.94. NMR revealed that the product co-eluted with ~20% of starting material **206**. The mixture was carried forward without additional purification.

(208) (E)-6-benzylchroman-4-one oxime

Followed procedure for compound **111** with **207** (0.023 g, 0.097 mmol) to give product as an oil (0.020 g, 83%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.2, 1H), 7.30 – 7.23 (m, 2H), 7.23 – 7.15 (m, 3H), 7.07 (dd, *J* = 8.5, 2.3, 1H), 6.82 (d, *J* = 8.5, 1H), 4.21 (t, *J* = 6.2, 2H), 3.90 (s, 2H), 2.96 (t, *J* = 6.2, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 155.25, 150.27, 141.24, 134.28, 132.03, 128.93, 128.63, 126.22, 124.10, 118.00, 65.10, 41.35, 23.53.

(209) 6-benzylchroman-4-amine

Followed procedure for compound **113** with **208** (0.020 g, 0.079 mmol) shaking at 40 psi for 22 h to give product as an oil (0.0062 g, 33%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.21 (m, 3H), 7.16 (d, *J* = 7.6, 3H), 6.98 (dd, *J* = 8.4, 2.1, 1H), 6.74 (d, *J* = 8.4, 1H), 4.26 (ddd, *J* = 12.1, 9.8, 2.6, 1H), 4.18 – 4.11 (m, 2H), 3.86 (s, 2H), 2.22 – 2.11 (m, 1H), 2.02 – 1.93 (m, 1H).

(210) (2S)-2-amino-N-(6-benzylchroman-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **115** with **209** (0.0062 g, 0.026 mmol) to give product as a white solid. (**210E**): MS(EI): 453.2 (M+Na), Retention Time: 37.69 min. (**210L**): MS(EI): 453.2 (M+Na), Retention Time: 38.49 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.26 – 7.19 (m, 2H), 7.17 – 7.09 (m, 3H), 6.82 (dd, *J* = 8.5, 2.2, 1H), 6.60 (d, *J* = 8.4, 1H), 6.55 (s, 2H), 6.46 (d, *J* = 2.2, 1H), 4.76 – 4.70 (m, 1H), 4.17 – 4.09 (m, 1H), 4.03 – 3.95

(m, 1H), 3.89 – 3.74 (m, 3H), 3.27 – 3.21 (m, 1H), 2.97 (dd, *J* = 13.8, 4.6, 1H), 2.29 (s, 6H), 2.17 – 2.07 (m, 1H), 2.05 – 1.95 (m, 1H).

(211) 6-(bromomethyl)thiochroman-4-one

Followed procedure for compound **23** with 6-methylthiochroman-4-one (0.96 g, 5.4 mmol) to give product as a white solid (0.17 g, 12%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 2.2, 1H), 7.40 (dd, J = 7.8, 1.9, 1H), 7.25 (d, J = 8.3, 1H), 4.44 (s, 2H), 3.22 (t, J = 6.3, 2H), 2.96 (t, J = 6.3, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 193.41, 142.62, 134.74, 133.79, 130.91, 129.33, 128.29, 39.30, 32.56, 26.52.

(212) 6-benzylthiochroman-4-one

Followed procedure for compound **159** with **211** (0.079 g, 0.31 mmol) to give product as a white solid (0.060 g, 77%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.98 (m, 1H), 7.29 (t, J = 7.5, 2H), 7.24 – 7.15 (m, 5H), 3.95 (s, 2H), 3.21 (t, J = 6.5, 2H), 2.96 (t, J = 6.3, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 194.15, 140.36, 139.77, 138.30, 134.11, 130.86, 129.26, 128.79, 128.60, 127.87, 126.33, 41.31, 39.67, 26.64.

(213) (R)-N-((R)-6-benzylthiochroman-4-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **212** (0.060 g, 0.24 mmol) to give product as a slightly yellow oil (0.038 g, 45%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 7.21 – 7.14 (m, 4H), 7.03 (d, J = 8.1, 1H), 6.97 (dd, J = 8.1, 2.0, 1H), 4.60 (q, J = 3.1, 1H), 3.90 (s, 2H), 3.28 (td, J = 12.6, 2.8, 1H), 3.16 (d, J = 2.3, 1H), 2.79 (dt, J = 12.5, 4.0, 1H), 2.50 – 2.41 (m, 1H), 2.05 – 1.96 (m, 1H), 1.22 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 140.85, 137.82, 132.54, 131.65, 131.06, 129.15, 128.78, 128.50, 126.91, 126.14, 55.59, 50.76, 41.25, 28.05, 22.62, 21.01.

(214) (S)-2-amino-N-((R)-6-benzylthiochroman-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **213** (0.038 g, 0.11 mmol) to give product as a white solid. MS(EI): 447.2 (M+H), Retention Time: 39.76 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.23 (t, J = 7.5, 2H), 7.17 – 7.09 (m, 4H), 7.03 (s, 1H), 6.93 (s, 1H), 6.50 (s, 2H), 5.03 (t, J = 4.0, 1H), 3.85 (dd, J = 11.9, 5.3, 1H), 3.83 (s, 2H), 3.26 (dd, J = 13.6, 11.7, 1H), 3.01 (dd, J = 13.6, 5.1, 1H), 2.51 (dt, J = 13.3, 4.2, 1H), 2.28 (s, 6H), 2.21 (td, J = 12.7, 2.8, 1H), 1.89 – 1.83 (m, 1H), 1.82 – 1.73 (m, 1H).

(215) 6-benzylthiochroman-4-one 1,1-dioxide

Compound **212** (0.048 g, 0.19 mmol) was dissolved in glacial AcOH (4 mL). 30% H_2O_2 solution (1 mL) was then added. The mixture was stirred at 80 °C for 2 h, after which time the mixture was diluted with H_2O. Aqueous layer was extracted with DCM. Combined organic extracts were washed with brine, and dried with $MgSO_4$. Solvents were filtered and removed under reduced pressure to give product as a colorless oil (0.050 g, 93%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 1.8, 1H), 7.91 (d, J = 8.0, 1H), 7.61 (dd, J = 8.0, 1.8, 1H), 7.31 (t, J = 7.4, 2H), 7.27 – 7.21 (m, 1H), 7.15 (d, J = 7.1, 2H), 4.08 (s, 2H), 3.66 (t, J = 6.2, 2H), 3.38 (t, J = 6.4, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 190.32, 147.60, 139.20, 138.79, 135.30, 130.32, 128.90, 128.88, 126.87, 124.00, 49.25, 41.77, 36.78.

(216) (R)-N-((R)-6-benzyl-1,1-dioxidothiochroman-4-yl)-2-methylpropane-2-sulfinamide

Followed procedure for compound **46** with **215** (0.050 g, 0.18 mmol) to give product as a colorless oil (0.030 g, 43%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, J = 8.2, 1.2, 1H),

7.44 (s, 1H), 7.35 – 7.25 (m, 3H), 7.24 – 7.20 (m, 1H), 7.15 (d, J = 7.5, 2H), 4.69 (q, J = 4.1, 1H), 4.01 (s, 2H), 3.70 – 3.61 (m, 1H), 3.35 (d, J = 3.4, 1H), 3.30 – 3.23 (m, 1H), 2.76 – 2.68 (m, 1H), 2.63 – 2.55 (m, 1H), 1.21 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 147.47, 139.28, 136.62, 136.17, 130.43, 130.24, 128.85, 128.77, 126.68, 124.16, 56.10, 50.87, 46.13, 41.75, 27.74, 22.53.

(217) (S)-2-amino-N-((R)-6-benzyl-1,1-dioxidothiochroman-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **216** (0.030 g, 0.077 mmol) to give product as a white solid. MS(EI): 479.2 (M+H), Retention Time: 31.03 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.71 (d, J = 8.2, 1H), 7.34 (dd, J = 8.2, 1.7, 1H), 7.30 – 7.23 (m, 3H), 7.21 – 7.13 (m, 3H), 6.52 (s, 2H), 5.24 (t, J = 5.0, 1H), 4.00 (s, 2H), 3.83 (dd, J = 11.5, 5.3, 1H), 3.26 (dd, J = 14.0, 11.5, 1H), 3.18 – 3.10 (m, 1H), 3.05 (dd, J = 13.7, 5.3, 1H), 2.86 – 2.75 (m, 1H), 2.42 – 2.32 (m, 1H), 2.28 (s, 6H), 2.02 – 1.93 (m, 1H).

(218) 1-(3-benzylphenyl)ethan-1-one

Followed procedure for compound **207** with 1-(3-bromophenyl)ethan-1-one (0.12 g, 0.62 mmol) stirring at 110 °C for 75 min to give product as a colorless oil (0.058 g, 44%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.38 (d, *J* = 5.2, 1H), 7.29 (t, *J* = 7.4, 2H), 7.23 – 7.15 (m, 3H), 4.03 (s, 2H), 2.57 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 198.40, 141.81, 140.52, 137.46, 133.85, 128.98, 128.85, 128.76, 128.73, 126.46, 41.88, 26.84.

(219) 6-benzyl-2,3-dihydro-1H-inden-1-one

Followed procedure for compound **207** with 6-bromo-2,3-dihydro-1H-inden-1-one (0.14 g, 0.65 mmol) stirring at 110 °C for 70 min to give product as a white solid (0.10 g,

70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.45 – 7.36 (m, 2H), 7.31 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 4.02 (s, 2H), 3.09 (t, *J* = 6.0, 2H), 2.68 (t, *J* = 6.0, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 207.22, 153.37, 140.84, 140.57, 137.48, 135.75, 128.95, 128.73, 126.81, 126.44, 123.71, 41.67, 36.68, 25.59.

(220) (E)-1-(3-benzylphenyl)ethan-1-one oxime

Followed procedure for compound **111** with **218** (0.052 g, 0.25 mmol) to give product as an oil (0.056 g, 100%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.30 (td, *J* = 7.5, 3.1, 3H), 7.22 – 7.19 (m, 4H), 4.02 (s, 2H), 2.28 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 156.23, 141.52, 140.87, 136.82, 130.01, 129.03, 128.79, 128.65, 126.73, 126.30, 124.07, 42.02, 12.54.

(221) 1-(3-benzylphenyl)ethan-1-amine

Followed procedure for compound **113** with **220** (0.054 g, 0.24 mmol), shaking at 40 psi for 16 h to give product as a colorless oil (0.040 g, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 3H), 7.22 – 7.16 (m, 5H), 7.06 (d, *J* = 7.4, 1H), 4.09 (q, *J* = 6.6, 1H), 3.98 (s, 2H), 3.01 (br s, 2H), 1.39 (d, *J* = 6.6, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.13, 141.50, 141.16, 129.04, 128.81, 128.59, 127.75, 126.56, 126.21, 123.58, 51.33, 42.10, 25.27.

(222) 6-benzyl-2,3-dihydro-1H-inden-1-amine

Compound **219** (0.045 g, 0.20 mmol) was suspended in anhydrous absolute EtOH (2 mL) in a 10 mL microwave tube. NH_4OAc (0.23 g, 3.04 mmol) and $NaBH_3CN$ (0.015 g, 0.24 mmol) were then added. The mixture was stirred under microwave irradiation at 130 °C for 5 min, after which time EtOH was removed under reduced pressure, and residue was redissolved in DCM. 2M HCl was added. Organic layer was discarded, and aqueous layer

was basified with solid NaOH pellets (pH 14). Aqueous layer was extracted with DCM (3x). Combined organic layers were dried with $MgSO_4$, and solvents were filtered and removed under reduced pressure to give product as an oil (0.017 g, 38%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.22 – 7.10 (m, 5H), 7.03 (d, *J* = 7.6, 1H), 4.31 (t, *J* = 7.5, 1H), 3.97 (s, 2H), 2.91 (ddd, *J* = 15.8, 8.6, 3.3, 1H), 2.81 – 2.70 (m, 1H), 2.53 – 2.43 (m, 1H), 1.73 – 1.64 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.80, 141.55, 141.02, 139.72, 129.01, 128.59, 128.10, 126.13, 124.74, 123.94, 57.28, 42.03, 37.61, 29.87.

(223) (2S)-2-amino-N-(1-(3-benzylphenyl)ethyl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **115** with **221** (0.053 g, 0.25 mmol) to give product as a white solid. (**223E**): MS(EI): 403.3 (M+H), Retention Time: 37.57 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.26 – 7.19 (m, 2H), 7.19 – 7.12 (m, 4H), 7.05 (d, *J* = 7.6, 1H), 6.88 (s, 1H), 6.65 (d, *J* = 7.6, 1H), 6.32 (s, 2H), 4.95 – 4.91 (m, 1H), 3.93 (d, *J* = 3.9, 2H), 3.87 – 3.74 (m, 1H), 3.12 (t, *J* = 12, 1H), 2.86 (d, *J* = 13.5, 1H), 2.02 (s, 6H), 1.31 (d, *J* = 6.9, 3H). (**223L**): MS(EI): 403.3 (M+H), Retention Time: 38.68 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.25 – 7.00 (m, 9H), 6.52 (s, 2H), 4.78 (t, *J* = 7.2, 1H), 3.90 (s, 2H), 3.77 (dd, *J* = 11.6, 4.6, 1H), 3.25 – 3.15 (m, 1H), 2.99 (d, *J* = 13.8, 4.6, 1H), 2.27 (s, 6H), 1.09 (d, *J* = 7.0, 3H).

(224) (2S)-2-amino-N-(6-benzyl-2,3-dihydro-1H-inden-1-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **115** with **222** (0.012 g, 0.054 mmol) to give product as a white solid. MS(EI): 437.2 (M+Na), Retention Time: 39.35 min. ^{1}H-NMR (500

MHz, CD_3OD) δ 7.27 – 7.01 (m, 14H), 6.97 (d, *J* = 6.4, 1H), 6.59 (s, 2H), 6.52 (s, 1H), 6.50 (s, 2H), 5.26 (q, *J* = 6.8, 1H), 5.16 – 5.09 (m, 1H), 3.96 – 3.78 (m, 6H), 3.30 – 3.20 (m, 2H), 3.01 (dt, *J* = 13.7, 4.9, 2H), 2.85 (ddd, *J* = 15.8, 8.7, 3.9, 1H), 2.81 – 2.65 (m, 3H), 2.53 (dtd, *J* = 11.9, 7.7, 4.0, 1H), 2.29 (s, 6H), 2.27 (s, 6H), 2.26 – 2.20 (m, 1H), 1.80 – 1.70 (m, 1H), 1.41 – 1.30 (m, 1H) (both diastereomers).

(225) tert-butyl 7-chloro-5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepine-1-carboxylate

Followed procedure for compound **15** with 7-chloro-1,2,3,4-tetrahydro-5H-benzo[b]azepin-5-one (0.046 g, 0.24 mmol) to give product as a white solid (0.060 g, 43%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.44 – 7.33 (m, 2H), 3.74 (br s, 2H), 2.76 (t, *J* = 6.7, 2H), 2.16 (p, *J* = 6.9, 2H), 1.49 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 199.80, 153.68, 142.79, 134.22, 132.24, 131.73, 129.55, 128.70, 81.70, 48.84, 40.08, 28.33, 24.66.

(226) tert-butyl 7-benzyl-5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepine-1-carboxylate

To a dry 10 mL microwave vessel was added K_2CO_3 (0.084 g, 0.61 mmol), SPhos (0.016 g, 0.040 mmol) and $Pd_2(dba)_3$ (0.019 g, 0.020 mmol). The vessel was placed under an inert atmosphere, and **225** (0.060 g, 0.20 mmol) dissolved in 10:1 1,4-dioxane/H_2O (3 mL, degassed and saturated with Ar gas) was added via syringe. Benzylboronic acid pinacol ester (0.066 g, 0.30 mmol) was then added via syringe. The mixture was stirred under microwave irradiation at 140 °C for 30 min, after which time solvents were removed under reduced pressure, and crude residue was purified by column chromatography (10:1 hex/EtOAc) to give product as a colorless oil (0.029 g, 28%). ^{1}H-

NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.31 – 7.25 (m, 3H), 7.22 – 7.16 (m, 3H), 3.98 (s, 2H), 3.72 (br s, 2H), 2.74 (t, *J* = 6.6, 2H), 2.16 – 2.08 (m, 2H), 1.47 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 201.34, 154.12, 140.45, 139.12, 133.09, 132.48, 129.11, 129.01, 128.69, 128.20, 126.42, 81.28, 48.82, 41.40, 40.27, 28.40, 24.69.

(227) tert-butyl (R)-7-benzyl-5-(((R)-tert-butylsulfinyl)amino)-2,3,4,5-tetrahydro-1H-benzo[b]azepine-1-carboxylate

Followed procedure for compound **46** with **226** (0.029 g, 0.083 mmol) to give a colorless oil that was not characterized and used without further purification.

(228) (S)-2-amino-N-((R)-7-benzyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **68** with **227** (0.007 g, 0.015 mmol) to give product as a white solid. MS(EI): 444.3 (M+H), Retention Time: 26.04 min. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.26 – 7.22 (m, 2H), 7.18 – 7.13 (m, 4H), 7.08 – 7.02 (m, 2H), 6.53 (s, 2H), 5.05 (dd, *J* = 8.4, 2.3, 1H), 3.95 (dd, *J* = 11.6, 4.8, 1H), 3.91 (s, 2H), 3.23 (dd, *J* = 13.7, 11.7, 1H), 3.18 – 3.12 (m, 1H), 3.11 – 3.02 (m, 2H), 2.28 (s, 6H), 1.81 – 1.71 (m, 1H), 1.61 – 1.50 (m, 2H), 1.48 – 1.39 (m, 1H).

(229) 6-benzyl-N-methyl-1,2,3,4-tetrahydroquinolin-4-amine

To a stirring solution of methylamine hydrochloride (1.78 g, 26.4 mmol), Et_3N (3.68 mmol, 26.4 mmol) and **14** (3.14 g, 13.2 mmol) in absolute EtOH (70 mL) was added $Ti(OiPr)_4$ (7.81 mL, 26.4 mmol). The reaction was allowed to stir at r.t for 24 h. $NaBH_4$ (0.749 g, 19.8 mmol) was then added to the reaction mixture, and was allowed to stir for an additional 8 h. The reaction was then quenched by pouring into aqueous ammonia (10 mL). The resulting inorganic precipitate was filtered off and washed with DCM. The

organic layer was separated, and the aqueous layer was washed again with DCM. The organic layers were combined and extracted once with 1M HCl. The acidic aqueous extract was washed once with DCM then treated with 2M NaOH until the solution reached pH 12. The aqueous layer was then extracted with DCM (3x). The combined organic extracts were washed with brine, dried with $MgSO_4$, and solvents were removed under reduced pressure to give a yellow oil (1.05 g) which was used without any further purification.

(230) 6-benzyl-N-cyclopropyl-1,2,3,4-tetrahydroquinolin-4-amine

To a 10 mL microwave vessel was added **14** (0.11 g, 0.46 mmol) and absolute EtOH (2 mL). Cyclopropylamine (0.27 g, 4.6 mmol) was then added via syringe. $NaBH_3CN$ (0.035 g, 0.56 mmol) was then added. The mixture was stirred under microwave irradiation at 130 °C for 10 min, after which time EtOH was removed under reduced pressure, and crude residue was redissolved in DCM. 1M HCl was added, and the organic layer was removed. Aqueous layer was basified with solid NaOH pellets (pH 14), and was extracted with DCM (3x). Combined organic extracts were dried with $MgSO_4$. Solvents were filtered and removed, and crude residue was purified by column chromatography (20:1 DCM/MeOH) to give product as a white solid (0.011 g, 9%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H), 7.22 – 7.12 (m, 3H), 6.97 (d, *J* = 2.1, 1H), 6.85 (dd, *J* = 8.2, 2.1, 1H), 6.44 (d, *J* = 8.2, 1H), 3.87 – 3.81 (m, 3H), 3.39 (td, *J* = 11.6, 3.1, 1H), 3.23 (dt, *J* = 11.4, 4.2, 1H), 2.25 – 2.09 (m, 2H), 1.97 – 1.87 (m, 1H), 0.57 – 0.37 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 142.72, 142.25, 130.39, 129.29, 129.03, 128.90, 128.43, 125.89, 122.26, 114.76, 53.77, 41.20, 37.42, 28.57, 26.93, 7.16, 5.90.

(231) (2S)-2-amino-N-(6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)-N-methylpropanamide

Followed procedure for compound **115** with **229** (0.10 g, 0.41 mmol) to give product as a white solid. (**231E**): MS(EI): 466.2 (M+Na), Retention Time: 27.25 min. (**231L**): MS(EI): 466.2 (M+Na), Retention Time: 29.16 min.

(232) (2S)-2-amino-N-(6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-N-cyclopropyl-3-(4-hydroxy-2,6-dimethylphenyl)propanamide

Followed procedure for compound **115** with **230** (0.011 g, 0.041 mmol) to give product as a white solid. (**232E**): MS(EI): 492.3 (M+Na), Retention Time: 28.05 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.23 – 7.16 (m, 2H), 7.13 – 7.03 (m, 3H), 6.80 (dd, *J* = 8.1, 1.9, 1H), 6.67 (s, 1H), 6.56 (d, *J* = 8.2, 1H), 6.52 (s, 2H), 5.67 – 5.59 (m, 1H), 5.07 (dd, *J* = 11.6, 4.7, 1H), 3.77 (s, 2H), 3.39 – 3.33 (m, 3H), 3.17 (dd, *J* = 13.8, 4.8, 1H), 2.32 (s, 6H), 2.25 – 2.10 (m, 1H), 1.83 – 1.71 (m, 1H), 1.35 – 1.24 (m, 1H), 0.88 – 0.78 (m, 1H), 0.59 – 0.49 (m, 1H), 0.42 – 0.30 (m, 2H). (**232L**): MS(EI): 492.3 (M+Na), Retention Time: 30.18 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.26 – 7.18 (m, 2H), 7.16 – 7.06 (m, 3H), 6.82 (dd, *J* = 8.2, 1.9, 1H), 6.62 (d, *J* = 8.2, 1H), 6.56 (s, 2H), 6.35 (s, 1H), 5.49 – 5.41 (m, 1H), 5.06 (dd, *J* = 11.5, 4.5, 1H), 3.82 (d, *J* = 6.1, 2H), 3.40 (dd, *J* = 13.7, 11.5, 1H), 3.27 (dd, *J* = 8.0, 3.5, 2H), 3.09 (dd, *J* = 13.7, 4.5, 1H), 2.35 (s, 6H), 1.82 – 1.72 (m, 1H), 0.88 – 0.74 (m, 1H), 0.68 – 0.56 (m, 1H), 0.52 – 0.37 (m, 1H), 0.24 – 0.11 (m, 1H).

3.6.2 Microsomal Stability

To a mixture of 10 μL of pooled mouse liver microsomes (20 mg/mL, Xenotech, lot#105861) and 366 μL 0.1 M phosphate buffer containing 3.3 mM $MgCl_2$ are added 4 μL test compound (at 100 μM in $MeOH/H_2O$). The solution mixture is pre-incubated in a

water bath at 37 °C for 3 min. Next, a solution of 16.7 mg/mL (20 mM) NADPH in 0.1 M phosphate buffer containing 3.3 mM $MgCl_2$ is made. Following preparation, 20 μL of the NADPH solution is added to the solution containing the test compound to initiate the reaction (the final concentration of test compound 1 μM). The stability of the compound is tested at T (min)= 0,1,3,5,10,30 and 60 by removing a 30 μL aliquot, and quenching it with 90 μL of cold MeCN. The quenched samples are centrifuged at 14000 rpm for 5 min, and then 5 μL of the supernatant is used for LC/MS/MS analysis.

CHAPTER 4

SYNTHESIS OF 2',6'-DIMETHYL-L-TYROSINE DERIVATIVES AND INCORPORATION INTO OPIOID PEPTIDOMIMETICS[c]

4.1 Introduction

The unnatural amino acid 2',6'-dimethyl-L-tyrosine (Dmt)[9] has found widespread use in the synthesis of opioid peptides and small molecules.[36,39,57,95] Typically, opioid ligands containing Dmt in place of tyrosine (Tyr) at the N-terminus display increased affinity for the mu opioid receptor (MOR)[27,96,97] and many Dmt-containing ligands reported in the literature are potent and efficacious analgesics in preclinical pain models.[31,59] Additionally, Dmt is a component of Dmt-Tic, a delta opioid receptor (DOR) antagonist pharmacophore that is incorporated in many biologically active compounds.[98] Dmt is also an important building block for the synthesis of the mixed Mu-Delta opioid ligand Eluxadoline®, a small molecule opioid recently approved for the treatment of irritable bowl syndrome.[64,99] Moreover, peptides containing this amino acid have also been shown to have antioxidant properties.[100]

Several synthetic routes to Dmt have previously been published. In one such synthesis, the key step for installing the desired L stereochemistry is the asymmetric hydrogenation of (Z)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-2-propenoate, using

[c] See reference 109. In vitro assays were performed by Nick Griggs, Tyler Trask, and Chao Gao. In vivo work was done by Jessica Anand.

the expensive chiral catalyst [Rh(1,5-COD)(R,R-DIPAMP)]BF_4.[101] Other strategies involve the alkylation of a Ni(II) complex of the chiral Schiff base derived from glycine and (S)-o-[N-(N-benzylprolyl)amino]benzophenone[102] and a stereocontrolled alkylation of a chiral 2,5-diketopiperazine synthon.[103] Although these routes are synthetically viable, we sought to develop a shorter and more direct approach for the expedient synthesis of Dmt and other novel unnatural Tyr derivatives. Additionally, the development of a synthesis in which the desired L stereochemistry is incorporated from the beginning, and does not need to be installed with the use of a chiral auxiliary or catalyst, would be desirable.

RESULTS AND DISCUSSION

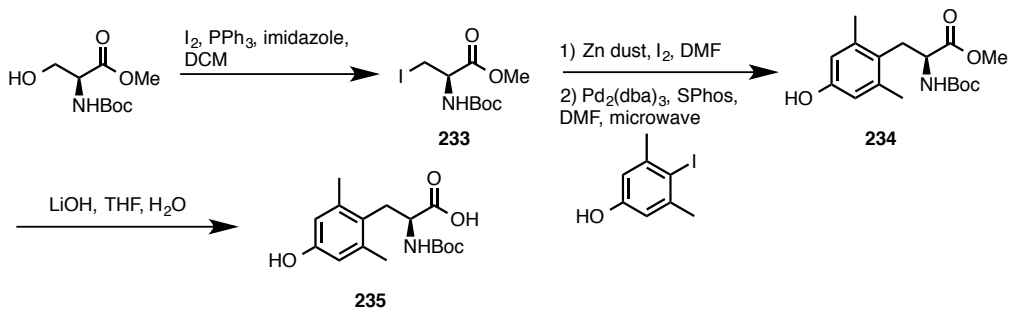
4.2 Synthesis of 2',6'-dimethyl-L-tyrosine Analogues via Negishi Coupling

Jackson and colleagues have disclosed that the use of $Pd_2(dba)_3$ and SPhos[104] in a 1:2 molar ratio is a highly efficient precatalyst for the Negishi coupling of aryl halides with an organozinc reagent derived from iodoalanine intermediate **233**.[105] This strategy was shown to be effective for both aryl iodides and bromides, as well as aryl halides featuring unprotected phenols and ortho substitutions. Given the synthetic utility of this approach, it was reasoned that a Negishi coupling between **233** and commercially available 3,5-dimethyl-4-iodophenol was a feasible approach toward the synthesis of Dmt.

Iodoalanine intermediate **233** was synthesized under Appel conditions as previously reported starting from commercially available Boc-protected L-serine methyl ester (Boc-Ser-OMe) (Scheme 22).[106] After the synthesis of **233**, conditions for the

Negishi coupling with 3,5-dimethyl-4-iodophenol were explored. Jackson and colleagues observed that the best yields for the coupling of mono-ortho-substituted aryl halides with **233** were obtained by using 2.5 mol % of $Pd_2(dba)_3$ and 5 mol % of SPhos with stirring at room temperature overnight. For the coupling between **233** and 3,5-dimethyl-4-iodophenol, these conditions led to the formation of desired product **234** in 16% yield. It was reasoned that the additional steric hindrance of this system contributed to the observed low yield, and a more efficient approach was desired.

Scheme 22. Synthesis of Boc-2',6'-dimethyl-L-tyrosine

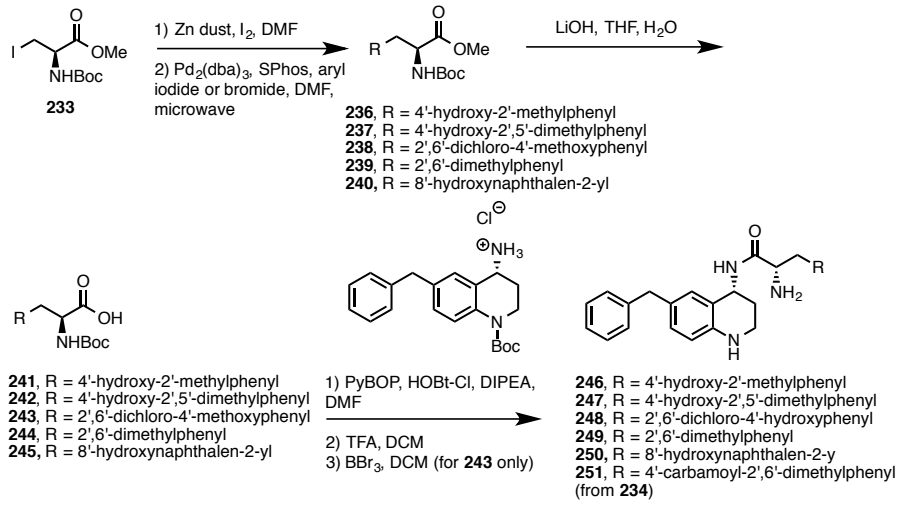


The use of microwave-assisted synthesis has been shown to be highly effective for challenging Negishi cross-coupling reactions[107,108] and the reaction was next run under microwave irradiation at 110 °C to give **234** in 40% yield. Increasing the mol % of $Pd_2(dba)_3$ and SPhos to 5% and 10% respectively under these conditions gave **234** in 56% yield.[109] Subsequent methyl ester hydrolysis gave Boc-2',6'-dimethyl-L-tyrosine **235**. Attention was next turned to using the microwave-assisted Negishi cross coupling reaction for the synthesis of other unnatural tyrosine and phenylalanine derivatives (Scheme 23).

4'-hydroxy-2'-methylphenyl (Mmt) analogue **241** has been previously reported in synthetic endomorphin[110] and DALDA-based[85] peptides, and showed comparable binding

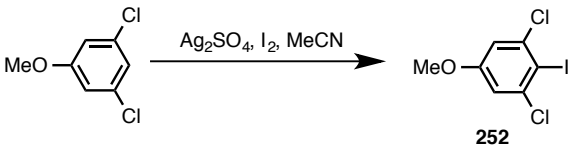
affinity at MOR relative to the Dmt counterpart compounds. 2',6'-dimethyl-L-phenylalanine (Dmp) analogue **244** has also been incorporated into the endomorphin scaffold, and has been shown to improve binding affinity at MOR and DOR compared to the naturally occurring endomorphins when substituted at the third position.[111] Additionally, phenylalanine and derivatives can sometimes serve as suitable replacements for the N-terminal tyrosine in opioid peptides, while still maintaining biological activity.[112,113] Compounds **242**, **243** and **245** had not been examined as Tyr replacements in opioid ligands. The synthesis of all analogues using the microwave-assisted Negishi coupling proved straightforward. In the case of analogue **238**, aryl iodide **252** was synthesized from 3,5-dichloroanisole as previously described (Scheme 24).[114] In the case of analogue **240**, aryl bromide **253** was synthesized via halogenation and aromatization of commercially available 7-bromo-3,4-dihydronaphthalen-1(2H)-one (Scheme 25). After methyl ester hydrolysis, all analogues were coupled to 6-benzyl-1-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride (Chapter 2) under standard amide coupling conditions (Scheme 23) to give final tetrahydroquinolines **246-250** after Boc-deprotection, and in the case of **248**, after an additional deprotection of the aryl methoxy group with BBr_3 (Scheme 23).

Scheme 23. Synthesis of Analogues **246-251**

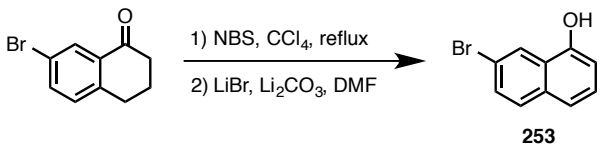


Additionally, **234** was carried forward using previously described chemistry[99] and coupled to 6-benzyl-1-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride to give carboxamido analogue **251**, a replacement that has been shown to be an effective bioisostere for phenol moieties (Scheme 23).[115] Lastly, in an attempt to further explore chloro substitutents and phenol replacements, 6-benzyl-1-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride was coupled to commercially available Boc-2'4'-dichloro-L-phenylalanine and deprotected under standard conditions to give final analogue **254** (Scheme 26). Final analogues were then purified by semipreparative RP-HPLC and lyophilized to give enough material for in vitro testing.

Scheme 24. Synthesis of Intermediate **252**

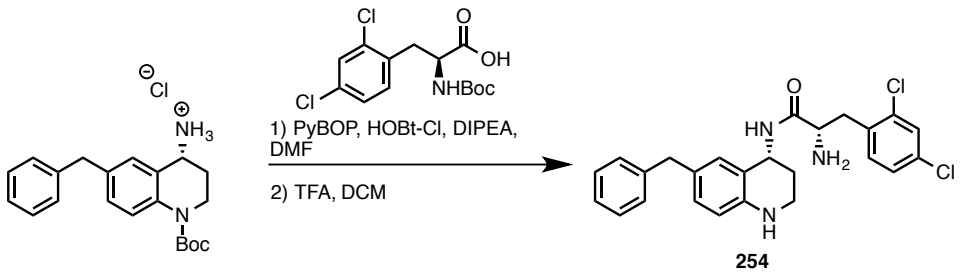


Scheme 25. Synthesis of Intermediate **253**



253

Scheme 26. Synthesis of Analogue **254**

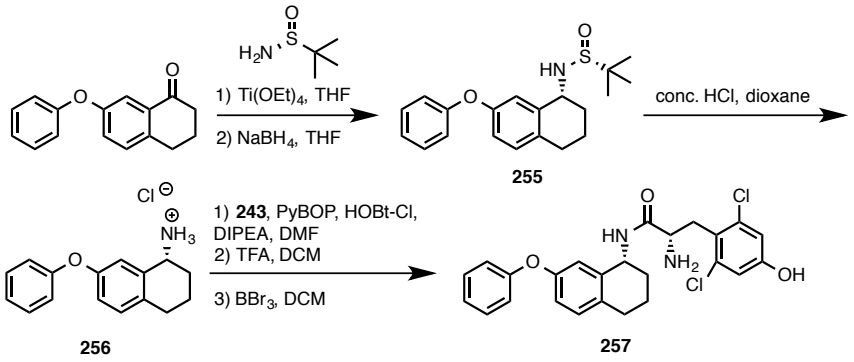


254

As seen in Table 8, MOR binding affinity is reduced by approximately an order of magnitude for analogues **246** and **247** in which the 2'-methyl group is maintained, and the second aryl methyl is either deleted (**246**) or moved to the 5' position (**247**). MOR affinity for 2',6-dichloro analogue **248** is comparable to the parent peptidomimetic **1** (Chapter 2), which is not entirely surprising given the similar size of the methyl and chloro substituents. Analogues **249** and **250** display a more pronounced decrease in MOR binding, and analogues **247**, **249** and **250** lose significant binding affinity at DOR. The data in Table 8 show that analogues **246-249** and **251** all maintain a high level of agonist efficacy (as measured by [^{35}S]GTPγS binding) compared to DAMGO at MOR, but with reduced potency as compared to **1**. In particular, carboxamido analogue **251** maintains high binding affinity and good potency at MOR, further highlighting the utility of this phenol bioisostere for the development of opioid ligands. The 2',5'-dimethyl analogue

247 displays reduced potency at DOR as compared to **1**, but with higher maximal stimulation (53% compared to the full agonist DPDPE). The naphthol analogue **250** shows a significant decrease in binding affinity for all three receptors, and thus was not evaluated in the [^{35}S]GTPγS assay.

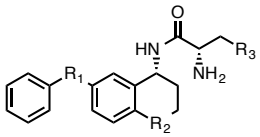
Scheme 27. Synthesis of Analogue **257**



With its ability to maintain the high MOR affinity and potency in this series and provide considerable selectivity over DOR and KOR, the results show that Boc-2',6'-dichloro-L-tyrosine may prove useful for the development of opioids with improved metabolic stability toward benzylic oxidation.

In an attempt to combine this unnatural chlorinated amino acid with previously discussed modifications aimed at improving metabolic stability (see Chapter 3), **243** was also coupled to amine scaffold **256** (prepared from chiral sulfonamide **255** from commercially available 7-phenoxy-3,4-dihydronaphthalen-1(2H)-one, Scheme 27) to give final diarylether analogue **257** (Table 8), a compound which displays reduced binding affinity for both MOR and DOR as compared to **1**. Unfortunately, $t_{1/2}$ for analogue **257** was also found to be < 5 min in mouse liver microsomes.

Table 8. Opioid Receptor Binding Affinities and Efficacies for Analogues **246-251**, **254** and **257**[a]



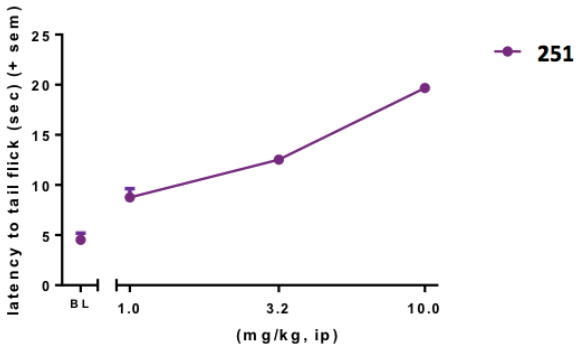
				MOR			DOR			KOR		
	R_1	R_2	R_3	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
1	CH_2	NH		0.22 ± 0.02	1.6 ± 0.3	81 ± 2	9.4 ± 0.8	110 ± 6	16 ± 2	68 ± 2	540 ± 72	22 ± 2
246	CH_2	NH		1.7 ± 0.2	44 ± 20	69 ± 6	42 ± 9	dns	dns	96 ± 20	2350 ± 80	41 ± 8
247	CH_2	NH		6.5 ± 2	39 ± 8	89 ± 8	390 ± 120	5900 ± 2200	53 ± 8	730 ± 80	370 ± 200	22 ± 6
248	CH_2	NH		0.47 ± 0.04	33 ± 4	83 ± 3	37 ± 8	dns	dns	35 ± 5	1150 ± 290	32 ± 4
249	CH_2	NH		18 ± 4	280 ± 50	86 ± 8	660 ± 120	dns	dns	130 ± 50	4750 ± 1100	38 ± 5
250	CH_2	NH		440 ± 70	-	-	1620 ± 120	-	-	2500 ± 450	-	-
251	CH_2	NH		0.6 ± 0.1	9.2 ± 5	98 ± 5	33 ± 8	1590 ± 740**	25 ± 3**	170 ± 50	dns	dns
254	CH_2	NH		51 ± 10	>1000**	>13**	2087*	dns*	dns*	-	-	-
257	O	CH_2		1.5 ± 0.6	118 ± 80	21 ± 3	105 ± 10	dns	dns	-	-	-

[a.] dns = does not stimulate. See Table 1 for further in vitro details. Dashed line indicates compound was not tested. * = n of 1, ** = n of 2.

4.3 In Vivo Studies on Analogue 251

On the basis of its good binding affinity and potent [^{35}S]GTPγS simulation of MOR, compound **251** was chosen for in vivo studies. In the mouse warm water tail withdrawal (WWTW) assay, **251** was fully efficacious, and produced dose-dependent increases in latency to tail flick (Figure 21).

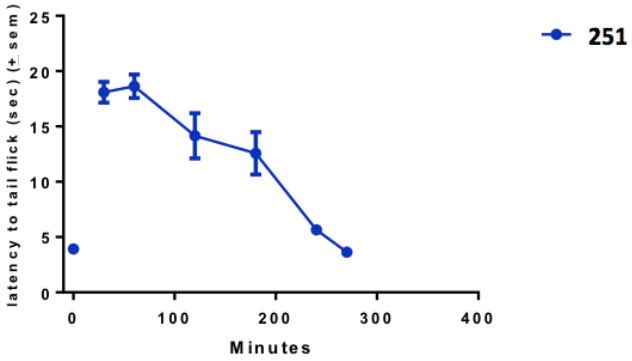
Figure 21. Cumulative Antinociceptive Dose-Response Curve for Analogue **251** in the Mouse WWTW Assay After ip Administration (n = 3)[a]



[a.] Data are plotted as mean ± SEM.

To determine the duration of action of compound **251**, tail withdrawal latencies were measured at intervals following the administration of the 10 mg/kg dose (Figure 22). Compound **251** showed a full antinociceptive response for just under 100 minutes before returning to baseline. Compared with compounds **86** and **102** (Figure 17, Chapter 2) and compound **214** (Figure 20, Chapter 3) this compound displayed a shorter total duration of action (Figure 22), comparable to compound **1** (Figure 17, Chapter 2).

Figure 22. Time Course of Antinociceptive Response For Analogue **251** in the Mouse WWTW Assay After ip Administration of a 10 mg/kg Dose



In this chapter, a 3-step synthesis of Boc-2',6'-dimethyl-L-tyrosine (Dmt) featuring a microwave-assisted Negishi coupling is described, which ultimately led to the expedient synthesis of a number of novel tyrosine analogues that were incorporated into the peptidomimetic scaffold. Of particular interest is 2',6'-dichloro-L-tyrosine intermediate **243**, which may be useful for the development of peptidomimetics with reduced liability for oxidative metabolism on the aryl methyl groups, and carboxamido peptidomimetic **251**, which shows a total duration of action in vivo that is comparable to lead compound **1**. Given this result, this carboxamido substitution may prove useful as a substitution on other peptidomimetic scaffolds reported in previous chapters as a means to improve upon the duration of action in vivo, by preventing phase 2 metabolic glucoronidation on the 4' hydroxyl.

4.4 Experimental Procedures

4.4.1 Chemistry

Specific rotations were recorded on a Jasco P2000 instrument at 589 nm with a path length of 100 mm. Chiral purity of analogues Boc-protected amino acid derivatives was determined with a Lux 5μ Amylose-2 column by Phenomenex, with a linear gradient of 0% solvent B (acetonitrile with 0.1% AcOH and 0.02% TFA) in Solvent A (water with 0.1% AcOH and 0.02% TFA) to 70% solvent B, with a flow rate of 1 mL/min (gradient was optimized using a sample of Boc-DL-2',4',6'-trimethylphenylalanine which gave good separation, t_1 = 45.04 min, t_2 = 46.17 min). Data was analyzed with a Waters Alliance 2690 analytical HPLC at 230 nm. For further general chemistry, *in vitro* and *in vivo* experimental detail, see section 2.4.

(233) methyl (R)-2-((tert-butoxycarbonyl)amino)-3-iodopropanoate

To a dry flask was added PPh_3 (2.96 g, 11.3 mmol) and imidazole (0.77 g, 11.3 mmol). The flask was placed under an inert atmosphere, and DCM (30 mL) was added via syringe. After dissolution of solids, I_2 (3.45 g, 13.6 mmol) was added portionwise. The mixture was allowed to stir for 5 min, after which time Boc-L-Ser-OMe (2.49 g, 11.3 mmol) was dissolved in DCM (20 mL) and added dropwise via syringe. The mixture was stirred at r.t. for 4 h, after which time it was transferred to a separatory funnel and washed with H_2O, sat. sodium thiosulfate, and brine. The organic layer was dried with $MgSO_4$, and solvents were filtered and removed. Crude residue was purified by column chromatography (5:1 hex/EtOAc) to give product as a colorless oil that solidified upon standing (2.66 g, 72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.47 (d, J = 7.8, 1H), 4.53 (dt, J = 7.9, 4.0, 1H), 3.80 (s, 3H), 3.61 – 3.53 (m, 2H), 1.46 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 169.96, 154.77, 80.32, 53.70, 52.97, 28.25, 7.80.

(234) methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)propanoate

To a dry 10 mL microwave flask equipped with a stir bar was added Zn dust (0.13 g, 1.93 mmol) and placed under an inert atmosphere. DMF (0.5 mL) was added via syringe, followed by a catalytic amount of I_2 (30 mg). The mixture was stirred vigorously, during which time the color changed to yellow and back to colorless. Compound **233** (0.21 g, 0.64 mmol) in DMF (2 mL) was added via syringe, immediately followed by another portion of catalytic I_2 (30 mg). The mixture was stirred vigorously for 10 min, after which time $Pd_2(dba)_3$ (0.029 g, 0.032 mmol), SPhos (0.026 g, 0.064 mmol) and 3,5-dimethyl-4-iodophenol (0.21 g, 0.84 mmol) were added quickly. The resulting mixture

was transferred to the microwave reactor under an inert atmosphere, and stirred for 2 h at 110 °C, after which time the reaction mixture was added directly to a silica column and purified (4:1 to 2:1 hex/EtOAc) to give product as a colorless oil (0.12 g, 56%). MS(EI): 346.2 (M+Na). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.48 (s, 2H), 5.29 (brs, 1H), 5.08 (d, J = 8.7, 1H), 4.48 (q, J = 8.1, 1H), 3.65 (s, 3H), 3.08 – 2.86 (m, 2H), 2.27 (s, 6H), 1.41 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.49, 155.17, 154.18, 138.73, 125.31, 115.18, 80.15, 53.34, 52.43, 32.75, 28.40, 20.40.

(235) (S)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)propanoic acid

To a solution of **234** (0.11 g, 0.34 mmol) in THF (2 mL) was added a solution of LiOH (0.044 g, 1.71 mmol) in H_2O (2 mL) dropwise. The mixture was stirred at r.t. for 1 h, after which time 1M HCl was added until the solution reached pH 4. The mixture was transferred to a separatory funnel, and the aqueous layer was extracted with EtOAc. Combined organic extracts were dried with $MgSO_4$, and solvents were filtered and removed to give product as a colorless oil (0.10 g, 94%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.60 (d, J = 8.3), 5.20 (d, J = 8.7) (1H), 6.51, 6.48 (2s, 2H), 4.56 – 4.34 (m, 1H), 3.11 (dd, J = 14.4, 5.4), 2.96 (dd, J = 14.4, 9.6) (2H), 2.29, 2.27 (2s, 6H), 1.37, 1.19 (2s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 177.33, 176.42, 156.64, 155.59, 154.22, 138.93, 138.72, 125.73, 125.01, 115.34, 115.26, 81.73, 80.68, 54.41, 53.58, 33.33, 32.39, 28.36, 27.85, 20.45, 20.40. $[\alpha]_D^{20}$ -9.74° (c 1.0, MeOH), literature value $[\alpha]_D^{20}$ -11.7° (c 1.0, MeOH)[116]. Elution times (Lux 5μ Amylose-2): t_{major}: 31.42 min, t_{minor}: 30.36 min, e.r. 96:4.

(236) methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-2-methylphenyl)propanoate

Followed procedure for compound **234** with **233** (0.15 g, 0.44 mmol) and 4-iodo-3-methylphenol (0.14 g, 0.58 mmol) to give product as a colorless oil (0.074 g, 54%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.87 (d, J = 8.3, 1H), 6.64 (d, J = 2.7, 1H), 6.57 (d, J = 7.7, 1H), 6.34 (br s, 1H), 5.06 (d, J = 8.5, 1H), 4.51 (q, J = 7.3, 1H), 3.68 (s, 3H), 3.06 (dd, J = 14.2, 6.1, 1H), 2.92 – 2.84 (m, 1H), 2.25 (s, 3H), 1.40 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 173.04, 155.27, 155.09, 138.11, 130.92, 125.82, 117.38, 112.87, 80.17, 53.95, 52.26, 35.27, 28.28, 19.41.

(237) methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-2,5-dimethylphenyl)propanoate

Followed procedure for compound **234** with **233** (0.13 g, 0.41 mmol) and 4-iodo-2,5-dimethylphenol (0.13 g, 0.53 mmol) to give product as a colorless oil (0.052 g, 39%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.54 (s, 1H), 5.76 (br s, 1H), 5.07 (d, J = 8.4, 1H), 4.50 (q, J = 7.6, 1H), 3.69 (s, 3H), 3.04 (dd, J = 14.3, 6.1, 1H), 2.85 (dd, J = 14.2, 7.1, 1H), 2.21 (s, 3H), 2.15 (s, 3H), 1.41 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.13, 155.23, 153.00, 135.25, 132.48, 125.73, 121.21, 116.84, 80.07, 54.01, 52.31, 35.24, 28.28, 18.97, 15.38.

(238) methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2,6-dichloro-4-methoxyphenyl)propanoate

Followed procedure for compound **234** with **233** (0.21 g, 0.64 mmol) and **252** (0.19 g, 0.64 mmol) to give product as a colorless oil (0.038 g, 16%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 2H), 5.15 (d, J = 9.1, 1H), 4.68 (td, J = 9.3, 5.9, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.32 (dd, J = 13.9, 5.9, 1H), 3.22 (dd, J = 13.8, 9.5, 1H), 1.35 (s, 9H); ^{13}C-NMR

(101 MHz, $CDCl_3$) δ 172.41, 158.71, 154.96, 136.34, 124.74, 114.26, 79.74, 55.69, 52.50, 33.54, 28.20.

(239) methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2,6-dimethylphenyl)propanoate

Followed procedure for compound **234** with **233** (0.16 g, 0.48 mmol) and 2-iodo-1,3-dimethylbenzene (0.14 g, 0.62 mmol) to give product as a colorless oil (0.053 g, 36%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.07 – 6.96 (m, 3H), 5.09 (d, J = 8.7, 1H), 4.54 (q, J = 8.1, 1H), 3.63 (s, 3H), 3.15 – 3.00 (m, 2H), 2.34 (s, 6H), 1.36 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.32, 155.00, 137.14, 133.37, 128.41, 126.81, 79.92, 53.05, 52.33, 33.40, 28.36, 20.30.

(240) methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(8-hydroxynaphthalen-2-yl)propanoate

Followed procedure for compound **234** with **233** (0.16 g, 0.47 mmol) and **253** (0.14 g, 0.62 mmol) to give product as a yellow oil (0.068 g, 42%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.72 (d, J = 8.4, 1H), 7.35 (d, J = 8.2, 1H), 7.29 – 7.21 (m, 2H), 7.19 (br s, 1H), 6.84 (d, J = 7.5, 1H), 5.08 (d, J = 8.3, 1H), 4.67 (q, J = 7.2, 1H), 3.72 (s, 3H), 3.33 – 3.17 (m, 2H), 1.40 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 172.70, 155.42, 152.17, 133.91, 132.62, 128.05, 127.73, 125.98, 124.75, 122.39, 119.73, 108.84, 80.20, 54.74, 52.41, 38.77, 28.40.

(241) (S)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-2-methylphenyl)propanoic acid

Followed procedure for compound **235** with **236** (0.073 g, 0.24 mmol) to give product as a white solid (0.050 g, 71%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.93 (d, J = 8.3, 1H), 6.64 (d, J = 6.2, 1H), 6.55 (d, J = 9.5, 1H), 6.25 (d, J = 8.0), 5.10 (d, J = 8.4) (1H), 4.53 (q, J =

7.2), 4.36 (q, J = 7.2) (1H), 3.14 (dd, J = 14.3, 5.6), 2.95 – 2.90 (m) (2H), 2.26, 2.24 (2s, 3H), 1.40, 1.30 (2s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 176.39, 176.10, 156.63, 155.75, 154.84, 138.49, 138.31, 131.73, 131.20, 126.48, 126.20, 117.59, 117.52, 113.14, 81.91, 80.76, 55.03, 54.10, 36.03, 34.96, 28.44, 28.12, 19.60. $[\alpha]_D^{20}$ -4.60° (c 0.81, MeOH), literature value $[\alpha]_D^{25}$ -8.0° (c 0.813, MeOH)[110]. Elution times (Lux 5µ Amylose-2): t_{major}: 29.36 min, t_{minor}: 30.05 min, e.r. 98:2.

(242) (S)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-2,5-dimethylphenyl)propanoic acid

Followed procedure for compound **235** with **237** (0.052 g, 0.16 mmol) to give product as a slightly yellow oil (0.043 g, 86%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.84 (d, J = 13.2, 1H), 6.56 (d, J = 9.5, 1H), 6.36 (d, J = 8.0), 5.06 (d, J = 8.3) (1H), 4.51 (q, J = 7.2), 4.35 (br s) (1H), 3.13 (dd, J = 14.2, 5.4), 2.91 – 2.70 (m) (2H), 2.22 (s, 3H), 2.14 (s, 3H), 1.40, 1.26 (2s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 176.61, 176.29, 156.53, 155.66, 152.97, 135.57, 135.46, 133.06, 132.67, 126.62, 126.04, 121.37, 117.15, 117.06, 81.60, 80.55, 55.31, 54.05, 36.28, 35.01, 28.42, 28.01, 19.08, 15.42. $[\alpha]_D^{20}$ +1.29 (c 0.50, MeOH). Elution times (Lux 5µ Amylose-2): t_{major}: 32.67 min, t_{minor}: 31.71 min, e.r. 98:2.

(243) (S)-2-((tert-butoxycarbonyl)amino)-3-(2,6-dichloro-4-methoxyphenyl)propanoic acid

Followed procedure for compound **235** with **238** (0.038 g, 0.10 mmol) to give product as a colorless oil (0.037 g, 100%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 2H), 5.14 (d, J = 8.9, 1H), 4.74 – 4.60 (m, 1H), 3.78 (s, 3H), 3.46 – 3.21 (m, 2H), 1.35 (s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 176.59, 175.86, 158.96, 155.48, 136.80, 136.52, 125.29, 124.73, 114.51, 114.48, 81.22, 80.30, 55.90, 55.86, 53.73, 52.83, 34.38, 33.22, 28.34, 28.04.

$[\alpha]_D^{20}$ -14.34° (c 0.72, MeOH). Elution times (Lux 5µ Amylose-2): t_{major}: 46.87 min, t_{minor}: 47.74 min, e.r. 91:9.

(244) (S)-2-((tert-butoxycarbonyl)amino)-3-(2,6-dimethylphenyl)propanoic acid

Followed procedure for compound **235** with **239** (0.057 g, 0.19 mmol) to give product as a colorless oil (0.054 g, 100%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.2), 5.05 (d, J = 8.6) (1H), 7.09 – 6.98 (m, 3H), 4.57 (ddd, J = 11.6, 8.1, 3.6, 1H), 3.26 – 3.07 (m, 2H), 2.41 (s, 6H), 1.35, 1.04 (2s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 175.69, 156.99, 137.58, 134.58, 128.43, 126.67, 81.38, 54.19, 34.88, 27.64, 20.54. $[\alpha]_D^{20}$ -14.43 (c 0.41, MeOH), literature value $[\alpha]_D^{25}$ -17.85° (c 0.41, MeOH)[111]. Elution times (Lux 5µ Amylose-2): t_{major}: 43.04 min, t_{minor}: 41.73 min, e.r. 99:1.

(245) (S)-2-((tert-butoxycarbonyl)amino)-3-(8-hydroxynaphthalen-2-yl)propanoic acid

Followed procedure for compound **235** with **240** (0.068 g, 0.20 mmol) to give product as a yellow oil (0.049 g, 75%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.69 (d, J = 8.6, 1H), 7.36 – 7.24 (m, 2H), 7.21 (t, J = 7.7, 1H), 6.82 (d, J = 7.7, 1H), 5.15 (d, J = 8.2, 1H), 4.70 (q, J = 6.6, 1H), 3.36 – 3.19 (m, 2H), 1.38, 1.27 (2s, 9H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 175.99, 155.92, 152.04, 133.89, 132.70, 128.97, 128.87, 128.06, 127.59, 126.02, 124.88, 122.82, 122.26, 119.81, 109.57, 109.19, 81.89, 80.55, 56.23, 54.76, 39.00, 38.32, 28.40, 28.11. $[\alpha]_D^{20}$ +40.21 (c 0.37, MeOH). Elution times (Lux 5µ Amylose-2): t_{major}: 40.52 min, t_{minor}: 39.15 min, e.r. 99:1.

(246) (S)-2-amino-N-((R)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2-methylphenyl)propanamide

To a dry flask containing **241** (0.028 g, 0.095 mmol) was added DMF (9 mL) via syringe. DIPEA (0.17 mL, 0.95 mmol) was then added dropwise via syringe, followed by PyBOP (0.049 g, 0.095 mmol) and 6-Cl-HOBt (0.016 g, 0.095 mmol). 6-benzyl-1-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-4-aminium chloride (0.036 g, 0.095 mmol) was then dissolved in DMF (3 mL) and added dropwise via syringe. The resulting mixture was allowed to stir at r.t. for 15 h, after which time DMF was removed under reduced pressure, and the crude residue was passed through silica (1:1 hex/EtOAc). The crude residue was redissolved in a 1:1 mixture of TFA and DCM (10 mL) and stirred at r.t. for 20 min. DCM and TFA were then removed under reduced pressure, and crude residue was purified by semi-prep RP-HPLC and lyophilized to give product as a white solid. Retention Time: 23.21 min. (MS)EI: 438.2 (M+Na). ^{1}H-NMR (500 MHz, CD_3OD) δ 8.40 (d, J = 7.6, 1H), 7.24 – 7.20 (m, 2H), 7.16 – 7.11 (m, 3H), 7.01 (d, J = 2.0, 1H), 6.98 – 6.94 (m, 2H), 6.69 (d, J = 8.2, 1H), 6.64 (d, J = 2.6, 1H), 6.58 (dd, J = 8.2, 2.6, 1H), 4.94 (t, J = 4.7, 1H), 3.88 (t, J = 8.2, 1H), 3.83 (s, 2H), 3.09 (dt, J = 12.3, 4.3, 1H), 3.04 (d, J = 8.2, 2H), 2.70 – 2.62 (m, 1H), 2.28 (s, 3H), 1.86 – 1.77 (m, 1H), 1.66 – 1.59 (m, 1H).

(247) (S)-2-amino-N-((R)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,5-dimethylphenyl)propanamide

Followed procedure for compound **246** with **242** (0.043 g, 0.14 mmol) to give product as a white solid. Retention Time: 25.52 min. (MS)EI: 430.2 (M+H). ^{1}H-NMR (500 MHz, CD_3OD) δ 8.40 (d, J = 7.8, 1H), 7.25 – 7.19 (m, 2H), 7.16 – 7.10 (m, 3H), 7.03 (d, J = 2.0, 1H), 6.99 (dd, J = 8.3, 2.0, 1H), 6.83 (s, 1H), 6.73 (d, J = 8.2, 1H), 6.59 (s, 1H), 4.95 (t, J = 4.6, 1H), 3.88 – 3.85 (m, 1H), 3.84 (s, 2H), 3.13 – 3.06 (m, 1H), 3.06 – 2.95 (m,

2H), 2.69 – 2.61 (m, 1H), 2.24 (s, 3H), 2.12 (s, 3H), 1.87 – 1.79 (m, 1H), 1.64 – 1.56 (m, 1H).

(248) (S)-2-amino-N-((R)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(2,6-dichloro-4-hydroxyphenyl)propanamide

Followed procedure for compound **246** with **243** (0.043 g, 0.12 mmol) with the following modification: after semi-prep RP-HPLC purification, residue was dissolved in DCM (5 mL) and cooled to 0 °C. BBr_3 (0.11 mL, 1.0 M solution in DCM) was then added dropwise. The solution was warmed to r.t. and stirred for 1 h, after which time it was quenched with the slow addition of MeOH. Further purification by RP-HPLC gave product as a white solid. Retention Time: 26.90 min. MS(EI): 492.1 (M+Na). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.25 – 7.18 (m, 2H), 7.16 – 7.10 (m, 3H), 7.04 – 6.96 (m, 1H), 6.96 – 6.88 (m, 1H), 6.86 (s, 2H), 6.67 (d, J = 8.2, 1H), 5.04 (t, J = 5.2, 1H), 4.00 (dd, J = 10.7, 4.6, 1H), 3.82 (d, J = 5.3, 2H), 3.55 (dd, J = 13.5, 10.9, 1H), 3.26 – 3.12 (m, 2H), 2.89 – 2.75 (m, 1H), 1.98 – 1.88 (m, 1H), 1.88 – 1.78 (m, 1H).

(249) (S)-2-amino-N-((R)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(2,6-dimethylphenyl)propanamide

Followed procedure for compound **246** with **244** (0.014 g, 0.048 mmol) to give product as a white solid. Retention Time: 30.98 min. MS(EI): 436.2 (M+Na). ^{1}H-NMR (400 MHz, CD_3OD) δ 8.17 (d, J = 7.9, 1H), 7.25 – 7.19 (m, 2H), 7.16 – 7.00 (m, 6H), 7.00 – 6.96 (m, 1H), 6.92 (dd, J = 8.3, 2.0, 1H), 6.63 (d, J = 8.2, 1H), 4.99 – 4.92 (m, 1H), 3.92 (dd, J = 11.6, 5.0, 1H), 3.81 (s, 2H), 3.41 – 3.33 (m, 1H), 3.11 (dd, J = 13.5, 5.0, 1H), 3.00 (dt, J = 12.2, 4.3, 1H), 2.52 – 2.40 (m, 1H), 2.35 (s, 6H), 1.80 – 1.68 (m, 1H), 1.53 – 1.41 (m, 1H).

(250) (S)-2-amino-N-((R)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(8-hydroxynaphthalen-2-yl)propanamide

Followed procedure for compound **246** with **245** (0.029 g, 0.088 mmol) to give product as a white solid. Retention Time: 30.35 min. MS(EI): 452.2 (M+H). ^{1}H-NMR (500 MHz, CD_3OD) δ 8.06 (s, 1H), 7.78 (d, J = 8.4, 1H), 7.36 – 7.27 (m, 3H), 7.23 – 7.19 (m, 2H), 7.15 – 7.09 (m, 3H), 6.94 (d, J = 2.0, 1H), 6.90 (dd, J = 8.3, 2.1, 1H), 6.84 (dd, J = 7.3, 1.2, 1H), 6.57 (d, J = 8.3, 1H), 4.91 (t, J = 4.5, 1H), 4.04 (dd, J = 8.7, 6.7, 1H), 3.80 (s, 2H), 3.27 (dd, J = 7.7, 5.6, 2H), 2.61 (dt, J = 12.2, 4.3, 1H), 2.29 (td, J = 11.7, 2.8, 1H), 1.75 – 1.65 (m, 1H), 1.64 – 1.55 (m, 1H).

(251) 4-((S)-2-amino-3-(((R)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)-3-oxopropyl)-3,5-dimethylbenzamide

Followed procedure for compound **246** with (S)-2-((tert-butoxycarbonyl)amino)-3-(4-carbamoyl-2,6-dimethylphenyl)propanoic acid[99] (0.028 g, 0.083 mmol) to give product as a white solid. Retention Time: 22.24 min. MS(EI): 457.3 (M+H). ^{1}H-NMR (500 MHz, CD_3OD) δ 8.24 (d, J = 7.8, 1H), 7.55 (s, 2H), 7.21 (t, J = 7.5, 2H), 7.15 – 7.08 (m, 3H), 6.98 (d, J = 2.0, 1H), 6.93 (dd, J = 8.3, 2.0, 1H), 6.64 (d, J = 8.3, 1H), 4.98 – 4.91 (m, 1H), 3.93 (dd, J = 11.7, 5.0, 1H), 3.81 (s, 2H), 3.42 (dd, J = 13.3, 11.7, 1H), 3.17 (dd, J = 13.4, 5.0, 1H), 3.00 (dt, J = 12.3, 4.6, 1H), 2.42 (s, 6H), 2.41 – 2.35 (m, 1H), 1.79 – 1.70 (m, 1H), 1.48 – 1.41 (m, 1H).

(252) 1,3-dichloro-2-iodo-5-methoxybenzene

To a stirring solution of 3,5-dichloroanisole (0.54 g, 3.02 mmol) in MeCN (20 mL) was added Ag_2SO_4 (1.41 g, 4.53 mmol) and I_2 (0.84 g, 3.34 mmol). The resulting mixture was stirred at r.t. under an inert atmosphere for 3 days, after which time MeCN was removed

under reduced pressure, and residue was redissolved in DCM. Sat. sodium thiosulfate was added, and the aqueous layer was extracted with DCM. Combined organic extracts were washed with brine, and dried with $MgSO_4$. Solvents were filtered and removed to give product as a tan solid (0.71 g, 77%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 3.77 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.10, 140.62, 113.82, 92.22, 55.93.

(253) 7-bromonaphthalen-1-ol

To a dry flask was added 7-bromo-3,4-dihydronaphthalen-1(2H)-one (0.53 g, 2.36 mmol) and NBS (0.44 g, 2.48 mmol) and placed under an inert atmosphere. CCl_4 (20 mL) was then added via syringe, and the mixture was stirred at reflux for 18 h. After cooling to r.t., the mixture was filtered through a plug of Celite with DCM. Organic extract was washed with sat. $NaHCO_3$ and brine, and dried with $MgSO_4$. Solvents were filtered and removed, and crude residue was purified by column chromatography (8:1 hex/EtOAc) to give product as a white solid (0.50 g, 70%), which was confirmed by NMR analysis to be the desired α-brominated intermediate. This intermediate was redissolved in DMF (15 mL). LiBr (0.046 g, 5.25 mmol) and Li_2CO_3 (0.026 g, 3.45 mmol) were then added, and the mixture was stirred at 140 °C for 2 h, after which time it was cooled to r.t. Solids were removed by filtration, and washed with EtOAc. Filtrate was washed with H_2O (3x) and brine, and organic layer was dried with $MgSO_4$. Solvents were filtered and removed, and crude residue was purified by column chromatography (5:1 hex/EtOAc) to give product as a light brown solid (0.29 g, 78%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 2.2, 1H), 7.65 (d, J = 8.7, 1H), 7.54 (dd, J = 8.8, 2.1, 1H), 7.38 (d, J = 8.3, 1H), 7.31 – 7.29 (m, 1H), 6.81 (d, J = 7.4, 1H), 5.45 (s, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 150.69, 133.24, 129.96, 129.43, 126.41, 125.61, 124.47, 120.63, 119.42, 109.62.

(254) (S)-2-amino-N-((R)-6-benzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(2,4-dichlorophenyl)propanamide

Followed procedure for compound **246** with (S)-2-((tert-butoxycarbonyl)amino)-3-(2,4-dichlorophenyl)propanoic acid (0.029 g, 0.088 mmol) to give product as a white solid. Retention Time: 32.65 min. MS(EI): 476.1 (M+Na). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.53 (d, J = 2.0, 1H), 7.34 (dd, J = 8.3, 2.1, 1H), 7.29 (d, = 8.3, 1H), 7.24 – 7.18 (m, 2H), 7.15 – 7.09 (m, 3H), 6.98 (d, J = 2.0, 1H), 6.93 (dd, J = 8.3, 2.1, 1H), 6.64 (d, J = 8.2, 1H), 4.97 (t, J = 4.7, 1H), 4.02 (dd, J = 9.6, 6.1, 1H), 3.81 (s, 2H), 3.27 – 3.08 (m, 3H), 2.75 – 2.65 (m, 1H), 1.87 – 1.83 (m, 1H), 1.72 – 1.61 (m, 1H).

(255) (R)-2-methyl-N-((R)-7-phenoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propane-2-sulfinamide

Followed procedure for compound **46** with 7-phenoxy-3,4-dihydronaphthalen-1(2H)-one (0.10 g, 0.42 mmol) to give product as a colorless oil (0.049 g, 34%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 2H), 7.11 (d, *J* = 2.4, 1H), 7.10 – 7.04 (m, 2H), 6.97 (d, *J* = 7.8, 2H), 6.86 (dd, *J* = 8.4, 2.5, 1H), 4.52 (q, *J* = 3.5, 1H), 3.22 (d, *J* = 2.6, 1H), 2.80 (dt, *J* = 16.7, 5.0, 1H), 2.70 (ddd, *J* = 16.4, 8.9, 5.6, 1H), 2.09 – 2.00 (m, 1H), 1.99 – 1.87 (m, 2H), 1.82 – 1.72 (m, 1H), 1.20 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.59, 155.49, 138.45, 132.85, 130.68, 129.80, 123.14, 119.88, 118.84, 118.56, 55.61, 52.56, 30.25, 28.64, 22.76, 18.37.

(256) (R)-7-phenoxy-1,2,3,4-tetrahydronaphthalen-1-aminium chloride

Compound **255** (0.049 g, 0.14 mmol) was dissolved in 1,4-dioxane (7 mL). Conc. HCl (0.071 mL, 0.86 mmol) was added dropwise. The resulting solution was stirred at r.t. for 1.5 h, after which time dioxane and HCl were removed under reduced pressure. Et_2O was

added, precipitating a white solid, which was subsequently washed 3x with Et_2O and dried (0.028 g, 72%) and used without further purification.

(257) (S)-2-amino-3-(2,6-dichloro-4-hydroxyphenyl)-N-((R)-7-phenoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propanamide

Followed procedure for compound **68** with **256** (0.008 g, 0.029 mmol) and **243** (0.011 g, 0.029 mmol) with the following modification: after TFA deprotection and RP-HPLC purification, residue was dissolved in dry DCM (3 mL) and cooled to 0 °C under an inert atmosphere. BBr_3 (0.062 mL, 1.0 M solution in DCM) was then added dropwise via syringe. The solution was allowed to warm to r.t. and was stirred overnight. The reaction mixture was then quenched with the addition of MeOH, and solvents were removed under reduced pressure. Crude residue was purified by RP-HPLC to give product as a white solid. MS(EI): 493.1 (M+Na).

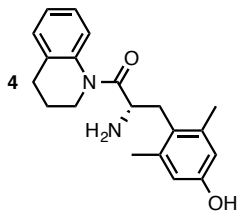
CHAPTER 5

4-SUBSTITUTED PIPERIDINES AND PIPERAZINES AS MIXED EFFICACY MOR/DOR LIGANDS[d]

5.1 Introduction

In an effort to further develop drug-like MOR/DOR bifunctional ligands, we turned our attention to compound **258** (Figure 23) a previously synthesized opioid ligand that displays equal binding affinity for both MOR and DOR, as well as KOR (K_i (MOR) = 25.8 nM; (DOR) = 33.0 nM; (KOR) = 36.5 nM, unpublished observations). Given the relative simplicity of the compound and its nonselective binding profile, it was reasoned that the compound would be a good starting point for derivatization. Computational modeling suggested that position 4 would be the optimal point for diversification (Figure 23), as an aromatic moiety at this position would be ideally situated to interact with Asn^{125}, Thr^{218}, and Lys^{303} in the MOR active site, and the resulting compound would thus function as a MOR agonist.[40,59]

Figure 23. Chemical Structure of Compound **258**

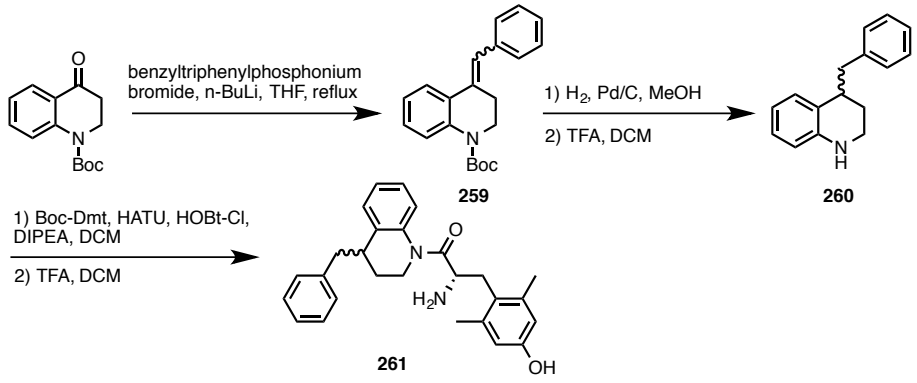


[d] See reference 95. In vitro assays were performed by Mary Clark. Compound 285 was synthesized by Michael Agius.

5.2 Synthesis and Evaluation of 4-Substituted Piperidine and Piperazine Opioid Ligands

Compound **258** was initially substituted with a benzyl group at the 4 position to give analogue **261**. The synthesis of **261** began by subjecting tert-butyl 4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (synthesized in a similar manner as compound **22** in Scheme 3, Chapter 2) to a Wittig reaction to yield alkene **259** as a mixture of *E* and *Z* isomers, which was subsequently hydrogenated and deprotected to give amine **260**, to which was coupled Boc-L-Dmt and deprotected with TFA in DCM (Scheme 28). Compared to **258**, the resulting compound **261** displayed no significant change in binding affinity for MOR and DOR, but showed decreased affinity for KOR (Table 9).

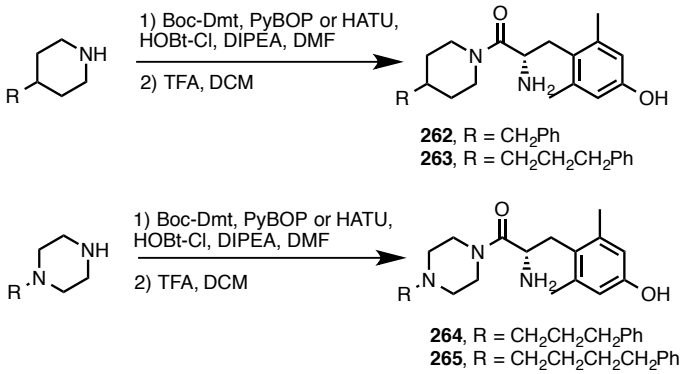
Scheme 28. Synthesis of Analogue **261**



Unfortunately, **261** also displayed no notable efficacy at MOR as determined by the [^{35}S]GTPγS assay. Because the synthesis of **261** proved somewhat laborious, and the resulting diastereomers could not be resolved by RP-HPLC, it was reasoned that synthesis of further analogues could be simplified by the replacement of the tetrahydroquinoline (THQ) core of **261** with a piperidine, effectively eliminating a

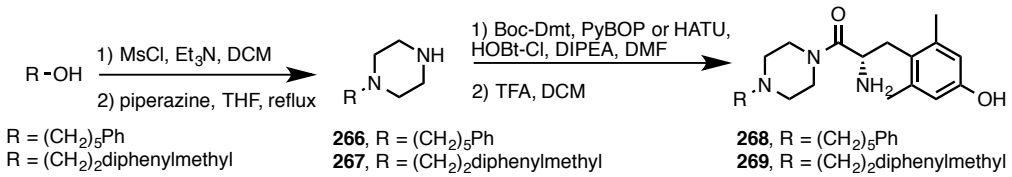
stereocenter. The resulting compound **262** displayed roughly a tenfold increase in binding affinity for MOR and DOR, but still lacked any efficacy at MOR. The remainder of the SAR campaign was focused on changing the length and flexibility profile of the side chain in an attempt to not only retain strong binding affinity for both MOR and DOR, but to increase efficacy at MOR. For purposes of synthetic utility as well as increased solubility, the piperidine core was also replaced with a piperazine for most of the analogues, the results of which are summarized in Table 9.

Scheme 29. Synthesis of Analogues **262-265**



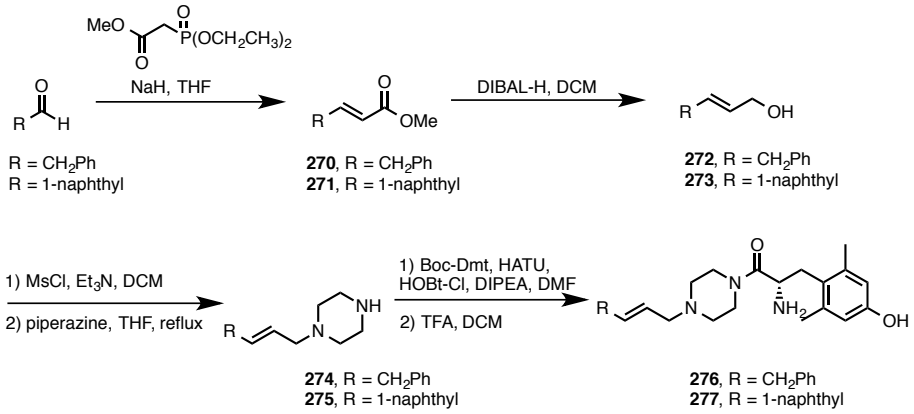
Compounds **262-265** were synthesized by coupling a commercially available piperidine or piperazine derivative with Boc-2',6'-dimethyl-L-tyrosine, followed by TFA-mediated deptrotection and RP-HPLC purification to yield the final compounds (Scheme 29). In the case of **268** and **269**, a commercially available primary alcohol was first mesylated and refluxed with excess piperazine[117] to give intermediates **266** and **267**, which were then coupled with Boc-2',6'-dimethyl-L-tyrosine and deprotected under similar conditions (Scheme 30).

Scheme 30. Synthesis of Analogues **268** and **269**

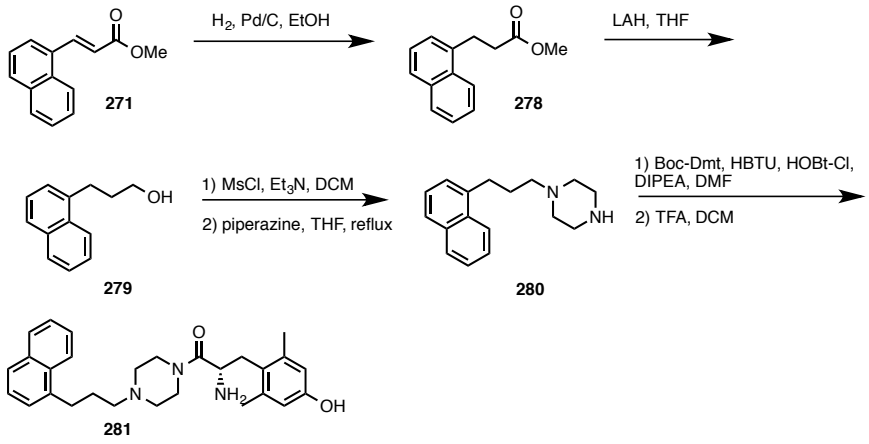


Unsaturated analogues **276** and **277** were synthesized as shown in Scheme 31. The appropriate commercially available aldehyde was subjected to a Horner–Wadsworth–Emmons type olefination to give **270** and **271**, which were then reduced to the corresponding alcohols using either DIBAL-H (for the formation of allylic alcohols) or LAH (for the formation of saturated alcohols). Additionally, before reduction, alkene **271** was first hydrogenated to give saturated ester **278**, ultimately leading to final analogue **281** (Scheme 32). All intermediates were then carried forward in a similar manner as in Schemes 29 and 30 to give finished products.

Scheme 31. Synthesis of Analogues **276** and **277**

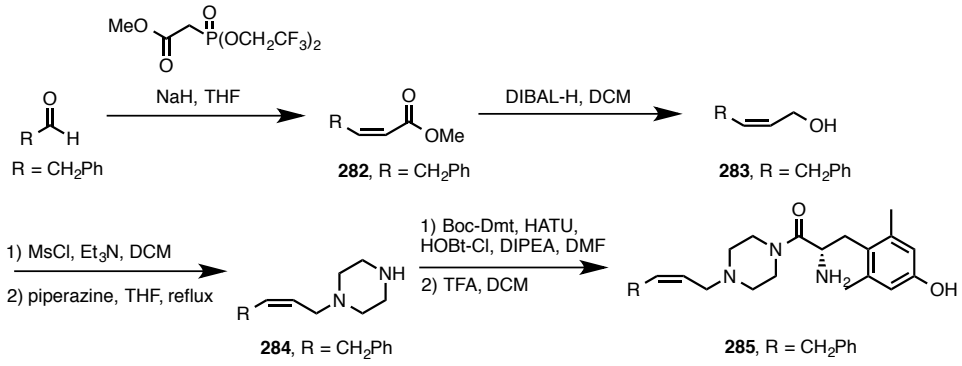


Scheme 32. Synthesis of Analogue **281**

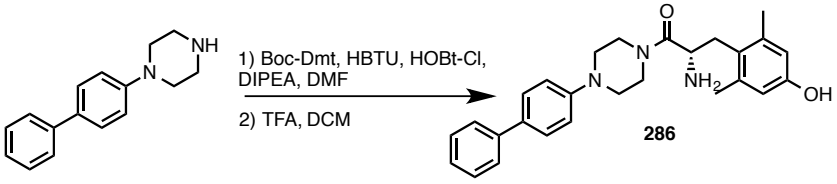


Z-alkene analogue **285** was synthesized as shown in Scheme 33 by subjecting a commercially available aldehyde (the same as in the case of intermediate **270**) to a Still-modified Horner-Wadsworth-Emmons olefination.[118] Lastly, commercially available 1-([1,1'-biphenyl]-4-yl)piperazine was coupled to Boc-L-Dmt (Scheme 34) to give final analogue **286**.

Scheme 33. Synthesis of Analogue **285**



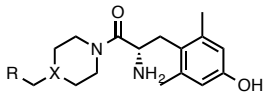
Scheme 34. Synthesis of Analogue **286**

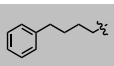
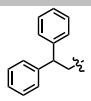
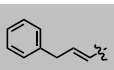
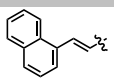
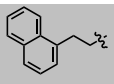
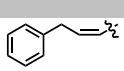


The synthesized analogues in Table 9 display a broad range of binding affinities for MOR (29–0.29 nM), and to a lesser extent, DOR (115–6.6 nM). Extension of the side chain of **262** from 1 to 3 methylene units did little to change binding at MOR or DOR, but encouragingly, the resulting compound (**263**) behaved as a weak partial agonist at MOR. Replacement of the piperidine core of **263** with a piperazine (**264**) proved inconsequential, and the continued balanced MOR/DOR binding profile of this analogue led to the pursuit of other aromatic moieties separated by three methylene units from the piperazine core. Analogue **281** in particular showed an improved balanced MOR/DOR binding profile, and also displayed a partial agonist profile at MOR. Interestingly, compound **277**, in which the 1-naphthyl side chain of **281** is constrained with an additional double bond, showed no efficacy in the [^{35}S]GTPγS assay at all three receptors, with an additional loss of binding affinity for KOR. The insertion of an extra aromatic moiety as in the case of the diphenylmethyl analogue **269** did little to increase binding affinity for either MOR or DOR. Further extension of the distance between the aromatic side chain and the piperazine core (**265**) resulted in a boost in MOR binding, without drastically affecting DOR. Although these 4 carbon analogues (**265, 276, 285**) suffered a slight loss of MOR/DOR affinity balance, all displayed good efficacy at MOR,

particularly the unsaturated analogues **276** and **285** (20 and 41 nM, respectively). Side chain extension to 5 methylene units (**268**) did little to improve upon the profile of **276** or **285**.

Table 9. Opioid Receptor Binding Affinities and Efficacies for Analogues **261-265**, **268**, **269, 276, 277, 281, 285, 286**[a]



			MOR			DOR			KOR		
	R	**x**	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim	K_i (nM)	EC_{50} (nM)	% stim
261	Scheme 28		29 ± 9	dns	11 ± 6	14 ± 2	dns	dns	310 ± 50	dns	dns
262		CH	1.4 ± 0.1	dns	dns	7.8 ± 0.9	dns	dns	140 ± 24	dns	dns
263		CH	2.0 ± 0.8	119 ± 39	26 ± 2	12 ± 2	dns	dns	110 ± 11	dns	dns
264		N	3.8 ± 0.8	150 ± 49	23 ± 2	36 ± 4	dns	dns	250 ± 51	dns	dns
265		N	0.45 ± 0.3	64 ± 3	43 ± 6	9.9 ± 2	dns	dns	30 ± 6	dns	12 ± 1
268		N	0.42 ± 0.15	53 ± 23	42 ± 1	6.9 ± 1.7	dns	dns	39 ± 15	660 ± 80	12 ± 5
269		N	1.1 ± 0.2	dns	dns	21 ± 7	dns	dns	150 ± 42	dns	dns
276		N	0.29 ± 0.07	20 ± 3.6	36 ± 4	23 ± 8.9	dns	dns	89 ± 23	1500 ± 120	16 ± 3
277		N	6.4 ± 0.1	dns	dns	11 ± 0.65	dns	dns	330 ± 92	dns	dns
281		N	1.1 ± 0.3	85 ± 10	17 ± 3	6.6 ± 2	dns	dns	78 ± 15	dns	dns
285		N	0.3 ± 0.1	41 ± 15	49 ± 5	28 ± 6.8	dns	dns	54 ± 3.2	dns	11 ± 7
286	Scheme 34		11 ± 2	2500 ± 800	15 ± 8	115 ± 42	dns	dns	320 ± 80	dns	dns

[a] dns = does not stimulate. See Table 1 for further in vitro details.

Structurally, these analogues exhibit some similarities to the class of trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonists originally described by Zimmerman[119] and explored by others.[120] In this series, the 3-hydroxyphenyl moiety is replaced by 2',6'-dimethyl-L-tyrosine, and the piperidine (or piperazine) core is left unsubstituted. In both series, receptor selectivity is modulated by the nature of the lipophilic side chain attached *para* to the phenolic component of the molecule. The piperidine and piperazine analogues of THQ compound **258** described here display a favorable balance between binding affinity at MOR and DOR, and several display improved potency at MOR as compared to morphine (K_i (MOR) = 6.3 nM, (DOR) = 171 nM; EC_{50} (MOR) = 194 nM).[42] Unfortunately, compound **268** proved to be inactive in the WWTW assay at 10 mg/kg, and further in vivo studies on this class of analogues were not pursued.

5.3 Experimental Section

5.3.1 Chemistry

For further general chemistry, *in vitro* and *in vivo* experimental detail, see section 2.4.

(259) tert-butyl 4-benzylidene-3,4-dihydroquinoline-1(2H)-carboxylate

To a suspension of triphenylphosphoniumbenzyl bromide (2.44 g, 5.6 mmol) in dry THF (20 mL) was added n-BuLi (2.70 mL, 6.8 mmol) dropwise at 0°C. The red mixture was allowed to stir for 1 h. tert-butyl 4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (1.46 g, 5.9 mmol) was then added dropwise at 0 °C. The mixture was then warmed to 70 °C, and refluxed overnight. The mixture was then quenched with sat. ammonium chloride (5 mL) and the aqueous layer was extracted with EtOAc. Combined organic extracts were

washed with brine and dried with $MgSO_4$. Residue was purified by column chromatography (9:1 hexanes/EtOAc) to give product as a colorless oil (0.44 g, 50%). ^{1}H-NMR (400 MHz, $CDCl_3$) revealed an inseparable 3:1 mixture of E:Z isomers, which was carried forward without additional purification.

(260) 4-benzyl-1,2,3,4-tetrahydroquinoline

Compound **259** (0.286 g, 0.89 mmol) was dissolved in MeOH (40 mL) and added to 10% Pd/C (400 mg) in a hydrogenation vessel. The mixture was shaken under 50 psi H_2 gas for 24 h, after which time the mixture was filtered through a plug of Celite, and MeOH was removed. Residue was redissolved in EtOAc, and H_2O was added. Aqueous layer was extracted with EtOAc, and combined organic layers were dried with $MgSO_4$. Solvents were filtered and removed to afford a colorless oil which was dissolved in a 1:1 mixture of TFA/DCM (6 mL) and stirred for 30 min. Solvents were removed, and residue was extracted from 2M NaOH with EtOAc and dried with $MgSO_4$. Solvents were filtered and removed to give product as a colorless oil (0.12 g, 61%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.4, 2H), 7.21 (t, J = 8.8, 3H), 7.04 – 6.95 (m, 2H), 6.61 (t, J = 7.4, 1H), 6.49 (d, J = 7.9, 1H), 3.41 – 3.32 (m, 1H), 3.21 (dt, J = 9.7, 4.6, 1H), 3.12 (dd, J = 13.3, 5.1, 1H), 3.08 – 3.00 (m, 1H), 2.71 (dd, J = 13.3, 10.0, 1H), 1.82 – 1.66 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.42, 140.58, 129.43, 128.43, 127.13, 126.12, 124.79, 116.87, 114.36, 43.33, 38.29, 37.55, 25.33.

(261) (2S)-2-amino-1-(4-benzyl-3,4-dihydroquinolin-1(2H)-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propan-1-one

To a solution of Boc-L-Dmt (0.056 g, 0.14 mmol) and 5Å molecular sieves in anhydrous DMF (2 mL) and DCM (5 mL) was added DIPEA (0.20 mL, 1.1 mmol), followed by 10

min of stirring. HATU (0.043 g, 0.11 mmol) and HOBt-Cl (0.019 g, 0.11 mmol) were then added, followed by an additional 20 min of stirring. Compound **260** (0.025 g, 0.11 mmol) in DMF (2 mL) was then added *via* syringe. The reaction was heated to 40 °C and allowed to stir overnight. Solvents were removed, and crude residue was redissolved in EtOAc. H_2O was added, and extracted with EtOAc. Combined organic extracts were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed, and residue was purified by column chromatography (7:1 hexanes/EtOAc). Purified residue was then redissolved in a 1:1 mixture of DCM/TFA (10 mL), and allowed to stir for 1 h. Solvents were removed to give product as an oily solid. Retention Time: 39.60 min. MS(EI): 437.2 (M+Na).

(262) (S)-2-amino-1-(4-benzylpiperidin-1-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propan-1-one

To a solution of 4-benzylpiperidine (0.100 g, 0.57 mmol), Boc-L-Dmt (0.234 g, 0.57 mmol) and DIPEA (1.00 mL, 5.7 mmol) was added HATU (0.217 g, 0.571 mmol) and HOBt-Cl (0.097 g, 0.57 mmol) and allowed to stir at r.t. for 15 h. H_2O was then added, and extracted with EtOAc. Combined organic layers were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed, and residue was redissolved in 1:1 DCM/TFA (6 mL) and allowed to stir for 1 h. Solvents were removed, and residue was purified by RP-HPLC to give product as a white solid. Retention Time: 32.45 min. MS(EI): 389.2 (M+Na). ^{1}H-NMR (400 MHz, $CDCl_3$) revealed a 2:1 ratio of conformers.

(263) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-(4-(3-phenylpropyl)piperidin-1-yl)propan-1-one

Followed procedure for compound **262** with 4-(3-phenylpropyl)piperidine (0.087 g, 0.42 mmol) with the following modification: reaction was stirred at r.t. for 2 h and purified by RP-HPLC to give product as a white solid. Retention Time: 39.15 min. MS(EI): 394.2 (M+H). ^{1}H-NMR (400 MHz, $CDCl_3$) revealed a 3:2 ratio of conformers.

(264) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-(4-(3-phenylpropyl)piperazin-1-yl)propan-1-one

Followed procedure for compound **262** with 1-(3-phenylpropyl)piperazine (0.091 g, 0.45 mmol) to give product as a white solid. Retention Time: 20.29 min. MS(EI): 396.3 (M+H). ^{1}H-NMR (500 MHz, CD_3OD) δ 7.30 – 7.21 (m, 2H), 7.21 – 7.12 (m, 3H), 6.55 (s, 2H), 4.55 (dd, J = 11.8, 4.8, 1H), 3.37 – 2.87 (m, 12H), 2.63 (t, J = 7.6, 2H), 2.24 (s, 6H), 2.00 – 1.87 (m, 2H).

(265) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-(4-(4-phenylbutyl)piperazin-1-yl)propan-1-one

Followed procedure for compound **262** with 1-(4-phenylbutyl)piperazine (0.045 g, 0.21 mmol) to give product as a white solid. Retention Time: 26.71 min. MS(EI): 410.3 (M+H). ^{1}H-NMR (500 MHz, CD_3OD) δ 7.27 (t, *J* = 7.5, 2H), 7.23 – 7.15 (m, 3H), 6.57 (s, 2H), 4.56 (dd, *J* = 12.1, 4.6, 1H), 3.54 – 2.87 (m, 12H), 2.67 (t, *J* = 6.7, 2H), 2.28 (s, 6H), 1.69 – 1.61 (m, 4H).

(266) 1-(5-phenylpentyl)piperazine

5-phenylpentanol (0.506 g, 3.08 mmol) was dissolved in DCM (15 mL). Et_3N (0.86 mL, 6.2 mmol) was then added *via* syringe. The mixture was cooled to 0 °C, and MsCl (0.406 mL, 5.2 mmol) was added dropwise. The yellow mixture was stirred at 0 °C for 1 h, after which time it was washed with H_2O (15 mL). Aqueous layer was discarded, and the

organic solvents were filtered and removed to give crude mesylate as a yellow oil. Mesylate was redissolved in THF (15 mL) and piperazine (1.32 g) was added. The mixture was refluxed at 70 °C for 16 h, after which time THF was removed and residue was redissolved in DCM. 2M HCl was added, and the organic layer was discarded. Aqueous layer was basified with solid NaOH to pH 14, and extracted with DCM. Combined organic extracts were dried with $MgSO_4$, and solvents were filtered and removed to afford product as a colorless oil (0.50 g, 69%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 2H), 7.19 – 7.12 (m, 3H), 2.86 (t, *J* = 5.0, 4H), 2.59 (t, *J* = 7.6, 2H), 2.37 (brs, 4H), 2.31 – 2.23 (m, 2H), 1.62 (p, *J* = 7.6, 2H), 1.51 (p, *J* = 7.6, 2H), 1.33 (p, *J* = 7.7, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 142.37, 128.14, 128.00, 125.39, 59.11, 54.37, 45.85, 35.67, 31.21, 27.04, 26.33.

(267) 1-(3,3-diphenylpropyl)piperazine

Followed procedure for compound **266** with 3,3-diphenylpropan-1-ol (0.54 g, 2.56 mmol) to give product as a colorless oil (0.56 g, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 8H), 7.19 – 7.11 (m, 2H), 3.99 (t, *J* = 6.8, 1H), 2.86 (t, *J* = 4.9, 4H), 2.36 (s, 4H), 2.27 – 2.22 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.85, 128.47, 127.84, 126.14, 57.42, 54.41, 49.06, 45.97, 32.55.

(268) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-(4-(5-phenylpentyl)piperazin-1-yl)propan-1-one

Followed procedure for compound **262** with **266** (0.058 g, 0.25 mmol) with the following modifications: reaction was stirred at r.t. for 8 h with PyBOP instead of HATU and purified by RP-HPLC to give product as a white solid. Retention time: 28.63 min. MS(EI): 424.3 (M+H). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.25 (t, *J* = 7.4, 2H), 7.20 – 7.11

(m, 3H), 6.57 (s, 2H), 4.57 (dd, *J* = 12.1, 4.6, 1H), 3.22 (t, *J* = 12.8, 1H), 3.12 (dd, *J* = 13.6, 4.5, 1H), 3.07 – 2.85 (m, 10H), 2.63 (t, *J* = 7.5, 2H), 2.27 (s, 6H), 1.74 – 1.58 (m, 4H), 1.43 – 1.29 (m, 2H).

(269) (S)-2-amino-1-(4-(3,3-diphenylpropyl)piperazin-1-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propan-1-one

Followed procedure for compound **262** with **267** (0.091 g, 0.33 mmol) with the following modifications: reaction was stirred at r.t. for 2 h with HBTU instead of HATU and purified by RP-HPLC to give product as a white solid. Retention Time: 32.23 min. MS(EI): 472.3 (M+H). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.33 – 7.26 (m, 10H), 6.53 (s, 2H), 4.53 (dd, *J* = 12.0, 4.7, 1H), 3.97 (t, *J* = 7.9, 1H), 3.25 – 2.34 (m, 14H), 2.24 (s, 6H).

(270) (E)-methyl 4-phenylbut-2-enoate

To 60% NaH (0.190 g, 4.8 mmol) in THF (12 mL) was added methyl diethylphosphonoacetate (0.87 mL, 4.8 mmol) dropwise at 0 °C. The mixture was allowed to stir for 5 min, after which time the ice bath was removed and phenylacetaldehyde (0.56 mL, 4.8 mmol) was added dropwise over a period of 10 min. The mixture was stirred for 1 h, and was then quenched with sat. ammonium chloride. The aqueous layer was extracted with Et_2O. Combined organic extracts were dried with $MgSO_4$, and solvents were filtered and removed. Residue was purified by column chromatography (8:1 hexanes/EtOAc) to afford product as a colorless oil (0.62 g, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.23 – 7.17 (m, 1H), 7.16 – 7.04 (m, 3H), 5.80 (dt, *J* = 15.6, 1.4, 1H), 3.67 (s, 3H), 3.46 (dd, *J* = 6.9, 0.8, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 166.78, 147.59, 137.65, 128.78, 128.69, 126.68, 121.94, 51.40, 38.43.

(271) (E)-methyl 3-(naphthalen-1-yl)acrylate

Followed procedure for compound **270** with 1-naphthaldehyde (0.74 g, 4.76 mmol) to afford product as a colorless oil (0.88 g, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 15.8, 1H), 8.08 (d, *J* = 8.0, 1H), 7.80 – 7.71 (m, 2H), 7.59 (d, *J* = 7.2, 1H), 7.51 – 7.38 (m, 2H), 7.33 (t, *J* = 7.7, 1H), 6.46 (d, *J* = 16.0, 1H), 3.78 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.08, 141.57, 133.48, 131.41, 131.22, 130.39, 128.57, 126.69, 126.04, 125.26, 124.80, 123.13, 120.15, 51.59.

(272) (E)-4-phenylbut-2-en-1-ol

To a solution of compound **270** (0.60 g, 3.4 mmol) in anhydrous DCM (10 mL) was added DIBAL (15 mL, 15 mmol, 1.0 M in THF) at -78°C. The mixture was allowed to stir at -78 °C for 15 min, after which time the mixture was quenched with EtOAc (5 mL) and H_2O (5 mL) and allowed to stir for 1 h at r.t. The mixture was filtered through a plug of Celite, and the aqueous layer was extracted with EtOAc. Combined organic extracts were washed with brine and dried with $MgSO_4$. Solvents were filtered and removed, and residue was purified by column chromatography (3:1 hexanes/EtOAc) to afford product as a colorless oil (0.26 g, 52%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.20 – 7.13 (m, 3H), 5.85 – 5.75 (m, 1H), 5.69 – 5.59 (m, 1H), 4.04 (dd, *J* = 5.8, 0.9 2H), 3.40 (d, *J* = 6.7, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 140.08, 131.36, 130.39, 128.59, 128.49, 126.16, 63.30, 38.67.

(273) (E)-3-(naphthalen-1-yl)prop-2-en-1-ol

Followed procedure for compound **272** with **271** (0.86 g, 4.04 mmol) to give product as a colorless oil (0.62 g, 83%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 1H), 7.76 – 7.70 (m, 1H), 7.65 (d, *J* = 8.2, 1H), 7.43 (d, *J* = 7.2, 1H), 7.40 – 7.32 (m, 2H), 7.31 – 7.21 (m, 2H), 6.29 – 6.19 (m, 1H), 4.18 (dd, *J* = 5.6, 1.2, 2H); ^{13}C-NMR (101 MHz, CDCl3) δ

134.34, 133.51, 131.69, 131.04, 128.44, 127.85, 127.66, 125.97, 125.68, 125.55, 123.75, 123.66, 63.46.

(274) (E)-1-(4-phenylbut-2-en-1-yl)piperazine

Followed procedure for compound **266** with **272** (0.14 g, 0.96 mmol) to give product as a colorless oil (0.11 g, 51%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 2H), 7.24 – 7.14 (m, 3H), 5.82 – 5.71 (m, 1H), 5.63 – 5.51 (m, 1H), 3.47 (s, 2H), 3.38 (d, *J* = 6.4, 2H), 3.03 – 2.91 (m, 4H), 2.47 (s, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 140.30, 133.44, 128.60, 128.53, 127.57, 126.15, 61.24, 53.58, 45.67, 38.97.

(275) (E)-1-(3-(naphthalen-1-yl)allyl)piperazine

Followed procedure for compound **266** with **273** (0.62 g, 3.34 mmol) to give product as a colorless oil (0.40 g, 48%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.2, 1H), 7.79 (d, *J* = 7.6, 1H), 7.72 (d, *J* = 8.2, 1H), 7.58 (d, *J* = 7.1, 1H), 7.50 – 7.36 (m, 3H), 7.24 (d, *J* = 15.6, 1H), 6.27 (dt, *J* = 15.5, 6.8, 1H), 3.20 (d, *J* = 6.8, 2H), 2.87 (t, *J* = 4.9, 4H), 2.47 (s, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 134.49, 133.43, 130.89, 129.98, 129.67, 128.38, 127.68, 125.85, 125.58, 125.51, 123.67, 123.58, 61.78, 54.33, 45.92.

(276) (S,E)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-(4-(4-phenylbut-2-en-1-yl)piperazin-1-yl)propan-1-one

Followed procedure for compound **262** with **274** (0.070 g, 0.32 mmol) to give product as a white solid. Retention Time: 26.28 min. MS(EI): 408.3 (M+H). ^{1}H-NMR (500 MHz, CD_3OD) δ 7.30 (t, *J* = 7.5, 2H), 7.21 (t, *J* = 6.4, 3H), 6.55 (s, 2H), 6.25 – 6.16 (m, 1H), 5.53 – 5.44 (m, 1H), 4.55 (dd, *J* = 12.1, 4.6, 1H), 3.80 (d, *J* = 7.2, 1H), 3.65 – 2.86 (m, 13H), 2.26 (s, 6H).

(277) (S,E)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-(4-(3-(naphthalen-1-yl)allyl)piperazin-1-yl)propan-1-one

Followed procedure for compound **262** with **275** (0.12 g, 0.47 mmol) to give product as a white solid. Retention Time: 30.95 min. MS(EI): 444.3 (M+H). ^{1}H-NMR (500 MHz, CD_3OD) δ 8.20 (d, *J* = 8.4, 1H), 7.90 (t, *J* = 7.8, 2H), 7.76 – 7.68 (m, 2H), 7.62 – 7.47 (m, 3H), 6.61 (s, 2H), 6.28 – 6.18 (m, 1H), 4.57 (dd, *J* = 12.1, 4.6, 1H), 3.98 – 3.89 (m, 1H), 3.77 – 3.00 (m, 11H), 2.28 (s, 6H).

(278) methyl 3-(naphthalen-1-yl)propanoate

Compound **271** (0.574 g, 2.7 mmol) was dissolved in abs. EtOH, and added slowly to 10% Pd/C (200 mg). The mixture was allowed to shake under 15 psi H_2 gas for 2 h, after which time it was filtered through a plug of Celite, and EtOH was removed. Residue was redissolved in EtOAc, and H_2O was added. Aqueous layer was extracted with EtOAc. Combined organic extracts were dried with $MgSO_4$, and solvents were filtered and removed to give pure product as a colorless oil (0.555 g, 96%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2, 1H), 7.90 (d, *J* = 7.9, 1H), 7.78 (d, *J* = 8.0, 1H), 7.61 – 7.49 (m, 2H), 7.48 – 7.37 (m, 2H), 3.74 (s, 3H), 3.48 (t, *J* = 7.9, 2H), 2.82 (t, *J* = 7.9, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.35, 136.43, 133.85, 131.56, 128.86, 127.12, 126.05, 125.87, 125.57, 125.54, 123.33, 51.61, 34.91, 28.07.

(279) 3-(naphthalen-1-yl)propan-1-ol

To a stirring suspension of LAH (0.197 g, 5.2 mmol) in dry THF (15 mL) was added compound **278** (0.555 g, 2.6 mmol) in THF (10 mL) dropwise at 0 °C. The reaction mixture was warmed to r.t., and was stirred vigorously for 1 h, after which time it was quenched with H_2O (10 mL) and was filtered through a plug of Celite with Et_2O.

Aqueous layer was extracted with Et_2O, and combined organic extracts were dried with $MgSO_4$. Solvents were filtered and removed to afford pure product as a colorless oil (0.450 g, 95%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.96 (m, 1H), 7.81 – 7.76 (m, 1H), 7.65 (d, *J* = 8.1, 1H), 7.47 – 7.37 (m, 2H), 7.32 (t, *J* = 6.8, 1H), 7.25 (d, *J* = 6.7, 1H), 3.61 (t, *J* = 6.4, 2H), 3.07 (t, *J* = 7.6, 2H), 1.98 – 1.86 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 137.97, 133.88, 131.82, 128.78, 126.66, 125.97, 125.80, 125.55, 125.48, 123.78, 62.25, 33.43, 29.14.

(280) 1-(3-(naphthalen-1-yl)propyl)piperazine

Followed procedure for compound **266** with **279** (0.46 g, 2.46 mmol) to give product as a colorless oil (0.49 g, 79%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.1, 1H), 7.85 – 7.78 (m, 1H), 7.67 (d, *J* = 8.1, 1H), 7.50 – 7.40 (m, 2H), 7.35 (t, *J* = 7.2, 1H), 7.29 (d, *J* = 6.8, 1H), 3.05 (t, *J* = 8.0, 2H), 2.89 (t, *J* = 4.9, 4H), 2.50 – 2.34 (m, 6H), 1.95 – 1.84 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 138.15, 133.75, 131.76, 128.65, 126.49, 125.84, 125.63, 125.42, 125.34, 123.72, 58.51, 53.51, 45.33, 30.55, 27.63.

(281) (S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-(4-(3-(naphthalen-1-yl)propyl)piperazin-1-yl)propan-1-one

Followed procedure for compound **262** with **280** (0.088 g, 0.35 mmol) with the following modifications: reaction was stirred at r.t. for 3 h with HBTU instead of HATU and purified by RP-HPLC to give product as a white solid. Retention Time: 30.22 min. MS(EI): 446.3 (M+H). ^{1}H-NMR (400 MHz, CD_3OD) δ 8.06 (d, J = 8.5, 1H), 7.86 (d, *J* = 7.9, 1H), 7.75 (d, *J* = 8.0, 1H), 7.51 (dt, *J* = 23.7, 7.0, 2H), 7.44 – 7.33 (m, 2H), 6.56 (s, 2H), 4.54 (dd, *J* = 11.8, 4.4, 1H), 3.26 – 2.91 (m, 14H), 2.55 (s, 6H), 2.11 – 2.02 (m, 2H).

(282) (Z)-methyl 4-phenylbut-2-enoate

Followed procedure for compound **270** with phenylacetaldehyde (0.38 g, 3.14 mmol) with the following modifications: methyl P,P-bis(2,2,2-trifluoroethyl)phosphonoacetate was used instead of methyl diethylphosphonoacetate and the reaction was allowed to stir for 30 minutes to give product as a colorless oil (0.43 g, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.25 – 7.17 (m, 3H), 6.40 – 6.30 (m, 1H), 5.86 (d, *J* = 11.4, 1H), 4.02 (d, *J* = 7.3, 2H), 3.74 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 166.85, 148.41, 139.45, 128.71, 128.69, 126.43, 119.54, 51.26, 35.22.

(283) (Z)-4-phenylbut-2-en-1-ol

Followed procedure for compound **272** with **282** (0.43 g, 2.42 mmol) to give product as a colorless oil (0.26 g, 72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.22 – 7.14 (m, 3H), 5.74 – 5.69 (m, 2H), 4.30 – 4.27 (m, 2H), 3.42 (d, *J* = 5.8, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 140.26, 130.97, 129.43, 128.60, 128.37, 126.18, 58.49, 33.70.

(284) (Z)-1-(4-phenylbut-2-en-1-yl)piperazine

Followed procedure for compound **266** with **283** (0.23 g, 1.54 mmol) to give product as a colorless oil (0.23 g, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 2H), 7.23 – 7.13 (m, 3H), 5.82 – 5.70 (m, 1H), 5.67 – 5.55 (m, 1H), 3.43 (s, 2H), 3.22 – 3.08 (m, 2H), 3.01 – 2.71 (m, 4H), 2.48 (s, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 140.49, 131.54, 128.48, 128.30, 126.88, 126.02, 55.63, 54.19, 45.82, 33.76.

(285) (S,Z)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-(4-(4-phenylbut-2-en-1-yl)piperazin-1-yl)propan-1-one

Followed procedure for compound **262** with **284** (0.065 g, 0.30 mmol) to give product as a white solid. Retention Time: 25.09 min. MS(EI): 408.3 (M+H). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.30 (m, 2H), 7.24 – 7.16 (m, 3H), 6.54 (s, 2H), 6.19 (m, 1H), 5.52 (m, 1H),

4.57 (dd, *J* = 11.9, 4.7, 1H), 3.77 (d, *J* = 7.4, 2H), 3.50 (d, *J* = 7.7, 2H), 3.38 – 2.93 (m, 10H), 2.25 (s, 6H).

(286) (S)-1-(4-([1,1'-biphenyl]-4-yl)piperazin-1-yl)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propan-1-one

Followed procedure for compound **262** with 1-([1,1'-biphenyl]-4-yl)piperazine (0.047 g, 0.20 mmol) with the following modifications: reaction was reaction was stirred at r.t. for 3 h with HBTU instead of HATU and purified by RP-HPLC to give product as a white solid. Retention Time: 37.86 min. MS(EI): 430.3 (M+H). ^{1}H-NMR (500 MHz, CD_3OD) δ 7.54 (d, *J* = 7.6, 2H), 7.50 (d, *J* = 7.2, 2H), 7.38 (t, *J* = 6.0, 2H), 7.26 (t, *J* = 7.4, 1H), 6.93 (d, *J* = 6.8, 2H), 6.53 (s, 2H), 4.57 (dd, *J* = 12.1, 4.3, 1H), 3.91 – 3.83 (m, 1H), 3.56 – 3.47 (m, 1H), 3.29 – 3.06 (m, 4H), 2.90 – 2.80 (m, 2H), 2.80 – 2.73 (m, 1H), 2.29 (s, 6H), 2.04 – 1.96 (m, 1H).

CHAPTER 6

CONCLUSIONS AND FUTURE DIRECTIONS

General Summary. The previous chapters have described both (1) the synthesis, in vitro and in vivo evaluation of a class of mixed efficacy opioid ligands based on compound **1** (Figure 11, Chapter 2) featuring 2',6'-dimethyl-L-tyrosine (Dmt) attached to a tetrahydroquinoline (THQ) or related core (Chapters 2-4) and (2) the synthesis, in vitro and in vivo evaluation of a class of opioids featuring piperidine and piperazine cores (Chapter 5). The SAR campaign for both classes of compounds has yielded analogues that are potent MOR agonists (and DOR antagonists) in vitro, as well as several analogues that display potent, dose-dependent antinociception in mouse models, particularly isoindoline **86**, tetrahydroisoquinoline **102**, thiochroman **214** and carboxamide **251**. These analogues are therefore promising candidates for further dependence and tolerance studies in mice.

Binding Affinity and Sodium. Because it is known that sodium ions can bind to an allosteric site in DOR and reduce the binding affinity of certain DOR ligands,[121] **86**, **102**, **214** and **251** were tested for DOR binding affinity in the presence of 100 mM Na, which is roughly the physiological concentration. Under these conditions, it was found that the DOR binding affinity of **86** is 102.4 nM, a 6.8 fold decrease in affinity from 15 nM in Tris buffer. Conversely, the binding affinity for **102** in the presence of Na was

found to be 2.8 nM, only a 3.1 fold decrease from 0.89 nM. It was found that in the presence of Na, the DOR binding affinity for **214** became 34.6 nM, a roughly 7-fold decrease from 4.8 nM in Tris buffer. Preliminary studies on the binding of carboxamide **251** in the presence of 100 mM sodium at DOR have shown the compound's binding affinity to be 91 nM, comparable to isoindoline **86**. If the theory that MOR agonist/DOR antagonist ligands with superior binding affinity at both MOR and DOR under physiological conditions are able to mitigate the negative side effects associated with selective MOR agonists, **102** may be an especially promising candidate for future in vivo studies.

Synthesis of New THQ Core-Based Analogues (Chapters 2-4). The analogues synthesized in Chapter 2 feature a substituent at the 6 position of a THQ or substituted THQ core. It would therefore be an interesting endeavor to combine a 6-position pendant substitution that yielded good dose-dependent antinociception in vivo (tetrahydroisoquinoline **102**, isoindoline **86**, see Chapter 2) with the *thiochroman* core of analogue **214** (Chapter 3). Such an analogue may show a cumulative effect and be even more potent in vivo than either of its parent compounds, or may conversely show no effect at all (in keeping with the unpredictable results seen in vivo thus far). Either way, the synthesis of this type of additive compound has not yet been attempted, and the results would provide new information concerning the efficacy of this type of scaffold in vivo.

Given the robust dose-dependent analgesia exhibited by carboxamide compound **251** (Chapter 4), this analogue is also an interesting candidate for further in vivo studies, particularly chronic tolerance and dependence in mice. Additionally, this unnatural amino

acid (S)-2-((tert-butoxycarbonyl)amino)-3-(4-carbamoyl-2,6-dimethylphenyl)propanoic acid[99] could also be examined on scaffolds featuring different pendant modifications at the 6 position (see Chapter 2), particularly the aforementioned pendant modifications that also gave good dose-pendent analgesia in mice (**86** and **102**).

Additionally, because ligands with selectivity for MOR and KOR over DOR (with KOR agonist activity) such as nalbuphine have shown promise for the treatment of drug dependence (specifically cocaine self administration),[83] further SAR studies on analogue **89** (Chapter 2) are warranted. **89** shows potent stimulation of KOR in the [^{35}S]GTPγS binding assay, but does not stimulate MOR. Using similar LAH-reduction chemistry on different commercially available imides (see Scheme 6) other saturated spiro amines of varying ring sizes could be synthesized (2-azaspiro[4.5]decane, 8-azaspiro[4.5]decane, 7-azaspiro[4.5]decane, etc.).[77] These types of substitutions would serve as a useful starting point for the development of an analogue that retains or improves on the potent KOR stimulation of compound **89**, while maintaining selective affinity for MOR and KOR over DOR.

Synthesis of New Piperazine Core-Based Analogues (Chapter 5). Although the extension of the lipophilic side chain to 5 methylene units of piperazine analogue **268** (Chapter 5) did not improve upon the MOR agonist/DOR antagonist profile of compound **265**, bulkier aromatic groups were not examined on chain lengths of 4 methylene units or greater from the piperazine core in this series of analogues. Such compounds could feasibly be synthesized by refluxing the appropriate commercially available 1-naphthyl or 2-naphthyl derivatized alcohol or halide with piperazine in THF.[117] Additionally, alternative nitrogen-containing heterocycles have not yet been examined in place of the

piperazine core. Replacement with a 7-membered piperazine derivative (homopiperazine) or similarly larger or smaller saturated nitrogen-containing heterocycles would provide interesting analogues in which the angle of the lipophilic side chain would necessarily be changed relative to the Dmt-containing portion of the ligand. Such analogues could potentially boost the modest MOR agonist activity of the previously synthesized compounds.

Negishi Coupling Optimization. Although the microwave-assisted Negishi coupling described in Chapter 4 can provide access to Dmt and its derivatives in a rapid manner, the reaction does require further optimization. The modest yield of 56% could potentially be improved with the use of a different Pd catalyst/ligand system, and further screening of commercially available catalytic systems would provide further insight into strategies for yield improvement. Additionally, although this reaction is effective on a relatively small scale (< 400 mg of serine derivative **233**), operation of the reaction on a gram scale has proven difficult, and only trace amounts of product have thus far been isolated. Optimization of the reaction setup and microwave conditions (reaction time, temperature) will therefore require further study for large batches of these useful intermediates.

Peripherally Active Compounds for the Treatment of IBS. Although many of the THQ-based peptidomimetics discussed in Chapters 2 and 3 show optimal MOR agonist/DOR antagonist profiles in vitro, only a select few of the compounds showed dose-dependent antinociception in mice after ip administration. Alternatively, compounds with no activity after this route of administration (meaning no BBB penetration) are promising candidates for the treatment of IBS (see the development of Eluxadoline,

Chapter 1.5). Representative analogues modified at the 6-position that would be viable candidates for such studies are 2-benzofuranyl compound **75**, tetrahydroisoquinoline compounds **82** and **83**, and decahydroisoquinoline compound **87** (Chapter 2). All of these compounds have good binding affinities at MOR and DOR (with some selectivity for MOR), and show potent stimulation of MOR in the [^{35}S]GTPγS assay. Many of the analogues with modifications to the THQ core discussed in Chapter 3 would also be good candidates for further studies in the area of peripherally active MOR agonist/DOR antagonists, namely sulfone analogue **217**. **217** shows especially potent stimulation of MOR (EC_{50} 0.72 nM, 94% stimulation), and good binding affinity at DOR (2.3 nM). Furthermore, the sulfone moiety (in place of the THQ aniline) prevents oxidative aromatization of the molecule's core, and lends the compound an especially high polar surface area (109.5), which is favorable for a lack of BBB penetration and overall metabolic stability.

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