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Article

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Structural Simplification of a Tetrahydroquinoline Core Peptidomimetic μ-Opioid Receptor (MOR) Agonist/ δ-Opioid Receptor (DOR) Antagonist Produces Improved Metabolic Stability

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Abstract:

We have previously reported a series of μ-opioid receptor (MOR) agonist/ δ-opioid receptor (DOR) antagonist ligands to serve as potential nonaddictive opioid analgesics. These ligands have been shown to be active *in vivo*, do not manifest withdrawal syndromes or reward behavior in conditioned-place preference assays in mice, and do not produce dependence. While these attributes are promising, these analogs exhibit poor metabolic stability in mouse liver microsomes, likely due to the central tetrahydroquinoline scaffold in this series. As such, an SAR campaign was pursued to improve their metabolic stability. This resulted in a shift from our original bicyclic tetrahydroquinoline core to a monocyclic benzylic core system. By eliminating one of the rings in this scaffold and exploring the SAR of this new core, two promising analogs were discovered. These analogs (**5l** and **5m**) had potency and efficacy values at MOR better or comparable to morphine, retain their DOR antagonist properties, and showed a 10-fold improvement in metabolic stability.

Introduction:

Mu-opioid analgesics, such as morphine and oxycodone, are the most clinically relevant drugs used for the treatment of chronic pain. Despite their widespread use, tolerance develops to their analgesic actions and patients suffer from undesirable side effects, such as dependence, addiction, constipation, and respiratory depression. A growing body of pre-clinical evidence has emerged suggesting that compounds that stimulate the μ-opioid receptor (MOR) in conjunction with antagonism at the δ-opioid receptor (DOR) can produce the desired analgesic effects without producing analgesic tolerance or dependence. For instance, rats given morphine and co-treated with the DOR-antagonists TIPP[Ψ][1] or naltrindole[2-3] displayed antinociception with significantly diminished chronic antinociceptive tolerance and dependence as measured by reduced withdrawal symptoms. These trends are supported by experiments wherein DOR knockout mice[4] did not develop chronic tolerance to the analgesic effects of morphine. Furthermore, mice treated with antisense DOR oligodeoxynucleotide[5] did not develop acute dependence or chronic tolerance to the analgesic effects of morphine.

Many ligands have been synthesized that possess this MOR-agonist/DOR-antagonist profile,[6,7] and some small molecule bifunctional MOR-agonist/DOR-antagonists have been reported that show reduced side-effect profiles (**Figure 1**). Some of these are based on the classical morphinan scaffold (**Figure 1A, I and II**), and show attenuated chronic tolerance and dependence.[8–10] Mitragynine pseudoindoxyl (**Figure 1B, III**), derived from the kratom alkaloid mitragynine, was found to elicit reduced withdrawal and respiratory depression, and does not produce conditioned-place preference.[11] Others still are derived from opioid peptides (**Figure 1C-D**). DIPP[Ψ]-NH_2 **(Figure 1C, IV**), an endomorphin derivative, produces antinociception in murine models without acute tolerance and chronic physical dependence.[12] AAH8 (**Figure 1C, V**) has also been shown to produce antinociception in murine models without developing tolerance to antinociceptive effects, physical dependence, nor does it evoke conditioned-place preference, suggesting it does not have reward properties.[13] While a large number of derivatives of this last compound have been reported,[14–20] these ligands show poor metabolic stability in mouse liver microsomes (MLM) ($T_{1/2}$~5 min), suggesting they will be too short acting *in vivo* for clinical

development. We therefore sought to improve their metabolic stability while maintaining the desired bifunctional opioid profile.

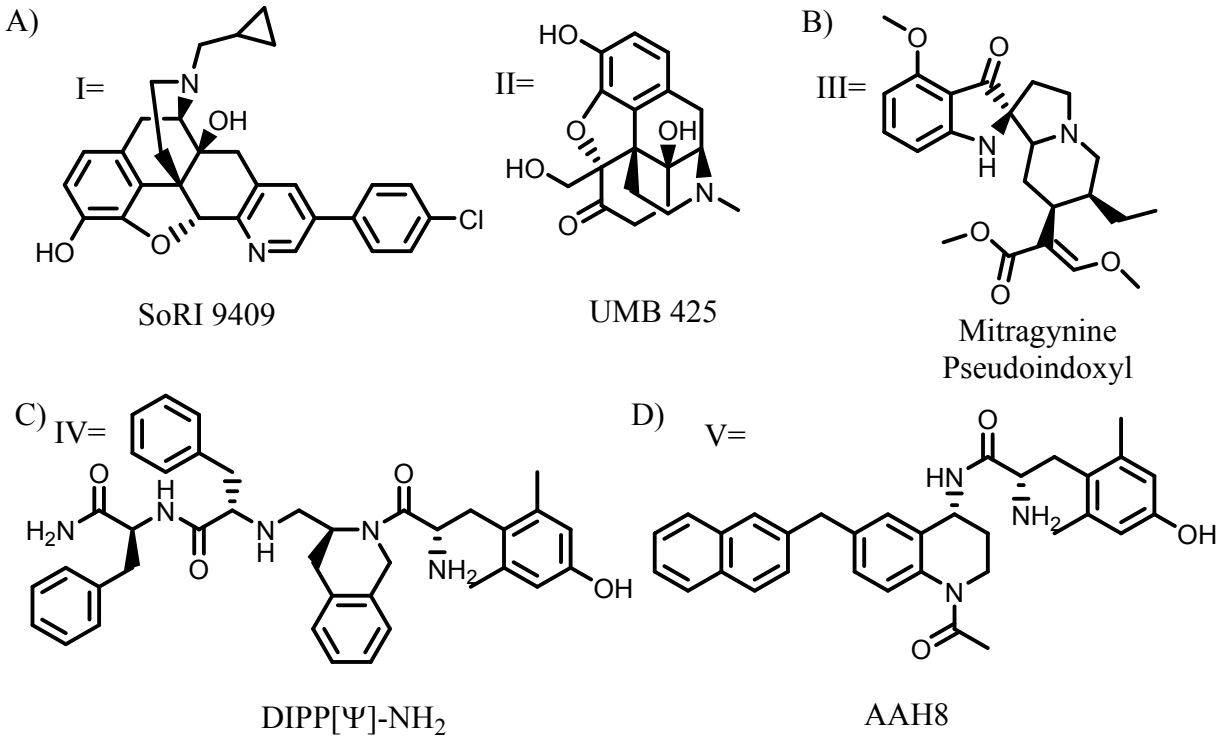
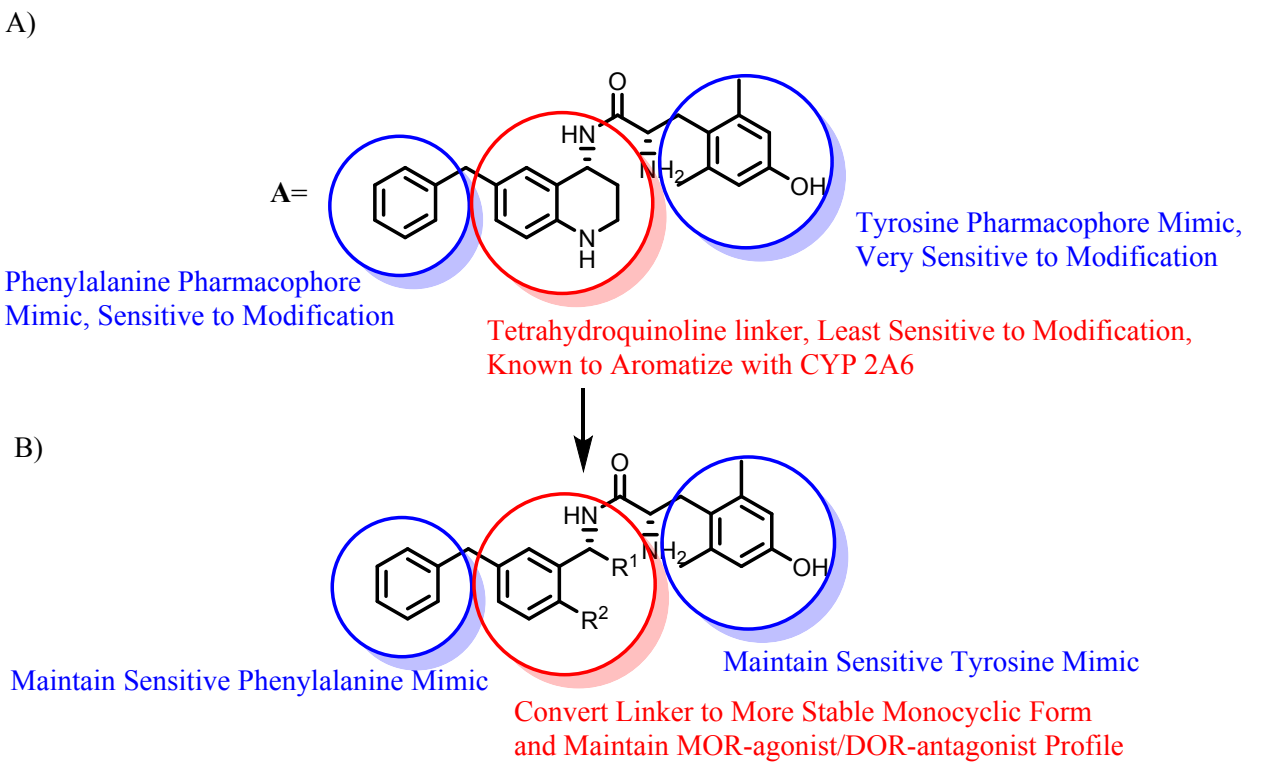


Figure 1: Notable structures that exhibit a MOR-agonist/DOR-antagonist profile. Some of these compounds utilize the morphinan scaffold shared by many opioids (A), or is a derivative of kratom alkaloids (B), while others are derived from endomorphins (C), or cyclic opioid peptides (D).

With this goal in mind, we sought to identify regions that would be most amenable to modifications aimed at improving metabolic stability. Here, we used our original lead peptidomimetic KSKPP1E (**Figure 2A**, **A**)[21] as a reference point on which to base our initial design choices. Tetrahydroquinolines (THQ) have been shown to aromatize upon action by CYP2A6 enzymes,[22] commonly found in mouse liver microsomes. This aromatization could in part explain the metabolic instability of our peptidomimetic series, an instability that persists for almost all compounds that contain a bicyclic core akin to the THQ system. Given the role of the THQ core as linker for the 2'6'-dimethyltyrosine (DMT) and benzyl pharmacophores, an SAR campaign aimed at transforming this core

into a more stable form was pursued. Initially, we sought to remove the aliphatic ring of the THQ system, producing more conformationally flexible ligands while removing the metabolically labile cycle (**Figure 2B**). We were encouraged by other opioids that relied on similar strategies to connect these two pharmacophore elements together, such as a urea,[23] piperidine or piperazine,[24] pyrazinone,[25–28] alkyl diamine,[29,30] or long alkyl chains.[31] Herein, we describe our initial SAR study that eliminates the bicyclic system of the THQ core to both produce our desired MOR-agonist/DOR-antagonist profile and to improve metabolic stability.



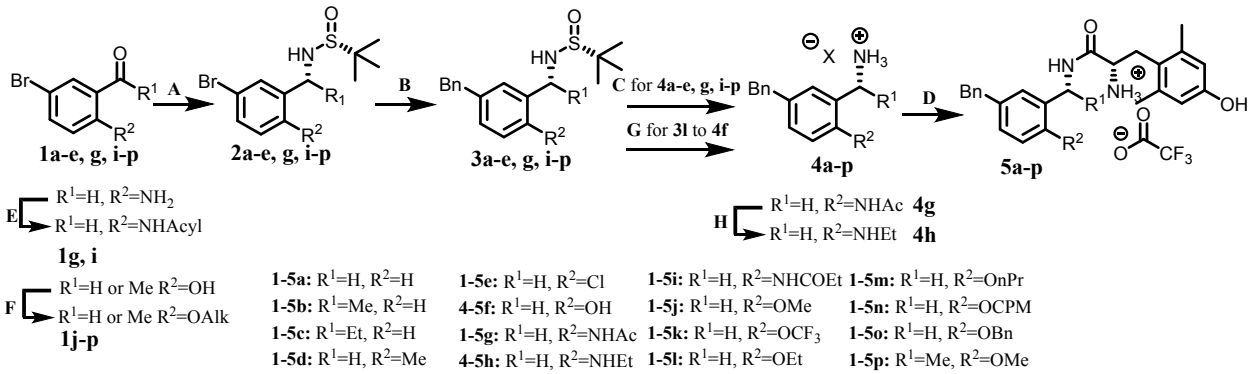
5a: R^1=H, R^2=H	**5e:** R^1=H, R^2=Cl	**5i:** R^1=H, R^2=NHCOEt	**5m:** R^1=H, R^2=OnPr
5b: R^1=Me, R^2=H	**5f:** R^1=H, R^2=OH	**5j:** R^1=H, R^2=OMe	**5n:** R^1=H, R^2=OCPM
5c: R^1=Et, R^2=H	**5g:** R^1=H, R^2=NHAc	**5k:** R^1=H, R^2=OCF_3	**5o:** R^1=H, R^2=OBn
5d: R^1=H, R^2=Me	**5h:** R^1=H, R^2=NHEt	**5l:** R^1=H, R^2=OEt	**5p:** R^1=Me, R^2=OMe

Figure 2: A.) Pharmacophore and linker elements of our peptidomimetic lead.[19,21] The pharmacophore elements include 2',6'-dimethyltyrosine and benzyl pendants that are sensitive to modification, and the linker consists of a tetrahydroquinoline (THQ) core. B.) New analogs lacking the THQ core.

Results:

General Chemistry: All of the described monocyclic compounds were synthesized according to **Scheme 1**. Before engaging in the main route of synthesis, the ethers and the anilines were diversified at the beginning. To synthesize functionalized anilines, 2-amino-5-bromobenzaldehyde was subjected to acylation using the appropriate neat anhydride at 100 °C, producing the acetyl and propionyl anilines **1g** and **1i** respectively. To produce aromatic ethers, 5-bromo-2-hydroxybenzaldehyde was functionalized using an alkyl bromide or iodide, producing the methyl, ethyl, n-propyl, cyclopropyl methyl, and benzyl ethers **1j, l-o**. The exceptions here are trifluoromethoxy ether **1k**, which was purchased, and **1p**, which used 1-(5-bromo-2-hydroxyphenyl)ethan-1-one as starting material instead of 5-bromo-2-hydroxybenzaldehyde. The functionalized aromatic bromo ketone or aldehydes **1a-e, g, i-p** were then reduced through imine formation with an Ellman's chiral sulfonamide and subsequent reduction with sodium borohydride, producing compounds **2a-e, g, i-p**. The Ellman's chiral sulfonamide both enables enantioselective amine formation (if applicable) as used previously,[18] and protects the amine during subsequent Suzuki coupling to generate compounds **3a-e, g, i-p**. This was followed by Ellman deprotection using concentrated HCl and dioxane to produce **4a-e, g, i-p**. The exception here being the synthesis of the 6-phenol (**4f)** which utilized BBr_3 to both remove the Ellman's chiral sulfonamide and cleave the 6-position ether **3l**. The ethyl aniline analog **4h** was synthesized by reduction of the acetyl aniline **4g** with borane-dimethylsulfide complex (BH_3*Me_2S). Finally, Boc-protected DMT was coupled to the free primary amine of structures **4a-p** using PyBOP, followed by removal of the Boc groups using trifluoroacetic acid to yield the final peptidomimetics **5a-p**.

Scheme 1: Synthesis of Substituted Monocyclic Core Analogs **5a-p**



A) 1. (R)-(+)-2-methyl-propane-2-sulfinamide, $Ti(OEt)_4$, THF, 75 °C 2. $NaBH_4$. B) BnBPin, K_2CO_3, $Pd(dppf)Cl_2$, 3:1 Acetone:Water, 80-100 °C. C) HCl conc., Dioxane. D) 1. DiBocDMT, DIEA, PyBOP, 6-Cl-HOBt, DMF. 2. TFA, DCM. E) Neat acyl anhydride, 100 °C. F) MeI or Alk-Br, K_2CO_3, DMF. G) BBr_3, DCM. H) BH_3*Me_2S, THF, 75 °C.

SAR: Our studies began by first probing the structural components of the aliphatic ring of the THQ core. These studies focused on binding affinity, efficacy, and potency at MOR and DOR, though the κ-opioid receptor (KOR) was also examined to determine compound selectivity. The binding affinity data can be found in **Table 1**, whereas the efficacy and potency data can be found in **Table 2** (see footnotes of each table for how these values were measured). Initially, all substituents and functional groups comprising this aliphatic ring were removed, yielding **5a**. This conversion had little effect on binding affinity compared to the original lead **A**, but had a significant effect on efficacy. Indeed, **5a** did not stimulate any of the three classical opioid receptors. We then began to restore different portions of the original aliphatic ring to elucidate the importance of each component. The incorporation of short linear alkyl chains (**5b-c**) on the benzylic position (R^1) connecting the aromatic core to the DMT pharmacophore partially restored MOR agonism (41 % stimulation for compound **5b**). In this case, the methyl group (**5b**) was superior to an ethyl group (**5c**), however MOR efficacy was less than that of morphine (57 % stimulation), which serves here as a benchmark for MOR activity. It should be noted that morphine's intrinsic activity of 57 % should not be interpreted as poor MOR efficacy, only that the standard agonist DAMGO in this assay has exceptional efficacy. DOR affinity was found to decrease when these alkyl chains are incorporated,

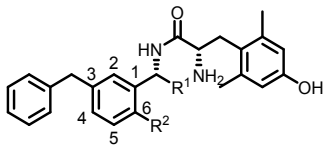
though these compounds still did not stimulate DOR. KOR binding improved with increasing chain size, and weak KOR agonism was observed with both alkyl groups.

In parallel with the analogs described above, an assortment of compounds was made with functional groups at the 6-position, corresponding to that of the THQ nitrogen. Initially, a few simple substituents were incorporated at this position. These included methyl, chloro, and hydroxy groups (**5d-f**). Each of these managed to restore MOR agonism to between 17 % and 39 %, but much less than that seen with the parent compound. None of these ligands produced agonism at DOR, though the hydroxy (**5f**) significantly reduced the binding at DOR compared to **5a**.

A small number of nitrogen containing substituents were also incorporated at the 6-position, resulting in ethyl, acetyl, and propionyl anilines (**5g-i**). These were made to mimic the substituents of the original THQ core without ring cyclization, or to mimic some N-acyl compounds that had utility in our previously reported THQ series.[16] These ligands were all weak partial MOR agonists and had reduced binding affinity at DOR compared to **5a**. The ethyl aniline also displayed reduced affinity at MOR.

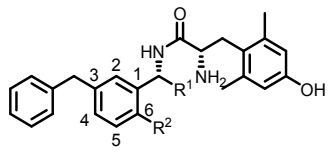
Several ethers were examined due to their synthetic accessibility, their ability to be rapidly diversified, and to probe the effect of hydrogen bond acceptors at the 6-position. The alkyl ethers included methyl, trifluoromethyl, ethyl, n-propyl, cyclopropyl methyl (CPM), and benzyl (**5j-o**). Here, an activity maximum was observed between the ethyl ether (**5l**), and the n-propyl ether (**5m**). Both ethers proved to be more potent than morphine and displayed similar levels of efficacy to morphine at MOR. This, in combination with the high DOR affinity and the lack of DOR efficacy of these two compounds, demonstrates that these monocyclic core compounds can retain our desired *in vitro* profile.

A final compound was synthesized to determine if a combination of R^1 and R^2 substituents could yield additive effects. To this end, **5p** was synthesized, in which R^1=-Me and R^2=-OMe. These substituents were selected as they have the same number of large atoms as the original THQ core, while



			Binding Affinity, K_i (nM)			***Selectivity***
Name	**-R¹**	**-R²**	**MOR**	**DOR**	**KOR**	**MOR:DOR:KOR**
A	**-CH_2CH_2NH-**		**0.22**±0.02[a]	**9.4**±0.8[a]	**68**±2[a]	**1:43:309**
Morphine	**-**	**-**	**6.3**±2.5[b]	**171**±19[b]	**61**±17[b]	**1:27:9.7**
5a	**H**	**H**	**1.0**±0.2	**14.7**±0.6	**410**±47	**1:15:410**
5b	**Me**	**H**	**1.1**±0.3	**46**±10	**201**±36	**1:42:180**
5c	**Et**	**H**	**3.2**±0.6	**61**±10	**49.5**±1.7	**1:19:15**
5d	**H**	**Me**	**5.2**±0.9	**33.9**±4.9	**360**±60	**1:6.5:69**
5e	**H**	**Cl**	**5.6**±0.8	**38.1**±3.9	**528**±49	**1:6.8:94**
5f	**H**	**OH**	**9.48**±0.50	**175**±26	**307**±34	**1:18:32**
5g	**H**	**NHAc**	**7.9**±1.1	**387**±31	**1550**±130	**1:49:200**
5h	**H**	**NHEt**	**23.5**±6.5	**63.8**±5.2	**408**±54	**1:2.7:17**
5i	**H**	**NHCOEt**	**4.2**±1.1	**108**±27	**1090**±290	**1:26:260**
5j	**H**	**OMe**	**3.58**±0.10	**21.5**±4.5	**610**±100	**1:6.0:170**
5k	**H**	**OCF_3**	**1.4**±0.5	**7.3**±0.5	**370**±83	**1:5.2:260**
5l	**H**	**OEt**	**2.8**±0.5	**23.8**±3.3	**1180**±120	**1:8.5:420**
5m	**H**	**OnPr**	**0.91**±0.06	**5.3**±1.0	**390**±150	**1:5.8:430**
5n	**H**	**OCPM**	**2.7**±0.6	**13.9**±1.8	**319**±51	**1:5.1:120**
5o	**H**	**OBn**	**8.0**±1.5	**70.4**±5.4	**575**±80	**1:8.8:71**
5p	**Me**	**OMe**	**8.0**±0.8	**6.8**±1.1	**330**±150	**1:0.85:41**

Table 1: Affinity of the benzylic core compounds at MOR, DOR, and KOR. Binding affinities (K_i) were obtained by competitive displacement of radiolabeled [^{3}H] diprenorphine in membrane preparations. Included are morphine and the original lead peptidomimetic (**A**) for comparison. All data were from three separate experiments, performed in duplicate. These data are reported as the average ± standard error of the mean. Selectivity was calculated by dividing the K_i of each receptor by the K_i at MOR for a given compound. DNS=Does Not Stimulate. [a]From Reference[21]. [b]From Reference[32].



			Potency, EC_{50} (nM)			***Efficacy, (% Stimulation)***		
Name	**-R^1**	**-R^2**	**MOR**	**DOR**	**KOR**	**MOR**	**DOR**	**KOR**
A	-CH_2CH_2NH-		**1.6**±0.3[a]	**110**±6[a]	**540**±72[a]	**81**±2[a]	**16**±2[a]	**22**±2[a]
Morphine	-	-	**194**±21[b]	**ND**	**DNS**	**57**±5[b]	**ND**	**DNS**
5a	H	H	**DNS**	**DNS**	**DNS**	**DNS**	**DNS**	**DNS**
5b	Me	H	**44.4**±7.5	**DNS**	**>1700**	**41**±12	**DNS**	**>40**
5c	Et	H	**158**±17	**DNS**	**2200**±500	**15.0**±2.6	**DNS**	**26.6**±3.0
5d	H	Me	**111**±29	**DNS**	**DNS**	**21.9**±5.3	**DNS**	**DNS**
5e	H	Cl	**250**±24	**DNS**	**DNS**	**39.2**±1.0	**DNS**	**DNS**
5f	H	OH	**552**±90	**DNS**	**DNS**	**17.0**±1.1	**DNS**	**DNS**
5g	H	NHAc	**117**±13	**DNS**	**DNS**	**32.5**±2.6	**DNS**	**DNS**
5h	H	NHEt	**156**±20	**DNS**	**>2440**	**25.9**±5.8	**DNS**	**>40**
5i	H	NHCOEt	**84**±26	**DNS**	**>4000**	**28.7**±7.1	**DNS**	**>35**
5j	H	OMe	**264**±21	**DNS**	**DNS**	**37.2**±1.7	**DNS**	**DNS**
5k	H	OCF_3	**342**±80	**DNS**	**DNS**	**45.0**±6.1	**DNS**	**DNS**
5l	H	OEt	**77**±10	**DNS**	**DNS**	**65.9**±5.2	**DNS**	**DNS**
5m	H	OnPr	**68**±10	**DNS**	**DNS**	**54.9**±4.0	**DNS**	**DNS**
5n	H	OCPM	**71**±13	**DNS**	**DNS**	**37.5**±1.3	**DNS**	**DNS**
5o	H	OBn	**107**±19	**DNS**	**DNS**	**34.7**±3.8	**DNS**	**DNS**
5p	Me	OMe	**296**±69	**DNS**	**DNS**	**20.2**±1.4	**DNS**	**DNS**

Table 2: Efficacy and potency of the benzylic core compounds at MOR, DOR, and KOR. Efficacy and potency data were obtained using agonist induced stimulation of [^{35}S] GTPγS binding. Potency is represented as EC50 (nM) and efficacy as percent maximal stimulation relative to standard agonist DAMGO (MOR), DPDPE (DOR), or U69,593 (KOR) at 10 μM. Included are morphine and the original lead peptidomimetic (**A**) for comparison. All data were from three separate experiments, performed in duplicate. These data are reported as the average ± standard error of the mean. DNS=Does Not Stimulate. ND =Not Determined. [a]From Reference[19]. [b]From Reference[33].

also utilizing the more desirable ethers. When compared to **5b**, this compound appears to have reduced binding affinity, efficacy, and potency at MOR. DOR binding, however, shows a modest improvement over **5b** and retains an antagonist profile at DOR.

With regards to KOR, most of the ligands express reduced binding affinity at this receptor compared to **A**, with the exception of **5c**. Similarly, only **5c**, **5h**, and **5i** were shown to have weak, partial efficacy at KOR; the rest have no efficacy at this receptor. Since we were interested in balancing the binding affinity between MOR and DOR, and since we were screening KOR for selectivity, we calculated binding ratios between MOR, DOR, and KOR normalized to MOR. Most of these ligands show an improved balance between MOR and DOR compared to the lead compound **A**, the exception of **5g**. The greatest balance can be found with various functional groups at the R^2-position, namely the methyl (**5d**), chloro (**5e**), ethyl aniline (**5h**), and all the ethers (**5j-p**). When comparing MOR and KOR for selectivity, only the unfunctionalized compound **5a**, and the ethyl (**5l**) and n-propyl (**5m**) ethers contained greater selectivity than **A**.

Antagonist Potency of Representative Analogs: Finally, while analogs displaying reasonably high DOR affinity (~20 nM or less) and no DOR efficacy are presumptive DOR antagonists, this was tested explicitly for **5l**, **5m**, and **5n**. DOR antagonism was confirmed for all three analogs, which effected rightward shifts in the EC_{50} of the standard DOR agonist DPDPE that equated to K_e values of 20.2 nM, 7.4 nM, and 20.5 nM, respectively (calculated as described in Methods).

Metabolic Stability: In tandem with the SAR described above, the metabolic stability of these monocyclic core compounds was characterized in mouse liver microsomes (MLM) (**Table 3**) using verapamil as the positive control. Because of the variability between the measures of metabolic half-life for verapamil (from 13.8 to 22.6 min) in the different assay preparations, the ratio of $T_{1/2}$ for the compound and verapamil was calculated as a stability ratio. This was to ensure consistent comparisons between different analogs.

Name	*R¹*	*R²*	*$T_{1/2}$ (min)*	*Verapamil $T_{1/2}$ (min)*	*Stability Ratio*	*cLogP*
A	CH_2CH_2NH		**3.1**±0.1	**14.7**±2.0	**0.21**±0.03	**3.74**
5a	H	H	**13.0**±2.6	**14.6**±1.0	**0.89**±0.19	**4.30**
5b	Me	H	**8.5**±0.8	**22.6**±1.4	**0.38**±0.04	**4.61**
5c	Et	H	**4.1**±0.2	**13.8**±1.6	**0.29**±0.04	**5.14**
5d	H	Me	**12.2**±0.0	**22.6**±1.4	**0.54**±0.03	**4.75**
5e	H	Cl	**16.3**±2.5	**22.6**±1.4	**0.72**±0.12	**5.01**
5f	H	OH	**15.4**±1.3	**14.4**±1.0	**1.1**±0.1	**3.58**
5g	H	NHAc	**10.2**±0.4	**14.4**±1.0	**0.71**±0.06	**2.45**
5h	H	NHEt	**12.1**±1.5	**22.6**±1.4	**0.54**±0.07	**4.33**
5j	H	OMe	**19.7**±2.0	**13.8**±1.6	**1.4**±0.2	**4.22**
5k	H	OCF_3	**5.7**±0.0	**14.6**±1.0	**0.39**±0.03	**5.33**
5l	H	OEt	**23.7**±5.9	**14.6**±1.0	**1.6**±0.4	**4.75**
5m	H	OnPr	**33.1**±2.8	**19.6**±2.3	**1.7**±0.2	**5.28**
5n	H	OCPM	**56.3**±10.1	**22.6**±1.4	**2.5**±0.5	**5.19**
5o	H	OBn	**15.6**±0.1	**22.6**±1.4	**0.69**±0.04	**5.99**
5p	Me	OMe	**4.3**±0.0	**14.6**±1.0	**0.30**±0.02	**4.53**

Table 3: Metabolic stability of monocyclic compounds in MLM. Included are the compound half-life ($T_{1/2}$), the half-life of the positive control verapamil, and the stability ratio between the compound and the positive control. The stability ratio was calculated by dividing the half-life of the analog of interest by the half-life of the positive control in that assay. Individual compounds were tested once, with errors representing the SE in the decay curve regressed onto the data collected in 15 minute intervals. Finally, the cLogP of these analogs are included and were calculated using PerkinElmer's ChemDraw® Professional Software.

To evaluate the improvement in stability of these compounds, the original lead compound **A** is included in **Table 3**. This compound displays the poorest metabolic stability, with a ratio of 0.21 compared to verapamil and is characteristic of the other THQ containing analogs in our previously

reported series. Stripping away all the substituents that make up the aliphatic portion of the tetrahydroquinoline ring (**5a**) improves the ratio 4-fold to 0.89. However, introducing alkyl chains off this benzylic position (R^1, **5b-c**) reduces the stability of these compounds back to that of **A**.

Next, we examined our analogs at the 6-position (R^2). The small substituents at this position (**5d-f**) did not improve the stability of these compounds, even though some of these modifications are polar (which would reduce cLogP[34]) or are electron withdrawing groups (which would inhibit free radical formation during the CYP catalytic cycle). This also extends to the acetyl and ethyl anilines (**5g-h**), in which no improvements were observed.

The ethers (**5j-o**), generally produced significant improvements in metabolic stability. This is particularly true for cyclopropyl methyl ether (**5n**), which was 2.5 fold more stable than verapamil, reflecting a half-life of 56 minutes. This was not true of all the ethers however, as the trifluoromethyl ether (**5k**) showed lower stability levels than **5a**. Finally, the hybrid analog **5p** had low stability, similar to compound **5b**.

Discussion and Conclusions:

SAR: Using **A** as a baseline, it appears that moving to **5a** causes a loss in MOR agonism and affinity. This may in part be explained by increased conformational flexibility that occurs upon elimination of the aliphatic portion of the tetrahydroquinoline ring. This activity can be partially regained through the introduction of small alkyl chains at the benzylic position (**5b-c**), likely due to restoring interactions that favor interaction with the active state of the receptor.

Introducing the methyl, chloro, or hydroxy group to the 6-position of the benzylic core (**5d-f**) produced partial MOR agonism compared to **5a**. The hydroxyl group (**5f**) was the least potent and efficacious of the three, suggesting that either an electron donating group on the benzylic core or a hydrogen bond donor at the 6-position interferes with the ability of substituents at this position to activate MOR. This trend is also seen with binding affinity at DOR, as the hydroxy substituent possesses the

lowest affinity. The chloro substituent (**5e**) is similar to the methyl (**5d**) substituent in its activity at the three receptors, and differed only from **5d** in that it had twice the efficacy at MOR. This reinforces the electronics argument, as the chloro group is more electron withdrawing than the methyl group due to induction.

The 6-position ethers produced some of the most promising ligands in this series. These ligands generally had high MOR and DOR affinity, except for the benzyl ether at DOR (**5o**). However, the potency and efficacy of these compounds at MOR vary greatly. The optimum here appears to be with the ethyl (**5l**) and n-propyl (**5m**) ethers, which proved comparable to morphine in efficacy and potency. This is particularly interesting when these data are compared to the 6-anilines (**5g-i**) and the 6-hydroxyl (**5f**), as they suggest that the hydrogen bond donor present in these latter compounds is detrimental for MOR efficacy, rather than the presence of electron donating groups. The orientation of the hydrogen bond donor may be important, as the lead compound **A** displays high MOR efficacy. From the data illustrated in compounds **5g-i**, it appears that orientating the hydrogen bond donor toward the DMT pendant is detrimental to MOR agonism. Since these ethers also antagonize DPDPE, these data suggest that the small chain ethers are best for producing our desired MOR-agonist/DOR-antagonist profile.

It should be noted that the ethers **5l** and **5m** do not possess the potency or efficacy at MOR of the original lead compound **A**. Since we are ultimately interested in determining if MOR-agonist/DOR-antagonist ligands are suitable for use as opioid analgesics without abuse liabilities, the stability improvements of **5l** and **5m** represents a necessary developmental step toward this end. This is particularly true considering the instability of the THQ core compounds such as **A**. However, **5l** and **5m** have improved potency and similar efficacy at MOR compared to morphine, which is the classic opioid analgesic. As such, sacrificing some potency and efficacy at MOR to improve pharmacokinetic parameters is worthwhile, especially if they still perform better than morphine *in vitro*.

The hybrid compound **5p** is also notable due to its poor MOR efficacy and potency. While the potency of this compound was akin to the simple 6-OMe precursor (**5j**), the efficacy here was less than

either precursor analog **5b** and **5j**. This suggests that steric effects within the ligand may be detrimental to activation of MOR, a problem that vanishes when these two groups are tied together in the bicyclic ring of the original THQ core.

With regard to selectivity, two notable trends can be observed. Selectivity for MOR over KOR can be reduced compared to our original lead **A** through two different means. Extending alkyl chains off the benzylic position (R^1, **5b-c**) do this largely through improving KOR binding which peaks with the ethyl group (**5c**) in this series, whereas some substituents containing a hydrogen bond donor off the 6-position (R^2), namely the hydroxyl (**5f**) and ethyl aniline (**5h**) do this through reduced MOR binding. Conversely, the ethyl and n-propyl ethers (**5l-m**) show the best selectivity over KOR, largely due to reduced KOR binding compared to **A**. While almost all of the compounds show improved MOR/DOR affinity balance, possibly due to elimination of the bicyclic ring system, all of the ethers (**5j-p**) have among the best balance. Overall, the ethers **5l** and **5m** show the best selectivity over KOR, and are among the compounds that best balance MOR and DOR affinities.

Metabolic Stability: Stripping away all the components of the THQ core (**5a**) produced a 4-fold improvement in metabolic stability over **A**. When incorporating alkyl chains onto the benzylic position (**5b-c**, and **5p**), this improvement is lost, suggesting that this benzylic position in both this series and in the original THQ series is a metabolic hot spot. This is consistent with the mechanism of CYP metabolism, namely that the benzylic methyne present in compounds **5b-c**, and **5p** can greater stabilize the radical formed upon interaction with the enzyme than can the methylene alone. Simple chloro (**5e**) and hydroxyl (**5f**) functional groups at the 6-position were no different than the unfunctionalized system (**5a**). The ethers (**5j-o**), apart from the trifluoro (**5k**) and benzyl (**5o**) ethers, displayed the greatest levels of stability, reaching stability ratios of 2.5 and half-lives near an hour, as determined for **5n**.

Interestingly, these ethers were more stable than the functionalized anilines, despite their greater cLogP, which is commonly associated with reduced stability.[34] Amines are better electron donating substituents than ethers. As such, they may further stabilize metabolism at the adjacent benzylic positions

on the aromatic ring. Notably, the most stable ether contained a cyclopropyl moiety. This can likely be attributed to a combination of steric effects and ring strain, as the cyclopropyl group can both block metabolism at adjacent positions and the ring strain destabilizes free radical formation on the cyclopropyl group itself.

Fortunately, the SAR regarding the restoration of our MOR-agonist/DOR-antagonist profile overlapped with the SAR aimed at improving metabolic stability. This suggests that these 6-position ethers are a promising new direction for the development of these peptidomimetics. As such, our future derivatization of these analogs will follow the lead provided by these promising ethers.

Conclusion: Addiction to prescription opioids remains a major challenge for millions of Americans. This problem is driven largely by the widespread use of opioids to treat chronic pain. Consequently, there is a growing need for potent analgesics that lack these abuse liabilities. To this end, agonism at MOR with simultaneous antagonism at DOR may be able to produce analgesia without these side effects. Our previously reported peptidomimetics and their bicyclic analogs display such a profile, however their metabolic instability represents a major hurdle in their development. The results presented here show that the metabolically labile THQ core can be changed to a monocyclic core to improve metabolic stability. Initial modification of the simplified benzyl core yielded analogs (**5l** and **5m**) which display similar potency and efficacy as morphine at MOR, are antagonists at DOR, possess a more balanced affinity between MOR and DOR, are more selective over KOR, and show improved metabolic stability in mouse liver microsome assays compared to our original THQ core ligands. These monocyclic compounds represent an attractive new direction through which more stable MOR-agonist/DOR-antagonist ligands may be developed.

Experimental:

Chemistry

General Methods: All reagents and solvents were obtained commercially and were used without further purification. Intermediates were purified by flash chromatography using a Biotage Isolera One instrument. Most purification methods utilized a hexanes/ethyl acetate solvent system in a Biotage SNAP KP-Sil column, with a linear gradient between 0 and 100% ethyl acetate. Reverse phase column chromatography using a linear gradient of 0 % to 100 % solvent B (0.1 % TFA in acetonitrile) in solvent A (0.1 % TFA in water) using a Biotage SNAP Ultra C18 column was utilized for some intermediate amine salts. 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 0 % to 100 % solvent B in solvent A at a rate 1 % per minute, monitoring UV absorbance at 230 nm. The purity of final compounds was assessed using a Waters Alliance 2690 analytical HPLC instrument with a Vydac protein and peptide C18 reverse phase column. A linear gradient (gradient A) of 0 % to 70 % solvent B in solvent A in 70 min, measuring UV absorbance at 230 nm was used to determine purity. All final compounds used for testing were ≥95 % pure, as determined by analytical HPLC. ^{1}H NMR and ^{13}C NMR data were obtained on a 500 or 400 MHz Varian spectrometer using $CDCl_3$ or CD_3OD solvents. The identities of final compounds were verified by mass spectrometry using an Agilent 6130 LC–MS mass spectrometer in the positive ion mode, or an Agilent 6230 TOF HPLC-MS in the positive ion mode. Suzuki couplings using microwave irradiation were performed on a Discover S-class (CEM) microwave in a closed vessel with maximum power input of 300 W and temperature set to 100 °C for 30 min under the standard method using their Synergy software.

General Procedure for Ellman Reductions (Procedure A): A flamed-dried round bottom flask containing 1 equivalent of aldehyde or ketone and 3 equivalents of (R)-(+)-2-methyl-propane-2-sulfinamide was attached to a reflux condenser and flushed with argon. 4 mL of THF was added and cooled to 0 °C. 6 or 7.5 equivalents of titanium (IV) ethoxide was added, followed by an additional 4 mL of THF. The solution was stirred and heated to 75 °C overnight with TLC monitoring until all ketone or aldehyde was consumed. A separate flame-dried flask containing 6 equivalents of sodium borohydride was flushed with

argon. 4 mL of THF was added, at which point the solution was cooled to -78 °C. The solution containing Ellman adduct was cooled to room temperature and slowly transferred to the sodium borohydride solution via syringe. This final solution was then allowed to warm to room temperature and stirred for 2 hours, at which point the reaction mixture was quenched with methanol to consume the sodium borohydride, followed by DI water to precipitate the titanium. The solution was vacuum filtered, and the precipitate was washed with ethyl acetate. The filtrate was then concentrated in vacuo and purified via column chromatography (0-100 % EtOAc in Hexanes).

General Procedure for Suzuki Couplings Using Microwave Irradiation (Procedure Ba): To a microwave vessel containing the protected amine was added 2 equivalents of benzylboronic acid pinacol ester, 3 equivalents of potassium carbonate, and 0.1 equivalents of 1,1′-Bis(diphenylphosphino)ferrocene] dichloropalladium. The vessel was purged with argon and 2.5 mL of degassed 3:1 Acetone:Water was added. The vessel was then subject to microwave irradiation to a temperature of 100 °C for 30 min. The solution was cooled, partitioned between brine and ethyl acetate, and extracted with ethyl acetate. The organic layer was then dried with magnesium sulfate, filtered, and concentrated in vacuo. Column chromatography was then performed (0-100 % ethyl acetate in hexanes), yielding the desired Suzuki coupled derivatives.

General Procedure for Suzuki Couplings without Microwave Irradiation (Procedure Bb): To a round bottom flask containing protected amine, 2 equivalents of potassium carbonate, and 0.1 equivalents of 1,1′-Bis(diphenylphosphino)ferrocene] dichloropalladium was added 2.5 equivalents of benzylboronic acid pinacol ester. The flask was equipped with a reflux condenser, purged with argon, and 5 mL of degassed 3:1 Acetone:Water was added. The vessel was then heated to a temperature of 80 °C overnight. The solution was cooled, partitioned between brine and ethyl acetate, and extracted with ethyl acetate. The organic layer was then dried with magnesium sulfate, filtered, and concentrated in vacuo. Column chromatography was then performed (0-100 % ethyl acetate in hexanes), yielding the desired Suzuki coupled derivatives.

General Procedure for Removal of Ellman's chiral sulfonamide (Procedure C): To a flask containing Ellman protected amine was added 2 mL of Dioxane and 0.2 mL concentrated HCl. The solution was stirred at room temperature for 1 minute and concentrated in vacuo. The ensuing salt was then purified via one of two methods. If the product is insoluble in diethyl ether, it was triturated with diethyl ether, and the precipitate was concentrated in vacuo to dryness, yielding the product as an HCl salt. If the product was soluble in diethyl ether, it was purified using a reverse phase chromatography (0-100% B in A), yielding the product as a TFA salt.

General Procedure for the Coupling of 2',6'-Dimethyltyrosine to Functionalized Amine Salt (Procedure D): To a dried flask containing the amine salt under argon was added 3 mL of DMF and 10 equivalents of Hunig's base. 1 equivalent of PyBOP and 1 equivalent of 6-Cl-HOBt was added, followed by 1 equivalent of N-Boc-O-Boc-2',6'-dimethyl-L-tyrosine in 1.5 mL DMF. The solution was stirred overnight at room temperature and concentrated in vacuo. 2 mL of TFA and 2 mL of DCM were then added, and the solution was stirred for an additional hour. The reaction mixture was concentrated in vacuo and purified via semipreparative reverse phase HPLC (0.1% TFA in water: 0.1% TFA in acetonitrile). The product was concentrated in vacuo and lyophilized overnight to yield the final peptidomimetic.

General procedure for the acylation of 2-amino-5-bromobenzaldehyde (Procedure E): To a dried flask containing 2-amino-5-bromobenzaldehyde under argon was added neat acyl anhydride. The reaction was stirred overnight at 100 °C and concentrated in vacuo. The product was then partitioned between sat. $NaHCO_3$ and DCM. The compound was extracted with DCM, filtered, and concentrated in vacuo yielding the desired acylated compound.

General Procedure for the Synthesis of 6-position Ethers (Procedure F): To a flame dried flask containing phenolic aldehyde or ketone was added 3 equivalents of potassium carbonate. The flask was purged with argon and 4 mL of DMF was added. 3 equivalents of an alkyl iodide or bromide was then added, and the solution was stirred at room temperature overnight. The solution was then concentrated in vacuo,

partitioned between ethyl acetate and saturated sodium bicarbonate, and extracted with ethyl acetate. The organic layers were combined, dried with magnesium sulfate, filtered, and concentrated in vacuo, yielding the desired ether.

General procedure for the Cleavage of Phenolic Ethers (Procedure G): To a flame dried flask containing 1 equivalent of phenolic ether under argon was added 5 mL DCM and 3.02 equivalents of 1M BBr_3 in DCM was added dropwise. The solution was stirred at room temperature for 4 hours and quenched with methanol. The solution was concentrated in vacuo, suspended in diethyl ether, and filtered. The precipitate was then dissolved in methanol and filtered. The product in methanol was then concentrated in vacuo, yielding the desired phenol.

General procedure for the Reduction of Acyl Anilines (Procedure H): To a dried flask containing the desired acyl aniline under argon was added 2M BH_3*Me_2S in THF and additional THF. The solution was heated to 75 °C for 3 hours, at which point the solution was quenched with methanol and stirred an additional 15 minutes at 75 °C. The solution was cooled, concentrated in vacuo, yielding the reduced alkyl aniline.

N-(4-bromo-2-formylphenyl)acetamide (1g): See Procedure E: 74 mg (0.37 mmol) of 2-amino-5-bromobenzaldehyde, and 3 mL of acetic anhydride. The compound was purified after aqueous workup via column chromatography (0-10% ethyl acetate in hexanes) to produce compound **1g** (59 mg, 65.9 % yield) which was isolated as an orange solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.00 (br s, 1H), 9.84 (s, 1H), 8.65 (d, *J* = 8.9 Hz, 1H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.67 (dd, *J* = 9.0, 2.4 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 194.22, 169.53, 139.84, 138.80, 137.98, 122.78, 121.70, 114.91, 25.38.

N-(4-bromo-2-formylphenyl)propionamide (1i): See Procedure E: 98 mg (0.49 mmol) of 2-amino-5-bromobenzaldehyde, and 3 mL of propionic anhydride. Compound **1i** (113 mg, 90.1 % yield) was isolated as an orange solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.00 (s, 1H), 9.81 (s, 1H), 8.65 (d,

J = 9.0 Hz, 1H), 7.72 (d, *J* = 2.5 Hz, 1H), 7.64 (dd, *J* = 9.0, 2.4 Hz, 1H), 2.46 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 194.21, 173.28, 139.94, 138.75, 137.95, 122.83, 121.70, 114.71, 31.48, 9.33.

5-bromo-2-methoxybenzaldehyde (**1j**): See Procedure F: 157 mg (0.78 mmol) of 5-bromosalicylaldehyde, 320 mg (2.3 mmol, 3.0 eq.) of K_2CO_3, 150 µL (342 mg, 2.4 mmol, 3.1 eq) of MeI, 3 mL of DMF. Compound **1j** (170 mg, Quantitative Yield) was isolated as a yellow solid. ^{1}H-NMR (400MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.86 (d, *J*=2.3 Hz, 1H), 7.58 (dd, *J*=8.9, 2.3 Hz, 1H), 6.86 (d, *J*=8.9 Hz, 1H) 3.89 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 183.3, 169.7, 138.3, 130.9, 126.0, 113.7, 113.4, 56.0.

5-bromo-2-ethoxybenzaldehyde (1l): See Procedure F: 451 mg (1.5 mmol) of 5-bromosalicylaldehyde, 608 mg (4.4 mmol, 3.0 eq.) of K_2CO_3, 330 µL (482 mg, 4.4 mmol, 3.0 eq.) of EtBr, 4 mL of DMF. Compound **1l** (495 mg, 96.3 % yield) was isolated as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.36 (s, 1H), 7.85 (d, *J* = 2.6 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.4, 160.2, 138.2, 130.7, 126.0, 114.5, 113.2, 64.6, 14.5.

5-bromo-2-propoxybenzaldehyde (**1m**): See Procedure F: 123 mg (0.61 mmol) of 5-bromosalicylaldehyde, 251 mg (1.8 mmol, 3.0 eq.) of K_2CO_3, 160 µL (217 mg, 1.8 mmol, 2.9 eq.) of nPrBr, 4 mL of DMF. Compound **1m** (155 mg, Quantitative Yield) was isolated as a white waxy solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.41 (s, 1H), 7.89 (d, *J* = 2.6 Hz, 1H), 7.58 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.86 (d, *J* = 8.9 Hz, 1H), 4.01 (t, *J* = 6.4 Hz, 2H), 1.86 (h, *J* = 7.3 Hz, 2H), 1.06 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.4, 160.4, 138.2, 130.7, 126.1, 114.5, 113.2, 70.4, 22.4, 10.5.

5-bromo-2-(cyclopropylmethoxy)benzaldehyde (**1n**): See Procedure F: 99 mg (0.49 mmol) of 5-bromosalicylaldehyde, 204 mg (1.5 mmol, 3.0 eq.) of K_2CO_3, 140 µL (195 mg, 1.4 mmol, 2.9 eq.) of (bromomethyl)cyclopropane, 3 mL of DMF. Compound **1n** (128 mg, Quantitative Yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.42 (s, 1H), 7.87 (s, 1H), 7.55 (d, *J* = 8.9 Hz, 1H),

6.82 (d, *J* = 8.7 Hz, 1H), 3.89 (d, *J* = 6.6 Hz, 2H), 1.27 (m, 1H), 0.65 (m, 2H), 0.36 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 188.5, 160.3, 138.2, 130.7, 126.3, 114.9, 113.3, 73.7, 10.0, 3.2.

2-(benzyloxy)-5-bromobenzaldehyde (**1o**): See Procedure F: 401 mg (2.0 mmol) of 5-bromosalicylaldehyde, 828 mg (6.0 mmol, 3.0 eq.) of K_2CO_3, 710 µL (1021 mg, 6.0 mmol, 3.0 eq.) of BnBr, 5 mL of DMF. Compound **1m** (569 mg, 97.9 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.46 (s, 1H), 7.94 (d, *J* = 2.6 Hz, 1H), 7.60 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.45 – 7.33 (m, 5H), 6.95 (d, *J* = 8.9 Hz, 1H), 5.18 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 188.2, 159.9, 138.2, 135.5, 131.0, 128.8, 128.5, 127.3, 126.5, 115.2, 113.8, 70.9.

1-(5-bromo-2-methoxyphenyl)ethan-1-one (**1p**): See Procedure F: 198 mg (0.92 mmol) of 1-(5-bromo-2-hydroxyphenyl)ethan-1-one, 380 mg (2.8 mmol, 3.0 eq.) of K_2CO_3, 0.170 mL (388 mg, 2.7 mmol, 3.0 eq.) of MeI, 3 mL of DMF. Compound **1p** (205 mg, 97.2 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 2.7 Hz, 1H), 7.48 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 1H), 3.86 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 198.1, 157.9, 136.0, 132.8, 129.5, 113.6, 113.0, 55.8, 31.7.

(R)-N-(3-bromobenzyl)-2-methylpropane-2-sulfinamide (**2a**): See Procedure A: 90 mg (0.49 mmol) of 3-bromobenzaldehyde, 179 mg (1.5 mmol, 3.0 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 600 µL (653 mg, 2.9 mmol, 5.9 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 115 mg (3.0 mmol, 6.3 eq.) of sodium borohydride in 4 mL THF. Compound **2a** (111 mg, 78.6 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ7.47 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.1 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 4.30 (dd, *J* = 14.2, 5.1 Hz, 1H), 4.22 (dd, *J* = 14.2, 7.5 Hz, 1H), 3.56 (t, *J* = 6.3 Hz, 1H), 1.23 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.8, 131.1, 130.7, 130.2, 126.6, 122.6, 56.0, 48.7, 22.7.

(R)-N-((R)-1-(3-bromophenyl)ethyl)-2-methylpropane-2-sulfinamide (**2b**): See Procedure A: 155 mg (0.78 mmol) of 3'-bromoacetophenone, 261 mg (2.2 mmol, 2.8 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 1.00 mL (1.09 g, 4.8 mmol, 6.1 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 179 mg (4.7 mmol, 6.1 eq.) of sodium borohydride in 4 mL THF. Compound **2b** (125 mg, 62.5 % yield) was isolated as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (t, *J* = 1.8 Hz, 1H), 7.39 (ddd, *J* = 7.8, 2.0, 1.2 Hz, 1H),

7.26 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 4.48 (qd, *J* = 6.6, 3.1 Hz, 1H), 3.41 (d, *J* = 3.2 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.21 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.3, 130.9, 130.4, 129.6, 125.4, 122.7, 55.6, 53.6, 22.8, 22.6.

(R)-N-((R)-1-(3-bromophenyl)propyl)-2-methylpropane-2-sulfinamide (**2c**): See Procedure A: 106 mg (0.50 mmol) of 1-(3-bromophenyl)propan-1-one, 185 mg (1.5 mmol, 3.1 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 800 µL (870 mg, 3.8 mmol, 7.7 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 111 mg (2.9 mmol, 5.9 eq.) of sodium borohydride in 4 mL THF. Compound **2c** (125 mg, 78.9 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 (t, *J* = 1.8 Hz, 1H), 7.39 (dt, *J* = 7.6, 1.7 Hz, 1H), 7.25 – 7.16 (m, 2H), 4.21 (ddd, *J* = 8.9, 5.4, 4.1 Hz, 1H), 3.40 (d, *J* = 4.0 Hz, 1H), 2.01 (dtd, *J* = 14.7, 7.4, 5.5 Hz, 1H), 1.77 – 1.65 (m, 1H), 1.21 (s, 9H), 0.79 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.7, 130.9, 130.20, 130.15, 126.1, 122.7, 60.1, 55.8, 29.4, 22.6, 10.0.

(R)-N-(5-bromo-2-methylbenzyl)-2-methylpropane-2-sulfinamide (**2d**): See Procedure A: 77 mg (0.39 mmol) of 5-bromo-2-methylbenzaldehyde, 143 mg (1.2 mmol, 3.1 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 490 µL (533 mg, 2.3 mmol, 6.0 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 89 mg (2.4 mmol, 6.1 eq.) of sodium borohydride in 4 mL THF. Compound **2d** (108 mg, 91.8 % yield) was isolated as a colorless oil that solidified on standing. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 4.27 (dd, *J* = 13.9, 3.7 Hz, 1H), 4.16 (dd, *J* = 13.7, 8.4 Hz, 1H), 3.43 (dt, *J* = 8.4, 3.7 Hz, 1H), 2.26 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 138.4, 135.5, 132.1, 131.4, 130.7, 119.5, 56.0, 46.7, 22.7, 18.6.

(R)-N-(5-bromo-2-chlorobenzyl)-2-methylpropane-2-sulfinamide (**2e**): See Procedure A: 104 mg (0.47 mmol) of 5-bromo-2-chlorobenzaldehyde, 162 mg (1.3 mmol, 2.8 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 600 µL (653 mg, 2.9 mmol, 6.0 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 107 mg (2.8 mmol, 6.0 eq.) of sodium borohydride in 4 mL THF. Compound **2e** (134 mg, 87.1 % yield) was isolated as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 2.3 Hz, 1H), 7.33 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 4.40 (dd, *J* = 15.0, 5.8 Hz, 1H), 4.28 (dd, *J* = 15.0, 7.5 Hz, 1H), 3.68 (t, *J* =

6.7 Hz, 1H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 138.3, 132.7, 132.6, 131.9, 131.0, 120.6, 56.2, 46.9, 22.6.

(R)-N-(4-bromo-2-(((tert-butylsulfinyl)amino)methyl)phenyl)acetamide (2g): See Procedure A: 93 (0.38 mmol) of **1g**, 144 mg (1.2 mmol, 3.1 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 600 µL (653 mg, 2.9 mmol, 7.5 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 87 mg (2.3 mmol, 6.0 eq.) of sodium borohydride in 3 mL THF. This compound was purified using 0-10 % methanol in DCM as the mobile phase during column chromatography. Compound **2g** (130 mg, 97.5 % yield) was isolated as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 4.22 (dd, *J* = 13.5, 5.8 Hz, 1H), 4.11 (dd, *J* = 13.5, 4.5 Hz, 1H), 3.72 (t, *J* = 5.1 Hz, 1H), 2.19 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.53, 135.72, 133.03, 132.03, 130.51, 126.03, 117.34, 56.50, 44.54, 24.08, 22.85.

(R)-N-(4-bromo-2-(((tert-butylsulfinyl)amino)methyl)phenyl)propionamide (2i): See Procedure A: 84 (0.33 mmol) of **1i**, 123 mg (1.0 mmol, 3.1 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 410 µL (446 mg, 2.0 mmol, 6.0 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 76 mg (2.0 mmol, 6.1 eq.) of sodium borohydride in 4 mL THF. Compound **2i** (78 mg, 65.8 % yield) was isolated as a colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 4.20 (dd, *J* = 13.4, 5.9 Hz, 1H), 4.08 (dd, *J* = 13.1, 4.5 Hz, 1H), 3.67 (t, *J* = 5.1 Hz, 1H), 2.44 (q, *J* = 7.6 Hz, 2H), 1.22 (m, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.14, 135.81, 133.02, 132.07, 130.19, 125.87, 117.15, 56.47, 44.52, 30.22, 22.82, 9.69.

(R)-N-(5-bromo-2-methoxybenzyl)-2-methylpropane-2-sulfinamide (**2j**): See Procedure A: 142 mg (0.66 mmol) of **1j**, 240 mg (2.0 mmol, 3.0 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 1.00 mL (1.09 g, 4.8 mmol, 7.2 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 152 mg (4.0 mmol, 6.1 eq.) of sodium borohydride in 4 mL THF. Compound **2j** (159 mg, 75.2 % yield) was isolated as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 2.5 Hz, 1H), 7.33 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.72 (d, *J* = 8.6 Hz,

1H), 4.34 (dd, *J* = 14.4, 5.6 Hz, 1H), 4.11 (dd, *J* = 14.5, 7.6 Hz, 1H), 3.80 (s, 3H), 3.66 (t, *J* = 6.9 Hz, 1H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.4, 131.9, 131.4, 129.3, 112.6, 112.0, 55.9, 44.8, 22.6.

(R)-N-(5-bromo-2-(trifluoromethoxy)benzyl)-2-methylpropane-2-sulfinamide (**2k**): See Procedure A: 70 µL (119 mg, 0.44 mmol) of 5-bromo-2-(trifluoromethoxy)benzaldehyde, 163 mg (1.3 mmol, 3.0 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 700 µL (762 mg, 3.3 mmol, 7.5 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 103 mg (2.7 mmol, 6.1 eq.) of sodium borohydride in 4 mL THF. Compound **2k** (128 mg, 77.1 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 2.4 Hz, 1H), 7.43 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.11 (dd, *J* = 8.7, 1.6 Hz, 1H), 4.38 (dd, *J* = 15.1, 5.8 Hz, 1H), 4.27 (dd, *J* = 15.1, 7.4 Hz, 1H), 3.61 (t, *J* = 6.6 Hz, 1H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.2 (q, *J* = 1.7 Hz), 133.5, 133.0, 132.0, 122.2 (q, *J* = 1.7 Hz), 121.4, 120.2, 119.3, 56.2, 43.7, 22.6.

(R)-N-(5-bromo-2-ethoxybenzyl)-2-methylpropane-2-sulfinamide (**2l**): See Procedure A: 73 mg (0.32 mmol) of **1l**, 116 mg (0.96 mmol, 3.0 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 500 µL (544 mg, 2.4 mmol, 7.5 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 74 mg (2.0 mmol, 6.1 eq.) of sodium borohydride in 3 mL THF. Compound **2l** (97 mg, 91.1 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 2.5 Hz, 1H), 7.30 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 4.35 (dd, *J* = 14.3, 5.6 Hz, 1H), 4.12 (dd, *J* = 14.4, 7.9 Hz, 1H), 4.00 (q, *J* = 7.0 Hz, 2H), 3.72 (t, *J* = 6.8 Hz, 1H,), 1.40 (t, *J* = 7.0 Hz, 3H), 1.20 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.8, 131.8, 131.3, 129.4, 112.8, 112.5, 63.9, 55.9, 45.0, 22.6, 14.8.

(R)-N-(5-bromo-2-propoxybenzyl)-2-methylpropane-2-sulfinamide (**2m**): See Procedure A: 133 mg (0.55 mmol) of **1m**, 98 mg (0.81 mmol, 1.5 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 420 µL (457 mg, 2.0 mmol, 3.7 eq.) of $Ti(OEt)_4$, and 3+3 mL THF. 121 mg (3.2 mmol, 5.9 eq.) of sodium borohydride in 3 mL THF. Compound **2m** (169 mg, 88.7 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.35 (d, *J* = 2.5 Hz, 1H), 7.28 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 1H), 4.33 (dd, *J* = 14.4, 5.6 Hz, 1H), 4.11 (dd, *J* = 14.4, 7.8 Hz, 1H), 3.88 (t, *J* = 6.5 Hz, 2H), 3.72 (dd, *J*

= 7.8, 5.6 Hz, 1H), 1.78 (h, *J* = 7.4 Hz, 2H), 1.18 (s, 9H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.8, 131.8, 131.3, 129.4, 112.8, 112.4, 69.8, 55.9, 44.9, 22.6, 22.5, 10.6.

(R)-N-(5-bromo-2-(cyclopropylmethoxy)benzyl)-2-methylpropane-2-sulfinamide (**2n**): See Procedure A: 135 mg (0.53 mmol) of **1n**, 197 mg (1.6 mmol, 3.1 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 840 µL (914 mg, 4.0 mmol, 7.6 eq.) of $Ti(OEt)_4$, and 4+4 mL THF. 115 mg (3.0 mmol, 5.8 eq.) of sodium borohydride in 3 mL THF. Compound **2n** (165 mg, 86.5 % yield) was isolated as a colorless oil that solidifies to a white solid on standing. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 2.5 Hz, 1H), 7.30 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 4.39 (dd, *J* = 14.4, 5.7 Hz, 1H), 4.14 (dd, *J* = 14.4, 7.9 Hz, 1H), 3.88 – 3.75 (m, 3H), 1.21 (s, 9H), 0.62 (dt, *J* = 8.9, 3.2 Hz, 2H), 0.32 (dd, *J* = 4.7, 2.1 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.9, 131.8, 131.3, 129.6, 113.0, 112.5, 73.1, 55.9, 45.3, 22.6, 10.2, 3.24, 3.18.

(R)-N-(2-(benzyloxy)-5-bromobenzyl)-2-methylpropane-2-sulfinamide (**2o**): See Procedure A: 440 mg (1.5 mmol) of **1o**, 558 mg (4.6 mmol, 3.1 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 2.4 mL (2.6 g, 11.4 mmol, 7.6 eq.) of $Ti(OEt)_4$, and 5+5 mL THF. 341 mg (9.0 mmol, 6.0 eq.) of sodium borohydride in 4 mL THF. Compound **2o** (582 mg, 97.2 % yield) was isolated as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 (d, *J* = 2.5 Hz, 1H), 7.27 – 7.18 (m, 4H), 7.18 – 7.11 (m, 2H), 6.62 (d, *J* = 8.7 Hz, 1H), 4.98 (s, 2H), 4.32 (dd, *J* = 14.6, 5.7 Hz, 1H), 4.18 (dd, *J* = 14.6, 7.2 Hz, 1H), 4.12 (dd, *J* = 7.2, 5.8 Hz, 1H), 1.14 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.3, 136.2, 131.7, 131.0, 129.9, 128.5, 128.1, 128.0, 127.2, 126.7, 113.3, 112.8, 70.0, 55.7, 44.5, 22.5.

(R)-N-((R)-1-(5-bromo-2-methoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide (**2p**): See Procedure A: 129 mg (0.59 mmol) of **1p**, 193 mg (1.6 mmol, 2.7 eq.) of (R)-(+)-2-methyl-propane-2-sulfinamide, 720 µL (783 mg, 3.4 mmol, 5.8 eq.) of $Ti(OEt)_4$, 4+4 mL THF, 137 mg (3.6 mmol, 6.1 eq.) of sodium borohydride in 4 mL THF. Compound **2p** (173 mg, 91.9 % yield) was isolated as a colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 2.5 Hz, 1H), 7.26 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.69 (d, *J* = 8.7 Hz, 1H), 4.69 (p, *J* = 6.5 Hz, 1H), 3.77 (s, 3H), 3.75 (d, *J* = 5.8 Hz, 1H), 1.40 (d, *J* = 6.7 Hz, 3H),

1.16 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.6, 134.5, 131.1, 129.7, 113.0, 112.6, 55.6, 49.6, 23.6, 22.6, 21.0.

(R)-N-(3-benzylbenzyl)-2-methylpropane-2-sulfinamide (**3a**): See Procedure Bb: 55 mg (0.19 mmol) of **2a**, 120 µL (118 mg, 0.54 mmol, 2.8 eq.) of benzyl boronic acid pinacol ester, 54 mg (0.39 mmol, 2.1 eq.) of potassium carbonate, 17 mg (0.023 mmol, 0.12 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 4 mL of 3:1 Acetone:Water. Compound **3a** (38 mg, 66.5% yield) was isolated as a colorless oil that solidified to a white solid on standing. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.24 (m, 3H), 7.23 – 7.10 (m, 6H), 4.31 (dd, *J* = 13.8, 4.6 Hz, 1H), 4.21 (dd, *J* = 13.8, 7.8 Hz, 1H), 3.98 (s, 2H), 3.45 (dd, *J* = 7.6, 4.6 Hz, 1H), 1.22 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 141.6, 140.8, 138.7, 128.9, 128.7, 128.6, 128.5, 128.3, 126.2, 125.8, 55.9, 49.3, 41.8, 22.7.

(R)-N-((R)-1-(3-benzylphenyl)ethyl)-2-methylpropane-2-sulfinamide (**3b**): See Procedure Bb: 98 mg (0.32 mmol) of **2b**, 180 µL (176 mg, 0.81 mmol, 2.5 eq.) of benzyl boronic acid pinacol ester, 86 mg (0.62 mmol, 1.9 eq.) of potassium carbonate, 21 mg (0.029 mmol, 0.089 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 5 mL of 3:1 Acetone:Water. Compound **3b** (58 mg, 57.1 % yield) was isolated as a colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.23 (m, 3H), 7.24 – 7.14 (m, 5H), 7.11 (dt, *J* = 7.7, 1.4 Hz, 1H), 4.51 (qd, *J* = 6.5, 2.6 Hz, 1H), 3.99 (s, 2H), 3.39 (d, *J* = 2.6 Hz, 1H), 1.49 (d, *J* = 6.5 Hz, 3H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.3, 141.7, 140.8, 128.91, 128.87, 128.5, 128.3, 127.2, 126.1, 124.2, 55.4, 53.8, 41.9, 22.8, 22.6.

(R)-N-((R)-1-(3-benzylphenyl)propyl)-2-methylpropane-2-sulfinamide (**3c**): See Procedure Ba: 83 mg (0.28 mmol) of **2c**, 130 µL (127 mg, 0.58 mmol, 2.1 eq.) of benzyl boronic acid pinacol ester, 116 mg (0.84 mmol, 3.0 eq.) of potassium carbonate, 20 mg (0.027 mmol, 0.098 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 2.5 mL of 3:1 Acetone:Water. Compound **3c** (81 mg, 94.3 % yield) was isolated as a colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.23 (m, 3H), 7.21 – 7.07 (m, 6H), 4.23 (dt, *J* = 8.5, 4.6 Hz, 1H), 3.98 (s, 2H), 2.02 (dp, *J* = 13.2, 7.4 Hz, 1H), 1.73

(dq, *J* = 21.7, 7.3 Hz, 1H), 1.20 (s, 9H), 0.77 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.4, 141.4, 140.9, 128.9, 128.7, 128.5, 128.4, 127.9, 126.1, 124.9, 60.2, 55.7, 41.8, 29.3, 22.6, 10.0.

(R)-N-(5-benzyl-2-methylbenzyl)-2-methylpropane-2-sulfinamide (**3d**): See Procedure Bb: 89 mg (0.29 mmol) of **2d**, 200 µL (196 mg, 0.90 mmol, 3.1 eq.) of benzyl boronic acid pinacol ester, 82 mg (0.59 mmol, 2.0 eq.) of potassium carbonate, 22 mg (0.030 mmol, 0.10 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 4 mL of 3:1 Acetone:Water. Compound **3d** (65 mg, 70.4 % yield) was isolated as a tan solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.26 (m, 2H), 7.19 (t, *J* = 8.7 Hz, 3H), 7.12 – 7.07 (m, 2H), 7.05 (dd, *J* = 7.8, 1.9 Hz, 1H), 4.30 (dd, *J* = 13.3, 3.9 Hz, 1H), 4.18 (dd, *J* = 13.3, 8.8 Hz, 1H), 3.94 (s, 2H), 3.27 (dd, *J* = 9.1, 3.9 Hz, 1H), 2.31 (s, 3H), 1.20 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.0, 139.0, 136.2, 134.4, 130.6, 129.4, 128.9, 128.5, 128.3, 126.1, 55.9, 47.4, 41.5, 22.7, 18.6.

(R)-N-(5-benzyl-2-chlorobenzyl)-2-methylpropane-2-sulfinamide (**3e**): See Procedure Bb: 59 mg (0.18 mmol) of **2e**, 100 µL (98 mg, 0.45 mmol, 2.5 eq.) of benzyl boronic acid pinacol ester, 47 mg (0.34 mmol, 1.9 eq.) of potassium carbonate, 13 mg (0.018 mmol, 0.098 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 4 mL of 3:1 Acetone:Water. Compound **3e** (45 mg, 73.7 % yield) was isolated as a colorless oil that solidifies to a white solid on standing. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.24 (m, 3H), 7.21-7.18 (m, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 1H), 4.40 (dd, *J* = 14.4, 5.1 Hz, 1H), 4.27 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.93 (s, 2H), 3.60 (t, *J* = 6.8 Hz, 1H), 1.18 (d, *J* = 1.4 Hz, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.3, 136.0, 131.4, 130.5, 129.6, 129.5, 128.9, 128.6, 126.3, 56.1, 47.3, 41.2, 22.6.

(R)-N-(4-benzyl-2-(((tert-butylsulfinyl)amino)methyl)phenyl)acetamide (3g): See Procedure Ba: 125 mg (0.36 mmol) of **2g**, 140 µL (137 mg, 0.63 mmol, 1.8 eq.) of benzyl boronic acid pinacol ester, 136 mg (0.98 mmol, 2.7 eq.) of potassium carbonate, 29 mg (0.040 mmol, 0.11 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 3.2 mL of 3:1 Acetone:Water. Compound **3g** (94 mg, 72.8 % yield) was isolated as a yellow oil ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 7.79 (d,

J = 8.3 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.20 – 7.12 (m, 4H), 7.04 (d, *J* = 2.1 Hz, 1H), 4.20 (dd, *J* = 13.2, 6.0 Hz, 1H), 4.12 (dd, *J* = 13.3, 4.4 Hz, 1H), 3.90 (s, 2H), 3.65 (t, *J* = 5.3 Hz, 1H), 2.18 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.48, 140.67, 137.91, 134.64, 130.73, 129.71, 128.89, 128.74, 128.51, 126.19, 124.72, 56.34, 45.48, 41.28, 24.05, 22.84.

(R)-N-(4-benzyl-2-(((tert-butylsulfinyl)amino)methyl)phenyl)propionamide (3i): See Procedure Bb: 76 mg (0.21 mmol) of **2i**, 120 µL (118 mg, 0.54 mmol, 2.6 eq.) of benzyl boronic acid pinacol ester, 59 mg (0.43 mmol, 2.0 eq.) of potassium carbonate, 15 mg (0.020 mmol, 0.098 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 5 mL of 3:1 Acetone:Water. Compound 3i (68 mg, 86.8 % yield) was isolated as a yellow oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.23 – 7.11 (m, 4H), 7.05 (s, 1H), 4.19 (dd, *J* = 13.1, 6.2 Hz, 1H), 4.11 (dd, *J* = 13.1, 4.3 Hz, 1H), 3.92 (s, 2H), 3.55 (t, *J* = 5.2 Hz, 1H), 2.44 (q, *J* = 7.6 Hz, 2H), 1.25 – 1.21 (m, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.06, 140.73, 137.67, 134.78, 130.73, 129.71, 128.88, 128.50, 128.46, 126.18, 124.49, 56.27, 45.47, 41.28, 30.28, 22.83, 9.87.

(R)-N-(5-benzyl-2-methoxybenzyl)-2-methylpropane-2-sulfinamide (**3j**): See Procedure Bb: 149 mg (0.47 mmol) of **2j**, 200 µL (196 mg, 0.90 mmol, 1.9 eq.) of benzyl boronic acid pinacol ester, 193 mg (1.4 mmol, 3.0 eq.) of potassium carbonate, 33 mg (0.045 mmol, 0.096 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 3 mL of 3:1 Acetone:Water. Compound **3j** (98 mg, 63.5 % yield) was isolated. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 (ddd, *J* = 7.6, 6.3, 1.3 Hz, 2H), 7.20 – 7.13 (m, 3H), 7.09 – 7.04 (m, 2H), 6.77 (d, *J* = 9.0 Hz, 1H), 4.36 (dd, *J* = 13.8, 5.1 Hz, 1H), 4.10 (dd, *J* = 13.8, 8.0 Hz, 1H), 3.90 (s, 2H), 3.79 (s, 3H), 3.76 (dd, *J* = 8.0, 5.3 Hz, 1H), 1.17 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.8, 141.3, 133.2, 129.9, 129.0, 128.8, 128.4, 126.9, 126.0, 110.4, 55.9, 55.4, 45.5, 41.0, 22.6.

(R)-N-(5-benzyl-2-(trifluoromethoxy)benzyl)-2-methylpropane-2-sulfinamide (**3k**): See Procedure Bb: 141 mg (0.38 mmol) of **2k**, 110 µL (108 mg, 0.49 mmol, 1.3 eq.) of benzyl boronic acid pinacol ester, 94 mg (0.68 mmol, 1.8 eq.) of potassium carbonate, 28 mg (0.038 mmol, 0.10 eq.) of 1,1′-

Bis(diphenylphosphino)ferrocene]dichloropalladium, 5 mL of 3:1 Acetone:Water. Compound **3k** (105 mg, 72.3 % yield) was isolated as a tan solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 2H), 7.26 (s, 1H), 7.25 – 7.11 (m, 5H), 4.39 (dd, *J* = 14.5, 5.4 Hz, 1H), 4.26 (dd, *J* = 14.5, 7.7 Hz, 1H), 3.97 (s, 2H), 3.53 (dd, *J* = 7.7, 5.4 Hz, 1H), 1.19 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 145.6 (q, *J* = 1.5 Hz), 140.2, 140.1, 131.1, 130.5, 129.3, 128.9, 128.6, 126.4, 121.6, 120.6 (q, *J* = 1.4 Hz), 119.5, 56.03, 44.1, 41.2, 22.5.

(R)-N-(5-benzyl-2-ethoxybenzyl)-2-methylpropane-2-sulfinamide (**3l)**: See Procedure Ba: 119 mg (0.36 mmol) of **2l**, 160 µL (157 mg, 0.72 mmol, 2.0 eq.) of benzyl boronic acid pinacol ester, 151 mg (1.1 mmol, 3.1 eq.) of potassium carbonate, 29 mg (0.040 mmol, 0.11 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene] dichloropalladium, 2.5 mL of 3:1 Acetone:Water. Compound **3l** (87 mg, 70.7 % yield) was isolated as a colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.24 (m, 2H), 7.20 – 7.15 (m, 3H), 7.07 (d, *J* = 2.3 Hz, 1H), 7.05 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 4.39 (dd, *J* = 13.8, 5.1 Hz, 1H), 4.11 (dd, *J* = 13.8, 8.1 Hz, 1H), 4.02 (qd, *J* = 7.0, 1.1 Hz, 2H), 3.91 (s, 2H), 3.76 (dd, *J* = 8.3, 5.2 Hz, 1H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.2, 141.4, 133.0, 129.9, 129.0, 128.8, 128.4, 127.1, 126.0, 111.2, 63.6, 55.8, 45.6, 41.0, 22.6, 15.0.

(R)-N-(5-benzyl-2-propoxybenzyl)-2-methylpropane-2-sulfinamide (**3m**): See Procedure Ba: 122 mg (0.35 mmol) of **2m**, 130 µL (127 mg, 0.58 mmol, 1.7 eq.) of benzyl boronic acid pinacol ester, 135 mg (0.98 mmol, 2.8 eq.) of potassium carbonate, 25 mg (0.034 mmol, 0.098 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 2.5 mL of 3:1 Acetone:Water. Compound **3m** (92 mg, 73.1 % yield) was isolated as a yellow oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.26 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.20 – 7.14 (m, 3H), 7.08 (d, *J* = 2.3 Hz, 1H), 7.05 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 4.39 (dd, *J* = 13.8, 5.2 Hz, 1H), 4.12 (dd, *J* = 13.8, 8.2 Hz, 1H), 3.91 (t, *J* = 6.5 Hz, 2H), 3.90 (s, 2H) 3.76 (dd, *J* = 8.2, 5.2 Hz, 1H), 1.80 (h, *J* = 7.2 Hz, 2H), 1.17 (s, 9H), 1.04 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.3, 141.4, 133.0, 129.9, 129.0, 128.8, 128.4, 127.1, 126.0, 111.2, 69.6, 55.8, 45.6, 41.0, 22.7, 22.6, 10.7.

(R)-N-(5-benzyl-2-(cyclopropylmethoxy)benzyl)-2-methylpropane-2-sulfinamide (**3n**): See Procedure Ba: 48 mg (0.13 mmol) of **2n**, 60 µL (59 mg, 0.27 mmol, 2.0 eq.) of benzyl boronic acid pinacol ester, 56 mg (0.41 mmol, 3.1 eq.) of potassium carbonate, 10 mg (0.014 mmol, 0.10 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 3.25 mL of 3:1 Acetone:Water. Compound **3n** (41 mg, 82.8 % yield) was isolated as a colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 7.08 (d, *J* = 2.3 Hz, 1H), 7.04 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 4.43 (dd, *J* = 13.8, 5.1 Hz, 1H), 4.13 (dd, *J* = 13.8, 8.1 Hz, 1H), 3.91 (s, 2H), 3.86 (dd, *J* = 8.0, 5.3 Hz, 1H), 3.80 (qd, *J* = 9.9, 6.9 Hz, 2H), 1.28 – 1.22 (m, 1H), 1.20 (s, 9H), 0.68 – 0.58 (m, 2H), 0.33 (tdd, *J* = 4.8, 3.3, 2.2 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.3, 141.4, 133.1, 129.9, 128.9, 128.8, 128.4, 127.3, 126.0, 111.4, 72.8, 55.7, 45.9, 41.0, 22.6, 10.4, 3.2, 3.1.

(R)-N-(5-benzyl-2-(benzyloxy)benzyl)-2-methylpropane-2-sulfinamide (**3o**): See Procedure Ba: 500 mg (1.3 mmol) of **2o**, 590 µL (578 mg, 2.7 mmol, 2.0 eq.) of benzyl boronic acid pinacol ester, 564 mg (4.1 mmol, 3.1 eq.) of potassium carbonate, 98 mg (0.13 mmol, 0.10 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 2.5 mL of 3:1 Acetone:Water. Compound **3o** (363 mg, 70.6 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.35 (m, 4H), 7.34 – 7.25 (m, 3H), 7.21 – 7.15 (m, 3H), 7.12 (d, *J* = 2.2 Hz, 1H), 7.06 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 5.06 (s, 2H), 4.41 (dd, *J* = 14.0, 5.4 Hz, 1H), 4.20 (dd, *J* = 14.0, 7.8 Hz, 1H), 3.92 (s, 2H), 3.81 (dd, *J* = 7.8, 5.4 Hz, 1H), 1.13 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 154.9, 141.3, 136.9, 133.6, 130.0, 129.0, 128.9, 128.6, 128.5, 128.0, 127.32, 127.29, 126.1, 111.7, 70.1, 55.9, 45.6, 41.1, 22.6.

(R)-N-((R)-1-(5-benzyl-2-methoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide (**3p**): See Procedure Bb: 134 mg (0.40 mmol) of **2p**, 240 µL (235 mg, 1.1 mmol, 2.7 eq.) of benzyl boronic acid pinacol ester, 101 mg (0.73 mmol, 1.8 eq.) of potassium carbonate, 28 mg (0.038 mmol, 0.096 eq.) of 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium, 4 mL of 3:1 Acetone:Water. Compound **3p** (75 mg, 54.2 % yield) was isolated as a colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.23 (m, 2H), 7.21 – 7.13 (m, 3H), 7.09 (d, *J* = 2.2 Hz, 1H), 7.02 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.78 (d, *J* = 8.4 Hz,

1H), 4.75 (p, *J* = 6.5 Hz, 1H), 3.92 (s, 2H), 3.80 (s, 3H), 3.77 (d, *J* = 5.0 Hz, 1H), 1.44 (d, *J* = 6.7 Hz, 3H), 1.17 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 154.9, 141.4, 133.3, 132.2, 128.9, 128.6, 128.4, 127.4, 126.0, 110.9, 55.40, 55.37, 49.9, 41.1, 22.6, 21.9.

(3-benzylphenyl)methanaminium chloride (**4a**): See Procedure C: 123 mg (0.41 mmol) of **3a**, 0.4 mL HCl conc., 2 mL dioxane. Compound **4a** (85 mg, 89.1 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.38 – 7.32 (m, 2H), 7.32 – 7.23 (m, 4H), 7.23 – 7.19 (m, 2H), 7.19 – 7.12 (m, 1H), 4.07 (s, 2H), 4.00 (s, 2H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 142.6, 140.8, 133.2, 129.4, 129.1, 128.9, 128.5, 128.1, 126.3, 125.8, 42.9, 41.2.

(R)-1-(3-benzylphenyl)ethan-1-aminium chloride (**4b**): See Procedure C: 43 mg (0.14 mmol) of **3b**, 0.2 mL HCl conc., 2 mL dioxane. Compound **4b** (35 mg, Quantitative Yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.39 – 7.33 (m, 2H), 7.31 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.29 – 7.23 (m, 3H), 7.23 – 7.19 (m, 2H), 7.19 – 7.14 (m, 1H), 4.41 (q, *J* = 6.9 Hz, 1H), 4.01 (s, 2H), 1.61 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 142.6, 140.8, 138.4, 129.3, 129.0, 128.5, 128.1, 126.8, 125.8, 123.9, 51.0, 41.3, 19.4.

(R)-1-(3-benzylphenyl)propan-1-aminium chloride (**4c**): See Procedure C: 81 mg (0.25 mmol) of **3c**, 0.4 mL HCl conc., 2 mL dioxane. Compound **4c** (26 mg, 40.4 % yield) was isolated as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.38 (dd, *J* = 8.2, 6.9 Hz, 1H), 7.31 (t, *J* = 1.7 Hz, 1H), 7.29 – 7.23 (m, 4H), 7.23 – 7.14 (m, 3H), 4.11 (dd, *J* = 9.3, 5.9 Hz, 1H), 4.01 (s, 2H), 2.09 – 1.85 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 142.7, 140.8, 136.9, 129.4, 129.0, 128.5, 128.1, 127.5, 125.8, 124.5, 56.9, 41.3, 27.3, 9.1.

(5-benzyl-2-methylphenyl)methanaminium chloride (**4d**): See Procedure C: 65 mg (0.21 mmol) of **3d**, 0.3 mL HCl conc., 3 mL dioxane. Compound **4d** (42 mg, 82.3 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.29 (d, *J* = 1.7 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.21 – 7.10 (m, 5H), 4.11 (s, 2H), 3.94 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 141.0, 139.9, 134.3, 131.3, 130.7, 129.5, 129.4, 128.5, 128.1, 125.7, 40.9, 40.2, 17.2.

(5-benzyl-2-chlorophenyl)methanaminium chloride (**4e**): See Procedure C: 45 mg (0.30 mmol) of **3e**, 0.2 mL HCl conc., 2 mL dioxane. Compound **4e** (33 mg, 91.8 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.45 – 7.40 (m, 2H), 7.30 – 7.25 (m, 3H), 7.24 – 7.16 (m, 3H), 4.22 (s, 2H), 4.00 (s, 2H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 141.7, 140.3, 131.4, 131.1, 130.6, 129.6, 128.5, 128.3, 126.0, 40.6, 40.3.

(5-benzyl-2-hydroxyphenyl)methanaminium bromide (**4f**): See Procedure G: 103 mg (0.298 mmol) of **3l**, 900 µL 1M BBr_3 in DCM (0.90 mmol, 3.02 eq.), 5 mL DCM. Compound **4f** (64 mg, 73.0 % yield) was isolated as a yellow solid as the bromide salt. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.27 – 7.21 (m, 2H), 7.20 – 7.11 (m, 4H), 7.09 (dd, J = 8.2, 2.3 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 4.04 (s, 2H), 3.88 (s, 2H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 154.1, 141.5, 132.8, 130.8, 130.6, 128.4, 128.0, 125.6, 119.1, 114.8, 40.4, 39.4.

(2-acetamido-5-benzylphenyl)methanaminium chloride (**4g**): See Procedure C: 94 mg (0.26 mmol) of **3g**, 0.4 mL HCl conc., 2 mL dioxane. Compound **4g** (69 mg, 90.6 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.43 (s, 1H), 7.30 – 7.24 (m, 3H), 7.24 – 7.20 (m, 2H), 7.20 – 7.15 (m, 2H), 4.00 (s, 2H), 3.99 (s, 2H), 2.20 (s, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 173.9, 142.6, 142.1, 135.3, 132.2, 131.7, 130.2, 130.0, 129.7, 127.9, 127.4, 42.2, 40.9, 23.2.

(5-benzyl-2-(ethylamino)phenyl)methanaminium chloride (**4h**): See Procedure H: 21 mg (0.072 mmol) of **4g**, 260 µL (0.52 mmol, 7.2 eq.) of 2M BH_3*Me_2S in THF, and 4 mL of THF. Compound **4h** continued to the next step without further purification.

(5-benzyl-2-propionamidophenyl)methanaminium chloride (**4i**): See Procedure C: 68 mg (0.18 mmol) of **3i**, 0.2 mL HCl conc., 2 mL dioxane. Compound **4i** (50 mg, 89.9 % yield) was isolated as a yellow oil. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.38 (s, 1H), 7.31 – 7.12 (m, 7H), 3.99 (s, 2H), 3.94 (s, 2H), 2.46 (q, J = 7.0 Hz, 2H), 1.22 (t, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 176.1, 141.0, 140.5, 133.9, 130.8, 130.4, 128.7, 128.6, 128.2, 126.4, 126.0, 40.9, 40.0, 29.1, 9.0.

(5-benzyl-2-methoxyphenyl)methanaminium chloride (**4j**): See Procedure C: 98 mg (0.30 mmol) of **3j**, 0.3 mL HCl conc., 1 mL dioxane. Compound **4j** (44 mg, 56.4 % yield) was isolated as a

white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.27-7.23 (m, 3H), 7.21 – 7.12 (m, 4H), 6.99 (d, J = 8.3 Hz, 1H), 4.05 (s, 2H), 3.92 (s, 2H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 156.2, 141.3, 133.9, 131.0, 130.9, 128.4, 128.1, 125.7, 120.7, 110.5, 54.8, 40.4, 39.2.

(5-benzyl-2-(trifluoromethoxy)phenyl)methanaminium chloride (**4k**): See Procedure C: 105 mg (0.27 mmol) of **3k**, 0.2 mL HCl conc., 2 mL dioxane. Compound **4k** (76 mg, 87.8 % yield) was isolated as a yellow-white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.50 (d, J = 2.0 Hz, 1H), 7.39 (dd, J = 8.5, 1.9 Hz, 1H), 7.33 (dq, J = 8.5, 1.8 Hz, 1H), 7.31 – 7.14 (m, 5H), 4.18 (s, 2H), 4.04 (s, 2H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 145.6, 141.6, 140.2, 131.1, 130.9, 128.6, 128.3, 126.1, 125.4, 121.8, 120.5, 119.2, 40.5, 37.2.

(5-benzyl-2-ethoxyphenyl)methanaminium chloride (**4l**): See Procedure C: 70 mg (0.20 mmol) of **3l**, 0.4 mL HCl conc., 2 mL dioxane. Compound **4l** (37 mg, 65.7 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.24 (d, J = 7.0 Hz, 3H), 7.21 – 7.12 (m, 4H), 6.98 (d, J = 8.3 Hz, 1H), 4.13 (q, J = 6.6 Hz, 2H), 4.06 (s, 2H), 3.92 (s, 2H), 1.44 (t, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 155.4, 141.3, 133.8, 130.9, 130.7, 128.4, 128.1, 125.7, 120.8, 111.4, 63.7, 40.4, 39.0, 13.6.

(5-benzyl-2-propoxyphenyl)methanaminium chloride (**4m**): See Procedure C: 37 mg (0.10 mmol) of **3m**, 0.4 mL HCl conc., 2 mL dioxane. Compound **4m** (27 mg, 71.0 % yield) was purified via reverse phase chromatography and isolated as a colorless oil. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.27 – 7.22 (m, 3H), 7.20 – 7.13 (m, 4H), 6.98 (d, J = 8.4 Hz, 1H), 4.06 (s, 2H), 4.03 (t, J = 6.6 Hz, 2H), 3.92 (s, 2H), 1.86 (h, J = 7.2 Hz, 2H), 1.06 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 155.4, 141.3, 133.8, 130.9, 130.6, 128.4, 128.1, 125.7, 120.8, 111.4, 69.6, 40.4, 38.8, 22.0, 9.4.

(5-benzyl-2-(cyclopropylmethoxy)phenyl)methanaminium chloride (**4n**): See Procedure D: 43 mg (0.12 mmol) of **3n**, 0.2 mL HCl conc., 2 mL dioxane. Compound **4n** (20 mg, 56.9 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.27 – 7.21 (m, 3H), 7.21 – 7.13 (m, 4H), 6.97 (d, J = 8.4 Hz, 1H), 4.09 (s, 2H), 3.94 – 3.90 (m, 4H), 1.36 – 1.27 (m, 1H), 0.66 – 0.60 (m, 2H), 0.38 (dt, J = 6.1, 4.5 Hz, 2H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 155.5, 141.3, 133.9, 130.9, 130.6, 128.4, 128.1, 125.7, 120.9, 111.8, 73.0, 40.4, 38.9, 9.7, 2.2.

(5-benzyl-2-(benzyloxy)phenyl)methanaminium chloride (**4o**): See Procedure D: 57 mg (0.14 mmol) of **3o**, 0.3 mL HCl conc., 2 mL dioxane. Compound **4o** (31 mg, 65.3 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.50 – 7.45 (m, 2H), 7.41 – 7.36 (m, 2H), 7.35 – 7.30 (m, 1H), 7.28 – 7.21 (m, 4H), 7.21 – 7.14 (m, 3H), 7.07 – 7.01 (m, 1H), 5.19 (s, 2H), 4.10 (s, 2H), 3.92 (s, 2H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 155.1, 141.2, 136.8, 134.3, 130.9, 130.7, 128.4, 128.3, 128.1, 127.7, 127.3, 125.7, 121.1, 112.2, 70.0, 40.4, 38.8.

(R)-1-(5-benzyl-2-methoxyphenyl)ethan-1-aminium chloride (**4p**): See Procedure D: 29 mg (0.084 mmol) of **3p**, 0.4 mL HCl conc., 2 mL dioxane. Compound **4p** (20 mg, 85.8 % yield) was isolated as an off-yellow colorless oil (insoluble in diethyl ether). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.27 – 7.22 (m, 3H), 7.21 – 7.13 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 4.59 (q, J = 6.6 Hz, 1H), 3.93 (s, 2H), 3.89 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 155.3, 141.3, 134.1, 130.4, 128.4, 128.1, 127.5, 125.7, 125.3, 111.0, 54.8, 40.5, 17.6.

(S)-1-((3-benzylbenzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5a**): See Procedure D: Step 1: 16 mg (0.068 mmol) of **4a**, 120 µL (89 mg, 0.69 mmol, 10.1 eq.) of N,N-diisopropylethylamine, 39 mg (0.075 mmol, 1.1 eq.) of PyBOP, 12 mg (0.071 mmol, 1.0 eq.) of 6-Cl-HOBt, 28 mg (0.068 mmol, 1.0 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5a** (10 mg, 29.1 % yield) was isolated as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.25-7.21 (m, 2H), 7.18-7.12 (m, 4H), 7.06 (d, J = 7.7 Hz, 1H), 6.93 (s, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.46 (s, 2H), 4.30 (d, J = 14.7 Hz, 1H), 4.11 (d, J = 14.7 Hz, 1H), 3.92 (s, 2H), 3.83 (dd, J = 11.3, 4.8 Hz, 1H), 3.19 (dd, J = 13.6, 11.5 Hz, 1H), 2.96 (dd, J = 13.8, 4.8 Hz, 1H), 2.18 (s, 6H). No ^{13}C Data Acquired. ESI-MS: 389.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 36.25 min.

(S)-1-(((R)-1-(3-benzylphenyl)ethyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5b**): See Procedure D: Step 1: 14 mg (0.057 mmol) of **4b**, 100 µL (74 mg, 0.57 mmol, 10.2 eq.) of N,N-diisopropylethylamine, 31 mg (0.060 mmol, 1.1 eq.) of PyBOP, 11 mg (0.065 mmol, 1.2 eq.) of 6-Cl-HOBt, 26 mg (0.063 mmol, 1.1 eq.) of Boc-O-Boc-L-2',6'-

dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5b** (14.4 mg, 49.3 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.27 – 7.20 (m, 2H), 7.21 – 7.11 (m, 4H), 7.11 (s, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.54 (s, 2H), 4.79 (q, J = 6.7 Hz, 1H), 3.91 (s, 2H), 3.79 (dd, J = 11.5, 4.6 Hz, 1H), 3.21 (dd, J = 13.7, 11.6 Hz, 1H), 3.01 (dd, J = 13.8, 4.7 Hz, 1H), 2.28 (s, 6H), 1.10 (d, J = 7.0 Hz, 3H). No ^{13}C Data Acquired. ESI-MS: 403.2 $[M + H]^+$, HPLC (gradient A): Retention Time: 38.26 min.

(S)-1-(((R)-1-(3-benzylphenyl)propyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5c**): See Procedure D: Step 1: 18 mg (0.069 mmol) of **4c**, 140 µL (103 mg, 0.80 mmol, 11.7 eq.) of N,N-diisopropylethylamine, 45 mg (0.086 mmol, 1.3 eq.) of PyBOP, 14 mg (0.083 mmol, 1.2 eq.) of 6-Cl-HOBt, 30 mg (0.073 mmol, 1.1 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5c** (10 mg, 27.4 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.12 (d, J = 8.0 Hz, 1H), 7.25 – 7.11 (m, 6H), 7.10 (s, 1H), 7.09 – 7.00 (m, 2H), 6.52 (s, 2H), 4.51 (dd, J = 8.8, 6.5 Hz, 1H), 3.92 (s, 2H), 3.83 (dd, J = 11.5, 4.6 Hz, 1H), 3.23 (dd, J = 13.8, 11.5 Hz, 1H), 2.98 (dd, J = 13.8, 4.6 Hz, 1H), 2.29 (s, 6H), 1.47 (tt, J = 9.2, 4.6 Hz, 2H), 0.56 (t, J = 7.4 Hz, 3H). No ^{13}C Data Acquired. ESI-MS: 417.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 40.94 min.

(S)-1-((5-benzyl-2-methylbenzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5d**): See Procedure D: 20 mg (0.081 mmol) of **4d**, 170 µL (126 mg, 0.98 mmol, 12.1 eq.) of N,N-diisopropylethylamine, 54 mg (0.10 mmol, 1.3 eq.) of PyBOP, 20 mg (0.12 mmol, 1.5 eq.) of 6-Cl-HOBt, 39 mg (0.095 mmol, 1.3 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5d** (6 mg, 14.4 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.99 (s, 1H), 7.23 (t, J = 7.5 Hz, 2H), 7.14 (dd, J = 15.9, 7.6 Hz, 3H), 7.03 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.94 (s, 1H), 6.41 (s, 2H), 4.25 (dd, J = 14.7, 4.7 Hz, 1H), 4.16 (dd, J = 14.5, 5.0 Hz, 1H), 3.88 (s, 2H), 3.82 (dd, J = 11.3, 4.7 Hz, 1H), 3.15 (dd, J = 13.5, 11.5 Hz, 1H), 2.93 (dd, J = 13.7, 4.7 Hz, 1H), 2.10 (s, 6H), 2.03 (s, 3H). No ^{13}C Data Acquired. ESI-MS: 403.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 38.13 min.

(S)-1-((5-benzyl-2-chlorobenzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5e**): See Procedure D: 20 mg (0.075 mmol) of **4e**, 150 µL (111 mg, 0.86 mmol, 11.5 eq.) of N,N-diisopropylethylamine, 47 mg (0.090 mmol, 1.2 eq.) of PyBOP, 16 mg (0.094 mmol, 1.3 eq.) of 6-Cl-HOBt, 39 mg (0.095 mmol, 1.3 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5e** (18 mg, 44.9 % yield) was isolated as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.69-7.66 (m, 3H), 7.61-7.58 (m, 3H), 7.53 – 7.44 (m, 2H), 6.81 (s, 2H), 4.82 (d, J = 14.9 Hz, 1H), 4.67 (d, J = 14.8 Hz, 1H), 4.35 (s, 2H), 4.30 (dd, J = 11.4, 4.8 Hz, 1H), 3.57 (dd, J = 13.4, 11.6 Hz, 1H), 3.36 (dd, J = 13.9, 5.0 Hz, 1H), 2.53 (s, 6H). No ^{13}C Data Acquired. ESI-MS: 423.2 $[M + H]^+$, HPLC (gradient A): Retention Time: 38.05 min.

(S)-1-((5-benzyl-2-hydroxybenzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5f**): See Procedure D: 12 mg (0.041 mmol) of **4f**, 90 µL (67 mg, 0.52 mmol, 12.7 eq.) of N,N-diisopropylethylamine, 26 mg (0.050 mmol, 1.2 eq.) of PyBOP, 9 mg (0.053 mmol, 1.3 eq.) of 6-Cl-HOBt, 20 mg (0.049 mmol, 1.2 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5f** (7 mg, 28.1 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.88 (t, J = 5.7 Hz, 1H), 7.23 (t, J = 7.5 Hz, 2H), 7.18 – 7.07 (m, 3H), 6.92 (dd, J = 8.2, 2.2 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.39 (s, 2H), 4.20 (d, J = 3.8 Hz, 2H), 3.89 – 3.81 (m, 3H), 3.14 (dd, J = 14.0, 11.2 Hz, 1H), 2.94 (dd, J = 13.9, 4.8 Hz, 1H), 2.12 (s, 6H). No ^{13}C Data Acquired. ESI-MS: 405.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 33.69 min.

(S)-1-((2-acetamido-5-benzylbenzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5g**): See Procedure D: 31 mg (0.11 mmol) of **4g**, 190 µL (141 mg, 1.1 mmol, 10.2 eq.) of N,N-diisopropylethylamine, 58 mg (0.11 mmol, 1.0 eq.) of PyBOP, 19 mg (0.11 mmol, 1.1 eq.) of 6-Cl-HOBt, 44 mg (0.11 mmol, 1.0 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5g** (12 mg, 20.1 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.42 (d, J = 8.2 Hz, 1H), 7.27 – 7.20 (m, 2H), 7.20 – 7.09 (m, 4H), 6.89 (d, J = 2.0 Hz, 1H), 6.42 (s, 2H), 4.14 (d, J = 2.8 Hz, 2H), 3.93 (d, J = 2.9 Hz, 2H),

3.80 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.15 (dd, *J* = 13.9, 11.2 Hz, 1H), 2.96 (dd, *J* = 13.9, 5.0 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 6H). No ^{13}C Data Acquired. ESI-MS: 446.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 31.27 min.

(S)-1-((5-benzyl-2-(ethylamino)benzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5h**): See Procedure D: Step 1: 0.072 mmol of **4h**, 130 µL (96 mg, 0.75 mmol, 10.3 eq.) of N,N-diisopropylethylamine, 40 mg (0.077 mmol, 1.1 eq.) of PyBOP, 14 mg (0.083 mmol, 1.1 eq.) of 6-Cl-HOBt, 30 mg (0.073 mmol, 1.0 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5h** (15.9 mg, 40.4 % yield) was isolated as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.42 – 7.32 (m, 2H), 7.31 – 7.22 (m, 2H), 7.23 – 7.14 (m, 3H), 7.00 (d, *J* = 1.8 Hz, 1H), 6.35 (s, 2H), 4.22 (d, *J* = 15.0 Hz, 1H), 4.12 (d, *J* = 15.0 Hz, 1H), 4.03 (d, *J* = 3.4 Hz, 2H), 3.88 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.48 (qd, *J* = 7.2, 1.7 Hz, 2H), 3.12 (dd, *J* = 13.9, 11.5 Hz, 1H), 2.99 (dd, *J* = 13.9, 5.0 Hz, 1H), 2.03 (s, 6H), 1.45 (t, *J* = 7.2 Hz, 3H). No ^{13}C Data Acquired. ESI-MS:: 432.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 28.11 min.

(S)-1-((5-benzyl-2-propionamidobenzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5i**): See Procedure D: Step 1: 6 mg (0.020 mmol) of **4i**, 40 µL (30 mg, 0.23 mmol, 11.3 eq.) of N,N-diisopropylethylamine, 12 mg (0.023 mmol, 1.1 eq.) of PyBOP, 11 mg (0.065 mmol, 3.2 eq.) of 6-Cl-HOBt, 11 mg (0.027 mmol, 1.3 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5i** (6.4 mg, 56.7 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.20 (t, *J* = 6.1 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.18 – 7.11 (m, 4H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.41 (s, 2H), 4.12 (d, *J* = 3.1 Hz, 2H), 3.93 (d, *J* = 3.1 Hz, 2H), 3.80 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.15 (dd, *J* = 13.9, 11.3 Hz, 1H), 2.96 (dd, *J* = 13.9, 4.9 Hz, 1H), 2.44 (q, *J* = 7.6 Hz, 2H), 2.11 (s, 6H), 1.23 (t, *J* = 7.6 Hz, 3H). No ^{13}C Data Acquired. ESI-MS:: 460.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 32.89 min.

(S)-1-((5-benzyl-2-methoxybenzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5j**): See Procedure D: 22 mg (0.083 mmol) of **4j**, 170 µL (126 mg, 0.98 mmol, 11.8 eq.) of N,N-diisopropylethylamine, 51 mg (0.098 mmol, 1.2 eq.) of PyBOP, 19 mg (0.11

mmol, 1.4 eq.) of 6-Cl-HOBt, 43 mg (0.11 mmol, 1.3 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5j** (18 mg, 40.5 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.63 (t, J = 5.9 Hz, 1H), 7.25 (t, J = 7.6 Hz, 2H), 7.21 – 7.17 (m, 2H), 7.15 (tt, J = 7.2, 1.3 Hz, 1H), 7.10 (dd, J = 8.4, 2.3 Hz, 1H), 6.96 (d, J = 2.2 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.31 (s, 2H), 4.37 – 4.26 (m, 1H), 4.12 (dd, J = 14.2, 4.6 Hz, 1H), 3.89 – 3.83 (m, 3H), 3.67 (s, 3H), 3.10 (dd, J = 13.8, 11.6 Hz, 1H), 2.92 (dd, J = 13.8, 4.5 Hz, 1H), 2.03 (s, 6H). No ^{13}C Data Acquired. ESI-MS: 419.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 37.07 min.

(S)-1-((5-benzyl-2-(trifluoromethoxy)benzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5k**): See Procedure D: 19 mg (0.060 mmol) of **4k**, 110 µL (82 mg, 0.63 mmol, 10.5 eq.) of N,N-diisopropylethylamine, 32 mg (0.061 mmol, 1.0 eq.) of PyBOP, 11 mg (0.065 mmol, 1.1 eq.) of 6-Cl-HOBt, 29 mg (0.071 mmol, 1.2 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5k** (19 mg, 54.2 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.10 (t, J = 5.7 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.20 – 7.12 (m, 5H), 7.01 (s, 1H), 6.43 (s, 2H), 4.39 (dd, J = 15.1, 6.4 Hz, 1H), 4.23 (dd, J = 15.2, 4.7 Hz, 1H), 3.95 (d, J = 3.7 Hz, 2H), 3.89 (dd, J = 11.1, 5.0 Hz, 1H), 3.16 (dd, J = 13.9, 11.1 Hz, 1H), 2.97 (dd, J = 13.9, 5.0 Hz, 1H), 2.15 (s, 6H). No ^{13}C Data Acquired. ESI-MS: 473.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 42.11 min.

(S)-1-((5-benzyl-2-ethoxybenzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5l**): See Procedure D: 18 mg (0.065 mmol) of **4l**, 120 µL (89 mg, 0.69 mmol, 10.6 eq.) of N,N-diisopropylethylamine, 38 mg (0.073 mmol, 1.1 eq.) of PyBOP, 13 mg (0.077 mmol, 1.2 eq.) of 6-Cl-HOBt, 26 mg (0.063 mmol, 0.98 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5l** (15 mg, 42.4 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.35 (t, J = 5.7 Hz, 1H), 7.23 (t, J = 7.5 Hz, 2H), 7.21 – 7.16 (m, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.07 (dd, J = 8.4, 2.3 Hz, 1H), 6.93 (d, J = 2.2 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.30 (s, 2H), 4.33 (dd, J = 14.3, 7.0 Hz, 1H), 4.14 (dd, J = 14.3, 4.6 Hz, 1H), 3.93 – 3.84 (m,

5H), 3.08 (dd, *J* = 13.8, 11.6 Hz, 1H), 2.91 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.01 (s, 6H), 1.27 (t, *J* = 7.0 Hz, 3H). No ^{13}C Data Acquired. ESI-MS: 433.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 39.20 min.

(S)-1-((5-benzyl-2-propoxybenzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5m**): See Procedure D: 24 mg (0.065 mmol) of **4m**, 110 µL (82 mg, 0.63 mmol, 9.7 eq.) of N,N-diisopropylethylamine, 37 mg (0.071 mmol, 1.1 eq.) of PyBOP, 14 mg (0.083 mmol, 1.3 eq.) of 6-Cl-HOBt, 30 mg (0.073 mmol, 1.1 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5m** (17 mg, 46.7 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.31 (t, *J* = 5.8 Hz, 1H), 7.25-7.22 (m, 2H), 7.20 – 7.16 (m, 2H), 7.13 (t, *J* = 7.1 Hz, 1H), 7.06 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.30 (s, 2H), 4.36 (dd, *J* = 14.4, 7.0 Hz, 1H), 4.15 (dd, *J* = 14.4, 4.4 Hz, 1H), 3.89 – 3.85 (m, 3H), 3.80 (td, *J* = 6.6, 4.5 Hz, 2H), 3.08 (dd, *J* = 13.8, 11.6 Hz, 1H), 2.92 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.02 (s, 6H), 1.67 (h, *J* = 7.1 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). No ^{13}C Data Acquired. ESI-MS: 447.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 42.13 min.

(S)-1-((5-benzyl-2-(cyclopropylmethoxy)benzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5n**): See Procedure D: 17 mg (0.045 mmol) of **4n**, 140 µL (104 mg, 0.80 mmol, 18.0 eq.) of N,N-diisopropylethylamine, 35 mg (0.067 mmol, 1.5 eq.) of PyBOP, 13 mg (0.077 mmol, 1.7 eq.) of 6-Cl-HOBt, 28 mg (0.068 mmol, 1.5 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5n** (4 mg, 12.5 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.23 (t, *J* = 7.6 Hz, 2H), 7.20 – 7.16 (m, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.06 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.29 (s, 2H), 4.37 (d, *J* = 14.4 Hz, 1H), 4.18 (d, *J* = 14.4 Hz, 1H), 3.87 (s, 2H), 3.84 (dd, *J* = 11.7, 4.8 Hz, 1H), 3.74 – 3.61 (m, 2H), 3.08 (dd, *J* = 13.8, 11.5 Hz, 1H), 2.90 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.03 (s, 6H), 1.12 (ddd, *J* = 12.7, 8.0, 5.6 Hz, 1H), 0.56 (d, *J* = 7.5 Hz, 2H), 0.27 (dd, *J* = 7.1, 5.0 Hz, 2H). No ^{13}C Data Acquired. ESI-MS: 459.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 42.68 min.

(S)-1-((5-benzyl-2-(benzyloxy)benzyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5o**): See Procedure D: 17 mg (0.050 mmol) of **4o**, 100 µL (74

mg, 0.57 mmol, 11.5 eq.) of N,N-diisopropylethylamine, 31 mg (0.060 mmol, 1.2 eq.) of PyBOP, 10 mg (0.059 mmol, 1.2 eq.) of 6-Cl-HOBt, 24 mg (0.059 mmol, 1.2 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5o** (11 mg, 36.1 % yield) was isolated as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.44 – 7.38 (m, 1H), 7.36 (d, J = 4.4 Hz, 4H), 7.32 – 7.27 (m, 1H), 7.26 – 7.21 (m, 2H), 7.21 – 7.16 (m, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.08 (dd, J = 8.3, 2.2 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.29 (s, 2H), 4.95 (d, J = 4.3 Hz, 2H), 4.40 (dd, J = 14.4, 7.0 Hz, 1H), 4.17 (dd, J = 14.4, 4.3 Hz, 1H), 3.88 (s, 2H), 3.80 (dd, J = 11.4, 4.6 Hz, 1H), 3.06 (dd, J = 13.4, 11.8 Hz, 1H), 2.89 (dd, J = 13.8, 4.7 Hz, 1H), 1.98 (s, 6H). No ^{13}C Data Acquired. ESI-MS: 495.3 $[M + H]^+$, HPLC (gradient A): Retention Time: 44.98 min.

(S)-1-(((R)-1-(5-benzyl-2-methoxyphenyl)ethyl)amino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropan-2-aminium trifluoroacetate (**5p**): See Procedure D: 12 mg (0.043 mmol) of **4p**, 76 µL (56 mg, 0.44 mmol, 10.1 eq.) of N,N-diisopropylethylamine, 24 mg (0.046 mmol, 1.1 eq.) of PyBOP, 8 mg (0.047 mmol, 1.1 eq.) of 6-Cl-HOBt, 19 mg (0.046 mmol, 1.1 eq.) of Boc-O-Boc-L-2',6'-dimethyltyrosine, 3+1.5 mL of DMF. Step 2: 2 mL TFA and 2 mL DCM. Compound **5p** (7 mg, 29.6 % yield) was isolated as a white solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.52 (d, J = 8.0 Hz, 1H), 7.22 (dd, J = 8.2, 7.0 Hz, 2H), 7.16 – 7.09 (m, 3H), 7.02 – 6.94 (m, 2H), 6.82 (d, J = 8.3 Hz, 1H), 6.55 (s, 2H), 5.08 (p, J = 6.9 Hz, 1H), 3.87 (dd, J = 11.6, 4.7 Hz, 1H), 3.84 (s, 2H), 3.76 (s, 3H), 3.20 (dd, J = 13.7, 11.7 Hz, 1H), 3.02 (dd, J = 13.8, 4.8 Hz, 1H), 2.29 (s, 6H), 1.06 (d, J = 6.9 Hz, 3H). No ^{13}C Data Acquired. ESI-MS: 433.4 $[M + H]^+$, HPLC (gradient A): Retention Time: 40.43 min.

In Vitro Pharmacology

Cell Lines and Membrane Preparations.

All tissue culture reagents were purchased from Gibco Life Sciences (Grand Island, NY, U.S.) unless otherwise noted. C6-rat glioma cells stably expressing rat MOR (C6-MOR) or rat DOR (C6-DOR) and Chinese hamster ovary (CHO) cells stably expressing human KOR (CHO-KOR) were used for all *in*

vitro assays. Cells were grown to confluence at 37 °C in 5 % CO_2 in Dulbecco's modified Eagle medium (DMEM) containing 10 % fetal bovine serum and 5 % penicillin/streptomycin. Membranes were prepared by washing confluent cells three times with ice cold phosphate buffered saline (0.9 % NaCl, 0.61 mM Na_2HPO_4, 0.38 mM KH_2PO_4, pH 7.4). Cells were detached from the plates by incubation in warm harvesting buffer (20 mM HEPES, 150 mM NaCl, 0.68 mM EDTA, pH 7.4) and pelleted by centrifugation at 1600 rpm for 3 min. The cell pellet was suspended in ice-cold 50 mM Tris- HCl buffer, pH 7.4, and homogenized with a Tissue Tearor (Biospec Products, Inc., Bartlesville, OK, U.S.) for 20 s. The homogenate was centrifuged at 15,000 rpm for 20 min at 4 °C. The pellet was rehomogenized in 50 mM Tris-HCl with a Tissue Tearor for 10 s, followed by recentrifugation. The final pellet was resuspended in 50 mM Tris-HCl and frozen in aliquots at -80 °C. Protein concentration was determined via a BCA protein assay (Thermo Scientific Pierce, Waltham, MA, U.S.) using bovine serum albumin as the standard.

Radioligand Competition Binding Assays.

Radiolabeled compounds were purchased from Perkin-Elmer (Waltham, MA, U.S.). Opioid ligand binding assays were performed by competitive displacement of 0.2 nM [^{3}H]-diprenorphine (250 μCi, 1.85 TBq/mmol) by the peptidomimetic from membrane preparations containing opioid receptors as described above. The assay mixture, containing membranes (20 μg protein/tube) in 50 mM Tris-HCl buffer (pH 7.4), 0.2 nM [^{3}H]-diprenorphine, and various concentrations of test peptidomimetic, was incubated at room temperature on a shaker for 1 h to allow binding to reach equilibrium. The samples were rapidly filtered through Whatman GF/C filters using a Brandel harvester (Brandel, Gaithersburg, MD, U.S.) and washed three times with 50 mM Tris-HCl buffer, pH 7.4. Bound radioactivity on dried filters was determined by liquid scintillation counting, after saturation with EcoLume liquid scintillation cocktail, in a Wallac 1450 MicroBeta (Perkin-Elmer, Waltham, MA, U.S.). Nonspecific binding was determined using 10 μM naloxone. The results presented are the mean ± standard error (S.E.M.) from at least three separate assays performed in duplicate. K_i (nM) values were calculated using nonlinear

regression analysis to fit a logistic equation to the competition data using GraphPad Prism, version 6.0c, (GraphPad Software Inc., La Jolla, CA).

[^{35}S]-GTPγS Binding Assays.

Agonist stimulation of [^{35}S]guanosine 5′-O-[γ- thio]triphosphate ([^{35}S]-GTPγS, 1250 Ci, 46.2 TBq/mmol) binding to G protein was measured as described previously.[35] Briefly, membranes (10 μg of protein/well) were incubated for 1 h at 25°C in GTPγS buffer (50 mM Tris-HCl, 100 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.4) containing 0.1 nM [^{35}S]-GTPγS, 30 μM guanosine diphosphate (GDP), and varying concentrations of test peptidomimetic. G protein activation following receptor activation by peptidomimetic was compared with 10 μM of the standard compounds [D-Ala2,N-MePhe4,Gly-ol]enkephalin (DAMGO) at MOR, D-Pen2,5- enkephalin (DPDPE) at DOR, or U69,593 at KOR. The reaction was terminated by vacuum filtration through GF/C filters that were washed 5 times with GTPγS buffer. Bound radioactivity was measured as described above. The results are presented as the mean ± standard error (S.E.M.) from at least three separate assays performed in duplicate; potency (EC_{50} (nM)) and percent stimulation were determined using nonlinear regression analysis with GraphPad Prism 6, as above.

K_e Determination.

Agonist stimulation of [^{35}S]GTPγS binding by the known standard agonist DPDPE at delta opioid receptor was measured as described above. This was then compared to [^{35}S]GTPγS binding stimulated by DPDPE in the presence of test compound. Both conditions produced 100% stimulation relative to DPDPE. The fold difference between the EC_{50} of DPDPE alone and in the presence of test compound is defined as the shift in dose response. The K_e was then calculated as K_e = (concentration of test compound)/ (Dose response shift – 1). The results presented are the mean ± SEM from three individual assays performed in duplicate and then averaged. The data were fitted to a non-linear regression curve (sigmoidal dose response curve for agonist stimulation) using GraphPad Prism v8.01.

Mouse Liver Microsome Stability Assays

All liver microsome assays were performed by Quintara Biosciences. Metabolic stability of testing compounds was evaluated using mouse liver microsomes to predict intrinsic clearance. Mouse liver microsome tissue fractions were obtained from Corning or BioreclamationIVT. The assay was carried out in 96-well microtiter plates at 37°C. Reaction mixtures (25 μL) contained a final concentration of 1 μM test compound, 0.1 mg/mL liver microsome protein, and 1 mM NADPH in 100 mM potassium phosphate, pH 7.4 buffer with 3 mM $MgCl_2$. At each of the time points (0, 15, 30, and 60 minutes), 150 μL of quench solution (acetonitrile with 0.1% formic acid) with internal standard (bucetin) was transferred to each well. Verapamil was included as a positive control to verify assay performance. Plates were sealed, vortexed, and centrifuged at 4°C for 15 minutes at 4000 rpm. The supernatant was transferred to fresh plates for LC/MS/MS analysis. All samples were analyzed on LC/MS/MS using an AB Sciex API 4000 instrument, coupled to a Shimadzu LC-20AD LC Pump system. Analytical samples were separated using a Waters Atlantis T3 dC18 reverse phase HPLC column (20 mm x 2.1 mm) at a flow rate of 0.5 mL/min. The mobile phase consists of 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B). The extent of metabolism was calculated as the disappearance of the test compound, compared to the 0-min time incubation. Initial rates were calculated for the compound concentration and used to determine $t_{1/2}$ values and subsequently, the intrinsic clearance.

Supporting Information:

Molecular Formula Strings (CSV)

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Author Contributions:

Synthesis was carried out by S.P.H. The research project was designed by S.P.H., J.R.T, and H.I.M. In vitro assays were carried out by T.J.F., J.P.A., and N.W.G.

Conflicts of Interest:

The authors declare no competing financial interest.

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Abbreviations Used:

Alk-Br, Alkyl bromide; BCA, bicinchoninic acid; BH_3*Me_2S, borane dimethyl sulfide complex; BnBPin, benzylboronic acid pinacol ester; CHO, Chinese hamster ovary; CL_{INT}, intrinsic clearance; CPM, cyclopropyl methyl; DAMGO, [D-Ala2,N-MePhe4,Gly-ol]enkephalin; DI, deionized; DiBocDMT, N-Boc-O-Boc-2',6'-dimethyl-L-tyrosine; DIEA, N,N-diisopropylethylamine; DPDPE, D-Pen2,5- enkephalin; DMEM, Dulbecco's modified Eagle medium; DMT, 2',6'-dimethyl-L-tyrosine; DNS, does not stimulate; DOR, δ-opioid receptor; GTPγS, guanosine 5′-O-[γ- thio]triphosphate; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; 6-Cl-HOBt, 6-chloro-1-hydroxybenzotriazole; KOR, κ-opioid receptor; MLM, mouse liver microsome; MOR, μ-opioid receptor; $Pd(dppf)Cl_2$, [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride; PyBOP, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate; SEM, standard error of the mean; TEA, triethylamine; THQ, 1,2,3,4-tetrahydroquinoline; DIPP[Ψ]-NH_2, H-Dmt-TicΨ[CH_2NH]Phe-Phe-NH_2.

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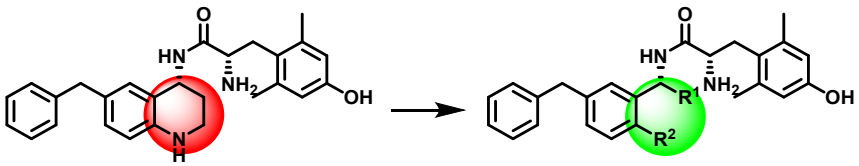
Table of Contents Graphic



Tetrahydroquinoline Lead Peptidomimetic in Bicyclic Core Opioid Series MLM $T_{1/2}$=3.1±0.1 min.

This Work: Monocyclic Core Opioid Series R=Alkyl, Hydroxyl, Ethers, Anilines, Chloro R^2=Ethers Retain Opioid Profile, Improved Metabolic Stability