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Design, Synthesis, and Structure−Activity Relationship Studies of (4-Alkoxyphenyl)glycinamides and Bioisosteric 1,3,4-Oxadiazoles as GPR88 Agonists

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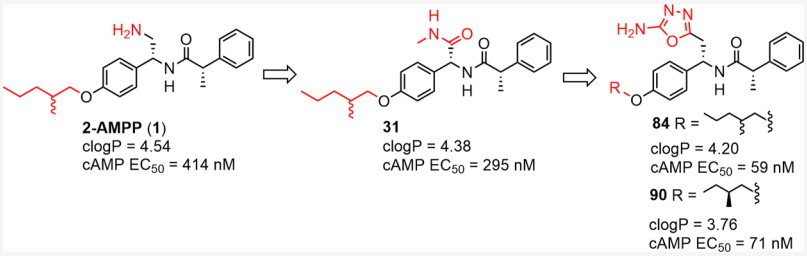

ABSTRACT: Increasing evidence implicates the orphan G protein-coupled receptor 88 (GPR88) in a number of striatal-associated disorders. In this study, we report the design and synthesis of a series of novel (4-alkoxyphenyl)glycinamides (e.g., **31**) and the corresponding 1,3,4-oxadiazole bioisosteres derived from the 2-AMPP scaffold (**1**) as GPR88 agonists. The 5-amino-1,3,4-oxadiazole derivatives (**84**, **88**−**90**) had significantly improved potency and lower lipophilicity compared to 2-AMPP. Compound **84** had an EC_{50} of 59 nM in the GPR88 overexpressing cell-based cAMP assay. In addition, **84** had an EC_{50} of 942 nM in the [^{35}S]GTPγS binding assay using mouse striatal membranes but was inactive in membranes from GPR88 knockout mice, even at a concentration of 100 μM. In vivo pharmacokinetic testing of **90** in rats revealed that the 5-amino-1,3,4-oxadiazole analogues may have limited brain permeability. Taken together, these results provide the basis for further optimization to develop a suitable agonist to probe GPR88 functions in the brain.

INTRODUCTION

The orphan G protein-coupled receptor 88 (GPR88) has recently attracted considerable interest in studying its biological functions, mainly through genetic interference. GPR88 is highly expressed in the striatum of the brain and is involved in both the striatonigral and striatopallidal pathways, suggesting that the receptor may play a role in regulating striatal functions.[1−5] Genetic knockout[6−15] and transcriptional profiling studies[3,16−20] in rodents have suggested that GPR88 plays an important role in regulating the dopaminergic system and is implicated in a number of disorders such as Parkinson's disease, schizophrenia, anxiety, and drug addiction. Additionally, human genetic studies have demonstrated positive associations between the *Gpr88* gene and schizophrenia[21] and evidence that a *Gpr88* variant was linked to childhood speech delay, learning disabilities, and chorea, indicating the relevance of GPR88 in the genetic risk for these diseases.[22] Taken together, both animal and human data suggest that GPR88 is a potential novel drug target.

To date, the endogenous ligand for GPR88 has not been discovered. GPR88 is most closely related to the biogenic amine receptors and has the highest sequence homology with the 5-HT_{1d} receptor and the β_3 adrenergic receptor (27 and 21% identity, respectively).[1] Chemogenomic analysis, based on the alignment of 30 critical residues predicted to line the binding cavity of G protein-coupled receptors, clustered GPR88 with metabotropic glutamate and $GABA_B$ receptors.[23] In order to characterize GPR88 signaling mechanisms and biological functions, our laboratory, as well as others, has carried out a medicinal chemistry campaign to develop GPR88 synthetic agonist probes.[24−32] We have previously reported that a synthetic small-molecule, 2-PCCA [(1*R*,2*R*)-2-(pyridin-2-yl)cyclopropane carboxylic acid ((2*S*,3*S*)-2-amino-3-methylpentyl)-(4′-propylbiphenyl-4-yl)amide, Figure 1], was able to activate GPR88 through a Gα_i-coupled signaling pathway in our time-resolved fluorescence energy transfer (TR-FRET)-based Lance cAMP assay in GPR88 overexpressing CHO cells.[26] Recently, we have demonstrated that a potent, selective,

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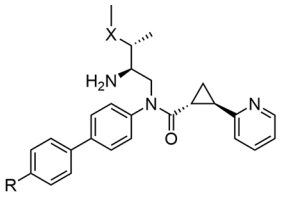

2-PCCA, R = *n*-Pr, X = CH_2, cAMP EC_{50} = 56 nM
RTI-13951-33, R = CH_3OCH_2, X = O, cAMP EC_{50} = 25 nM

Figure 1. 2-PCCA scaffold-based GPR88 agonists.

and brain-penetrant GPR88 agonist RTI-13951-33 (Figure 1), derived from the 2-PCCA scaffold, significantly reduced alcohol self-administration and alcohol intake in a dose-dependent manner in rats when administered intraperitoneally and at doses that did not affect the locomotor activity and sucrose self-administration.[29] These findings support the development and pharmacological validation of GPR88 agonists as a potential therapeutic to treat alcohol addiction.

2-AMPP [(2*S*)-*N*-((1*R*)-2-amino-1-(4-(2-methylpentyloxy)-phenyl)ethyl)-2-phenylpropanamide (**1**, Figure 2)] is another

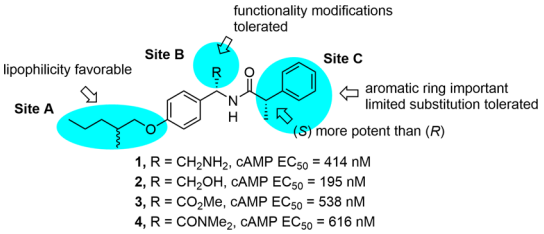

Figure 2. Structures of 2-AMPP (**1**) and **2**−**4** and preliminary SAR.

promising GPR88 agonist scaffold for medicinal chemistry optimization.[14,28,31] Early structure−activity relationship (SAR) studies of **1** have provided a preliminary understanding of receptor tolerances at three distinct sites for agonist activity (Figure 2).[28,31,32] For example, the lipophilicity of the alkoxy group on site A is favorable for potency. The amino group on site B can be replaced by other functionalities (e.g., hydroxyl **2**, ester **3**, and amide **4**), all of which have comparable or slightly improved EC_{50} values relative to **1**. Site C, on the other hand, has limited space for structural modifications, possibly involving a sterically defined aromatic stacking interaction with the GPR88 receptor.

2-AMPP was moderately potent with an EC_{50} of 414 nM in our TR-FRET-based Lance cAMP assay[28] and was reported to have a poor brain penetration because of its high lipophilicity (clog *P* = 4.53, calculated using Instant JChem 5.4.0, ChemAxon Ltd.).[31] Recently, 2-AMPP (referring to compound 19 in the literature[33]) was shown to have an EC_{50} of 634 nM in the BRET-based cAMP assay in GPR88 overexpressing HEK293 cells, which is in line with our EC_{50} value of this compound. We faced two major challenges for the development of 2-AMPP-based agonists as in vivo probes: (a) potency and (b) brain bioavailability. To address these questions, we planned to further explore the SAR on sites A and B and reasoned that both potency and brain permeability can be improved by fine-tuning the lipophilicity on site A and modifying the functionality on site B. Herein, we report the design, synthesis, and pharmacological evaluation of a series of (4-alkoxyphenyl)glycinols, (4-alkoxyphenyl)glycinamides, and the corresponding bioisosteric 1,3,4-oxadiazoles as GPR88 agonists.

RESULTS AND DISCUSSION

Chemistry. The overall synthetic approach followed the methods detailed in our earlier publication.[28] All the synthesized target compounds were characterized by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectra (HRMS) and determined to be >95% pure by high-performance liquid chromatography (HPLC) analyses. The characterization data are in agreement with the assigned structures. The reaction yield is presented in the Experimental Section. Compounds **12**−**28** were synthesized following procedures depicted in Scheme 1. Boc-protection of the amino group in (*R*)-2-phenylglycine methyl ester (**5**) afforded **6**. *O*-Alkylation of **6** with an appropriate alcohol under Mitsunobu conditions or via S_N2 substitution with an alkyl *p*-toluenesulfonate gave ethers **7**. Reduction of the methyl ester with sodium borohydride in the presence of lithium chloride, followed by the Boc group deprotection with HCl led to amino alcohols **8**. Boc-removal of **7**, followed by 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)-mediated coupling with (*S*)-2-phenylpropionic acid provided amides **11**. Alternatively, TIPS-protection of phenol **6** afforded **9**, which was subjected to Boc-deprotection, followed by HBTU-mediated coupling with (*S*)-2-phenylpropionic acid and TIPS-deprotection to furnish phenol **10**. Subsequent O-alkylation of the phenol group also provided the common intermediate **11**. Finally, coupling of **8** with (*S*)-2-phenylpropionic acid using HBTU or reduction of the ester function in **11** furnished the target alcohols **12**−**28**.

Synthesis of amides **30**−**69** is outlined in Scheme 2. Briefly, acids **29**, synthesized according to the procedure in our previous publication,[28] were coupled with an appropriate amine using the standard amide coupling reagents, such as Boc anhydride, EDC/HOBt, or by forming an acid chloride to give the target amides **30**−**69**.

Synthesis of 5-alkyl- and 5-amino-1,3,4-oxadiazoles is outlined in Schemes 3 and 4. As depicted in Scheme 3, the reaction of ester **3** or **11h**,[28] derived from 4-hydroxyphenylacetic acid, with hydrazine hydrate in refluxing ethanol afforded the corresponding hydrazides **70a,b**. Coupling of **70a,b** with trimethyl orthoformate or trimethyl orthoacetate in the presence of catalytic acid provided target 1,3,4-oxadiazoles **71**−**74**. On the other hand, oxadiazoles derived from 4-hydroxyphenylpropanoic acid were synthesized according to the procedure shown in Scheme 4. The reaction of acid **75** with acetyl chloride in methanol at 65 °C afforded the methyl ester **76**, which was protected with Boc anhydride to provide the Boc-protected amine **77**. The Mitsunobu reaction of **77** with the appropriate alcohol furnished the corresponding alkyl ethers **78a**−**f**. The removal of the Boc group from the amine followed by HBTU-mediated coupling with (*S*)-2-phenylpropionic acid provided amides **80a**−**f**. The ester function in **80** was converted to the corresponding hydrazide by heating the ester with hydrazine hydrate in ethanol. Finally, hydrazides **81a**−**f** were condensed with trimethyl orthoformate, trimethyl orthoacetate, or cyanogen bromide to furnish the target 1,3,4-oxadiazoles **82**−**91**.

Pharmacological Evaluation and SAR Study. All synthesized compounds in this study were evaluated for the GPR88 agonist activity in our previously established in vitro GPR88 Lance TR-FRET cAMP assay.[26] The TR-FRET signal

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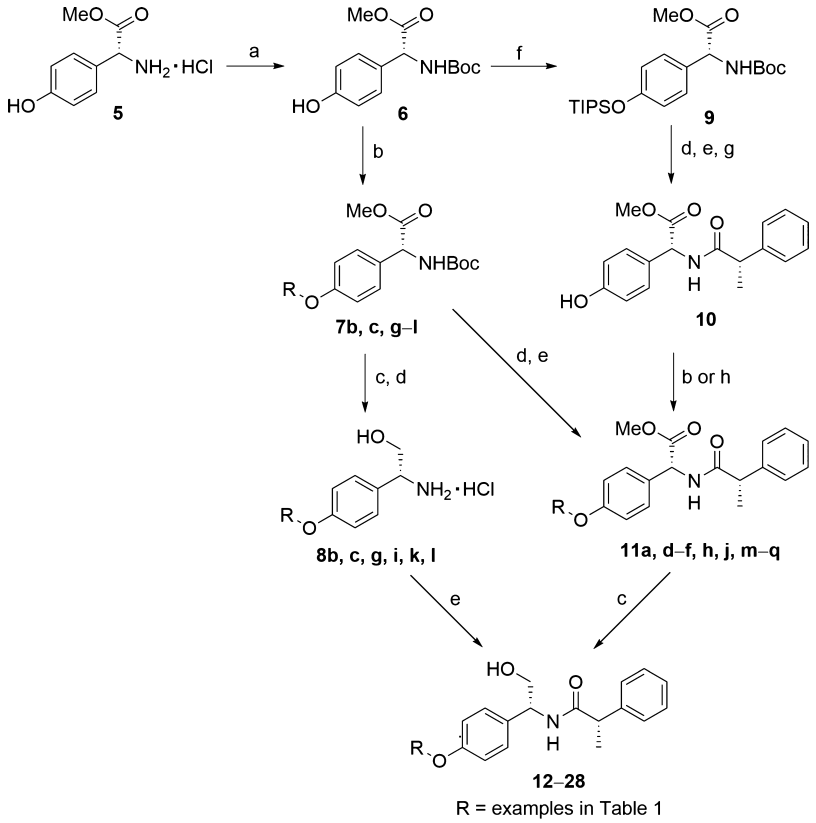
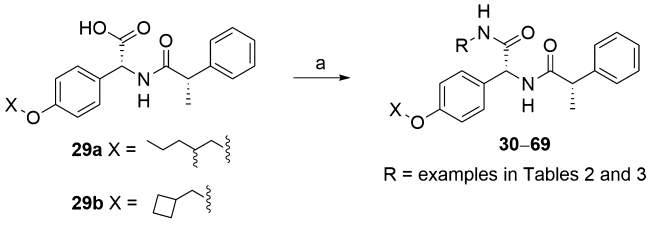
Scheme 1. Synthesis of Target Compounds 12−28[a]



[a]Reagents and conditions: (a) Boc_2O, DIPEA, DCM, rt, overnight; (b) PPh_3, DEAD, alcohol, THF, rt, overnight; (c) $NaBH_4$, LiCl, THF-EtOH (1:1), rt, 3 h; (d) 4 M HCl in dioxane, DCM, rt, 16 h; or TFA: DCM, rt, 6 h; (e) (*S*)-2-phenylpropionic acid, HBTU, TEA, MeCN, rt, 5 h; (f) TIPSCl, imidazole, DCM, rt, overnight; (g) TBAF, THF, 0 °C, 3 h; (h) alkyl *p*-toluenesulfonate, K_2CO_3 MeCN, 65 °C, overnight.

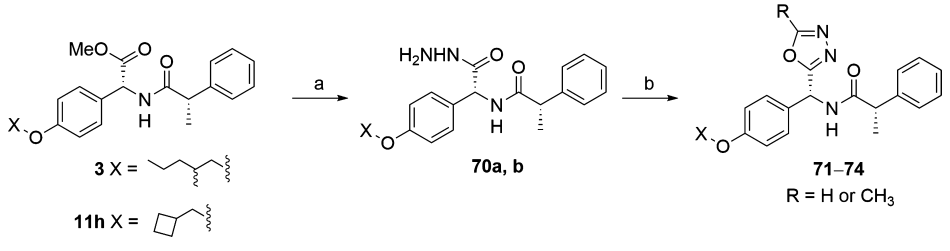
Scheme 2. Synthesis of Target Compounds 30−69[a]



[a]Reagents and conditions: Method A (a) pyridine, dioxane, NH_4HCO_3, Boc_2O, rt, overnight; Method B (a) EDC hydrochloride, HOBt, DIPEA, amine, DMF, rt, overnight; Method C (a) oxalyl chloride, DMF (cat.), DCM, rt; then amine, Et_3N, rt, overnight.

(665 nm) was converted to fmol cAMP by interpolating from the standard cAMP curve. fmol cAMP was plotted against the log of compound concentration, and data were fit to a three-parameter logistic curve to generate the maximum response (E_{max}) and EC_{50} values. In our assay, 2-PCCA had an E_{max} of 100 ± 2 (mean ± S.E.M.) and RTI-13951-33 had an E_{max} of 103 ± 2 relative to 2-PCCA. Collectively, all of the active compounds in this study had E_{max} values comparable to 2-PCCA and RTI-13951-33, except for compounds **28** and **43**, which had E_{max} values of 84 and 83%, respectively. These values might indicate that the compounds are partial agonists; however, it is important to note that E_{max} was calculated against synthetic agonists because the endogenous ligand for GPR88 has not yet been discovered. Figure 3 displays the concentration−response curves of representative compounds

Scheme 3. Synthesis of Target Compounds 71−74[a]



[a]Reagents and conditions: (a) hydrazine monohydrate, EtOH, reflux, 3 h; (b) $CH(OMe)_3$, PTSA, 85 °C, 2 h or $CH_3C(OMe)_3$, HOAc, *m*-xylene, reflux, 6 h.

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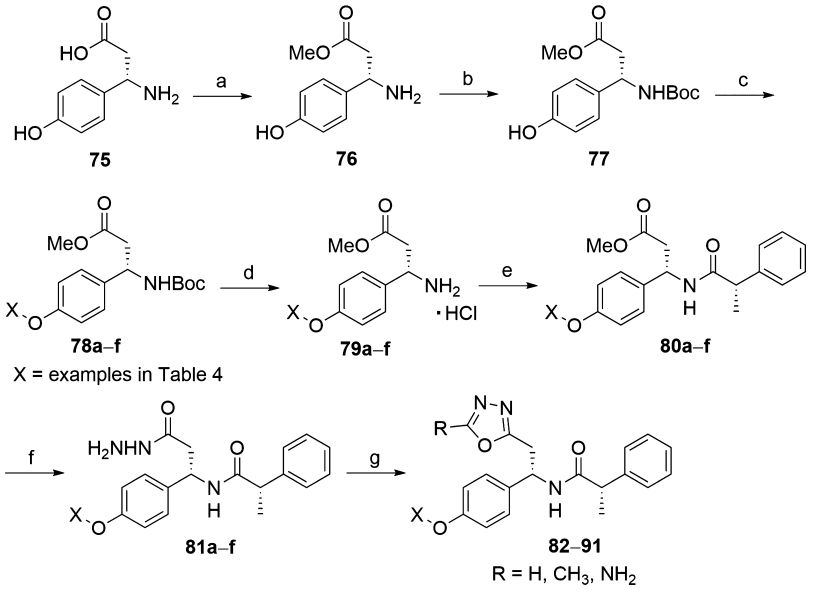
Scheme 4. Synthesis of Target Compounds 82−91[a]



[a]Reagents and conditions: (a) acetyl chloride, MeOH, reflux, overnight; (b) Boc_2O, DIPEA, DCM, rt, overnight; (c) PPh_3, DEAD, alcohol, rt, overnight; or alkyl *p*-toluenesulfonate, K_2CO_3, MeCN, 65 °C, overnight; (d) 4 M HCl in dioxane, DCM, rt, overnight; (e) (*S*)-2-phenylpropionic acid, HBTU, TEA, MeCN, rt, 5 h; (f) hydrazine monohydrate, EtOH, reflux, 3 h; (g) $CH(OMe)_3$, PTSA, 85 °C, 2 h; or $CH_3C(OMe)_3$, HOAc, *m*-xylene, reflux, 6 h; or CNBr, MeOH, reflux, 3 h.

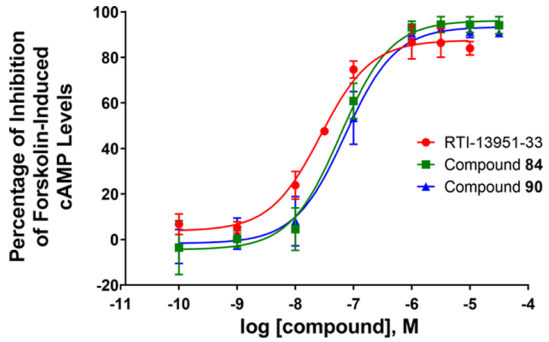


Figure 3. Concentration−response curves of RTI-13951-33, **84**, and **90** in the GPR88 Lance TR-FRET cAMP assay. The TR-FRET signal (665 nm) was converted to fmol cAMP by interpolating from the standard cAMP curve. Percent inhibition of forskolin-induced (300 nM) cAMP levels was plotted against the log of compound concentration, and data were fit to a three-parameter logistic curve to generate EC_{50} values. Each data point is the mean ± S.D. of at least three independent experiments performed in duplicate.

(RTI-13951-33, **84**, and **90**). Given the importance of an alkoxy substitution on site A in the 2-AMPP scaffold for GPR88 activity reported earlier, we first examined a series of ether analogues **12**−**28** by varying the length, shape, and steric and electronic properties, with the aim of identifying a side chain that can lower the lipophilicity while maintaining the potency of 2-{4-[(2-methylpentyl)oxy]phenyl}glycinol **2** (clog *P* = 4.64, EC_{50} = 195 nM). As can be seen from Table 1, the GPR88 agonist activity of this series was sensitive to the branching and length of the alkoxy side chain. First, the position of methyl branching was important for activity, as both 1-methylpentyl **12** (EC_{50} = 380 nM) and 4-methylpentyl **13** (EC_{50} = 282 nM) were less potent than the 2-methylpentyl analogue **2**. Second, the branched alkyl was more potent than the linear alkyl group, as exemplified by **16** (EC_{50} = 174 nM) relative to **14** (EC_{50} = 295 nM). Third, the length of the alkyl group was important as potency decreased from *n*-pentyl to *n*-propyl (**14**, **18**, and **20**). Among the three cyclic alkyl analogues (**17**, **19**, and **21**), only the cyclobutylmethyl **19** was favored with an EC_{50} of 234 nM. Attempts to add an additional oxygen atom into the side chain to reduce clog *P* resulted in a 10-fold loss of activity (**22**, **23**). In general, the GPR88 agonist activity was correlated with the lipophilicity of the compounds. The potency decreased as the clog *P* of compounds **12**−**23** decreased. Compounds **16** and **19** with an (*S*)-2-methylbutyl and a cyclobutylmethyl group, respectively, provided the best balance between potency and lipophilicity. To further explore SAR of the cyclobutylmethyl **19**, we synthesized and tested a series of substituted analogues **24**−**28**. Unfortunately, all of these compounds suffered from loss of potency; in particular, **24**, **26**, and **27** were completely inactive, suggesting that there is a limited steric tolerance in this side-chain position.

We next investigated site B with a rationale that modification of the amide functionality on this site would improve the potency of **4** (EC_{50} = 616 nM, Figure 2). In addition, amide formation with a variety of readily available amines can rapidly expand the structural diversity for SAR. To this end, we performed an in-depth examination of the substitution effects on the amide nitrogen by varying the size, lipophilicity, polarity, and electronic properties. The study began with the aliphatic substitutions on the amide nitrogen, as shown in Table 2. The primary amide **30** was equipotent to the tertiary *N*-dimethyl **4**, whereas a monomethyl group (**31**) improved the potency by twofold. The agonist activity increased further with an ethyl group (**32**), decreased with an *n*-propyl group (**33**), and then maintained a moderate potency (EC_{50} = 200−300 nM) with small-to-large-sized alkyl substitutions (**34**−**42**) except for cyclohexyl (**43**). The *N*-ethyl analogue **32** (EC_{50} = 120 nM) emerged as the most potent compound in the amide series. Further modifications by adding polar functionalities at the terminal end of *N*-ethyl, such as ester (**44**), hydroxyl (**45**), ether (**46**, **47**), carbamate (**48**, **50**), and amine (**49**), led to a

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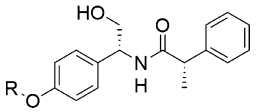
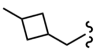
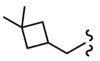
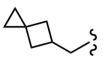
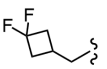
Table 1. Biological Data of 4-Alkoxyphenylglycinols



Compound	R	clogP[a]	cAMP pEC_{50} (EC_{50}, nM)[b]	E_{max}[c]
2-PCCA		6.19	7.14 ± 0.02 (73)	100 ± 2
RTI-13951-33		3.34	7.33 ± 0.05 (47)	103 ± 2
2	2-Methylpentyl	4.64	6.71 ± 0.09 (195)	100 ± 4
12	1-Methylpentyl	4.69	6.42 ± 0.03 (380)	96 ± 6[d]
13	4-Methylpentyl	4.56	6.55 ± 0.05 (282)	96 ± 1
14	*n*-Pentyl	4.28	6.53 ± 0.08 (295)	98 ± 3
15	2-Methylbutyl	4.20	6.60 ± 0.10 (251)	103 ± 2[d]
16	(*S*)-2-Methylbutyl	4.20	6.76 ± 0.08 (174)	97 ± 3[d]
17	Cyclopentylmethyl	4.18	6.59 ± 0.01 (257)	104 ± 1[d]
18	*n*-Butyl	3.83	6.42 ± 0.07 (380)	105 ± 13
19	Cyclobutylmethyl	3.73	6.63 ± 0.05 (234)	91 ± 8
20	*n*-Propyl	3.39	6.25 ± 0.04 (562)	98 ± 3
21	Cyclopropylmethyl	3.29	6.20 ± 0.04 (631)	96 ± 5
22	4-Methoxybutyl	3.04	5.33 ± 0.08 (4677)	95 ± 1
23	3-Methoxypropyl	2.52	5.23 ± 0.06 (5888)	94 ± 3
24		4.11	<5.00	N.D.
25		4.02	6.51 ± 0.04 (309)	97 ± 4[d]
26		4.32	<5.00	N.D.
27		3.86	<5.00	N.D.
28		3.22	5.89 ± 0.05 (1288)	84 ± 3[d]

[a]clog *P* was calculated using Instant JChem 5.4.0 (ChemAxon Ltd.). [b]pEC_{50} values are means ± standard error of at least three independent experiments performed in duplicate. [c]E_{max} value is % of 2-PCCA (mean ± standard error). [d]E_{max} value is % of RTI-13951-33 (mean ± standard error). N.D., not determined.

significant loss of potency. Interestingly, compounds (**49**, **51**−**54**) with a protonatable nitrogen had the least activity. This SAR trend was also observed in the amide analogues with aromatic substitutions (Table 3). Phenyl and benzyl groups (**55**, **56**) were favorable with an EC_{50} of 245 and 219 nM, respectively, whereas pyridine rings (**57**−**59**), capable of forming a salt to improve aqueous solubility, were less active. Other polar five-membered heterocycles (**60**−**69**) were also poorly tolerated. It appeared that the activity deteriorated with heterocycles containing more heteroatoms. It should be noted that although two different side chains (2-methylpentyl and cyclobutylmethyl) on site B were used in Table 3, there was little difference in potency contributions between the two groups (**60** vs **61**). Overall, the SAR suggested that compounds with a lipophilic alkyl substitution on the amide nitrogen tend to have better potency.

Bioisosteric replacement is an essential tool in the SAR study to improve potency, selectivity, and pharmacokinetics (PKs).[34] The oxadiazole moiety is stable to chemical and enzymatic degradation and capable of forming a hydrogen bond; therefore, it has been broadly used as a nonclassical bioisostere for ester and amide functionalities.[35] Because the 1,3,4-oxadiazoles have a lower lipophilicity (in general, an order of magnitude of clog *P*) compared to its 1,2,4-isomers, we selected 1,3,4-oxadiazole as our initial testing set. Replacement of the amide group in **4** with a 1,3,4-oxadiazole or a 5-methyl-1,3,4-oxadiazole moiety gave analogues **71** and **72**, respectively, which were equipotent to **4** with EC_{50} values in the 500−600 nM range (Table 4). There was no difference in potency between the 2-methylpentyl and cyclobutylmethyl side chains (**73**, **74** vs **71**, **72**). Interestingly, the addition of a methylene linker between the oxadiazole moiety and the benzylic carbon led to a 5-fold increase in potency (**82**, **83** vs **71**, **72**). Further modification by attaching an amino group to the 5-position gave the most potent compound **84** (EC_{50} = 59 nM) in the series. Attempts to lower the lipophilicity by exchanging the 2-methylpentyl side chain in **82**−**84** with the cyclobutylmethyl group, unfortunately, resulted in less active compounds **85**−**87**. After identifying a favorable 1,3,4-oxadiazole pharmacophore on site B, we turned our attention back to the side chain on site A, in which we reasoned that the chiral center of the methyl branching might have an impact on the potency. The (*S*)-isomer **88** and the (*R*)-isomer **89** had equivalent GPR88 activity with EC_{50} values of 78 and 74 nM, respectively, in line with the EC_{50} value of the racemic mixture **84**. However, in the case of the 2-methylbutyl side chain, (*S*)-**90** was approximately twofold more potent than (*R*)-**91**, which is consistent with the observation in the corresponding hydroxyl (on site B)

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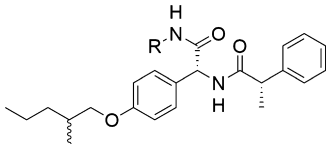
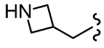
Table 2. Biological Data of 4-Alkoxyphenylglycinamides



Compound	R	cAMP pEC_{50} (EC_{50}, nM)[a]	E_{max}[b]
4		6.21 ± 0.08 (616)	97 ± 4
30	H	6.24 ± 0.07 (575)	97 ± 7
31	Methyl	6.53 ± 0.08 (295)	116 ± 4
32	Ethyl	6.92 ± 0.11 (120)	99 ± 4[c]
33	*n*-Propyl	6.40 ± 0.04 (398)	113 ± 8
34	*i*-Propyl	6.74 ± 0.04 (182)	102 ± 3
35	*t*-Butyl	6.50 ± 0.01 (316)	109 ± 10[c]
36	Butan-2-yl	6.61 ± 0.04 (245)	96 ± 3
37	3-Methylbutan-2-yl	6.67 ± 0.07 (214)	93 ± 6[c]
38	Cyclopropyl	6.62 ± 0.04 (240)	98 ± 4
39	Cyclopropylmethyl	6.68 ± 0.09 (209)	94 ± 4[c]
40	Cyclobutyl	6.55 ± 0.04 (282)	98 ± 2
41	1-Methylcyclobutyl	6.63 ± 0.04 (234)	91 ± 4[c]
42	Cyclopentyl	6.68 ± 0.01 (209)	107 ± 4[c]
43	Cyclohexyl	6.25 ± 0.07 (562)	83 ± 2[c]
44	$MeOOCCH_2$	6.33 ± 0.05 (468)	103 ± 8
45	$HOCH_2CH_2$	6.37 ± 0.12 (427)	99 ± 4
46	$MeOCH_2CH_2$	6.27 ± 0.02 (537)	107 ± 11
47		6.33 ± 0.04 (468)	110 ± 1[c]
48	$BocNHCH_2CH_2$	6.05 ± 0.07 (891)	97 ± 7[c]
49	$NH_2CH_2CH_2$	5.10 ± 0.05 (7943)	129 ± 4[c]
50	$MeN(Boc)CH_2CH_2$	6.29 ± 0.03 (513)	111 ± 1[c]
51	$MeNHCH_2CH_2$	5.26 ± 0.06 (5495)	122 ± 4[c]
52	$Me_2NCH_2CH_2$	5.26 ± 0.06 (5495)	103 ± 4[c]
53		5.47 ± 0.07 (3388)	120 ± 5[c]
54		<5.00	N.D.

[a] pEC_{50} values are means ± standard error of at least three independent experiments performed in duplicate. [b] E_{max} value is % of 2-PCCA (mean ± standard error). [c] E_{max} value is % of RTI-13951-33 (mean ± standard error). N.D., not determined.

analogues that (*S*)-2-methylbutyl **16** is slightly more potent than racemic **15** (Table 1).

To further characterize the GPR88 agonist activity, we tested our best compound in the [^{35}S]GTPγS binding assay using mouse striatal membrane preparations. RTI-13951-33 (cAMP: EC_{50} = 25 nM) increased [^{35}S]GTPγS binding with an EC_{50} = 535 nM (E_{max} = 200%).[29] E_{max} is expressed as percentage of activation above the basal binding, which is set as 100%, and the basal binding refers to binding in the absence of the agonist. Compound **84** also exhibited strong enhancement of the [^{35}S]GTPγS binding activity (EC_{50} = 942 nM, E_{max} = 229%) in mouse striatal membranes (Figure 4). Importantly, the compound was inactive in membranes prepared from GPR88 KO mice at concentrations tested up to 100 μM, indicating that it had a GPR88-specific agonist signaling activity in the striatum. It is worth noting that although the GPR88 agonist activity in the [^{35}S]GTPγS binding assay using a native tissue system is approximately 10- to 20-fold less potent than the cAMP assay in a GPR88 overexpressing cell line, the rank order of the potency of compounds is consistent between the two assay systems.

Solubility and Preliminary PK Studies. One of the major challenges for the development of GPR88 probes is their ability to cross the blood−brain barrier (BBB) and have sufficient brain exposure to modulate receptor functions. Calculated physicochemical properties, such as lipophilicity (clog *P*) and topological polar surface area (TPSA), are useful indicators of a successful CNS drug. In general, a balance between clog *P* (2−4)[36] and TPSA (<76 Å^2)[37] would lead to good solubility and BBB permeability. Therefore, we tested the kinetic aqueous solubility (at pH = 7.4) and PK properties of select compounds to determine their drug-likeness. PK data for the in vivo effective agonist RTI-13951-33 are also presented for comparison.[29] As shown in Table 5, both compounds **1** and **84** have a poor solubility of <1 μM, which is expected for compounds with a high clog *P* (4.53 and 4.20, respectively). Compound **90** (clog *P* = 3.76) has an increased solubility of 2.9 ± 0.3 μM, which confirms that while solubility is a challenge we still face, lowering lipophilicity does improve

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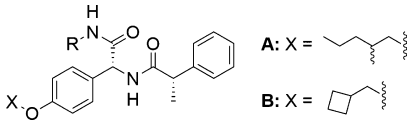
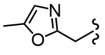
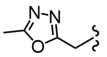
Table 3. Biological Data of 4-Alkoxyphenylglycinamides Containing Aromatics



Compound	Structure	R	cAMP pEC$_{50}$ (EC$_{50}$, nM)[a]	E_{max}[b]
55	A		6.61 ± 0.02 (245)	90 ± 9
56	A		6.66 ± 0.08 (219)	93 ± 4
57	A		6.21 ± 0.02 (617)	95 ± 5
58	A		6.23 ± 0.08 (589)	103 ± 4
59	A		6.06 ± 0.05 (871)	104 ± 2
60	A		6.57 ± 0.09 (269)	98 ± 4
61	B		6.26 ± 0.06 (550)	90 ± 2
62	B		6.14 ± 0.03 (724)	103 ± 0
63	B		6.34 ± 0.03 (457)	104 ± 3
64	B		6.17 ± 0.05 (676)	94 ± 5
65	B		6.13 ± 0.04 (741)	103 ± 3
66	B		6.00 ± 0.05 (1000)	116 ± 9
67	B		5.44 ± 0.04 (3631)	111 ± 0
68	B		5.31 ± 0.04 (4898)	114 ± 6
69	B		5.29 ± 0.08 (5129)	108 ± 4

[a]pEC$_{50}$ values are means ± standard error of at least three independent experiments performed in duplicate. [b]E_{max} value is % of RTI-13951-33 (mean ± standard error).

solubility. Compound **90** was further evaluated in a preliminary PK study to assess whether this compound has sufficient brain exposure. Following an intraperitoneal (i.p.) dose of 10 mg/kg in rats, **90** reached the peak plasma concentration of 270 ng/mL at 30 min (the first time point tested). The brain concentration also peaked at 30 min with a C_{max} of 39 ng/mL (92 nM), which is slightly above its EC$_{50}$ of 71 nM in the cAMP functional assay. The overall brain to plasma AUC ratio (B/P), as determined by AUC$_{0-inf}$ ratio, was 0.1, indicating that **90** has limited brain penetration. As a comparison, RTI-13951-33 has a brain C_{max} of 287 ng/mL (539 nM) and a B/P ratio of 0.5 in rats (i.p., 10 mg/kg dose).[29] Compound **90** has a clog *P* of 3.76 but a high TPSA of 103 Å^2, which likely limits its brain permeability. Further optimization of the 1,3,4-oxadiazole analogues is required to improve brain permeability.

CONCLUSIONS

The orphan receptor GPR88 plays important roles in mediation of dopaminergic activity and striatal functions. To explore the therapeutic potential of this novel drug target, our group has carried out a medicinal chemistry campaign to develop GPR88 small-molecule agonist probes based on the 2-PCCA and 2-AMPP scaffolds.[25−29] The present study describes a series of novel (4-alkoxyphenyl)glycinols, (4-alkoxyphenyl)glycinamides and the corresponding bioisosteric 1,3,4-oxadiazoles derived from 2-AMPP and explores their SAR requirements for high potency at the GPR88 receptor. Notably, 5-amino-1,3,4-oxadiazoles **84** (EC$_{50}$ = 59 nM) and **90** (EC$_{50}$ = 71 nM) emerged as the most potent compounds in this study. Compound **84** exhibited a significant [^{35}S]GTPγS binding activity (EC$_{50}$ = 942 nM) using the native tissue sample from mouse striatum but was inactive in GPR88 KO mouse striatal membranes, even at a concentration of 100 μM, demonstrating that this type of compound has GPR88-specific agonist activity in the striatum. However, a preliminary PK study of **90** indicates limited brain permeability. Chemical modifications of 2-AMPP on site B (Figure 2) with other five-membered heterocycles, as well as on site C, to further improve potency and ADME properties are currently underway. These studies will facilitate the identification of highly

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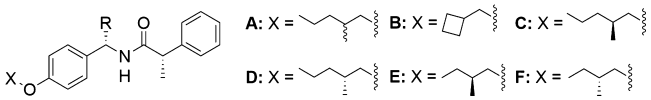
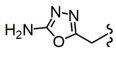
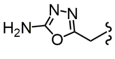
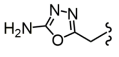
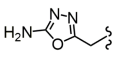
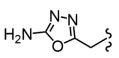
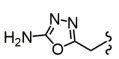
Table 4. Biological Data of Bioisosteric 1,3,4-Oxadiazoles



Compound	Structure	R	clogP[a]	cAMP pEC$_{50}$ (EC$_{50}$, nM)[b]	E_{max}[c]
71	A		4.26	6.27 ± 0.01 (537)	103 ± 5[d]
72	A		4.39	6.28 ± 0.06 (525)	101 ± 5[d]
73	B		3.35	6.32 ± 0.09 (479)	94 ± 0
74	B		3.48	6.26 ± 0.06 (550)	96 ± 4
82	A		4.35	6.95 ± 0.10 (112)	96 ± 4
83	A		4.47	6.83 ± 0.08 (148)	95 ± 3
84[e]	A		4.20	7.23 ± 0.03 (59)	99 ± 0
85	B		3.56	6.53 ± 0.03 (295)	104 ± 3
86	B		3.44	6.43 ± 0.01 (372)	98 ± 3
87[e]	B		3.29	6.86 ± 0.01 (138)	92 ± 9
88[e]	C		4.20	7.11 ± 0.02 (78)	97 ± 3
89[e]	D		4.20	7.13 ± 0.08 (74)	103 ± 3
90[e]	E		3.76	7.15 ± 0.08 (71)	101 ± 1
91[e]	F		3.76	6.86 ± 0.04 (138)	107 ± 2

[a]clog *P* was calculated using Instant JChem 5.4.0 (ChemAxon Ltd.). [b]pEC$_{50}$ values are means ± standard error of at least three independent experiments performed in duplicate. [c]E_{max} value is % of RTI-13951-33 (mean ± standard error). [d]E_{max} value is % of 2-PCCA (mean ± standard error). [e]Compounds were tested as the HCl salt.

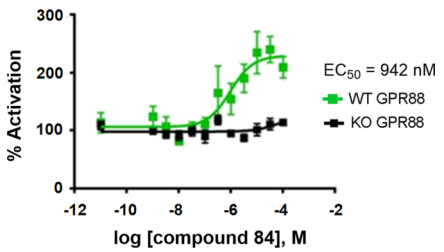


Figure 4. [^{35}S]GTPγS binding of compound **84** in WT mouse striatal membranes vs GPR88 KO mouse striatal membranes. The data are the means of triplicate measurements with standard deviation shown as error bars.

potent and brain-penetrant agonists to probe GPR88 functions in the brain.

EXPERIMENTAL SECTION

Chemistry. *General Methods.* All solvents and chemicals were of reagent grade. Unless otherwise mentioned, all reagents and solvents were purchased from commercial vendors and used as received. Flash column chromatography was carried out on a Teledyne ISCO CombiFlash Rf system using prepacked columns. Solvents used include hexane, ethyl acetate (EtOAc), dichloromethane, and methanol. Purity and characterization of compounds were established by a combination of NMR, mass spectrometry, TLC, and HPLC analyses. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer and were determined in $CDCl_3$, DMSO-d_6, or CD_3OD with tetramethylsilane (TMS) (0.00 ppm) or solvent peaks as the internal reference. Chemical shifts are reported in ppm relative to the reference signal and coupling constant (*J*) values are reported in hertz (Hz). Nominal mass spectra were obtained using an Agilent InfinityLab MSD single quadrupole mass spectrometer system (ESI). HRMS were obtained using Agilent 1290 Infinity UHPLC-6230 TOF mass spectrometer (ESI). Thin-layer chromatography (TLC) was performed on EMD precoated silica gel 60 F254 plates, and spots were visualized with UV light or iodine staining. CMA80 for column chromatography is a mixture of 80:18:2 chloroform/MeOH/NH_4OH. All final compounds were greater than 95% pure as determined by HPLC on a Waters 2695 Separation Module equipped with a Waters 2996 Photodiode Array Detector and a Phenomenex Synergi 4 mm Hydro-RP 80A C18 250 × 4.6 mm column using a flow rate of 1 mL/min starting with 1 min at 5% solvent B, followed by a 15 min gradient of 5−95% solvent B, followed by 9 min at 95% solvent B (solvent A, water with 0.1% TFA; solvent B, acetonitrile with 0.1% TFA and 5% water; absorbance monitored at 280 nm). All the synthesized target compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS and determined to be >95% pure by HPLC analyses.

*Methyl (2R)-2-{[(tert-Butoxy)carbonyl]amino}-2-(4-hydroxyphenyl)acetate (**6**).* To a solution of (*R*)-2-phenylglycine methyl ester hydrochloride (5 g, 23 mmol) in DCM (175 mL) at 0

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Table 5. Physicochemical, Solubility, and PK Properties of Compounds 1, 84, and 90

					rat PK (i.p., 10 mg/kg)				
					plasma		brain		
compound[a]	cAMP EC_{50} (nM)	clog P[b]	TPSA[b]	kinetic solubility at pH 7.4 (μM)	C_{max} (ng/mL)	AUC_{0-inf} (ng/mL·h)	C_{max} (ng/mL)	AUC_{0-inf} (ng/mL·h)	B/P
1	414	4.53	64.3	<1					
84	59	4.20	103.3	<1					
90	71	3.76	103.3	2.9 ± 0.3	270	1001	39	95	0.1
RTI-13951-33[c]	25	3.34	77.7		874	1510	287	825	0.5

[a]All compounds were tested as the HCl salt. [b]clog P and TPSA were calculated using Instant JChem 5.4.0 (ChemAxon Ltd.). [c]Data were obtained from ref 29.

°C under nitrogen was added DIPEA (12 mL, 69 mmol), followed by di-*tert*-butyldicarbonate (5.2 g, 23 mmol). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL), washed with 10% citric acid (3 × 50 mL) and brine (3 × 50 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded crude **6** (6.45 g, 100% yield) as a colorless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.16 (d, J = 9.0 Hz, 2H), 7.13 (d, J = 9.0 Hz, 2H), 6.44 (s, 1H), 5.60 (br d, J = 6.0 Hz, 1H), 5.22 (d, J = 6.0 Hz, 1H), 3.71 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 172.0, 156.3, 155.0, 128.5, 128.4, 115.8, 80.5, 57.1, 52.7, 28.3; MS (ESI) [M + H]$^+$ m/z: 282.3.

*Methyl (2R)-2-{[(tert-Butoxy)carbonyl]amino}-2-{4-[(4-methylpentyl)oxy]phenyl}acetate (**7b**).* To a solution of **6** (200 mg, 0.71 mmol), 4-methylpentanol (177 μL, 1.42 mmol), and PPh_3 (316 mg, 1.21 mmol) in THF (10 mL) at room temperature under nitrogen was slowly added DEAD (0.19 mL, 1.21 mmol) dropwise, while keeping the reaction temperature below 35 °C. After addition, the reaction mixture was stirred at room temperature overnight and quenched with H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel using 0−20% EtOAc in hexanes to afford **7b** (130 mg, 50% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 5.50 (br d, J = 6.0 Hz, 1H), 5.24 (d, J = 6.0 Hz, 1H), 3.92 (t, J = 6.0 Hz, 2H), 3.71 (s, 3H), 1.86−1.71 (m, 2H), 1.67−1.53 (m, 1H), 1.43 (s, 9H), 1.40−1.25 (m, 2H), 0.91 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 159.3, 154.8, 128.7, 128.3, 114.8, 80.0, 68.4, 57.1, 52.5, 35.1, 28.3, 27.8, 27.1, 22.5; MS (ESI) m/z: 366.6 [M + H]$^+$.

*Methyl (2R)-2-{[(tert-Butoxy)carbonyl]amino}-2-[4-(pentyloxy)-phenyl]acetate (**7c**).* The procedure for the synthesis of **7b** was followed starting with **6** and *n*-pentanol to give **7c** (50% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.50 (br d, J = 6.0 Hz, 1H), 5.25 (d, J = 9.0 Hz, 1H), 3.93 (t, J = 7.5 Hz, 2H), 3.71 (s, 3H), 1.82−1.71 (m, 2H), 1.43 (s, 9H), 1.42−1.25 (m, 4H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 159.3, 154.8, 128.7, 128.3, 114.8, 80.0, 68.0, 57.1, 52.5, 28.9, 28.3, 28.2, 22.4, 14.0; MS (ESI) m/z: 352.3 [M + H]$^+$.

*Methyl (2R)-2-{[(tert-Butoxy)carbonyl]amino}-2-[4-(butoxy)-phenyl]acetate (**7g**).* The procedure for the synthesis of **7b** was followed starting with **6** and *n*-butanol to give **7g** (57% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.53 (br d, J = 9.0 Hz, 1H), 5.25 (d, J = 9.0 Hz, 1H), 3.94 (t, J = 7.5 Hz, 2H), 3.70 (s, 3H), 1.81−1.68 (m, 2H), 1.52−1.44 (m, 2H), 1.43 (s, 9H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 159.3, 154.8, 128.7, 128.3, 114.8, 80.0, 67.7, 57.1, 52.5, 31.3, 28.3, 19.2, 13.8; MS (ESI) m/z: 338.6 [M + H]$^+$.

*Methyl (2R)-2-{[(tert-Butoxy)carbonyl]amino}-2-[4-(cyclobutylmethoxy)phenyl]acetate (**7h**).* The procedure for the synthesis of **7b** was followed starting with **6** and cyclobutylmethanol to give **7h** (71% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 5.50 (br d, J = 6.0 Hz, 1H), 5.25 (d, J = 9.0 Hz, 1H), 3.90 (d, J = 6.0 Hz, 2H), 3.70 (s, 3H), 2.84−1.68 (m, 1H), 2.19−2.06 (m, 2H), 2.01−1.80 (m, 4H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 159.4, 154.8, 128.8, 128.3, 114.9, 80.0, 72.1, 57.0, 52.6, 34.6, 28.3, 24.8, 18.6; MS (ESI) m/z: 350.2 [M + H]$^+$.

*Methyl (2R)-2-{[(tert-Butoxy)carbonyl]amino}-2-(4-propoxyphenyl)acetate (**7i**).* The procedure for the synthesis of **7b** was followed starting with **6** and *n*-propanol to give **7i** (57% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.54 (br d, J = 9.0 Hz, 1H), 5.25 (d, J = 9.0 Hz, 1H), 3.89 (t, J = 7.5 Hz, 2H), 3.70 (s, 3H), 1.85−1.72 (m, 2H), 1.43 (s, 9H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 159.3, 154.8, 128.7, 128.3, 114.8, 80.0, 69.5, 57.1, 52.5, 28.3, 22.5, 10.5; MS (ESI) m/z: 324.3 [M + H]$^+$.

*Methyl (2R)-2-{[(tert-Butoxy)carbonyl]amino}-2-[4-(cyclopropylmethoxy)phenyl]acetate (**7j**).* The procedure for the synthesis of **7b** was followed starting with **6** and cyclopropylmethanol to give **7j** (76% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 5.54 (br d, J = 9.0 Hz, 1H), 5.25 (d, J = 9.0 Hz, 1H), 3.78 (d, J = 9.0 Hz, 2H), 3.70 (s, 3H), 1.43 (s, 9H), 1.32−1.16 (m, 1H), 0.67−0.58 (m, 2H), 0.39−0.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 159.1, 154.8, 128.9, 128.4, 114.9, 80.0, 72.8, 57.0, 52.5, 28.3, 10.2, 3.2; MS (ESI) m/z: 336.3 [M + H]$^+$.

*Methyl (2R)-2-{[(tert-Butoxy)carbonyl]amino}-2-[4-(4-methoxybutoxy)phenyl]acetate (**7k**).* The procedure for the synthesis of **7b** was followed starting with **6** and 4-methoxybutan-1-ol to give **7k** (63% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.56 (br d, J = 6.0 Hz, 1H), 5.25 (d, J = 9.0 Hz, 1H), 3.96 (t, J = 6.0 Hz, 2H), 3.70 (s, 3H), 3.43 (t, J = 6.0 Hz, 2H), 3.33 (s, 3H), 1.91−1.68 (m, 4H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 159.1, 154.8, 128.8, 128.3, 114.8, 80.0, 72.3, 67.7, 58.5, 57.0, 52.5, 28.3, 26.2, 26.0; MS (ESI) m/z: 368.4 [M + H]$^+$.

*Methyl (2R)-2-{[(tert-Butoxy)carbonyl]amino}-2-[4-(4-methoxypropoxy)phenyl]acetate (**7l**).* The procedure for the synthesis of **7b** was followed starting with **6** and 3-methoxypropan-1-ol to give **7l** (68% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 5.55 (br d, J = 6.0 Hz, 1H), 5.25 (d, J = 9.0 Hz, 1H), 4.03 (t, J = 6.0 Hz, 2H), 3.70 (s, 3H), 3.54 (t, J = 6.0 Hz, 2H), 3.34 (s, 3H), 2.08−1.97 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 159.1, 154.8, 128.9, 128.3, 114.8, 80.0, 69.1, 64.9, 58.6, 57.0, 52.5, 29.5, 28.3; MS (ESI) m/z: 354.5 [M + H]$^+$.

*(2R)-2-Amino-2-{4-[(4-methylpentyl)oxy]phenyl}ethan-1-ol Hydrochloride (**8b**).* To a suspension of $NaBH_4$ (35 mg, 0.93 mmol) in EtOH (1.5 mL) at 0 °C under nitrogen was added LiCl (39 mg, 0.93 mmol). After stirring at 0 °C for 10 min, a solution of **7b** (130 mg, 0.36 mmol) in THF (1.5 mL) was added. The reaction mixture was stirred at room temperature for 3 h and quenched with saturated NH_4Cl solution (5 mL), followed by addition of H_2O (5 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give 125 mg of the crude intermediate alcohol. The Boc group was then deprotected with 4 M HCl in dioxane (2 mL) and DCM (5 mL). The reaction mixture was

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stirred at room temperature overnight and concentrated to give crude **8b** (93 mg, 100% over two steps) as an off-white foamy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 4.01−3.84 (m, 3H), 3.74−3.60 (m, 1H), 3.51 (t, J = 9.0 Hz, 1H), 1.84−1.70 (m, 2H), 1.66−1.51 (m, 1H), 1.38−1.21 (m, 3H), 0.92 (d, J = 9.0 Hz, 6H); MS (ESI) free base m/z: 238.3 $[M + H]^+$.

*(2R)-2-Amino-2-[4-(pentyloxy)phenyl]ethan-1-ol Hydrochloride (**8c**).* The procedure for the synthesis of **8b** was followed starting with **7c** to give crude **8c** (100% yield over two steps) as an off-white foamy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 4.05−3.84 (m, 3H), 3.75−3.61 (m, 1H), 3.51 (t, J = 9.0 Hz, 1H), 1.84−1.70 (m, 2H), 1.50−1.29 (m, 5H), 0.93 (t, J = 7.5 Hz, 3H); MS (ESI) free base m/z: 224.3 $[M + H]^+$.

*(2R)-2-Amino-2-(4-butoxyphenyl)ethan-1-ol Hydrochloride (**8g**).* The procedure for the synthesis of **8b** was followed starting with **7g** to give crude **8g** (100% yield over two steps) as an off-white foamy solid. ^{1}H NMR (300 MHz, CD_3OD): δ 7.35 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 4.32−4.21 (m, 1H), 3.99 (t, J = 6.0 Hz, 2H), 3.87−3.72 (m, 2H), 1.82−1.67 (m, 2H), 1.58−1.42 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); MS (ESI) free base m/z: 210.3 $[M + H]^+$.

*(2R)-2-Amino-2-(4-propoxyphenyl)ethan-1-ol Hydrochloride (**8i**).* The procedure for the synthesis of **8b** was followed starting with **7i** to give crude **8i** (100% yield over two steps) as an off-white foamy solid. ^{1}H NMR (300 MHz, CD_3OD): δ 7.33 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 4.30−4.14 (m, 1H), 3.97−3.69 (m, 4H), 1.86−1.66 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H); MS (ESI) free base m/z: 196.2 $[M + H]^+$.

*(2R)-2-Amino-2-[4-(4-methoxybutoxy)phenyl]ethan-1-ol Hydrochloride (**8k**).* The procedure for the synthesis of **8b** was followed starting with **7k** to give crude **8k** (100% yield over two steps) as an off-white foamy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 5.54−5.28 (m, 1H), 4.53−4.30 (m, 1H), 4.00−3.60 (m, 4H), 3.49−3.36 (m, 2H), 3.32 (s, 3H), 1.86−1.57 (m, 4H); MS (ESI) free base m/z: 240.4 $[M + H]^+$.

*(2R)-2-Amino-2-[4-(3-methoxypropoxy)phenyl]ethan-1-ol Hydrochloride (**8l**).* The procedure for the synthesis of **8b** was followed starting with **7l** to give crude **8l** (100% yield over two steps) as an off-white foamy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 5.47−5.36 (m, 1H), 4.47−4.33 (m, 1H), 3.98−3.84 (m, 3H), 3.80−3.68 (m, 1H), 3.49 (t, J = 6.0 Hz, 2H), 3.31 (s, 3H), 2.05−1.91 (m, 2H); MS (ESI) free base m/z: 226.2 $[M + H]^+$.

*Methyl (2R)-2-{[(tert-Butoxy)carbonyl]amino}-2-(4-{[tris(propan-2-yl)silyl]oxy}phenyl)acetate (**9**).* To a solution of **6** (1 g, 3.55 mmol) in dry DCM (20 mL) were added imidazole (532 mg, 7.82 mmol) and TIPS−Cl (837 mg, 3.91 mmol) at 0 °C. After stirring at room temperature for 16 h, the reaction was quenched with H_2O (2 mL), and the layers were separated. The aqueous layer was extracted with additional DCM (3 × 20 mL), and the combined organic layers were washed with brine (3 × 30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was subjected to chromatography on silica gel using 0−30% EtOAc in hexanes to furnish **9** (1.47 g, 95% yield) as a thick colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.42 (d, J = 6.3 Hz, 1H), 5.23 (d, J = 7.3 Hz, 1H), 3.71 (s, 3H), 1.43 (s, 9H), 1.31−1.16 (m, 3H), 1.12−1.05 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 156.3, 155.0, 129.1, 128.3, 120.2, 80.1, 57.1, 52.5, 28.3, 17.9, 12.6; MS (ESI) m/z: 460.0 $[M + Na]^+$.

*Methyl (2R)-2-(4-Hydroxyphenyl)-2-[(2S)-2-phenylpropanamido]acetate (**10**).* To a solution of **9** (968 mg, 2.25 mmol) in DCM (25 mL) was added TFA (2 mL) at 0 °C. After stirring for 16 h, the reaction was quenched with saturated $NaHCO_3$ (20 mL) and the layers were separated. The aqueous layer was extracted with additional DCM (3 × 20 mL), and the combined organic layers were washed with brine (3 × 20 mL), dried (Na_2SO_4), and concentrated. The residue was subjected to chromatography on silica gel using 0−30% EtOAc in hexanes (containing 1.5% Et_3N) to afford the free amine (650 mg, 85% yield) as a foamy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.58 (s, 1H), 3.69 (s, 3H), 2.33 (br s, 2H), 1.35−1.15 (m, 3H), 1.15−0.97 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 156.0, 132.2, 127.9, 120.1, 58.1, 52.3, 17.9, 12.6; MS (ESI) m/z: 322.0 $[M + H^+ - NH_3]^+$. To a solution of the amine intermediate (620 mg, 1.84 mmol) in MeCN (20 mL) at room temperature were added TEA (0.77 mL, 5.52 mmol), (*S*)-2-phenylpropionic acid (0.36 g, 2.39 mmol), and HBTU (1.05 g, 2.76 mmol). After stirring for 5 h, the reaction was quenched by H_2O (10 mL), followed by addition of EtOAc (50 mL). The layers were separated. The organic layer was washed with saturated $NaHCO_3$ (10 mL) and brine (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel using 0−30% EtOAc in hexanes to give the corresponding amide as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.16 (m, 5H), 7.02 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 6.32 (d, J = 7.0 Hz, 1H), 5.46 (d, J = 7.1 Hz, 1H), 3.73−3.52 (m, 4H), 1.49 (d, J = 7.1 Hz, 3H), 1.30−1.14 (m, 3H), 1.11−1.04 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 171.6, 156.2, 141.1, 128.8, 128.6, 128.2, 127.6, 127.2, 120.1, 55.9, 52.6, 46.7, 18.4, 17.9, 12.6; MS (ESI) m/z: 470.0 $[M + H]^+$. To a solution of the amide (864 mg, 1.84 mmol) in THF (20 mL) at 0 °C was added TBAF (1.0 M in THF, 2.76 mL, 2.76 mmol) via a syringe. After stirring at 0 °C for 4 h, the reaction was quenched by H_2O (15 mL) and diluted with EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with additional EtOAc (2 × 20 mL). The combined organic layers were washed with brine (2 × 2 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel using 0−100% EtOAc in hexanes to furnish **10** (576 mg, 85% over two steps) as a yellowish waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48−7.16 (m, 5H), 6.96 (d, J = 8.5 Hz, 2H), 6.78 (br s, 1H), 6.60 (d, J = 8.6 Hz, 2H), 6.48 (d, J = 6.6 Hz, 1H), 5.40 (d, J = 6.7 Hz, 1H), 3.73−3.51 (m, 4H), 1.51 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 169.1, 153.9, 138.2, 126.4, 125.7, 125.1, 124.9, 113.3, 53.6, 50.3, 44.3, 15.7; MS (ESI) m/z: 314.0 $[M + H]^+$.

*Methyl (2R)-2-[4-(Hexan-2-yloxy)phenyl]-2-[(2S)-2-phenylpropanamido]acetate (**11a**).* The procedure for the synthesis of **7b** was followed starting with **10** and 2-hexanol to give **11a** (46% yield) as a sticky solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.17 (m, 5H), 7.11−7.00 (m, 2H), 6.83−6.68 (m, 2H), 6.33 (d, J = 6.9 Hz, 1H), 5.44 (d, J = 7.0 Hz, 1H), 4.39−4.23 (m, 1H), 3.67 (s, 3H), 3.66−3.55 (m, 1H), 1.80−1.63 (m, 1H), 1.63−1.52 (m, 1H), 1.50 (d, J = 7.2 Hz, 3H), 1.43−1.28 (m, 4H), 1.25 (d, J = 6.1 Hz, 3H), 0.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 171.6, 158.3, 141.1, 128.8, 128.2, 127.9, 127.6, 127.2, 115.9, 73.9, 56.0, 53.0, 46.8, 36.1, 27.7, 22.6, 19.7, 18.4, 14.0; MS (ESI) m/z: 398.0 $[M + H]^+$.

*Methyl (2R)-2-[4-(2-Methylbutoxy)phenyl]-2-[(2S)-2-phenylpropanamido]acetate (**11d**).* The procedure for the synthesis of **7b** was followed starting with **10** and 2-methyl-1-butanol to give **11d** (29% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.20 (m, 5H), 7.19−7.01 (m, 2H), 6.86−6.75 (m, 2H), 6.31 (d, J = 7.0 Hz, 1H), 5.44 (d, J = 6.9 Hz, 1H), 3.82−3.53 (m, 6H), 1.89−1.75 (m, 1H), 1.63−1.42 (m, 4H), 1.37−1.10 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 171.6, 159.4, 128.8, 128.2, 127.6, 127.2, 114.8, 72.9, 56.0, 52.6, 46.8, 34.7, 26.1, 18.4, 16.5, 11.2; MS (ESI) m/z: 384.0 $[M + H]^+$.

*Methyl (2R)-2-{4-[(2S)-2-Methylbutoxy]phenyl}-2-[(2S)-2-phenylpropanamido]acetate (**11e**).* The procedure for the synthesis of **7b** was followed with **10** and (*S*)-2-methyl-1-butanol to give **11e** (41% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.18 (m, 5H), 7.07 (t, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.34 (d, J = 6.6 Hz, 1H), 5.44 (d, J = 6.9 Hz, 1H), 3.84−3.52 (m, 6H), 1.92−1.70 (m, 1H), 1.64−1.44 (m, 4H), 1.35−1.11 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 171.6, 159.4, 141.1, 128.8, 128.2, 128.1, 127.6, 127.2, 114.8, 72.9, 56.0, 53.0, 46.8, 34.7, 26.1, 18.4, 16.5, 11.2; MS (ESI) m/z: 384.0 $[M + H]^+$.

*Methyl (2R)-2-[4-(Cyclopentylmethoxy)phenyl]-2-[(2S)-2-phenylpropanamido]acetate (**11f**).* The procedure for the synthesis of **7b** was followed with **11** and (*S*)-2-methyl-1-butanol to furnish **9f** (27% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (ddd, J = 9.7, 7.3, 3.1 Hz, 5H), 7.08 (d, J = 8.7 Hz, 2H), 6.78 (d, J =

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8.7 Hz, 2H), 6.35 (d, J = 6.9 Hz, 1H), 5.44 (d, J = 6.9 Hz, 1H), 3.77 (d, J = 6.9 Hz, 1H), 3.72−3.52 (m, 4H), 2.41−2.22 (m, 1H), 1.91−1.70 (m, 2H), 1.70−1.51 (m, 4H), 1.49 (d, J = 7.2 Hz, 3H), 1.43−1.14 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 171.6, 159.4, 141.1, 128.8, 128.2, 127.6, 127.2, 114.8, 72.2, 56.0, 52.6, 46.8, 39.0, 29.4, 25.4, 18.4; MS (ESI) m/z: 396.0 $[M + H]^+$.

*Methyl (2R)-2-[4-(Cyclobutylmethoxy)phenyl]-2-[(2S)-2-phenylpropanamido]acetate (**11h**).* To a solution of **7h** (175 mg, 0.5 mmol) in DCM (5 mL) at room temperature was added 4 M HCl in dioxane (3 mL). The reaction mixture was stirred at room temperature overnight and concentrated to give crude amine hydrochloride. The crude amine (90 mg, 0.35 mmol) was then dissolved in MeCN (10 mL), followed by addition of TEA (0.16 mL, 1.1 mmol), (*S*)-2-phenylpropionic acid (56 mg, 0.37 mmol), and HBTU (170 mg, 0.45 mmol). After stirring for 5 h, the reaction was quenched by H_2O (5 mL), followed by addition of EtOAc (50 mL). The layers were separated. The organic layer was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel using 0−30% EtOAc in hexanes to furnish **11h** (87 mg, 65% yield over two steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.20 (m, 5H), 7.08 (d, J = 9.0 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H), 6.36 (d, J = 6.0 Hz, 1H), 5.44 (d, J = 6.0 Hz, 1H), 3.87 (d, J = 9.0 Hz, 2H), 3.67 (s, 3H), 3.66−3.56 (m, 1H), 2.81−2.65 (m, 1H), 2.18−2.05 (m, 2H), 2.02−1.72 (m, 4H), 1.49 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 171.6, 159.4, 141.1, 128.9, 128.2, 127.6, 127.3, 114.9, 101.6, 72.1, 55.1, 52.6, 46.8, 34.6, 24.8, 18.6, 18.5; MS (ESI) m/z: 382.5 $[M + H]^+$.

*Methyl (2R)-2-[4-(Cyclopropylmethoxy)phenyl]-2-[(2S)-2-phenylpropanamido]acetate (**11j**).* The procedure for the synthesis of **11h** was followed starting with **7j** to give **11j** (63% yield over two steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33−7.20 (m, 5H), 7.08 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 6.43 (d, J = 6.0 Hz, 1H), 5.44 (d, J = 6.0 Hz, 1H), 4.74 (d, J = 9.0 Hz, 2H), 3.66 (s, 3H), 3.65−3.56 (m, 1H), 1.49 (d, J = 9.0 Hz, 3H), 1.30−1.14 (m, 1H), 0.66−0.57 (m, 2H), 0.34−0.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 171.6, 159.1, 141.1, 128.9, 128.3, 127.6, 127.3, 114.8, 72.7, 56.0, 52.7, 46.7, 18.5, 10.2, 3.2; MS (ESI) m/z: 368.5 $[M + H]^+$.

*Methyl (2R)-2-{4-[(1-Methylcyclobutyl)methoxy]phenyl}-2-[(2S)-2-phenylpropanamido]acetate (**11m**).* To a solution of **10** (200 mg, 0.64 mmol) in anhydrous DMF (15 mL) at room temperature were added (1-methylcyclobutyl)methyl 4-methylbenzene-1-sulfonate (189 mg, 0.7 mmol) and K_2CO_3 (264 mg, 1.92 mmol). After stirring for 16 h at 60 °C, the reaction was quenched by H_2O (10 mL), followed by addition of EtOAc (15 mL). The layers were separated, and the aqueous layer was extracted with additional EtOAc (2 × 10 mL). The combined organic layers were washed with brine (4 × 15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using 0−50% EtOAc in hexanes to furnish **11m** (15 mg, 6% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.23 (m, 5H), 7.17 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.30 (d, J = 6.7 Hz, 1H), 5.43 (d, J = 6.9 Hz, 1H), 3.73 (s, 2H), 3.66 (s, 3H), 3.59 (q, J = 7.2 Hz, 1H), 2.12−1.82 (m, 4H), 1.82−1.66 (m, 2H), 1.51 (d, J = 7.2 Hz, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 171.5, 159.8, 140.9, 128.9, 128.3, 127.7, 127.3, 114.9, 75.6, 56.0, 52.6, 46.9, 38.7, 30.1, 24.5, 18.4, 15.0; MS (ESI) m/z: 396.0 $[M + H]^+$.

*Methyl (2R)-2-{4-[(3-Methylcyclobutyl)methoxy]phenyl}-2-[(2S)-2-phenylpropanamido]acetate (**11n**).* The procedure for the synthesis of **7b** was followed starting with **10** and (3-methylcyclobutyl)methanol to give **11n** (27% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.19 (m, 5H), 7.08 (dd, J = 8.7, 2.2 Hz, 2H), 6.85−6.70 (m, 2H), 6.32 (d, J = 6.6 Hz, 1H), 5.44 (d, J = 6.9 Hz, 1H), 3.91 (d, J = 7.1 Hz, 1H), 3.80 (d, J = 6.3 Hz, 1H), 3.71−3.54 (m, 4H), 2.85−2.12 (m, 3H), 2.04−1.92 (m, 1H), 1.84−1.67 (m, 1H), 1.49 (d, J = 7.2 Hz, 3H), 1.45−1.35 (m, 1H), 1.12 (d, J = 6.9 Hz, 1.4 H), 1.04 (d, J = 6.1 Hz, 1.6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 171.6, 159.3, 141.1, 128.8, 128.2, 127.6, 1272, 114.8, 72.7, 72.2, 56.0, 52.6, 46.8, 31.2, 31.5, 30.6, 30.3, 27.0, 26.8, 22.3, 22.1, 18.4; MS (ESI) m/z: 396.0 $[M + H]^+$.

*Methyl (2R)-2-{4-[(3,3-Dimethylcyclobutyl)methoxy]phenyl}-2-[(2S)-2-phenylpropanami do]acetate (**11o**).* The procedure for the synthesis of **11m** was followed starting with **10** and (3,3-dimethylcyclobutyl)methyl-4-methylbenzene-1-sulfonate to give **11o** (21% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.23 (m, 5H), 7.16 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 6.34 (d, J = 6.8 Hz, 1H), 5.43 (d, J = 6.9 Hz, 1H), 3.86 (d, J = 6.6 Hz, 2H), 3.65 (s, 3H), 3.59 (q, J = 7.2 Hz, 1H), 2.75−2.50 (m, 1H), 1.96−1.81 (m, 2H), 1.68−1.54 (m, 2H), 1.50 (d, J = 7.2 Hz, 3H), 1.17 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 171.4, 159.4, 140.9, 128.9, 128.3, 127.7, 127.3, 114.9, 73.0, 56.0, 52.6, 46.9, 37.7, 31.9, 30.9, 28.9, 27.2, 18.4; MS (ESI) m/z: 410.0 $[M + H]^+$.

*Methyl (2R)-2-[(2S)-2-Phenylpropanamido]-2-[4-({spiro[2.3]-hexan-5-yl}methoxy)phenyl]acetate (**11p**).* The procedure for the synthesis of **11m** (except, MeCN was used instead of DMF) was followed starting with **10** and (3-methylidenecyclobutyl)methyl 4-methylbenzene-1-sulfonate to give the corresponding olefin intermediate methyl (2*R*)-2-{4-[(3-methylidenecyclobutyl)methoxy]-phenyl}-2-[(2*S*)-2-phenylpropanamido] acetate (12% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.21 (m, 5H), 7.16 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.39 (d, J = 6.7 Hz, 1H), 5.42 (d, J = 6.9 Hz, 1H), 4.88−4.68 (m, 2H), 3.93 (d, J = 6.7 Hz, 2H), 3.64 (s, 3H), 3.58 (q, J = 7.2 Hz, 1H), 2.92−2.78 (m, 2H), 2.78−2.62 (m, 1H), 2.56−2.44 (m, 2H), 1.49 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 171.4, 159.2, 146.3, 140.9, 128.9, 128.6, 128.4, 127.7, 127.3, 114.9, 106.7, 71.6, 56.0, 52.6, 46.8, 34.6, 29.2, 18.5; MS (ESI) m/z: 394.0 $[M + H]^+$. The olefin function of this material was transformed into the corresponding cyclopropyl function under Shi[38] modified Simmons−Smith[39] reaction. To a solution of Et_2Zn (171.5 μL, 0.17 mmol) in DCM (1 mL) at 0 °C was added TFA (13.1 μL, 0.17 mmol). After stirring at 0 °C for 1 h, diiodomethane (13.8 μL, 0.17 mmol) was added and stirred for another 40 min at 0 °C. At that time, the olefin intermediate (27 mg, 0.07 mmol) was dissolved in DCM (1 mL) and added slowly to the above reaction via a syringe at 0 °C. The reaction, which resulted, was stirred under N_2 at room temperature for 2 h. After that, the reaction was quenched by cold saturated NH_4Cl (2 mL) and diluted with EtOAc (5 mL). The layers were separated, and the aqueous layer was extracted with additional EtOAc (2 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (5 mL) and brine (3 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using 0−25% EtOAc in hexanes to furnish **11p** (20 mg, 72% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.22 (m, 5H), 7.17 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.30 (d, J = 6.7 Hz, 1H), 5.43 (d, J = 6.9 Hz, 1H), 4.01 (d, J = 7.1 Hz, 2H), 3.66 (s, 3H), 3.59 (q, J = 7.2 Hz, 1H), 2.92−2.73 (m, 1H), 2.37−2.14 (m, 2H), 1.93 (dd, J = 12.3, 5.8 Hz, 2H), 1.51 (d, J = 7.2 Hz, 3H), 0.41 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 171.4, 159.4, 140.9, 128.9, 128.4, 128.3, 127.7, 127.3, 115.0, 72.5, 56.0, 52.6, 46.9, 33.4, 29.8, 18.4, 16.9, 12.1, 11.7; MS (ESI) m/z: 408.0 $[M + H]^+$.

*Methyl (2R)-2-{4-[(3,3-Difluorocyclobutyl)methoxy]phenyl}-2-[(2S)-2-phenylpropanamido]acetate (**11q**).* The procedure for the synthesis of **11m** was followed starting with **10** and (3,3-difluorocyclobutyl)methyl 4-methylbenzene-1-sulfonate to give **11q** (8% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.21 (m, 5H), 7.09 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.34 (d, J = 6.8 Hz, 1H), 5.45 (d, J = 6.9 Hz, 1H), 3.94 (d, J = 5.8 Hz, 2H), 3.72−3.54 (m, 4H), 2.84−2.34 (m, 5H), 1.49 (d, J = 7.1 Hz, 3H); MS (ESI) m/z: 418.0 $[M + H]^+$.

*(2S)-N-[(1R)-1-[4-(Hexan-2-yloxy)phenyl]-2-hydroxyethyl]-2-phenylpropanamide (**12**).* To a suspension of $NaBH_4$ (20.9 mg, 0.55 mmol) in EtOH (6 mL) at 0 °C under nitrogen was added LiCl (23.4 mg, 0.55 mmol). After stirring at 0 °C for 10 min, a solution of **11a** (88 mg, 0.22 mmol) in THF (6 mL) was added. The reaction mixture was stirred at room temperature for 3 h and quenched with saturated NH_4Cl solution (5 mL), followed by the addition of H_2O (10 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined

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organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using 0−30% EtOAc in hexanes to furnish **12** (45 mg, 55% yield) as a white waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44−7.20 (m, 5H), 6.93 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.14 (d, J = 7.1 Hz, 1H), 4.94 (dd, J = 11.2, 6.0 Hz, 1H), 4.42−4.04 (m, 1H), 3.73 (d, J = 5.5 Hz, 2H), 3.62 (q, J = 7.1 Hz, 1H), 2.98 (br s, 1H), 1.79−1.61 (m, 1H), 1.61−1.46 (m, 4H), 1.46−1.28 (m, 4H), 1.25 (d, J = 6.1 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 157.7, 141.3, 130.6, 128.9, 127.6, 127.3, 116.0, 73.9, 66.5, 55.3, 47.0, 36.2, 27.7, 22.6, 19.7, 18.5, 14.0; HRMS (ESI) m/z: calcd for $C_{23}H_{31}NO_3$ $[M + H]^+$, 370.2377, m/z: found, 370.2371.

*(2S)-N-[(1R)-2-Hydroxy-1-{4-[(4-methylpentyl)oxy]phenyl}ethyl]-2-phenylpropanamide (**13**).* To a solution of **8b** (96 mg, 0.35 mmol) in MeCN (10 mL) at room temperature were added TEA (0.16 mL, 1.1 mmol), (*S*)-2-phenylpropionic acid (56 mg, 0.37 mmol), and HBTU (170 mg, 0.45 mmol). After stirring for 5 h, the reaction was quenched by H_2O (5 mL), followed by addition of EtOAc (50 mL). The layers were separated. The organic layer was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel using 0−30% EtOAc in hexanes to provide **13** (55 mg, 43% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.20 (m, 5H), 6.95 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 6.08 (d, J = 9.0 Hz, 1H), 4.99−4.90 (m, 1H), 3.88 (t, J = 7.5 Hz, 2H), 3.75 (br s, 2H), 3.68−3.56 (m, 1H), 2.83 (br s, 1H), 1.81−1.69 (m, 2H), 1.64−1.54 (m, 1H), 1.51 (d, J = 9.0 Hz, 3H), 1.36−1.23 (m, 2H), 0.91 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 158.6, 141.2, 130.6, 128.9, 127.5, 127.3, 114.7, 68.3, 66.6, 55.3, 47.0, 35.1, 27.8, 27.1, 22.5, 18.4; HRMS (ESI) m/z: calcd for $C_{23}H_{31}NO_3$ $[M + H]^+$, 370.2377; m/z: found, 370.2375.

*(2S)-N-{(1R)-2-Hydroxy-1-[4-(pentyloxy)phenyl]ethyl}-2-phenylpropanamide (**14**).* The procedure for the synthesis of **13** was followed starting with **8c** to give **14** (43% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.20 (m, 5H), 6.95 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 9.0 Hz, 2H), 6.03 (d, J = 6.0 Hz, 1H), 5.00−4.89 (m, 1H), 3.89 (t, J = 6.0 Hz, 2H), 3.76 (d, J = 6.0 Hz, 2H), 3.68−3.55 (m, 1H), 2.73 (br s, 1H), 1.85−1.67 (m, 2H), 1.51 (d, J = 6.0 Hz, 3H), 1.46−1.25 (m, 4H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 158.7, 141.2, 130.6, 128.9, 127.6, 127.5, 127.3, 114.7, 68.0, 66.7, 55.4, 47.1, 28.9, 28.2, 22.4, 18.4, 14.0; HRMS (ESI) m/z: calcd for $C_{22}H_{29}NO_3$ $[M + H]^+$, 356.2220; m/z: found, 356.2219.

*(2S)-N-[(1R)-2-Hydroxy-1-[4-(2-methylbutoxy)phenyl]ethyl]-2-phenylpropanamide (**15**).* The procedure for the synthesis of **12** was followed starting with **11d** to give **15** (67% yield) as a white waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.16 (m, 5H), 6.95 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 5.98 (d, J = 6.9 Hz, 1H), 4.95 (dd, J = 11.8, 5.0 Hz, 1H), 3.81−3.72 (m, 3H), 3.71−3.57 (m, 2H), 2.61 (t, J = 5.7 Hz, 1H), 1.94−1.73 (m, 1H), 1.64−1.44 (m, 4H), 1.37−1.12 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 158.9, 141.2, 130.5, 128.9, 127.6, 127.5, 127.3, 114.8, 72.9, 66.8, 55.4, 47.1, 34.7, 26.1, 18.4, 16.5, 11.2; HRMS (ESI) m/z: calcd for $C_{22}H_{29}NO_3$ $[M + H]^+$, 356.2220; m/z: found, 356.2213.

*(2S)-N-[(1R)-2-Hydroxy-1-{4-[(2S)-2-methylbutoxy]phenyl}ethyl]-2-phenylpropanamide (**16**).* The procedure for the synthesis of **12** was followed starting with **11e** to give **16** (69% yield) as a white waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.19 (m, 5H), 6.94 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.7 Hz, 2H), 6.11 (d, J = 7.1 Hz, 1H), 4.93 (dd, J = 11.9, 5.3 Hz, 1H), 3.82−3.51 (m, 5H), 2.90 (br s, 1H), 1.94−1.72 (m, 1H), 1.61−1.43 (m, 4H), 1.33−1.14 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 158.8, 141.3, 130.6, 128.9, 127.6, 127.5, 127.3, 114.7, 72.9, 66.6, 55.3, 47.0, 34.7, 26.1, 18.4, 16.5, 11.3; HRMS (ESI) m/z: calcd for $C_{22}H_{29}NO_3$ $[M + H]^+$, 356.2220; m/z: found, 356.2214.

*(2S)-N-[(1R)-1-[4-(Cyclopentylmethoxy)phenyl]-2-hydroxyethyl]-2-phenylpropanamide (**17**).* The procedure for the synthesis of **12** was followed starting with **11f** to give **17** (58% yield) as a white waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44−7.17 (m, 5H), 6.95 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.01 (d, J = 6.9 Hz, 1H), 4.95 (dd, J = 11.9, 5.0 Hz, 1H), 3.76 (dd, J = 6.0, 3.2 Hz, 4H), 3.62 (q, J = 7.1 Hz, 1H), 2.67 (t, J = 6.0 Hz, 1H), 2.45−2.20 (m, 1H), 1.90−1.69 (m, 3H), 1.69−1.55 (m, 3H), 1.52 (t, J = 6.2 Hz, 3H), 1.34 (dt, J = 11.6, 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 158.8, 141.2, 130.6, 128.9, 127.6, 127.5, 127.3, 114.8, 72.3, 66.7, 55.4, 47.1, 39.0, 29.4, 25.4, 18.4; HRMS (ESI) m/z: calcd for $C_{23}H_{29}NO_3$ $[M + H]^+$, 368.2220; m/z: found, 368.2215.

*(2S)-N-[(1R)-1-(4-Butoxyphenyl)-2-hydroxyethyl]-2-phenylpropanamide (**18**).* The procedure for the synthesis of **13** was followed starting with **8g** to give **18** (33% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.23 (m, 5H), 6.96 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 5.99 (d, J = 6.0 Hz, 1H), 5.00−4.89 (m, 1H), 3.91 (t, J = 7.5 Hz, 2H), 3.76 (d, J = 3.0 Hz, 2H), 3.69−3.57 (m, 1H), 2.62 (br s, 1H), 1.82−1.66 (m, 2H), 1.52 (d, J = 6.0 Hz, 3H), 1.51−1.37 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 158.7, 141.2, 130.6, 128.9, 127.6, 127.5, 127.3, 114.8, 67.7, 66.8, 55.4, 47.1, 31.3, 19.2, 18.4, 13.8; HRMS (ESI) m/z: calcd for $C_{21}H_{27}NO_3$ $[M + H]^+$, 342.2064; m/z: found, 342.2071.

*(2S)-N-{(1R)-1-[4-(Cyclobutylmethoxy)phenyl]-2-hydroxyethyl}-2-phenylpropanamide (**19**).* The procedure for the synthesis of **12** was followed starting with **11h** to give **19** (83% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.22 (m, 5H), 6.95 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 9.0 Hz, 2H), 6.09 (d, J = 6.0 Hz, 1H), 4.98−4.88 (m, 1H), 3.86 (d, J = 6.0 Hz, 2H), 3.74 (br s, 2H), 3.68−3.56 (m, 1H), 2.86 (br t, J = 6.0 Hz, 1H), 2.81−2.65 (m, 2H), 2.20−2.04 (m, 2H), 2.20−1.75 (m, 4H), 1.51 (d, J = 9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 158.8, 141.2, 130.7, 128.9, 127.5, 127.3, 114.8, 72.1, 66.6, 55.3, 47.0, 34.6, 24.8, 18.5, 18.4; HRMS (ESI) m/z: calcd for $C_{22}H_{27}NO_3$ $[M + H]^+$, 354.2064; m/z: found, 354.2064.

*(2S)-N-[(1R)-2-Hydroxy-1-(4-propoxyphenyl)ethyl]-2-phenylpropanamide (**20**).* The procedure for the synthesis of **13** was followed starting with **8i** to give **20** (32% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.22 (m, 5H), 6.95 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 9.0 Hz, 2H), 6.08 (d, J = 6.0 Hz, 1H), 4.99−4.90 (m, 1H), 3.96 (t, J = 7.5 Hz, 2H), 3.75 (br s, 2H), 3.67−3.56 (m, 1H), 2.83 (br t, J = 4.5 Hz, 1H), 1.83−1.68 (m, 2H), 1.51 (d, J = 9.0 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 158.6, 141.2, 130.6, 128.9, 127.5, 127.3, 114.7, 69.5, 66.6, 55.3, 47.0, 22.5, 18.4, 10.4; HRMS (ESI) m/z: calcd for $C_{20}H_{25}NO_3$ $[M + H]^+$, 328.1907; m/z: found, 328.1911.

*(2S)-N-{(1R)-1-[4-(Cyclopropylmethoxy)phenyl]-2-hydroxyethyl}-2-phenylpropanamide (**21**).* The procedure for the synthesis of **12** was followed starting with **11j** to give **21** (82% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.19 (m, 5H), 6.94 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 9.0 Hz, 2H), 6.11 (d, J = 6.0 Hz, 1H), 4.99−4.88 (m, 1H), 3.73 (d, J = 6.0 Hz, 3H), 3.68−3.54 (m, 1H), 2.89 (br t, J = 6.0 Hz, 1H), 1.50 (d, J = 6.0 Hz, 4H), 1.32−1.14 (m, 1H), 0.69−0.56 (m, 2H), 0.36−0.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 158.5, 141.2, 130.8, 128.9, 127.5, 127.3, 114.8, 72.7, 66.5, 55.2, 47.0, 18.4, 10.2, 3.1; HRMS (ESI) m/z: calcd for $C_{21}H_{25}NO_3$ $[M + H]^+$, 340.1907; m/z: found, 340.1910.

*(2S)-N-[(1R)-2-Hydroxy-1-[4-(4-methoxybutoxy)phenyl]ethyl}-2-phenylpropanamide (**22**).* The procedure for the synthesis of **13** was followed starting with **8k** to give **22** (82% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.20 (m, 5H), 6.94 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 6.29 (d, J = 6.0 Hz, 1H), 4.97−4.86 (m, 1H), 3.90 (t, J = 6.0 Hz, 2H), 3.70 (br s, 2H), 3.66−3.55 (m, 1H), 3.41 (t, J = 6.0 Hz, 2H), 3.32 (s, 3H), 3.27 (br s, 1H), 1.86−1.63 (m, 4H), 1.48 (d, J = 9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 158.3, 141.2, 130.8, 128.8, 127.4, 127.1, 114.5, 72.2, 67.5, 66.2, 58.4, 55.1, 46.8, 26.1, 25.9, 18.4; HRMS (ESI) m/z: calcd for $C_{22}H_{29}NO_4$ $[M + H]^+$, 372.2169; m/z: found, 372.2173.

*(2S)-N-[(1R)-2-Hydroxy-1-[4-(3-methoxypropoxy)phenyl]ethyl}-2-phenylpropanamide (**23**).* The procedure for the synthesis of **13** was followed starting with **8l** to give **23** (73% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.20 (m, 5H), 6.93 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.36 (d, J = 6.0 Hz, 1H), 4.96−4.87 (m, 1H), 3.97 (t, J = 6.0 Hz, 2H), 3.76−3.55 (m, 3H), 3.51 (t, J

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= 6.0 Hz, 2H), 3.45 (br s, 1H), 3.32 (s, 3H), 2.05−1.93 (m, 2H), 1.47 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 158.2, 141.2, 130.9, 128.7, 127.4, 127.1, 114.5, 69.1, 66.0, 64.7, 58.5, 55.0, 48.8, 29.4, 18.3; HRMS (ESI) m/z: calcd for $C_{21}H_{27}NO_4$ $[M + H]^+$, 358.2013; m/z: found, 358.2017.

*(2S)-N-[(1R)-2-Hydroxy-1-{4-[(1-methylcyclobutyl)methoxy]-phenyl}ethyl]-2-phenylpropanamide (**24**).* The procedure for the synthesis of **12** was followed starting with **11m** to give **24** (83% yield) as a white waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46−7.21 (m, 5H), 7.08 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.91 (d, J = 6.5 Hz, 1H), 4.96 (dd, J = 11.1, 5.9 Hz, 1H), 3.86−3.67 (m, 4H), 3.60 (q, J = 7.2 Hz, 1H), 2.58 (t, J = 6.0 Hz, 1H), 2.09−1.81 (m, 4H), 1.81−1.68 (m, 2H), 1.54 (d, J = 7.2 Hz, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 159.4, 141.2, 130.6, 129.0, 127.6, 127.5, 127.4, 114.9, 75.7, 66.8, 55.7, 47.2, 38.7, 30.1, 24.5, 18.5, 15.0; HRMS (ESI) m/z: calcd for $C_{23}H_{29}NO_3$ $[M + H]^+$, 368.2220; m/z: found, 368.2214.

*(2S)-N-[(1R)-2-Hydroxy-1-{4-[(3-methylcyclobutyl)methoxy]-phenyl}ethyl]-2-phenylpropanamide (**25**).* The procedure for the synthesis of **12** was followed starting with **11n** to give **25** (65% yield) as a white waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.09 (m, 5H), 6.94 (dd, J = 8.6, 2.0 Hz, 2H), 6.81−6.72 (m, 2H), 6.08 (d, J = 6.5 Hz, 1H), 4.94 (dd, J = 11.3, 5.5 Hz, 1H), 3.90 (d, J = 7.1 Hz, 1H), 3.80 (d, J = 6.4 Hz, 1H), 3.74 (br s, 2H), 3.61 (q, J = 7.1 Hz, 1H), 2.90−2.80 (m, 1H), 2.78−2.60 (m, 0.5 H), 2.60−2.35 (m, 1H), 2.35−2.14 (m, 1.5 H), 2.07−1.91 (m, 1H), 1.82−1.67 (m, 1H), 1.50 (d, J = 7.1 Hz, 3H), 1.46−1.31 (m, 1H), 1.12 (d, J = 6.8 Hz, 1.4H), 1.04 (d, J = 6.1 Hz, 1.6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 158.8, 158.8, 141.3, 130.7, 130.7, 128.9, 127.6, 127.5, 127.3, 114.8, 72.8, 72.2, 66.6, 55.3, 47.1, 33.2, 31.5, 30.6, 30.3, 27.0, 26.8, 22.3, 22.1, 18.4; HRMS (ESI) m/z: calcd for $C_{23}H_{29}NO_3$ $[M + H]^+$, 368.2220; m/z: found, 368.2213.

*(2S)-N-[(1R)-1-{4-[(3,3-Dimethylcyclobutyl)methoxy]phenyl}-2-hydroxyethyl]-2-phenylpropanamide (**26**).* The procedure for the synthesis of **12** was followed starting with **11o** to give **26** (75% yield) as a white waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44−7.20 (m, 5H), 7.06 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.95 (d, J = 6.7 Hz, 1H), 4.94 (dd, J = 11.4, 5.5 Hz, 1H), 3.86 (d, J = 6.6 Hz, 2H), 3.80−3.65 (m, 2H), 3.58 (q, J = 7.2 Hz, 1H), 2.75−2.44 (m, 2H), 1.98−1.76 (m, 2H), 1.67−1.57 (m, 2H), 1.52 (d, J = 7.2 Hz, 3H), 1.17 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 158.9, 141.2, 130.7, 129.0, 127.6, 127.5, 127.4, 114.9, 73.1, 66.7, 55.6, 47.2, 37.7, 31.9, 30.9, 28.9, 27.2, 18.5; HRMS (ESI) m/z: calcd for $C_{24}H_{31}NO_3$ $[M + H]^+$, 382.2377; m/z: found, 382.2368.

*(2S)-N-[(1R)-2-Hydroxy-1-[4-({spiro[2.3]hexan-5-yl}methoxy)-phenyl]ethyl]-2-phenylpropanamide (**27**).* The procedure for the synthesis of **12** was followed starting with **11p** to give **27** (80% yield) as a white waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44−7.22 (m, 5H), 7.08 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.93 (d, J = 6.7 Hz, 1H), 4.96 (dd, J = 11.4, 5.5 Hz, 1H), 4.01 (d, J = 7.1 Hz, 2H), 3.86−3.67 (m, 2H), 3.60 (q, J = 7.1 Hz, 1H), 2.93−2.71 (m, 1H), 2.56 (t, J = 6.0 Hz, 1H), 2.32−2.11 (m, 2H), 2.04−1.81 (m, 2H), 1.54 (d, J = 7.2 Hz, 3H), 0.58−0.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 159.0, 141.2, 130.7, 129.0, 127.7, 127.5, 127.4, 115.0, 72.6, 66.7, 55.7, 47.2, 33.4, 29.8, 18.5, 16.9, 12.1, 11.7; HRMS (ESI) m/z: calcd for $C_{24}H_{29}NO_3$ $[M + H]^+$, 380.2220; m/z: found, 380.2214.

*(2S)-N-[(1R)-1-{4-[(3,3-Difluorocyclobutyl)methoxy]phenyl}-2-hydroxyethyl]-2-phenylpropanamide (**28**).* The procedure for the synthesis of **12** was followed starting with **11q** to give **28** (50% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.22 (m, 5H), 6.97 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.00 (d, J = 7.0 Hz, 1H), 4.96 (dd, J = 11.8, 4.9 Hz, 1H), 3.94 (d, J = 5.9 Hz, 2H), 3.77 (d, J = 5.1 Hz, 2H), 3.63 (q, J = 7.1 Hz, 1H), 2.82−2.61 (m, 2H), 2.61−2.33 (m, 4H), 1.52 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 158.2, 141.2, 131.4, 128.9, 127.6, 127.6, 127.3, 114.8, 70.1 (m), 55.2, 47.1, 37.7 (t, J = 23.0 Hz), 22.5 (dd, J = 12.0, 7.4 Hz), 18.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ −83.8 (d, J = 193 Hz), −93.2 (d, J = 196 Hz); HRMS (ESI) m/z: calcd for $C_{22}H_{25}F_2NO_3$ $[M + H]^+$, 390.1875; m/z: found, 390.1867.

*(2R)-2-{4-[(2-Methylpentyl)oxy]phenyl}-2-[(2S)-2-phenylpropanamido]acetic Acid (**29a**).*[28] To a solution of **3** (1.2 g, 3.02 mmol) in THF/H_2O (10 mL, 1:1, v/v) was added 1 N NaOH (6.04 mL, 6.04 mmol) at room temperature. After stirring for 1 h, the reaction was cooled (ice bath) and acidified (pH = ∼4) with 1 N HCl and extracted with EtOAc (3 × 20 mL). The combined EtOAc layers were washed with brine (3 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to furnish **29a** (1.06 g, 92%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.17 (m, 5H), 7.11 (d, J = 8.1 Hz, 2H), 6.79 (d, J = 8.2 Hz, 2H), 6.21 (d, J = 6.1 Hz, 1H), 5.43 (d, J = 6.3 Hz, 1H), 3.82−3.72 (m, 1H), 3.71−3.57 (m, 2H), 2.01−1.78 (m, 1H), 1.49 (d, J = 7.1 Hz, 3H), 1.45−1.07 (m, 4H), 0.99 (d, J = 6.6 Hz, 3H), 0.91 (t, J = 6.7 Hz, 3H); MS (ESI) m/z: 384.4 $[M + H]^+$.

*(2R)-2-[4-(Cyclobutylmethoxy)phenyl]-2-[(2S)-2-phenylpropanamido]acetic Acid (**29b**).* The procedure for the synthesis of **29a** was followed starting with **11h** to give **29b** (100% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32−7.20 (m, 6H), 7.10 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 6.25 (d, J = 6.6 Hz, 1H), 5.43 (d, J = 6.7 Hz, 1H), 3.87 (d, J = 6.7 Hz, 2H), 3.63 (q, J = 7.1 Hz, 1H), 2.82−2.62 (m, 1H), 2.22−2.03 (m, 2H), 2.03−1.73 (m, 4H), 1.49 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 174.1, 159.5, 140.7, 128.9, 128.3, 127.6, 127.4, 127.4, 114.9, 72.1, 56.1, 46.7, 34.5, 24.8, 18.5, 18.2; MS (ESI) m/z: 368.0 $[M + H]^+$.

*(2S)-N-[(R)-Carbamoyl({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide (**30**).* To a solution of **29a** (230 mg, 0.6 mmol) in dioxane (10 mL) at room temperature were added pyridine (0.1 mL, 1.2 mmol), NH_4HCO_3 (95 mg, 1.2 mmol), and Boc anhydride (262 mg, 1.2 mmol). The reaction mixture was stirred for 4 h. Another portion of NH_4HCO_3 (95 mg, 1.2 mmol) and Boc anhydride (262 mg, 1.2 mmol) was added, and the mixture was stirred overnight. The reaction was quenched by 10% citric acid (10 mL) and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with 10% citric acid (10 mL), $NaHCO_3$ (2 × 10 mL), and brine (10 mL), dried ($NaSO_4$), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using 0−3% MeOH in DCM to provide **30** (100 mg, 44% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.15 (m, 5H), 7.09 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 6.61 (s, 1H), 5.85 (s, 1H), 5.54 (d, J = 6.0 Hz, 1H), 3.84−3.54 (m, 3H), 1.98−1.81 (m, 1H), 1.44 (d, J = 9.0 Hz, 3H), 1.41−1.08 (m, 4H), 0.98 (d, J = 9.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 172.8, 159.2, 141.1, 129.4, 128.7, 128.1, 127.5, 127.1, 114.7, 73.2, 56.0, 46.6, 35.7, 32.8, 20.0, 18.3, 16.9, 14.3; HRMS (ESI) m/z: calcd for $C_{23}H_{30}N_2O_3$ $[M + H]^+$, 383.2329; m/z: found, 383.2332.

*(2S)-N-[(R)-(Methylcarbamoyl)({4-[(2-methylpentyl)oxy]phenyl})-methyl]-2-phenylpropanamide (**31**).* To a solution of **29a** (115 mg, 0.3 mmol) in DMF (5 mL) under nitrogen were added EDC hydrochloride (63 mg, 0.33 mmol), HOBt (45 mg, 0.33 mmol), and DIPEA (0.16 mL, 0.9 mmol). After cooling to 0 °C, methylamine hydrochloride (22 mg, 0.33 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with 10% citric acid solution (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using 0−100% EtOAc in hexanes to furnish **31** (56 mg, 47% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.18 (m, 5H), 7.17−6.96 (m, 4H), 6.68 (d, J = 9.0 Hz, 2H), 5.62 (d, J = 9.0 Hz, 1H), 3.79−3.54 (m, 3H), 2.70 (d, J = 6.0 Hz, 2H), 1.99−1.81 (m, 1H), 1.55−1.12 (m, 5H), 1.48 (d, J = 9.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 171.0, 159.0, 141.2, 129.9, 128.7, 128.0, 127.5, 127.1, 114.6, 73.1, 56.2, 46.6, 35.7, 32.8, 26.3, 20.0, 18.4, 16.9, 14.2; HRMS (ESI) m/z: calcd for $C_{24}H_{32}N_2O_3$ $[M + H]^+$, 397.2486; m/z: found, 397.2482.

*(2S)-N-((1R)-2-(Ethylamino)-1-(4-((2-methylpentyl)oxy)phenyl)-2-oxoethyl)-2-phenylpropanamide (**32**).* The procedure for the

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synthesis of **31** was followed starting with **29a** and ethylamine to give **32** (53% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.17 (m, 5H), 7.08 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 6.5 Hz, 1H), 5.64 (br s, 1H), 5.28 (d, J = 6.6 Hz, 1H), 3.76 (dd, J = 8.8, 5.8 Hz, 1H), 3.70−3.54 (m, 2H), 3.35−3.08 (m, 2H), 2.03−1.77 (m, 1H), 1.53−1.11 (m, 7H), 1.05 (t, J = 7.3 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 170.2, 159.0, 141.2, 130.0, 128.8, 128.1, 127.5, 127.1, 114.7, 73.2, 56.4, 46.7, 35.7, 34.6, 32.9, 20.0, 18.4, 17.0, 14.5, 14.3; HRMS (ESI) m/z: calcd for $C_{25}H_{34}N_2O_3$ $[M + H]^+$, 411.2642; m/z: found, 411.2639.

*(2S)-N-[(R)-{4-[(2-Methylpentyl)oxy]phenyl}(propylcarbamoyl)-methyl]-2-phenylpropanamide (**33**).* The procedure for the synthesis of **31** was followed starting with **29a** and propylamine hydrochloride to give **33** (39% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.17 (m, 5H), 7.06 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 6.0 Hz, 1H), 6.70 (d, J = 9.0 Hz, 2H), 6.68−6.55 (m, 1H), 5.63 (d, J = 9.0 Hz, 1H), 3.78−3.55 (m, 3H), 3.23−3.03 (m, 2H), 1.98−1.81 (m, 1H), 1.55−1.10 (m, 6H), 1.48 (d, J = 9.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H), 0.79 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 170.3, 159.0, 141.2, 130.0, 128.7, 128.0, 127.5, 127.1, 114.6, 73.2, 56.4, 46.7, 41.4, 35.7, 32.8, 22.6, 20.0, 18.4, 16.9, 14.2, 11.2; HRMS (ESI) m/z: calcd for $C_{26}H_{36}N_2O_3$ $[M + H]^+$, 425.2799; m/z: found, 425.2798.

*(2S)-N-[(R)-{4-[(2-Methylpentyl)oxy]phenyl}[(propan-2-yl)-carbamoyl]methyl]-2-phenylpropanamide (**34**).* The procedure for the synthesis of **31** was followed starting with **29a** and isopropylamine to give **34** (41% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.16 (m, 5H), 7.03 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 1H), 6.68 (d, J = 9.0 Hz, 2H), 6.39 (d, J = 9.0 Hz, 1H), 5.49 (d, J = 6.0 Hz, 1H), 4.07−3.90 (m, 1H), 3.80−3.57 (m, 3H), 1.98−1.81 (m, 1H), 1.52−1.14 (m, 4H), 1.48 (d, J = 9.0 Hz, 3H), 1.12 (d, J = 6.0 Hz, 3H), 1.00 (d, J = 6.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 169.4, 158.9, 141.2, 130.0, 128.7, 128.0, 127.5, 127.1, 114.6, 73.2, 56.3, 46.7, 41.7, 35.7, 32.9, 22.5, 22.3, 20.0, 18.5, 16.9, 14.2; HRMS (ESI) m/z: calcd for $C_{26}H_{36}N_2O_3$ $[M + H]^+$, 425.2799; m/z: found, 425.2804.

*(2S)-N-((1R)-2-(tert-Butylamino)-1-(4-((2-methylpentyl)oxy)-phenyl)-2-oxoethyl)-2-phenylpropanamide (**35**).* To a solution of **29a** (50 mg, 0.13 mmol) in THF (2 mL) were added 2-chloro-4,6-dimethoxy-1,3,5-triazine (22.9 mg, 0.13 mmol) and *N*-methylmorpholine (15 μL, 13.5 mmol). The reaction that resulted was stirred at room temperature. After 1 h, *tert*-butylamine (21 μL, 0.2 mmol) was added to the above cloudy solution, and the reaction that resulted was stirred overnight at room temperature. The solvent was evaporated, and the residue was subjected to column chromatography on silica gel using 0−50% EtOAc in hexanes to furnish **35** (28 mg, 49% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.13 (m, 5H), 7.08 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 6.6 Hz, 1H), 5.30 (br s, 1H), 5.19 (d, J = 6.7 Hz, 1H), 3.82−3.71 (m, 1H), 3.71−3.50 (m, 2H), 2.05−1.72 (m, 1H), 1.46 (d, J = 7.1 Hz, 3H), 1.44−1.13 (m, 13H), 1.00 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 169.2, 159.1, 141.4, 130.3, 128.7, 128.2, 127.5, 127.0, 114.8, 73.2, 56.9, 51.7, 46.8, 35.8, 32.9, 28.6, 20.0, 18.5, 17.0, 14.3; HRMS (ESI) m/z: calcd for $C_{27}H_{38}N_2O_3$ $[M + H]^+$, 439.2955; m/z: found, 439.2957.

*(2S)-N-[(R)-[(Butan-2-yl)carbamoyl]({4-[(2-methylpentyl)oxy]-phenyl})methyl]-2-phenylpropanamide (**36**).* The procedure for the synthesis of **31** was followed starting with **29a** and butan-2-amine to give **36** (42% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.16 (m, 5H), 7.07 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 5.94−5.83 (m, 1H), 5.40 (d, J = 6.0 Hz, 1H), 3.90−3.55 (m, 4H), 1.99−1.83 (m, 1H), 1.53−1.12 (m, 6H), 1.48 (d, J = 6.0 Hz, 3H), 1.09 (d, J = 6.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 169.6, 159.0, 141.2, 130.2, 128.8, 128.1, 127.5, 127.1, 114.7, 73.2, 56.6, 47.0, 46.8, 35.7, 32.9, 29.4, 20.4, 20.0, 18.5, 17.0, 14.3, 10.0; HRMS (ESI) m/z: calcd for $C_{27}H_{38}N_2O_3$ $[M + H]^+$, 439.2955; m/z: found, 439.2952.

*(2S)-N-((1R)-2-((3-Methylbutan-2-yl)amino)-1-(4-((2-methylpentyl)oxy)phenyl)-2-oxoethyl)-2-phenylpropanamide (**37**).* The procedure for the synthesis of **31** was followed starting with **29a** and 1,2-dimethylpropylamine to give **37** (44% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.16 (m, 5H), 7.08 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 6.5 Hz, 1H), 6.76 (d, J = 8.7 Hz, 2H), 5.53 (d, J = 9.0 Hz, 1H), 5.30 (d, J = 6.5 Hz, 1H), 3.87−3.69 (m, 2H), 3.69−3.41 (m, 2H), 2.04−1.75 (m, 1H), 1.73−1.10 (m, 8H), 1.01 (dd, J = 13.6, 6.7 Hz, 6H), 0.91 (t, J = 7.0 Hz, 3H), 0.69−0.58 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 169.4, 159.1, 141.2, 130.3, 128.8, 128.1, 127.5, 127.1, 114.8, 73.3, 56.8, 50.4, 46.9, 35.7, 32.9, 32.9, 20.0, 18.4, 18.3, 18.0, 17.6, 16.9, 14.3; HRMS (ESI) m/z: calcd for $C_{28}H_{40}N_2O_3$ $[M + H]^+$, 453.3112; m/z: found, 453.3110.

*(2S)-N-[(R)-(Cyclopropylcarbamoyl)({4-[(2-methylpentyl)oxy]-phenyl})methyl]-2-phenylpropanamide (**38**).* The procedure for the synthesis of **31** was followed starting with **29a** and cyclopropylamine to give **38** (35% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.16 (m, 5H), 7.06−6.93 (m, 3H), 6.86 (d, J = 6.0 Hz, 1H), 6.88 (d, J = 9.0 Hz, 2H), 5.49 (d, J = 6.0 Hz, 1H), 3.79−3.56 (m, 3H), 2.68−2.57 (m, 1H), 1.98−1.85 (m, 1H), 1.51−1.10 (m, 4H), 1.48 (d, J = 6.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H), 0.76−0.57 (m, 2H), 0.52−0.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 171.7, 159.0, 141.1, 129.7, 128.8, 128.0, 127.5, 127.1, 114.6, 73.2, 56.1, 46.7, 35.7, 32.9, 22.7, 20.0, 18.4, 17.0, 14.2, 6.4, 6.2; HRMS (ESI) m/z: calcd for $C_{26}H_{34}N_2O_3$ $[M + H]^+$, 423.2642; m/z: found, 423.2647.

*(2S)-N-((1R)-2-((Cyclopropylmethyl)amino)-1-(4-((2-methylpentyl)oxy)phenyl)-2-oxoethyl)-2-phenylpropanamide (**39**).* The procedure for the synthesis of **31** was followed starting with **29a** and cyclopropylmethylamine hydrochloride to give **39** (49% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.18 (m, 5H), 7.07 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 7.2 Hz, 1H), 6.70 (d, J = 8.7 Hz, 2H), 6.57 (t, J = 5.4 Hz, 1H), 5.53 (d, J = 7.2 Hz, 1H), 3.82−3.52 (m, 3H), 3.15−2.92 (m, 2H), 2.04−1.78 (m, 1H), 1.48 (d, J = 7.1 Hz, 3H), 1.45−1.11 (m, 4H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H), 0.88−0.77 (m, 1H), 0.47−0.35 (m, 2H), 0.15−0.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 170.3, 159.1, 141.3, 130.0, 128.8, 128.1, 127.5, 127.1, 114.7, 73.2, 56.4, 46.8, 44.3, 35.7, 32.9, 20.0, 18.5, 17.0, 14.3, 10.5, 3.3, 3.2; HRMS (ESI) m/z: calcd for $C_{27}H_{36}N_2O_3$ $[M + H]^+$, 437.2799; m/z: found, 437.2793.

*(2S)-N-[(R)-(Cyclobutylcarbamoyl)({4-[(2-methylpentyl)oxy]-phenyl})methyl]-2-phenylpropanamide (**40**).* The procedure for the synthesis of **31** was followed starting with **29a** and cyclobutylamine to give **40** (35% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.17 (m, 5H), 7.04 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 6.0 Hz, 1H), 6.70 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 9.0 Hz, 1H), 5.45 (d, J = 6.0 Hz, 1H), 4.36−4.20 (m, 1H), 3.80−3.56 (m, 3H), 2.35−2.13 (m, 2H), 1.97−1.57 (m, 5H), 1.54−1.10 (m, 4H), 1.49 (d, J = 6.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 169.3, 159.0, 141.2, 129.9, 128.8, 128.1, 127.5, 127.1, 114.7, 73.2, 58.3, 46.8, 45.0, 35.7, 32.9, 30.8, 30.7, 20.0, 18.4, 17.0, 15.0, 14.3; HRMS (ESI) m/z: calcd for $C_{27}H_{36}N_2O_3$ $[M + H]^+$, 437.2799; m/z: found, 437.2806.

*(2S)-N-((1R)-2-((1-Methylcyclobutyl)amino)-1-(4-((2-methylpentyl)oxy)phenyl)-2-oxoethyl)-2-phenylpropanamide (**41**).* The procedure for the synthesis of **31** was followed starting with **29a** and 1-methylcyclobutylamine to give **41** (48% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.13 (m, 5H), 7.07 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 5.89 (s, 1H), 5.29 (d, J = 6.8 Hz, 1H), 3.76 (dd, J = 8.9, 5.8 Hz, 1H), 3.71−3.54 (m, 2H), 2.26−2.03 (m, 2H), 2.03−1.85 (m, 3H), 1.83−1.67 (m, 2H), 1.54−1.10 (m, 10H), 1.00 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 168.9, 159.1, 141.3, 130.2, 128.8, 128.2, 127.5, 127.1, 114.8, 73.2, 56.6, 54.5, 46.8, 35.7, 34.4, 34.3, 32.9, 25.0, 20.0, 18.5, 17.0, 14.5, 14.3; HRMS (ESI) m/z: calcd for $C_{28}H_{38}N_2O_3$ $[M + H]^+$, 451.2955; m/z: found, 451.2950.

*(2S)-N-[(R)-(Cyclopentylcarbamoyl)({4-[(2-methylpentyl)oxy]-phenyl})methyl]-2-phenylpropanamide (**42**).* The procedure for the synthesis of **31** was followed starting with **29a** and cyclopentylamine to give **42** (33% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$):

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δ 7.38−7.15 (m, 5H), 7.06 (d, J = 8.6 Hz, 2H), 6.87−6.64 (m, 3H), 5.90 (d, J = 7.3 Hz, 1H), 5.35 (d, J = 6.9 Hz, 1H), 4.28−4.02 (m, 1H), 3.75 (dd, J = 8.9, 5.8 Hz, 1H), 3.70−3.55 (m, 2H), 2.04−1.76 (m, 3H), 1.66−1.28 (m, 11H), 1.27−1.10 (m, 2H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 169.7, 159.1, 141.2, 130.0, 128.8, 128.1, 127.5, 127.1, 114.8, 73.2, 56.5, 51.5, 46.8, 35.7, 32.9, 32.8, 32.8, 23.7, 23.6, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) *m/z*: calcd for $C_{28}H_{38}N_2O_3$ $[M + H]^+$, 451.2955; *m/z*: found, 451.2952.

*(2S)-N-[(R)-(Cyclohexylcarbamoyl)({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide (**43**).* The procedure for the synthesis of **31** was followed starting with **29a** and cyclohexylamine to give **43** (54% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.15 (m, 5H), 7.06 (d, J = 8.7 Hz, 2H), 6.85−6.64 (m, 3H), 5.75 (d, J = 7.6 Hz, 1H), 5.33 (d, J = 6.9 Hz, 1H), 3.83−3.53 (m, 4H), 2.01−1.77 (m, 2H), 1.76−1.51 (m, 5H), 1.48 (d, J = 7.1 Hz, 3H), 1.46−1.03 (m, 8H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 169.2, 159.1, 141.2, 130.1, 128.8, 128.2, 127.5, 127.1, 114.8, 73.2, 56.6, 48.6, 46.9, 35.7, 32.9, 32.8, 32.6, 25.4, 24.7, 24.6, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) *m/z*: calcd for $C_{29}H_{40}N_2O_3$ $[M + H]^+$, 465.3122; *m/z*: found, 465.3111.

*Methyl 2-[(2R)-2-{4-[(2-Methylpentyl)oxy]phenyl}-2-[(2S)-2-phenylpropanamido]acetamido]acetate (**44**).* The procedure for the synthesis of **31** was followed starting with **29a** and methyl 2-aminoacetate hydrochloride to give **44** (46% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.16 (m, 5H), 7.10 (d, J = 9.0 Hz, 2H), 6.88 (t, J = 4.5 Hz, 1H), 6.82−6.67 (m, 3H), 5.54 (d, J = 6.0 Hz, 1H), 3.93 (t, J = 6.0 Hz, 2H), 3.79−3.58 (m, 6H), 1.97−1.85 (m, 1H), 1.54−1.13 (m, 4H), 1.47 (d, J = 9.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 170.6, 169.8, 159.2, 141.1, 129.3, 128.8, 128.2, 127.5, 127.1, 114.7, 73.2, 56.4, 52.3, 46.7, 41.3, 35.7, 32.8, 20.0, 18.4, 16.9, 14.3; HRMS (ESI) *m/z*: calcd for $C_{26}H_{34}N_2O_5$ $[M + H]^+$, 455.2540; *m/z*: found, 455.2541.

*(2S)-N-[(R)-[(2-Hydroxyethyl)carbamoyl]({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide (**45**).* To a suspension of $NaBH_4$ (11 mg, 0.29 mmol) in EtOH (2 mL) at 0 °C under nitrogen was added LiCl (12 mg, 0.29 mmol). After stirring at 0 °C for 10 min, a solution of **44** (50 mg, 0.11 mmol) in THF (2 mL) was added. The reaction mixture was stirred at room temperature for 3 h and quenched with saturated NH_4Cl solution (5 mL), followed by addition of H_2O (10 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using 20−70% EtOAc in hexanes to afford **45** (38 mg, 81% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28−7.08 (m, 5H), 7.07−6.88 (m, 3H), 6.76 (d, J = 6.0 Hz, 1H), 6.65 (d, J = 9.0 Hz, 2H), 5.39 (d, J = 6.0 Hz, 1H), 3.71−3.44 (m, 4H), 3.44−3.26 (m, 1H), 3.20−3.04 (m, 1H), 1.92−1.74 (m, 1H), 1.46−1.01 (m, 6H), 1.40 (d, J = 9.0 Hz, 3H), 0.92 (d, J = 9.0 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 171.2, 159.2, 141.0, 129.2, 128.8, 128.1, 127.5, 127.2, 114.8, 73.2, 61.6, 56.7, 46.7, 42.5, 35.7, 32.9, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) *m/z*: calcd for $C_{25}H_{34}N_2O_4$ $[M + H]^+$, 427.2591; *m/z*: found, 427.2589.

*(2S)-N-[(R)-[(2-Methoxyethyl)carbamoyl]({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide (**46**).* The procedure for the synthesis of **31** was followed starting with **29a** and 2-methoxyethan-1-amine to give **46** (42% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29−7.09 (m, 5H), 7.00 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 6.0 Hz, 1H), 6.66 (d, J = 9.0 Hz, 2H), 6.37 (br s, 1H), 5.35 (d, J = 6.0 Hz, 1H), 3.73−3.62 (m, 1H), 3.61−3.50 (m, 2H), 3.42−3.18 (m, 4H), 3.17 (s, 3H), 1.91−1.74 (m, 1H), 1.49−1.05 (m, 4H), 1.40 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.0 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 170.3, 159.1, 141.2, 129.8, 128.7, 128.1, 127.5, 127.1, 114.7, 73.2, 70.8, 58.7, 56.5, 46.7, 39.4, 35.7, 32.8, 20.0, 18.4, 16.9, 14.2; HRMS (ESI) *m/z*: calcd for $C_{26}H_{36}N_2O_4$ $[M + H]^+$, 441.2748; *m/z*: found, 441.2743.

*(2S)-N-[(R)-{4-[(2-Methylpentyl)oxy]phenyl}({[(oxolan-2-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**47**).* The procedure for the synthesis of **31** was followed starting with **29a** and tetrahydrofurfurylamine to give **47** (88% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.18 (m, 5H), 7.08 (d, J = 8.6 Hz, 2H), 6.82−6.66 (m, 3H), 6.19−6.03 (m, 1H), 5.35 (t, J = 7.2 Hz, 1H), 3.95−3.49 (m, 6H), 3.50−3.32 (m, 1H), 3.32−3.06 (m, 1H), 2.01−1.64 (m, 3H), 1.64−1.08 (m, 8H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 173.2, 170.4, 170.3, 159.2, 159.2, 141.3, 141.2, 130.2, 129.8, 128.8, 128.2, 128.1, 127.6, 127.1, 114.8, 77.3, 73.3, 73.2, 68.1, 68.1, 56.8, 56.7, 46.8, 43.2, 42.9, 35.7, 32.9, 28.5, 28.2, 25.8, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) *m/z*: calcd for $C_{28}H_{38}N_2O_4$ $[M + H]^+$, 467.2904; *m/z*: found, 467.2905.

*tert-Butyl N-{2-[(2R)-2-{4-[(2-Methylpentyl)oxy]phenyl}-2-[(2S)-2-phenylpropanamido]acetamido]ethyl}carbamate (**48**).* The procedure for the synthesis of **31** was followed starting with **29a** and *N*-Boc-ethylenediamine hydrochloride to give **48** (55% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.17 (m, 5H), 7.06 (d, J = 8.7 Hz, 2H), 6.84−6.65 (m, 4H), 5.35 (d, J = 6.7 Hz, 1H), 4.92 (d, J = 5.5 Hz, 1H), 3.74 (dd, J = 8.9, 5.8 Hz, 1H), 3.69−3.55 (m, 2H), 3.40−3.04 (m, 4H), 2.05−1.73 (m, 1H), 1.47 (d, J = 7.1 Hz, 3H), 1.45−1.11 (m, 13H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 170.8, 159.2, 141.2, 129.6, 128.8, 128.1, 127.5, 127.2, 114.8, 79.7, 73.2, 56.8, 46.8, 40.8, 40.0, 35.7, 32.9, 28.3, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) *m/z*: calcd for $C_{30}H_{43}N_3O_5$ $[M + H]^+$, 526.3275; *m/z*: found, 526.3267.

*(2S)-N-[(R)-[(2-Aminoethyl)carbamoyl]({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide Hydrochloride (**49**).* To a solution of **48** (14.1 mg, 0.03 mmol) in DCM, HCl (4 M in dioxane, 67 μL, 0.27 mmol) was added at 0 °C. The reaction that resulted was warmed to room temperature and stirred until completion. After the completion of the reaction, the solvent was evaporated, and the residue was redissolved in DCM and evaporated under reduced pressure (three times). The residue was dried *in vacuo* to furnish **49** as hydrochloride salt (9.7 mg, 78%) as a thick colorless oil. ^{1}H NMR (300 MHz, CD_3OD): δ 7.36−7.15 (m, 7H), 6.86 (d, J = 8.7 Hz, 2H), 5.11 (s, 1H), 3.84−3.53 (m, 4H), 3.37−3.22 (m, 1H), 3.19−2.94 (m, 2H), 2.00−1.76 (m, 1H), 1.57−1.14 (m, 7H), 1.00 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 177.3, 174.4, 161.0, 142.8, 130.2, 129.5, 129.1, 128.5, 128.0, 115.8, 74.3, 59.4, 48.4, 41.0, 38.3, 36.9, 34.1, 21.1, 18.9, 17.3, 14.6; HRMS (ESI) free base *m/z*: calcd for $C_{25}H_{35}N_3O_3$ $[M + H]^+$, 426.2751; *m/z*: found, 426.2750.

*tert-Butyl N-Methyl-N-{2-[(2R)-2-{4-[(2-methylpentyl)oxy]phenyl}-2-[(2S)-2-phenylpropanamido]acetamido]ethyl}carbamate (**50**).* The procedure for the synthesis of **31** was followed starting with **29a** and *N*-Boc-*N*-methylethylenediamine to give **50** (32% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.15 (m, 5H), 7.06 (d, J = 8.6 Hz, 2H), 6.97 (br s, 1H), 6.84 (d, J = 6.7 Hz, 1H), 6.72 (d, J = 8.6 Hz, 2H), 5.62−4.88 (m, 1H), 3.80−3.57 (m, 3H), 3.27 (br s, 4H), 2.74 (br s, 3H), 2.01−1.78 (m, 1H), 1.46 (d, J = 7.2 Hz, 3H), 1.44−1.10 (m, 13H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 170.6, 159.1, 156.8, 141.3, 129.9, 128.8, 128.1, 127.5, 127.1, 114.7, 79.9, 73.2, 56.6, 47.6, 46.7, 39.1, 35.7, 35.0, 32.9, 28.4, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) *m/z*: calcd for $C_{31}H_{45}N_3O_5$ $[M + H]^+$, 540.3432; *m/z*: found, 540.3424.

*(2S)-N-[(R)-{[2-(Methylamino)ethyl]carbamoyl}({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide Hydrochloride (**51**).* The procedure for the synthesis of **49** was followed starting with **50** to give **51** as hydrochloride salt (94%) as a thick colorless oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.62−8.38 (m, 1H), 7.37−7.12 (m, 7H), 6.85 (d, J = 8.7 Hz, 2H), 5.17−5.06 (m, 1H), 3.89−3.61 (m, 4H), 3.40−3.32 (m, 1H), 3.26−3.03 (m, 2H), 2.73 (s, 3H), 2.05−1.75 (m, 1H), 1.57−1.13 (m, 7H), 0.99 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 179.9, 176.9, 163.6, 145.3, 132.7, 132.1, 131.6, 131.0, 130.5, 118.3, 76.9, 62.0, 53.0, 49.3, 39.6, 39.4, 36.6, 36.4, 23.6, 21.4, 19.8, 17.2; HRMS

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(ESI) free base m/z: calcd for $C_{26}H_{37}N_3O_3$ $[M + H]^+$, 440.2908; m/z: found, 440.2923.

*(2S)-N-[(R)-{[2-(Dimethylamino)ethyl]carbamoyl}({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide (**52**).* A solution of **29a** (77 mg, 0.20 mmol) in DCM (5 mL) was cooled to 0 °C. To that above solution oxalyl chloride (0.4 mmol, 34 μL) and DMF (catalytic) were added sequentially. The reaction that resulted was stirred at room temperature for 2 h. At that time, the solvent was removed, and the residue was dried *in vacuo* for 1 h. The yellow color residue was redissolved in DCM (5 mL) and DIPEA (350 μL, 2.0 mmol), and *N*,*N*-dimethylethylenediamine (88.5 mg, 1.0 mmol) was added. The reaction that resulted was stirred at room temperature for 14 h. The solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using 0−50% CMA80 in DCM to furnish the amide **52** (37 mg, 41%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.08 (m, 6H), 6.95 (d, J = 6.7 Hz, 1H), 6.79 (dd, J = 18.1, 8.7 Hz, 2H), 6.69 (s, 1H), 5.33 (d, J = 6.7 Hz, 1H), 3.82−3.52 (m, 3H), 3.47−3.28 (m, 1H), 3.28−2.97 (m, 1H), 2.56−2.32 (m, 2H), 2.32−2.16 (m, 6H), 2.03−1.78 (m, 1H), 1.62−1.09 (m, 8H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 170.0, 158.8, 140.7, 129.5, 128.3, 128.0, 127.3, 126.7, 114.4, 72.8, 57.0, 56.4, 46.5, 44.2, 36.0, 35.3, 32.4, 19.6, 18.1, 16.5, 13.8; HRMS (ESI) m/z: calcd for $C_{27}H_{39}N_3O_3$ $[M + H]^+$, 454.3064; m/z: found, 454.3059.

*(2S)-N-[(R)-{4-[(2-Methylpentyl)oxy]phenyl}({[(pyrrolidin-2-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**53**).* The procedure for the synthesis of **31** was followed starting with **29a** and 1-Boc-2-(aminomethyl)pyrrolidine to give *N*-Boc-**53** (68% yield). The *N*-Boc compound (100.0 mg, 0.18 mmol) was dissolved in DCM (2 mL) and cooled to 0 °C. To that above solution, HCl (4 M in dioxane, 440 μL, 1.77 mmol) was added, and the reaction that resulted was stirred at room temperature until complete conversion. After that, the reaction was diluted with DCM (10 mL) and basified with saturated $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with additional DCM (2 × 10 mL). The combined organic layers were washed with brine, dried (K_2CO_3), and evaporated to furnish the free base **53** (72 mg, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.18 (m, 5H), 7.08 (d, J = 8.6 Hz, 2H), 6.96 (dd, J = 6.8, 2.3 Hz, 1H), 6.90−6.81 (m, 1H), 6.72 (d, J = 8.6 Hz, 2H), 5.42 (dd, J = 6.9, 2.0 Hz, 1H), 3.82−3.53 (m, 3H), 3.37−2.90 (m, 3H), 2.90−2.57 (m, 2H), 2.32 (br s, 1H), 2.07−1.82 (m, 1H), 1.79−1.06 (m, 11H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 173.4, 170.5, 170.4, 159.1, 141.3, 130.1, 130.1, 128.7, 128.1, 127.5, 127.1, 114.7, 73.2, 57.4, 57.4, 56.6, 46.7, 46.4, 46.3, 44.0, 43.8, 35.7, 32.9, 29.0, 28.8, 25.6, 25.6, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) m/z: calcd for $C_{28}H_{39}N_3O_3$ $[M + H]^+$, 466.3064; m/z: found, 464.3077.

*(2S)-N-[(R)-{[(Azetidin-3-yl)methyl]carbamoyl}({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide (**54**).* The procedure for the synthesis of **53** was followed starting with **29a** and 1-Boc-3-(aminomethyl)azetidine to furnish ***N*-Boc-54** (88% yield) as a colorless oil. The amide, ***N*-Boc-54** (75 mg, 0.13 mmol) was dissolved in DCM (6 mL) and cooled to 0 °C. To that above solution, TFA (0.4 mL) was added dropwise with a syringe, and the reaction, which resulted, was stirred at 0 °C for 30 min. At that time, the reaction was diluted with DCM (10 mL) and basified with saturated aqueous $NaHCO_3$ (15 mL). The organic layer was separated, and the aqueous layer was extracted with additional DCM (2 × 5 mL). The combined organic layers were dried with K_2CO_3, and the residue was subjected to column chromatography on silica gel using 0−40% CMA80/DCM to furnish **54** (38 mg, 62%) as a free base. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68−8.74 (br s, 2H), 8.53 (s, 1H), 7.40−7.08 (m, 6H), 6.95 (d, J = 6.6 Hz, 1H), 6.76 (dd, J = 26.9, 8.7 Hz, 2H), 5.59 (d, J = 6.6 Hz, 1H), 4.22−3.82 (m, 3H), 3.77−3.47 (m, 4H), 3.27−3.04 (m, 1H), 3.03−2.84 (m, 1H), 2.72−2.24 (m, 1H), 1.96−1.78 (m, 1H), 1.59−1.05 (m, 7H), 0.96 (d, J = 6.7 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 171.8, 159.3, 140.9, 128.8, 128.1, 127.5, 127.3, 114.8, 73.2, 57.0, 48.7, 46.5, 40.1, 35.7, 32.8, 32.0, 20.0, 18.2, 16.9, 14.3; HRMS (ESI) m/z: calcd for $C_{27}H_{37}N_3O_3$ $[M + H]^+$, 452.2908; m/z: found, 452.2908.

*(2S)-N-[(R)-{4-[(2-Methylpentyl)oxy]phenyl}(phenylcarbamoyl)methyl]-2-phenylpropanamide (**55**).* The procedure for the synthesis of **35** was followed starting with **29a** and aniline to give **55** (65% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.37−7.19 (m, 7H), 7.15 (d, J = 8.7 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 7.2 Hz, 1H), 6.75 (d, J = 8.7 Hz, 2H), 5.67 (d, J = 7.0 Hz, 1H), 3.83−3.52 (m, 3H), 2.01−1.78 (m, 1H), 1.51 (d, J = 7.1 Hz, 3H), 1.47−1.07 (m, 4H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 168.5, 159.4, 141.0, 137.4, 129.0, 128.9, 128.3, 127.6, 127.3, 124.5, 120.0, 115.0, 73.3, 57.3, 46.9, 35.7, 32.8, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) m/z: calcd for $C_{29}H_{34}N_2O_3$ $[M + H]^+$, 459.2642; m/z: found, 459.2642.

*(2S)-N-[(R)-(Benzylcarbamoyl)({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide (**56**).* The procedure for the synthesis of **31** was followed starting with **29a** and benzylamine to give **56** (45% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.15 (m, 8H), 7.09 (d, J = 8.8 Hz, 4H), 6.80−6.68 (m, 3H), 6.12 (t, J = 5.6 Hz, 1H), 5.39 (d, J = 6.7 Hz, 1H), 4.51−4.13 (m, 2H), 3.88−3.44 (m, 3H), 2.06−1.63 (m, 1H), 1.60−1.08 (m, 7H), 0.99 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 170.2, 159.3, 141.2, 137.6, 129.7, 128.8, 128.6, 128.3, 127.5, 127.4, 127.1, 114.9, 73.3, 56.8, 46.8, 43.7, 35.7, 32.9, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) m/z: calcd for $C_{30}H_{36}N_2O_3$ $[M + H]^+$, 473.2799; m/z: found, 473.2797.

*(2S)-N-[(R)-{4-[(2-Methylpentyl)oxy]phenyl}({[(pyridin-2-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**57**).* The procedure for the synthesis of **31** was followed starting with **29a** and 2-picolylamine to give **57** (75% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, J = 4.3 Hz, 1H), 7.61 (td, J = 7.7, 1.8 Hz, 1H), 7.36−7.19 (m, 5H), 7.19−7.06 (m, 4H), 6.93 (d, J = 4.4 Hz, 1H), 6.78 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 6.6 Hz, 1H), 5.43 (d, J = 6.6 Hz, 1H), 4.63−4.36 (m, 2H), 3.79−3.71 (m, 1H), 3.70−3.48 (m, 2H), 1.94−1.82 (m, 1H), 1.47 (d, J = 7.1 Hz, 3H), 1.45−1.09 (m, 4H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 170.2, 159.2, 155.7, 149.0, 141.2, 136.7, 129.8, 128.8, 128.2, 127.6, 127.1, 122.4, 121.7, 114.9, 73.2, 56.8, 46.9, 44.5, 35.7, 32.9, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) m/z: calcd for $C_{29}H_{35}N_3O_3$ $[M + H]^+$, 474.2751; m/z: found, 474.2749.

*(2S)-N-[(R)-{4-[(2-Methylpentyl)oxy]phenyl}({[(pyridin-3-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**58**).* The procedure for the synthesis of **31** was followed starting with **29a** and 3-picolylamine to give **58** (71% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (dd, J = 4.8, 1.5 Hz, 1H), 8.39 (d, J = 1.8 Hz, 1H), 7.45−7.38 (m, 1H), 7.34−7.22 (m, 3H), 7.22−7.10 (m, 3H), 7.05 (d, J = 8.7 Hz, 2H), 7.02−6.94 (m, 1H), 6.79−6.68 (m, 3H), 5.54 (d, J = 7.0 Hz, 1H), 4.48−4.19 (m, 2H), 3.74 (dd, J = 8.9, 5.8 Hz, 1H), 3.69−3.53 (m, 2H), 1.98−1.84 (m, 1H), 1.58−1.07 (m, 7H), 0.99 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 170.6, 159.3, 148.9, 148.8, 141.0, 135.1, 133.5, 129.3, 128.8, 128.1, 127.5, 127.2, 123.4, 114.8, 73.3, 56.6, 46.8, 41.1, 35.7, 32.9, 20.0, 18.3, 17.0, 14.3; HRMS (ESI) m/z: calcd for $C_{29}H_{35}N_3O_3$ $[M + H]^+$, 474.2751; m/z: found, 474.2744.

*(2S)-N-[(R)-{4-[(2-Methylpentyl)oxy]phenyl}({[(pyridin-4-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**59**).* The procedure for the synthesis of **31** was followed starting with **29a** and 4-picolylamine to give **59** (74% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (d, J = 5.8 Hz, 2H), 7.39−7.20 (m, 4H), 7.19−7.13 (m, 2H), 7.08 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 5.7 Hz, 2H), 6.85 (d, J = 7.1 Hz, 1H), 6.73 (d, J = 8.5 Hz, 2H), 5.66 (d, J = 7.2 Hz, 1H), 4.33 (ddd, J = 48.7, 16.1, 6.0 Hz, 2H), 3.81−3.70 (m, 1H), 3.70−3.50 (m, 2H), 2.09−1.72 (m, 1H), 1.57−1.08 (m, 7H), 1.00 (d, J = 6.7 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 170.8, 159.4, 149.9, 147.0, 140.9, 129.3, 128.9, 128.1, 127.5, 127.3, 121.9, 114.8, 73.3, 56.5, 46.7, 42.3, 35.7, 32.9, 20.0, 18.3, 17.0, 14.3; HRMS (ESI) m/z: calcd for $C_{29}H_{35}N_3O_3$ $[M + H]^+$, 474.2751; m/z: found, 474.2750.

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*(2S)-N-[(R)-{[(Furan-2-yl)methyl]carbamoyl}({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide (**60**).* The procedure for the synthesis of **31** was followed starting with **29a** and furfurylamine to give **60** (75% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.12 (m, 6H), 7.06 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.6 Hz, 3H), 6.46−6.15 (m, 2H), 6.09 (d, J = 3.1 Hz, 1H), 5.43 (d, J = 6.9 Hz, 1H), 4.56−4.20 (m, 2H), 3.86−3.49 (m, 3H), 1.99−1.81 (m, 1H), 1.54−1.09 (m, 7H), 0.99 (d, J = 6.7 Hz, 3H), 0.90 (t, J = 7.0, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 170.1, 159.2, 150.7, 142.2, 141.1, 129.5, 128.8, 128.3, 127.5, 127.2, 114.8, 110.4, 107.4, 73.2, 56.6, 46.8, 36.8, 35.7, 32.9, 20.0, 18.4, 17.0, 14.3; HRMS (ESI) m/z: calcd for $C_{28}H_{34}N_2O_4$ $[M + H]^+$, 463.2591; m/z: found, 463.2585.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl]({[(furan-2-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**61**).* The procedure for the synthesis of **31** was followed starting with **29b** and furfurylamine to give **61** (73% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44−7.12 (m, 6H), 7.04 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 7.1 Hz, 1H), 6.76 (t, J = 5.6 Hz, 1H), 6.70 (d, J = 8.7 Hz, 2H), 6.25 (dd, J = 3.1, 1.9 Hz, 1H), 6.08 (d, J = 2.7 Hz, 1H), 5.54 (d, J = 7.1 Hz, 1H), 4.35 (qd, J = 15.6, 5.6 Hz, 2H), 3.85 (d, J = 6.7 Hz, 2H), 3.61 (q, J = 7.1 Hz, 1H), 2.82−2.64 (m, 1H), 2.20−2.04 (m, 2H), 2.02−1.66 (m, 4H), 1.43 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 170.2, 159.1, 150.8, 142.1, 141.1, 129.7, 128.8, 128.2, 127.5, 127.2, 114.8, 110.4, 107.3, 72.1, 56.4, 46.8, 36.7, 34.6, 24.8, 18.5, 18.3; HRMS (ESI) m/z: calcd for $C_{27}H_{30}N_2O_4$ $[M + H]^+$, 447.2278; m/z: found, 447.2277.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl]({[(thiophen-2-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**62**).* The procedure for the synthesis of **31** was followed starting with **29b** and 2-thiophenemethylamine to give **62** (80% yield) as a white waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.23 (m, 3H), 7.23−7.14 (m, 3H), 7.07 (d, J = 8.7 Hz, 2H), 6.89 (dd, J = 5.1, 3.5 Hz, 1H), 6.86−6.80 (m, 1H), 6.76 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 6.8 Hz, 1H), 6.26−6.17 (m, 1H), 5.38 (d, J = 6.7 Hz, 1H), 4.67−4.36 (m, 2H), 3.87 (d, J = 6.7 Hz, 2H), 3.61 (q, J = 7.1 Hz, 1H), 2.88−2.52 (m, 1H), 2.20−2.04 (m, 2H), 2.03−1.73 (m, 4H), 1.45 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 169.9, 159.2, 141.1, 140.2, 129.5, 128.8, 128.3, 127.5, 127.2, 126.8, 125.9, 125.2, 114.9, 72.1, 56.7, 46.8, 38.6, 34.6, 24.8, 18.5, 18.4; HRMS (ESI) m/z: calcd for $C_{27}H_{30}N_2O_3S$ $[M + H]^+$, 463.2050; m/z: found, 463.2046.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl]({[(1H-pyrrol-2-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**63**).* The procedure for the synthesis of **31** was followed starting with **29b** and (1*H*-pyrrol-2-yl)methanamine to give **63** (58% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (br s, 1H), 7.45−7.15 (m, 5H), 7.11 (t, J = 5.7 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 6.79−6.55 (m, 4H), 6.04 (dd, J = 5.8, 2.8 Hz, 1H), 5.97−5.92 (m, 1H), 5.45 (d, J = 7.1 Hz, 1H), 4.33 (dd, J = 15.1, 6.0 Hz, 1H), 4.21−4.08 (m, 1H), 3.84 (d, J = 6.7 Hz, 2H), 3.60 (q, J = 7.1 Hz, 1H), 2.81−2.61 (m, 1H), 2.20−2.04 (m, 2H), 2.00−1.73 (m, 4H), 1.44 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 171.3, 159.2, 141.0, 129.3, 128.9, 128.5, 128.1, 127.5, 127.3, 118.2, 114.9, 107.7, 106.8, 72.1, 56.6, 46.7, 37.1, 34.6, 24.8, 18.5, 18.4, HRMS (ESI) m/z: calcd for $C_{27}H_{31}N_3O_3$ $[M + H]^+$, 446.2438; m/z: found, 446.2437.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl]({[(5-methyl-1,3-oxazol-2-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**64**).* The procedure for the synthesis of **31** was followed starting with **29b** and (5-methyloxazol-2-yl)methanamine to give **64** (46% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.15 (m, 5H), 7.09 (d, J = 8.7 Hz, 2H), 6.87 (t, J = 5.4 Hz, 1H), 6.81−6.67 (m, 3H), 6.59 (d, J = 1.2 Hz, 1H), 5.50 (d, J = 7.0 Hz, 1H), 4.51 (dd, J = 16.4, 5.8 Hz, 1H), 4.32 (dd, J = 16.4, 5.1 Hz, 1H), 3.86 (d, J = 6.7 Hz, 2H), 3.62 (q, J = 7.1 Hz, 1H), 2.84−2.52 (m, 1H), 2.24 (d, J = 1.1 Hz, 3H), 2.19−2.03 (m, 2H), 2.03−1.70 (m, 4H), 1.45 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 170.4, 159.2, 158.8, 149.4, 141.2, 129.5, 128.8, 128.3, 127.6, 127.2, 122.7, 114.8, 72.1, 56.5, 46.8, 37.0, 34.6, 24.8, 18.5, 18.4, 10.7; HRMS (ESI) m/z: calcd for $C_{27}H_{31}N_3O_4$ $[M + H]^+$, 462.2387; m/z: found, 462.2385.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl]({[(1,2-oxazol-3-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**65**).* The procedure for the synthesis of **31** was followed starting with **29b** and isoxazol-3-ylmethanamine hydrochloride to give **65** (60% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, J = 1.6 Hz, 1H), 7.50−7.36 (m, 1H), 7.35−7.12 (m, 5H), 7.04 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 8.7 Hz, 2H), 6.13 (d, J = 1.6 Hz, 1H), 5.60 (d, J = 7.2 Hz, 1H), 4.51−4.31 (m, 2H), 3.84 (d, J = 6.7 Hz, 2H), 3.64 (q, J = 7.1 Hz, 1H), 2.84−2.60 (m, 1H), 2.23−2.02 (m, 2H), 2.02−1.69 (m, 4H), 1.43 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 170.8, 160.0, 159.2, 158.7, 141.0, 129.3, 128.8, 128.1, 127.5, 127.2, 114.8, 103.6, 72.1, 56.4, 46.7, 35.2, 34.6, 24.8, 18.5, 18.3; HRMS (ESI) m/z: calcd for $C_{26}H_{29}N_3O_4$ $[M + H]^+$, 448.2231; m/z: found, 448.2229.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl]({[(1,3-thiazol-2-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**66**).* The procedure for the synthesis of **31** was followed starting with **29b** and 1,3-thiazol-2-ylmethylamine hydrochloride to give **66** (65% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J = 3.3 Hz, 1H), 7.49−7.14 (m, 6H), 7.07 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 7.1 Hz, 1H), 6.72 (d, J = 8.7 Hz, 2H), 5.58 (d, J = 7.1 Hz, 1H), 4.66 (d, J = 5.9 Hz, 2H), 3.85 (d, J = 6.7 Hz, 2H), 3.62 (q, J = 7.1 Hz, 1H), 2.95−2.50 (m, 1H), 2.23−2.03 (m, 2H), 2.03−1.64 (m, 4H), 1.43 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 167.0, 159.2, 142.4, 141.1, 129.3, 128.8, 128.3, 127.5, 127.2, 126.2, 119.5, 114.9, 72.1, 56.5, 46.7, 41.2, 34.6, 24.8, 18.5, 18.4; HRMS (ESI) m/z: calcd for $C_{26}H_{29}N_3O_3S$ $[M + H]^+$, 464.2002; m/z: found, 448.2000.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl]({[(1H-imidazol-2-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**67**).* The procedure for the synthesis of **31** was followed starting with **29b** and (1*H*-imidazol-2-yl)methanamine hydrochloride to give **67** (53% yield) as a waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (t, J = 5.7 Hz, 1H), 7.38−7.15 (m, 6H), 7.02 (d, J = 8.7 Hz, 2H), 6.89−6.82 (m, 3H), 6.70 (d, J = 8.7 Hz, 2H), 5.41 (d, J = 6.8 Hz, 1H), 4.42 (dd, J = 15.3, 6.3 Hz, 1H), 4.22 (dd, J = 15.3, 5.5 Hz, 1H), 3.83 (d, J = 6.7 Hz, 2H), 3.66 (q, J = 7.1 Hz, 1H), 2.81−2.52 (m, 1H), 2.18−1.66 (m, 6H), 1.46 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 229.0, 174.1, 171.9, 159.3, 145.2, 141.1, 128.8, 128.2, 127.5, 127.2, 122.0, 114.9, 72.1, 57.0, 46.6, 37.4, 34.6, 24.8, 18.5, 18.4; HRMS (ESI) m/z: calcd for $C_{26}H_{30}N_4O_3$ $[M + H]^+$, 447.2391; m/z: found, 447.2387.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl]({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**68**).* The procedure for the synthesis of **31** was followed starting with **29b** and (5-methyl-1,3,4-oxadiazol-2-yl)methanamine oxalate to give **68** (55% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.16 (m, 5H), 7.10 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.59 (d, J = 6.4 Hz, 2H), 5.44 (d, J = 6.7 Hz, 1H), 4.57 (ddd, J = 38.1, 16.6, 5.8 Hz, 2H), 3.87 (d, J = 6.6 Hz, 2H), 3.63 (q, J = 7.1 Hz, 1H), 2.81−2.65 (m, 1H), 2.48 (s, 3H), 2.21−2.02 (m, 2H), 2.02−1.73 (m, 4H), 1.47 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 229.0, 173.6, 170.6, 164.4, 163.0, 159.4, 141.0, 128.9, 128.4, 127.5, 127.2, 115.0, 77.2, 72.1, 56.7, 46.8, 34.6, 34.5, 24.8, 18.5, 18.4, 10.9; HRMS (ESI) m/z: calcd for $C_{26}H_{30}N_4O_4$ $[M + H]^+$, 463.2340; m/z: found, 463.2337.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl]({[(1H-1,2,4-triazol-3-yl)methyl]carbamoyl})methyl]-2-phenylpropanamide (**69**).* The procedure for the synthesis of **31** was followed starting with **29b** and (4*H*-1,2,4-triazol-3-yl)methanamine hydrochloride to give **69** (47% yield) as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ 8.20 (s, 1H), 7.39−7.06 (m, 7H), 6.80 (d, J = 8.7 Hz, 2H), 5.37 (s, 1H), 4.52 (dd, J = 52.1, 15.8 Hz, 2H), 3.89 (d, J = 6.6 Hz, 2H), 3.80 (q, J = 7.0 Hz, 1H), 2.85−2.58 (m, 1H), 2.19−2.03 (m, 2H), 2.03−1.75 (m, 4H), 1.46 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 176.6, 173.1, 160.7, 158.4, 148.1, 142.9, 130.3, 129.9, 129.6, 128.5, 128.0, 115.7, 73.2, 58.4, 47.0, 37.2, 36.1, 25.7, 19.4, 18.8; HRMS (ESI) m/z: calcd for $C_{25}H_{29}N_5O_3$ $[M + H]^+$, 448.2343; m/z: found, 448.2342.

*(2S)-N-[(R)-(Hydrazinecarbonyl)({4-[(2-methylpentyl)oxy]phenyl})methyl]-2-phenylpropanamide (**70a**).* A mixture of **3** (596 mg, 1.5 mmol) and hydrazine hydrate (2 mL) in EtOH (10 mL) was

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refluxed for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was crystallized from MeOH/hexanes to give **70a** (572 mg, 96% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.42−7.16 (m, 5H), 7.07 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 6.61 (d, J = 6.0 Hz, 1H), 5.43 (d, J = 6.0 Hz, 1H), 3.81 (s, 2H), 3.80−3.69 (m, 1H), 3.69−3.55 (m, 2H), 2.01−1.81 (m, 1H), 1.56−1.12 (m, 4H), 1.50 (d, J = 9.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); MS (ESI) m/z: 398.4 $[M + H]^+$.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl](hydrazinecarbonyl)-methyl]-2-phenylpropanamide (**70b**).* The procedure for the synthesis of **70a** was followed starting with **11h** to give **70b** (90% yield) as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ 7.33−7.19 (m, 5H), 7.16 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 5.28 (s, 1H), 3.87 (d, J = 6.6 Hz, 2H), 3.78 (q, J = 7.1 Hz, 1H), 2.85−2.63 (m, 1H), 2.19−2.02 (m, 2H), 2.02−1.77 (m, 4H), 1.44 (d, J = 7.1 Hz, 3H); ^{1}H NMR (300 MHz, CD_3OD): δ 176.5, 172.2, 160.7, 142.9, 130.4, 129.6, 129.6, 128.5, 128.0, 115.7, 73.2, 56.8, 47.0, 36.1, 25.7, 19.3, 18.8; MS (ESI) m/z: 382.0 $[M + H]^+$.

*(2S)-N-[(R)-{4-[(2-Methylpentyl)oxy]phenyl}(1,3,4-oxadiazol-2-yl)methyl]-2-phenylpropanamide (**71**).* A mixture of **70a** (70 mg, 0.18 mmol), trimethyl orthoformate (5 mL), and PTSA (45 mg, 0.23 mmol) was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was diluted with EtOAc (50 mL), washed with $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using 0−20% CMA80 in DCM to furnish **71** (40 mg, 56% yield) as an off-white solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.31 (s, 1H), 7.43−7.19 (m, 5H), 7.05 (d, J = 9.0 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H), 6.54 (d, J = 9.0 Hz, 1H), 6.33 (d, J = 6.0 Hz, 1H), 3.80−3.60 (m, 3H), 1.98−1.81 (m, 1H), 1.56−1.09 (m, 4H), 1.51 (d, J = 6.0 Hz, 3H), 0.98 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 165.9, 159.9, 163.2, 140.8, 128.9, 128.2, 127.7, 127.6, 127.4, 115.0, 73.3, 49.5, 46.7, 35.7, 32.8, 20.0, 18.4, 16.9, 14.2; HRMS (ESI) m/z: calcd for $C_{24}H_{29}N_3O_3$ $[M + H]^+$, 408.2282; m/z: found, 408.2278.

*(2S)-N-[(R)-(5-Methyl-1,3,4-oxadiazol-2-yl)({4-[(2-methylpentyl)-oxy]phenyl})-2-phenylpropanamide (**72**).* A mixture of **70a** (100 mg, 0.25 mmol), trimethyl orthoacetate (0.065 mL, 0.5 mmol), and acetic acid (0.1 mL) in m-xylene (5 mL) was refluxed for 6 h. After cooling to room temperature, the mixture was diluted with EtOAc (50 mL), washed with $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried ($NaSO_4$), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using 0−20% CMA80 in DCM to provide **72** (60 mg, 57% yield) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.21 (m, 5H), 7.06 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 6.60 (d, J = 9.0 Hz, 1H), 6.25 (d, J = 6.0 Hz, 1H), 3.79−3.60 (m, 3H), 2.44 (s, 3H), 1.95−1.83 (m, 1H), 1.53−1.12 (m, 4H), 1.50 (d, J = 6.0 Hz, 3H), 0.98 (d, J = 9.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 165.8, 164.2, 159.5, 140.8, 128.8, 128.2, 127.5, 127.2, 114.8, 73.1, 49.4, 46.8, 35.6, 32.7, 20.0, 18.4, 16.8, 14.2, 10.8; HRMS (ESI) m/z: calcd for $C_{25}H_{31}N_3O_3$ $[M + H]^+$, 422.2438; m/z: found, 422.2440.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl](1,3,4-oxadiazol-2-yl)-methyl]-2-phenylpropanamide (**73**).* The procedure for the synthesis of **71** was followed starting with **70b** and trimethyl orthoformate to give **73** (65% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.43−7.18 (m, 5H), 7.05 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 6.52 (d, J = 7.6 Hz, 1H), 6.33 (d, J = 7.7 Hz, 1H), 3.86 (d, J = 6.6 Hz, 2H), 3.67 (q, J = 7.1 Hz, 1H), 2.90−2.53 (m, 1H), 2.22−2.02 (m, 2H), 2.02−1.66 (m, 4H), 1.51 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 165.9, 159.7, 153.2, 140.8, 128.9, 128.2, 127.8, 127.6, 127.4, 115.1, 72.1, 49.5, 46.8, 34.5, 24.8, 18.5, 18.4; HRMS (ESI) m/z: calcd for $C_{23}H_{25}N_3O_3$ $[M + H]^+$, 392.1969; m/z: found, 392.1967.

*(2S)-N-[(R)-[4-(Cyclobutylmethoxy)phenyl](5-methyl-1,3,4-oxadiazol-2-yl)methyl]-2-phenylpropanamide (**74**).* The procedure for the synthesis of **72** was followed starting with **70b** and trimethyl orthoacetate to give **74** (72% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.18 (m, 5H), 7.06 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.55 (d, J = 7.7 Hz, 1H), 6.24 (d, J = 7.7 Hz, 1H), 3.87 (d, J = 6.6 Hz, 2H), 3.66 (q, J = 7.1 Hz, 1H), 2.86−2.61 (m, 1H), 2.45 (s, 3H), 2.20−2.04 (m, 2H), 2.04−1.68 (m, 4H), 1.50 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 165.8, 164.3, 159.5, 140.9, 128.9, 128.3, 128.2, 127.6, 127.3, 115.0, 72.1, 49.5, 46.8, 34.5, 24.8, 18.5, 18.5, 10.9; HRMS (ESI) m/z: calcd for $C_{24}H_{27}N_3O_3$ $[M + H]^+$, 406.2125; m/z: found, 406.2123.

*Methyl (3S)-3-Amino-3-(4-hydroxyphenyl)propanoate (**76**).* (*S*)-3-Amino-3-(4-hydroxyphenyl)propanoic acid (**75**) (6.0 g, 33.15 mmol) was dissolved in dry MeOH (60 mL). Acetyl chloride (5 mL) was added to that above solution slowly via a syringe. The reaction that resulted was stirred at 65 °C for 12 h. After that, the solvent was evaporated under reduced pressure, and the residue was dried *in vacuo* to furnish the methyl ester **76** as hydrochloride salt (8.63 g, 115% crude yield) as a foamy solid which was used for the next transformation without purification. ^{1}H NMR (300 MHz, CD_3OD): δ 7.35−7.24 (m, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.63 (t, J = 7.2 Hz, 1H), 3.68 (s, 3H), 3.12 (ddd, J = 16.8, 7.9, 1.6 Hz, 1H), 2.98 (dd, J = 16.8, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 171.8, 159.8, 129.8, 127.8, 117.0, 52.8, 52.7, 39.2; MS (ESI) m/z: 196.0 $[M + H]^+$.

*Methyl (3S)-3-{[(tert-Butoxy)carbonyl]amino}-3-(4-hydroxyphenyl)propanoate (**77**).* To a solution of **76** (8.6 g, 37.1 mmol) in DCM (200 mL), DIPEA (38.8 mL, 0.22 mol) was added slowly via a syringe at 0 °C. To that above solution, Boc_2O (8.09 g, 37.1 mmol) was added, and the reaction which resulted was stirred at room temperature under nitrogen for 12 h. At that time, water (100 mL) was added to the reaction and the organic layer was separated. The aqueous layer was extracted with additional DCM (2 × 50 mL) and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was crystallized with DCM/hexanes to furnish **77** (11.5 g, 78%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04 (t, J = 9.2 Hz, 3H), 6.67 (d, J = 8.1 Hz, 2H), 5.54 (br s, 1H), 5.00 (br s, 1H), 3.61 (s, 3H), 2.96−2.60 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 155.7, 155.4, 132.4, 127.3, 115.6, 80.0, 51.8, 50.9, 40.9, 28.3; MS (ESI) m/z: 318.0 $[M + Na]^+$.

*Methyl (3S)-3-{[(tert-Butoxy)carbonyl]amino}-3-{4-[(2-methylpentyl)oxy]phenyl}propanoate (**78a**).* The procedure for the synthesis of **7b** was followed starting with **77** and 2-methylpentanol to give **78a** (87% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.32 (br s, 1H), 5.04 (br s, 1H), 3.79 (dd, J = 9.0, 5.8 Hz, 1H), 3.69 (dd, J = 8.9, 6.7 Hz, 1H), 3.61 (s, 3H), 2.82 (qd, J = 15.3, 6.2 Hz, 2H), 2.07−1.78 (m, 1H), 1.55−1.11 (m, 13H), 1.00 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); MS (ESI) m/z: 402.0 $[M + Na]^+$.

*Methyl (3S)-3-{[(tert-Butoxy)carbonyl]amino}-3-[4-(cyclobutylmethoxy)phenyl]propanoate (**78b**).* The procedure for the synthesis of **7b** was followed starting with **77** and cyclobutylmethanol to give **78b** (87% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, J = 8.6 Hz, 2H), 6.90−6.77 (m, 2H), 5.36 (s, 1H), 5.04 (d, J = 5.0 Hz, 1H), 3.90 (d, J = 6.7 Hz, 2H), 3.61 (s, 3H), 2.94−2.59 (m, 3H), 2.23−2.04 (m, 2H), 2.01−1.78 (m, 4H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 158.7, 155.0, 133.1, 127.2, 114.7, 79.6, 72.1, 51.7, 50.9, 40.9, 34.6, 28.3, 24.8, 18.5; MS (ESI) m/z: 386.0 $[M + Na]^+$.

*Methyl (3S)-3-{[(tert-Butoxy)carbonyl]amino}-3-(4-{[(2S)-2-methylpentyl]oxy}phenyl)propanoate (**78c**).* The procedure for the synthesis of **7b** was followed starting with **77** and (*S*)-2-methylpentanol to give **78c** (30% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.35 (br s, 1H), 5.04 (br s, 1H), 3.79 (dd, J = 9.0, 5.8 Hz, 1H), 3.69 (dd, J = 8.9, 6.7 Hz, 1H), 3.61 (s, 3H), 2.82 (qd, J = 15.3, 6.2 Hz, 2H), 2.01−1.77 (m, 1H), 1.55−1.09 (m, 13H), 1.00 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); MS (ESI) m/z: 402.0 $[M + Na]^+$.

*Methyl (3S)-3-{[(tert-Butoxy)carbonyl]amino}-3-(4-{[(2R)-2-methylpentyl]oxy}phenyl)propanoate (**78d**).* The procedure for the synthesis of **11m** was followed starting with **77** and (2*R*)-2-methylpentyl 4-methylbenzene-1-sulfonate to give **78d** (35% yield) as

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a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.38 (br s, 1H), 5.03 (br s, J = 5.4 Hz, 1H), 3.78 (dd, J = 9.0, 5.8 Hz, 1H), 3.68 (dd, J = 9.0, 6.7 Hz, 1H), 3.61 (s, 3H), 2.82 (qd, J = 15.3, 6.3 Hz, 2H), 2.00−1.76 (m, 1H), 1.56−1.11 (m, 13H), 1.00 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 158.7, 155.0, 133.1, 127.2, 114.6, 79.6, 73.2, 51.6, 50.9, 40.9, 35.7, 32.9, 28.3, 20.0, 17.0, 14.3; MS (ESI) m/z: 402.0 $[M + Na]^+$.

*Methyl (3S)-3-{[(tert-Butoxy)carbonyl]amino}-3-{4-[(2S)-2-methylbutoxy]phenyl}propanoate (**78e**).* The procedure for the synthesis of **7b** was followed starting with **77** and (*S*)-2-methylbutanol to give **78e** (95% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.42 (br s, 1H), 5.03 (br s, 1H), 3.79 (dd, J = 9.0, 6.0 Hz, 1H), 3.70 (dd, J = 9.0, 6.6 Hz, 1H), 3.61 (s, 3H), 2.82 (qd, J = 15.3, 6.3 Hz, 2H), 1.90−1.75 (m, 1H), 1.564−1.48 (m, 1H), 1.42 (s, 9H), 1.33−1.15 (m, 4H), 1.00 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 158.7, 155.0, 133.1, 127.2, 114.6, 79.5, 72.8, 51.6, 50.9, 40.9, 34.7, 28.3, 26.1, 16.5, 11.2; MS (ESI) m/z: 388 $[M + Na]^+$.

*Methyl (3S)-3-{[(tert-Butoxy)carbonyl]amino}-3-{4-[(2R)-2-methylbutoxy]phenyl}propanoate (**78f**).* The procedure for the synthesis of **11m** was followed starting with **77** and (2*R*)-2-methylbutyl 4-methylbenzene-1-sulfonate to give **78f** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.34 (br s, 1H), 5.04 (br s, 1H), 3.83−3.66 (m, 2H), 3.61 (s, 3H), 2.82 (qd, J = 15.3, 6.2 Hz, 2H), 1.96−1.71 (m, 1H), 1.65−1.48 (m, 1H), 1.42 (br s, 9H), 1.33−1.16 (m, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 158.7, 155.0, 133.0, 127.3, 114.6, 79.6, 72.9, 51.7, 50.9, 40.9, 34.7, 28.3, 26.1, 16.5, 11.3; MS (ESI) m/z: 388 $[M + Na]^+$.

*Methyl (3S)-3-Amino-3-{4-[(2-methylpentyl)oxy]phenyl}-propanoate Hydrochloride (**79a**).* A solution of **78a** (1.63 g, 4.29 mmol) in DCM (20 mL) was cooled to 0 °C. To that above solution, HCl (4 M in dioxane, 10.74 mL, 42.95 mmol) was added via a syringe. The reaction which resulted was stirred at room temperature for overnight. At that time, the solvent was removed under reduced pressure, and the residue was redissolved in DCM and evaporated (repeated three times). The residue was dried in vacuo to furnish **79a** (1.35 g, 99%) as a foamy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (br s, 3H), 7.42 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.1 Hz, 2H), 4.64 (br s, 1H), 3.87−3.64 (m, 2H), 3.60 (s, 3H), 3.35−3.15 (m, 1H), 3.00 (dd, J = 16.4, 6.5 Hz, 1H), 2.00−1.82 (m, 1H), 1.55−1.09 (m, 4H), 1.00 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); MS (ESI) free base m/z: 263.0 $[M + H^+ - NH_3]^+$.

*Methyl (3S)-3-Amino-3-[4-(cyclobutylmethoxy)phenyl]-propanoate Hydrochloride (**79b**).* The procedure for the synthesis of **79a** was followed starting with **78b** to give **79b** as a waxy solid. MS (ESI) free base m/z: 247.0 $[M + H^+ - NH_3]^+$. This material was used for the next transformation without further characterization.

*Methyl (3S)-3-Amino-3-(4-{[(2S)-2-methylpentyl]oxy}phenyl)-propanoate Hydrochloride (**79c**).* The procedure for the synthesis of **79a** was followed starting with **78c** to give **79c** as a waxy solid. MS (ESI) free base m/z: 263.0 $[M + H^+ - NH_3]^+$. This material was used for the next transformation without further characterization.

*Methyl (3S)-3-Amino-3-(4-{[(2R)-2-methylpentyl]oxy}phenyl)-propanoate Hydrochloride (**79d**).* The procedure for the synthesis of **79a** was followed starting with **78d** to give **79d** as a waxy solid. MS (ESI) free base m/z: 263.0 $[M + H^+ - NH_3]^+$. This material was used for the next transformation without further characterization.

*Methyl (3S)-3-Amino-3-{4-[(2S)-2-methylbutoxy]phenyl}-propanoate Hydrochloride (**79e**).* The procedure for the synthesis of **79a** was followed starting with **78e** to give **79e** as a waxy solid. MS (ESI) free base m/z: 249.0 $[M + H^+ - NH_3]^+$. This material was used for the next transformation without further characterization.

*Methyl (3S)-3-Amino-3-{4-[(2R)-2-methylbutoxy]phenyl}-propanoate Hydrochloride (**79f**).* The procedure for the synthesis of **79a** was followed starting with **78f** to give **79f** as a waxy solid. MS (ESI) free base m/z: 249.0 $[M + H^+ - NH_3]^+$.

*Methyl (3S)-3-{4-[(2-Methylpentyl)oxy]phenyl}-3-[(2S)-2-phenylpropanamido]propanoate (**80a**).* To a solution of **79a** (1.35 g, 4.27 mmol) in MeCN (50 mL), HBTU (2.43 g, 6.41 mmol), Et_3N (1.80 mL, 12.82 mmol), and (*S*)-(+)-2-phenylpropionic acid (642 mg, 4.27 mmol) were added, and the reaction that resulted was stirred at room temperature 5 h. After the completion of the reaction, EtOAC (20 mL) and saturated $NaHCO_3$ (20 mL) were added, and the organic layer was separated. The aqueous layer was extracted with additional EtOAc, and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using 0−50% EtOAc in hexanes to furnish **80a** (1.60 g, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.19 (m, 5H), 6.95 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.38 (d, J = 8.4 Hz, 1H), 5.31 (dt, J = 8.3, 5.9 Hz, 1H), 3.75 (dd, J = 8.9, 5.8 Hz, 1H), 3.69−3.57 (m, 2H), 3.55 (s, 3H), 2.77 (qd, J = 15.5, 5.9 Hz, 2H), 2.00−1.77 (m, 1H), 1.51 (d, J = 57.2 Hz, 3H), 1.48−1.09 (m, 4H), 0.98 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 171.5, 158.6, 141.3, 132.3, 128.9, 127.6, 127.2, 127.0, 114.5, 73.2, 51.7, 49.0, 47.1, 40.0, 35.7, 32.9, 20.0, 18.3, 17.0, 14.3; MS (ESI) m/z: 412.0 $[M + H]^+$.

*Methyl (3S)-3-[4-(Cyclobutylmethoxy)phenyl]-3-[(2S)-2-phenylpropanamido]propanoate (**80b**).* The procedure for the synthesis of **80a** was followed starting with **79b** to give **80b** (65% yield over 2 steps) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (dd, J = 13.5, 6.6 Hz, 5H), 6.95 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.50 (d, J = 8.4 Hz, 1H), 5.31 (dt, J = 8.3, 6.0 Hz, 1H), 3.85 (d, J = 6.7 Hz, 2H), 3.59 (q, J = 7.1 Hz, 1H), 3.54 (s, 3H), 2.91−2.64 (m, 3H), 2.18−2.00 (m, 2H), 1.96−1.63 (m, 4H), 1.50 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2, 171.5, 158.5, 141.3, 132.4, 128.9, 127.6, 127.2, 127.0, 114.6, 72.1, 51.7, 49.0, 47.1, 40.0, 34.6, 24.8, 18.5, 18.3; MS (ESI) m/z: 396.0 $[M + H]^+$.

*Methyl (3S)-3-(4-{[(2S)-2-Methylpentyl]oxy}phenyl)-3-[(2S)-2-phenylpropanamido]propanoate (**80c**).* The procedure for the synthesis of **80a** was followed starting with **79c** to give **80c** (61% yield) as a sticky solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.21 (m, 5H), 6.95 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 6.46 (d, J = 8.4 Hz, 1H), 5.32 (dt, J = 8.2, 5.9 Hz, 1H), 3.74 (dd, J = 8.9, 5.8 Hz, 1H), 3.69−3.58 (m 2H), 3.55 (s, 3H), 2.78 (qd, J = 15.5, 5.9 Hz, 2H), 2.01−1.80 (m, 1H), 1.52 (d, J = 7.2 Hz, 3H), 1.49−1.02 (m, 4H), 0.98 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); MS (ESI) m/z: 412.0 $[M + H]^+$.

*Methyl (3S)-3-(4-{[(2R)-2-Methylpentyl]oxy}phenyl)-3-[(2S)-2-phenylpropanamido]propanoate (**80d**).* The procedure for the synthesis of **80a** was followed starting with **79d** to give **80d** (63% yield over two steps) as a sticky solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.15 (m, 5H), 6.95 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.43 (d, J = 8.4 Hz, 1H), 5.36−5.25 (m, 1H), 3.79−3.70 (m, 1H), 3.69−3.56 (m, 2H), 3.54 (s, 3H), 2.77 (qd, J = 15.5, 5.9 Hz, 2H), 1.98−1.81 (m, 1H), 1.51 (d, J = 7.2 Hz, 3H), 1.49−1.11 (m, 4H), 0.98 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 171.5, 158.6, 141.3, 132.3, 128.9, 127.6, 127.2, 127.0, 114.5, 73.2, 51.7, 49.0, 47.1, 40.0, 35.7, 32.9, 20.0, 18.3, 17.0, 14.3; MS (ESI) m/z: 412.0 $[M + H]^+$.

*Methyl (3S)-3-{4-[(2S)-2-Methylbutoxy]phenyl}-3-[(2S)-2-phenylpropanamido]propanoate (**80e**).* The procedure for the synthesis of **80a** was followed starting with **79e** to give **80e** (64% yield over two steps) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48−7.03 (m, 5H), 6.95 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.43 (d, J = 8.4 Hz, 1H), 5.30 (dd, J = 14.2, 6.0 Hz, 1H), 3.79−3.66 (m, 3H), 3.54 (s, 3H), 2.77 (qd, J = 15.5, 6.0 Hz, 2H), 1.90−1.75 (m, 1H), 1.64−1.37 (m, 4H), 1.36−1.08 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 171.5, 158.6, 141.3, 132.3, 128.8, 127.6, 127.2, 127.1, 114.5, 72.8, 51.7, 49.0, 47.1, 40.0, 34.7, 26.1, 18.3, 16.5, 11.3; MS (ESI) m/z: 398.0 $[M + H]^+$.

*Methyl (3S)-3-{4-[(2R)-2-Methylbutoxy]phenyl}-3-[(2S)-2-phenylpropanamido]propanoate (**80f**).* The procedure for the synthesis of **80a** was followed starting with **79f** to give **80f** (54% yield over two steps) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.20 (m, 5H), 6.99−6.88 (m, 2H), 6.80−6.69 (m, 2H), 6.38 (d, J = 8.4 Hz, 1H), 5.35−5.25 (m, 1H), 3.79−3.71 (m, 1H), 3.70−3.56 (m, 2H), 3.55 (s, 6H), 2.77 (qd, J = 15.5, 5.9 Hz, 2H), 1.89−1.72 (m,

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1H), 1.62−1.45 (m, 4H), 1.32−1.13 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 171.5, 158.6, 141.3, 132.3, 128.9, 127.6, 127.2, 127.0, 114.5, 72.9, 51.7, 49.0, 47.1, 40.0, 34.7, 26.1, 18.3, 16.5, 11.3; MS (ESI) m/z: 398.0 $[M + H]^+$.

*(2S)-N-[(1S)-2-(Hydrazinecarbonyl)-1-{4-[(2-methylpentyl)oxy]-phenyl}ethyl]-2-phenylpropanamide (**81a**).* The procedure for the synthesis of **70a** was followed starting with **80a** to give **81a** (92% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.21 (m, 5H), 6.93 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 6.68 (br s, 1H), 5.27−5.14 (m, 1H), 3.79−3.57 (m, 3H), 2.59 (qd, J = 14.6, 5.5 Hz, 2H), 1.99−1.82 (m, 1H), 1.65−1.09 (m, 9H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); MS (ESI) m/z: 412.0 $[M + H]^+$.

*(2S)-N-[(1S)-1-[4-(Cyclobutylmethoxy)phenyl]-2-(hydrazinecarbonyl)ethyl]-2-phenylpropanamide (**81b**).* The procedure for the synthesis of **70a** was followed starting with **80b** to give **81b** (90% yield) as a white solid. MS (ESI) m/z: 396.0 $[M + H]^+$. This material was used for the next transformation without further characterization.

*(2S)-N-[(1S)-2-(Hydrazinecarbonyl)-1-(4-{[(2S)-2-methylpentyl]-oxy}phenyl)ethyl]-2-phenylpropanamide (**81c**).* The procedure for the synthesis of **70a** was followed starting with **80c** to give **81c** (67% yield) as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ 7.30−7.06 (m, 5H), 6.94 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 5.15 (t, J = 7.1 Hz, 1H), 3.72−3.49 (m, 3H), 2.58−2.39 (m, 2H), 1.87−1.62 (m, 1H), 1.44−0.93 (m, 7H), 0.88 (d, J = 6.7 Hz, 3H), 0.82 (t, J = 7.1 Hz, 3H); MS (ESI) m/z: 412.0 $[M + H]^+$.

*(2S)-N-[((1S)-2-Hydrazinecarbonyl)-1-(4-{[(2R)-2-methylpentyl]-oxy}phenyl)ethyl]-2-phenylpropanamide (**81d**).* The procedure for the synthesis of **70a** was followed starting with **80d** to give **81d** (75% yield) as a white solid. MS (ESI) m/z: 412.0 $[M + H]^+$. This material was used for the next transformation without further characterization.

*(2S)-N-[(1S)-2-(Hydrazinecarbonyl)-1-{4-[(2S)-2-methylbutoxy]-phenyl}ethyl]-2-phenylpropanamide (**81e**).* The procedure for the synthesis of **70a** was followed starting with **80e** to give **81e** (97% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.17 (m, 5H), 6.95 (m, 4H), 6.73 (d, J = 8.7 Hz, 2H), 5.26−5.15 (m, 1H), 3.80−3.45 (m, 4H), 2.58 (qd, J = 14.6, 5.6 Hz, 2H), 1.91−1.41 (m, 6H), 1.34−1.12 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 171.2, 158.6, 141.3, 132.3, 128.8, 127.6, 127.2, 126.9, 114.6, 72.9, 49.9, 47.2, 40.1, 34.7, 26.1, 18.2, 16.5, 11.3; (ESI) m/z: 398.0 $[M + H]^+$.

*(2S)-N-[(1S)-2-(Hydrazinecarbonyl)-1-{4-[(2R)-2-methylbutoxy]-phenyl}ethyl]-2-phenylpropanamide (**81f**).* The procedure for the synthesis of **70a** was followed starting with **80f** to give **81f** (90% yield) as a white solid. MS (ESI) m/z: 398.0 $[M + H]^+$. This material was used for the next transformation without further characterization.

*(2S)-N-[(1S)-1-{4-[(2-Methylpentyl)oxy]phenyl}-2-(1,3,4-oxadiazol-2-yl)ethyl]-2-phenylpropanamide (**82**).* The procedure for the synthesis of **71** was followed starting with **81a** and trimethyl orthoformate to give **82** (35% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.28 (m, 5H), 6.96 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.6 Hz, 2H), 6.29 (d, J = 8.3 Hz, 1H), 5.42 (dd, J = 14.1, 7.3 Hz, 1H), 3.78−3.69 (m, 1H), 3.68−3.51 (m, 2H), 3.43−3.15 (m, 2H), 1.99−1.80 (m, 1H), 1.46 (d, J = 7.2 Hz, 3H), 1.43−1.07 (m, 4H), 0.98 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 164.0, 158.9, 153.0, 141.0, 131.2, 128.9, 127.6, 127.2, 127.1, 114.7, 73.2, 50.0, 47.0, 35.7, 32.8, 31.7, 20.0, 18.3, 17.0, 14.3; HRMS (ESI) m/z: calcd for $C_{25}H_{31}N_3O_3$ $[M + H]^+$, 422.2438; m/z: found, 422.2432.

*(2S)-N-[(1S)-2-(5-Methyl-1,3,4-oxadiazol-2-yl)-1-{4-[(2-methylpentyl)oxy]phenyl}ethyl]-2-phenylpropanamide (**83**).* The procedure for the synthesis of **72** was followed starting with **81a** and trimethyl orthoacetate to give **83** (93% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.16 (m, 5H), 6.97 (d, J = 8.6 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 6.41 (d, J = 8.4 Hz, 1H), 5.46−5.29 (m, 1H), 3.78−3.69 (m, 1H), 3.68−3.48 (m, 2H), 3.35−3.07 (m, 2H), 2.42 (s, 3H), 1.98−1.79 (m, 1H), 1.52−1.10 (m, 7H), 0.98 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 164.0, 163.9, 158.8, 141.1, 131.6, 128.8, 127.6, 127.2, 127.2, 114.7, 73.2, 49.9, 47.0, 35.7, 32.8, 31.8, 20.0, 18.3, 17.0, 14.3, 10.8; HRMS (ESI) m/z: calcd for $C_{26}H_{33}N_3O_3$ $[M + H]^+$, 436.2595; m/z: found, 436.2609.

*(2S)-N-[(1S)-2-(5-Amino-1,3,4-oxadiazol-2-yl)-1-{4-[(2-methylpentyl)oxy]phenyl}ethyl]-2-phenylpropanamide Hydrochloride (**84**).* To a solution of **81a** (28 mg, 0.07 mmol) in dry MeOH (2.5 mL), cyanogen bromide (8 mg, 0.075 mmol) was added, and the reaction that resulted was heated to reflux under nitrogen for 4 h. The reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was subjected to column chromatography on silica gel using 0−50% CMA80 in DCM to furnish **84** (free base, 22 mg, 75% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.17 (m, 5H), 6.99 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.51 (d, J = 8.5 Hz, 1H), 5.45 (br s, 2H), 5.37 (dd, J = 14.4, 7.6 Hz, 1H), 3.73 (dd, J = 8.9, 5.8 Hz, 1H), 3.68−3.48 (m, 2H), 3.26−3.01 (m, 2H), 1.96−1.80 (m, 1H), 1.52−1.05 (m, 7H), 0.98 (d, J = 6.7 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H). The above solid was suspended in DCM (2 mL) and cooled to 0 °C. To that above suspension, HCl (126 μL, 2.0 M in diethyl ether) was added dropwise. The solution that resulted was stirred for 30 min at 0 °C. The solvent was evaporated, and the solid was triturated with MeOH and hexanes to furnish the hydrochloride salt **84** as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ 8.52 (d, J = 8.3 Hz, 1H), 7.34−7.19 (m, 5H), 7.16 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.37−5.18 (m, 1H), 3.86−3.59 (m, 3H), 3.24 (d, J = 7.3 Hz, 2H), 2.05−1.78 (m, 1H), 1.61−1.30 (m, 6H), 1.30−1.11 (m, 1H), 1.01 (d, J = 6.7 Hz, 3H), 0.97−0.87 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 176.5, 163.3, 160.4, 159.4, 142.7, 133.0, 129.5, 128.7, 128.4, 127.9, 115.7, 74.3, 51.4, 47.3, 36.9, 34.1, 32.8, 21.1, 18.8, 17.3, 14.6; HRMS (ESI) free base m/z: calcd for $C_{25}H_{32}N_4O_3$ $[M + H]^+$, 437.2547; m/z: found, 437.2546.

*(2S)-N-[(1S)-1-[4-(Cyclobutylmethoxy)phenyl]-2-(1,3,4-oxadiazol-2-yl)ethyl]-2-phenylpropanamide (**85**).* The procedure for the synthesis of **71** was followed starting with **81b** and trimethyl orthoformate to give **85** (57% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.39−7.17 (m, 5H), 6.96 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 6.17 (d, J = 8.3 Hz, 1H), 5.42 (dd, J = 14.0, 7.3 Hz, 1H), 3.85 (d, J = 6.6 Hz, 2H), 3.56 (q, J = 7.1 Hz, 1H), 3.45−3.22 (m, 2H), 2.79−2.63 (m, 1H), 2.24−1.98 (m, 2H), 1.97−1.70 (m, 4H), 1.47 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 164.0, 158.9, 153.0, 141.0, 131.3, 128.9, 127.6, 127.3, 127.1, 114.8, 72.1, 50.0, 47.0, 34.6, 31.7, 24.8, 24.5, 18.6, 18.3; HRMS (ESI) m/z: calcd for $C_{24}H_{27}N_3O_3$ $[M + H]^+$, 406.2125; m/z: found, 406.2122.

*(2S)-N-[(1S)-1-[4-(Cyclobutylmethoxy)phenyl]-2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-2-phenylpropanamide (**86**).* The procedure for the synthesis of **72** was followed starting with **81b** and trimethyl orthoacetate to give **86** (88% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.17 (m, 5H), 6.96 (d, J = 8.6 Hz, 2H), 6.83−6.65 (m, 2H), 6.25 (d, J = 8.3 Hz, 1H), 5.39 (dd, J = 14.7, 6.6 Hz, 1H), 3.85 (d, J = 6.6 Hz, 2H), 3.57 (q, J = 7.1 Hz, 1H), 3.39−3.09 (m, 2H), 2.80−2.63 (m, 1H), 2.44 (s, 3H), 2.20−2.02 (m, 2H), 2.02−1.65 (m, 4H), 1.47 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 163.9, 158.8, 141.1, 131.6, 128.9, 127.6, 127.2, 127.1, 114.7, 72.1, 49.9, 47.0, 34.6, 31.9, 24.8, 18.5, 18.3, 10.8; HRMS (ESI) m/z: calcd for $C_{25}H_{29}N_3O_3$ $[M + H]^+$, 420.2282; m/z: found, 420.2281.

*(2S)-N-[(1S)-2-(5-Amino-1,3,4-oxadiazol-2-yl)-1-[4-(cyclobutylmethoxy)phenyl]ethyl]-2-phenylpropanamide Hydrochloride (**87**).* The procedure for the synthesis of **84** was followed starting with **81b** and cyanogen bromide to give **87** (80% yield) as a white solid. ^{1}H NMR [free base] (300 MHz, CD_3OD): δ 7.36−7.14 (m, 5H), 7.10 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 5.28 (t, J = 7.6 Hz, 1H), 3.87 (d, J = 6.6 Hz, 2H), 3.65 (q, J = 7.0 Hz, 1H), 3.16 (d, J = 7.6 Hz, 2H), 2.84−2.46 (m, 1H), 2.19−2.03 (m, 2H), 2.03−1.64 (m, 4H), 1.39 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 176.3, 165.8, 160.2, 159.3, 142.8, 133.6, 129.5, 128.6, 128.4, 127.9, 115.6, 73.2, 51.6, 47.4, 36.1, 32.9, 25.7, 19.3, 18.9;

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HRMS (ESI) free base m/z: calcd for $C_{24}H_{28}N_4O_3$ $[M + H]^+$, 421.2234; m/z: found, 421.2231.

*(2S)-N-[(1S)-2-(5-Amino-1,3,4-oxadiazol-2-yl)-1-(4-{[(2S)-2-methylpentyl]oxy}phenyl)ethyl]-2-phenylpropanamide Hydrochloride (**88**).* The procedure for the synthesis of **84** was followed starting with **81c** and cyanogen bromide to give **88** (60% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.16 (m, 5H), 6.98 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.6 Hz, 2H), 6.30 (d, J = 8.4 Hz, 1H), 5.35 (dd, J = 14.8, 6.8 Hz, 1H), 5.06 (br s, 2H), 3.81−3.45 (m, 3H), 3.13 (d, J = 6.7 Hz, 2H), 1.95−1.76 (m, 1H), 1.46 (d, J = 7.2 Hz, 3H), 1.43−1.10 (m, 4H), 0.98 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 162.8, 158.8, 158.2, 141.1, 131.7, 128.8, 127.6, 127.2, 127.1, 114.7, 73.2, 49.9, 47.0, 35.7, 32.8, 32.0, 20.0, 18.3, 17.0, 14.3; HRMS (ESI) free base m/z: calcd for $C_{25}H_{32}N_4O_3$ $[M + H]^+$, 437.2547; m/z: found, 437.2537.

*(2S)-N-[(1S)-2-(5-Amino-1,3,4-oxadiazol-2-yl)-1-(4-{[(2R)-2-methylpentyl]oxy}phenyl)ethyl]-2-phenylpropanamide Hydrochloride (**89**).* The procedure for the synthesis of **84** was followed starting with **81d** and cyanogen bromide to give **89** (75% yield) as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ 7.33−7.16 (m, 5H), 7.12 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 5.30 (t, J = 7.6 Hz, 1H), 3.84−3.60 (m, 3H), 3.18 (d, J = 7.5 Hz, 2H), 1.97−1.88 (m, 1H), 1.57−1.12 (m, 7H), 1.01 (d, J = 6.7 Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 176.3, 165.8, 160.2, 159.3, 142.8, 133.5, 129.5, 128.6, 128.4, 127.9, 115.6, 74.3, 51.6, 47.0, 36.9, 34.1, 32.9, 21.1, 18.9, 17.3, 14.6; HRMS (ESI) free base m/z: calcd for $C_{25}H_{32}N_4O_3$ $[M + H]^+$, 437.2547; m/z: found, 437.2539.

*(2S)-N-[(1S)-2-(5-Amino-1,3,4-oxadiazol-2-yl)-1-{4-[(2S)-2-methylbutoxy]phenyl}ethyl]-2-phenylpropanamide Hydrochloride (**90**).* The procedure for the synthesis of **84** was followed starting with **81e** and cyanogen bromide to give **90** (94% yield) as a white solid. ^{1}H NMR [free base] (300 MHz, $CDCl_3$): δ 7.36−7.11 (m, 5H), 7.10−6.97 (m, 3H), 6.71 (d, J = 8.6 Hz, 2H), 6.20 (br s, 2H), 5.41 (dt, J = 14.2, 7.2 Hz, 1H), 3.71 (dd, J = 9.0, 6.0 Hz, 1H), 3.58 (ddd, J = 21.3, 11.5, 6.8 Hz, 2H), 3.16 (qd, J = 15.2, 7.2 Hz, 2H), 1.89−1.71 (m, 1H), 1.63−1.44 (m, 1H), 1.39 (d, J = 7.1 Hz, 3H), 1.30−1.11 (m, 1H), 0.97 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 163.7, 158.8, 157.9, 141.2, 132.0, 128.7, 127.6, 127.2, 127.0, 114.7, 72.9, 49.9, 46.8, 34.7, 32.1, 26.1, 18.4, 16.5, 11.3; HRMS (ESI) free base m/z: calcd for $C_{24}H_{30}N_4O_3$ $[M + H]^+$, 423.2391; m/z: found, 423.2388.

*(2S)-N-[(1S)-2-(5-Amino-1,3,4-oxadiazol-2-yl)-1-{4-[(2R)-2-methylbutoxy]phenyl}ethyl]-2-phenylpropanamide Hydrochloride (**91**).* The procedure for the synthesis of **84** was followed starting with **81f** and cyanogen bromide to give **91** (59% yield) as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ 7.32−7.02 (m, 5H), 6.93 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 5.14 (t, J = 7.1 Hz, 1H), 3.77−3.48 (m, 3H), 2.50 (d, J = 7.1 Hz, 2H), 1.76−1.60 (m, 1H), 1.53−1.37 (m, 1H), 1.32 (d, J = 7.1 Hz, 3H), 1.23−1.06 (m, 1H), 0.88 (d, J = 6.7 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 175.9, 172.0, 160.0, 142.9, 134.4, 129.5, 128.5, 128.5, 127.9, 115.4, 73.9, 51.4, 47.5, 41.3, 36.0, 27.2, 18.8, 16.8, 11.6; HRMS (ESI) free base m/z: calcd for $C_{24}H_{30}N_4O_3$ $[M + H]^+$, 423.2391; m/z: found, 423.2383.

Pharmacology. *Materials.* Cell culture materials were purchased from Fisher SSI. Forskolin was purchased from Sigma-Aldrich. The Lance Ultra kit (TRF0262) was purchased from PerkinElmer.

Lance Ultra cAMP Assay Using Stable PPLS-HA-GPR88 CHO Cells. All cAMP assays were performed using our previously published methods.[26] Stimulation buffer containing 1× Hank's balanced salt solution, 5 mM HEPES, 0.1% BSA stabilizer, and 0.5 mM final IBMX was prepared and titrated to pH 7.4 at room temperature. Serial dilutions of the test compounds (5 μL) and 300 nM forskolin (5 μL), both prepared at 4× the desired final concentration in 2% DMSO/stimulation buffer, were added to a 96-well white 1/2 area microplate (PerkinElmer). A cAMP standard curve was prepared at 4× the desired final concentration in stimulation buffer and 5 μL was added to the assay plate. Stable PPLS-HA-GPR88 CHO cells were lifted with versene and spun at 270g for 10 min. The cell pellet was resuspended in stimulation buffer and 4000 cells (10 μL) were added to each well except for wells containing the cAMP standard curve. After incubating for 30 min at room temperature, Eu-cAMP tracer and uLIGHT-anti-cAMP working solutions were added per the manufacturer's instructions. After incubation at room temperature for 1 h, the TR-FRET signal (ex 337 nm) was read on a CLARIOstar multimode plate reader (BMG Biotech, Cary, NC).

Data Analysis. The TR-FRET signal (665 nm) was converted to fmol cAMP by interpolating from the standard cAMP curve. fmol cAMP was plotted against the log of compound concentration, and data were fit to a three-parameter logistic curve to generate EC_{50} values (Prism, version 6.0, GraphPad Software, Inc., San Diego, CA). The E_{max} value for each test compound relative to the control compounds RTI-13951-33 or 2-PCCA was calculated using the equation % control E_{max} = (maximal test compound signal/maximal control signal) × 100.

[^{35}S]GTPγS Binding Assay. [^{35}S]GTPγS binding assays were performed on membrane preparations from wild-type (WT) mice or GPR88 KO mice, following our previously published methods.[14,15] To assess [^{35}S]GTPγS binding in the whole striatal region, brains were quickly removed after cervical dislocation and the whole striatal region was dissected out, frozen, and stored at −80 °C until use. Membranes were prepared by homogenizing brain samples in ice-cold 0.25 M sucrose solution 10 vol (mL/g wet weight of tissue). The obtained suspensions were then centrifuged at 2500g for 10 min. Supernatants were collected and diluted 10 times in buffer containing 50 mM Tris HCl (pH 7.4), 3 mM $MgCl_2$, 100 mM NaCl, and 0.2 mM EGTA and then centrifuged at 23,000g for 30 min. The pellets were homogenized in 800 μL ice-cold sucrose solution (0.32 M), aliquoted, and kept at −80 °C. For [^{35}S]GTPγS binding assays, 2 μg of protein was used per well. Samples were incubated with and without the test compound for 1 h at 25 °C in an assay buffer containing 30 mM GDP and 0.1 nM [^{35}S]GTPγS. Bound radioactivity was quantified using a liquid scintillation counter. Nonspecific binding was defined as binding in the presence of 10 μM GTPγS; basal binding refers to binding in the absence of the agonist. Data were expressed as a mean percentage of activation above the basal binding. GTPγS binding by the agonist was plotted with X-axis representing concentration and Y-axis representing the percentage of activation against background. EC_{50} values were calculated using GraphPad Prism software.

Solubility Determination. For kinetic solubility experiments, 10 mM DMSO stocks of compounds were directly diluted into 10 mM phosphate buffer at pH 7.4 and shaken for 90 min at room temperature. The final concentration of DMSO was 1%. After the incubation, samples were filtered through a 0.4 μm filter plate (Millipore). Filtrates were carefully collected. On each experimental occasion, tamoxifen and caffeine were assessed as reference compounds for low and high solubilities, respectively. All samples were assessed in triplicate and analyzed by LC−MS/MS using electrospray ionization against standards prepared in the same matrix.

PK Analysis. PK study of **90** was performed using male Long-Evans rats (Paraza Pharma Inc., Montreal, Canada). Doses were formulated in 5% dimethylacetamide in sesame oil. On the morning of the PK study, animals were weighed, and dosing formulation volumes were calculated accordingly. The compound was injected intraperitoneally to all animals. At selected time points (0.5, 1, 2, 4, and 8 h postdose), animals were anesthetized to perform a cardiac puncture to collect blood for pooled plasma analysis, followed by whole-body perfusion with phosphate saline buffer (pH 7.4) to wash out any remaining blood from the organs. Brains were harvested and homogenized by polytron 1:4 (w/v) in 25% isopropanol in water. Brain homogenates were further pooled per corresponding time point and extracted for drug quantification of LC−MS/MS. Samples were prepared and analyzed as follows: Plasma (10 μL) was mixed with 10 μL of 0.5% formic acid in water and 100 μL of internal standard working solution (0.1 μM Glyburide/Labetalol in 0.5% ammonium formate in methanol/acetonitrile), vortexed, and centrifuged at 10,000g for 10 min at 4 °C. The supernatant (100 μL) was transferred to a 2 mL deepwell plate and diluted with 200 μL of 30% acetonitrile/water. Brain homogenate (25 μL) was mixed with 25 μL of 0.5% formic acid in water and 150 μL of internal standard working

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solution (0.1 μM Glyburide/Labetalol in methanol/acetonitrile), vortexed, and centrifuged at 10,000*g* for 10 min at 4 °C. The supernatant (100 μL) was transferred to a 2 mL deepwell plate and diluted with 100 μL of water. LC−MS/MS was conducted using an Applied Biosystems API 4000 HPLC system. Chromatography was performed with an Xbridge BEH C18 (2.1 × 30 mm, 2.5 μm) column. Mobile phases were 0.1% formic acid in water (A), and 0.1% formic acid in 25% isopropanol/acetonitrile (B). Initial conditions were 5% B and held for 0.5 min, followed by a linear gradient to 95% B over 1.8 min. 95% B was held for 2.6 min before returning to initial conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c01581.

^{1}H NMR, ^{13}C NMR, and HPLC analysis results of target compounds (PDF)

Molecular formula strings with biological data (CSV)

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

ADME, absorption, distribution, metabolism, and excretion; 2-AMPP, (2*S*)-*N*-((1*R*)-2-amino-1-(4-(2-methyl-pentyloxy)-phenyl)ethyl)-2-phenylpropanamide; cAMP, cyclic adenosine monophosphate; BBB, blood−brain barrier; BRET, bioluminescence resonance energy transfer; CHO cells, Chinese hamster ovary cells; DCM, dichloromethane; DEAD, diethyl azodicarboxylate; DIPEA, *N*,*N*-diisopropylethylamine; DMF, *N*,*N*-dimethylformamide; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; GPCR, G protein-coupled receptor; HA, human influenza hemagglutinin; HBTU, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HEK293 cells, human embryonic kidney cells; HOBt, hydroxybenzotriazole; KO, knockout; MS, mass spectroscopy; 2-PCCA, (1*R*,2*R*)-2-(pyridin-2-yl)cyclopropane carboxylic acid((2*S*,3*S*)-2-amino-3-methylpentyl)-(4′-propylbiphenyl-4-yl)amide; Pgp, P-glycoprotein; PPLS, pre-prolactin leader sequence; PTSA, *p*-toluenesulfonic acid; TBAF, tetrabutylammonium fluoride; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TIPSCl, triisopropylsilyl chloride; TLC, thin-layer chromatography; TPSA, topological polar surface area; SAR, structure−activity relationship

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