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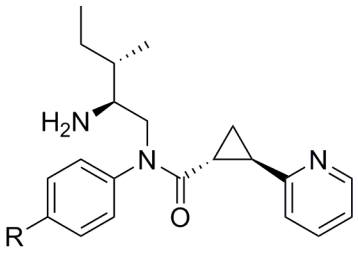
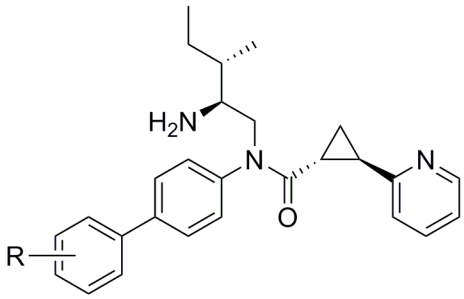


R = H, hexyl, Cy, Ph, PhO, Bn, $PhCH_2CH_2$



R = alkyl, alkoxy, F, Cl, CN, NO_2, OH, amine, amide, ester, etc.

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Abstract

GPR88, an orphan receptor richly expressed in the striatum, is implicated in a number of basal ganglia-associated disorders. In order to elucidate the functions of GPR88, an *in vivo* probe appropriate for CNS investigation is required. We previously reported that 2-PCCA was able to modulate GPR88–mediated cAMP production through a $G\alpha_i$–coupled pathway. Early structure-activity relationship (SAR) studies suggested that the aniline moiety of 2-PCCA is a suitable site for diverse modifications. Aimed at elucidating structural requirements in this region, we have designed and synthesized a series of analogues bearing a variety of substituents at the phenyl ring of the aniline moiety. Several compounds (e.g., **5j**, **5o**) showed improved or comparable potency, but have lower lipophilicity than 2-PCCA (clogP 6.19). These compounds provide the basis for further optimization to probe GPR88 *in vivo* functions. Computational studies confirmed the SAR trends and supported the notion that 4'-substituents on the biphenyl ring exit through a largely hydrophobic binding site to the extracellular loop.

Keywords: Orphan GPR88, 2-PCCA, SAR, molecular modeling

INTRODUCTION

The G protein-coupled receptors (GPCRs) constitute the largest family of membrane proteins and mediate most cellular responses to hormones and neurotransmitters. GPCRs also play important roles in disease pathogenesis and account for more than 30% of targets of marketed drugs.[1] Analysis of the human genome revealed more than 800 GPCR sequences, of which around 140 GPCRs, excluding olfactory receptors, are still classified as orphan receptors for which endogenous ligands are unknown.[2] The complex biology and potential for drug therapy within this class provide strong incentives for small molecule probe development to enable modulation of individual receptors and facilitate elucidation of their biological functions.[3]

GPR88 is an orphan receptor highly expressed in the CNS, with particularly robust expression in the striatum throughout the dorsal and ventral areas.[4] Transcriptional profiling studies have revealed *Gpr88* gene expression is altered by conditions related to Parkinson's disease,[4c] schizophrenia,[5] bipolar disorder,[6]

depression,[7] and drug addiction.[8] Interestingly, both receptor up- and down-regulation have been observed depending on the treatment and brain region. For example, in dopamine-depleted striatum, *Gpr88* expression was differentially regulated in striatonigral and striatopallidal medium spinal neurons (MSNs), and L-DOPA treatment normalized *Gpr88* expression levels.[4c] *Gpr88* gene expression was up-regulated in the prefrontal cortex following methamphetamine exposure[6b] and down-regulated in the amygdala following treatment with the NMDA receptor antagonist MK-801.[5]

More direct evidence of GPR88 function was obtained from GPR88 knockout studies. GPR88 knockout mice demonstrated disrupted prepulse inhibition of startle response, a phenotype of schizophrenia, and exhibited D_2 receptor hypersensitivity, which were normalized to control levels by antipsychotic drug administration.[9] In another study, the GPR88 knockout animals exhibited increased locomotion, poor motor coordination and impaired cue-based learning.[10] Examination of MSNs electrophysiology in brain slices revealed decreased tonic GABAergic inhibition and increased glutamatergic excitation, which promoted enhanced firing rates observed *in vivo*.[10] In addition, GPR88 re-expression normalized these impaired behaviors and electrophysiological properties, indicating that GPR88 dysfunction may contribute to abnormal behaviors observed in basal ganglia-associated disorders such as Parkinson's disease and schizophrenia. Interestingly, a recent study showed that the GPR88-deficient mice performed better in spatial tasks and reduced levels of anxiety, indicating GPR88 may also play a role in cognitive and anxiety disorders.[11]

Despite emerging pharmacological implications of GPR88, the signaling mechanisms and biological functions of this orphan receptor are still largely unknown due to the lack of potent and selective native or synthetic ligands. We previously reported that 2-PCCA [(1*R**,2*R**)-2-(pyridin-2-yl)cyclopropanecarboxylic acid ((2S,3S)-2-amino-3-methylpentyl)-(4′-propylbiphenyl-4-yl)-amide (**1**); Figure 1] was able to modulate GPR88-mediated cAMP production through a $G\alpha_i$–coupled pathway.[12] Unfortunately, 2-PCCA has a high calculated lipophilicity (clogP 6.19) and was reported to be a P-glycoprotein substrate, which might limit its effectiveness as a tool.[13] In order to elucidate the functions of GPR88, an improved *in vivo* agonist probe appropriate for CNS investigation is required. Early structure-activity relationship (SAR) studies suggest that the aniline moiety of 2-PCCA is a suitable site for diverse modifications.[12-13] Aimed at elucidating SAR

requirements in this region, we have designed and synthesized a series of analogues (**4a–g**, Figure 1 and **5a–aa**, Figure 2) bearing a variety of substituents at the phenyl ring of the aniline moiety. In this paper, we report the SAR and computational studies of these compounds with the goal of improving potency and lowering the lipophilicity.

RESULTS AND DISCUSSION

Chemistry. The overall approach to the synthesis followed methods detailed in our earlier work.[12] Synthesis of the designed compounds **4a–g** is outlined in Scheme 1. Reductive amination of aldehyde **7**, prepared by Dess-Martin oxidation of commercially available (−)-(2*S*,3*S*)-*N*-Boc-2-amino-3-methyl-1-pentanol, with 4-substituted aniline **6a–h** afforded amine **8a–h** in 46–77% yields. Amide formation with the acid chloride of racemic (±)-*trans*-2-(pyridin-2-yl)cyclopropanecarboxylic acid gave **9a–h** in 32–72% yields. Removal of the Boc protecting group of **9b–h** with 4 M HCl in dioxane provided target compounds **4a-g** in 83–97% yields.

Synthesis of the biphenyl derivatives **5a–aa** is illustrated in Scheme 2. Suzuki coupling of the bromo compound **9a** with an appropriate arylboronic acid under microwave conditions gave intermediates **10a–aa** in the range of 51−81% yields. Deprotection of the Boc group furnished **5a–aa** in 86−100% yields. Target compounds **4a–g** and **5a–aa** were determined to be 1:1 mixture of (1*R*,2*R*)- and (1*S*,2*S*)-enantiomers, differentiating at the configuration of the *trans*-substituted cyclopropane ring, by ^{1}H NMR and HPLC analyses.

Biological Results and SAR Studies. We previously demonstrated that 2-PCCA (**1**, Figure 1) inhibited isoproterenol-stimulated cAMP accumulation with EC_{50} = 911 nM in HEK293 cells stably expressing the human GPR88 receptor and the GloSensor^{TM}–22F cAMP construct, indicating that GPR88 is coupled to the $G\alpha_i$ subunits.[12] Recently, Bi et al. reported that the (1*R*,2*R*)-enantiomer of 2-PCCA exhibited an EC_{50} of 3.1 nM in a HTRF (Cisbio Bioassays) cAMP assay.[13] The discrepancy between the EC_{50} values of 2-PCCA is possibly due to the sensitivity of the two different assay systems. In order to facilitate the SAR study and discovery of potent GPR88 ligands, a reliable and sensitive assay is needed. Thus, we created a Chinese

Hamster Ovary (CHO) cell line stably expressing the PPLS-HA-GPR88 construct and measured cAMP levels using the Lance assay platform (PerkinElmer). A pre-prolactin leader sequence (PPLS) and an influenza hemagglutinin (HA) tag were used in the construct to facilitate membrane expression and immunostaining of GPR88 in CHO cells. In the stable PPLS-HA-GPR88 CHO cells, 2-PCCA and its pure enantiomer **2** had EC_{50} values of 116 nM and 56 nM, respectively, shown in Figure 1. The phenyl analogue **3** possessed an EC_{50} of 233 nM.

Early SAR studies suggest that the aniline moiety of 2-PCCA is a suitable site for optimization.[12-13] It appears that the phenyl ring of the aniline moiety can tolerate substitution at the 4-position, in some cases leading to improved potency. In order to gain additional information about the structural requirements in this region for obtaining high potency ligands with possibly improved drug-like properties (e.g., clogP <5), we have synthesized a series of analogues (**4a–g**, Figure 1 and **5a–aa**, Figure 2) and tested their agonist activity in the Lance cAMP assay. These compounds bear a variety of substituents at the phenyl ring of the aniline moiety to systematically evaluate the effects of size, polarity, lipophilicity, and steric and electronic tolerance. The unsubstituted analogue **4a** was significantly less potent than 2-PCCA (2760 nM vs. 116 nM, Figure 1). Addition of a hexyl group at the 4-position of the phenyl ring led to **4b**, which regained most of the potency (EC_{50} = 421 nM), indicating a hydrophobic pocket may be present in the binding site to interact with this region. Replacing the hexyl group with cyclohexyl (**4c**) or phenyl (**4d**) further improved the EC_{50} to 283 nM. However, moving the distal phenyl group in **4d** away from the aniline phenyl ring by replacement with phenoxy (**4e**), benzyl (**4f**) or phenethyl (**4g**) resulted in deteriorated activity. These findings suggested that an aromatic stacking interaction between the biphenyl moiety and the receptor might contribute to the agonist activity of 2-PCCA.

Substituent effect of the distal phenyl ring of **4d** was next examined and the results are summarized in Table 1. Consistent with the previous findings,[12] the 4-position of the distal phenyl ring tolerated small to medium sized alkyl substitutions with the ethyl analogue **5c** (EC_{50} = 85 nM) being the most potent compound and the bulk *t*-butyl **5f** (EC_{50} = 515 nM) being the least potent compound in the series. Interestingly, the large alkyl substitutions, such as hexyl (**5g**), cyclohexyl (**5h**) and phenyl (**5i**), were also well tolerated giving good

to moderate (EC_{50} = 136–289 nM) activity. This provided further evidence to support the previous hypothesis[13] that the 4'-substitution at the biphenyl group likely extends into a hydrophobic pocket.

Improvement of the potency of **4d** was also observed by adding small alkoxy groups at the 4-position (**5j–m**). Attachment of an additional methoxy group at the 3-position of **5j** led to the 3,4-dimethoxy analogue **5n**, resulting in approximately 10-fold loss of activity (96 nM vs. 917 nM). The loss in potency of **5n** was probably due to the limited steric tolerance proximal to the distal phenyl ring, as evidenced in **5f**. Somewhat surprisingly, the 3,4-methylenedioxy analogue **5o** possessed good activity with an EC_{50} of 204 nM. The electron-withdrawing groups (**5b**, **5p-u**) were well tolerated at the 4-postion, with EC_{50} values ranging from 187 nM to 351 nM. However, substituents containing a hydrogen-bond donor (**5v** and **5w**) led to a significant decrease in activity. The dimethylamino group (**5x**) had an improved potency compared to the amino group in **5w** (294 nM vs. 1120 nM), suggesting that both basicity and lipophilicity of the substituents at the 4-postion may have a marked influence on the activity. Finally, substitution at the 4-position with an amide group (**5y**, **5z** and **5aa**) gave the least activity in the series.

Calculated physiochemical properties such as lipophilicity (clogP), topological polar surface area (TPSA), and derived values such as logBB are useful indicators of a compound's potential to penetrate the brain. In general, CNS drugs have clogP in the range of 2–4,[14] TPSA less than 76 $Å^2$,[15] and logBB greater than −1.[16] These molecular descriptors were calculated for 2-PCCA, as well as selected compounds **5a**, **5c**, **5j**, **5l**, **5m**, and **5o** (Table 2). 2-PCCA has the highest clogP value of 6.19. All other calculated compounds have clogP greater than 4, among which **5o** has the lowest clogP = 4.41. 2-PCCA and all of the analogues, except **5o**, have TPSA less than 76 $Å^2$. Even **5o** has a TPSA = 77.68 $Å^2$, just above the recommended threshold (a TPSA cutoff of 90 $Å^2$ has also been suggested for CNS drugs[17]). All compounds have logBB values greater than −1, predicting potential brain penetration.

QSAR Analysis. In a complementary effort to assess the SAR, we computed a series of properties of the substituents and analyzed their importance in explaining the observed variations in $\ln EC_{50}$ values. We computed optimized geometries of the hydrogen capped substituted biphenyl fragments using MOPAC7[18] and

then computed shape/steric (Sterimol parameters/globularity),[19] polar surface area (PSA), volume, solvent accessible area, total hydrophobicity (TotalHyd) and HOMO/LUMO frontier orbital energetics using these semiempirical results in addition to GRAPHA assessments of the varied substituted biphenyl fragments.[20] LogP and Molar refractivity and number of rotatable bonds were computed using OpenBabel 2.3.2.[21] Isotropic polarizabilities of the substituents were computed using GAMESS-UK[22] at 6-31G** B3LYP DFT optimized geometries.

The covariance matrix of all the descriptors was computed to facilitate exploring QSAR employing descriptors with reasonable 'orthogonality' in variance. In this way we maximized the linear independence of the descriptors and sought to explain the $\ln EC_{50}$ variations via the QSAR description with the smallest number of possible terms while probing multiple facets of each of the substitutions. While many models were explored in an attempt to find explanations for the $\ln EC_{50}$'s in terms of all the computed metrics, we focused on a buildup of three models and examined at each stage the impact of an additional descriptor.

Table 3 reports the best (model C) of three successive models, while the Supporting Information contains the description and statistics for the other two models A and B upon which model C was based. In the model C, $\ln EC_{50} \sim -1.0\ L + 1.7\ TotalHyd + 0.04\ V\_S + 0.1\ PSA - 0.9\ LogP + 1.1\ B4 + 8.0$. The significance of both the 'metric' within the given QSAR model as well as the ANOVA computations allowed one to decide on the significance of any improvement in the multivariate-linear least squares with model expansion. The model table provides the coefficients of the metrics in the model QSAR equation, the standard error (an error level of the model computed from the sums-of-squares of deviations from the theoretical fit and the number of cases), the t-value (the t-statistic providing an indication of whether the coefficient is different than zero), and Pr (the p-value for the hypothesis test for which the t-value is the test statistic). As shown in Table 3, the p-value was < 0.05 and indicated significance. At a 95% confidence limit, the model had significance in explaining the variations of $\ln EC_{50}$ in terms of the physiochemical descriptors probed. The R^2 value illustrated reasonable correlations in the fit described by the theoretical QSAR equation to the observed $\ln EC_{50}$ value, and this coefficient of determination showed that the variables employed provided a

68% explanation for the variations in $lnEC_{50}$. Figure 3 shows a plot of the predicted versus the experimental $lnEC_{50}$ values.

The model C contains six physiochemical descriptors. PSA, logP, and total hydrophobicity are common features used in the assessment of drug candidates, but the L- and B4-Sterimol (L and B4, respectively) and the vibrational thermochemical (V_S) descriptors are much less well known. An example of the L- and B4-Sterimol metrics for two ligands **5j** and **5o** is shown in Figure 4. The L-Sterimol axis is the longest dimension spanning the molecular surface of the substituent. The B4-Sterimol descriptor is orthogonal to this L-dimension and provides a metric of a width of the substituent to the L-axis. Such orthogonal descriptor captures the width of the binding pocket orthogonal to the long axis of the substituent.

The vibrational parameter (V_S) is a descriptor that captures a dynamical aspect of the ligand and possibly indicates a propensity for cooperative binding. While differential binding to the orthosteric site of a GPCR is not likely to result in significant receptor structural changes near the orthosteric site, small changes in a ligand's architecture may result in differential stabilization of activated conformations of the GPCR. The effect of the local fluctuations in a portion of a ligand substituent may bias larger cooperative structural changes at the intracellular side to conformations constituting an 'active state'.[23-24] Small changes in a ligand's dynamics may in this way alter ionic locks/loop and helical structure at the intracellular region that modifies interactions with GPCR partners (e.g., G proteins, β-arrestin). While such a rationale for V_S remains speculative, there was a plausible connection of the vibrational parameter to the $lnEC_{50}$ in our QSAR model.

Docking Analysis of (1*R*,2*R*)-2-PCCA. While the QSAR model compared reasonably with the qualitative facets of the SAR deductions at the aniline moiety, we sought to discover if a homology model, based on existing crystallographic templates, would give useful information about the receptor binding site characteristics for this region. The focus of this limited structural exploration was to ascertain whether the QSAR is consistent with structural principles/orthosteric ligand binding site based on the docking and MMGBSA (Molecular Mechanics Generalized Born Surface Area)[25] scoring analysis of (1*R*,2*R*)-2-PCCA.

Sequence alignments of human GPR88 with selected GPCR templates of known structure were performed using a BLOSUM62 matrix. While no GPCR crystal structures with high or moderate sequence identity (>40% by our own experience) to GPR88 have yet been solved, the β1-adrenergic receptor (PDB: 5A8E) has a 26% sequence identity to GPR88 deduced from a pairwise alignment. This template also has one of the highest sequence identities in the alignment of 9 GPCRs with GPR88 (~20%, see Supporting Information). The β1-adrenergic receptor template was used to construct an initial backbone model of GPR88 employing Sali's MODELLER v9.11,[26] refining the backbone model 'energetically' using simulated annealing with topological constraints. We next employed SCWRL[27] rotamer exploration to find non-clashing sidechain orientations for non-conserved residues with conserved residues between the target and template employing conservation assessments shown in the alignment. Conserved residue sidechain from the β1-adrenergic receptor template were initially retained in the SCWRL rotamer exploration. This initial level model was then energy minimized using AMBER12[28] to provide a homology model for docking and free-energy scoring.

We docked (1*R*,2*R*)-2-PCCA using both Autodock VINA[29] with AMBER12 MMGBSA rescoring as well as GLIDE-SP (Schrödinger)[30] followed by Prime-MMGBSA rescoring. As shown in Figure 5, the 4'-propylbiphenyl group in (1*R*,2*R*)-2-PCCA pointed out of the orthosteric site into the extracellular loop region. The residue character along the binding site region housing the biphenyl is quite hydrophobic. The initial GPR88 homology model appears to be consistent with the results of QSAR analysis in that the long-spatial axis, parameterized at the L-Sterimol, is an important facet as is the overall hydrophobicity. The model is not, at this stage, predictive of $\ln EC_{50}$. Refinement of the model using pure (*R*,*R*)-diastereomers is currently under investigation.

CONCLUSIONS

In summary, we have designed and synthesized a series of 2-PCCA analogues bearing a variety of substituents at the phenyl ring of the aniline moiety to determine the SAR in this region. The target compounds were evaluated in a Lance cAMP assay using stable PPLS-HA-GPR88 CHO cells. SAR studies

suggested that there is a hydrophobic pocket in the GPR88 binding site interacting with the aniline region of 2-PCCA. In addition, the 4'-position of the biphenyl group was well tolerated with alkyl, alkoxy and electron-withdrawing groups, but less tolerated with the substituents having a hydrogen-bond donor. Several compounds had a slightly improved or comparable potency, but lower calculated lipophilicity than 2-PCCA. Combined with calculated TPSA and logBB values, compound **5j** may provide the basis for further optimization to develop an *in vivo* probe for GPR88 functional studies.

Exploration of both a computational QSAR and an initial homology model and docking of (1*R*,2*R*)-2-PCCA supported the SAR conclusions. The findings of statistically sound models including both L- and B4-Sterimol parameters in the QSAR were consistent with the positioning of the 4'-substituted biphenyl encased in a largely hydrophobic GPR88 homology model binding site.

EXPERIMENTAL SECTION

Chemistry. *General Methods*. Melting points were determined using a MEL-TEMP II capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were obtained on a Bruker Avance DPX-300 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. ^{13}C NMR data of diastereomeric mixtures were not reported due to the complicity of the spectra. Mass spectra (MS) were run on a Perkin-Elmer Sciex API 150 EX mass spectrometer. HRMS spectra were run on a Waters Synapt G2 HDMS Q-TOF mass spectrometer, using electrospray ionization in positive ion mode. Analytical thin-layer chromatography (TLC) was carried out using EMD silica gel 60 F_{254} TLC plates. TLC visualization was achieved with a UV lamp or in an iodine chamber. Flash column chromatography was done on a CombiFlash Companion system using Isco prepacked silica gel columns. Unless otherwise stated, reagent-grade chemicals were obtained from commercial sources and were used without further purification. All moisture- and air-sensitive reactions and reagent transfers were carried out under dry nitrogen. Synthesis and characterization of compounds **1–3**, **5a–c**, **5e**, **5h**, **5p**, **5q** and **5t** have been previously reported.[12] All synthesized compounds were ≥95% pure as determined by HPLC analyses (see Supporting Information).

*tert-Butyl {(2S,3S)-1-[(4-Bromophenyl)amino]-3-methylpentan-2-yl}carbamate (**8a**).* To a solution of (−)-(2*S*,3*S*)-*N*-Boc-2-amino-3-methyl-1-pentanol (2.17 g, 10.0 mmol) in water-saturated CH_2Cl_2 (10 mL) at room temperature was added Dess-Martin reagent (8.90 g, 21.0 mmol) and the reaction was stirred for 1 h. Additional water-saturated CH_2Cl_2 (5 mL) was added every 15 min during the reaction time. The mixture was diluted with Et_2O (100 mL) and poured into a solution of $Na_2S_2O_3$ (17 g) in 80% saturated $NaHCO_3$ (100 mL). After stirring for 10 min, the layers were separated and the aqueous layer was extracted with Et_2O (100 mL). The combined organic layers were washed with ice-cold saturated $NaHCO_3$ (30 mL) and water (30 mL). The solution was dried (Na_2SO_4) and concentrated under reduced pressure to give the crude aldehyde **7**. To a solution of 4-bromoaniline (**6a**) (1.72 g, 10.0 mmol) in dichloroethane (60 mL) was added the above crude aldehyde, followed by $NaBH(OAc)_3$ (4.24 g, 20.0 mmol). The mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0–30% EtOAc in hexanes afforded **8a** (2.78 g, 75%) as a white solid: mp 103–105 ºC; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.24 (d, *J* = 9.0 Hz, 2H), 6.45 (d, *J* = 9.0 Hz, 2H), 4.52 (d, *J* = 9.0 Hz, 1H), 4.20 (br s, 1H), 3.82–3.65 (m, 1H), 3.30–3.14 (m, 1H), 3.05–2.89 (m, 1H), 1.60–1.47 (m, 1H), 1.44 (s, 9H), 1.23–1.10 (m, 1H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 154.9, 145.7, 130.1, 112.4, 106.9, 77.9, 52.9, 45.0, 35.7, 26.6, 23.6, 13.8, 9.9;MS (ESI) *m/z* 371.3 $[M + H]^+$ (^{79}Br), 373.3 $[M + H]^+$ (^{81}Br).

*tert-Butyl [(2S,3S)-1-Phenylamino-3-methylpentan-2-yl]carbamate (**8b**).* The procedure for **8a** was followed using 140 mg (1.5 mmol) of **6b** to give 336 mg (77%) of **8b** as a white solid: mp 77–79 ºC; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.16 (t, *J* = 7.5 Hz, 2H), 6.69 (t, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 9.0 Hz, 2H), 4.57 (d, *J* = 9.0 Hz, 1H), 4.13 (br s, 1H), 3.82–3.68 (m, 1H), 3.26 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.02 (t, *J* = 10.5 Hz, 1H), 1.68–1.46 (m, 1H), 1.45 (s, 9H), 1.28–1.10 (m, 1H), 0.98-0.89 (m, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 156.6, 148.3, 129.2, 117.4, 112.8, 79.5, 54.7, 46.6, 37.5, 28.4, 25.4, 15.5, 11.7; MS (ESI) *m/z* 293.3 $[M + H]^+$.

*tert-Butyl {(2S,3S)-1-[(4-Hexylphenyl)amino]-3-methylpentan-2-yl}carbamate (**8c**).* The procedure for **8a** was followed using 355 mg (2.0 mmol) of **6c** to give 526 mg (70%) of **8c** as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.98 (d, *J* = 9.0 Hz, 2H), 6.53 (d, *J* = 9.0 Hz, 2H), 4.52 (d, *J* = 9.0 Hz, 1H), 3.86 (br s, 1H), 3.80–3.66 (m, 1H), 3.30–3.18 (m, 1H), 3.06–2.90 (m, 1H), 2.48 (t, *J* = 6.0 Hz, 2H), 1.70–1.53 (m, 2H), 1.44 (s, 9H), 1.38–1.10 (m, 8H), 1.00–0.80 (m, 9H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 156.5, 146.5, 131.8, 129.1, 112.8, 79.4, 54.8, 46.7, 37.5, 35.1, 31.9, 31.8, 29.0, 28.4, 25.4, 22.7, 15.5, 14.1, 11.7; MS (ESI) *m/z* 377.3 $[M + H]^+$.

*tert-Butyl {(2S,3S)-1-[(4-Cyclohexylphenyl)amino]-3-methylpentan-2-yl}carbamate (**8d**).* The procedure for **8a** was followed using 263 mg (1.5 mmol) of **6d** to give 345 mg (61%) of **8d** as a white solid: mp 108–110 ºC; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.02 (d, *J* = 9.0 Hz, 2H), 6.55 (d, *J* = 9.0 Hz, 2H), 4.53 (d, *J* = 9.0 Hz, 1H), 4.00 (br s, 1H), 3.80–3.66 (m, 1H), 3.32–3.20 (m, 1H), 3.10–2.90 (m, 1H), 2.46–2.31 (m, 1H), 1.90-1.70 (m, 5H), 1.70–1.10 (m, 16H), 0.98–0.90 (m, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 156.5, 146.5, 137.3, 127.5, 122.8, 79.4, 54.8, 46.7, 43.7, 37.4, 34.8, 28.4, 27.1, 26.3, 25.4, 15.5, 11.7; MS (ESI) *m/z* 375.2 $[M + H]^+$.

*tert-Butyl [(2S,3S)-1-Biphenylamino-3-methylpentan-2-yl]carbamate (**8e**).* The procedure for **8a** was followed using 545 mg (2.5 mmol) of **6e** to give 560 mg (76%) of **8e** as a white solid: mp 98–100 ºC; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.56–7.50 (m, 2H), 7.46–7.34 (m, 4H), 7.28–7.21 (m, 1H), 6.66 (d, *J* = 9.0 Hz, 2H), 4.47 (d, *J* = 9.0 Hz, 1H), 4.18 (br s, 1H), 3.81–3.71 (m, 1H), 3.32–3.22 (m, 1H), 3.10–2.96 (m, 1H), 1.68–1.46 (m, 1H), 1.45 (s, 9H), 1.30–1.10 (m, 1H), 0.98 (d, *J* = 9.0 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 156.7, 148.1, 141.4, 130.2, 128.7, 127.6, 126.6, 126.1, 133.0, 79.6, 54.8, 46.6, 37.5, 28.5, 25.5, 15.6, 11.7; MS (ESI) *m/z* 369.4 $[M + H]^+$.

*tert-Butyl {(2S,3S)-1-[(4-Phenoxyphenyl)amino]-3-methylpentan-2-yl}carbamate (**8f**).* The procedure for **8a** was followed using 370 mg (2.0 mmol) of **6f** to give 350 mg (46%) of **8f** as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.32–7.25 (m, 2H), 7.05–6.98 (m, 1H), 6.96–6.86 (m, 4H), 6.59 (d, *J* = 9.0 Hz, 2H), 4.56 (d, *J* = 9.0 Hz, 1H), 4.02 (br s, 1H), 3.81–3.72 (m, 1H), 3.31–3.20 (m, 1H), 3.06–2.95 (m, 1H), 1.66–1.50 (m, 1H), 1.45

(s, 9H), 1.26–1.10 (m, 1H), 1.02–0.90 (m, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 159.3, 156.7, 147.5, 145.3, 129.9, 121.9, 121.3, 117.1, 113.7, 79.4, 54.8, 46.9, 37.5, 28.5, 25.4, 15.6, 11.7; MS (ESI) *m/z* 385.4 $[M + H]^+$.

*tert-Butyl {(2S,3S)-1-[(4-Benzylphenyl)amino]-3-methylpentan-2-yl}carbamate (**8g**).* The procedure for **8a** was followed using 275 mg (1.5 mmol) of **6g** to give 390 mg (68%) of **8g** as an off- white solid: mp 65–66 ºC; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.30–7.15 (m, 5H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.54 (d, *J* = 9.0 Hz, 2H), 4.54 (d, *J* = 9.0 Hz, 1H), 3.95 (br s, 1H), 3.87 (s, 2H), 3.83–3.70 (m, 1H), 3.30–3.18 (m, 1H), 3.06–2.95 (m, 1H), 1.65–1.50 (m, 1H), 1.44 (s, 9H), 1.28–1.10 (m, 1H), 1.01–0.90 (m, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 156.5, 146.6, 142.1, 130.0, 129.7, 128.8, 128.3, 125.8, 113.0, 79.5, 54.7, 46.8, 41.1, 37.5, 28.4, 25.4, 15.5, 11.7; MS (ESI) *m/z* 383.5 $[M + H]^+$.

*tert-Butyl {(2S,3S)-1-[(4- Phenethylphenyl)amino]-3-methylpentan-2-yl}carbamate (**8h**).* The procedure for **8a** was followed using 290 mg (1.5 mmol) of **6h** to give 325 mg (55%) of **8h** as a white solid: mp 55–57 ºC; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.30–7.10 (m, 5H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.59 (d, *J* = 9.0 Hz, 2H), 4.62 (d, *J* = 9.0 Hz, 1H), 3.95 (br s, 1H), 3.80–3.68 (m, 1H), 3.25 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.02 (t, *J* = 10.5 Hz, 1H), 2.90–2.76 (, 4H), 1.65–1.50 (m, 1H), 1.44 (s, 9H), 1.23–1.10 (m, 1H), 0.98–0.88 (m, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 156.6, 145.9, 142.1, 131.4, 129.2, 128.5, 128.3, 125.8, 113.5, 79.5, 54.6, 47.2, 38.3, 37.5, 37.1, 28.4, 25.4, 15.5, 11.7; MS (ESI) *m/z* 397.5 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{4-Bromophenyl-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**9a**).* To a solution of (±)-*trans*-2-(pyridin-2-yl)cyclopropanecarboxylic acid (0.40 g, 2.0 mmol) in CH_2Cl_2 (20 mL) at room temperature was added oxalyl chloride (0.35 mL, 4.0 mmol) and DMF (50 µL). The mixture was stirred at 40 °C for 2 h, then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and treated with **8a** (0.74 g, 2.0 mmol) and Et_3N (1.1 mL, 8.0 mmol). The resulting solution was stirred at room temperature overnight. Saturated $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (3 x 20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using

0–25% EtOAc in hexanes afforded **9a** (0.74 g, 72%, 1:1 diastereomeric mixture) as a light yellow foam: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30 (d, J = 6.0 Hz, 1H), 7.58–7.34 (m, 3H), 7.22–6.98 (m, 4H), 4.96 (d, J = 9.0 Hz, 1H), 4.45–4.25 (m, 1H), 3.80–3.78 (m, 1H), 3.21–3.06 (m, 1H), 2.71–2.62 (m, 0.5H), 2.58–2.48 (m, 0.5H), 1.98–1.86 (m, 1H), 1.75–1.62 (m, 1H), 1.60–1.35 (m, 3H), 1.45 and 1.40 (2s, 9H), 1.15–1.02 (m, 1H), 0.92–0.80 (m, 6H); MS (ESI) *m/z* 516.7 $[M + H]^+$ (^{79}Br), 518.6 $[M + H]^+$ (^{81}Br).

tert-Butyl [(2S,3S)-1-{Phenyl-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**9b**).* The procedure for **9a** was followed using 102 mg (0.35 mmol) of **8b** to give 85 mg (56%) of **9b** (1:1 diastereomeric mixture) as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.26 (d, J = 6.0 Hz, 1H), 7.54–7.46 (m, 1H), 7.38–7.10 (m, 6H), 7.03–6.96 (m, 1H), 4.96 (t, J = 7.5 Hz, 1H), 4.48–4.32 (m, 1H), 3.81–3.62 (m, 1H), 3.22–3.08 (m, 1H), 2.72–2.62 (m, 0.5H), 2.58–2.48 (m, 0.5H), 2.00–1.88 (m, 1H), 1.72–1.48 (m, 4H), 1.46 and 1.42 (2s, 9H), 1.15–1.00 (m, 1H), 0.91–0.78 (m, 6H); MS (ESI) *m/z* 438.5 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{4-Hexylphenyl-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**9c**).* The procedure for **9a** was followed using 188 mg (0.5 mmol) of **8c** to give 140 mg (54%) of **9c** (1:1 diastereomeric mixture) as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.22 (m, 1H), 7.53–7.45 (m, 1H), 7.20–6.92 (m, 6H), 5.10 (t, J = 9.0 Hz, 1H), 4.45–4.31 (m, 1H), 3.80–3.60 (m, 1H), 3.18–3.06 (m, 1H), 2.70–2.61 (m, 0.5H), 2.60–2.47 (m, 2.5H), 2.00–1.89 (m, 1H), 1.71–1.30 (m, 24H), 1.20–1.02 (m, 1H), 0.96–0.80 (m, 6H); MS (ESI) *m/z* 522.6 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{4-Cyclohexylphenyl-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**9d**).* The procedure for **9a** was followed using 131 mg (0.35 mmol) of **8d** to give 104 mg (57%) of **9d** (1:1 diastereomeric mixture) as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.20 (m, 1H), 7.52–7.45 (m, 1H), 7.20–6.92 (m, 6H), 5.12 (dd, J = 12.0, 9.0 Hz, 1H), 4.46–4.30 (m, 1H), 3.80–3.60 (m, 1H), 3.20–3.06 (m, 1H), 2.70–2.60 (m, 0.5H), 2.58–2.47 (m, 1.5H), 2.00–1.65 (m, 7H), 1.55–1.20 (m, 17H), 1.18–1.00 (m, 1H), 0.92–0.78 (m, 6H); MS (ESI) *m/z* 520.6 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{Biphenyl-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**9e**).* The procedure for **9a** was followed using 184 mg (0.5 mmol) of **8e** to give 130 mg (51%) of **9e** (1:1 diastereomeric mixture) as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.29–8.23 (m, 1H), 7.60–7.15 (m, 11H), 7.01–6.95 (m, 1H), 5.11 (t, *J* = 9.0 Hz, 1H), 4.50–4.37 (m, 1H), 3.86–3.68 (m, 1H), 3.26–3.17 (m, 1H), 2.75–2.68 (m, 0.5H), 2.60–2.51 (m, 0.5H), 2.10–1.98 (m, 1H), 1.75–1.67 (m, 0.5H), 1.66–1.58 (m, 0.5H), 1.57–1.40 (m, 3H), 1.47 and 1.43 (2s, 9H), 1.20–1.03 (m, 1H), 0.93–0.80 (m, 6H); MS (ESI) *m/z* 514.7 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{4-Phenoxyphenyl-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**9f**).* The procedure for **9a** was followed using 130 mg (0.34 mmol) of **8f** to give 57 mg (32%) of **9f** (1:1 diastereomeric mixture) as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.33–8.27 (m, 1H), 7.52–7.43 (m, 1H), 7.40–7.30 (m, 2H), 7.22–7.10 (m, 4H), 7.02–6.78 (m, 5H), 5.08 (t, *J* = 9.0 Hz, 1H), 4.55–4.40 (m, 1H), 3.82–3.66 (m, 1H), 3.20–3.02 (m, 1H), 2.68–2.60 (m, 0.5H), 2.52–2.43 (m, 0.5H), 2.02–1.90 (m, 1H), 1.75–1.45 (m, 4H), 1.44 and 1.41 (2s, 9H), 1.18–1.00 (m, 1H), 0.92–0.80 (m, 6H); MS (ESI) *m/z* 530.7 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{4-Benzylphenyl-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**9g**).* The procedure for **9a** was followed using 100 mg (0.26 mmol) of **8g** to give 65 mg (47%) of **9g** (1:1 diastereomeric mixture) as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.26 (m, 1H), 7.60–7.52 (m, 1H), 7.38–6.95 (m, 11H), 5.06 (t, *J* = 9.0 Hz, 1H), 4.48–4.30 (m, 1H), 3.92 and 3.88 (2s, 2H), 3.80–3.66 (m, 1H), 3.20–3.05 (m, 1H), 2.70–2.62 (m, 0.5H), 2.50–2.42 (m, 0.5H), 1.98–1.90 (m, 1H), 1.76–1.46 (m, 4H), 1.44 and 1.42 (2s, 9H), 1.20–1.02 (m, 1H), 0.93–0.82 (m, 6H); MS (ESI) *m/z* 528.8 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{4-Phenethylphenyl-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**9h**).* The procedure for **9a** was followed using 139 mg (0.35 mmol) of **8h** to give 96 mg (51%) of **9h** (1:1 diastereomeric mixture) as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.25 (m, 1H), 7.55–7.46 (m, 1H), 7.30–6.96 (m, 11H), 5.10 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.46–4.32 (m, 1H), 3.80–3.62

(m, 1H), 3.20–3.06 (m, 1H), 2.90–2.80 (m, 4H), 2.71–2.632 (m, 0.5H), 2.56–2.47 (m, 0.5H), 1.98–1.90 (m, 1H), 1.72–1.47 (m, 4H), 1.46 and 1.42 (2s, 9H), 1.16–1.02 (m, 1H), 0.90–0.78 (m, 6H); MS (ESI) *m/z* 528.8 $[M + H]^+$.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(phenyl-4-yl)amide (**4a**).* A solution of **9b** (85 mg, 0.19 mmol) and 4 M HCl in dioxane (2 mL) in CH_2Cl_2 (5 mL) was stirred at room temperature for 6 h. The solvent was removed under reduced pressure. The resulting residue was triturated with hexanes to give **4a** dihydrochloride (76 mg, 96%, 1:1 diastereomeric mixture) as an off-white solid: ^{1}H NMR (300 MHz; CD_3OD) δ 8.66–8.56 (m, 1H), 8.40–8.28 (m, 1H), 7.85–7.74 (m, 1H), 7.61–7.33 (m, 6H), 4.40 (dd, *J* = 15.0, 9.0 Hz, 0.5H), 4.29 (dd, *J* = 15.0, 9.0 Hz, 0.5H), 3.78–3.56 (m, 1.5H), 3.39–3.30 (m, 0.5H), 3.08–2.99 (m, 0.5H), 2.98–2.89 (m, 0.5H), 2.11–1.84 (m, 2H), 1.82–1.58 (m, 2H), 1.40–1.10 (m, 2H), 1.00–0.76 (m, 6H); HRMS (ESI) calcd. for $C_{21}H_{27}N_3O$ $[M + H]^+$: 338.2227. Found: 338.2241.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-hexylphenyl-4-yl)amide (**4b**).* The procedure for **4a** was followed using 135 mg (0.26 mmol) of **9c** to give 121 mg (95%) of **4b** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.26–8.16 (m, 1H), 7.70–7.56 (m, 1H), 7.28–7.08 (m, 6H), 4.32–4.16 (m, 1H), 3.70–3.58 (m, 1H), 3.36–3.20 (m, 1H), 2.66–2.50 (m, 3H), 1.92–1.80 (m, 1H), 1.78–1.48 (m, 4H), 1.48–1.10 (m, 9H), 1.00–0.76 (m, 9H); HRMS (ESI) calcd. for $C_{27}H_{39}N_3O$ $[M + H]^+$: 422.3166. Found: 422.3170.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-cyclohexylphenyl-4-yl)amide (**4c**).* The procedure for **4a** was followed using 104 mg (0.2 mmol) of **9d** to give 93 mg (95%) of **4c** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.63–8.52 (m, 1H), 8.38–8.24 (m, 1H), 7.85–7.72 (m, 1H), 7.60–7.48 (m, 1H), 7.48–7.20 (m, 4H), 4.36 (dd, *J* = 15.0, 9.0 Hz, 0.5H), 4.25 (dd, *J* = 15.0, 9.0 Hz, 0.5H), 3.78–3.56 (m, 1.5H), 3.40–3.30 (m, 0.5H), 3.04–2.95 (m, 0.5H), 2.94–2.83 (m, 0.5H), 2.60–2.42 (m, 1H), 2.10–2.00 (m, 1H), 1.98–1.52 (m, 7H), 1.52–1.05 (m, 8H), 1.00–0.76 (m, 6H); HRMS (ESI) calcd. for $C_{27}H_{37}N_3O$ $[M + H]^+$: 420.3009. Found: 420.3022.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(biphenyl-4-yl)amide (**4d**).* The procedure for **4a** was followed using 125 mg (0.24 mmol) of **9e** to give 115 mg (97%) of **4d** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.28–8.21 (m, 1H), 7.72–7.52 (m, 5H), 7.48–7.32 (m, 5H), 7.30–7.23 (m, 1H), 7.19–7.10 (m, 1H), 4.40–4.22 (m, 1H), 3.80–3.66 (m, 1H), 3.40–3.22 (m, 1H), 2.70–2.53 (m, 1H), 2.05–1.90 (m, 1H), 1.84–1.62 (m, 2H), 1.50–1.15 (m, 3H), 0.99 and 0.97 (2d, J = 6.0 Hz, 3H), 0.90–0.80 (m, 3H); HRMS (ESI) calcd. for $C_{27}H_{31}N_3O$ $[M + H]^+$: 414.2540. Found: 414.2541.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-phenoxyphenyl-4-yl)amide (**4e**).* The procedure for **4a** was followed using 50 mg (0.09 mmol) of **9f** to give 46 mg (97%) of **4e** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.60–8.46 (m, 1H), 8.32–8.20 (m, 1H), 7.78–7.64 (m, 1H), 7.60–7.20 (m, 5H), 7.12–7.02 (m, 1H), 7.00–6.76 (m, 4H), 4.32 (dd, J = 15.0, 9.0 Hz, 0.5H), 4.13 (dd, J = 15.0, 9.0 Hz, 0.5H), 3.68–3.40 (m, 1.5H), 3.35–3.25 (m, 0.5H), 3.02–2.90 (m, 0.5H), 2.88–2.78 (m, 0.5H), 2.08–1.54 (m, 4H), 1.42–1.08 (m, 2H), 0.98–0.68 (m, 6H); HRMS (ESI) calcd. for $C_{27}H_{31}N_3O$ $[M + H]^+$: 430.2489. Found: 430.2505.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-benzylphenyl-4-yl)amide (**4f**).* The procedure for **4a** was followed using 65 mg (0.12 mmol) of **9g** to give 51 mg (83%) of **4f** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.52–8.46 (m, 1H), 8.22–8.10 (m, 1H), 7.70–7.60 (m, 1H), 7.50–7.32 (m, 3H), 7.30–7.06 (m, 7H), 4.32 (dd, J = 15.0, 9.0 Hz, 0.5H), 4.21 (dd, J = 15.0, 9.0 Hz, 0.5H), 3.92 and 3.90 (2s, 2H), 3.75–3.65 (m, 1.5H), 3.38–3.26 (m, 0.5H), 3.00–2.90 (m, 0.5H), 2.88–2.80 (m, 0.5H), 2.08–1.58 (m, 4H), 1.42–1.12 (m, 2H), 0.98–0.72 (m, 6H); HRMS (ESI) calcd. for $C_{28}H_{33}N_3O$ $[M + H]^+$: 428.2696. Found: 428.2711.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-phenethylphenyl-4-yl)amide (**4g**).* The procedure for **4a** was followed using 96 mg (0.18 mmol) of **9h** to give 87 mg (95%) of **4g** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.66–8.56 (m, 1H), 8.38–8.25 (m, 1H), 7.82–7.70 (m, 1H), 7.58–7.42 (m, 1H), 7.40–7.30 (m, 2H), 7.30–7.05

(m, 7H), 4.42 (dd, *J* = 15.0, 9.0 Hz, 0.5H), 4.27 (dd, *J* = 15.0, 9.0 Hz, 0.5H), 3.75–3.56 (m, 1.5H), 3.38–3.28 (m, 0.5H), 3.06–2.96 (m, 0.5H), 2.96–2.78 (m, 4.5H), 2.10–1.82 (m, 2H), 1.80–1.58 (m, 2H), 1.40–1.10 (m, 2H), 1.00–0.70 (m, 6H); HRMS (ESI) calcd. for $C_{29}H_{35}N_3O$ $[M + H]^+$: 442.2853. Found: 442.2859.

tert-Butyl [(2S,3S)-1-{(4'-Methylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10a**).* A mixture of **9a** (30 mg, 0.058 mmol), 4-methylphenylboronic acid (12 mg, 0.087 mmol), Pd(dppf)Cl_2•CH_2Cl_2 (4.35 mg, 0.0058 mmol) and K_3PO_4 (38 mg, 2.7 mmol) in dimethoxyethane (1 mL) and water (0.3 mL) was heated in a sealed vessel by microwave irradiation at 160 °C for 6 min. The resulting mixture was poured into 1 N NaOH solution (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 20% EtOAc in hexanes afforded **10a** (20 mg, 65%) as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.29–8.22 (m, 1H), 7.58–7.38 (m, 5H), 7.37–7.16 (m, 5H), 7.02–6.92 (m, 1H), 5.13–5.06 (m, 1H), 4.48–4.37 (m, 1H), 3.83–3.68 (m, 1H), 3.24–3.12 (m, 1H), 2.73–2.65 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.39 (s, 3H), 2.08–1.96 (m, 1H), 1.76–1.55 (m, 1H), 1.54–1.37 (m, 3H), 1.47 and 1.43 (2s, 9H), 1.17–1.00 (m, 1H), 0.92–0.78 (m, 6H); MS (ESI) *m/z* 528.7 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Trifluoromethylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10b**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 17 mg (0.087 mmol) of 4-trifluoromethylphenylboronic acid to give 25 mg (74%) of **10b** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.22 (m, 1H), 7.72–7.40 (m, 7H), 7.38–7.16 (m, 3H), 7.02–6.93 (m, 1H), 5.13–5.02 (m, 1H), 4.50–4.38 (m, 1H), 3.84–3.65 (m, 1H), 3.28–3.15 (m, 1H), 2.76–2.65 (m, 0.5H), 2.61–2.48 (m, 0.5H), 2.08–1.96 (m, 1H), 1.76–1.55 (m, 1H), 1.54–1.37 (m, 3H), 1.47 and 1.43 (2s, 9H), 1.18–1.00 (m, 1H), 0.94–0.78 (m, 6H); MS (ESI) *m/z* 582.7 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Ethylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10c**).* The procedure for **10a** was followed

using 30 mg (0.058 mmol) of **9a** and 13 mg (0.087 mmol) of 4-ethylphenylboronic acid to give 25 mg (80%) of **10c** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.23 (m, 1H), 7.58–7.38 (m, 5H), 7.37–7.15 (m, 5H), 7.04–6.95 (m, 1H), 5.15–5.05 (m, 1H), 4.50–4.37 (m, 1H), 3.85–3.68 (m, 1H), 3.25–3.14 (m, 1H), 2.76–2.66 (m, 2.5H), 2.60–2.48 (m, 0.5H), 2.10–1.96 (m, 1H), 1.76–1.54 (m, 1H), 1.53–1.37 (m, 3H), 1.47 and 1.43 (2s, 9H), 1.28 (t, J = 7.5 Hz, 3H), 1.17–1.00 (m, 1H), 0.93–0.78 (m, 6H); MS (ESI) *m/z* 542.6 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Isopropylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10d**).* The procedure for **10a** was followed using 68 mg (0.13 mmol) of **9a** and 34 mg (0.2 mmol) of 4-isopropylphenylboronic acid to give 50 mg (69%) of **10d** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.26–8.20 (m, 1H), 7.54–7.38 (m, 5H), 7.35–7.12 (m, 5H), 7.03–6.92 (m, 1H), 5.14–5.05 (m, 1H), 4.48–4.35 (m, 1H), 3.88–3.68 (m, 1H), 3.26–3.17 (m, 1H), 3.02–2.88 (m, 1H), 2.72–2.66 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.10–1.95 (m, 1H), 1.76–1.40 (m, 4H), 1.47 and 1.43 (2s, 9H), 1.29 (d, J = 6.0 Hz, 6H), 1.18–1.02 (m, 1H), 0.95–0.82 (m, 6H); MS (ESI) *m/z* 556.9 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Isobutylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10e**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 16 mg (0.087 mmol) of 4-isobutylphenylboronic acid to give 23 mg (77%) of **10e** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.23 (m, 1H), 7.60–7.38 (m, 5H), 7.34–7.15 (m, 5H), 7.04–6.95 (m, 1H), 5.14–5.05 (m, 1H), 4.50–4.36 (m, 1H), 3.86–3.68 (m, 1H), 3.24–3.14 (m, 1H), 2.74–2.65 (m, 0.5H), 2.60–2.46 (m, 2.5H), 2.10–1.82 (m, 2H), 1.76–1.54 (m, 1H), 1.53–1.36 (m, 3H), 1.47 and 1.43 (2s, 9H), 1.16–1.00 (m, 1H), 0.98–0.78 (m, 12H); MS (ESI) *m/z* 570.6 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-tert-butylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10f**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 16 mg (0.087 mmol) of 4-*tert*-butylphenylboronic acid to give 20 mg

(61%) of **10f** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.20 (m, 1H), 7.58–7.45 (m, 7H), 7.30–7.12 (m, 3H), 7.00–6.92 (m, 1H), 5.12–5.04 (m, 1H), 4.45–4.33 (m, 1H), 3.82–3.66 (m, 1H), 3.25–3.15 (m, 1H), 2.72–2.65 (m, 0.5H), 2.60–2.48 (m, 0.5H), 2.08–1.95 (m, 1H), 1.75–1.40 (m, 4H), 1.47 and 1.43 (2s, 9H), 1.36 (s, 9H), 1.16–1.02 (m, 1H), 0.96–0.80 (m, 6H); MS (ESI) *m/z* 570.8 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-hexylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10g**).* The procedure for **10a** was followed using 68 mg (0.13 mmol) of **9a** and 42 mg (0.2 mmol) of 4-hexylphenylboronic acid to give 40 mg (51%) of **10g** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.21 (m, 1H), 7.58–7.40 (m, 5H), 7.36–7.15 (m, 5H), 7.05–6.94 (m, 1H), 5.16–5.08 (m, 1H), 4.50–4.38 (m, 1H), 3.88–3.68 (m, 1H), 3.27–3.15 (m, 1H), 2.76–2.50 (m, 3H), 2.10–1.95 (m, 1H), 1.72–1.22 (m, 12H), 1.47 and 1.43 (2s, 9H), 1.18–1.02 (m, 1H), 0.98–0.80 (m, 9H); MS (ESI) *m/z* 599.0 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Cyclohexylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10h**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 18 mg (0.087 mmol) of 4-cyclohexylphenylboronic acid to give 28 mg (81%) of **10h** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.21 (m, 1H), 7.58–7.40 (m, 5H), 7.32–7.12 (m, 5H), 7.02–6.92 (m, 1H), 5.15–5.05 (m, 1H), 4.50–4.36 (m, 1H), 3.88–3.68 (m, 1H), 3.26–3.13 (m, 1H), 2.75–2.64 (m, 0.5H), 2.60–2.48 (m, 1.5H), 2.05–1.71 (m, 7H), 1.69–1.25 (m, 8H), 1.47 and 1.43 (2s, 9H), 1.17–1.00 (m, 1H), 0.96–0.80 (m, 6H); MS (ESI) *m/z* 596.9 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Phenylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10i**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 18 mg (0.087 mmol) of 4-biphenylboronic acid to give 22 mg (65%) of **10i** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.22 (m, 1H), 7.70–7.42 (m, 10H), 7.42–7.16 (m, 5H), 7.03–6.95 (m, 1H), 5.15–5.05 (m, 1H), 4.50–4.38 (m, 1H), 3.88–3.68 (m, 1H), 3.30–3.18 (m, 1H), 2.78–2.65 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.10–1.98 (m, 1H), 1.80–1.40 (m, 4H), 1.48 and 1.44 (2s, 9H), 1.20–1.02 (m, 1H), 0.95–0.80 (m, 6H); MS (ESI) *m/z* 590.4 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Methoxybiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10j**).* The procedure for **10a** was followed using 68 mg (0.13 mmol) of **9a** and 30 mg (0.2 mmol) of 4-methoxyphenylboronic acid to give 52 mg (74%) of **10j** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.25 (m, 1H), 7.56–7.36 (m, 5H), 7.32–7.16 (m, 3H), 7.04–6.93 (m, 3H), 5.15–5.06 (m, 1H), 4.50–4.37 (m, 1H), 3.85 (s, 3H), 3.84–3.68 (m, 1H), 3.28–3.12 (m, 1H), 2.76–2.68 (m, 0.5H), 2.60–2.52 (m, 0.5H), 2.10–1.98 (m, 1H), 1.76–1.40 (m, 4H), 1.47 and 1.43 (2s, 9H), 1.20–1.02 (m, 1H), 0.95–0.80 (m, 6H); MS (ESI) *m/z* 544.7 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Trifluoromethoxybiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10k**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 18 mg (0.087 mmol) of 4-trifluoromethoxyphenylboronic acid to give 18 mg (52%) of **10k** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.22 (m, 1H), 7.58–7.40 (m, 5H), 7.38–7.16 (m, 5H), 7.04–6.96 (m, 1H), 5.10–5.03 (m, 1H), 4.50–4.38 (m, 1H), 3.82–3.68 (m, 1H), 3.28–3.16 (m, 1H), 2.76–2.68 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.08–1.94 (m, 1H), 1.75–1.40 (m, 4H), 1.47 and 1.43 (2s, 9H), 1.20–1.05 (m, 1H), 0.96–0.82 (m, 6H); MS (ESI) *m/z* 598.9 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Ethoxybiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10l**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 14 mg (0.087 mmol) of 4-ethoxyphenylboronic acid to give 22 mg (68%) of **10l** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.20 (m, 1H), 7.55–7.40 (m, 5H), 7.30–7.12 (m, 3H), 7.02–6.92 (m, 3H), 5.12–5.05 (m, 1H), 4.48–4.38 (m, 1H), 4.15–4.04 (m, 2H), 3.86–3.68 (m, 1H), 3.26–3.15 (m, 1H), 2.76–2.68 (m, 0.5H), 2.60–2.52 (m, 0.5H), 2.08–1.96 (m, 1H), 1.78–1.40 (m, 4H), 1.47 and 1.42 (2s, 9H), 1.20–1.04 (m, 1H), 0.94–0.82 (m, 9H); MS (ESI) *m/z* 558.8 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Isopropoxybiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10m**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 16 mg (0.087 mmol) of 4-isopropoxyphenylboronic acid to

give 20 mg (60%) of **10m** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.22 (m, 1H), 7.54–7.38 (m, 5H), 7.32–7.15 (m, 3H), 7.05–6.92 (m, 3H), 5.15–5.06 (m, 1H), 4.68–4.55 (m, 1H), 4.50–4.38 (m, 1H), 3.86–3.68 (m, 1H), 3.25–3.15 (m, 1H), 2.76–2.68 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.10–1.96 (m, 1H), 1.77–1.40 (m, 4H), 1.47 and 1.43 (2s, 9H), 1.37 (d, *J* = 6.0 Hz, 6H), 1.20–1.05 (m, 1H), 0.95–0.80 (m, 6H); MS (ESI) *m/z* 572.9 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(3',4'-Dimethoxybiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10n**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 16 mg (0.087 mmol) of 3,4-dimethoxyphenylboronic acid to give 19 mg (57%) of **10n** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.20 (m, 1H), 7.55–7.40 (m, 2H), 7.32–6.90 (m, 8H), 5.15–5.08 (m, 1H), 4.50–4.38 (m, 1H), 3.96 (s, 3H), 3.33 (s, 3H), 3.85–3.68 (m, 1H), 3.26–3.15 (m, 1H), 2.78–2.68 (m, 0.5H), 2.62–2.53 (m, 0.5H), 2.10–1.98 (m, 1H), 1.76–1.40 (m, 4H), 1.47 and 1.43 (2s, 9H), 1.20–1.03 (m, 1H), 0.96–0.80 (m, 6H); MS (ESI) *m/z* 574.9 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(3',4'-Methylenedioxybiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10o**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 14 mg (0.087 mmol) of 3,4-methylenedioxyphenylboronic acid to give 20 mg (62%) of **10o** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.22 (m, 1H), 7.56–7.33 (m, 3H), 7.32–7.15 (m, 3H), 7.08–6.92 (m, 3H), 6.90–6.85 (m, 1H), 6.01 (s, 2H), 5.10–5.04 (m, 1H), 4.50–4.38 (m, 1H), 3.85–3.68 (m, 1H), 3.26–3.16 (m, 1H), 2.76–2.66 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.10–1.98 (m, 1H), 1.76–1.40 (m, 4H), 1.47 and 1.42 (2s, 9H), 1.20–1.02 (m, 1H), 0.96–0.80 (m, 6H); MS (ESI) *m/z* 558.7 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Fluorobiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10p**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 12 mg (0.087 mmol) of 4-fluorophenylboronic acid to give 20 mg (74%) of **10p** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.22 (m, 1H), 7.56–7.48 (m, 4H), 7.30–7.18 (m, 6H), 7.02–6.92 (m, 1H), 5.12–5.05 (m, 1H), 4.52–4.38 (m, 1H), 3.82–3.65 (m, 1H), 3.25–3.12

(m, 1H), 2.76–2.65 (m, 0.5H), 2.61–2.48 (m, 0.5H), 2.08–1.95 (m, 1H), 1.78–1.55 (m, 1H), 1.54–1.37 (m, 3H), 1.47 and 1.43 (2s, 9H), 1.18–1.00 (m, 1H), 0.95–0.80 (m, 6H); MS (ESI) *m/z* 532.5 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Chlorobiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10q**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 14 mg (0.087 mmol) of 4-chlorophenylboronic acid to give 22 mg (74%) of **10q** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.21 (m, 1H), 7.55–7.36 (m, 6H), 7.30–7.15 (m, 4H), 7.02–6.95 (m, 1H), 5.10–5.00 (m, 1H), 4.50–4.35 (m, 1H), 3.80–3.62 (m, 1H), 3.26–3.15 (m, 1H), 2.76–2.65 (m, 0.5H), 2.61–2.48 (m, 0.5H), 2.08–1.95 (m, 1H), 1.75–1.55 (m, 1H), 1.54–1.37 (m, 3H), 1.47 and 1.42 (2s, 9H), 1.16–1.00 (m, 1H), 0.95–0.80 (m, 6H); MS (ESI) *m/z* 548.5 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Cyanobiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10r**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 13 mg (0.087 mmol) of 4-cyanophenylboronic acid to give 20 mg (64%) of **10r** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.20 (m, 1H), 7.76–7.42 (m, 7H), 7.40–7.16 (m, 3H), 7.02–6.92 (m, 1H), 5.10–5.00 (m, 1H), 4.50–4.38 (m, 1H), 3.80–3.64 (m, 1H), 3.26–3.14 (m, 1H), 2.76–2.66 (m, 0.5H), 2.61–2.52 (m, 0.5H), 2.08–1.95 (m, 1H), 1.75–1.40 (m, 4H), 1.47 and 1.42 (2s, 9H), 1.18–1.00 (m, 1H), 0.96–0.80 (m, 6H); MS (ESI) *m/z* 539.3 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Nitrobiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10s**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 15 mg (0.087 mmol) of 4-nitrophenylboronic acid to give 21 mg (65%) of **10s** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.35–8.21 (m, 3H), 7.75–7.44 (m, 5H), 7.40–7.16 (m, 3H), 7.02–6.95 (m, 1H), 5.08–4.98 (m, 1H), 4.50–4.38 (m, 1H), 3.80–3.62 (m, 1H), 3.28–3.18 (m, 1H), 2.76–2.66 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.08–1.94 (m, 1H), 1.76–1.40 (m, 4H), 1.47 and 1.42 (2s, 9H), 1.17–1.00 (m, 1H), 0.95–0.80 (m, 6H); MS (ESI) *m/z* 559.4 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Acetylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10t**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 14 mg (0.087 mmol) of 4-acetylphenylboronic acid to give 25 mg (76%) of **10t** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.21 (m, 1H), 8.06–7.98 (m, 2H), 7.68–7.48 (m, 5H), 7.38–7.15 (m, 3H), 7.02–6.93 (m, 1H), 5.10–5.00 (m, 1H), 4.50–4.36 (m, 1H), 3.80–3.62 (m, 1H), 3.28–3.15 (m, 1H), 2.75–2.65 (m, 0.5H), 2.64 (s, 3H), 2.61–2.48 (m, 0.5H), 2.08–1.95 (m, 1H), 1.76–1.55 (m, 1H), 1.54–1.37 (m, 3H), 1.47 and 1.43 (2s, 9H), 1.16–0.98 (m, 1H), 0.92–0.78 (m, 6H); MS (ESI) *m/z* 557.2 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Ethoxycarbonylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10u**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 17 mg (0.087 mmol) of 4-ethoxycarbonylphenylboronic acid to give 22 mg (65%) of **10u** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.22 (m, 1H), 8.16–8.08 (m, 2H), 7.66–7.48 (m, 5H), 7.38–7.16 (m, 3H), 7.02–6.95 (m, 1H), 5.10–5.02 (m, 1H), 4.50–4.36 (m, 3H), 3.85–3.66 (m, 1H), 3.28–3.16 (m, 1H), 2.75–2.65 (m, 0.5H), 2.62–2.50 (m, 0.5H), 2.10–1.98 (m, 1H), 1.76–1.37 (m, 4H), 1.47 and 1.43 (2s, 9H), 1.20–1.02 (m, 1H), 0.95–0.81 (m, 9H); MS (ESI) *m/z* 586.5 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Hydroxybiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10v**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 25 mg (0.087 mmol) of 4-(*tert*-butoxycarboxy)phenylboronic acid to give 22 mg (72%) of **10v** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.52 (br s, 1H), 8.28–8.18 (m, 1H), 7.60–7.50 (m, 1H), 7.38–7.10 (m, 7H), 7.08–7.00 (m, 1H), 7.76–6.68 (m, 2H), 5.26–5.18 (m, 1H), 4.52–4.40 (m, 1H), 3.82–3.68 (m, 1H), 3.20–3.08 (m, 1H), 2.78–2.68 (m, 0.5H), 2.62–2.52 (m, 0.5H), 2.15–2.08 (m, 1H), 1.76–1.40 (m, 4H), 1.51 and 1.46 (2s, 9H), 1.20–1.02 (m, 1H), 0.96–0.80 (m, 6H); MS (ESI) *m/z* 530.9 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{[4'-(tert-Butoxycarbonylamino)biphenyl-4-yl]-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10w**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 21 mg (0.087 mmol) of 4-(*tert*-butoxycarbonylamino)phenylboronic acid to give 22 mg (60%) of **10w** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.20 (m, 1H), 7.52–7.40 (m, 7H), 7.30–7.12 (m, 3H), 7.02–6.94 (m, 1H), 6.68 (s, 1H), 5.12–5.06 (m, 1H), 4.48–4.38 (m, 1H), 3.82–3.67 (m, 1H), 3.25–3.15 (m, 1H), 2.76–2.68 (m, 0.5H), 2.58–2.48 (m, 0.5H), 2.08–1.98 (m, 1H), 1.77–1.40 (m, 4H), 1.53 (s, 9H), 1.47 and 1.43 (2s, 9H), 1.20–1.02 (m, 1H), 0.95–0.80 (m, 6H); MS (ESI) *m/z* 629.8 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{[4'-(Dimethylamino)biphenyl-4-yl]-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10x**).* The procedure for **10a** was followed using 68 mg (0.13 mmol) of **9a** and 35 mg (0.2 mmol) of 4-(dimethylamino)phenylboronic acid to give 52 mg (72%) of **10x** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.22 (m, 1H), 7.55–7.36 (m, 5H), 7.30–7.12 (m, 3H), 7.02–6.96 (m, 1H), 6.84–6.76 (m, 2H), 5.18–5.10 (m, 1H), 4.50–4.38 (m, 1H), 3.88–3.70 (m, 1H), 3.26–3.16 (m, 1H), 2.99 (s, 6H), 2.76–2.68 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.10–1.98 (m, 1H), 1.72–1.40 (m, 4H), 1.47 and 1.43 (2s, 9H), 1.20–1.02 (m, 1H), 0.98–0.82 (m, 6H); MS (ESI) *m/z* 557.8 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Acetamidobiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10y**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 15.6 mg (0.087 mmol) of 4-acetamidophenylboronic acid to give 18 mg (54%) of **10y** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.20 (m, 1H), 7.96–7.80 (m, 1H), 7.62–7.34 (m, 7H), 7.30–7.15 (m, 3H), 7.02–6.96 (m, 1H), 5.18–5.08 (m, 1H), 4.50–4.38 (m, 1H), 3.82–3.66 (m, 1H), 3.28–3.15 (m, 1H), 2.76–2.67 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.18 (s, 3H), 2.08–1.95 (m, 1H), 1.76–1.40 (m, 4H), 1.47 and 1.43 (2s, 9H), 1.20–1.02 (m, 1H), 0.96–0.80 (m, 6H); MS (ESI) *m/z* 571.6 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{(4'-Carbamoylbiphenyl-4-yl)-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10z**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 14 mg (0.087 mmol) of 4-carbamoylphenylboronic acid to give 18 mg (56%) of **10z** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.30–8.21 (m, 1H), 7.92–7.86 (m, 2H), 7.66–7.46 (m, 5H), 7.40–7.18 (m, 3H), 7.05–6.98 (m, 1H), 6.16 (br s, 1H), 5.80 (br s, 1H), 5.10–5.05 (m, 1H), 4.50–4.38 (m, 1H), 3.82–3.64 (m, 1H), 3.28–3.16 (m, 1H), 2.76–2.68 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.08–1.96 (m, 1H), 1.76–1.40 (m, 4H), 1.47 and 1.42 (2s, 9H), 1.20–1.02 (m, 1H), 0.95–0.81 (m, 6H); MS (ESI) *m/z* 558.1 $[M + H]^+$.

tert-Butyl [(2S,3S)-1-{[4'-(Dimethylcarbamoyl)biphenyl-4-yl]-[(1R,2R*)-2-(pyridin-2-yl)cyclopropanecarbonyl]amino}-3-methylpentan-2-yl]carbamate (**10aa**).* The procedure for **10a** was followed using 30 mg (0.058 mmol) of **9a** and 17 mg (0.087 mmol) of 4-(dimethylcarbamoyl)phenylboronic acid to give 20 mg (56%) of **10aa** as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.28–8.22 (m, 1H), 7.60–7.38 (m, 7H), 7.32–7.12 (m, 3H), 7.02–6.95 (m, 1H), 5.10–5.00 (m, 1H), 4.50–4.38 (m, 1H), 3.82–3.65 (m, 1H), 3.28–3.16 (m, 1H), 3.14 (s, 3H), 3.04 (s, 3H), 2.75–2.66 (m, 0.5H), 2.60–2.50 (m, 0.5H), 2.08–1.96 (m, 1H), 1.76–1.40 (m, 4H), 1.47 and 1.43 (2s, 9H), 1.20–1.02 (m, 1H), 0.96–0.80 (m, 6H); MS (ESI) *m/z* 585.8 $[M + H]^+$.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-methylbiphenyl-4-yl)amide (**5a**).* The procedure for **4a** was followed using 20 mg (0.038 mmol) of **10a** and 1 mL of 4 M HCl in dioxane to give 18 mg (95%) of **5a** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.68–8.55 (m, 1H), 8.42–8.30 (m, 1H), 7.88–7.40 (m, 8H), 7.30–7.20 (m, 2H), 4.50–4.40 (m, 0.5H), 4.40–4.28 (m, 0.5H), 3.88–3.56 (m, 1H), 3.48–3.38 (m, 1H), 3.12–3.05 (m, 0.5H), 3.05–2.96 (m, 0.5H), 2.37 (s, 3H), 2.22–2.10 (m, 1H), 2.10–1.88 (m, 1H), 1.87–1.60 (m, 2H), 1.48–1.15 (m, 2H), 1.06–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{28}H_{33}N_3O$ $[M + H]^+$: 428.2696. Found: 428.2701.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-trifluoromethylbiphenyl-4-yl)amide (**5b**).* The procedure for **4a** was followed using 20 mg (0.034 mmol) of

10b and 1 mL of 4 M HCl in dioxane to give 18 mg (95%) of **5b** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.70–8.58 (m, 1H), 8.42–8.30 (m, 1H), 7.90–7.50 (m, 10H), 4.55–4.40 (m, 0.5H), 4.40–4.26 (m, 0.5H), 3.90–3.60 (m, 1H), 3.50–3.38 (m, 1H), 3.15–3.05 (m, 0.5H), 3.05–2.92 (m, 0.5H), 2.25–2.10 (m, 1H), 2.10–1.92 (m, 1H), 1.92–1.62 (m, 2H), 1.50–1.15 (m, 2H), 1.08–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{28}H_{30}F_3N_3O$ $[M + H]^+$: 482.2414. Found: 482.2416.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-ethylbiphenyl-4-yl)amide (**5c**).* The procedure for **4a** was followed using 20 mg (0.037 mmol) of **10c** and 1 mL of 4 M HCl in dioxane to give 18 mg (95%) of **5c** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.70–8.58 (m, 1H), 8.45–8.30 (m, 1H), 7.88–7.45 (m, 8H), 7.32–7.20 (m, 2H), 4.52–4.40 (m, 0.5H), 4.38–4.28 (m, 0.5H), 3.88–3.56 (m, 1H), 3.48–3.35 (m, 1H), 3.15–3.05 (m, 0.5H), 3.05–2.95 (m, 0.5H), 2.80–2.60 (m, 2H), 2.25–2.10 (m, 1H), 2.10–1.90 (m, 1H), 1.87–1.60 (m, 2H), 1.50–1.10 (m, 5H), 1.08–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{29}H_{35}N_3O$ $[M + H]^+$: 442.2853. Found: 442.2867.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-isopropylbiphenyl-4-yl)amide (**5d**).* The procedure for **4a** was followed using 45 mg (0.08 mmol) of **10d** and 2 mL of 4 M HCl in dioxane to give 40 mg (95%) of **5d** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.60–8.50 (m, 1H), 8.30–8.18 (m, 1H), 7.70–7.48 (m, 8H), 7.36–7.28 (m, 2H), 4.48–4.22 (m, 1H), 3.83–3.62 (m, 1H), 3.46–3.38 (m, 1H), 3.06–2.88 (m, 2H), 2.20–2.10 (m, 1H), 2.00–1.84 (m, 1H), 1.84–1.72 (m, 1H), 1.72–1.60 (m, 1H), 1.50–1.20 (m, 2H), 1.28 (d, J = 9.0 Hz, 6H), 1.05–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{30}H_{37}N_3O$ $[M + H]^+$: 456.3009. Found: 456.3014.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-isobutylbiphenyl-4-yl)amide (**5e**).* The procedure for **4a** was followed using 20 mg (0.035 mmol) of **10e** and 1 mL of 4 M HCl in dioxane to give 17 mg (90%) of **5e** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.68–8.58 (m, 1H), 8.40–8.28 (m, 1H), 7.92–7.43 (m, 8H), 7.30–7.20 (m, 2H), 4.50–4.40 (m, 0.5H), 4.38–4.25 (m, 0.5H), 3.88–3.60 (m, 1H), 3.50–3.38 (m, 1H), 3.13–3.05 (m, 0.5H),

3.05–2.90 (m, 0.5H), 2.51 (d, J = 6.0 Hz, 2H), 2.25–2.10 (m, 1H), 2.05–1.60 (m, 4H), 1.50–1.20 (m, 2H), 1.10–0.76 (m, 12H); HRMS (ESI) calcd. for $C_{31}H_{39}N_3O$ $[M + H]^+$: 470.3166. Found: 470.3178.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-tert-butylbiphenyl-4-yl)amide (**5f**).* The procedure for **4a** was followed using 20 mg (0.035 mmol) of **10f** and 1 mL of 4 M HCl in dioxane to give 18 mg (95%) of **5f** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.68–8.58 (m, 1H), 8.42–8.30 (m, 1H), 7.88–7.46 (m, 10H), 4.50–4.38 (m, 0.5H), 4.38–4.22 (m, 0.5H), 3.88–3.60 (m, 1H), 3.46–3.38 (m, 1H), 3.14–3.05 (m, 0.5H), 3.05–2.94 (m, 0.5H), 2.22–2.08 (m, 1H), 2.08–1.90 (m, 1H), 1.88–1.65 (m, 2H), 1.50–1.20 (m, 2H), 1.35 (s, 9H), 1.05–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{31}H_{39}N_3O$ $[M + H]^+$: 470.3166. Found: 470.3178.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-hexylbiphenyl-4-yl)amide (**5g**).* The procedure for **4a** was followed using 35 mg (0.058 mmol) of **10g** and 1 mL of 4 M HCl in dioxane to give 30 mg (90%) of **5g** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.52–8.42 (m, 1H), 8.22–8.10 (m, 1H), 7.65–7.32 (m, 8H), 7.25–7.10 (m, 2H), 4.40–4.28 (m, 0.5H), 4.28–4.16 (m, 0.5H), 3.75–3.55 (m, 1H), 3.36–3.25 (m, 1H), 2.98–2.86 (m, 0.5H), 2.86–2.68 (m, 0.5H), 2.60–2.45 (m, 2H), 2.10–1.95 (m, 1H), 1.90–1.60 (m, 2H), 1.60–1.45 (m, 3H), 1.40–1.05 (m, 8H), 0.95–0.68 (m, 9H); HRMS (ESI) calcd. for $C_{33}H_{43}N_3O$ $[M + H]^+$: 498.3479. Found: 498.3496.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-cyclohexylbiphenyl-4-yl)amide (**5h**).* The procedure for **4a** was followed using 20 mg (0.034 mmol) of **10h** and 1 mL of 4 M HCl in dioxane to give 19 mg (98%) of **5h** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.55–8.40 (m, 1H), 8.15–8.00 (m, 1H), 7.75–7.40 (m, 8H), 7.35–7.20 (m, 2H), 4.48–4.20 (m, 1H), 3.88–3.68 (m, 1H), 3.42–3.35 (m, 1H), 2.98–2.88 (m, 1H), 2.68–2.48 (m, 1H), 2.20–2.00 (m, 1H), 1.98–1.70 (m, 7H), 1.66–1.10 (m, 8H), 1.05–0.78 (m, 6H); HRMS (ESI) calcd. for $C_{33}H_{41}N_3O$ $[M + H]^+$: 496.3322. Found: 496.3323.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-phenylbiphenyl-4-yl)amide (**5i**).* The procedure for **4a** was followed using 22 mg (0.037 mmol) of **10i** and 1 mL of 4 M HCl in dioxane to give 20 mg (95%) of **5i** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.70–8.58 (m, 1H), 8.42–8.30 (m, 1H), 7.88–7.52 (m, 12H), 7.50–7.30 (m, 3H), 4.52–4.40 (m, 0.5H), 4.40–4.25 (m, 0.5H), 3.90–3.60 (m, 1H), 3.38–3.48 (m, 1H), 3.16–3.06 (m, 0.5H), 3.06–2.96 (m, 0.5H), 2.26–2.10 (m, 1H), 2.10–1.90 (m, 1H), 1.90–1.68 (m, 2H), 1.52–1.20 (m, 2H), 1.00–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{33}H_{35}N_3O$ $[M + H]^+$: 490.2853. Found: 490.2870.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-methoxybiphenyl-4-yl)amide (**5j**).* The procedure for **4a** was followed using 36 mg (0.066 mmol) of **10j** and 2 mL of 4 M HCl in dioxane to give 32 mg (94%) of **5j** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.60–8.52 (m, 1H), 8.32–8.20 (m, 1H), 7.76–7.48 (m, 8H), 7.05–6.96 (m, 2H), 4.46–4.26 (m, 1H), 3.83 (s, 3H), 3.80–3.62 (m, 1H), 3.45–3.32 (m, 1H), 3.10–2.98 (m, 0.5H), 2.98–2.88 (m, 0.5H), 2.22–2.06 (m, 1H), 2.00–1.82 (m, 1H), 1.82–1.58 (m, 2H), 1.46–1.15 (m, 2H), 1.05–0.75 (m, 6H); HRMS (ESI) calcd. for $C_{28}H_{33}N_3O_2$ $[M + H]^+$: 444.2646. Found: 444.2655.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-trifluoromethoxybiphenyl-4-yl)amide (**5k**).* The procedure for **4a** was followed using 18 mg (0.03 mmol) of **10k** and 1 mL of 4 M HCl in dioxane to give 16 mg (94%) of **5k** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.68–8.56 (m, 1H), 8.45–8.30 (m, 1H), 7.90–7.56 (m, 8H), 7.42–7.30 (m, 2H), 4.52–4.40 (m, 0.5H), 4.38–4.22 (m, 0.5H), 3.90–3.60 (m, 1H), 3.48–3.38 (m, 1H), 3.15–3.06 (m, 0.5H), 3.06–2.95 (m, 0.5H), 2.22–2.08 (m, 1H), 2.08–1.90 (m, 1H), 1.90–1.64 (m, 2H), 1.50–1.16 (m, 2H), 1.06–0.78 (m, 6H); HRMS (ESI) calcd. for $C_{28}H_{30}F_3N_3O_2$ $[M + H]^+$: 498.2363. Found: 498.2385.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-ethoxybiphenyl-4-yl)amide (**5l**).* The procedure for **4a** was followed using 22 mg (0.039 mmol) of **10l** and 1 mL of 4 M HCl in dioxane to give 21 mg (100%) of **5l** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H

NMR (300 MHz; CD_3OD) δ 8.70–8.58 (m, 1H), 8.42–8.30 (m, 1H), 7.88–7.76 (m, 1H), 7.76–7.38 (m, 7H), 7.02–6.90 (m, 2H), 4.52–4.40 (m, 0.5H), 4.38–4.24 (m, 0.5H), 4.07 (q, J = 6.0 Hz, 2H), 3.86–3.55 (m, 1H), 3.46–3.33 (m, 1H), 3.15–3.05 (m, 0.5H), 3.05–2.92 (m, 0.5H), 2.25–2.08 (m, 1H), 2.08–1.90 (m, 1H), 1.90–1.60 (m, 2H), 1.50–1.16 (m, 5H), 1.08–0.78 (m, 6H); HRMS (ESI) calcd. for $C_{29}H_{35}N_3O_2$ $[M + H]^+$: 458.2802. Found: 458.2812.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-isopropoxybiphenyl-4-yl)amide (**5m**).* The procedure for **4a** was followed using 20 mg (0.035 mmol) of **10m** and 1 mL of 4 M HCl in dioxane to give 19 mg (100%) of **5m** dihydrochloride as a 1:1 diastereomeric mixture: ^1H NMR (300 MHz; CD_3OD) δ 8.70–8.55 (m, 1H), 8.40–8.30 (m, 1H), 7.90–7.40 (m, 8H), 7.05–6.90 (m, 2H), 4.70–4.58 (m, 1H), 4.55–4.38 (m, 0.5H), 4.38–4.22 (m, 0.5H), 3.85–3.60 (m, 1H), 3.46–3.38 (m, 1H), 3.16–3.05 (m, 0.5H), 3.05–2.94 (m, 0.5H), 2.25–2.08 (m, 1H), 2.08–1.90 (m, 1H), 1.90–1.64 (m, 2H), 1.50–1.20 (m, 2H), 1.33 (d, J = 6.0 Hz, 6H), 1.06–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{30}H_{37}N_3O_2$ $[M + H]^+$: 472.2959. Found: 472.2957.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(3',4'-dimethoxybiphenyl-4-yl)amide (**5n**).* The procedure for **4a** was followed using 19 mg (0.033 mmol) of **10n** and 1 mL of 4 M HCl in dioxane to give 18 mg (100%) of **5n** dihydrochloride as a 1:1 diastereomeric mixture: ^1H NMR (300 MHz; CD_3OD) δ 8.68–8.58 (m, 1H), 8.46–8.32 (m, 1H), 7.90–7.78 (m, 1H), 7.78–7.53 (m, 5H), 7.20–7.10 (m, 2H), 7.08–6.98 (m, 1H), 4.52–4.40 (m, 0.5H), 4.40–4.25 (m, 0.5H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80–3.62 (m, 1H), 3.46–3.35 (m, 1H), 3.15–3.06 (m, 0.5H), 3.06–2.96 (m, 0.5H), 2.25–2.10 (m, 1H), 2.10–1.90 (m, 1H), 1.90–1.65 (m, 2H), 1.50–1.18 (m, 2H), 1.05–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{29}H_{35}N_3O_3$ $[M + H]^+$: 474.2751. Found: 474.2763.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(3',4'-methylenedioxybiphenyl-4-yl)amide (**5o**).* The procedure for **4a** was followed using 20 mg (0.036 mmol) of **10o** and 1 mL of 4 M HCl in dioxane to give 19 mg (100%) of **5o** dihydrochloride as a 1:1 diastereomeric mixture: ^1H NMR (300 MHz; CD_3OD) δ 8.68–8.56 (m, 1H), 8.42–8.28 (m, 1H), 7.85–7.73 (m, 1H),

7.73–7.50 (m, 5H), 7.12–7.00 (m, 2H), 6.92–6.82 (m, 1H), 5.99 (s, 2H), 4.50–4.35 (m, 0.5H), 4.34–4.20 (m, 0.5H), 3.85–3.60 (m, 1H), 3.45–3.32 (m, 1H), 3.12–3.02 (m, 0.5H), 3.02–2.90 (m, 0.5H), 2.22–2.08 (m, 1H), 2.08–1.88 (m, 1H), 1.88–1.60 (m, 2H), 1.50–1.15 (m, 2H), 1.06–0.78 (m, 6H); HRMS (ESI) calcd. for $C_{28}H_{31}N_3O_3$ $[M + H]^+$: 458.2438. Found: 458.2458.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-fluorobiphenyl-4-yl)amide (**5p**).* The procedure for **4a** was followed using 20 mg (0.038 mmol) of **10p** and 1 mL of 4 M HCl in dioxane to give 18 mg (94%) of **5p** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.70–8.58 (m, 1H), 8.45–8.35 (m, 1H), 7.90–7.50 (m, 8H), 7.25–7.10 (m, 2H), 4.52–4.40 (m, 0.5H), 4.40–4.25 (m, 0.5H), 3.90–3.60 (m, 1H), 3.52–3.40 (m, 1H), 3.16–3.06 (m, 0.5H), 3.05–2.92 (m, 0.5H), 2.25–2.10 (m, 1H), 2.10–1.92 (m, 1H), 1.92–1.60 (m, 2H), 1.50–1.18 (m, 2H), 1.10–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{27}H_{30}FN_3O$ $[M + H]^+$: 432.2446. Found: 432.2453.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-chlorobiphenyl-4-yl)amide (**5q**).* The procedure for **4a** was followed using 20 mg (0.036 mmol) of **10q** and 1 mL of 4 M HCl in dioxane to give 18 mg (96%) of **5q** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.72–8.58 (m, 1H), 8.45–8.35 (m, 1H), 7.90–7.55 (m, 8H), 7.55–7.40 (m, 2H), 4.55–4.42 (m, 0.5H), 4.40–4.25 (m, 0.5H), 3.90–3.60 (m, 1H), 3.50–3.40 (m, 1H), 3.18–3.07 (m, 0.5H), 3.06–2.96 (m, 0.5H), 2.25–2.10 (m, 1H), 2.08–1.90 (m, 1H), 1.90–1.68 (m, 2H), 1.58–1.12 (m, 2H), 1.10–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{27}H_{30}ClN_3O$ $[M + H]^+$: 448.2150. Found: 448.2162.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-cyanobiphenyl-4-yl)amide (**5r**).* The procedure for **4a** was followed using 20 mg (0.037 mmol) of **10r** and 1 mL of 4 M HCl in dioxane to give 18 mg (95%) of **5r** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.65–8.55 (m, 1H), 8.36–8.25 (m, 1H), 7.90–7.50 (m, 10H), 4.50–4.38 (m, 0.5H), 4.38–4.20 (m, 0.5H), 3.85–3.60 (m, 1H), 3.45–3.28 (m, 1H), 3.12–3.02 (m, 0.5H), 3.02–2.92 (m, 0.5H), 2.22–2.06 (m, 1H), 2.06–1.90 (m, 1H), 1.90–1.60 (m, 2H), 1.58–1.15 (m, 2H), 1.05–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{28}H_{30}N_4O$ $[M + H]^+$: 439.2492. Found: 439.2506.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-nitrobiphenyl-4-yl)amide (**5s**).* The procedure for **4a** was followed using 21 mg (0.037 mmol) of **10s** and 1 mL of 4 M HCl in dioxane to give 19 mg (95%) of **5s** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.65–8.55 (m, 1H), 8.45–8.20 (m, 2H), 7.95–7.55 (m, 9H), 4.50–4.30 (m, 1H), 3.85–3.60 (m, 1H), 3.45–3.35 (m, 1H), 3.12–3.02 (m, 0.5H), 3.02–2.95 (m, 0.5H), 2.25–2.10 (m, 1H), 2.10–1.90 (m, 1H), 1.89–1.60 (m, 2H), 1.50–1.15 (m, 2H), 1.10–0.82 (m, 6H); HRMS (ESI) calcd. for $C_{27}H_{30}N_4O_3$ $[M + H]^+$: 459.2391. Found: 459.2404.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-acetylbiphenyl-4-yl)amide (**5t**).* The procedure for **4a** was followed using 20 mg (0.036 mmol) of **10t** and 1 mL of 4 M HCl in dioxane to give 17 mg (90%) of **5t** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.35–8.22 (m, 1H), 8.05–7.92 (m, 2H), 7.90–7.75 (m, 1H), 7.72–7.60 (m, 4H), 7.52–7.40 (m, 2H), 7.35–7.22 (m, 2H), 4.38–4.16 (m, 1H), 3.80–3.55 (m, 1H), 3.38–3.20 (m, 1H), 2.80–2.60 (m, 1H), 2.54 (s, 3H), 2.00–1.88 (m, 1H), 1.78–1.60 (m, 2H), 1.50–1.10 (m, 3H), 0.95–0.70 (m, 6H); HRMS (ESI) calcd. for $C_{29}H_{33}N_3O_2$ $[M + H]^+$: 456.2646. Found: 456.2658.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-ethoxycarbonylbiphenyl-4-yl)amide (**5u**).* The procedure for **4a** was followed using 22 mg (0.038 mmol) of **10u** and 1 mL of 4 M HCl in dioxane to give 21 mg (100%) of **5u** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.65–8.48 (m, 1H), 8.35–8.18 (m, 1H), 8.15–8.10 (m, 2H), 7.85–7.50 (m, 8H), 4.50–4.20 (m, 3H), 3.85–3.62 (m, 1H), 3.45–3.35 (m, 1H), 3.12–3.00 (m, 0.5H), 3.00–2.90 (m, 0.5H), 2.20–2.03 (m, 1H), 2.03–1.55 (m, 3H), 1.45–1.12 (m, 5H), 1.08–0.78 (m, 6H); HRMS (ESI) calcd. for $C_{30}H_{35}N_3O_3$ $[M + H]^+$: 486.2751. Found: 486.2774.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-hydroxybiphenyl-4-yl)amide (**5v**).* The procedure for **4a** was followed using 22 mg (0.042 mmol) of **10v** and 1 mL of 4 M HCl in dioxane to give 21 mg (100%) of **5v** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.68–8.55 (m, 1H), 8.40–8.28 (m, 1H), 7.95–7.82 (m, 1H), 7.82–7.38 (m, 7H),

6.88–6.68 (m, 2H), 4.48–4.36 (m, 0.5H), 4.36–4.22 (m, 0.5H), 3.82–3.65 (m, 1H), 3.45–3.32 (m, 1H), 3.12–3.02 (m, 0.5H), 3.02–2.92 (m, 0.5H), 2.20–2.06 (m, 1H), 2.06–1.88 (m, 1H), 1.88–1.60 (m, 2H), 1.50–1.15 (m, 2H), 1.05–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{27}H_{31}N_3O_2$ $[M + H]^+$: 430.2489. Found: 430.2508.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-aminobiphenyl-4-yl)amide (**5w**).* The procedure for **4a** was followed using 22 mg (0.035 mmol) of **10w** and 1 mL of 4 M HCl in dioxane to give 20 mg (95%) of **5w** tri-hydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.61–8.55 (m, 1H), 8.40–8.30 (m, 1H), 7.84–7.47 (m, 10H), 4.52–4.42 (m, 0.5H), 4.40–4.28 (m, 0.5H), 3.80–3.65 (m, 1H), 3.42–3.32 (m, 1H), 3.12–3.00 (m, 0.5H), 3.00–2.93 (m, 0.5H), 2.22–2.08 (m, 1H), 2.08–1.88 (m, 1H), 1.88–1.60 (m, 2H), 1.50–1.16 (m, 2H), 1.06–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{27}H_{32}N_4O$ $[M + H]^+$: 429.2649. Found: 429.2661.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-[4'-(dimethylamino)biphenyl-4-yl]amide (**5x**).* The procedure for **4a** was followed using 46 mg (0.083 mmol) of **10x** and 2 mL of 4 M HCl in dioxane to give 40 mg (86%) of **5x** tri-hydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.55–8.45 (m, 1H), 8.25–8.12 (m, 1H), 7.70–7.40 (m, 10H), 4.42–4.28 (m, 0.5H), 4.28–4.15 (m, 0.5H), 3.82–3.65 (m, 1H), 3.55 (s, 6H), 3.32–3.22 (m, 1H), 3.02–2.90 (m, 0.5H), 2.90–2.82 (m, 0.5H), 2.10–1.95 (m, 1H), 1.95–1.50 (m, 3H), 1.45–1.10 (m, 2H), 0.95–0.70 (m, 6H); HRMS (ESI) calcd. for $C_{29}H_{36}N_4O$ $[M + H]^+$: 457.2962. Found: 457.2973.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-acetamidobiphenyl-4-yl)amide (**5y**).* The procedure for **4a** was followed using 18 mg (0.032 mmol) of **10y** and 1 mL of 4 M HCl in dioxane to give 17 mg (99%) of **5y** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.68–8.58 (m, 1H), 8.45–8.30 (m, 1H), 7.85–7.50 (m, 10H), 4.50–4.38 (m, 0.5H), 4.38–4.20 (m, 0.5H), 3.82–3.65 (m, 1H), 3.55–3.35 (m, 1H), 3.12–3.02 (m, 0.5H), 3.02–2.90 (m, 0.5H), 2.15 (s, 3H), 2.15–1.96 (m, 4H), 1.50–1.16 (m, 2H), 1.05–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{29}H_{34}N_4O_2$ $[M + H]^+$: 471.2755. Found: 471.2768.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-(4'-carbamoylbiphenyl-4-yl)amide (**5z**).* The procedure for **4a** was followed using 18 mg (0.032 mmol) of **10z** and 1 mL of 4 M HCl in dioxane to give 17 mg (99%) of **5z** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.68–8.55 (m, 1H), 8.45–8.30 (m, 1H), 8.00–7.50 (m, 10H), 4.50–4.38 (m, 0.5H), 4.38–4.22 (m, 0.5H), 3.85–3.65 (m, 1H), 3.46–3.35 (m, 1H), 3.12–3.02 (m, 0.5H), 3.02–2.92 (m, 0.5H), 2.25–2.10 (m, 1H), 2.10–1.90 (m, 1H), 1.90–1.55 (m, 2H), 1.50–1.16 (m, 2H), 1.08–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{28}H_{32}N_4O_2$ $[M + H]^+$: 457.2598. Found: 457.2616.

(1R,2R*)-2-(Pyridin-2-yl)cyclopropanecarboxylic Acid [(2S,3S)-2-Amino-3-methylpentyl]-[4'-(dimethylcarbamoyl)biphenyl-4-yl]amide (**5aa**).* The procedure for **4a** was followed using 20 mg (0.034 mmol) of **10aa** and 1 mL of 4 M HCl in dioxane to give 19 mg (100%) of **5aa** dihydrochloride as a 1:1 diastereomeric mixture: ^{1}H NMR (300 MHz; CD_3OD) δ 8.86–8.55 (m, 1H), 8.50–8.25 (m, 1H), 8.00–7.40 (m, 10H), 4.50–4.38 (m, 0.5H), 4.38–4.20 (m, 0.5H), 3.85–3.65 (m, 1H), 3.40–3.25 (m, 1H), 3.20–2.95 (m, 7H), 2.25–2.10 (m, 1H), 2.10–1.60 (m, 3H), 1.50–1.16 (m, 2H), 1.08–0.80 (m, 6H); HRMS (ESI) calcd. for $C_{30}H_{36}N_4O_2$ $[M + H]^+$: 485.2911. Found: 485.2931.

Pharmacology. *Materials.* Cell culture materials were purchased from Fisher SSI. Forskolin was purchased from Sigma-Aldrich. An expression plasmid containing a pre-prolactin leader sequence (PPLS) and an influenza hemagglutanin (HA) tag fused in frame upstream of the human GPR88 cDNA was prepared in a modified pcDNA3.1+ mammalian expression vector by GenScript (Piscataway, NJ). Midi-prep DNA was prepared and the PPLS-HA-GPR88 construct was verified by sequencing.

Lance™ cAMP Assay Using Stable PPLS-HA-GPR88 CHO Cells. A stable PPLS-HA-GPR88 CHO cell line was created by over-expressing the PPLS-HA-GPR88 construct in CHO cells. These cells were maintained in DMEM/F12 medium supplemented with 10% fetal bovine serum (FBS), 100 units each of penicillin and streptomycin, and 400 μg/mL geneticin (for antibiotic resistance). PerkinElmer's Lance Ultra kit (TRF0262) was used to detect cAMP accumulation. Stimulation buffer containing 1X Hank's Balanced Salt Solution (HBSS), 5 mM HEPES, 0.1% BSA stabilizer, and 0.5 mM final IBMX was prepared and titrated

to 7.4 at room temperature. Serial dilutions of the test compounds (5 μL) and 300 nM forskolin (5 μL), both prepared at 4x the desired final concentration in 2% DMSO/stimulation buffer, were added to a 96-well white ½ area microplate (PerkinElmer). A cAMP standard curve was prepared at 4x the desired final concentration in stimulation buffer and 5 μL was added to the assay plate. Cells were lifted with versene and spun at 270*g* for 10 minutes. The cell pellet was resuspended in stimulation buffer and 4,000 cells (10 μL) were added to each well except wells containing the cAMP standard curve. After incubating for 30 min at RT, Eu-cAMP tracer and u*LIGHT-anti-cAMP* working solutions were added per the manufacturer's instructions. After incubation at RT for 1 hour, 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).

Computational Studies. *Property Evaluation.* Properties of fragments in the SAR substitution region were evaluated using semiempirical QM (MOPAC7[18]) models at optimized geometries using this semiempirical Hamiltonian and with isotropic polarizabilities computed at B3LYP hybrid functional optimized geometries employing GAMESS-UK.[22] Postcomputation analysis of the results was done with GRAPHA, a utility that extracts QM-energetic, electrostatic, hydrophobic, frontier-orbital energetic, Sterimol, shape, polar−nonpolar surface area, volume, and thermodynamic descriptors.[20] Substituted biphenyls were used in the computations, capping the substituent at the biphenyl end where it attaches to the central N in the ligands with a hydrogen.

Fragment/2D/3D QSAR. Properties compiled were analyzed to develop quantitative structure relationships in an effort to ascertain the key physiochemical properties modulating GPR88 $\ln EC_{50}$ values as a function of substitution. Multivariate least squares approaches embodied in the R PROJECT software for Statistical Computing (http://www.r-project.org).

Homology Modeling. Multiple and pairwise sequence alignments were made using the human sequence

of GPR88 and sequences of known GPCR crystallographic template with their chimeric stabilizing proteins removed. Alignments were performed using Blosum scoring matrices employing CLUSTALX. An initial level homology model was developed using β1-adrenergic receptor template (PDB: 5A8E) first employing Sali's MODELLER v9.11[26] to obtain an initial backbone model through simulated annealing with topological constraints and employing the CHARMM potential function and then using SCWRL[27] to predict the rotameric sidechain states of non-conserved residues in the adrenergic receptor/GPR88 alignment. AMBER12 was then used to energy minimized the structure using the Simmerling modified AMBER99 potential function and SANDER.

VINA/GLIDE Docking and MMGBSA Scoring. (1*R*,2*R*)-2-PCCA was docked with both Autodock VINA[29] and GLIDE-SP[30] (Schrödinger) during an evaluation period. The Autodock VINA poses were MMGBSA rescored using AMBER12 GAFF+AMBER99SB potential functions and SANDER optimization, including SQM[28] deduced electrostatic charges using scripted workflow developed at RTI for parallelized CPU/GPU implementation analogous to literature reports,[31] while GLIDE-SP/XP-Prime-MMGBSA[30, 32] results were used to deduce the lowest free energy poses using that methodology. The low-free energy poses of these two approaches were largely self-consistent and indicated a common mode of binding of (1*R*,2*R*)-2-PCCA at the level of exploration of this early stage model.

SUPPORTING INFORMATION

Copies of HPLC results of **4a–g** and **5a–aa**, QSAR models A and B description, sequence alignment of GPR88 with selected GPCRs and β1-adrenergic receptor templates, PDB coordinates for GPR88 homology model. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENTS

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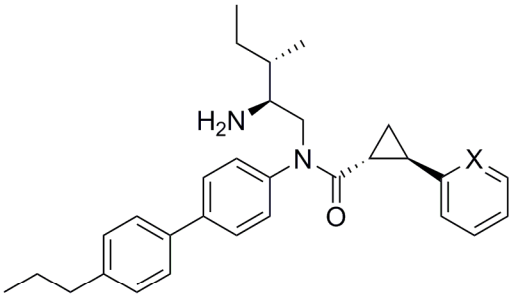
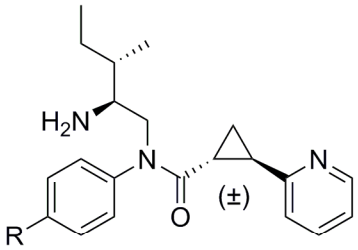
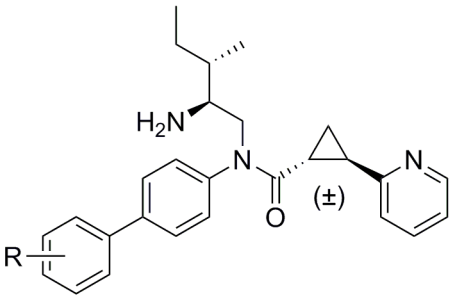


1 X = N, (±)-cyclopropyl, EC_{50} = 116 nM
2 X = N, (*R*,*R*)-cyclopropyl, EC_{50} = 56 nM
3 X = C, (*R*,*R*)-cyclopropyl, EC_{50} = 233 nM



4a R = H, EC_{50} = 2760 nM
4b R = hexyl, EC_{50} = 421 nM
4c R = Cy, EC_{50} = 356 nM
4d R = Ph, EC_{50} = 283 nM
4e R = PhO, EC_{50} = 439 nM
4f R = Bn, EC_{50} = 666 nM
4g R = $Ph(CH_2)_2$, EC_{50} = 553 nM

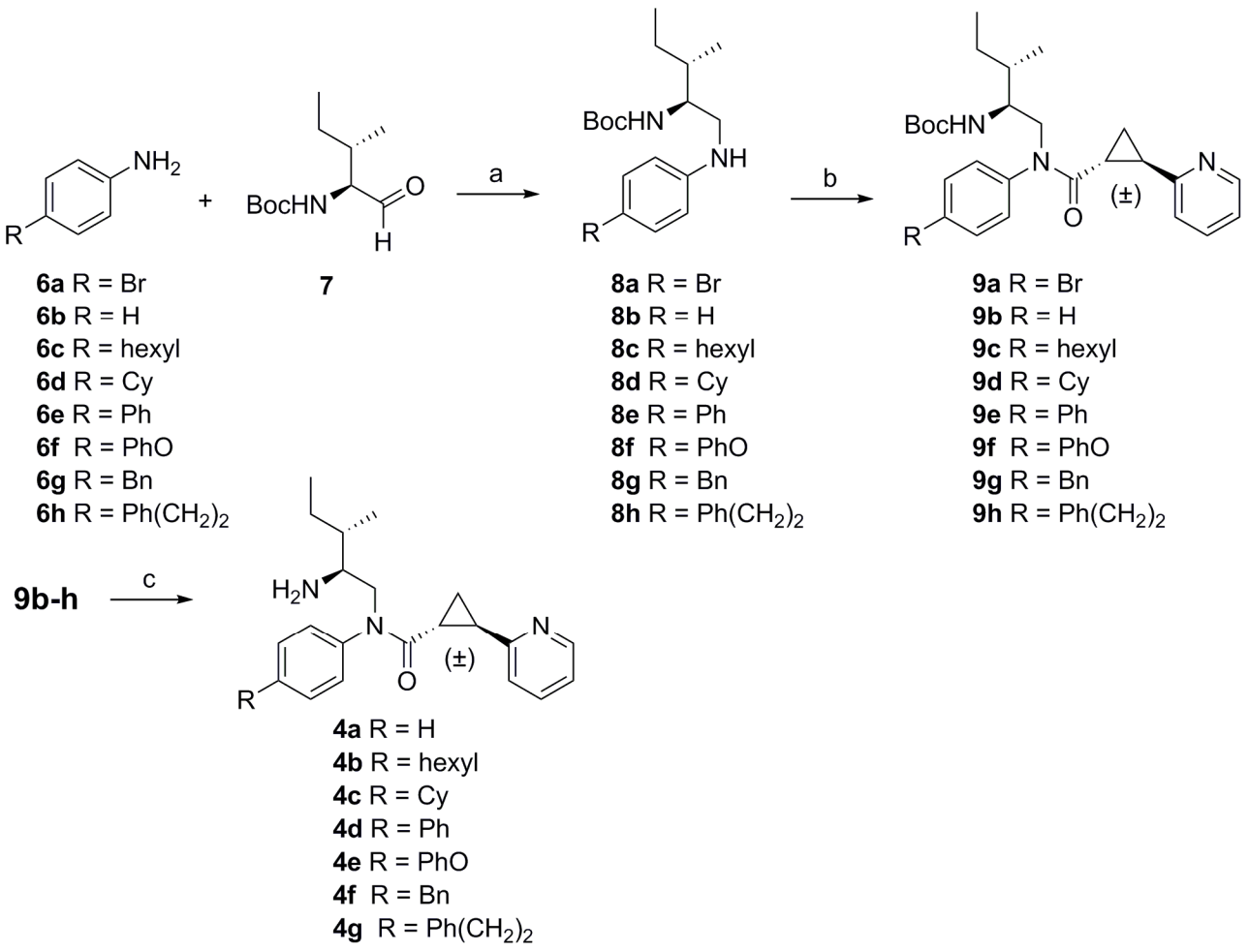
Figure 1. Structures of 2-PCCA (**1**), (1*R*,2*R*)-2-PCCA (**2**) and analogues **3**, **4a–g**.



5a	R = 4-Me	**5j**	R = 4-MeO	**5s**	R = 4-NO_2
5b	R = 4-CF_3	**5k**	R = 4-CF_3O	**5t**	R = 4-Ac
5c	R = 4-Et	**5l**	R = 4-EtO	**5u**	R = 4-CO_2Et
5d	R = 4-*i*-Pr	**5m**	R = 4-*i*-PrO	**5v**	R = 4-OH
5e	R = 4-*i*-Bu	**5n**	R = 3,4-diMeO	**5w**	R = 4-NH_2
5f	R = 4-*t*-Bu	**5o**	R = 3,4-MD	**5x**	R = 4-NMe_2
5g	R = 4-hexyl	**5p**	R = 4-F	**5y**	R = 4-NHAc
5h	R = 4-Cy	**5q**	R = 4-Cl	**5z**	R = 4-$CONH_2$
5i	R = 4-Ph	**5r**	R = 4-CN	**5aa**	R = 4-$CONMe_2$

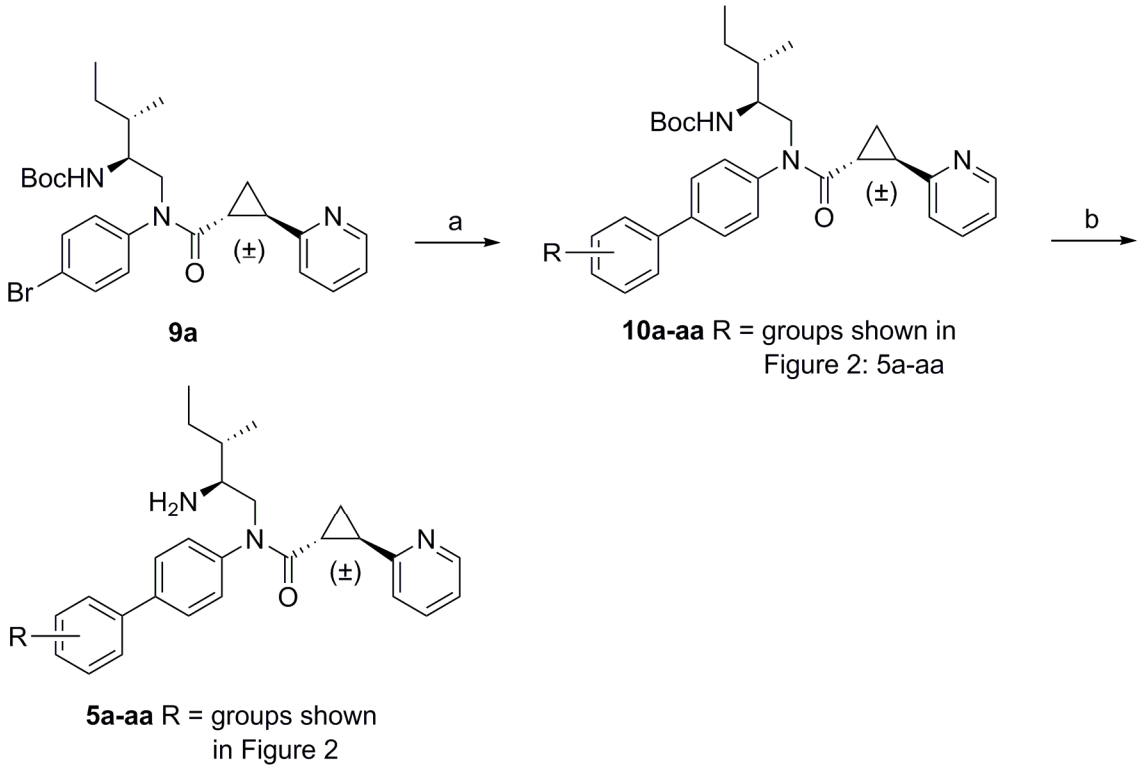
Figure 2. Structure of 2-PCCA analogues **5a–aa**.

Scheme 1[a]



[a] Reagents: (a) $NaBH(OAc)_3$, 1,2-dichloroethane, rt, overnight; (b) (±)-*trans*-2-(pyridin-2-yl)cyclopropanecarboxylic acid/oxalyl chloride/DCM/40 °C/2 h, concentrated, then **8a–h**/Et_3N/DCM, rt, overnight; (c) 4 M HCl/dioxane, DCM, rt, 6 h.

Scheme 2[a]



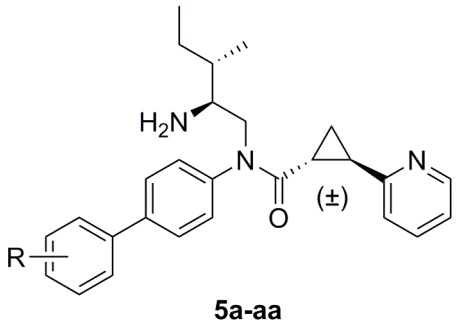
9a

10a-aa R = groups shown in Figure 2: 5a-aa

5a-aa R = groups shown in Figure 2

[a] Reagents: (a) arylboronic acid, Pd(dppf)Cl_2·DCM, K_3PO_4, DME/H_2O (3:1), microwave, 160 °C, 6 min; (b) 4 M HCl/dioxane, DCM, rt, 6 h.

Table 1. Structures and activities of compounds **5a–aa**.



5a-aa

Compd[a]	R	pEC_{50} (EC_{50}, nM)[b]	Compd[a]	R	pEC_{50} (EC_{50}, nM)[b]
1	4-Pr	6.94 ± 0.11 (116)	**5n**	3,4-diMeO	6.04 ± 0.01 (917)
4d	H	6.55 ± 0.03 (283)	**5o**	3,4-MD	6.69 ± 0.09 (204)
5a	4-Me	6.98 ± 0.09 (104)	**5p**	4-F	5.67 ± 0.04 (268)
5b	4-CF_3	6.73 ± 0.06 (187)	**5q**	4-Cl	6.67 ± 0.07 (213)
5c	4-Et	7.07 ± 0.01 (85)	**5r**	4-CN	6.71 ± 0.05 (197)
5d	4-*i*-Pr	6.59 ± 0.07 (260)	**5s**	4-NO_2	6.56 ± 0.06 (274)
5e	4-*i*-Bu	6.57 ± 0.02 (271)	**5t**	4-Ac	6.45 ± 0.05 (351)
5f	4-*t*-Bu	6.29 ± 0.07 (515)	**5u**	4-CO_2Et	6.59 ± 0.09 (257)
5g	4-hexyl	6.87 ± 0.11 (136)	**5v**	4-OH	5.54 ± 0.06 (2,860)
5h	4-Cy	6.76 ± 0.10 (176)	**5w**	4-NH_2	5.95 ± 0.02 (1,120)
5i	4-Ph	6.54 ± 0.03 (289)	**5x**	4-NMe_2	6.53 ± 0.04 (294)
5j	4-MeO	7.02 ± 0.08 (96)	**5y**	4-NHAc	8,500[c]
5k	4-CF_3O	6.86 ± 0.04 (139)	**5z**	4-$CONH_2$	NA[c]
5l	4-EtO	7.09 ± 0.02 (82)	**5aa**	4-$CONMe_2$	5.48 ± 0.05 (3,320)
5m	4-*i*-PrO	7.11 ± 0.09 (77)			

[a] All compounds were tested as the HCl salt. [b] pEC_{50} values are means ± standard error of at least three independent experiments performed in duplicate. [c] EC_{50} > 10 μM, mean of two independent experiments.

Table 2. Calculated physiochemical properties.

Compd	EC_{50} (nM)	clogP[a]	TPSA (Å^2)[a]	logBB
1	116	6.19	59.22	0.20
5a	104	5.30	59.22	0.07
5c	85	5.74	59.22	0.14
5j	96	4.63	68.45	–0.17
5l	82	4.99	68.45	–0.12
5m	77	5.40	68.45	–0.05
5o	204	4.41	77.68	–0.34

[a] cLogP and TPSA were calculated using Instant JChem 5.4.0 (ChemAxon Ltd).

Table 3. QSAR model description.

Model C: $\ln EC_{50} \sim L + TotalHyd + V\_S + PSA + logP + B4$

Descriptor	Estimate coefficients	Std. error	t-value	Pr (>|t|)
Intercept	8.05770	1.68999	4.768	5.23e–05
L	–1.01903	0.46050	–4.587	8.58e–05
TotalHyd	1.70887	0.46050	3.711	0.000907
V_S	0.04528	0.01001	4.523	0.000102
PSA	0.14556	0.02630	5.535	6.43e-06
logP	–0.88637	0.37052	–2.392	0.023701
B4	1.11513	0.41208	2.706	0.011461

Residual standard error = 0.7779 on 28 degrees of freedom, multiple $R^2 = 0.6797$, adjusted $R^2 = 0.6111$, F-statistic = 9.903 on 6 and 28 degrees of freedom, p-value = 7.063e–06.

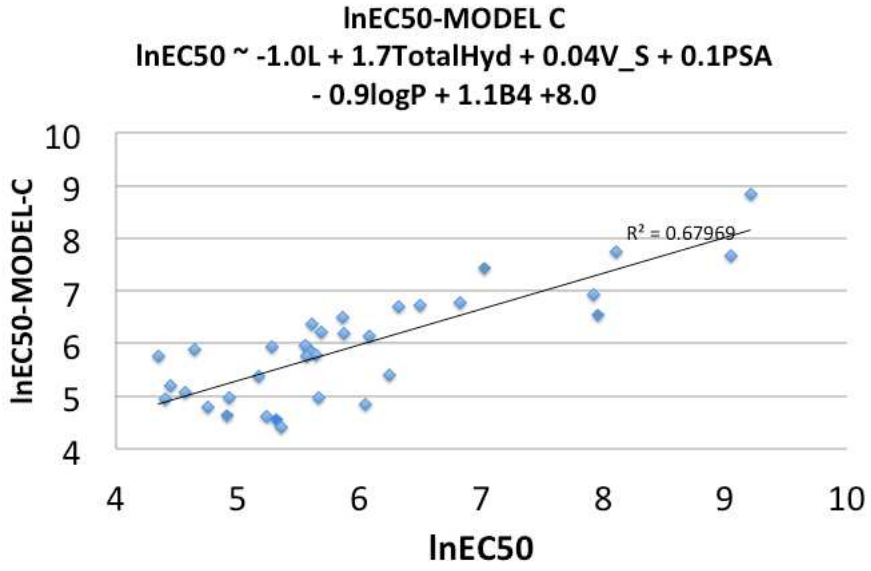


Figure 3. Plot of experimental $lnEC_{50}$ vs. model C $lnEC_{50}$.

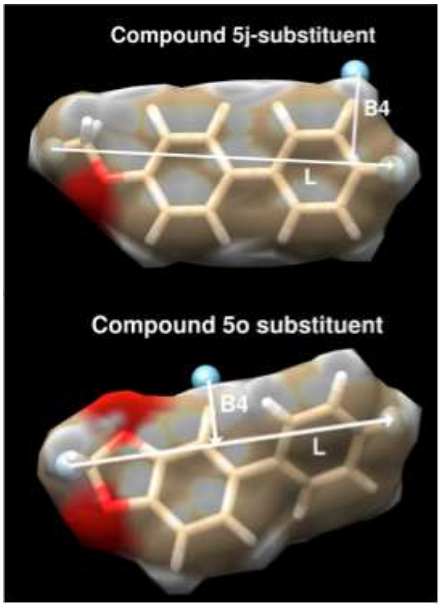


Figure 4. Illustrations of the L- and B4-Sterimol metrics for **5j** and **5o**.

(A) (B)

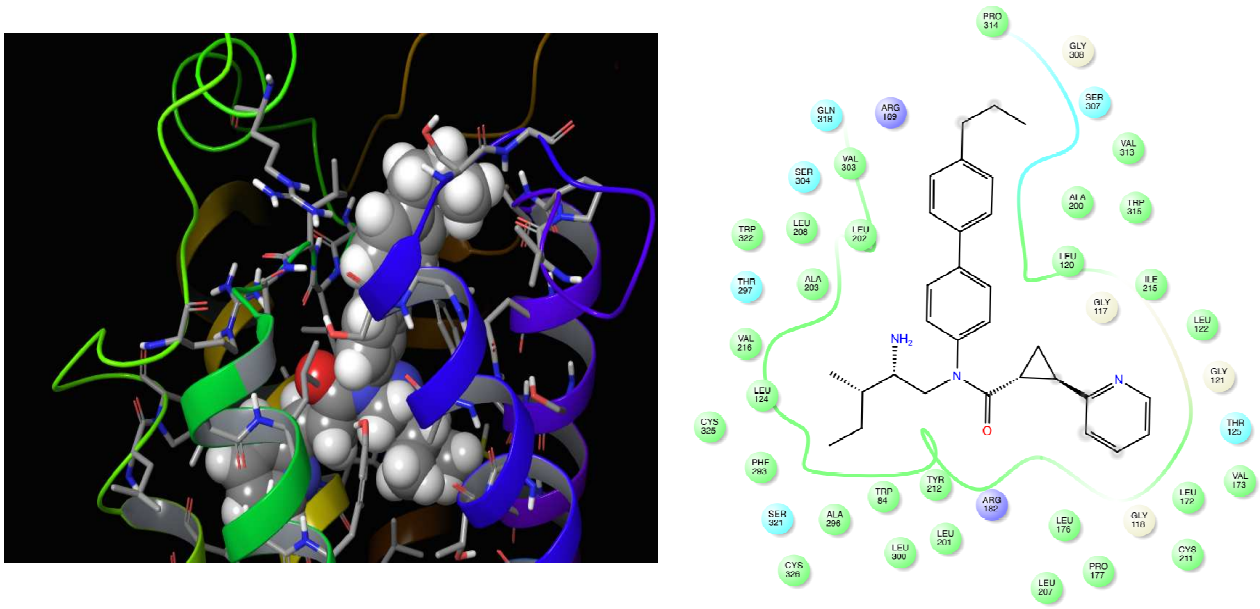
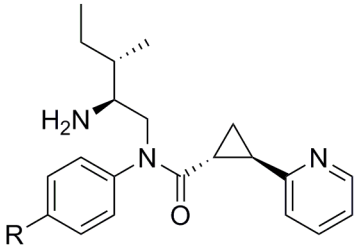
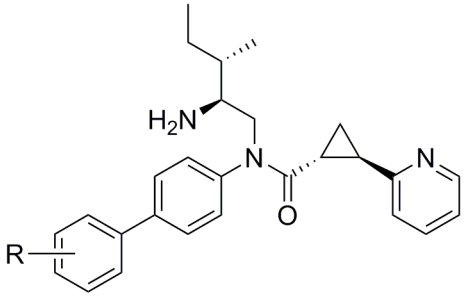


Figure 5. Examination of an early-stage homology model of GPR88 with (1*R*,2*R*)-2-PCCA lowest MMGBSA scored pose in 3D (**A**) and LIGPLOT (**B**) format. Note the largely hydrophobic residues around the biphenyl scaffold portion indicated by the green-line.

Table of Contents graphic



R = H, hexyl, Cy, Ph, PhO, Bn, $PhCH_2CH_2$



R = alkyl, alkoxy, F, Cl, CN, NO_2, OH, amine, amide, ester, etc.