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Biphenyl Acid Derivatives as APJ Receptor Agonists

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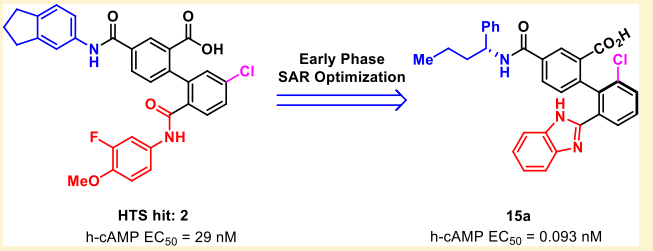
Supporting Information

ABSTRACT: The APJ receptor and its endogenous peptidic ligand apelin have been implicated as important modulators of cardiovascular function, and APJ receptor agonists may be beneficial in the treatment of heart failure. In this article, we describe the discovery of a series of biphenyl acid derivatives as potent APJ receptor agonists. Following the identification of initial high-throughput screen lead **2**, successive optimization led to the discovery of lead compound **15a**. Compound **15a** demonstrated comparable in vitro potency to apelin-13, the endogenous peptidic ligand for the APJ receptor. In vivo, compound **15a** demonstrated a dose-dependent improvement in the cardiac output in male Sprague Dawley rats with no significant changes in either mean arterial blood pressure or heart rate, consistent with the hemodynamic profile of apelin-13 in an acute pressure volume loop model.



INTRODUCTION

Heart failure (HF) and related complications have become an increasing concern to the world's population. In the US alone, HF affects approximately six million people and leads to increased morbidity, premature death, poor quality of life, and significant health-care expenditure.[1] HF is a clinical syndrome characterized by inadequate performance of the heart and inability to deliver sufficient blood and oxygen supply to meet the body's demands. Despite encouraging advances in HF management,[2] which focus primarily on inhibition and downregulation of the renin−angiotensin aldosterone system and co-medications including β-blockers, vasodilators, and diuretics, the prognosis remains poor. Patients display 10% mortality at 28 days posthospitalization for HF, and survival rates are approximately 50% within 5 years of diagnosis.[3] As a result, the development of novel therapeutic agents is necessary to further improve HF therapy.

The APJ receptor (APJ-R) was identified in 1993 as a member of the rhodopsin-like G-protein-coupled receptor family.[4] APJ-R is most closely related to the angiotensin AT_1 receptor, with 54% homology in the transmembrane domain, but lacks binding affinity for angiotensin II.[5a] APJ-R is widely expressed in various tissues, including the heart, kidney, and blood vessels. APJ-R was deorphanized following the discovery of its endogenous peptidic ligand, apelin.[5a] Recently, the Elabela peptide was also identified as an endogenous APJ-R ligand.[5b] Apelin is produced as a 77 amino acid pre-pro form and is progressively cleaved to smaller peptidic fragments.[6a] Among the biologically active apelin peptides, which include apelin-13, -17, and -36, as well as the pyroglutamate form of apelin-13 ((Pyr[1])apelin-13, Figure 1), (Pyr[1])apelin-13 has been reported as the most stable and most abundant form present in human plasma and cardiac tissue.[6b,c] Preclinical animal models indicate that APJ receptor agonists can improve cardiac function[7] and this notion is also supported by apelin studies in humans. Acute infusion of (Pyr[1])apelin-13 into healthy volunteers and into patients with HF resulted in improved cardiac output (CO) and increased ejection fraction without significant effects on blood pressure or heart rate.[8] Therefore, interest in APJ-R agonism as a potential therapeutic target for HF management has been widespread and is evidenced by the development of both peptido-mimetic[9] and small-molecule[10] APJ-R agonists. In this paper, the identification and optimization of a series of biphenyl acid (BPA)-based APJ agonists are described.

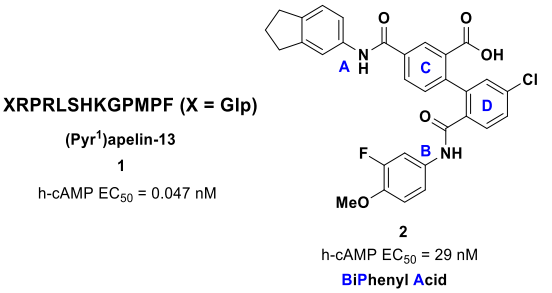


Figure 1. (Pyr[1])apelin-13 and HTS hit.

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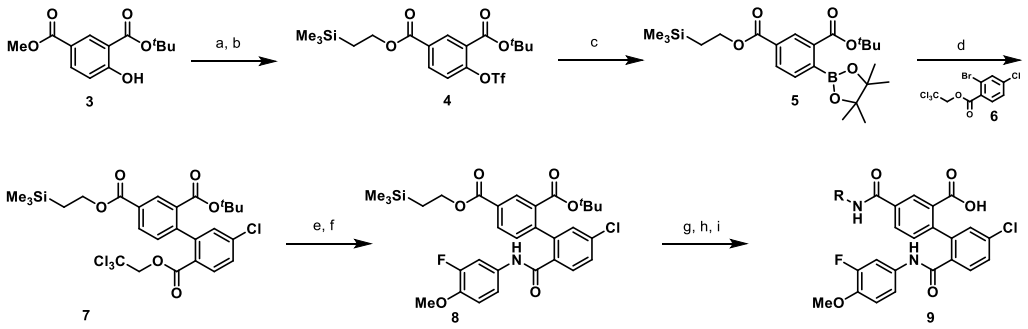
Scheme 1. Synthetic Route to Bis-Amides[a]



[a]Reagents and conditions: (a) 2-(trimethylsilyl)ethanol, NaH, toluene, 0−50 °C, 62%; (b) Tf_2O, pyridine, DCM, 0 °C, 99%; (c) bis(pinacolato)diborane, $PdCl_2$(dppf)-CH_2Cl_2, KOAc, 1,4-dioxane, 65 °C, 96%; (d) $PdCl_2$(dppf)−CH_2Cl_2, Na_2CO_3, toluene, H_2O, 65 °C, 57%; (e) Zn, sat. NH_4Cl solution, THF, rt, 97%; (f) 3-fluoro-4-methoxyaniline, HATU, DIEA, MeCN, rt, 81%; (g) TBAF, THF, rt, quant.; (h) RNH_2, HATU, DIEA, DCM, rt; (i) TFA, DCM, rt, 68−95% for two steps.

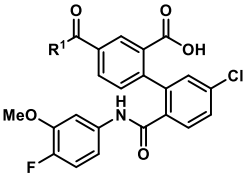
RESULTS AND DISCUSSION

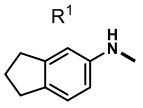
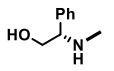
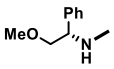
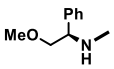
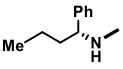
In an effort to identify small-molecule APJ-R agonists, a high-throughput screen (HTS) of 1.2 million compounds was undertaken using a homogeneous time-resolved fluorescence assay[11] in HEK293 cells stably expressing human APJ-R. Compounds that demonstrated ≥20% inhibition of forskolin-stimulated cAMP (Ymax) and ≤20% efficacy against a parental HEK293 cell line were further evaluated using confirmatory concentration response analysis. Confirmed hits were then screened against the AT_1 receptor to rule out any compounds with AT_1 activity. This led to the identification of a number of small-molecule agonists including bis-amide **2** (Figure 1), which contained a biphenyl core, a privileged structure for GPCRs,[12] and exhibited full agonism[13] of APJ-R with an EC_{50} of 29 nM.

Following the identification of compound **2**, an efficient synthetic sequence was developed and used to generate diverse BPA bis-amides through a key orthogonally protected biphenyl tricarboxylic ester intermediate **7** (Scheme 1). Starting with the known bis-ester **3**,[14] ester exchange followed by triflate formation produced intermediate **4**. Subsequent palladium-mediated borylation followed by Suzuki coupling generated tri-ester **7**. Each carboxylic ester on **7** could be cleaved selectively, providing a versatile starting point for array synthesis. For the re-synthesis of **2**, zinc-mediated reductive trichloroethyl ester cleavage of **7** and subsequent amide bond formation afforded bis-ester **8**. tetra-*n*-Butylammonium fluoride (TBAF)-mediated (trimethylsilyl)ethyl ester deprotection, amide coupling, and removal of the *t*-butyl group under acidic conditions generated bis-amides **9** in excellent yields.

One notable potential liability presented by **2** was the possible release of aniline as a result of amide hydrolysis under metabolic activation. Efforts were focused on replacement of the aniline and identification of analogues with improved potency. Following the synthetic route depicted in Scheme 1, a series of structurally diverse aliphatic amines were surveyed on amide A of the BPA core (Table 1). From these efforts, we found that the dihydroindene amine could be replaced with 2-phenylethanolamine to generate **9a** with comparable potency to compound **2**. Meanwhile, it was also noted that amides with lipophilic substituents afforded better potency compared to polar amides. Thus, the methylated 2-phenylethanolamine was incorporated resulting in **9b** with an EC_{50} of 0.19 nM, a 310-fold potency improvement compared to **9a**. It was determined that APJ activity resided primarily in the *R* enantiomer,

Table 1. SAR of Bis-Amide Examples[a]



compd	R^1	hAPJ EC_{50} (nM)
2		29 ± 12
9a		59 ± 9.9
9b		0.19 ± 1.0
9c		2.7 ± 0.64
9d		0.33 ± 0.10

[a]Data represent the mean SEM, n = 2 or more determinations.

whereas the *S* enantiomer **9c** showed reduced potency. An in vitro biotransformation study of an early analogue related to **9b** identified the methyl ether as the major site of metabolism.[15] The methoxy phenyl ethylene amine was replaced with isosteric *n*-butyl phenyl ethylene amine in an effort to address this liability, providing **9d** with comparable potency to **9b**.

Following the identification of **9d**, amide B of the BPA core was extensively surveyed. Array synthesis was executed by alternating the order of ester cleavage. However, a narrow structure−activity relationship (SAR) was observed at this position and all attempts to replace anilines with aliphatic amines were unproductive.[16] Subsequent efforts to replace the amide led to the identification of benzimidazole analogue **11a** (Table 2), the synthesis of which is depicted in Scheme 2. (Trimethylsilyl)ethyl ester deprotection of **7** followed by amide coupling provided intermediate **10**. Reductive cleavage of the trichloroethyl ester generated the corresponding

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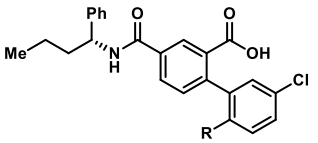
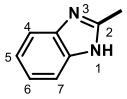
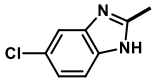
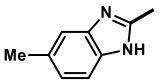
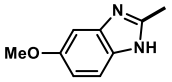
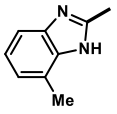
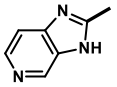
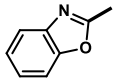
Table 2. Benzimidazole SAR[a]



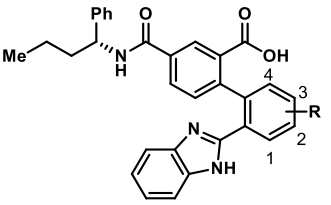
compd	R	hAPJ EC_{50} (nM)
11a		1.4 ± 0.47
11b		0.31 ± 0.14
11c		0.60 ± 0.32
11d		0.083 ± 0.025
11e		51 ± 2.0
11f		19 ± 5.8
11g		7.4 ± 3.2
11h		4900 ± 2600

[a]Data represent the mean SEM, n = 2 or more determinations.

carboxylic acid, which was subjected to amide coupling with *o*-phenylenediamine. The resulting regiosomeric mixture of amides was treated with acetic acid under elevated temperature to effect benzimidazole formation and *t*-butyl ester cleavage in one pot to generate **11**. Exploration of the benzimidazole substitution pattern indicated that various substituents at the 5 position were tolerated for potency. Both 5-Cl (**11b**) and 5-Me (**11c**) benzimidazole analogues exhibited slightly improved potency and the 5-OMe compound (**11d**) offered an additional potency boost. In contrast, as demonstrated by **11e** and **11f**, substitution with a methyl group at the 7 position and incorporation of N at the 6 position of the phenyl ring led to a significant loss in potency. In addition to benzimidazoles, heterocycles such as phenylimidazole and benzoxazole were also investigated. Whereas phenyl imidazole **11g** retained nM level potency, the benzoxazole analogue **11h** resulted in micromolar potency, indicating that the benzimidazole NH may play a pivotal role in the interaction with APJ-R.

Parallel to the exploration of the benzimidazole SAR, the substitution pattern of the D-ring was investigated (Table 3).

Table 3. D-Ring SAR[a]



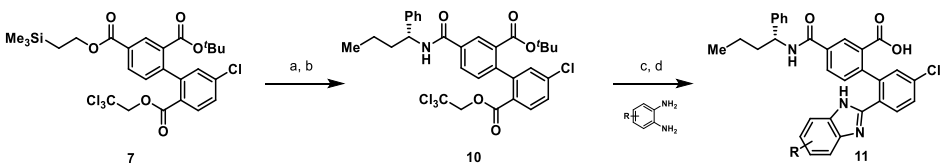
compd	R	hAPJEC_{50} (nM)
11a	3-Cl	1.4 ± 0.47
12a	3-H	5.7 ± 2.8
12b	3-Me	1.5 ± 0.64
12c	3-OMe	5.7 ± 2.2
12d	1-Cl	2100 ± 970
12e	2-Cl	9.0 ± 2.6
12f	4-Cl	0.20 ± 0.15
12g	4-F	0.51 ± 0.32
12h	4-Me	0.18 ± 0.013

[a]Data represent the mean SEM, *n* = 2 or more determinations.

Replacing the 3-Cl with a proton (**12a**) or methoxy group (**12c**) led to less potent compounds, whereas the 3-Me (**12b**) analogue retained potency. A chlorine walk on the D-ring was subsequently executed. Whereas 1-Cl (**12d**)- and 2-Cl (**11e**)-substituted analogues showed reduced potency, the 4-Cl analogue (**12f**) demonstrated improved potency by sevenfold compared to **11a**. Compound **12f** was determined to exist as a 1:1 mixture of atropisomers because of the steric encumbrance surrounding the biaryl bond. The corresponding 4-F (**12g**) and 4-Me analogues (**12h**) showed comparable potency to **12f**. The chlorine substitution was selected to be used for subsequent studies as it was considered to offer higher atropisomeric thermal stability compared to the 4-F analogue,[17] and afforded superior yield for the biaryl formation step compared to the 4-Me analogue. It is worth noting that the Suzuki coupling between boronic ester **5** and bromide **13** was challenging and only moderate yields were initially obtained. Extensive screening of reaction conditions afforded **14** in satisfactory yield (Scheme 3).[15]

The atropisomeric mixture **12f** was subjected to chiral supercritical fluid chromatography (SFC) separation and stable

Scheme 2. Syntheses of Benzimidazole-Substituted BPAs[a]



[a]Reagents and conditions: (a) TBAF, THF, rt, quant.; (b) (*R*)-1-phenylbutan-1-amine, HATU, DIEA, DCM, rt, 75%; (c) Zn, sat. NH_4Cl solution, THF, rt, 90%; (d) HATU, DIEA, DCM, rt, then AcOH, 85 °C, 68%–92%.

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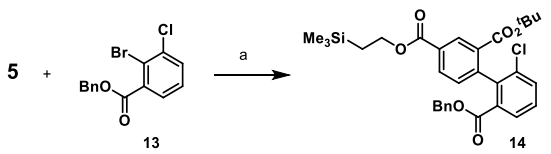
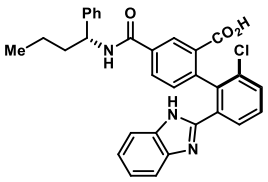
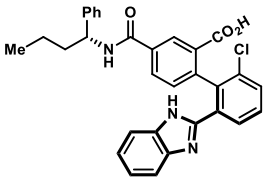
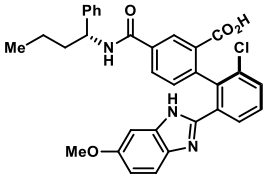
Scheme 3. Synthesis of Tri-Ester 14[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$, xantphos, 1 M K_3PO_4, toluene, 70 °C, 65−74%.

atropisomers **15a** and **15b** were obtained (Table 4). The absolute configurations of **15a** and **15b** were confirmed by X-ray crystallography of the individual atropisomers. The *S*-atropisomer **15a** was found to be 200-fold more potent than the corresponding *R*-atropisomer. The dihedral angle of the biphenyl system was nearly perpendicular in the crystalline form. The 15-fold potency boost compared to **11a** indicated that conformational restriction of the biphenyl ring system imposed a favorable bioactive conformation.[18]

Table 4[a]

compd	structure	APJ EC_{50} (nM) human/rat
1	(Pyr1)apelin-13	0.047 ± 0.071 0.062 ± 0.056
15a		0.093 ± 0.054 0.12 ± 0.049
15b		22 ± 20 43 ± 39
15c		0.062 ± 0.032 0.12 ± 0.15

[a]Data represent the mean SEM, n = 2 or more determinations.

The optimized BPA **15a** demonstrated agonist potency comparable to (Pyr[1])apelin-13 versus both human and rat APJ-R (0.093 vs 0.047 nM and 0.12 vs 0.062 nM, respectively). It is worth noting that, in contrast to the 3-Cl series (Table 2, compounds **11a** vs **11d**), installation of a methoxy group on the benzimidazole (Table 4, **15c**) failed to provide further potency improvement. It is hypothesized that the reinforced orthogonal orientation of the biphenyl core projected the methoxy group in a less favorable orientation. To understand the binding site of **15a**, competition studies between **15a** and [^{125}I]-apelin-13, as well as between [^{3}H]-**15a** and apelin-13, were performed (Figure 2). The nearly quantitative displacement of [^{125}I]-apelin-13 by **15a** and the displacement of [^{3}H]-**15a** by apelin-13 support the assumption that **15a** occupied the orthosteric site of APJ-R. Compared to **15c**, **15a** appeared to exhibit improved solubility at pH 7.4 (0.66 vs 0.18 mg/mL, amorphous) and was advanced to pressure−volume loop analysis (*PV*-loop)[19] in isoflurane-anesthetized male Sprague Dawley (SD) rats to evaluate its acute hemodynamic effect. When dosed via intravenous infusion at 100 μg/min/kg, **15a** induced a 10% increase in CO with minimal impact on blood pressure (<5% transient blood pressure drop)[15] and no effect on heart rate,[15] which was consistent with the hemodynamic effect of (Pyr[1])apelin-13 (**1**) in this model (Figure 3). Subsequent dose response studies revealed that **15a** exhibited a dose-dependent increase in CO without a significant effect on HR, consistent with a (Pyr[1])apelin-13 response in this model.

CONCLUSIONS

BPA bis-amide **2** was identified from HTS screening as an APJ-R agonist. Initial SAR exploration of the bis-amide series led to optimization of the upper amide, which resulted in an 80-fold increase in in vitro potency (**9d** vs **2**). The bis-amide series was further advanced by replacing the lower amide with a benzimidazole. Optimization of the benzimidazole C5 and C7 position substitution and subsequent biphenyl core C4 substitution afforded non-interconverting atropisomer **12f**. Separation of the respective atropisomers led to the

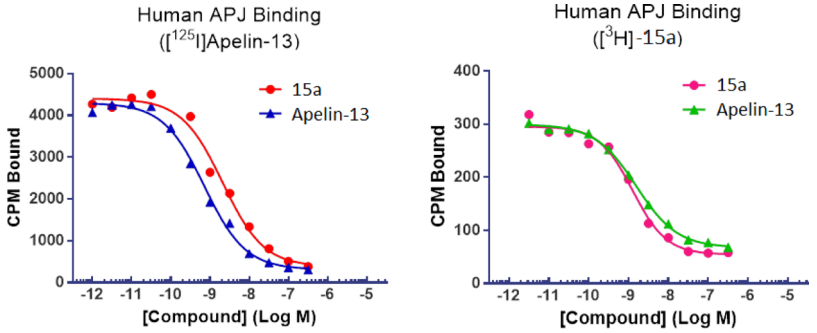


Figure 2. Radioligand binding experiments; 1 μg of the human APJ-R-expressing HEK293 cell membrane was incubated with increasing concentration of **1** or **15a** and 0.1 nM [^{125}I]-(Pyr[1])apelin-13 in a final volume of 200 μL assay buffer containing 25 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, 10 mM $MgCl_2$, 2 mM ethylene glycol-bis(2-aminoethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid, and 0.1% bovine serum albumin, pH = 7.2. The membrane was separated from free compounds with a 0.3% poly ethyleneimine-soaked UniFilter-96 GF/B plate after incubation at room temperature for 1 h; inhibition binding reaction was carried out at room temperature for 3 h when 1 nM of [^{3}H]-**15a** was used.

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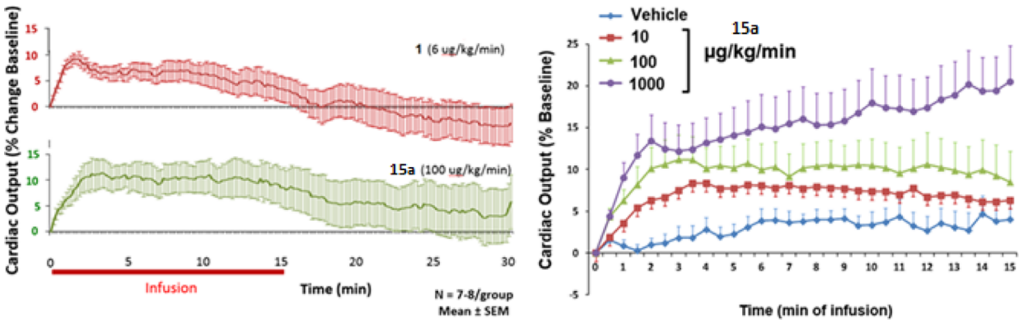

Figure 3. Rat pressure-volume loop analysis of **1** and **15a**. Isoflurane-anesthetized male SD rats with a Millar *PV*-loop catheter in LV and a Millar pressure catheter in the abdominal aorta. After establishing a stable baseline, **1** [6 μg/kg/min (3.92 nmol/kg/min), $n = 7$] or **15a** (10, 100, 1000 μg/kg/min (0.0157, 0.157, 1.57 μmol/kg/min), $n = 8$/dose) or *N*,*N*-Dimethylacetamide vehicle (100 μL/kg/min, $n = 10$) was infused into the jugular vein for 15 min with continuous monitoring of hemodynamics. Hemodynamics were monitored for an additional 15 min after terminating infusion. Separate rats were prepared to measure exposures in response to the same 15 min infusions of **15a** ($n = 3$/dose); washout samples were obtained after stopping the 10 and 1000 μg/kg/min infusions; plasma concentration of **15a** (μM) after 15 min of infusion: 0.44 ± 0.18 (10 μg/kg/min); 4.4 ± 0.28 (100 μg/kg/min); 82 ± 4.2 (1000 μg/kg/min).

identification of *S* antipode, **15a**, with in vitro potency consistent with that observed with the endogenous ligand, (Pyr[1])apelin-13 (**1**). Compound **15a** demonstrated significant improvement in CO in male SD rats with no significant changes in either mean arterial blood pressure or heart rate, which was consistent with the effect of **1** in this acute rat *PV*-loop model. The studies described herein demonstrate that the BPA chemotype shows promise as a novel scaffold for the development of potent APJ-R agonists for treatment of HF.

EXPERIMENTAL SECTION

General Information. All reagents and solvents used, including anhydrous solvents, were of commercial quality. All reactions were carried out under a static atmosphere of nitrogen and stirred magnetically unless otherwise stated. All flash chromatographic separations were performed using an ISCO RediSep on disposable silica gel columns, eluting with hexanes/ethyl acetate or methylene chloride/methanol. For diastereomeric mixtures, the desired compound was obtained via SFC on a PIC solution 200 SFC system using the following method: Chiralpak AD-H, 21 × 250 mm, 5 μm; 22% EtOH/78% CO_2; 45 mL/min, 150 bar, 40 °C. Final compounds were purified by reverse phase HPLC on a SunFire C18 preparative column using appropriate gradients of acetonitrile/water/0.1% trifluoroacetic acid (TFA) or methanol/water/0.1% TFA as the eluent. Reactions were monitored either by analytical Liquid chromatography−mass spectrometry (LCMS) or by thin-layer chromatography using 0.25 mm E. Merck silica gel plates (60 F254) and were visualized with UV light or by staining with various staining agents. LCMS data were recorded on a Shimadzu LC-10AT equipped with an SIL-10A injector, an SPD-10AV detector, running DISCOVERY VP software, and coupled with a Waters ZQ mass spectrometer running MassLynx, version 3.5, software using the following method: Phenomenex Luna C-18 2.0 mm × 30 mm column eluted with a 2 min linear gradient from 0 to 100% of B and then 1 min at 100% of B wherein A = 10% methanol/90% water/0.1% TFA and B = 90% methanol/10% water/0.1% TFA. The purity of all final compounds tested was determined to be ≥95% using the following orthogonal HPLC conditions: column-1: SunFire C18 3.5 μm, 3.0 × 150 mm; column-2: Xbridge Phenyl 3.5 μm, 3.0 × 150 mm; flow rate 1.0 mL/min, gradient 10−100% 95:5 AcCN/H_2O (0.05% TFA) in 5:95 AcCN/H_2O (0.05% TFA) over 12 min and then 100% of 95:5 AcCN/H_2O (0.05% TFA) over 3 min; wavelength 1 = 220 nm, wavelength 2 = 254 nm (method A); Column: Waters Acquity BEH C18 1.7 μm 2.1 × 50 mm; flow rate 1.1 mL/min, gradient 0−100% 95:5 AcCN/H_2O (0.1% TFA) in 5:95 AcCN/H_2O (0.1% TFA) over 3 min and then 100% of 95:5 AcCN/H_2O (0.1% TFA) over 0.75 min; and flow rate 1.1 mL/min, gradient 0−100% 95:5 AcCN/H_2O (10 mM ammonium acetate) in 5:95 AcCN/H_2O (10 mM ammonium acetate) over 3 min and then 100% of 95:5 AcCN/H_2O (10 mM ammonium acetate) over 0.75 min wavelength = 220 nm (method B). ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Bruker or a JEOL Fourier transform spectrometer operating at frequencies as follows: ^{1}H NMR, 400 MHz (Bruker or JEOL) or 500 MHz (JEOL); ^{13}C NMR, 101 MHz (Bruker or JEOL) or 125 MHz (JEOL). Spectra data are reported in the format chemical shift (multiplicity, coupling constants, and number of hydrogens). Chemical shifts are specified in ppm referenced to deuterated solvent peaks. All ^{13}C NMR spectra were proton decoupled. Most of the final compounds were confirmed for molecular weight using accurate mass LCMS (HRMS). A Thermo Fisher LTQ Orbitrap mass spectrometer in line with a Waters Acquity UPLC allowed collection of molecular ion data with accuracy of <5 ppm. Optical rotations were obtained on a JASCO P1010 Polarimeter.

*5′-Chloro-4-((2,3-dihydro-1H-inden-5-yl)carbamoyl)-2′-((3-fluoro-4-methoxyphenyl)-carbamoyl)-[1,1′-biphenyl]-2-carboxylic Acid (**2**).* Into the reaction vessel was added **8** (178 mg, 0.297 mmol), tetrahydrofuran (THF; 5 mL), and TBAF (0.89 mL, 1 M/L in THF, 0.89 mmol). The reaction was stirred at rt for 12 h, diluted with EtOAc (20 mL), and washed with 1 N HCl. The aqueous phase was extracted with additional EtOAc (10 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated to provide the corresponding carboxylic acid. m/z obs 499.9 $[M + H]^+$. A portion of this crude carboxylic acid (20 mg, 0.04 mmol) was dissolved in dichloromethane (DCM; 2 mL). 2,3-Dihydro-1*H*-inden-5-amine (16 mg, 0.12 mmol), *N*,*N*-diisopropylethylamine (DIEA; 0.021 mL, 0.12 mmol), and HATU (16.7 mg, 0.044 mmol) were added subsequently. The reaction was stirred at rt for 12 h, concentrated, and treated with DCM (1 mL) and TFA (0.10 mL). The reaction was stirred at rt for 12 h, concentrated, and subjected to prep-HPLC purification to produce **2** (17.8 mg, 0.032 mmol, 80% yield). ^{1}H NMR (500 MHz, methanol-d_4): δ 8.47 (d, $J = 1.8$ Hz, 1H), 8.06 (dd, $J = 8.0$, 1.9 Hz, 1H), 7.66 (d, $J = 8.2$ Hz, 1H), 7.57−7.51 (m, 2H), 7.41 (d, $J = 7.9$ Hz, 1H), 7.39−7.34 (m, 1H), 7.33−7.26 (m, 2H), 7.18 (d, $J = 8.1$ Hz, 1H), 7.01−6.91 (m, 2H), 3.80 (s, 3H), 2.90 (dt, $J = 14.8$, 7.5 Hz, 4H), 2.09 (quin, $J = 7.4$ Hz, 2H). Purity 99% (method A). HRMS (ESI): calcd for $C_{31}H_{25}ClFN_2O_5$ $[M + H]^+$, 559.1431; found, 559.1411.

*3-tert-Butyl 1-(2-(Trimethylsilyl)ethyl) 4-(((Trifluoromethyl)-sulfonyl) oxy)isophthalate (**4**).* Into the reaction vessel was added 2-(trimethylsilyl)ethanol (4.30 g, 36.4 mmol) and toluene (50 mL). The reaction was cooled to 0 °C and NaH (1.248 g, 31.2 mmol) was added. After 5 min, the mixture was warmed to rt and stirred for an additional 50 min. Compound **3** (2.623 g, 10.40 mmol) was then added and the reaction was heated at 50 °C for 30 min. The reaction was cooled to rt, washed with sat NH_4Cl (containing 31.2 mmol HCl), and extracted with EtOAc. The organic layer was dried over

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Na_2SO_4 and concentrated. Silica gel chromatography (0−20% EtOAc in hexanes) afforded the corresponding (trimethylsilyl)ethyl ester (2.18 g, 6.44 mmol, 62% yield) as a colorless oil. ^{1}H NMR (500 MHz, chloroform-*d*): δ 11.52 (s, 1H), 8.47 (d, *J* = 2.2 Hz, 1H), 8.08 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 4.44−4.38 (m, 2H), 1.63 (s, 9H), 1.15−1.09 (m, 2H), 0.09 (s, 9H). This intermediate (2.18 g, 6.44 mmol) was mixed with DCM (20 mL) and pyridine (2.60 mL, 32.2 mmol). After cooling to 0 °C, Tf_2O (1.63 mL, 9.66 mmol) was added. The reaction was warmed to rt, stirred at rt for 30 min, cooled to 0 °C, and 30 mL of DCM and 50 mL of water were added. The organic phase was collected, dried over Na_2SO_4, concentrated, and subjected to silica gel chromatography purification (0−10% EtOAc in hexanes) to produce **4** (3.00 g, 6.38 mmol, 99% yield) as a colorless oil. ^{1}H NMR (500 MHz, chloroform-*d*): δ 8.60 (d, *J* = 2.2 Hz, 1H), 8.22 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 4.49−4.45 (m, 2H), 1.64 (s, 9H), 1.18−1.13 (m, 2H), 0.11 (s, 9H).

*3-tert-Butyl 1-(2-(Trimethylsilyl)ethyl) 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)isophthalate (**5**).* Into the reaction vessel was added **4** (2.30 g, 4.89 mmol), 4,4,4′,4′,5,5, 5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (1.34 g, 5.28 mmol), and 1,4-dioxane (30 mL). $PdCl_2$(dppf)-CH_2Cl_2 (0.20 g, 0.244 mmol) and KOAc (1.20 g, 12.2 mmol) were subsequently added and the reaction mixture was degassed by bubbling N_2 for 10 min. The reaction was stirred at 65 °C for 3 h, cooled to rt, diluted with 1:1:0.01 EtOAc/hexane/Et_3N (50 mL), filtered through SiO_2 (15 g, 200 mL 1:1:0.01 EtOAc/hexane/Et_3N as eluent), and concentrated to produce **5** (2.10 g, 4.69 mmol, 96%) as a brown solid. Compound **5** was used in the next step without further purification. *m*/*z* obs 449.4 $[M + H]^+$. ^{1}H NMR (500 MHz, chloroform-*d*): δ 8.44 (d, *J* = 0.8 Hz, 1H), 8.12 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 4.47−4.44 (m, 2H), 1.61 (s, 9H), 1.43 (s, 12H), 1.17−1.14 (m, 2H).

*2-tert-Butyl 2′-(2,2,2-Trichloroethyl) 4-(2-(Trimethylsilyl)ethyl) 5′-Chloro-[1,1′-biphenyl]-2,2′,4-tricarboxylate (**7**).* To a reaction vessel containing **5** (1.55 g, 3.46 mmol) was added **6** (1.59 g, 4.33 mmol), toluene (42 mL), $PdCl_2$(dppf)-CH_2Cl_2 (0.127 g, 0.173 mmol), and Na_2CO_3 (2 M, 6.61 mL, 13.2 mmol). The reaction mixture was degassed by bubbling with N_2 for 10 min, stirred at 65 °C for 12 h, cooled to rt, concentrated, and subjected to silica gel chromatography purification (0−10% EtOAc in hexanes) to produce **7** (1.20 g, 1.97 mmol, 57% yield) as a white solid. *m*/*z* obs 606.7 $[M + H]^+$. ^{1}H NMR (500 MHz, chloroform-*d*): δ 8.63 (d, *J* = 1.7 Hz, 1H), 8.16 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.25 (d, *J* = 2.5 Hz, 2H), 4.72 (s, 2H), 4.49−4.45 (m, 2H), 1.26 (s, 9H), 1.19−1.15 (m, 2H), 0.11 (s, 9H).

*2-(tert-Butyl) 4-(2-(Trimethylsilyl)ethyl) 5′-chloro-2′-((3-fluoro-4-methoxyphenyl)-carbamoyl)-[1,1′-biphenyl]-2,4-dicarboxylate (**8**).* Into the reaction vessel was added **7** (250 mg, 0.411 mmol), THF (5 mL), sat NH_4Cl solution (2.5 mL), and Zn (134 mg, 2.06 mmol). The reaction was stirred vigorously at rt for 1 h and extracted with EtOAc (10 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated. This crude product was dissolved in DCM (10 mL) and filtered to remove insoluble impurities. After concentration, the crude acid was used in the subsequent step without further purification. *m*/*z* obs 477.1 $[M + H]^+$. The crude acid was dissolved in DCM (6 mL). 3-Fluoro-4-methoxyaniline (116 mg, 0.822 mmol), DIEA (0.215 mL, 1.23 mmol), and HATU (172 mg, 0.452 mmol) were added subsequently. After stirring at rt for 12 h, the mixture was concentrated and subjected to silica gel chromatography purification (0−90% EtOAc in hexanes) to produce **8** (178 mg, 0.297 mmol, 72% yield). *m*/*z* obs 600.1 $[M + H]^+$. ^{1}H NMR (500 MHz, chloroform-*d*): δ 8.44 (s, 1H), 8.40 (d, *J* = 1.7 Hz, 1H), 8.08 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.49 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.17−7.12 (m, 2H), 6.79−6.75 (m, 2H), 4.48−4.43 (m, 2H), 3.81 (s, 3H), 1.46 (s, 9H), 1.18−1.13 (m, 2H), 0.09 (s, 9H).

*(S)-5′-Chloro-2′-((3-fluoro-4-methoxyphenyl)carbamoyl)-4-((2-hydroxy-1-phenylethyl)carbamoyl)-[1,1′-biphenyl]-2-carboxylic Acid (**9a**).* ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.87 (br d, *J* = 8.2 Hz, 1H), 8.23 (br s, 1H), 7.85 (br d, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.44−7.36 (m, 3H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.24−7.19 (m, 1H), 7.18−7.04 (m, 4H), 7.02−6.97 (m, 1H), 5.10−5.02 (m, 1H), 4.94 (t, *J* = 6.0 Hz, 1H), 3.74 (s, 3H), 3.72−3.67 (m, 1H), 3.66−3.59 (m, 1H). Purity >99% (method A). HRMS (ESI): calcd for $C_{30}H_{25}ClFN_2O_6$ $[M + H]^+$, 563.1380; found, 563.1360.

*(S)-5′-Chloro-2′-((3-fluoro-4-methoxyphenyl)carbamoyl)-4-((2-methoxy-1-phenylethyl)-carbamoyl)-[1,1′-biphenyl]-2-carboxylic Acid (**9b**).* ^{1}H NMR (500 MHz, chloroform-*d*): δ 8.51−8.40 (m, 2H), 7.96−7.91 (m, 1H), 7.63 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.40−7.28 (m, 7H), 7.17−7.08 (m, 2H), 6.89−6.84 (m, 1H), 6.77−6.70 (m, 1H), 5.42−5.36 (m, 1H), 3.84−3.75 (m, 5H), 3.38 (s, 3H). Purity >99% (method A). HRMS (ESI): calcd for $C_{31}H_{27}ClFN_2O_6$ $[M + H]^+$, 577.1536; found, 577.1526.

*(R)-5′-Chloro-2′-((3-fluoro-4-methoxyphenyl)carbamoyl)-4-((2-methoxy-1-phenylethyl)carbamoyl)-[1,1′-biphenyl]-2-carboxylic Acid (**9c**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.41 (d, *J* = 1.7 Hz, 1H), 8.00 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.44−7.31 (m, 5H), 7.31−7.23 (m, 3H), 6.99−6.91 (m, 2H), 5.34 (dd, *J* = 8.6, 5.0 Hz, 1H), 3.80 (s, 3H), 3.76 (dd, *J* = 10.1, 8.6 Hz, 1H), 3.67 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.39 (s, 3H). Purity >99% (method B). HRMS (ESI): calcd for $C_{31}H_{27}ClFN_2O_6$ $[M + H]^+$, 577.1536; found, 577.1523.

*(R)-5′-Chloro-2′-((3-fluoro-4-methoxyphenyl)carbamoyl)-4-((1-phenylbutyl)carbamoyl)-[1,1′-biphenyl]-2-carboxylic Acid (**9d**).* ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.95 (d, *J* = 8.3 Hz, 1H), 8.32 (d, *J* = 1.1 Hz, 1H), 7.99−7.95 (m, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.57 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.45−7.37 (m, 3H), 7.34−7.25 (m, 4H), 7.24−7.19 (m, 1H), 7.16 (br d, *J* = 8.5 Hz, 1H), 7.03 (t, *J* = 9.4 Hz, 1H), 5.03 (td, *J* = 8.7, 6.2 Hz, 1H), 3.76 (s, 3H), 1.92−1.83 (m, 1H), 1.76−1.67 (m, 1H), 1.44−1.35 (m, 1H), 1.33−1.24 (m, 1H), 0.90 (t, *J* = 7.3 Hz, 3H). Purity 99% (method B). *m*/*z* obs 575.0 $[M + H]^+$.

*(R)-2-tert-Butyl 2′-(2,2,2-Trichloroethyl) 5′-Chloro-4-((1-phenylbutyl) carbamoyl)-[1,1′-biphenyl]-2,2′-dicarboxylate (**10**).* Into the reaction vessel was added **7** (600 mg, 0.986 mmol), THF (9.86 mL), and TBAF (4.93 mL, 4.93 mmol). The reaction was stirred at rt for 30 min, quenched with sat NH_4Cl (20 mL), and extracted with EtOAc (25 mL × 3). The combined organic phase was dried over sodium sulfate, filtered, and concentrated to yield the corresponding acid. Into the reaction vessel containing the crude acid was added (*R*)-1-phenylbutan-1-amine (147 mg, 0.986 mmol), DIEA (0.517 mL, 2.96 mmol), DCM (10 mL), and HATU (487 mg, 1.28 mmol). The reaction was stirred at rt for 12 h and concentrated. Silica gel chromatography (0−20% EtOAc in hexanes) produced **10** (475 mg, 0.743 mmol, 75% yield) as a white solid. *m*/*z* obs 637.8 $[M + H]^+$. ^{1}H NMR (500 MHz, chloroform-*d*): δ 8.31 (d, *J* = 9.4 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 8.05−7.97 (m, 1H), 7.52−7.48 (m, 1H), 7.38 (d, *J* = 5.0 Hz, 4H), 7.26−7.22 (m, 3H), 6.45 (br d, *J* = 6.1 Hz, 1H), 5.31 (s, 2H), 5.20 (q, *J* = 7.4 Hz, 1H), 4.74−4.69 (m, 2H), 1.99−1.87 (m, 2H), 1.46−1.41 (m, 2H), 1.21 (s, 9H), 0.98 (t, *J* = 7.3 Hz, 3H).

*2′-(1H-1,3-Benzodiazol-2-yl)-5′-chloro-4-{[(1R)-1-phenylbutyl]-carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**11a**).* Into the reaction vessel was added **10** (475 mg, 0.743 mmol), THF (7.43 mL), sat NH_4Cl solution (3 mL), and Zn (243 mg, 3.71 mmol). The reaction was stirred vigorously at rt for 1 h and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated to produce crude carboxylic acid as a white solid (339 mg, 0.667 mmol, 90% yield), which was used in the subsequent step without further purification. *m*/*z* obs 508.1 $[M + H]^+$. Into the reaction vessel was added crude carboxylic acid (18 mg, 0.035 mmol), 4-methoxy-benzene-1,2-diamine (9.79 mg, 0.071 mmol), DIEA (0.031 mL, 0.177 mmol), DCM (1 mL), and HATU (20.2 mg, 0.053 mmol). The reaction was stirred at rt for 12 h, concentrated, and dissolved in AcOH (1 mL)/water (0.1 mL). After stirring at 85 °C for 12 h, the reaction was cooled to rt, concentrated, and subjected to preparative HPLC purification to produce **11a** (16.3 mg, 0.024 mmol, 69% yield). ^{1}H NMR (500 MHz, methanol-d_4): δ 8.30 (s, 1H), 7.93 (br d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.70 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.58 (dd, *J* = 6.1, 3.2 Hz, 2H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.46−7.40 (m, 2H), 7.39−7.35 (m, 3H), 7.34−7.29 (m, 2H), 7.26−7.21 (m, 1H), 5.07 (dd, *J* = 8.8, 6.5 Hz, 1H), 1.93−1.86 (m, 1H),

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1.85−1.79 (m, 1H), 1.48−1.39 (m, 1H), 1.38−1.31 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H). Purity 95% (method B). HRMS (ESI): calcd for $C_{31}H_{27}ClN_3O_3$ $[M + H]^+$, 524.1735; found, 524.1722.

*5′-Chloro-2′-(5-chloro-1H-1,3-benzodiazol-2-yl)-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**11b**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.33 (d, J = 1.7 Hz, 1H), 7.98 (br d, J = 7.9 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 8.3, 2.1 Hz, 1H), 7.58 (d, J = 1.5 Hz, 1H), 7.55−7.51 (m, 2H), 7.43−7.36 (m, 4H), 7.34−7.29 (m, 2H), 7.26−7.21 (m, 1H), 5.08 (dd, J = 8.9, 6.6 Hz, 1H), 1.96−1.88 (m, 1H), 1.86−1.78 (m, 1H), 1.49−1.40 (m, 1H), 1.39−1.30 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H). Purity 96% (method B). HRMS (ESI): calcd for $C_{31}H_{26}Cl_2N_3O_3$ $[M + H]^+$, 558.1346; found, 558.1333.

*5′-Chloro-2′-(5-methyl-1H-1,3-benzodiazol-2-yl)-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**11c**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.32 (br d, J = 2.4 Hz, 1H), 7.99 (br t, J = 6.0 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.73 (dd, J = 8.3, 2.1 Hz, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.46−7.39 (m, 2H), 7.39−7.30 (m, 5H), 7.26−7.20 (m, 1H), 5.08 (dd, J = 8.9, 6.6 Hz, 1H), 2.48 (s, 3H), 1.94−1.88 (m, 1H), 1.85−1.78 (m, 1H), 1.48−1.40 (m, 1H), 1.39−1.32 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H). Purity 96% (method B). HRMS (ESI): calcd for $C_{32}H_{29}ClN_3O_3$ $[M + H]^+$, 538.1892; found, 538.1879.

*5′-Chloro-2′-(5-methoxy-1H-1,3-benzodiazol-2-yl)-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**11d**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.97 (br d, J = 8.3 Hz, 1H), 8.37 (dd, J = 4.8, 1.5 Hz, 1H), 8.08−8.01 (m, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.74 (dd, J = 8.4, 2.1 Hz, 1H), 7.59 (s, 1H), 7.53 (d, J = 9.1 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.40−7.36 (m, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.27−7.20 (m, 1H), 7.16 (dd, J = 9.1, 2.2 Hz, 1H), 7.08 (d, J = 2.2 Hz, 1H), 5.12−5.05 (m, 1H), 3.85 (s, 3H), 1.95−1.88 (m, 1H), 1.86−1.79 (m, 1H), 1.49−1.40 (m, 1H), 1.39−1.31 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H). Purity 100% (method A). HRMS (ESI): calcd for $C_{32}H_{29}ClN_3O_4$ $[M + H]^+$, 554.1841; found, 554.1827.

*5′-Chloro-2′-(4-methyl-1H-1,3-benzodiazol-2-yl)-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**11e**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.27 (s, 1H), 7.98 (br d, J = 7.2 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 8.3, 2.1 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.40−7.34 (m, 4H), 7.31 (t, J = 7.6 Hz, 3H), 7.27−7.21 (m, 1H), 5.07 (dd, J = 8.8, 6.5 Hz, 1H), 2.53 (s, 3H), 1.93−1.87 (m, 1H), 1.85−1.78 (m, 1H), 1.48−1.40 (m, 1H), 1.37−1.30 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H). Purity > 95% (method B). HRMS (ESI): calcd for $C_{32}H_{29}ClN_3O_3$ $[M + H]^+$, 538.1892; found, 538.1877.

*5′-Chloro-2′-{1H-imidazo[4,5-c]pyridin-2-yl}-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**11f**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 9.02 (s, 1H), 8.43 (d, J = 6.6 Hz, 1H), 8.34 (dd, J = 11.6, 1.7 Hz, 1H), 8.02−7.95 (m, 2H), 7.92 (d, J = 8.2 Hz, 1H), 7.67 (dd, J = 8.4, 2.1 Hz, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.43−7.37 (m, 3H), 7.33 (br t, J = 6.9 Hz, 2H), 7.27−7.20 (m, 1H), 5.13−5.08 (m, 1H), 1.98−1.90 (m, 1H), 1.88−1.79 (m, 1H), 1.53−1.43 (m, 1H), 1.42−1.32 (m, 1H), 0.99 (t, J = 7.2 Hz, 3H). Purity > 99% (method B). HRMS (ESI): calcd for $C_{30}H_{26}ClN_4O_3$ $[M + H]^+$, 525.1688; found, 525.1679.

*5′-Chloro-2′-(5-phenyl-1H-imidazol-2-yl)-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**11g**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.96 (br d, J = 8.3 Hz, 1H), 8.39 (br d, J = 1.4 Hz, 1H), 8.09 (br t, J = 7.3 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.73−7.69 (m, 2H), 7.62−7.55 (m, 3H), 7.50 (br d, J = 8.3 Hz, 1H), 7.45 (br s, 3H), 7.41−7.36 (m, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.26−7.21 (m, 1H), 5.15−5.07 (m, 1H), 1.97−1.89 (m, 1H), 1.87−1.80 (m, 1H), 1.50−1.41 (m, 1H), 1.41−1.33 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). Purity 98% (method B). m/z obs 550.0 $[M + H]^+$.

*(R)-2′-(Benzo[d]oxazol-2-yl)-5′-chloro-4-((1-phenylbutyl)-carbamoyl)-[1,1′-biphenyl]-2-carboxylic Acid (**11h**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.45 (d, J = 1.7 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.98 (dd, J = 7.9, 1.8 Hz, 1H), 7.60 (dd, J = 8.4, 2.1 Hz, 1H), 7.59−7.56 (m, 1H), 7.47−7.40 (m, 3H), 7.39−7.35 (m, 3H), 7.33−7.25 (m, 4H), 5.15 (dd, J = 8.9, 6.4 Hz, 1H), 2.03−1.95 (m, 1H), 1.92−1.84 (m, 1H), 1.57−1.47 (m, 1H), 1.47−1.39 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H). Purity 100% (method A). HRMS (ESI): calcd for $C_{31}H_{26}ClN_2O_4$ $[M + H]^+$, 525.1576; found, 525.1562.

*2′-(1H-1,3-Benzodiazol-2-yl)-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**12a**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.29 (s, 1H), 7.96 (br d, J = 7.8 Hz, 1H), 7.88 (dd, J = 7.6, 1.1 Hz, 1H), 7.82−7.77 (m, 1H), 7.74−7.69 (m, 1H), 7.64 (dd, J = 6.3, 3.2 Hz, 2H), 7.56−7.49 (m, 3H), 7.41 (d, J = 7.9 Hz, 1H), 7.39−7.35 (m, 2H), 7.34−7.29 (m, 2H), 7.26−7.20 (m, 1H), 5.08 (dd, J = 8.8, 6.5 Hz, 1H), 1.96−1.87 (m, 1H), 1.86−1.78 (m, 1H), 1.49−1.40 (m, 1H), 1.39−1.31 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H); purity 97% (method B). HRMS (ESI): calcd for $C_{31}H_{28}N_3O_3$ $[M + H]^+$, 490.2125; found, 490.2113.

*2′-(1H-1,3-Benzodiazol-2-yl)-5′-methyl-4-{[(1R)-1-phenylbutyl]-carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**12b**).* ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.96 (d, J = 8.3 Hz, 1H), 8.27 (d, J = 1.9 Hz, 1H), 8.00 (dd, J = 8.0, 1.4 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.55 (dd, J = 6.1, 3.0 Hz, 2H), 7.48 (d, J = 7.7 Hz, 1H), 7.41−7.37 (m, 2H), 7.35−7.29 (m, 5H), 7.25−7.19 (m, 2H), 5.07−4.98 (m, 1H), 2.45 (s, 3H), 1.92−1.82 (m, 1H), 1.76−1.67 (m, 1H), 1.43−1.33 (m, 1H), 1.31−1.23 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H). Purity 96% (method B). HRMS (ESI): calcd for $C_{32}H_{30}N_3O_3$ $[M + H]^+$, 504.2282; found, 504.2271.

*2′-(1H-1,3-Benzodiazol-2-yl)-5′-methoxy-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**12c**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.26 (s, 1H), 7.92 (br d, J = 7.8 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.67−7.59 (m, 2H), 7.53−7.48 (m, 2H), 7.40−7.32 (m, 5H), 7.28−7.23 (m, 2H), 7.06 (d, J = 2.4 Hz, 1H), 5.10 (dd, J = 8.9, 6.4 Hz, 1H), 3.95 (s, 3H), 1.98−1.89 (m, 1H), 1.87−1.78 (m, 1H), 1.50−1.42 (m, 1H), 1.40−1.33 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H). Purity 96% (method B). HRMS (ESI): calcd for $C_{32}H_{30}N_3O_4$ $[M + H]^+$, 520.2231; found, 520.2224.

*(R)-2′-(1H-Benzo[d]imidazole-2-yl)-3′-chloro-4-((1-phenylbutyl)-carbamoyl)-[1,1′-biphenyl]-2-carboxylic Acid (**12d**).* ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.85 (br d, J = 8.3 Hz, 1H), 8.17 (d, J = 1.4 Hz, 1H), 7.83−7.77 (m, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.63−7.54 (m, 1H), 7.48−7.42 (m, 2H), 7.35−7.26 (m, 5H), 7.24−7.19 (m, 2H), 7.15−7.11 (m, 2H), 5.00−4.88 (m, 1H), 1.85−1.75 (m, 1H), 1.71−1.62 (m, 1H), 1.39−1.26 (m, 1H), 1.24−1.18 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H). Purity 100% (method B). m/z obs 524.0 $[M + H]^+$.

*2′-(1H-1,3-Benzodiazol-2-yl)-4′-chloro-4-{[(1R)-1-phenylbutyl]-carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**12e**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.32 (s, 1H), 7.99 (br d, J = 7.2 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.79 (dd, J = 8.4, 2.3 Hz, 1H), 7.65−7.60 (m, 2H), 7.53−7.48 (m, 3H), 7.44 (d, J = 7.9 Hz, 1H), 7.38−7.34 (m, 2H), 7.34−7.28 (m, 2H), 7.25−7.21 (m, 1H), 5.07 (dd, J = 8.9, 6.6 Hz, 1H), 1.95−1.87 (m, 1H), 1.85−1.78 (m, 1H), 1.48−1.39 (m, 1H), 1.38−1.29 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H). Purity 96% (method B). HRMS (ESI): calcd for $C_{31}H_{27}ClN_3O_3$ $[M + H]^+$, 524.1735; found, 524.1724.

*2′-(1H-1,3-Benzodiazol-2-yl)-6′-chloro-4-{[(1R)-1-phenylbutyl]-carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**12f**).* Into the reaction vessel was added **SI14** (301 mg, 0.577 mmol), THF (10 mL), water (5 mL), and LiOH·H_2O (121 mg, 2.88 mmol). The reaction was stirred at rt for 1 day, diluted with EtOAc (30 mL), and washed with 20 mL of sat NH_4Cl containing 2.88 mmol HCl. The organic phase was dried over Na_2SO_4 and concentrated to produce crude 2′-(*tert*-butoxycarbonyl)-6-chloro-4′-(((*R*)-1-phenylbutyl)carbamoyl)-[1,1′-biphenyl]-2-carboxylic acid (293 mg, 0.577 mmol, 100% yield), which was used for the next step without further purification. Into the reaction vessel was added the crude carboxylic acid (293 mg, 0.577 mmol), benzene-1,2-diamine (125 mg, 1.154 mmol), DIEA (0.302 mL, 1.730 mmol), DCM (5 mL), and HATU (285 mg, 0.750 mmol). The reaction was stirred at rt for 12h, concentrated, and dissolved in AcOH (4.5 mL)/water (0.5 mL). After stirring at 85 °C for 12 h, the reaction was cooled to rt and concentrated. Preparative HPLC purification of the resulting residue produced **12f** (300 mg, 0.471 mmol, 82% yield). ^{1}H NMR (500 MHz, methanol-d_4): δ 8.34 (dd, J = 3.5, 1.8 Hz, 1H), 7.84−7.80 (m, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.74 (dd, J = 8.1, 1.1 Hz, 1H), 7.63−7.58 (m, 1H), 7.53−7.48 (m, 2H), 7.37−7.33 (m, 2H), 7.33−7.27 (m, 4H), 7.25−7.20 (m, 1H), 7.17 (d,

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J = 7.9 Hz, 1H), 5.08−5.02 (m, 1H), 1.93−1.84 (m, 1H), 1.83−1.75 (m, 1H), 1.48−1.39 (m, 1H), 1.36−1.32 (m, 1H), 0.98−0.93 (m, 3H). Purity >95% (method B). m/z obs 524.2 $[M + H]^+$.

*2′-(1H-1,3-Benzodiazol-2-yl)-6′-fluoro-4-{[(1R)-1-phenylbutyl]-carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**12g**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.47 (d, J = 1.8 Hz, 0.5H), 8.45 (d, J = 1.8 Hz, 0.5H), 7.93−7.88 (m, 1H), 7.76−7.71 (m, 2H), 7.64−7.60 (m, 2H), 7.57−7.52 (m, 1H), 7.51−7.46 (m, 2H), 7.38−7.34 (m, 2H), 7.33−7.29 (m, 3H), 7.26−7.20 (m, 1H), 5.10−5.04 (m, 1H), 1.93−1.86 (m, 1H), 1.84−1.77 (m, 1H), 1.48−1.40 (m, 1H), 1.38−1.31 (m, 1H), 0.99−0.93 (m, 3H). Purity 97% (method B). HRMS (ESI): calcd for $C_{31}H_{27}FN_3O_3$ $[M + H]^+$, 508.2031; found, 508.2026.

*2′-(1H-1,3-Benzodiazol-2-yl)-6′-methyl-4-{[(1R)-1-phenylbutyl]-carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**12h**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.34 (dd, J = 6.0, 1.8 Hz, 1H), 7.93 (ddd, J = 7.9, 5.9, 1.9 Hz, 1H), 7.68 (dd, J = 10.5, 7.5 Hz, 2H), 7.64−7.57 (m, 3H), 7.50 (ddd, J = 6.2, 3.2, 1.1 Hz, 2H), 7.37−7.29 (m, 5H), 7.25−7.20 (m, 1H), 5.10−5.04 (m, 1H), 2.10 (s, 3H), 1.93−1.85 (m, 1H), 1.84−1.77 (m, 1H), 1.46−1.38 (m, 1H), 1.36−1.29 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H). Purity >95% (method B). HRMS (ESI): calcd for $C_{32}H_{30}N_3O_3$ $[M + H]^+$, 504.2282; found, 504.2272.

Preparation of **15a** and **15b** via chiral SFC purification: **12f** was subjected to the chiral SFC purification condition below to afford optically pure compounds **15a** (second eluting peak) and **15b** (first eluting peak)—instrument: PIC solution 200 SFC; column: Chiralpak AD-H, 21 × 250 mm, 5 μm; mobile phase: 22% EtOH/78% CO_2; flow conditions: 45 mL/min, 150 bar, 40 °C; detector wavelength: 220 nm; injection details: 0.5 mL of ∼27 mg/mL in EtOH/MeCN. **15a**, RT = 8.37 min; **15b**, RT = 6.28 min.

*(S)-2′-(1H-1,3-Benzodiazol-2-yl)-6′-chloro-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**15a**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.43 (d, J = 1.8 Hz, 1H), 7.92 (dd, J = 8.0, 1.9 Hz, 1H), 7.84 (td, J = 8.5, 1.1 Hz, 2H), 7.69−7.65 (m, 1H), 7.63−7.58 (m, 2H), 7.49−7.46 (m, 2H), 7.36−7.28 (m, 5H), 7.24−7.20 (m, 1H), 5.05 (dd, J = 8.9, 6.6 Hz, 1H), 1.92−1.85 (m, 1H), 1.84−1.75 (m, 1H), 1.47−1.38 (m, 1H), 1.37−1.30 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, methanol-d_4): δ 167.6, 167.0, 148.7, 143.0, 140.3, 139.2, 135.5, 134.2, 132.9, 132.4, 132.3, 131.1, 130.3, 129.4, 129.3, 128.6, 128.1, 126.8, 126.3, 126.0, 125.9, 113.9, 54.1, 37.8, 19.5, 12.6. Purity: >99% (chiral analytical chromatographic condition: Berger analytical SFC; Chiralpak AD-H, 4.6 × 250 mm, 5 μm; 20% EtOH/80% CO_2; 2 mL/min, 150 bar, 40 °C; injection details: 5 μL of 1 mg/mL in ACN); HRMS (ESI): calcd for $C_{31}H_{27}ClN_3O_3$ $[M + H]^+$, 524.1735; found, 524.1727. $[\alpha]_D^{20}$ = −38.4° (C = 0.5, MeOH). Full crystallographic data for compound **15a** have been deposited to the Cambridge Crystallographic Data Center (CCDC reference no. CCDC 1918519) and can be obtained free of charge via the internet at http://www.ccdc.cam.ac.uk.

*(R)-2′-(1H-1,3-Benzodiazol-2-yl)-6′-chloro-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**15b**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.30 (d, J = 1.7 Hz, 1H), 7.78 (dd, J = 8.0, 1.9 Hz, 1H), 7.75 (dd, J = 7.6, 1.1 Hz, 1H), 7.69 (dd, J = 8.2, 1.1 Hz, 1H), 7.59−7.54 (m, 1H), 7.49−7.44 (m, 2H), 7.37−7.33 (m, 2H), 7.32−7.28 (m, 2H), 7.26−7.19 (m, 3H), 7.11 (d, J = 7.9 Hz, 1H), 5.05 (dd, J = 8.9, 6.5 Hz, 1H), 1.92−1.83 (m, 1H), 1.82−1.74 (m, 1H), 1.48−1.38 (m, 1H), 1.36−1.28 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, methanol-d_4): δ 169.9, 167.4, 150.6, 143.1, 139.8, 139.7, 136.5, 134.9, 134.5, 134.0, 131.1, 130.6, 130.2, 129.3, 129.0, 128.3, 128.1, 128.1, 126.7, 126.3, 123.3, 114.4, 53.9, 37.9, 19.5, 12.7. Purity: >99% (chiral analytical chromatographic condition: Berger analytical SFC; Chiralpak AD-H, 4.6 × 250 mm, 5 μm; 20% EtOH/80% CO_2; 2 mL/min, 150 bar, 40 °C; injection details—5 μL of 1 mg/mL in ACN); HRMS (ESI): calcd for $C_{31}H_{27}ClN_3O_3$ $[M + H]^+$, 524.1735; found, 524.1725. $[\alpha]_D^{20}$ = +43.3° (C = 0.43, MeOH). Full crystallographic data for compound **15b** have been deposited to the Cambridge Crystallographic Data Center (CCDC reference no. CCDC 1918520) and can be obtained free of charge via the internet at http://www.ccdc.cam.ac.uk.

*(S)-2′-Chloro-6′-(5-methoxy-1H-1,3-benzodiazol-2-yl)-4-{[(1R)-1-phenylbutyl]carbamoyl}-[1,1′-biphenyl]-2-carboxylic Acid (**15c**).* ^{1}H NMR (500 MHz, methanol-d_4): δ 8.97 (br d, J = 8.0 Hz, 1H), 8.47 (d, J = 1.9 Hz, 1H), 7.95 (dd, J = 8.0, 1.9 Hz, 1H), 7.88 (dd, J = 8.3, 1.1 Hz, 1H), 7.83 (dd, J = 7.7, 1.1 Hz, 1H), 7.74−7.66 (m, 1H), 7.52 (d, J = 9.4 Hz, 1H), 7.37−7.34 (m, 2H), 7.33−7.29 (m, 3H), 7.25−7.20 (m, 1H), 7.15 (dd, J = 9.1, 2.5 Hz, 1H), 7.07 (d, J = 2.2 Hz, 1H), 5.10−5.03 (m, 1H), 3.84 (s, 3H), 1.95−1.86 (m, 1H), 1.85−1.77 (m, 1H), 1.49−1.39 (m, 1H), 1.39−1.30 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H). Purity 95% (method A). HRMS (ESI): calcd for $C_{32}H_{29}ClN_3O_4$ $[M + H]^+$, 554.1841; found, 554.1828.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.9b01513.

Supplementary synthetic schemes, experimental protocols, synthesis of **12a−h**, synthesis of **15a** via intermediate **14**, assay condition, summary of *PV*-loop study, biotransformation study on the analogue of **9b**, details on HTP screening, and NMR spectra and HPLC traces (PDF).

Molecular formula strings for the final compounds (CSV)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

In memory of Atsu Apedo (1968−2017) and William Schumacher (1952−2018).

■ ABBREVIATIONS

HF, heart failure; CO, cardiac output; *PV*-loop, pressure−volume loop; SAR, structure−activity relationship; SFC, supercritical fluid chromatography; BPA, biphenyl acid; APJ-R, APJ receptor

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