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Potent, selective, and orally bioavailable matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis

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Abstract—Modification of α-biphenylsulfonamidocarboxylic acids led to potent and selective MMP-13 inhibitors. Compound **16** showed 100% oral bioavailability in rats and demonstrated >50% inhibition of bovine cartilage degradation at 10 ng/mL.

1. Introduction

Osteoarthritis (OA), characterized by the breakdown of the joint's cartilage, chronic joint pain, and inflammation, affects an estimated 20 million people in the United States. Current treatments, such as NSAIDs (including COX-2 inhibitors), although effective in relieving the pain of OA, fail to halt the progression of this disease. Matrix metalloproteinase-13 (MMP-13 or collagenase-3) efficiently and irreversibly cleaves type II collagen, the main structural component of the cartilage matrix, and is over-expressed in OA patient cartilage.[1,2] Agents that inhibit this enzyme therefore offer a potential therapy that could alter the progression of osteoarthritis.

Research on MMP inhibition has attracted tremendous attention in both academia and the pharmaceutical industry.[3–6] Biphenylsulfonamide carboxylate MMP inhibitors have been disclosed by a number of investigators.[7–9] At Wyeth, we have recently reported the structure-based design of a series of highly selective biphenylsulfonamide carboxylate MMP-13 inhibitors exemplified by **1**[10a] and **2**[10b] (Fig. 1). However, further development of these compounds was precluded by poor oral bioavailability, perhaps due to solubility and permeability issues.[11,12]

Herein, we report on the modification of the amide bond of the P1′ moiety of **1** and **2** as a means of improving pharmacokinetic (PK) properties with minimal structural change. Guided by evaluations of MMP-13 potency, rat iv clearance, and selectivity over MMP-2, our goal was to optimize the oral PK properties of this series of MMP-13 inhibitors, while retaining selectivity, to afford analogs suitable for further studies in animal models of OA. As MMP-2 is highly homologous to MMP-13 in and around the S1′ pocket, it was hoped that compounds that demonstrated selectivity over MMP-2 would also possess enhanced levels of selectivity over a wide variety of other MMPs.

2. Results

Table 1 compares the in vitro MMP-13 and MMP-2 inhibitory activities, as well as the rat iv clearance, of compounds **3**–**12** in which the linker joining the biphenyl sulfonamide and the benzofuran P1′ terminus has been varied. As compound **3**, the *R*-isomer of compound **1**, has a lower iv clearance (0.3 mL/min/kg) than **1** while

Keywords: MMP-13 inhibitor; Biphenylsulfonamide carboxylate; Benzofuran; Osteoarthritis.
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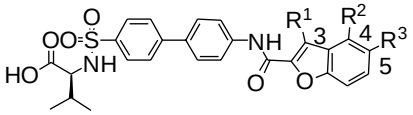
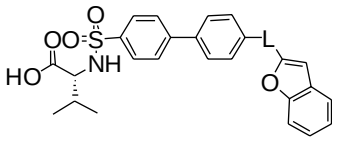
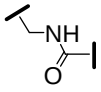
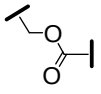
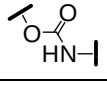


	R^1	R^2	R^3	MMP-13 IC_{50} (nM)
1	H	H	H	2.4
2	Me	OMe	Br	2.3

Figure 1. Biphenylsulfonamide carboxylate MMP-13 inhibitors.

Table 1. Modification of amide linkage



Compound	L	IC_{50} (nM)		
		MMP-13	MMP-2	Cl[a]
3		2.8	4.6	0.3
4		467	NT	NT
5		2.0	3.0	20
6		1.1	5.6	38
7		1.2	5.6	44
8		0.5	0.7	42
9		1.1	2.5	NT
10		1230	NT	NT
11		242	NT	NT
12		329	NT	NT

[a] Rat iv clearance (mL/min/kg). NT = not tested.

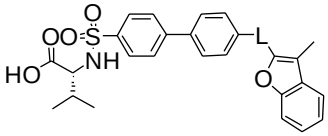
maintaining MMP-13 potency, all further structural modifications on the linker between the biphenyl backbone and the benzofuran were based on the D-valine biphenyl sulfonamide scaffold.

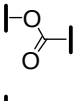
Interestingly, the *N*-methyl amide analog **4** was >150-fold less potent against MMP-13 than the NH-amide **3**, probably due to conformational change. However, other linkers, including sulfonate (**5**), sulfone (**6**), sulfoxide (**7**), ester (**8**), and ether (**9**) moieties, all provided potent inhibitors of MMP-13. Three-atom spacers (compounds **10**–**12**) between the biphenyl backbone and the benzofuran dramatically reduced MMP-13 inhibition.

While compounds **3** and **5**–**9** displayed good MMP-13 potency, they did not have appreciable selectivity over MMP-2. In addition, compounds **5**–**8** have a substantially higher rat iv clearance than amide-linked inhibitor **3**. The potential for a 3-substituent on the benzofuran ring to increase selectivity, as we had seen in the benzofuran 2-carboxamide series,[10b] and concomitantly affect clearance led to the synthesis of compounds **13**–**15**, which incorporate a methyl group at this position (Table 2). Selectivity for MMP-13 was modestly improved for all three analogs, but compound **15** also maintained potency against MMP-13 and displayed moderate clearance. Thus, compound **15** with its P1′ ether linkage was selected for further modification to improve selectivity against MMP-2.

In the series of amide-linked benzofuran P1′ inhibitors exemplified by structures **1** and **2**, 3,4,5-trisubstituted analogs such as **2** had excellent selectivity for MMP-13.[10b] We next sought to improve MMP-2 selectivity using a similar strategy by preparing analogs substituted at the 4- and 5-positions of the benzofuran ring (Table 3). Since the loop region of MMP-2 (e.g., PDB code 1QIB[13]) that forms its S1′ pocket is two amino acids shorter than the analogous region in MMP-13 (e.g., PDB code 830c[14]), the S1′ pocket of MMP-2 is constricted relative to that of MMP-13 (Fig. 2).[10] Molecular modeling suggested that incorporating a substituent at the 4-position of the benzofuran would take advantage of the difference in size between the S1′ pockets of MMP-2 and MMP-13, and enhance selectivity. Therefore, compounds **16**–**22** with an ether linkage to the benzofuran were synthesized.

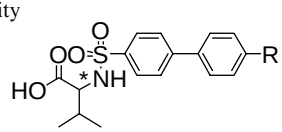
Table 2. C3-methylated benzofuran derivatives

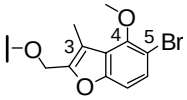
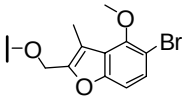
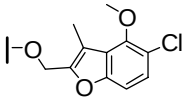
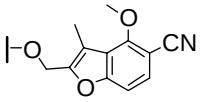
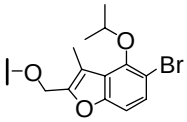
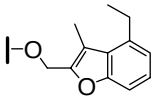
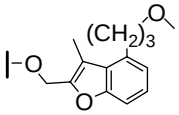
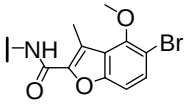


Compound	L	IC_{50} (nM)			
		MMP-13	MMP-2	MMP-2/ MMP-13	Cl[a]
13		17	164	10	NT
14		1.2	17	14	154
15		3.9	28	7	16

[a] Rat iv clearance (mL/min/kg). NT = not tested.

Table 3. Substitution on benzofuran for MMP-2 selectivity



Compound	R	*	IC_{50} (nM)			
			MMP-13	MMP-2	MMP-2/MMP-13	Cl[a]
16		*R*	1.8	135	75	5.2
17		*S*	1.4	136	95	NT
18		*S*	2.1	130	62	17
19		*S*	1.2	64	53	11
20		*R*	7.9	375	48	NT
21		*S*	1.2	207	177	NT
22		*S*	1.9	221	117	43
2		*S*	2.3	1700	740	21

[a] Rat iv clearance (mL/min/kg). NT = not tested.

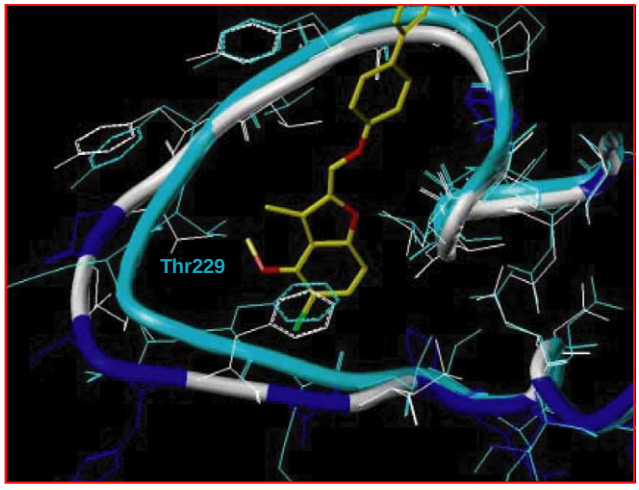


Figure 2. A close-up and schematic view of the predicted binding mode of compound **16** to MMP-13 overlaid with the catalytic domain of MMP-2. The white tube represents MMP-13, while the cyan tube represents MMP-2. The blue coloring in the MMP-13 tube highlights the positions of amino acid differences between the two proteins.

As shown in Table 3, analogs **16**–**20** with 3,4,5-trisubstitution of the benzofuran moiety improved selectivity over MMP-2 by approximately 10-fold relative to **15**. Contrary to what has been observed in the amide series,[10b] no significant difference in MMP-2 selectivity was observed for the two enantiomers **16** and **17**, possibly due to the flexibility of the ether linkage. A bulkier isopropoxy group at the 4-position of the benzofuran slightly reduced MMP-13 potency (**20**) and did not enhance selectivity. Interestingly, 3,4-disubstituted analogs **21** and **22** displayed improved selectivity over MMP-2, over 100-fold, relative to the 3,4,5-trisubstituted analogs while maintaining potency against MMP-13. Additional screening of compound **16** against a variety of MMPs showed moderate selectivity against MMP-2, -3, and -8, and greater than 500-fold selectivity over MMP-1, -7, -9, -14, and TACE (Table 4).[15]

Ether **16**[16] was further tested both iv and orally in male Sprague–Dawley rats.[11] This compound demonstrated low iv clearance (5.2 mL/min/kg at 2 mg/kg), significantly less than the iv clearance for amide **2**

Table 4. Inhibitory activities (IC_{50}, nM) of compound **16**

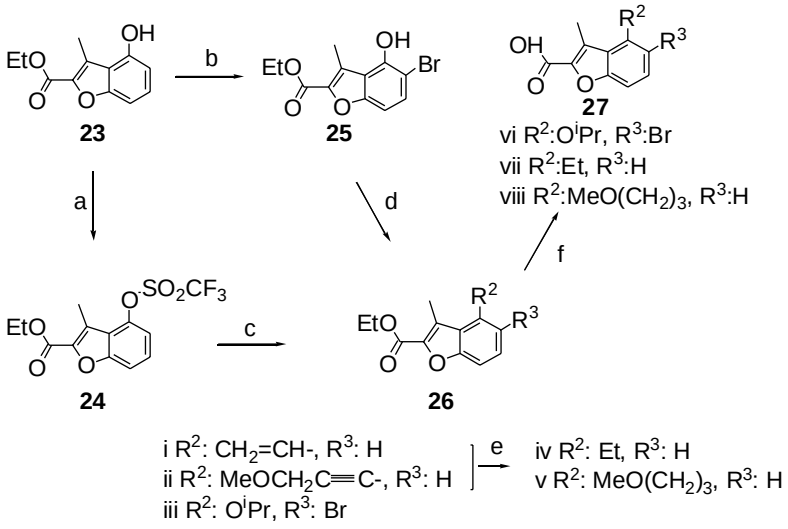
MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-14	TACE
>400,000	135	81	1100	42	>7000	5000	>25,000

(Table 3). Compound **16** was also 100% bioavailable when dosed orally at 20 mg/kg ($T_{1/2}$ = 197 min, C_{max} = 8.3 μg/mL, and AUC = 65.7 h*μg/mL). A 20 mg/kg oral dose maintained plasma levels at >1000 ng/mL for l2 h.

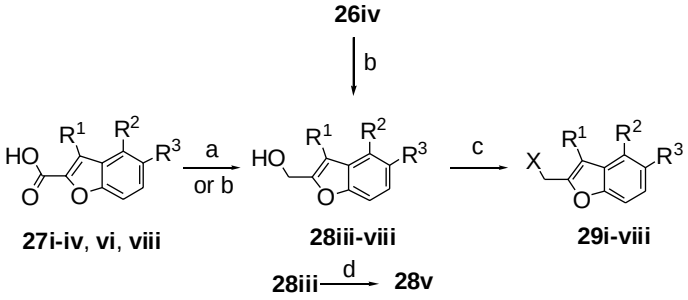
Because of its excellent potency and selectivity for MMP-13 and excellent oral bioavailability, compound **16** was further evaluated in a bovine cartilage explant assay[17] and demonstrated >50% inhibition of collagen degradation at a concentration of 10 ng/mL.

3. Synthesis

The compounds were synthesized as shown in Schemes 1–5. A variety of trisubstituted benzofuran carboxylates

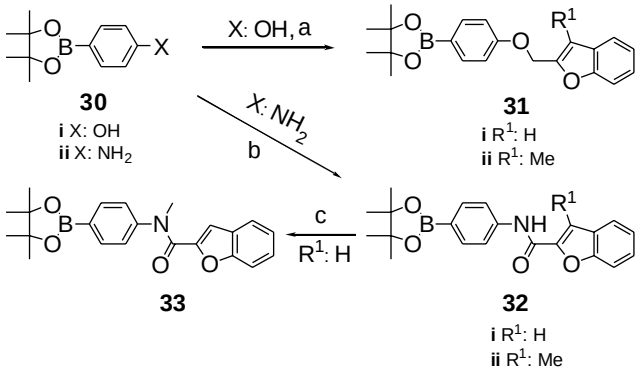


Scheme 1. Synthesis of substituted benzofuran carboxylates. Reagents and conditions: (a) Tf_2O, DIEA, DCM, 0 °C, 1 h (75%); (b) NBS, CCl_4, 0 °C, 6 h (67%); (c) **26i**, CH_2=$CHSnBu_3$, LiCl, $PdCl_2(PPh_3)_2$, DMF, 12 h (75%) and **26ii**, $MeOCH_2C$≡CH, $PdCl_2(PPh_3)_2$, DMF, 90 °C, 12 h (52%); (d) ^{i}PrBr, K_2CO_3, DMF, rt, 12 h (100%); (e) H_2, Pd/C, THF, 12 h (91–98%); (f) 1 N NaOH, MeOH, THF, 1 h (87–98%).

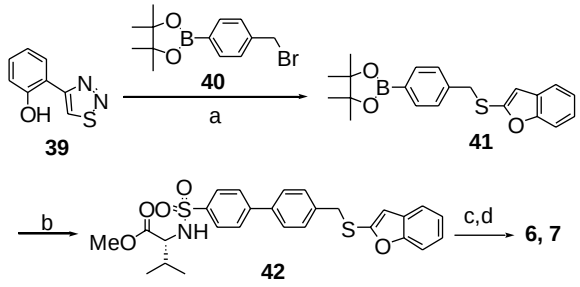


	R^1	R^2	R^3	X
i	H	H	H	Br
ii	Me	H	H	Cl
iii	Me	OMe	Br	Cl
iv	Me	OMe	Cl	Br
v	Me	OMe	CN	Br
vi	Me	O^{i}Pr	Br	Cl
vii	Me	Et	H	Br
viii	Me	$(CH_2)_3$OMe	H	Br

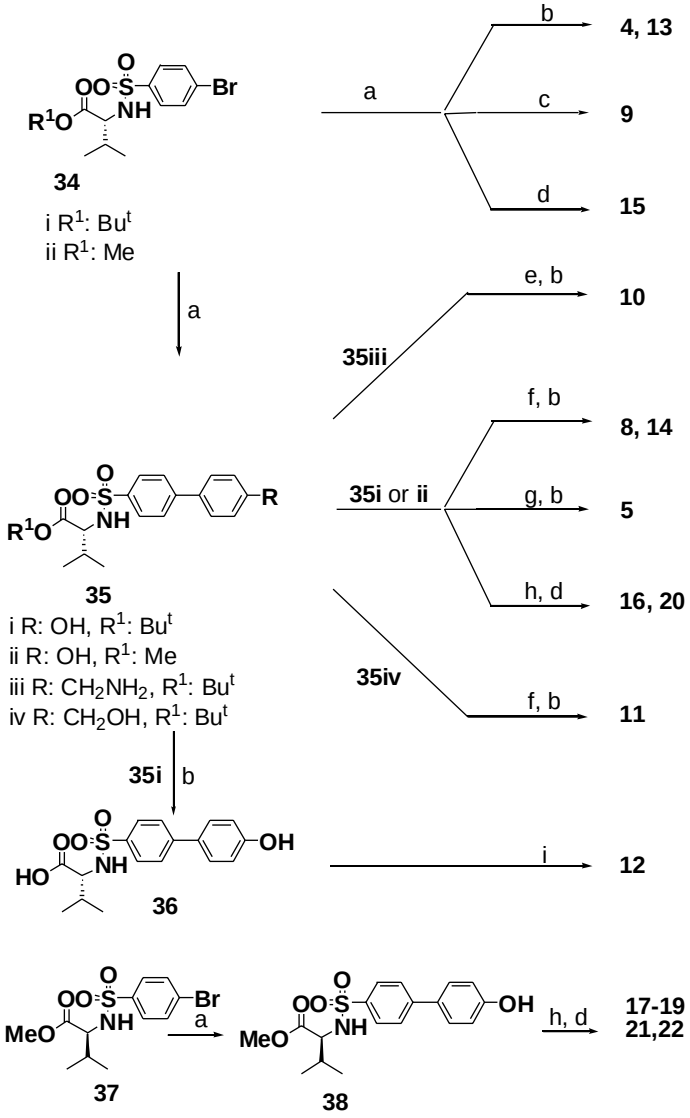
Scheme 2. Synthesis of substituted 2-(halomethyl)benzofuran derivatives. Reagents and conditions: (a) for **28iii**,**iv**, and **vi**, BH_3·THF, water bath, 12 h, (81–99%); (b) for **28vii**,**viii**, DIBAL, THF, 0 °C, 1 h (86–94%); (c) for **29iii**,**vi**, X = Cl, $SOCl_2$, DCM, 2 h, (92–100%) and for **29iv**,**v** and **29vii**–**viii**, X = Br, PBr_3, pyridine, DCM, 0 °C (82–99%); (d) for **28v**, CuCN, NMP, microwave, 200 °C, 10 min (67%).



Scheme 3. Synthesis of phenylboronic esters. Reagents and conditions: (a) K_2CO_3, **29i** or **ii**, CH_3CN, reflux, 12 h (**31i**, 63%; **31ii**, 96%); (b) EDC, **27i**,**ii**, DMAP, DMF, 3 h (**32i**, 83%; **32ii**, 55%); (c) i—NaH, DMF, 1 h; ii—MeI, 12 h (41%).



Scheme 5. Synthesis of sulfone and sulfoxide-linked benzofuran P1′ MMP-13 inhibitors. Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux, 12 h (40%); (b) $Pd(PPh_3)_4$, **34ii**, K_2CO_3, DME, 8 h (54%); (c) for **6**, *m*-CPBA (3 equiv), THF, 0 °C to rt, 12 h (70%) and for **7**, *m*-CPBA (1 equiv), DCM, 0 °C to rt, 12 h (83%); (d) LiOH/MeOH/H_2O, 12 h (92–97%).



Scheme 4. Synthesis of biphenylsulfonamide carboxylates. Reagents and conditions: (a) substituted boronic acid/ester, $Pd(PPh_3)_4$, K_2CO_3, DME/H_2O, 80 °C, 8 h (33–95%); (b) TFA/CH_2Cl_2 (1:1), rt, 3 h (95–100%); (c) $CeCl_3{\cdot}7H_2O$, KI, CH_3CN, reflux, 16 h (25%); (d) LiOH/MeOH/H_2O, 12 h (73–100%); (e) **27ii**, EDC, DMAP, DMF, 3 h (74%); (f) **27i** or **ii**, DCC, DMAP, DCM, 3.5 h (**8**, 31%; **11**, 95%; **14**, 71%); (g) benzofuran-2-SO_2Cl, DMAP, DCM, 12 h (31%); (h) **29iii**,**viii**, K_2CO_3, DMF, rt, 12 h (21–68%); (i) benzofuran-2-NCO, Et_3N, Et_2O/DCM, rt, 12 h (17%).

with a C4-oxygen linkage have been reported.[10b] Compound **26iii** was synthesized using a similar approach. Therefore, bromination of **23** followed by O-alkylation gave **26iii** in good yield. To synthesize compound with a C4 carbon-linked substitution, triflate **24** was prepared followed by Pd catalyzed Stille or Sonogashira coupling to give **26i**,**ii**, which were further hydrogenated to give **26iv**,**v**, respectively. Hydrolysis of ethyl carboxylate **26** gave acid **27** (Scheme 1). Borane or DIBAL reduction of **27** gave alcohol **28**. Alternatively, esters (e.g., **26iv**) could be directly reduced by DIBAL to give **28vii**. Cyanide coupling to **28iii** using microwave radiation gave **28v**. Chlorination or bromination of **28** gives halomethylbenzofuran **29** in excellent yield (Scheme 2).

Suzuki coupling of commercially available boronic acids with compound **34** gave a variety of biphenyl intermediates **35** to which benzofuran moieties were then introduced (Scheme 4). Alternatively, boronic esters **31**–**33** with various benzofuran moieties synthesized through alkylations (**31i**,**ii**) or amide couplings (Scheme 3, **32ii** and **33**) were used in Suzuki couplings with **34** to synthesize compounds **4**, **9**, **13**, and **15**. Most of the compounds reported herein were synthesized on the valine *tert*-butyl ester scaffold and the *tert*-butyl group was subsequently removed with TFA to afford the corresponding carboxylic acids. In cases where the valine methyl ester was used, basic hydrolysis using LiOH/MeOH/H_2O was performed.

General amide or acid coupling methods were used for the syntheses of **10** (EDC coupling), **8**, **11**, and **14** (DCC coupling). Compound **5** was synthesized through coupling of **35i** with the literature reported benzofuran-2-SO_2Cl.[18] Carbamate formation of **36** with benzofuran-2-NCO[19] gave **12**. Alkylation of substituted halomethylbenzofurans **29iii**–**viii** with either **35ii** or **38** gave compounds **16**–**22**, respectively (Scheme 4).

Compound **41** was prepared from 1,2,3-thiadiazole **39** using a nucleophilic intramolecular cyclization reaction (Scheme 5).[20] Suzuki coupling and oxidation using *m*-CPBA provided compounds **6** and **7** in good yields.

4. Conclusion

Modification of the amide bond of a biphenylsulfonamide carboxylate MMP-13 inhibitor led to a potent and selective MMP-13 inhibitor (**16**) with an ether-linked benzofuran P1′ moiety. Compound **16** showed moderate selectivity against MMP-2, -3 and -8, and greater than 500-fold selectivity over MMP-1, -7, -9, -14, and TACE. It also demonstrated excellent PK properties on both iv and oral dosing in rats, and good efficacy in a cartilage explant assay, making it a potential candidate for studies in in vivo OA efficacy models.

5. Experimental

5.1. General

All reagents and solvents were of commercial quality and used without further purification. Benzofuran-2-carboxylic acids (**27i**,**ii**) were purchased from Aldrich. Column chromatography was performed using Merck silica gel 60 (230–400 mesh). Proton nuclear magnetic spectroscopy ^{1}H NMR spectra (400 MHz) were obtained on a Bruker 400 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. Low-resolution mass spectra (MS) were obtained using a micromass platform electrospray ionization quadrupole mass spectrometer. High-resolution exact mass measurements (HRMS) were performed on a Bruker ApexIII 7T FT/ICR/MS. Chiral purities were determined using HP 1100 equipped with a Chiralpak AD column (4.6 × 250 mm, Chiral Technologies).[21] All intermediates were characterized by ^{1}H NMR. All new final SAR compounds were determined to be consistent with the proposed structure by ^{1}H NMR, MS, HRMS and were greater than 95% purity in two solvent systems (H_2O–CH_3CN and H_2O–MeOH) as determined using an Agilent 1100 HPLC instrument on a C18 column (see Supplementary data for details). Benzofuran-2-SO_2Cl,[18] benzofuran-2-NCO,[19] **2**, **3**, **23**, **27iii**,**iv**,[10b] **29i**,[22] **29ii**,[23] **34i**[8], and **39**[20] were synthesized according to the literature procedures.

6. Synthesis

6.1. Synthesis of ethyl benzofuran-2-carboxylates (24–26)

6.1.1. Ethyl 5-bromo-4-hydroxy-3-methylbenzofuran-2-carboxylate (25). To a mixture of **23**[10b] (2.00 g, 9.08 mmol) in CCl_4 (20 mL) was added *N*-bromosuccinimide (1.43 g, 8.03 mmol) under ice-water bath. The reaction mixture was allowed to react for 3 h. After solvent removal and column chromatography using CH_2Cl_2/CCl_4 (1:1, v/v) as eluent, **25** was obtained as a white solid in 67% yield (1.60 g). ^{1}H NMR ($CDCl_3$): δ 1.44 (t, J = 7.2 Hz, 3H), 2.75 (s, 3H), 4.45 (q, J = 7.2 Hz, 2H), 5.90 (s, 1H), 7.03 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H). MS *m*/*z*: 297.0 $(M-H)^-$. Anal. ($C_{12}H_{11}BrO_4$): C, H.

6.1.2. Ethyl 3-methyl-4-(trifluoromethylsulfonyloxy) benzofuran-2-carboxylate (24). To a mixture of **23** (6.34 g, 28.8 mmol) in CH_2Cl_2 (120 mL) was added diisopropylethylamine (12.6 mL, 72.3 mmol) under ice-water bath. Triflic anhydride (7.27 mL, 43.2 mmol) was added dropwise. The reaction was allowed to proceed for 1 h at 0 °C. After dilution with CH_2C1_2 (120 mL) and quenching with H_2O (30 mL), the reaction mixture was washed with H_2O (3 × 100 mL), the organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo. Column chromatography using CH_2Cl_2/CCl_4 (1:1, v/v) as eluent gave **24** as an off-white solid in 75% yield (7.61 g). ^{1}H NMR ($CDCl_3$): δ 1.45 (t, J = 7.2 Hz, 3H), 2.76 (s, 3H), 4.47 (q, J = 7.2 Hz, 2H), 7.25 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 8.3 Hz, 1H), 7.59 (dd, J = 8.3, 0.8 Hz, 1H). MS *m*/*z*: 353.0 $(M+H)^+$. Anal. ($C_{13}H_{11}F_3O_6S$): C, H.

6.1.3. Ethyl 3-methyl-4-vinylbenzofuran-2-carboxylate (26i). To a solution of **24** (2.48 g, 7.05 mmol) in 30 mL DMF were added vinyl tributyltin (2.16 mL,

7.40 mmol), lithium chloride (898 mg, 21.1 mmol), and $PdCl_2(PPh_3)_2$ (247 mg, 0.352 mmol). The reaction mixture was heated to 90 °C for 3 h and then cooled to room temperature. The reaction was diluted with H_2O and extracted with ether. The combined organic fractions were washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed eluting with EtOAc/hexanes (1:25, v/v) to give **26i** as a white solid in 75% yield (1.22 g). ^{1}H NMR (DMSO-d_6): δ 1.35 (t, J = 7.1 Hz, 3H), 2.74 (s, 3H), 4.36 (q, J = 7.1 Hz, 2H), 5.48 (dd, J = 10.8, 1.3 Hz, 1H), 5.87 (dd, J = 17.4, 1.3 Hz, 1H), 7.38–7.53 (m, 3H), 7.57–7.63 (m, 1H). MS m/z: 231.1 $(M+H)^+$.

6.1.4. Ethyl 4-(3-methoxy-prop-1-ynyl)-3-methylbenzofuran-2-carboxylate (26ii). To a solution of **24** (860 mg, 2.44 mmol) in DMF (7 mL) under nitrogen were added $PdCl_2(PPh_3)_2$ (98 mg, 0.14 mmol), 3-methoxy-propyne (0.42 mL, 4.97 mmol), and triethylamine (1.4 mL, 10.0 mmol). The reaction mixture was heated to 90 °C for 18 h. After aqueous workup (EtOAc/H_2O) and column chromatography (4% EtOAc/hexanes), **26ii** was obtained as an off-white solid in 52% yield (343 mg). ^{1}H NMR ($CDCl_3$): δ 1.41 (t, J = 7.2 Hz, 3H), 2.83 (s, 3H), 3.52 (s, 3H), 4.42 (s, 2H), 4.51 (q, J = 7.2 Hz, 2H), 7.43 (m, 2H), 7.54 (dd, J = 7.7, 1.6 Hz, 1H). MS m/z: 273.1 $(M+H)^+$. Anal. ($C_{16}H_{16}O_4$): C, H.

6.1.5. Ethyl 5-bromo-4-isopropoxy-3-methyl-1-benzofuran-2-carboxylate (26iii). To a mixture of **25** (500 mg, 1.67 mmol) in 7 mL DMF were added K_2CO_3 (510 mg, 3.69 mmol) and 2-bromopropane (0.48 mL, 5.11 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was concentrated in vacuo, and the residue was diluted with H_2O (30 mL) and extracted with EtOAc (150 mL). The organic layer was washed with H_2O (3 × 30 mL) and brine (3 × 30 mL), dried over sodium sulfate, filtered, and concentrated to provide **26iii** as a pink solid in 100% yield (438 mg). Mp: 48–50 °C. ^{1}H NMR ($CDCl_3$): δ 1.36–1.39 (m, 6H), 1.44 (t, J = 7.1 Hz, 3H), 2.74 (s, 3H), 4.45 (q, J = 7.1 Hz, 2H), 4.74–4.87 (m, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H). MS m/z: 341.0 $(M+H)^+$.

6.1.6. Ethyl 4-ethyl-3-methylbenzofuran-2-carboxylate (26iv). To a solution of **26i** (400 mg, 1.74 mmol) in 25 mL EtOAc under nitrogen was added 10% palladium on carbon (50 mg). The reaction mixture was shaken on a Parr shaker under 40 psi of hydrogen for 4 h. The reaction mixture was then filtered through a pad of Celite. The Celite was washed with an additional 150 mL EtOAc and the filtrate was concentrated in vacuo. The residue was chromatographed eluting with EtOAc/hexanes (1:30, v/v) to provide **26iv** as a white solid in 98% yield (395 mg). ^{1}H NMR (DMSO-d_6): δ 1.25 (t, J = 7.4 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.74 (s, 3H), 3.02 (q, J = 7.4 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2 H), 7.12 (d, J = 6.8 Hz, 1H), 7.37–7.45 (m, 1H), 7.45–7.51 (m, 1H). MS m/z: 233.1 $(M+H)^+$. Anal. ($C_{14}H_{16}O_3$): C, H.

6.1.7. Ethyl 4-(3-methoxy-propyl)-3-methylbenzofuran-2-carboxylate (26v). A mixture of **26ii** (2.66 g, 9.77 mmol) and 10% palladium on activated carbon (705 mg) and tetrahydrofuran (60 mL) was stirred under a hydrogen atmosphere (balloon) for 2 h. After filtering the mixture through a Celite pad followed by washing with EtOAc (100 mL), the filtrate was reduced to dryness, furnishing **26v** as a clear oil in 91% yield (2.46 g). ^{1}H NMR ($CDCl_3$): δ 1.44 (t, J = 7.2 Hz, 3H), 1.89–2.00 (m, 2H), 2.79 (s, 3H), 3.03–3.13 (m, 2H), 3.34–3.38 (m, 3H), 3.44 (t, J = 6.3 Hz, 2 H), 4.45 (q, J = 7.2 Hz, 2H), 7.05 (d, J = 7.3 Hz, 1 H), 7.29–7.36 (m, 1H), 7.37–7.42 (m, 1H). MS m/z: 277.1 $(M+H)^+$, 553.3 $(2M+H)^+$.

7. Synthesis of benzofuran-2-carboxylic acids (27)

General synthesis **1**, *hydrolysis of ethyl esters*: to a solution of ethyl benzofuran carboxylate **26** (1.50 mmol) in THF (15 mL) and MeOH (15 mL) was added NaOH (1 N, 8.5 mL). After 1 h of reaction, the reaction was quenched with saturated NH_4Cl solution (30 mL). The mixture was diluted with EtOAc (150 mL), washed with H_2O (3 × 30 mL) and brine (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give benzofurancarboxylic acid (**27**).

7.1. 5-Bromo-4-isopropoxy-3-methyl-1-benzofuran-2-carboxylic acid (27vi)

White solid: 87% yield (460 mg). Mp: 182–184 °C. ^{1}H NMR (DMSO-d_6): δ 1.31 (d, J = 6.3 Hz, 6H), 2.65 (s, 3H), 4.62–4.83 (m, 1H), 7.40 (d, J = 9.1 Hz, 1H), 7.67 (d, J = 9.1 Hz, 1H), 13.68 (br s, 1H). MS m/z: 311.0 $(M-H)^-$. Anal. ($C_{13}H_{13}BrO_4$): C, H.

7.2. 4-(3-Methoxypropyl)-3-methylbenzofuran-2-carboxylic acid (27viii)

White solid: 98% yield (1.98 g). ^{1}H NMR (DMSO-d_6): δ 1.79–1.89 (m, 2H), 2.72 (s, 3H), 3.02 (m, 2H), 3.26 (s, 3H), 3.38 (t, J = 6.2 Hz, 2H), 7.09 (d, J = 6.6 Hz, 1H), 7.35–7.41 (m, 1H), 7.43–7.48 (m, 1H), 13.36 (s, 1H). MS m/z: 247.1 $(M-H)^-$. HRMS: calcd for $[C_{14}H_{16}O_4 + H]^+$: 249.11214. Found: 24911161.

8. Synthesis of (benzofuran-2-yl)-methanols (28)

General synthesis **2**, *reduction of carboxylic acid to alcohol*: a solution of benzofuran-2-carboxylic acid **27** (1.00 mmol) in 6 mL THF under nitrogen was placed in water bath. BH_3·THF (1.0 M in THF, 3 mL, 3.00 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 12 h. Then the reaction was quenched with MeOH (3 mL). Solvent was removed in vacuo and the residue was subjected to column chromatography to give 2-hydroxymethylbenzofuran **28**.

8.1. (5-Bromo-4-methoxy-3-methylbenzofuran-2-yl)-methanol (28iii)

White solid: 81% yield (220 mg). Mp: 80–84 °C. ^{1}H NMR ($CDCl_3$): δ 1.80 (br s, 1H), 2.43 (s, 3H), 3.91 (s, 3H), 4.72 (s, 2H), 7.15 (d, J = 8.8 Hz, 1H), 7.41 (d,

$J = 8.8$ Hz, 1H). MS *m/z*: 269.0 $(M-H)^-$. Anal. ($C_{11}H_{11}BrO_3$): C, H.

8.2. (5-Chloro-4-methoxy-3-methylbenzofuran-2-yl)-methanol (28iv)

White solid: 99% yield (290 mg). This crude material was used for the following reaction without further purification.

8.3. (5-Bromo-4-isopropoxy-3-methyl-1-benzofuran-2-yl)-methanol (28vi)

Clear oil, 81% yield (330 mg). ^{1}H NMR ($CDCl_3$): δ 1.33–1.39 (m, 6H), 1.79 (br s, 1H), 2.39 (s, 3H), 4.66–4.78 (m, 3H), 7.07 (d, $J = 8.8$ Hz, 1H), 7.40 (d, $J = 8.8$ Hz, 1H). Anal. ($C_{13}H_{15}BrO_3$): C, H.

8.4. 2-Hydroxymethyl-4-methoxy-3-methylbenzofuran-5-carbonitrile (28v)

A suspension of **28iii** (310 mg, 1.14 mmol) and CuCN (210 g, 2.34 mmol) in *N*-methylpyrrolidinone (1.5 mL) was subjected to microwave radiation at 200 °C for 10 min. The reaction mixture was diluted with H_2O (10 mL) and EtOAc (10 mL), and filtered. The aqueous phase was extracted with EtOAc (30 mL). The combined organic layers were washed with H_2O (3×20 mL) and brine (1×30 mL). After drying over $MgSO_4$, filtration and concentration in vacuo gave the crude product. Chromatography eluting with EtOAc/hexanes (1:5, v/v) gave **28v** as a white solid in 67% yield (170 mg). ^{1}H NMR ($CDCl_3$): δ 1.85 (br s, 1H), 2.39 (s, 3H), 4.19 (s, 3H), 4.75 (s, 2H), 7.22 (d, $J = 9.0$ Hz, 1H), 7.43 (d, $J = 9.0$ Hz, 1H).

8.5. (4-Ethyl-3-methylbenzofuran-2-yl)-methanol (28vii)

To a solution of **26iv** (795 mg, 3.43 mmol) in THF (20 mL) at 0 °C was added diisobutylaluminum hydride (13.7 mL, 1.0 M in toluene) dropwise. After stirring for 1 h, MeOH (10 mL) was added followed by saturated aqueous sodium potassium tartrate (10 mL). The resulting mixture was stirred for 15 min and was then extracted with EtOAc (2×50 mL). The combined organic extracts were dried over $NaSO_4$, filtered, reduced to dryness, and the resulting residue was subjected to flash chromatography (EtOAc/hexanes 1:5, v/v) which furnished **28vii** as a white solid in 94% yield (612 mg). ^{1}H NMR ($CDCl_3$): δ 1.30 (t, $J = 7.6$ Hz, 3H), 1.78 (t, $J = 1.8$ Hz, 1H), 2.42 (s, 3H), 3.00 (q, $J = 7.6$ Hz, 2H), 4.75 (d, $J = 1.8$ Hz, 2H), 7.00 (d, $J = 6.6$ Hz, 1H), 7.14–7.23 (m, 1H), 7.23–7.32 (m, 1H). MS *m/z*: 190.1 ($M^{+\cdot}$).

8.6. [4-(3-Methoxypropyl)-3-methyl-1-benzofuran-2-yl]-methanol (28viii)

White solid, 86% yield (192 mg), made from **27viii** (235 mg, 0.95 mmol) using a procedure similar to that described for **28vii**. ^{1}H NMR (DMSO-d_6): δ 1.76–1.86 (m, 2H), 2.35 (s, 3H), 2.91–2.99 (m, 2H), 3.25 (s, 3H), 3.37 (t, $J = 6.3$ Hz, 2H), 4.52 (d, $J = 5.8$ Hz, 2H), 5.24 (t, $J = 5.8$ Hz, 1H), 6.97 (d, $J = 7.3$ Hz, 1H), 7.13–7.20 (m, 1H), 7.31 (d, $J = 8.3$ Hz, 1H). MS *m/z*: 234.1 ($M^{+\cdot}$). HRMS: calcd for $[C_4H_{18}O_3 + Na]^+$: 257.11481. Found: 257.11451.

9. Synthesis of 2-halomethylbenzofurans (29)

General synthesis **3***, synthesis of 2-chloromethylbenzofurans*: to a solution of (benzofuran-2-yl)-methanol **28** (5.00 mmol) in 12 mL CH_2Cl_2 was added 3 mL of thionyl chloride. After 2 h, the volatiles were removed to give 2-chloromethylbenzofuran (**29**).

9.1. 5-Bromo-2-chloromethyl-4-methoxy-3-methylbenzofuran (29iii)

Off-white solid, 92% yield (216 mg). ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H), 3.95 (s, 3H), 4.71 (s, 2H), 7.11 (d, $J = 8.6$ Hz, 1H), 7.42 (d, $J = 8.6$ Hz, 1 H). MS *m/z*: 288.0 ($M^{+\cdot}$).

9.2. 5-Bromo-4-isopropoxy-3-methyl-2-chloromethyl-1-benzofuran (29vi)

Off-white solid, 100% yield (330 mg). This crude material was used for the following reaction without further purification.

General synthesis **4***, synthesis of 2-bromomethylbenzofurans*: to a solution of (benzofuran-2-yl)-methanol 28 (1.30 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added neat PBr_3 (0.18 mL, 1.90 mmol) and pyridine (three drops). The ice bath was removed and the reaction mixture was allowed to react at room temperature for 12 h. Additional PBr_3 (0.09 mL; 0.95 mmol) was then added. After 2 h, the reaction was quenched with ice and extracted with EtOAc (3×50 mL). The combined organic layers were washed with H_2O (3×50 mL) and saturated sodium bicarbonate (3×50 mL), followed by drying over $MgSO_4$, filtration, and concentration in vacuo to give 2-bromomethylbenzofuran **29**.

9.3. 2-Bromomethyl-5-chloro-4-methoxy-3-methylbenzofuran (29iv)

White solid, 99% yield (370 mg). ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H), 3.95 (s, 3H), 4.58 (s, 2H), 7.12, (d, $J = 9.0$ Hz, 1H), 7.21 (d, $J = 9.0$ Hz, 1H).

9.4. 2-Bromomethyl-4-methoxy-3-methylbenzofuran-5-carbonitrile (29v)

Off-white solid, 95% yield (200 mg). This crude material was used for the following reaction without further purification.

9.5. 4-Ethyl-3-methyl-2-bromomethylbenzofuran (29vii)

White solid, 82% yield (83 mg). ^{1}H NMR ($CDCl_3$): δ 1.32 (t, $J = 7.6$ Hz, 3H), 2.42 (s, 3H), 3.01 (q, $J = 7.6$ Hz, 2H), 4.66 (s, 2H), 7.02 (d, $J = 7.3$ Hz, 1H), 7.20–7.26 (m, 1H), 7.29–7.33 (m, 1H).

9.6. 4-(3-Methoxypropyl)-3-methyl-2-bromomethyl-1-benzofuran (29viii)

Off-white solid, 82% yield (188 mg). This crude material was used for the following reaction without further purification.

10. Synthesis of boronic esters (31–33 and 41)

10.1. 2-[4-(4,4,5,5-Tetramethyl-[l,3,2]dioxaborolan-2-yl)-phenoxymethyl]-benzofuran (31i)

A mixture of **29i** (1.50 g, 7.11 mmol), 4-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-phenol **30i** (1.56 g, 7.09 mmol), K_2CO_3 (1.96 g, 14.2 mmol) in CH_3CN (50 mL) under argon was heated at 70 °C for 16 h. The reaction mixture was diluted with H_2O (50 mL). The aqueous phase was extracted with EtOAc (2×100 mL). The combined organic layers were washed with H_2O (3×50 mL) and brine (1×50 mL). After drying over $MgSO_4$, filtration, and concentration in vacuo gave the crude product. Chromatography eluting with EtOAc/hexanes (1:5, v/v) gave **31i** as a white solid in 63% yield (1.56 g). ^{1}H NMR (DMSO-d_6): δ 1.33 (s, 12H), 5.31 (s, 2H), 7.11 (m, 3H), 7.31 (m, 1H), 7.33 (m, 1H), 7.60 (m, 4H).

10.2. 3-Methyl-2-[4-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-phenoxymethyl]-benzofuran (31ii)

White solid, 96% yield (350 mg), made from **29ii** (181 mg, 1.00 mmol) using a procedure similar to that described for **30i**. ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 12H), 2.33 (s, 3H), 5.23 (s, 2H), 7.01 (d, J = 8.6 Hz, 2H), 7.32 (m, 2H), 7.54 (m, 2H), 7.83 (d, J = 8.8 Hz, 2H).

10.3. Benzofuran-2-carboxylic acid [4-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-phenyl]-amide (32i)

To a mixture of **27i** (1.03 g, 6.35 mmol), l-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.97 g, 10.3 mmol), and 4-dimethylaminopyridine (633 mg, 5.18 mmol) in 40 mL DMF under nitrogen was added 4-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-phenylamine **30ii** (1.08 g, 4.93 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with H_2O (50 mL). The aqueous phase was extracted with EtOAc (2×100 mL). The combined organic layers were washed with H_2O (3×50 mL) and brine (1×50 mL). After drying over $MgSO_4$, filtration, and concentration in vacuo gave the crude product. Chromatography eluting with EtOAc/hexanes (1:10, v/v) gave **32i** as a white solid in 83% yield (1.49 g). ^{1}H NMR (DMSO-d_6): δ 1.33 (s, 12H), 7.40 (m, 1H), 7.51 (m, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.71 (dd, J = 8.5, 0.9 Hz, 1H), 7.81 (m, 4H), 10.64 (s, 1H).

10.4. 3-Methyl-benzofuran-2-carboxylic acid [4-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-phenyl]-amide (32ii)

White solid, 55% yield (207 mg), made from **27ii** and **30ii** (219 mg, 1.00 mmol) using a procedure similar to that described for **32i**. ^{1}H NMR (DMSO-d_6): δ 1.31 (s, 12H), 2.61 (s, 3H), 7.40 (m, 1H), 7.53 (m, 1H), 7.71 (m, 3H), 7.83 (d, J = 7.3 Hz, 1H), 7.94 (d, J = 8.6 Hz, 2H), 10.51 (s, 1H).

10.5. Benzofuran-2-carboxylic acid methyl-[4-(4,4,5,5-tetramethyl-[l,3,2]dioxaborolan-2-yl)-phenyl]-amide (33)

To a solution of **32i** (195 mg, 0.54 mmol) in 3.5 mL DMF under nitrogen was added NaH (60% in mineral oil, 23 mg, 0.58 mmol). After 30 min, MeI (0.05 mL, 0.8 mmol) was added and the reaction was allowed to go on for 12 h. The reaction mixture was diluted with H_2O (30 mL). The aqueous phase was extracted with EtOAc (2×80 mL). The combined organic layers were washed with H_2O (3×30 mL) and brine (1×30 mL). After drying over $MgSO_4$, filtration, and concentration in vacuo gave the crude product. Chromatography eluting with EtOAc/hexanes (1:10, v/v) gave **33** (83 mg) as a white solid in 41% yield. ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 12H), 3.41 (s, 3H), 6.92 (d, J = 0.8 Hz, 1H), 7.02 (m, 4H), 7.24 (m, 2H), 8.11 (d, J = 8.3 Hz, 2H).

10.6. 2-[4-(4,4,5,5-Tetramethyl-[l,3,2]dioxaborolan-2-yl)-benzyl-sulfanyl]-benzofuran (41)

A mixture of 2-[l,2,3]thiadiazol-4-yl-phenol **39**[20] (241 mg, 1.35 mmol), 2-(4-bromomethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane **40** (406 mg, 1.37 mmol), and K_2CO_3 (396 mg, 2.87 mmol) in 8 mL CH_3CN was heated to reflux under a nitrogen atmosphere. After the reaction was complete as monitred by TLC (24 h), the mixture was filtered and the solvent was removed in vacuo. The resulting crude material was chromatographed eluting with ethyl acetate/hexane (1:5, v/v) to give **41** (198 mg) as a white solid in 40% yield. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 12H), 4.13 (s, 2H), 6.60 (d, J = 1.0 Hz, 1H), 7.20 (m, 4H), 7.41 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H).

11. *N*-[(4-Bromophenyl)sulfonyl]-valinate (34ii and 37)

11.1. Methyl *N*-[(4-bromophenyl)sulfonyl]-D-valinate (34ii)

White solid, 88% yield (5.73 g), synthesized according to the procedure reported for **34i**.[8] ^{1}H NMR (DMSO-d_6): δ 0.79 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H), 1.85–1.97 (m, 1H), 3.38 (s, 3H), 3.57 (dd, J = 9.4, 7.1 Hz, 1H), 7.65–7.70 (m, 2H), 7.77–7.83 (m, 2H), 8.40 (d, J = 9.4 Hz, 1H). MS m/z: 348.0 $(M-H)^-$.

11.2. Methyl *N*-[(4-bromophenyl)sulfonyl]-L-valinate (37)

White solid, 93% yield (4.45 g), synthesized according to the procedure reported for **34i**.[8] ^{1}H NMR (DMSO-d_6): δ 0.79 (d, J = 6.7 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H), 1.85–1.97 (m, 1H), 3.38 (s, 3H), 3.57 (dd, J = 9.2, 7.0 Hz, 1H), 7.65–7.70 (m, 2H), 7.78–7.82 (m, 2H), 8.39 (d, J = 9.2 Hz, 1H). MS m/z: 348.1 $(M-H)^-$.

12. Synthesis of *N*-(biphenylsulfonyl)-D-valinate (35 and 38)

General synthesis **5**, *Suzuki coupling*: a mixture of *N*-[(4-bromophenyl)sulfonyl]-valinate (**34** or **37**, 0.50 mmol), boronic acid or boronic ester (0.50 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), and K_2CO_3 (141 mg, 1.02 mmol) in 10 mL of 1,2-dimethoxyethane and 5 mL H_2O was heated to 90 °C under nitrogen. After 8 h, the reaction mixture was concentrated in vacuo, diluted with EtOAc (100 mL), washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), and dried over $MgSO_4$. The organic layer was concentrated in vacuo followed by column chromatography eluting with ethyl acetate/hexane (1:5, v/v) to give *N*-(biphenylsulfonyl)-D-valinate (**35** or **38**).

12.1. *tert*-Butyl *N*-[(4′-hydroxy-1,1′-biphenyl-4-yl)-sulfonyl]-D-valinate (35i)

White solid, 82% yield (9.04 g). ^{1}H NMR ($CDCl_3$): δ 0.86 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.20 (s, 9H), 1.99–2.13 (m, 1H), 3.66 (dd, J = 9.9, 4.6 Hz, 1H), 4.97 (s, 1H), 5.12 (d, J = 9.9 Hz, 1H), 6.90–6.95 (m, 2H), 7.42–7.50 (m, 2H), 7.59–7.67 (m, 2H), 7.82–7.90 (m, 2H). HRMS: calcd for $[C_{21}H_{27}NO_5S + H]^+$: 406.16827. Found: 406.1695.

12.2. Methyl *N*-[(4′-hydroxy-1,1′-biphenyl-4-yl)sulfonyl]-D-valinate (35ii)

White solid, 91% yield (1.41 g). ^{1}H NMR (DMSO-d_6): δ 0.79 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 1.84-1.95 (m, 1H),3.34(s, 3H), 3.55 (dd, J = 9.4, 7.1 Hz, 1H), 6.85–6.91 (m, 2H), 7.56–7.61 (m, 2H), 7.72–7.82 (m, 4H), 8.25 (d, J = 9.4 Hz, 1H), 9.74 (s, 1H). MS *m*/*z* 362.1 $(M-H)^-$ HRMS: calcd for $[C_{18}H_{21}NO_5S + H]^+$: 364.12132. Found: 364.12078. Anal. ($C_{18}H_{21}NO_5S$ 0.2H_2O): C, H, N. Chiral purity: 98.2% (21.7 min).[19]

12.3. *tert*-Butyl *N*-[(4′-aminomethyl-1,1′-biphenyl-4-yl)sulfonyl]-D-valinate (35iii)

White solid, synthesized from 4-(aminomethyl)phenylboronic acid and **34i** in 40% yield (347 mg). ^{1}H NMR (DMSO-d_6): δ 0.84 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 1.15 (s, 9H), 1.88–1.99 (m, 1H), 2.21 (br s, 2H), 3.47 (d, J = 6.32 Hz, 1H), 3.77 (s, 2H), 4.04 (m, 1H), 7.46 (d, J = 8.34 Hz, 2H), 7.63 (d, J = 8.08 Hz, 2H), 7.79–7.86 (m, 4H).

12.4. *tert*-Butyl *N*-{[4′-(hydroxymethyl)-1,1′-biphenyl-4-yl]sulfonyl}-D-valinate (35iv)

White solid, synthesized from 4-(hydroxymethyl)phenylboronic acid and **34i** in 95% yield (3.03 g). ^{1}H NMR (DMSO-d_6): δ 0.84 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 1.15 (s, 9H), 1.88–1.98 (m, 1H), 3.47 (dd, J = 9.7, 6.19 Hz, 1H), 4.55 (d, J = 5.8 Hz, 2H), 5.26 (t, J = 5.8 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.80–7.86 (m, 4H), 8.13 (d, J = 9.7 Hz, 1H).

12.5. Methyl *N*-[(4′-hydroxy-1,1′-biphenyl-4-yl)sulfonyl]-L-valinate (38)

White solid, synthesized from **37** in 85% yield (508 mg), ^{1}H NMR ($CDCl_3$): δ 0.89 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.99–2.11 (m, 1H), 3.43 (s, 3H), 3.78 (dd, J=10.2, 5.2 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 5.17 (s, 1H), 6.90–6.97 (m, 2H), 7.45–7.53 (m, 2H), 7.60–7.68 (m, 2H), 7.81–7.90 (m, 2H). MS *m*/*z*: 362.1 $(M-H)^-$. Chiral purity: 98.6% (27.5 min).[19]

13. Synthesis of α-biphenylsulfonamidocarboxylic acid MMP-13 inhibitors (4–22)

General synthesis **6**, *TFA cleavage of tert-butyl (biphenylsulfonyl)-valinates*: a mixture of *tert*-butyl ester (0.50 mmol), TFA (3 mL), and dichloromethane (6 mL) was allowed to react at room temperature for 3 h. After removal of volatiles, acid was obtained.

General synthesis **7**, *hydrolysis of methyl (biphenylsulfonyl)-valinates*: To a solution of methyl (biphenylsulfonyl)-valinate (0.50 mmol) in THF (8 mL) and MeOH (3 mL) was added LiOH (1 N, 3 mL). After 12 h of reaction, the reaction was quenched with saturated NH_4Cl solution (30 mL). The mixture was diluted with EtOAc (150 mL) and washed with H_2O (3 × 30 mL) and brine (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give the acid product.

13.1. *N*-({4′-[(1-Benzofuran-2-ylcarbonyl)(methyl)-amino]-1,1′-biphenyl-4-yl}sulfonyl)-D-valine (4)

Coupling of **33** with **34i** was carried out according to *General synthesis* **5** to give D-2-{4′-[(benzofuran-2-carbonyl)-methyl-amino]-biphenyl-4-sulfonylamino}-3-methyl-butyric acid *tert*-butyl ester as a white solid in 77% yield (190 mg). ^{1}H NMR (MeOH-d_4): δ 0.81 (m, 6H), 1.11 (s, 9H), 1.90 (m, 1H), 3.43 (s, 3H), 3.52 (d, J = 5.8 Hz, 1H), 6.60 (s, 1H), 7.12 (m, 1H), 7.24 (m, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 7.80 (m, 2H). Removal of *tert*-butyl ester (*General synthesis* **6**) gave compound **4** as a white solid in 98% yield (122 mg). Mp: 204–206 °C. ^{1}H NMR (MeOH-d_4): δ 0.81 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 1.89–1.99 (m, 1H), 3.42 (s, 3H), 3.58 (d, J = 5.8 Hz, 1H), 6.54 (s, 1H), 7.08–7.13 (m, 1H), 7.21–7.25 (m, 2H), 7.32–7.37 (m, 2H), 7.39–7.44 (m, 1H), 7.65–7.74 (m, 4H), 7.80–7.84 (m, 2H). HRMS: calcd for $[C_{27}H_{26}N_2O_6S + H]$: 507.1585. Found: 507.1588. Anal. ($C_{27}H_{26}N_2O_6S$·0.2H_2O): C, H, N.

13.2. *N*-({4′-[(1-Benzofuran-2-ylsulfonyl)oxy]-1,1′-biphenyl-4-yl}sulfonyl)-D-valine (5)

A mixture of **35i** (100 mg, 0.25 mmol), benzofuran-2-SO_2Cl[18] (60 mg, 0.28 mmol), and 4-dimethylaminopyridine (145 mg, 1.19 mmol) in CH_2Cl_2 (2 mL) at room temperature was allowed to react for 12 h. Removal of volatiles and column chromatography (CH_2Cl_2) gave

tert-butyl *N*-({4′-[(1-benzofuran-2-ylsulfonyl)oxy]-1,1′-biphenyl-4-yl}sulfonyl)-D-valinate as a white solid in 31% yield (48 mg). ^{1}H NMR ($CDCl_3$): δ 0.86 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.16–1.23 (m, 9H), 1.97–2.12 (m, 1H), 3.66 (dd, J = 10.1, 5.1 Hz, 1H), 5.12 (d, J = 10.1, 1H), 7.17–7.25 (m, 2H), 7.37–7.44 (m, 1H), 7.44–7.53 (m, 3H), 7.53–7.63 (m, 3H), 7.63–7.75 (m, 2H), 7.85–7.93 (m, 2H). Removal of *tert*-butyl ester (*General synthesis* **6**) gave compound **5** as a white solid in 100% yield (33 mg). ^{1}H NMR (DMSO-d_6): δ 0.80 (d, J = 6.82 Hz, 3H), 0.82 (d, J = 6.82 Hz, 3H), 1.89–1.98 (m, 1H), 3.53 (dd, J = 9.35, 6.06 Hz, 1H), 7.22–7.30 (m, 2H), 7.44–7.52 (m, 1H), 7.63–7.71 (m, 1H), 7.77–7.81 (m, 2H), 7.81–7.93 (m, 6H), 7.99 (d, J = 1.01 Hz, 1H), 8.09 (d, J = 9.35 Hz, 1H), 13.44 (br s, 1H). HRMS: calcd for $[C_{25}H_{23}NO_8S_2 + H]^+$: 530.0938. Found: 530.0955.

13.3. *N*-({4′-[(1-Benzofuran-2-ylsulfonyl)methyl]-1,1′-biphenyl-4-yl}sulfonyl)-D-valine (6) and *N*-({4′-[(1-benzofuran-2-ylsulfinyl)methyl]-1,1′-biphenyl-4-yl}sulfonyl)-D-valine (7)

Coupling of **34ii** with **41** was carried out according to *General synthesis* **5** to give **42** as a white solid in 54% yield (75 mg). ^{1}H NMR ($CDCl_3$): δ 0.71 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 1.93 (m, 1H), 3.0 (s, 3H), 4.02 (m, 3H), 5.04 (d, J = 10.1 Hz, 1H), 6.61 (d, J = 1.0 Hz, 1H), 7.13 (m, 4H), 7.3 (m, 6H), 7.31 (s, 1H), 7.44 (m, 1H).

A solution of **42** (75 mg, 0.15 mmol) in 4 mL THF was placed in an ice bath. *m*-Chloroperoxybenzoic acid (77%, 125 mg, 0.56 mmol) in 3 mL THF was added dropwise. After l0 min at 0 °C, the ice bath was removed. After 12 h of reaction, the mixture was diluted with EtOAc (150 mL) and washed with satd $NaHCO_3$ (3 × 30 mL) and brine (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with EtOAc/hexane (1:5, v/v), D-2-[4′-(benzofuran-2-sulfonylmethyl)-biphenyl-4-sulfonylamino]-3-methyl-butyric acid methyl ester (56 mg) was obtained as a white solid in 70% yield. ^{1}H NMR ($CDCl_3$): δ 0.86 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 2.03 (m, 1H), 3.43 (s, 3H), 3.84 (dd, J = 10.1, 5.3 Hz, 1H), 4.61 (s, 2H), 5.12 (d, J = 10.1 Hz, 1H), 7.41 (m, 4H), 7.53 (m, 3H), 7.61 (m, 1H), 7.73 (m, 3H), 7.91 (d, J = 8.8 Hz, 2H). Methyl ester hydrolysis (*General synthesis* **7**) gave compound **6** as a white solid in 92% yield (41 mg). Mp: 205–207 °C. ^{1}H NMR (DMSO-d_6): δ 0.78 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 1.91 (m, 1H), 3.53 (dd, J = 9.3, 6.1 Hz, 1H), 5.01 (s, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.42 (m, 1H), 7.61 (m, 1H), 7.72 (d, J = 1.0 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.81 (m, 6H), 8.10 (d, J = 9.3 Hz, 1H), 12.76 (br s, 1H). HRMS: calcd for $[C_{26}H_{25}NO_7S_2 + H]^+$: 528.1145. Found: 528.1147. Anal. ($C_{26}H_{25}NO_7S_2 \cdot 0.5H_2O$): C, H, N.

A solution of **42** (190 mg, 0.37 mmol) in 5 mL CH_2Cl_2 was placed in an ice bath. *m*-Chloroperoxybenzoic acid (77%, 88 mg, 0.39 mmol) in 3 mL CH_2Cl_2 was added dropwise. After 45 min, the mixture was diluted with EtOAc (150 mL) and washed with satd $NaHCO_3$ (3 × 30 mL) and brine (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with EtOAc/hexane (1:4, v/v) gave D-2-[4′-(benzofuran-2-sulfinylmethyl)-biphenyl-4-sulfonylamino]-3-methyl-butyric acid methyl ester (162 mg) as a white solid in 83% yield. ^{1}H NMR ($CDCl_3$): δ 0.86 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 2.00 (m, 1H), 3.43 (s, 3H), 3.81 (dd, J = 10.1, 5.1 Hz, 1H), 4.52 (m, 2H), 5.11 (d, J = 10.1 Hz, 1H), 7.12 (s, 1H), 7.31 (s, 2H), 7.32 (dd, J = 8.2, 7.2 Hz, 1H), 7.50 (m, 3H), 7.61 (m, 4H), 7.93 (d, J = 8.6 Hz, 2H). Methyl ester hydrolysis (*General synthesis* **7**) gave compound **7** as a white solid in 97% yield (118 mg). Mp: 220–223 °C. ^{1}H NMR (DMSO-d_6): δ 0.79 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H), 1.90 (m, 1H), 3.53 (dd, J = 9.3, 6.1 Hz, 1H), 4.71 (m, 2H), 7.41 (m, 3H), 7.53 (m, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.83 (m, 6H), 8.11 (d, J = 9.6 Hz, 1H), 12.62 (s, 1H). HRMS: calcd for $[C_{26}H_{25}NO_6S_2 + H]^+$: 512.1196. Found: 512.1197. Anal. ($C_{26}H_{25}NO_6S_2$): C, H, N.

13.4. *N*-({4′-[(1-Benzofuran-2-ylcarbonyl)oxy]-1,1′-bi-phenyl-4-yl}sulfonyl)-D-valine (8)

To a mixture of **27i** (401 mg, 2.47 mmol) in CH_2Cl_2 (50 mL) under nitrogen was added 1,3-dicyclohexylcarbodiimide (1.02 mg, 4.94 mmol). After 15 min, **35i** (1.00 g, 2.47 mmol) and 4-dimethylaminopyridine (50 mg, 0.41 mmol) were added. The mixture was allowed to stir at room temperature overnight. The reaction mixture was then diluted with CH_2Cl_2 (200 mL) washed with H_2O (3 × 100 mL) and brine (2 × 100 mL). The organic layer was dried over $MgSO_4$ and the solvent was concentrated in vacuo. The residue was purified by column chromatography eluting with EtOAc/hexane (1:5, v/v) to afford benzofuran-2-carboxylic acid 4′-(l-*tert*-butoxycarbonyl-2-methyl-propylsulfamoyl)-biphenyl-4-yl ester (325 mg) as a white solid in 31% yield. ^{1}H NMR ($CDCl_3$): δ 0.87 (d, J = 6.82 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 1.21 (s, 9H), 2.07 (m, 1H), 3.68 (dd, J = 9.9, 4.6 Hz, 1H), 5.15 (d, J = 9.9 Hz, 1H), 7.37 (m, 3H), 7.53 (t, J = 7.8 Hz, 1H), 7.66 (m, 5H), 7.77 (m, 2H), 7.92 (d, J = 8.3 Hz, 2H). Removal of *tert*-butyl ester (*General synthesis* **6**) gave compound **8** as a white solid in 100% yield (148 mg). Mp: 178–180 °C. ^{1}HNMR (DMSO-d_6): δ 0.80 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 2.04 (m, 1H), 3.24 (m, 1H), 7.43 (m, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.60 (m, 2H), 7.70 (d, J = 9.9 Hz, 1H), 7.85 (m, 7H), 8.08 (s, 1H), 13.11 (br s, 1H). HRMS: calcd for $[C_{26}H_{23}NO_7S + H]^+$: 494.1268. Found: 494.1284.

13.5. *N*-{[4′-(1-Benzofuran-2-ylmethoxy)-1,1′-biphenyl-4-yl]sulfonyl}-D-valine (9)

Coupling of **31i** with **34i** was carried out according to *General synthesis* **5** to give D-2-[4′-(benzofuran-2-ylmethoxy)-biphenyl-4-sulfonylamino]-3-methyl-butyric acid *tert*-butyl ester as a white solid in 33% yield (159 mg). ^{1}H NMR (DMSO-d_6): δ 0.78 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H), 1.23 (s, 9H), 1.90 (m,

1H), 3.51 (dd, J = 9.7, 6.2 Hz, 1H), 5.33 (s, 2H), 7.11 (s, 1H), 7.20 (d, J = 8.6 Hz, 2H), 7.30 (m, 1H), 7.34 (m, 1H), 7.61 (dd, J = 8.2, 0.6 Hz, 1H), 7.72 (m, 3H), 7.8 (m, 4H), 8.13 (d, J = 9.7 Hz, 1H). To this *tert*-butyl ester (126 mg, 0.23 mmol) in CH_3CN (10 mL) under argon were added cerium chloride heptahydrate (175 mg, 0.47 mmol) and KI (51 mg, 0.30 mmol). The reaction mixture was heated at reflux for 16 h. After filtration and concentration in vacuo, column chromatography of the residue eluting with 15% MeOH in CH_2Cl_2, **9** was obtained as a white solid in 25% yield (28 mg). ^{1}H NMR (DMSO-d_6): δ 0.78 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H), 2.03 (m, 1H), 3.51 (dd, J = 9.2, 5.9 Hz, 1H), 5.32 (s, 2H), 7.12 (s, 1H), 7.23 (d, J = 8.8 Hz, 2H), 7.31 (dd, J = 8.1, 0.8 Hz, 1H), 7.34 (m, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.70 (m, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.81 (m, 4H), 8.03 (d, J = 9.2 Hz, 1H), 14.01 (br s, 1H). HRMS: calcd for $[C_{26}H_{25}NO_6S + H]^+$: 480.1476. Found: 480.1474.

13.6. *N*-[(4′-{[(1-Benzofuran-2-ylcarbonyl)amino]-methyl}-1,1′-biphenyl-4-yl)sulfonyl]-D-valine (10)

Amide coupling of **35iii** (209 mg, 0.50 mmol) with **27i** (89 mg, 0.55 mmol) was carried out using a procedure similar to that described for **32i,** giving *tert*-butyl *N*-[(4′-{[(1-benzofuran-2-ylcarbonyl)amino]-methyl}-l,1′-biphenyl-4-yl)sulfonyl]-D-valinate as a white solid in 74% yield (173 mg). ^{1}H NMR (DMSO-d_6): δ 0.84 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 1.13 (s, 9H), 1.88–1.97 (m, 1H), 3.47 (dd, J = 9.6, 6.3 Hz, 1H), 4.54 (d, J = 6.1 Hz, 2H), 7.32–7.37 (m, 1H), 7.44–7.50 (m, 3H), 7.59 (d, J = 0.8 Hz, 1H), 7.64–7.69 (m, 3H), 7.77–7.80 (m, 1H), 7.80–7.86 (m, 4H), 8.13 (d, J = 9.6 Hz, 1H), 9.36 (t, J = 6.1 Hz, 1H). Removal of *tert*-butyl ester (*General synthesis* **6**) gave compound **10** as a white solid in 98% yield (138 mg). Mp: 263–265 °C. ^{1}H NMR (DMSO-d_6): δ 0.81 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 1.85–2.02 (m, 1H), 3.56 (dd, J = 9.4, 6.1 Hz, 1H), 4.55 (d, J = 6.3 Hz, 2H), 7.27–7.39 (m, 1H), 7.44–7.53 (m, 3H), 7.60 (d, J = 0.8 Hz, 1H), 7.65–7.69 (m, 1H), 7.69–7.75 (m, J = 8.3 Hz, 2H), 7.77–7.81 (m, 1H), 7.82–7.87 (m, 4H), 8.07 (d, J = 9.4 Hz, 1H), 9.36 (t, J = 6.3 Hz, 1H), 13.39 (br s, 1H). HRMS: calcd for $[C_{27}H_{26}N_2O_6S + H]^+$: 507.1585. Found 507.1578. Anal. ($C_{27}H_{26}N_2O_6S$): C, H, N.

13.7. *N*-[(4′-{[(1-Benzofuran-2-ylcarbonyl)oxy]-methyl}-1,1′-biphenyl-4-yl)sulfonyl]-D-valine (11)

Ester coupling of **35iv** (210 mg, 0.50 mmol) with **27i** (89 mg, 0.55 mmol) was carried out using a procedure similar to that described for compound **8**. *tert*-Butyl *N*-[(4′-{[(1-benzofuran-2-ylcarbonyl)oxy]-methyl}-1,1′-biphenyl-4-yl)sulfonyl]-D-valinate, white solid, 95% yield (144 mg). ^{1}H NMR ($CDCl_3$): δ 0.87 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.19 (s, 9H), 2.04–2.10 (m, 1H), 3.67 (dd, J = 9.9, 4.6 Hz, 1H), 5.13 (d, J = 9.9 Hz, 1H), 5.48 (s, 2H), 7.32 (m, 1H), 7.44–7.49 (m, 1H), 7.57–7.62 (m, 6H), 7.66–7.71 (m, 3H), 7.88–7.93 (m, 2H). Removal of *tert*-butyl ester (*General synthesis* **6**) gave compound **11** as a white solid in 97% yield (110 mg). Mp: 180–183 °C. ^{1}H NMR (MeOH-d_4): δ 0.81 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 1.90–2.00 (m, 1H), 3.58 (d, J = 5.3 Hz, 1H), 5.37 (s, 2H), 7.17–7.28 (m, 1H), 7.34–7.44 (m, 1H), 7.51 (dd, J = 8.2, 1.6 Hz, 3H), 7.56–7.60 (m, 1H), 7.61–7.68 (m, 3H) 7.68–7.74 (m, 2H), 7.77–7.87 (m, 2H). HRMS calcd for $[C_{27}H_{25}NO_7S + H]^+$: 508.1425. Found: 508.1426. Anal. ($C_{27}H_{25}NO_7S{\cdot}0.3H_2O$): C, H, N.

13.8. *N*-[(4′-{[(1-Benzofuran-2-ylamino)carbonyl]-oxy}-1,1′-biphenyl-4-yl)sulfonyl]-D-valine (12)

Removal of *tert*-butyl ester of compound **35i** gave *N*-[(4′-hydroxy-1,1′-biphenyl-4-yl)sulfonyl]-D-valine **36**: white solid, 100% yield (557 mg). ^{1}H NMR (MeOH-d_4): δ 0.81 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 1.88–2.00 (m, 1H), 3.57 (d, J = 5.6 Hz, 1H), 6.72–6.83 (m, 2H), 7.37–7.48 (m, 2H), 7.56–7.66 (m, 2H), 7.70–7.81 (m, 2H). HRMS: calcd for $[C_{17}H_{19}NO_5S + H]$: 350.1057. Found: 350.1057. To a mixture of **36** (314 mg, 0.90 mmol) in ethyl ether (20 mL) and CH_2Cl_2 (10 mL) was added benzofuran-2-NCO[17] (143 mg, 0.90 mmol) in ethyl ether (10 mL) followed by Et_3N (363 mg, 3.59 mmol). After 12 h of reaction, the volatiles were removed and the crude material was chromatographed eluting with 5% methanol in dichloromethane to give **12** as a white solid in 17% yield (76 mg). Mp: 184–186 °C. ^{1}H NMR (MeOH-d_4): δ 0.80 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 1.92–2.06 (m, 1H), 3.38 (m, 1H), 6.80–6.92 (m, 2H), 7.01–7.27 (m, 2H), 7.34–7.62 (m, 4H), 7.67–7.83 (m, 3H), 7.86 (s, 2H). HRMS: calcd for $[C_{26}H_{24}N_2O_7S + H]^+$: 509.1377. Found: 509.1383.

13.9. *N*-[(4′-{[(3-Methyl-1-benzofuran-2-yl)-carbonyl]-amino}-1,1′-biphenyl-4-yl)sulfonyl]-D-valine (13)

Coupling of **32ii** with **34i** was carried out according to *General synthesis* **5** to give *tert*-butyl *N*-[(4′-{[(3-methyl-1-benzofuran-2-yl)-carbonyl]-amino}-1,1′-biphenyl-4-yl)sulfonyl]-D-valinate as a white solid in 66% yield (485 mg). ^{1}H NMR ($CDCl_3$): δ 0.91 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 1.23 (s, 9H), 2.11 (m, 1H), 2.73 (s, 3H), 3.73 (dd, J = 9.9, 4.4 Hz, 1H), 5.12 (d, J = 9.9 Hz, 1H), 7.44 (m, 1H), 7.51 (m, 1H), 7.54 (m, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.73 (m, 3H), 7.82 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.6 Hz, 2H), 8.51 (s, 1H). Removal of *tert*-butyl ester (*General synthesis* **6**) gave compound **13** as a white solid in 100% yield (302 mg). Mp: 196–198 °C. ^{1}H NMR (MeOH-d_4): δ 0.77 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H), 1.92 (m, 1H), 2.61 (s, 3H), 3.62 (d, J = 5.8 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.41 (m, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.61 (m, 3H), 7.73 (d, J = 8.3 Hz, 2H), 7.81 (m, 4H), 10.11 (s, 1H). HRMS: calcd for $[C_{27}H_{26}N_2O_6S + H]^+$: 507.1585. Found: 507.1585. Anal. ($C_{27}H_{26}N_2O_6S{\cdot}0.5H_2O$): C, H, N.

13.10. *N*-[(4′-{[(3-Methyl-1-benzofuran-2-yl)-carbonyl]oxy}-1,1′-biphenyl-4-yl)sulfonyl]-D-valine (14)

Coupling of **35i** (305 mg, 0.75 mmol) with **27ii** (131 mg, 0.75 mmol) was carried out using a procedure similar to that described for compound **8**, giving *tert*-butyl

N-[(4′-{[(3-methyl-1-benzofuran-2-yl)-carbonyl]oxy}-1,1′-biphenyl-4-yl)sulfonyl]-D-valine as a white solid in 71% yield (300 mg). ^{1}H NMR ($CDCl_3$): δ 0.91 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.21 (s, 9H), 2.10 (m, 1H), 2.70 (s, 3H), 3.73 (dd, J = 9.9, 4.4 Hz, 1H), 5.13 (d, J = 9.9 Hz, 1H), 7.41 (m, 3H), 7.52 (m, 1H), 7.63 (m, 3H), 7.71 (m, 3H), 7.94 (d, J = 8.3 Hz, 2H). Removal of *tert*-butyl ester (*General synthesis* **6**) gave compound **14** as a white solid in 96% yield (188 mg). ^{1}H NMR (DMSO-d_6): δ 0.79 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 2.01 (m, 1H), 2.73 (s, 3H), 3.61 (dd, J = 9.2, 5.9 Hz, 1H), 7.42 (m, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.60 (m, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.91 (m, 7H), 8.10 (d, J = 9.2 Hz, 1H), 13.81 (br s, 1H). HRMS: calcd for $[C_{27}H_{25}NO_7S + H]^+$: 508.14245. Found: 508.1424.

13.11. *N*-({4′-[(3-Methyl-1-benzofuran-2-yl)-methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-D-valine (15)

Coupling of **34ii** with **31ii** was carried out according to *General synthesis* **5** to give methyl *N*-({4′-[(3-methyl-1-benzofuran-2-yl)-methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-D-valinate as a white solid in 75% yield (616 mg). ^{1}H NMR (MeOH-d_4): δ 0.81 (m, 6H), 1.93 (m, 1H), 2.21 (s, 3H), 3.23 (s, 3H), 3.50 (d, J = 6.6 Hz, 1H), 5.11 (s, 2H), 7.01 (d, J = 9.1 Hz, 2H), 7.14 (m, 1H), 7.21 (m, 1H), 7.33 (m, 1H), 7.41 (m, 1H), 7.52 (d, J = 9.1 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.71 (m, 2H). Methyl ester hydrolysis (*General synthesis* **7**) gave compound **15** as a white solid in 89% yield (354 mg). Mp: 178–180 °C. ^{1}H NMR (MeOH-d_4): δ 0.76 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 2.00 (m, 1H), 2.21 (s, 3H), 3.53 (d, J = 5.3 Hz, 1H), 5.11 (s, 2H), 7.11 (d, J = 9.1 Hz, 2H), 7.14 (m, 1H), 7.21 (m, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 9.1 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H). HRMS: calcd for $[C_{27}H_{27}NO_6S + H]^+$: 494.1632. Found: 494.164. Anal. ($C_{27}H_{27}NO_6S{\cdot}0.2H_2O$): C, H, N.

13.12. *N*-({4′-[(5-Bromo-4-methoxy-3-methyl-1-benzofuran-2-yl)methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-D-valine (16)

General synthesis **8**, alkylation: a mixture of **35ii** (155 mg, 0.43 mmol), **29iii** (120 mg, 0.42 mmol), and K_2CO_3 (137 mg, 0.99 mmol) in 8 mL DMF under nitrogen was stirred at room temperature. After 12 h, the mixture was diluted with EtOAc (150 mL) and washed with H_2O (3 × 50 mL) and brine (3 × 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography of the residue eluting with EtOAc/hexane (1:5, v/v) gave D-2-[4′-(5-bromo-4-methoxy-3-methylbenzofuran-2-ylmethoxy)-biphenyl-4-sulfonylamino]-3-methyl-butyric acid methyl ester (102 mg) as a white solid in 40% yield. Mp: 196–198 °C. ^{1}H NMR ($CDCl_3$): δ 0.86 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 2.11 (m, 1H), 2.51 (s, 3H), 3.40 (s, 3H), 3.82 (dd, J = 10.2, 5.2 Hz, 1H), 3.92 (s, 3H), 5.11 (d, J = 10.2 Hz, 1H), 5.23 (s, 2H), 7.10 (m, 3H), 7.41 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.6 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H). MS *m*/*z*: 616.1 $(M+H)^+$. Methyl ester hydrolysis (*General synthesis* **7**) gave compound **16** as a white solid in 88% yield (54 mg). Mp: 178–180 °C. ^{1}H NMR (DMSO-d_6): δ 0.79 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 2.03 (m, 1H), 2.41 (s, 3H), 3.51 (dd, J = 9.2, 5.9 Hz, 1H), 3.94 (s, 3H), 5.31 (s, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 9.1 Hz, 2H), 7.83 (m, 4H), 8.01 (d, J = 9.2 Hz, 1H), 13.38 (br s, 1H). MS *m*/*z*: 600.1 $(M-H)^-$, 1201.1 $(2M-H)^-$. HRMS: calcd for $[C_{28}H_{28}BrNO_7S + H]^+$: 602.0843. Found: 602.0826. Anal. ($C_{28}H_{28}BrNO_7S$): C, H, N. Chiral purity: 99.85% (13.4 min).[19]

13.13. *N*-({4′-[(5-Bromo-4-methoxy-3-methyl-1-benzofuran-2-yl)methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-L-valine (17)

Methyl *N*-({4′-[(5-bromo-4-methoxy-3-methyl-1-benzofuran-2-yl)methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-L-valinate, *General synthesis* **8**, white solid, 35% yield (105 mg). Mp: 205–207 °C. ^{1}H NMR ($CDCl_3$): δ 0.89 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.96–2.16 (m, 1H), 2.39 (s, 3H), 3.43 (s, 3H), 3.78 (dd, J = 10.07, 5.0 Hz, 1H), 3.90 (s, 3H), 5.09 (d, J = 10.1 Hz, 1H), 5.16 (s, 2H), 7.14 (m, 3H), 7.43 (d, J = 8.81 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.3 Hz, 2H). MS *m*/*z*: 616.1 $(M+H)^+$. Methyl ester hydrolysis (*General synthesis* **7**) gave compound **17** as a white solid in 96% yield (76 mg). Mp: 180–182 °C. ^{1}H NMR (DMSO-d_6): δ 0.80 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.83–2.08 (m, 1H), 2.43 (s, 3H), 3.50 (s, 1H), 3.88 (s, 3H), 5.31 (s, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.76–7.91 (m, 4H), 7.97 (s, 1H), 13.19 (br s, 1H). MS *m*/*z*: 600.0 $(M-H)^-$. HRMS: calcd for $[C_{28}H_{28}BrNO_7S + H]^+$: 602.0843. Found: 602.0828. Anal. ($C_{28}H_{28}BrNO_7S$): C, H, N.

13.14. *N*-({4′-[(5-Chloro-4-methoxy-3-methyl-1-benzofuran-2-yl)methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-L-valine (18)

Methyl *N*-({4′-[(5-chloro-4-methoxy-3-methyl-1-benzofuran-2-yl)methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-L-valinate, *General synthesis* **8**, off-white solid, 57% yield (410 mg). ^{1}H NMR (DMSO-d_6): δ 0.80 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H) 1.84–1.99 (m, 1H), 2.43 (s, 3H), 3.34 (s, 3H), 3.57 (dd, J = 9.3, 7.3 Hz, 1H), 3.90 (s, 3H), 5.30 (s, 2H), 7.15–7.26 (m, 2H), 7.40 (m, 2H), 7.68–7.90 (m, 6H), 8.27 (d, J = 9.3 Hz, 1H). MS *m*/*z*: 572.1 $(M-H)^-$. Methyl ester hydrolysis (*General synthesis* **7**) gave compound **18** as an off-white solid in 79% yield (320 mg). Mp: 174–177 °C. ^{1}H NMR (DMSO-d_6): δ 0.82 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 1.84–2.04 (m, 1H), 2.43 (s, 3H), 3.55 (dd, J = 9.3, 6.0 Hz, 1H), 3.90 (s, 3H), 5.30 (s, 2H), 7.11–7.27 (m, 2H), 7.37–7.42 (m, 2H), 7.68–7.78 (m, 2H), 7.82 (m, 4H), 8.03 (d, J = 9.3 Hz, 1H), 13.54 (br s, 1H). MS *m*/*z*: 556.1 $(M-H)^-$, 1113.2 $(2M-H)^-$. HRMS: calcd for $[C_{28}H_{28}ClNO_7S + H]^+$: 558.13478. Found: 558.1345. Anal. ($C_{28}H_{28}ClNO_7S{\cdot}0.2H_2O$): C, H, N.

13.15. *N*-({4′-[(5-Cyano-4-methoxy-3-methyl-1-benzofuran-2-yl)methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-L-valine (19)

Methyl *N*-({4′-[(5-cyano-4-methoxy-3-methyl-1-benzofuran-2-yl)methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-L-valinate, *General synthesis* **8**, white solid, 68% yield (280 mg). ^{1}H NMR (DMSO-d_6): δ 0.80 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.84–1.97 (m, 1H), 2.44 (s, 3H), 3.34 (s, 3H), 3.56 (dd, J = 9.3, 7.1 Hz, 1H), 4.11 (s, 3H), 5.33 (s, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.6 Hz, 1H), 7.64–7.90 (m, 7H), 8.27 (d, J = 9.3 Hz, 1H). MS *m*/*z*: 563.1 $(M+H)^+$. Methyl ester hydrolysis (*General synthesis* **7**) gave compound **19** as an off-white solid, 73% yield (200 mg). Mp: 175–178 °C. ^{1}H NMR (DMSO-d_6): δ 0.82 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 1.84–2.06 (m, 1H), 2.44 (s, 3H), 3.55 (dd, J = 9.3, 5.9 Hz, 1H), 4.11 (s, 3H), 5.33 (s, 2H), 7.19 (d, J = 9.1 Hz, 2H), 7.54 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.78–7.89 (m, 4H), 8.03 (d, J = 9.3 Hz, 1H), 14.10 (br s, 1H). MS *m*/*z*: 547.1 $(M-H)^-$, 1095.3 $(2M-H)^-$. HRMS: calcd for $[C_{29}H_{28}N_2O_7S + H]^+$: 549.169. Found: 549.1677. Anal. ($C_{29}H_{28}N_2O_7S$ 0.7H_2O): C, H, N.

13.16. *N*-({4′-[(5-Bromo-4-isopropoxy-3-methyl-1-benzofuran-2-yl)methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-D-valine (20)

Methyl *N*-({4′-[(5-bromo-4-isopropoxy-3-methyl-1-benzofuran-2-yl)methoxy]-l,1′-biphenyl-4-yl}sulfonyl)-D-valinate, *General synthesis* **8**, white solid, 21% yield (130 mg). Mp: 154–156 °C. ^{1}H NMR ($CDCl_3$): δ 0.89 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.37 (d, J = 6.0 Hz, 6H), 1.97–2.09 (m, 1H), 2.45 (s, 3H), 3.43 (s, 3H), 3.78 (dd, J = 10.2, 5.2 Hz, 1H), 4.70–4.79 (m, 1H), 5.09 (d, J = 10.2 Hz, 1H), 5.15 (s, 2H), 7.12 (d, J = 8.8 Hz, 3H), 7.43 (d, J = 8.8 Hz, 1H), 7.56–7.58 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 8.6 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H). MS *m*/*z*: 644 $(M+H)^+$, 661$(M + NH_4)^+$. Methyl ester hydrolysis (*General synthesis* **7**) gave compound **20** as an off-white solid in 83% yield (37 mg). Mp: 170–173 °C. ^{1}H NMR (MeOH-d_4): δ 0.78 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 6.3 Hz, 6H), 1.92–2.08 (m, 1H), 2.42 (s, 3H), 3.21 (s, 1H), 4.44–4.79 (m, 1H), 5.28 (s, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.80 (s, 4H). MS *m*/*z*: 628.1 $(M-H)^-$, 1257.1 $(2M-H)^-$. HRMS: calcd for $[C_{30}H_{32}BrN0_7S + H]^+$: 630.11556. Found: 630.1158.

13.17. *N*-({4′-[(4-Ethyl-3-methyl-1-benzofuran-2-yl)methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-L-valine (21)

Methyl *N*-({4′-[(4-ethyl-3-methyl-1-benzofuran-2-yl) methoxy]-1,1′-biphenyl-4-yl}sulfonyl)-L-valinate, *General synthesis* **8**, white solid, 51% yield (89 mg). ^{1}H NMR (DMSO-d_6): δ 0.80 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H), 1.25 (t, J = 7.4 Hz, 3H), 1.85–1.95 (m, 1H), 2.46 (s, 3H), 2.99 (q, J = 7.4 Hz, 2H), 3.34 (s, 3H), 3.56 (m, 1H), 5.30 (s, 2H), 7.04 (d, J = 7.3 Hz, 1H), 7.16–7.27 (m, 3H), 7.37 (d, J = 8.3 Hz, 1H), 7.69–7.87 (m, 6H), 8.27 (d, J = 9.1 Hz, 1H). MS *m*/*z*: 536.2 $(M+H)^+$, 1071.4 $(2M+H)^+$. Methyl ester hydrolysis (*General synthesis* **7**) gave compound **21** as an off-white solid in 79% yield (54 mg). Mp: 185–188 °C. ^{1}H NMR (DMSO-d_6): δ 0.80 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.25 (t, J = 7.6 Hz, 3H), 1.87–2.01 (m, 1H), 2.46 (s, 3H), 2.99 (q, J = 7.6 Hz, 2H), 3.47–3.57 (m, 1H), 5.29 (s, 2H), 7.04 (d, J = 7.3 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.24 (t, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.77–7.87 (m, 4H), 7.99 (d, J = 7.3 Hz, 1H), 13.91 (br s, 1H). MS *m*/*z*: 520.1 $(M-H)^-$, 1041.4 $(2M-H)^-$. HRMS: calcd for $[C_{29}H_{31}NO_6S + H]^+$: 522.1945. Found: 522.194.

13.18. *N*-[(4′-{[4-(3-Methoxypropyl)-3-methyl-1-benzofuran-2-yl]methoxy}-1,1′-biphenyl-4-yl)sulfonyl]-L-valine (22)

Methyl *N*-[(4′-{[4-(3-methoxypropyl)-3-methyl-1-benzofuran-2-yl]methoxy }-1,1′-biphenyl-4-yl)sulfonyl]-L-valinate, *General synthesis* **8**, white solid, 57% yield (210 mg). ^{1}H NMR (DMSO-d_6): δ 0.80 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.78–1.95 (m, 3H), 2.45 (s, 3H), 2.95–3.02 (m, 2H), 3.25 (s, 3H), 3.34 (s, 3H), 3.38 (t, J = 6.3 Hz, 2H), 3.56 (m, 1H), 5.29 (s, 2H), 7.03 (d, J = 7.3 Hz, 1H), 7.17–7.26 (m, 3H), 7.38 (d, J = 8.1 Hz, 1H), 7.70–7.79 (m, 4H), 7.81–7.87 (m, 2H), 8.27 (d, J = 9.1 Hz, 1H). MS *m*/*z*: 580.2 $(M+H)^+$. Methyl ester hydrolysis (*General synthesis* **7**) gave compound **21** as a white solid in 91% yield (171 mg). Mp: 168–170 °C. ^{1}H NMR (DMSO-d_6): δ 0.80 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.75–1.89 (m, 2H), 1.89–2.02 (m, 1H), 2.45 (s, 3H), 2.99 (t, 2H), 3.25 (s, 3H), 3.38 (t, J = 6.3 Hz, 2H), 3.54 (dd, J = 9.2, 5.9 Hz, 1H), 5.29 (s, 2H), 7.03 (d, J = 7.3 Hz, 1H), 7.14–7.27 (m, 3H), 7.38 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.77–7.87 (m, 4H), 8.02 (d, J = 9.2 Hz, 1H), 12.91 (br s, 1H). MS *m*/*z*: 564.2 $(M-H)^-$, 1129.4 $(2M-H)^-$. HRMS: calcd for $[C_{31}H_{35}NO_7S + H]^+$: 566.2207. Found: 566.2196. Anal. ($C_{31}H_{35}NO_7S$·0.4H_2O): C, H, N.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmc.2005.07.076.

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11. All pharmacokinetic studies were conducted at Wyeth Research (Andover MA). Male Sprague–Dawley rats were obtained with jugular vein catheters from Charles River Labs Wilmington MA. Test article was dosed through tail vein injection (iv 2 mg/kg) or oral gavage (PO). Blood samples (250 μL) were collected from the jugular vein (t = 0.08, 0.25, 0.5, 1, 2, 4, 6, 7, and 24 h). Plasma samples of 50 μL were diluted with 100 μL of acetonitrile containing a structurally similar molecule. Drug levels were determined by LC–MS/MS analysis. Pharmacokinetic parameters were calculated using the noncompartmental method in WINNONLIN v4.1 (Pharsight Mountain View CA).
12. Compound physicochemical properties and in vivo test information. Compound **1** solubility: 1 μg/mL at pH 7.4; permeability (PAMPA at pH 4.5): 0.20×10^{-6} cm/s; Cl: 1.9 mL/min/kg at 2 mg/kg dose; F: 7% at 25 mg/kg dose ($T_{1/2}$ = 207 min C_{max} = 3.4 μg/mL AUC = 16.2 h*μg/mL). Compound **2**: solubility: 41 μg/mL at pH 7.4; permeability (PAMPA at pH 4.5): 0.05×10^{-6} cm/s; Cl: 21 mL/min/kg.
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15. The inhibitory abilities of small molecules against different enzymes in this paper were tested using a continuous fluorescent assay For detailed information see Ref. 10 herein.
16. Physicochemical properties for compound **16**: solubility: 14 μg/mL at pH 7.4; permeability (PAMPA at pH 4.5): 1.10×10^{-6} cm/s.
17. Articular cartilage explant disks are harvested under sterile conditions from young bovine metacarpal phalangeal joints (Research 87 Hopkinton MA). Briefly full-thickness plugs are punched using a 8 mm cork borer and cartilage disks are generated by slicing 1 mm thick sections from the articular surface of the plugs. Disks are rinsed in PBS and subsequently cultured in medium. The medium consists of Dulbecco's Modified Eagle's medium (JRH Biosciences Lenexa KS) 50 μg/mL ascorbic acid (Wako Osaka Japan) 10 mM HEPES (Mediatech Herndon VA) 2 mM L-glutamine (Mediatech) antibiotic–antimycotic solution (Mediatech). Disks are cultured for 5 days with one media change in a 37 °C and 5% CO_2 environment to equilibrate the tissue prior to treatment. Following equilibration three disks are weighed together and placed in a 24-well tissue culture plate in 2 mL medium with and without 5 ng/mL IL-1α (Sigma St Louis MS). The compound in DMSO stock is added to cultures at different concentrations. Cultures are maintained for 18–21 days with media changes every 2–3 days. Conditioned medium is collected and analyzed for collagen release or stored at −20 °C for further analysis. Hydroxyproline assay is utilized for quantification of collagen release in the conditioned medium.
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21. Mobile-phase composition: 85% heptane/TFA: 15% ethanol for **35ii** and **38**; 5% heptane/TFA: 95% ethanol for **16**;

flow rate: 1.0 mL/min. No significant racemization of compounds was observed under the reaction conditions reported herein. For example, compound **16** was determined to be 99.85% pure (13.4 min) containing 0.15% of *S*-enantiomer (7.6 min).

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