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Identification of an Orally Efficacious Matrix Metalloprotease 12 Inhibitor for Potential Treatment of Asthma

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MMP-12 plays a significant role in airway inflammation and remodeling. Increased expression and production of MMP-12 have been observed in the lungs of asthmatic patients. Compound **27** was identified as a potent and selective MMP-12 inhibitor possessing good physicochemical properties. In pharmacological studies, the compound was orally efficacious in an MMP-12 induced ear-swelling inflammation model in the mouse with a good dose response. This compound also exhibited oral efficacy in a naturally *Ascaris*-sensitized sheep asthma model showing significant inhibition of the late phase response to allergen challenge. This compound has been considered for further development as a treatment therapy for asthma.

Introduction

Asthma is a chronic pulmonary disease that is characterized by airway inflammation, lung tissue remodeling, and progressive airflow obstruction that is reversible. This respiratory condition affects more than 300 million people worldwide, and this number is expected to grow due to increased prevalence with increasing age and environmental factors.[1] Presently, there are only symptomatic therapies, and no disease-modifying drugs are available for this disease.[2−4] Chronic inflammation and the pathologic degradation of the extracellular matrix (ECM[a]) of the bronchial wall may represent important causes of airflow obstruction in asthma. Matrix metalloproteinases (MMPs) have been suggested to be the major proteolytic enzymes that induce this airway remodeling.[5,6]

Macrophage metalloelastase (MMP-12) in particular, has been demonstrated to play a significant role in allergic airway inflammation and remodeling.[7] MMP-12 is the primary elastolytic enzyme of alveolar macrophages.[8] Preclinical studies support blocking MMP-12 as a valid approach for therapeutic intervention in asthma. Specifically, MMP-12 deficient mice display markedly reduced airway eosinophilia and airway hyper-responsiveness in response to allergen.[9,10] These mice also have less peribronchial fibrosis accompanied by reduced levels of α-smooth muscle actin and collagen type III deposition as detected by immunohistochemistry (IHC).[11] Furthermore, transgenic animals that overexpress IL-13 develop alveolar and lung enlargements, compliance alterations, respiratory failure, and death that are, in part, mediated by MMP-12. MMP-12 also makes a critical contribution to the accumulation of eosinophils and macrophages within the lungs of these mice and plays an important role in the IL-13-mediated induction of mRNA for MMP-2, -9, -13, and -14.[12] Significant increases in the expression of MMP-12 following antigen challenge or IL-13 exposure have been observed in both mouse and rat models of allergen-induced asthma.[13−15] IHC analyses in these studies revealed that MMP-12 was primarily expressed in airway epithelia and alveolar macrophages.[16] These findings are consistent with in vitro data that both human bronchial epithelial cells[17] and human airway smooth muscle cells[18] can also express and secrete MMP-12 upon stimulation with pro-inflammatory cytokines. Moreover, as detected by IHC, significantly increased levels of MMP-12 have been noted within airway smooth muscle of large airways in human fatal asthmatic patients when compared to nonasthmatics.[19] Collectively, these findings provide support for the potential involvement of MMP-12 in the inflammatory response and tissue remodeling in asthma and its role in contributing to the development of disease pathology.

Human MMP-12 is a 54 kDa proenzyme containing 470 amino acids composed of three domains: the pro-domain (9 kDa), the catalytic domain (22 kDa), and the hemopexin-like domain (23 kDa). The pro-domain includes a highly conserved cysteine residue that coordinates with the zinc ion to maintain the enzyme's latency. The catalytic domain

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[a] Abbreviations: ECM, extracellular matrix; MMP-12, matrix metalloprotease 12; MMP-13, matrix metalloprotease 13; MMP-2, matrix metalloprotease 2; COPD, chronic obstructive pulmonary disease; mCPBA: *meta*-chloroperoxybenzoic acid; TFA, trifluoroacetic acid; DBF, dibenzofuran; DBT, dibenzothiophene; DCM, dichloromethane; HTS, high-throughput screening; IHC, immunohistochemistry; ZCG, zinc chelating group; SAR, structure−activity relationship; PK, pharmacokinetics; HLM, human liver microsomes; MLM, mouse liver microsomes; hERG, human ether-a-go-go related gene; QD, quaque die (once a day); BID, bis in die (twice a day); PO, per os (by mouth); ID, intradermal; rh, recombinant human.

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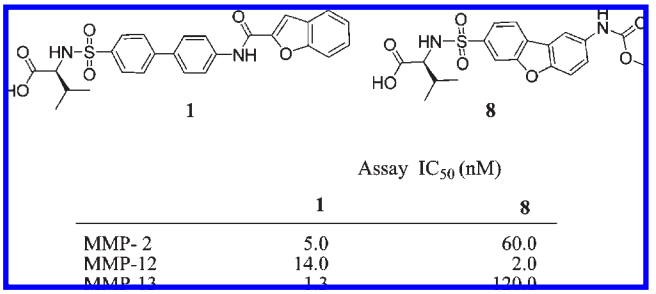


Figure 1. The structures of compounds **1** and **8**.

(22 kDa) bears the zinc-binding motif composed of three-conserved histidines coordinated with the zinc ion.[8] This is the domain that was used in our FRET assay for compound screening. The hemopexin domain[20] is attached to the catalytic domain by a hinge region. The functions of this domain include substrate recognition, tissue inhibitor binding, and localization of the enzyme in the extracellular matrix compartment.

Although MMP-12 is considered to be the most active MMP against elastin,[21] its substrates have been identified to include many other extracellular matrix components. Those include fibronectin, fibrillin-1, laminin, entactin, type IV collagen fragments, chondroitin sulfate, proteoglycans, and vitronectin.[22,23] In addition to inflammatory respiratory diseases, MMP-12 has been considered to be a therapeutic target for other chronic inflammatory, as well as musculoskeletal, neurological, cardiovascular, and neoplastic diseases.[24,25] Support for targeting these disease areas and MMP-12's role in their disease pathophysiology has been obtained largely with animal models, including gene knockout and transgene studies. These, in part, include in vivo studies in models of multiple sclerosis,[26,27] aortic aneurysm[28] and atherosclerosis,[29−32] and rheumatoid arthritis.[33] Herein, we report our drug discovery efforts focused on targeting MMP-12 for asthma with the identification of a potent and orally efficacious compound, MMP145 (**27**).

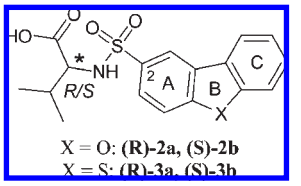
Development of SAR

Development of SAR was focused on modification of compounds composed of tricyclic cores, such as the dibenzofuran (DBF) or dibenzothiophene (DBT). One of the advanced DBF compounds, MMP408 (**8**, Figure 1), is a potent, selective, and orally available inhibitor with therapeutic potential for treatment of COPD.[34] SAR for this DBF series has been well-defined and could be used as a parallel frame of reference for the development of SAR of the structurally related DBT system. The tricyclic compound **8** was derived from a biphenyl MMP-13 inhibitor **1**[35] (Figure 1) via a traditional medicinal chemistry approach. The tricyclic DBF core has demonstrated the advantage of increased MMP-12 potency and selectivity over other MMPs. Therefore, the expansion of SAR to the DBT system was warranted. SAR developed for both DBT and DBF systems may provide more options for selecting lead candidates.

Before committing efforts into full SAR development activity, several C-ring unsubstituted DBT analogues were synthesized to assess the feasibility of this approach (Table 1). The SAR data provided primary information for comparison with the corresponding DBF analogues.

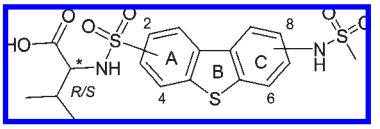
As seen in Table 1, the new DBT analogues are slightly less potent than the corresponding DBF counterparts (**3a** vs **2a**, 87 nM vs 38 nM; **3b**[36] vs **2b**, 750 nM vs 600 nM, respectively). However, the DBT analogues have better selectivity over MMP-13 than the corresponding DBF compounds (DBT **3a** with 158-fold vs DBF **2a** with 65-fold). A chiral recognition trend for the stereogenetic center of the amino acid is also observed. The (*R*)-enantiomer **3a** not only has better potency than the (*S*)-isomer **3b** (IC_{50}: 87 vs 750 nM) but also achieves better selectivity over MMP-13. For example, the (*R*)-**3a** is 158-fold selective over MMP-13, whereas the (*S*)-**3b** is only 80-fold selective.

Table 1. Selectivity Achieved with DBF and DBT Analogues



	IC_{50} (nM)		
compd	MMP-12	MMP-13	selectivity over MMP-13 (fold)
1	14	1.3	0.1
(*R*)-**2a**	38	2500	65
(*S*)-**2b**	600	25000	42
(*R*)-**3a**	87	13800	158
(*S*)-**3b**	750	60000	80

Table 2. SAR of the DBT Sulfonamide Analogues



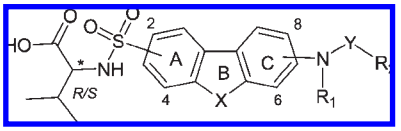
substituents A/C ring		compd	IC_{50} (nM) MMP-12	IC_{50} (nM) MMP-13
C2	C7	(*R*)-**4a**	4400	>25000
C2	C7	(*S*)-**4b**	2100	>25000
C3	C8	(*R*)-**5a**	60.0	277
C3	C8	(*S*)--**5b**	50.0	1135

With the preliminary favorable observations on potency, selectivity, and chiral recognition, full SAR was developed for the DBT system (Tables 2 and 3). New analogues from DBF were also investigated to maximize the likelihood of success in discovery of new drug candidates from these systems.

Derivatization on the DBT C-ring led to the preparation of the sulfonamide analogues (Table 2). As shown by the IC_{50} values, potencies of these new sulfonamide analogues against MMP-12 were reduced by comparison with the unsubstituted counterparts (**4a**/**b** over **3a**/**b**, respectively). Chiral recognition appears to be weak (**5a** vs **5b** for example). Although the C3/C8 regioisomers (**5a** and **5b**) have better potency over the C2/C7 counterparts (**4a** and **4b**), these preliminary data suggested that derivatization for sulfonamides was not the best approach for the SAR development.

Table 3 shows the SAR of the C-ring carbamate (Y = CO, R_2 = OR), and urea (Y = CO, R_2 = NRR′) analogues derived from modifications on the DBT and DBF C-ring. As shown by the IC_{50} values, potencies of some analogues have increased to single digit nanomolar or even subnanomolar (**7b**), with carbamates being more potent than the sulfonamides and ureas.

Table 3. SAR of Carbamate and Urea Analogues



substituents A/C ring		R_1	R_2	Y	X	compd	IC_{50} (nM) MMP-12	IC_{50} (nM) MMP-13
C2	C7	H	*O*-methyl	CO	S	(*R*)-**6a**	2900	> 25000
C2	C7	H	*O*-methyl	CO	S	(*S*)-**6b**	7300	> 25000
C3	C8	H	*O*-methyl	CO	S	(*R*)-**7a**	1.8	1.22
C3	C8	H	*O*-methyl	CO	S	(*S*)-**7b**	0.4	65
C3	C8	H	*O*-methyl	CO	O	(*S*)-**8**	2.0	120
C3	C7	H	*O*-methyl	CO	S	(*R*)-**9a**	29.0	1353
C3	C7	H	*O*-methyl	CO	S	(*R*)-**9b**	9.0	632
C3	C7	H	*O*-methyl	CO	O	(*R*)-**10a**	11.1	215
C3	C7	H	*O*-methyl	CO	O	(*R*)-**10b**	14.0	505
C3	C7	H		H	S	(*S*)-**11**	42.0	> 1000
C3	C7	H	*O*-ethyl	CO	S	(***R***)-**12a**	100.1	ND[a]
C3	C7	H	*O*-ethyl	CO	S	(*S*)-**12b**	6.3	56
C3	C7	H	*O*-isopropyl	CO	S	(*S*)-**13**	23.1	147
C3	C7	H	*O*-isobutyl	CO	S	(*S*)-**14**	20.2	334
C3	C7	H	*O*-2-(methylsulfonyl)ethyl	CO	S	(*S*)-**15**	7.6	40
C3	C7	H	*O*-(4)-butynyl	CO	S	(*S*)-**16**	6.1	23
C3	C7	H	*O*-phenyl	CO	S	(*S*)-**17**	25.0	225
C3	C7	H	*O*-*p*-tolyl	CO	S	(*S*)-**18**	36.3	235
C3	C7	H	*O*-(4-fluoro)phenyl	CO	S	(*S*)-**19**	28.0	217
C3	C7	H	*N*-ethyl	CO	S	(*S*)-**20**	260.0	809
C3	C7	H	*N*-cyclepentyl	CO	S	(*S*)-**21**	> 1000	> 1000
C3	C7	H	*N*-(thiophen-2-yl)ethyl	CO	S	(*S*)-**22**	187	456
C3	C7	H	*N*-(thiophen-2-yl)ethyl	CO	O	(*S*)-**23**	18.0	187
C3	C7	H	*N*-phenyl	CO	S	(*R*)-**24a**	1470	1286
C3	C7	H	*N*-phenyl	CO	S	(*S*)-**24b**	89.0	269
C3	C7	H	*N*-benzyl	CO	S	(*S*)-**25**	34.1	200
C3	C8	H	*O*-CH_2CH_3	CO	O	(*S*)-**26**	5.0	100
C3	C8	R_1, R_2 = $-CH_2CH_2O-$		CO	O	(*S*)-**27**	1.4	106
C3	C7	R_1, R_2 = $-CH_2CH_2O-$		CO	O	(*S*)-**28**	9.2	370
C3	C7	R_1, R_2 = $-CH_2CH_2O-$		CO	S	(*S*)-**29**	44.0	140
C3	C7	H		H	O	(*S*)-**30**	17.0	1093

[a] ND, not determined

The SAR for the carbamate analogues is well-defined. To determine the best regiochemistry, methyl carbamates were made for all regio combinations (C2/C7, C3/C8, and C3/C7). (D)- and (L)-Valines were also used to investigate the chiral recognition. Among the three regioisomers, the C3/C8 combination is more potent than its C2/C7 and C3/C7 counterparts. For example, the IC_{50} of **7b** (C3/C8) is 0.4 nM, whereas the **6b** (C2/C7) and **9b** (C3/C7) are 7300 and 9 nM, respectively. It is also notable that different regio combinations prefer different chiral configuration. For C2/C7 regioisomers, the (*R*)-enantiomer is more potent than the (*S*)-isomer (**6a** vs **6b**). For the C3/C8, the (*S*)-enantiomer **7b** is instead preferred over the (*R*)-**7a** (0.4 vs 1.8 nM), albeit both enantiomers are very potent. For the C3/C7 combination, the (*S*)-configuration is also preferred (**9b** vs **9a**, **12b** vs **12a**). It appears that the C3/C7 combination does prefer functionalized *O*-alkyl groups over simple alkyls (**15**, **16** vs **13**, **14**). *O*-Aryl carbamates (**17**, **18**, and **19**) also have reduced potency.

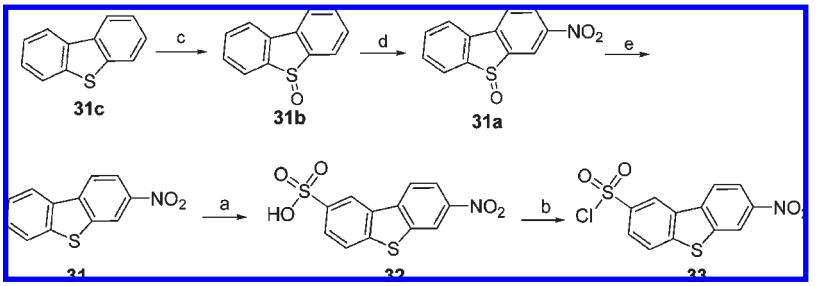
Efforts to improve potency through urea substituents were not successful. None of the urea analogues resulted in a notable increase in potency. For example, the IC_{50} of the most potent urea **25** is 34 nM, which was not a significant improvement over its parent aniline **11** (42 nM). A similar lack of potency improvement with the urea analogues was seen with the DBF system (**23** vs **30**), albeit the ureas from DBF C3/C7 are in general more potent than those of DBT (**23** vs **22**, 18 vs 187 nM, respectively). The C3/C7 ureas appear to prefer the *S*-configuration (**24b** vs **24a**, 89 vs 1470 nM, respectively). However, this preference did not lead to positive outcomes compared to the parent aniline **11**.

Because the carbamate analogues provided the best potency and selectivity, further SAR development on the carbamates was warranted. The investigation of SAR led to the preparation of cyclic carbamate derivatives (**27**−**29**). The DBF cyclic carbamate **27** with a C3/C8 regio combination has an IC_{50} value of 1.4 nM, which is a 3.5-fold increase in potency compared to that of the corresponding open chain ethyl carbamate **26** (5 nM). However, when the regio combination changed to C3/C7 (**28**), a 6.5-fold drop in potency was observed. It is also interesting to note that the DBT cyclic carbamate **29** (C3/C7) experienced an even greater reduction in activity (44 nM). Expanding the five-membered ring to six with an additional methylene also resulted in loss of potency (not shown).

Chemistry

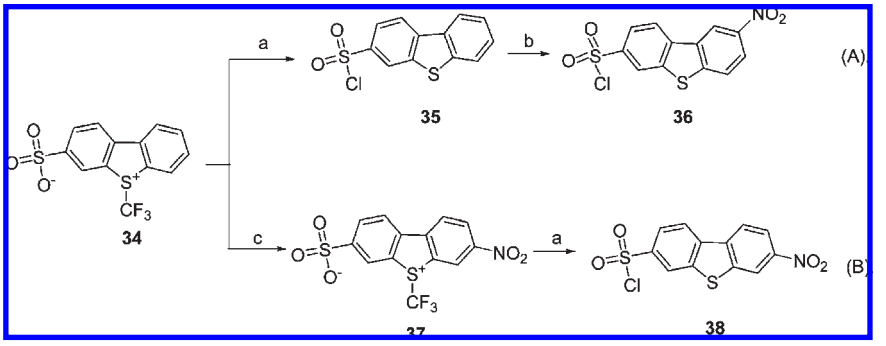
Preparation of the above analogues requires key nitro-DBT sulfonyl chlorides **33**, **36**, and **38** (Schemes 1 and 2). Synthetic

Scheme 1. Preparation of the Key DBF Intermediate **33**



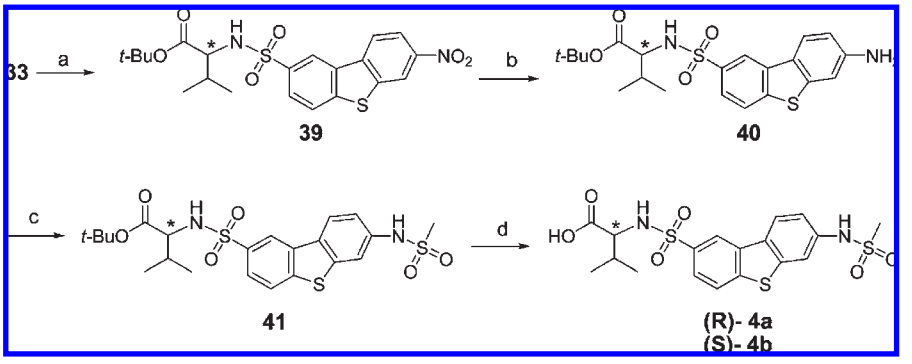
Reagents and conditions: (a) $ClSO_3H$, TFA, 97%; (b) $SOCl_2$, DMF (cat.) 90−100%; (c) mCPBA, DCM 79%; (d) HNO_3/TFA, 83%; (e) HOAc, conc HBr, 89%.

Scheme 2. Preparation of the Key DBF Intermediates **36** and **38**



Reagents and conditions: (a) $SOCl_2$, DMF (cat.), 90−100%; (b) HNO_3, TFA, 97%; (c) 30% oleum, 90% HNO_3, 94%.

Scheme 3. Preparation of C2/C7 Methyl Sulfonamides **4a** and **4b**



Reagents and conditions: (a) (D/L)-valine esters, TEA, DCM, 94%; (b) Pd/C, H_2, MeOH, 98%; (c) CH_3SO_2Cl, pyridine, DCM, 85%; (d) TFA, DCM, 98%.

routes with high overall yields for preparation of the three key nitro-DBT sulfonyl chlorides were developed according to their defined combinations. Another key feature for these developed routes is the high regioselectivity, which is crucial for synthetic efficiency.

Preparation of the sulfonyl chloride **33** (C2/C7 combination) was straightforward and required two steps from a known intermediate **31**.[37] Sulfonation of **31** with chlorosulfonic acid in chloroform afforded the desired C2-sulfonic acid **32**, which was treated with thionyl chloride to convert the acid to sulfonyl chloride **33** (Scheme 1) in high yield. Preparation of **31** is a three-step process from the commercially available dibenzothiophene. The first step involved an oxidation of the DBT to the corresponding sulfoxide **31b** using chlorine gas in DCM. However, overoxidation to sulfone was observed. A modified procedure using one equivalent *m*CPBA in DCM provided the selective oxidation to **31b** with high yield. The electron-deficient sulfoxide directed the nitration to the desired meta position to generate the isomer **31a**,[38] which was reduced by following the known procedure with HBr to afford **31**.[39] The overall yield was 58%, much better than the direct nitration on DBT, where the 3-nitro DBT was obtained as a minor isomer with only 15% yield.[40]

Preparation of the 8-nitro-DBT-3-sulfonyl chloride **36** (Scheme 2) would require a long route with many functional group manipulations if starting from the 3-nitro DBT **31** via reduction of $-NO_2$ to $-NH_2$, diazonium salt formation, displacement with SO_2, followed by conversion to **35**. We chose to investigate a new route based on a commercially available compound, 5-(trifluoromethyl)-5*H*-dibenzo[*b*, *d*]thiophenium-3-sulfonate (**34**), which has been developed as a unique electrophilic trifluoromethylating agent.[41] After

optimization of the reaction conditions, it was found that treatment of **34** with neat thionyl chloride at reflux in the presence of a catalytic amount of DMF generated the sulfonyl chloride **35** in quantitative yield. To our delight, the CF_3 group was removed simultaneously from the thiophene sulfur atom under the reaction conditions. Removal of the CF_3 group also set the stage for regioselective nitration (*para*-orientation to *S*), which led to the formation of the desired C8-nitro compound **36** upon treatment of **35** with nitric acid in TFA (Scheme 2, route A).

Preparation of the 7-nitrodibenzo[*b*,*d*]thiophene-3-sulfonyl chloride (**38**) takes advantage of the existing strong electron-withdrawing effect imparted by the trifluoromethylsulfonium cation (S^+-CF_3), which should direct the nitration at the desired C7 position (*meta*-orientation to *S*).[42] It came as no surprise that this group also substantially deactivates the C-ring, and harsh conditions (reaction carried out in 30% oleum, 90% HNO_3) had to be used to affect the nitration process to obtain the key intermediate **37** (Scheme 2, route B). Treatment of **37** with thionyl chloride in the presence of catalytic amount of DMF afforded **38** in excellent yield (94%).[43]

As illustrated in Scheme 2, preparation of the key intermediates **36** and **38** is an integral chemistry effort for maximizing synthetic efficiency; the same starting material **34** was used, but the reactivity was tempered at different stages to generate the desired regioisomers **36** and **37** from nitration.

With the three key intermediates **33**, **36**, and **38** in hand, preparation of the DBT analogues for SAR development was straightforward. Scheme 3 illustrates the synthesis of **4a** and **4b**. The amino acid moiety of **4a**/**4b** was installed via coupling of the sulfonyl chloride **33** with either (D)- or (L)-valine *t*-butyl ester in the presence of base to afford **39**. The nitro group on the C ring of **39** was reduced to the corresponding aniline analogue **40** in high yield via palladium catalyzed hydrogenolysis. Compound **40** was then derivatized by treatment with methyl sulfonyl chloride in the presence of base to generate the penultimate *t*-butyl ester **41**. The *t*-butyl was removed under acidic conditions to generate the desired acid products **4a**/**4b** in good overall yield from compound **33**.

The C3/C8 methyl sulfonamides analogues **5a** and **5b** were prepared similarly using the intermediate **36**.

Scheme 4 illustrates the synthesis of the methyl carbamate analogues. Compound **40** was treated with methyl chloroformate in the presence of pyridine at 0 °C in DCM to produce the *t*-butyl ester methyl carbamate. The *t*-butyl was removed by reacting with TFA (30% in DCM) to generate the desired carboxylic acids **6a**/**6b** as a white powder.

Originally, the valine methyl esters were used for the preparation of **6a**/**6b**. However, saponification of the corresponding penultimate methyl ester under basic conditions resulted in the desired acids but with contamination arising from the decomposition of the carbamate moiety. Thus, it was replaced with the *t*-butyl ester. Chiral analysis of **6a**/**6b** confirmed that there was no impurity from epimerization of the chiral center during the synthesis. Other carbamate and urea analogues in Table 3 were prepared similarly using different sulfonyl chloride and *N*-derivatization agents to afford analogues from **7a** to **26**.

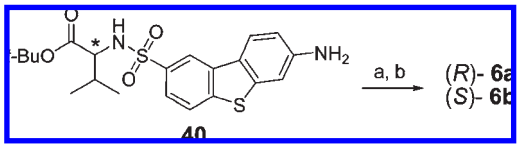
The cyclic carbamates **27**−**29** were prepared by a two-step process. For example, compound **27** was prepared by treatment of **46** with 2-bromoethyl chloroformate to form the open chain carbamate **48**, which was cyclized under basic conditions ($KHCO_3$/DMF) to generate **49**. Treatment of **49** with TFA resulted in the desired **27** as a white solid (Scheme 5).

Cyclic carbamates **28** and **29** were prepared similarly using the corresponding aniline substrates with good yields.

Profiling of the Leads. Further profiling was focused on the carbamate analogues due to their MMP-12 potencies. Pharmacokinetic data indicate that carbamate analogues **7a**, **7b**, and **27** exhibit decent exposure and moderate bioavailability in C57BL/6 mice (Table 4).

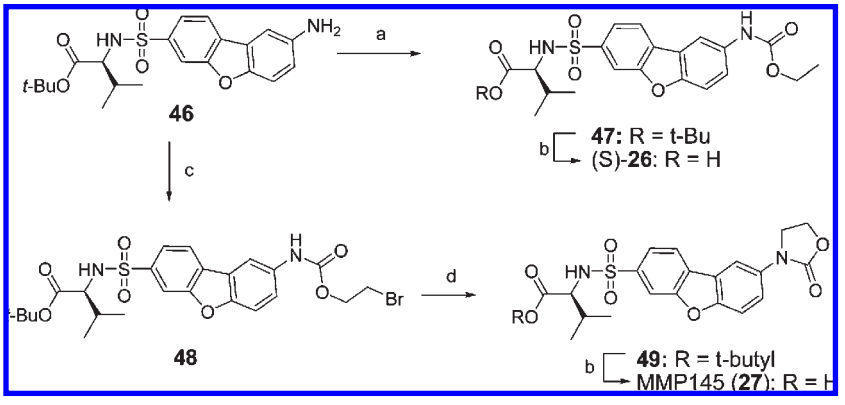
It is interesting to note that the (*S*)-enantiomer **7b** has better PK properties than the (*R*)-enantiomer **7a** (lower clearance, higher C_{max} and AUC). Compounds **8** and **27** have the lowest clearance among these analogues suggesting low metabolism. These compounds were further evaluated in the metabolic stability studies carried out in the liver microsomal system. All the compounds in Table 3 showed very good stability in mouse (C57BL/6, female), rat, and human liver microsomes ($t_{1/2}$ > 30 min). The acyl glucuronides and compounds from

Scheme 4. Preparation of C2/C7 Methyl Carbamates **6a** and **6b**



Reagents and conditions: (a) methyl chloroformate, TEA, DCM, 90−94%; (b) TFA, DCM, 95−98%.

Scheme 5. Preparation of the Cyclic Carbamate **27**



Reagents and conditions: (a) ethyl chloroformate, TEA, DCM, 92%; (b) TFA, DCM, 95−98%; (c) 2-bromoethyl chloroformate, TEA, DCM, 91%; (c) $KHCO_3$, DMF, 85%.

Table 4. Pharmacokinetic Data for Selected Compounds (C57BL/6 Mice)

compd	IV (mg/kg)	Vdss (L/kg)	CL (mL/min/kg)	PO (mg/kg)	$T_{1/2}$ (h)	C_{max} (ng/mL)	AUC/dose (ng·h/mL)/(mg/kg)	*F*%
7a	2	3.7	59.9	30	4.6	738	53.4	19
7b	2	1.7	31.2	30	3.1	1815	182.9	34
8	2	1.9	17.2	30	3.0	3084	249.2	27
27	2	0.8	18.0	10	3.1	456	152.4	17

Scheme 6. Plausible Pathway for the in Vitro Degradation of **8** to Aniline **51**

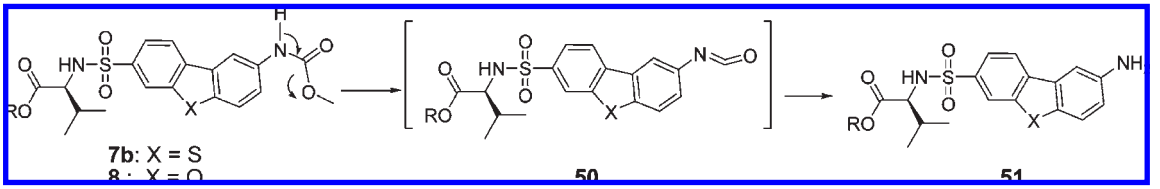


Table 5. Cross-Species Activity and Selectivity Profile of **27**

Cross Species MMP-12 Activity IC_{50} (nM)											
human			mouse			rat					sheep
1.4			27			72					2.0
Selectivity over Other Human MMPs IC_{50} (nM)											
MMP-1	-2	-3	-7	-8	-9	-12	-13	-14	TACE	Agg-1	Agg-2
5460	66	300	7830	37	318	1.4	46	2250	40000	18000	22600

amino acid side chain oxidation were the metabolites detected by LCMS techniques in all species at a very low level.

Further in vitro metabolic stability of **7b** and **8** was also determined in cryopreserved hepatocytes of dog, monkey, and human. In this system, the corresponding aniline metabolite from **7b** and **8** were detected. We hypothesized that the free −NH at the carbamate moiety might be responsible for the metabolic degradation to the anilines (Scheme 6).

The cyclic carbamate **27** was thus synthesized to replace the free N−H and tested under the same conditions as that of **7b** and **8**. No aniline metabolite **51** was detected. The improved metabolic stability of **27** supports the hypothesis that the free N−H is a liability for the biological degradation. Compound **27** did not inhibit CYP450 isoenzymes, such as 3A4, 2D6, and 2C9. Further drug safety studies for **27** were performed with favorable results. For example, it is negative in the screening Ames test and has no hERG activity at 10 μM in the IonWorks Assay.

Compound **27** was also profiled for cross-species MMP-12 activity and selectivity against other human MMPs (Table 5). Compared with human MMP-12, compound **27** has lower potency against rodent MMP-12 (19- and 51-fold less active for mouse and rat, respectively). However, it does have comparable sheep MMP-12 activity with an IC_{50} value of 2.0 nM, which is equipotent to human. The compound also maintains a good selectivity profile over other human MMPs.

In Vivo Pharmacology. Compound **27** was evaluated orally in two animal models: the mouse ear inflammation model and the sheep asthma model.

To evaluate the compounds initially in vivo, an MMP-12 dependent inflammatory response in the ear was induced in C57BL/6 mice by a single intradermal (ID) injection of recombinant human (rh) MMP-12.[44] A 2 h postadministration time point with rhMMP-12 was selected as the optimal period to measure the inhibitory activity of MMP-12 compounds. In this model, compound **27** was able to reproducibly

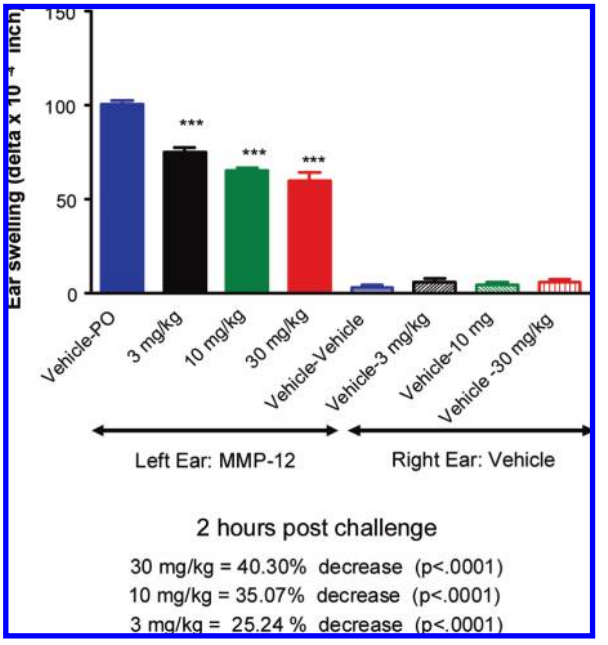


Figure 2. Compound **27** reduced edema in a mouse ear-swelling model. To induce an MMP-12 mediated edematous reaction, mice were challenged intradermally in the left ear with rhMMP-12. As a control, the contralateral right ear was challenged with vehicle alone. Edema was measured as an increase in ear thickness 2 h post challenge (mean ± SE, n = 7−8 mice/group). Compound **27** was administered orally (PO) the evening prior to challenge and again 2 h prior to challenge. Compound **27** significantly attenuated rhMMP-12 induced ear edema (*** $p < 0.0001$) by approximately 40%, 35%, and 25% when administered at 30 (red bar), 10 (green bar), and 3 (black bar) mg/kg PO, respectively, when compared to identically challenged vehicle treated control animals (blue bar). In each group of animals, the contralateral right ears that were challenged ID with vehicle alone did not mount an edematous reaction.

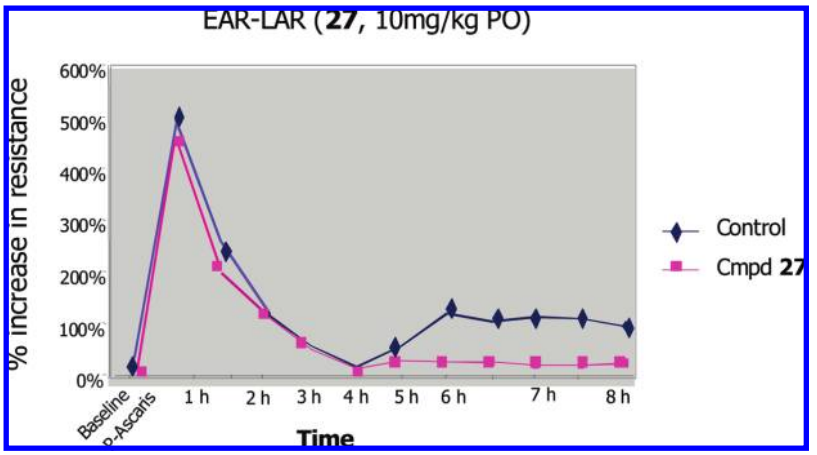


Figure 3. Compound **27** blocked the LAR in a sheep asthma model. To examine the effects on EAR and LAR, compound **27** was administered BID at 10 mg/kg PO the day prior to *Ascaris suum* airway challenge. Animals received a third dose of compound 1 h prior to allergen challenge. Airway resistance was measured throughout the course of the ensuing 8 h period ($N = 2$).

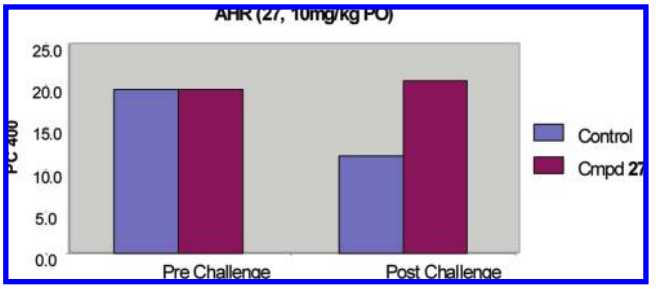


Figure 4. Compound **27** inhibited the AHR provoked by inhalation of the cholinergic agonist carbachol in a sheep asthma model. AHR was assessed by determining the cumulative carbachol concentration that increased specific lung resistance by 400% over the post saline value (PC_{400}) ($N = 2$).

inhibit rhMMP-12 induced inflammation when administered 16 and 2 h prior to the rhMMP-12 challenge. Specifically, comparative evaluation of 3, 10, and 30 mg/kg, PO, BID doses showed significant reductions in ear swelling at all the doses examined ($p < 0.0001$) when compared to vehicle controls. Histology studies suggested that the resulting decrease in edema with compounds appeared to be due (data not shown), at least in part, to a reduction in rhMMP-12-associated degranulation of resident mast cells present in the ear. The results of a representative study evaluating the efficacy of **27** in the mouse ear-swelling model are shown in Figure 2.

The oral efficacy of compound **27** was evaluated in a sheep asthma model. In this model, sheep that are naturally sensitized to the nematode *Ascaris suum* are challenged via the airways with an aerosol of *Ascaris suum* to induce an early phase airway bronchoconstriction (EAR) that occurs approximately 1 h post allergen challenge, followed by a late phase bronchoconstriction that occurs approximately 6−8 h post challenge. The airways of the challenged animals are also hyperresponsive to the muscarinic agonist, carbachol, resulting in airway bronchoconstriction at much lower concentrations of carbachol than is observed with nonchallenged animals. The airway hyperresponsiveness (AHR) can be assessed by determining the cumulative carbachol concentration that increases specific lung resistance by 400% over the post saline value (PC_{400}).

To evaluate whether or not compound **27** could attenuate the EAR and LAR phases of the bronchoconstrictive response, animals received three doses of compound (twice the day before allergen challenge and then 1 h prior to challenge, at 10 mg/kg per dose, PO). For the measurement of AHR, the sheep received a fourth dose of compound (8 h post allergen challenge). AHR to aerosolized carbachol was measured the day following *Ascaris suum* airway challenge. As dosed, compound **27** significantly inhibited the LAR to allergen challenge (Figure 3) and blocked the carbachol induced AHR (Figure 4).

Conclusion

In summary, molecules with drug-like properties for the MMP-12 program were obtained via SAR development of both DBT and DBF derivatives. Modification to increase the metabolic stability of the carbamate analogues resulted in **27**, which maintains the potency, selectivity, and bioavailability as compared to **8**. The key factor that stabilizes the carbamate group from metabolic degradation is the removal of the free −NH on the carbamate moiety via formation of the cyclic ring. The demonstrated ability of **27** in attenuating episodic and reversible airway narrowing supports further development of this compound as a potential therapeutic for asthma.

Experimental Section

Determination of IC_{50} against Human MMP-12. The assays for human MMP-12 and MMP-13 activity were performed by incubating 20 μM of the fluorogenic peptide substrate MCA-Pro-Leu-Gly-Leu-Dpa(DNP)-Ala-Arg (Anaspec, San Jose, CA) with 0.5 nM recombinant human MMP-12 or MMP-13 catalytic domain along with various concentrations of compound in 50 mM HEPES, pH 7.5, 100 mM NaCl, 5 mM $CaCl_2$, 0.005% Brij-35, and 10% DMSO. The rate of increase in fluorescent signal was measured on a Safire plate reader (Tecan, Mannedorf, Switzerland) exciting at a wavelength of 325 nm and measuring at an emission wavelength of 395 nm. The enzymes were expressed in *Escherichia coli*, refolded from insoluble inclusion bodies, and purified.

Determination of IC_{50} against Mouse MMP-12. The assay to measure potency in mouse MMP-12 catalytic domain was identical in format to the assay used for the human MMP enzymes with the exception that 3 nM mouse MMP-12 was required to obtain similar catalytic rates. Cleavage of 20 μM of the MCA-Pro-Leu-Gly-Leu-Dpa (DNP)-Ala-Arg peptide was

measured over time, monitoring λ_{ex} 325 nm and λ_{em} 395 nm (Tecan Safire 2, Tecan, Mannedorf, Switzerland).

Determination of IC_{50} against Sheep MMP-12. The assay to measure inhibitor potency in sheep MMP-12 catalytic domain was identical in format to the assay used for the human MMP enzymes. The concentration of sheep MMP-12 in the assay was 0.5 nM. Cleavage of 20 μM of the MCA-Pro-Leu-Gly-Leu-Dpa (DNP)-Ala-Arg peptide was measured over time, monitoring λ_{ex} 325 nm and λ_{em} 395 nm.

Evaluation of the Efficacy of a MMP-12 Inhibitor in a Mouse Ear-Swelling Model. Female C57BL/6 mice from Taconic (Germantown, NY) 8−10 weeks in age were received and allowed to acclimate at least one week prior to study. The mice were then randomly assigned to four groups. Standard mouse chow and water were offered ad libitum. The night prior to study, mice were pre-dosed with vehicle, 30, 10, or 3 mg/kg (PO).

The following morning, the mice were again dosed with vehicle (2% Tween 80 and 0.5% methylcellulose) or compound. The mice were anesthetized with isofluororane (Baxter Healthcare, Deefield, IL) until they exhibited shallow breathing. Baseline ear measurements were taken on all of the mice, left and right ears with a Mitutoyo Micrometer (Grainger, Boston, MA). Mice were then challenged intradermally in the left ear with 2.5 μg/25 μL of human MMP-12 protein with a Hamilton syringe and 30 gauge needle. Mice were also challenged with vehicle (MMP-12 diluent) in the right ear [20 mM Tris (pH 7.5), 200 mM NaCl, 5 mM $CaCl_2$ buffer]. Mice were placed back in their respective cages for recovery. The ear thickness measurements (extent of swelling) were taken at 2 h post challenge. The extent of ear swelling was expressed as the increment of the thickness ($\times 10^{-4}$ inch) pre- and postchallenge at each individual time point.

Evaluation of the Efficacy of a MMP-12 Specific Inhibitor in a Sheep Asthma Model. Compounds were dosed either intravenously or per oral route twice daily, the day before challenge, and then the following day (day of *Ascaris suum* challenge) 1 h prior to challenge and 8 h post challenge. Increases in airway resistance were measured throughout the day to capture both the early phase asthmatic response (EAR) and late phase asthmatic response (LAR). Airway hyper-responsiveness (AHR) to aerosolized carbachol was measured the following day (24 h post challenge). Following AHR measurements, lungs were lavaged and total cell counts were quantified in the BAL fluid.

Chemistry. All reagents and solvents were of commercial quality and used without further purification. Column chromatography was performed using Merck silica gel 60 (230−400 mesh). Proton nuclear magnetic spectroscopy ^{1}H NMR spectra were obtained on Bruker spectrometers. Low-resolution mass spectra (MS) were obtained using a micromass platform electrospray ionization quadrapole mass spectrometer. High resolution exact mass measurements (HRMS) were performed on a Bruker ApexIII 7T FT/ICR/MS. All intermediates were characterized by ^{1}H NMR. All new final SAR compounds were determined to be consistent with proposed structure by ^{1}H NMR, MS, and HRMS and were greater than 95% pure in two solvent systems (HPLC method 1: H_2O-CH_3CN; HPLC method 2: H_2O−MeOH) as determined using an Agilent 1100 HPLC instrument on a C18 column.

For detailed synthetic schemes and procedures, please see the Supporting Information section.

(*R*)-3-Methyl-2-(7-(methylsulfonamido)dibenzo[*b*,*d*]thiophene-2-sulfonamido)butanoic Acid (4a). The title compound **4a** was prepared from 3-nitrodibenzothiophene (see Supporting Information for detailed procedures) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.86−2.04 (m, 1H), 3.10 (s, 3H), 3.64 (dd, J = 5.8, 9.6 Hz, 1H), 7.39 (dd, J = 1.9, 8.7 Hz, 1H), 7.83 (dd, J = 1.8, 8.6 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 9.9 Hz, 1H), 8.19 (d, J = 8.6 Hz, 1H), 8.41 (d, J = 8.6 Hz, 1H), 8.61 (d, J = 1.5 Hz, 1H), 10.17 (s, 1H), 12.54 (s, 1H). HRMS: calcd for $C_{18}H_{20}N_2O_6S_3 + H^+$, 457.05562; found (ESI-FTMS, $[M + H]^+$), 457.0548.

(*S*)-3-Methyl-2-(7-(methylsulfonamido)dibenzo[*b*,*d*]thiophene-2-sulfonamido)butanoic Acid (4b). The title compound was prepared as a white solid following the procedures described for the preparation of **4a** using (*S*)-*tert*-butyl 2-amino-3-methylbutanoate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.87−2.03 (m, 1H), 3.10 (s, 3H), 3.64 (dd, J = 5.9, 9.5 Hz, 1H), 7.39 (dd, J = 2.0, 8.6 Hz, 1H), 7.83 (dd, J = 1.8, 8.6 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 8.03−8.14 (m, 1H), 8.19 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 8.6 Hz, 1H), 8.61 (d, J = 1.8 Hz, 1H), 10.16 (s, 1H), 12.55 (s, 1H). HRMS: calcd for $C_{18}H_{20}N_2O_6S_3 + H^+$, 457.05562; found (ESI-FTMS, $[M + H]^+$), 457.0555.

(*R*)-3-Methyl-2-(8-(methylsulfonamido)dibenzo[*b*,*d*]thiophene-3-sulfonamido)butanoic Acid (5a). The compound was obtained as a white solid (see Supporting Information for detailed procedures). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.82 Hz, 3H), 1.87−2.02 (m, 1H), 3.07 (s, 3H), 3.61 (dd, J = 5.9, 9.5 Hz, 1H), 7.46 (dd, J = 2.0, 8.7 Hz, 1H), 7.88 (dd, J = 1.5, 8.3 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 8.16 (d, J = 9.4 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.43 (d, J = 8.6 Hz, 1H), 8.46 (d, J = 1.8 Hz, 1H), 9.96 (s, 1H), 12.53 (s, 1H). HRMS: calcd for $C_{18}H_{20}N_2O_6S_3 + H^+$, 457.05562; found (ESI-FTMS, $[M + H]^+$), 457.0546.

(*S*)-3-Methyl-2-(8-(methylsulfonamido)dibenzo[*b*,*d*]thiophene-3-sulfonamido)butanoic Acid (5b). Following procedures for the preparation of **5a** and using (*S*)-*tert*-butyl 2-amino-3-methylbutanoate for the coupling reaction with the sulfonyl chloride **33**, compound **5b** was prepared as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H), 1.89−2.01 (m, 1H), 3.07 (s, 3H), 3.61 (dd, J = 5.9, 9.47 Hz, 1H), 7.46 (dd, J = 2.3, 8.6 Hz, 1H), 7.88 (dd, J = 1.8, 8.3 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 8.16 (d, J = 9.4 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.43 (d, J = 8.3 Hz, 1H), 8.47 (d, J = 1.5 Hz, 1H), 9.96 (s, 1H), 12.53 (s, 1H). HRMS: calcd for $C_{18}H_{20}N_2O_6S_3 + H^+$, 457.05562; found (ESI-FTMS, $[M + H]^+$), 457.0546.

(*R*)-2-(7-(Methoxycarbonylamino)dibenzo[*b*,*d*]thiophene-2-sulfonamido)-3-methylbutanoic Acid (6a). The title compound **6a** was prepared following the scheme and synthetic procedures described in the Supporting Information section. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.81 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.88−2.03 (m, 1H), 3.64 (dd, J = 5.9, 9.5 Hz, 1H), 3.72 (s, 3H), 7.56 (dd, J = 1.9, 8.7 Hz, 1H), 7.81 (dd, J = 1.8, 8.6 Hz, 1H), 8.10 (d, J = 9.6 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 8.22 (d, J = 1.8 z, 1H), 8.35 (d, J = 8.6 Hz, 1H), 8.57 (d, J = 1.5 Hz, 1H), 10.07 (s, 1H), 12.54 (s, 1H). HRMS: calcd for $C_{19}H_{20}N_2O_6S_2 + H^+$, 437.08355; found (ESI-FTMS, $[M + H]^+$), 437.0833.

(*S*)-2-(7-(Methoxycarbonylamino)dibenzo[*b*,*d*]thiophene-2-sulfonamido)-3-methylbutanoic Acid (6b). Following procedures for the preparation of **6a** and using the corresponding (*S*)-enantiomer isomer, (*S*)-2-(7-(methoxycarbonylamino)dibenzo-[*b*,*d*]thiophene-2-sulfonamido)-3-methylbutanoic acid, compound **6b** was prepared as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.88−2.03 (m, 1H), 3.64 (dd, J = 5.9, 9.5 Hz, 1H), 3.72 (s, 3H), 7.56 (dd, J = 1.9, 8.7 Hz, 1H), 7.81 (dd, J = 1.8, 8.3 Hz, 1H), 8.10 (d, J = 9.6 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 8.23 (d, J = 1.8 z, 1H), 8.35 (d, J = 8.8 Hz, 1H), 8.57 (d, J = 1.8 Hz, 1H), 10.07 (s, 1H), 12.54 (s, 1H). HRMS: calcd for $C_{19}H_{20}N_2O_6S_2 + H^+$, 437.08355; found (ESI-FTMS, $[M + H]^+$), 437.0833.

(*R*)-2-(8-(Methoxycarbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (7a). Following procedures for the preparation of **6a** and using the intermediate (*R*)-*tert*-butyl 2-(8-aminodibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoate (see preparation of **5a**), compound **7a** was prepared as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 1.87−2.01 (m, 1H), 3.61 (dd, J = 5.8, 9.6 Hz, 1H), 3.73 (s, 3H), 7.61 (dd, J = 2.0, 8.8 Hz, 1H), 7.87 (dd, J=1.8, 8.3 Hz, 1H), 8.01 (d, J=8.8 Hz,

1H), 8.15 (d, J = 9.6 Hz, 1H), 8.33 (d, J = 8.3 Hz, 1H), 8.44 (d, J = 1.5 Hz, 1H), 8.53 (d, J = 1.5 Hz, 1H), 9.95 (s, 1H), 12.54 (s, 1H). HRMS: calcd for $C_{19}H_{20}N_2O_6S_2 + H^+$, 437.08355; found (ESI-FTMS, $[M + H]^+$), 437.0822.

(*S*)-2-(8-(Methoxycarbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (7b). Following procedures for the preparation of **7a** and using the corresponding (*S*)-enantiomer, (*S*)-*tert*-butyl 2-(8-aminodibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoate, compound **7b** was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 1.88−2.02 (m, 1H), 3.61 (dd, J = 6.1, 9.6 Hz, 1H), 3.73 (s, 3H), 7.61 (dd, J = 2.2, 8.7 Hz, 1H), 7.87 (dd, J = 1.5, 8.3 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 9.6 Hz, 1H), 8.33 (d, J = 8.3 Hz, 1H), 8.44 (d, J = 1.5 Hz, 1H), 8.53 (d, J = 1.5 Hz, 1H), 9.95 (s, 1H), 12.54 (s, 1H). HRMS: calcd for $C_{19}H_{20}N_2O_6S_2 + H^+$, 437.08355; found (ESI-FTMS, $[M + H]^+$), 437.0833.

(*S*)-2-(8-(Methoxycarbonylamino)dibenzo[*b*,*d*]furan-3-sulfonamido)-3-methylbutanoic Acid (8). The title compound was obtained as a white solid following the procedures described for the preparation of compound **27** using methyl chloroformate for the *N*-derivatization step, compound **8** was obtained as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 0.93 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 2.01−2.13 (m, 1H), 3.75 (d, J = 5.6 Hz, 1H), 3.80 (s, 3H), 7.51−7.62 (m, 2H), 7.87 (dd, J = 8.2, 1.6 Hz, 1H), 8.07 (d, J = 1.0 Hz, 1H), 8.13 (d, J = 7.6 Hz, 1H), 8.27 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 17.6, 18.9, 30.3, 51.7, 61.3, 110.2, 110.7, 112.1, 120.6, 121.3, 121.4, 122.5, 127.0, 135.3, 140.0, 152.4, 154.2, 154.8, 172.0. HRMS: calcd for $C_{19}H_{20}N_2O_7S + H^+$, 421.10640; found (ESI-FTMS, $[M+H]^{1+}$), 421.1069. Anal. calcd for $C_{19}H_{20}N_2O_7S$, C 55.29%, H 5.10%, N 6.45%; found C 54.70%, H 5.03%, N 6.32%.

(*R*)-2-(7-(Methoxycarbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (9a). The title compound was prepared as a white solid following the procedures described for the preparation of **9b** and using the (*R*)-valine *t*-butyl ester. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H), 1.88−2.02 (m, 1H), 3.60 (dd, J = 8.9, 6.0 Hz, 1H), 3.73 (s, 3H), 7.58 (dd, J = 8.7, 1.9 Hz, 1H), 7.84 (dd, J = 8.5, 1.5 Hz, 1H), 8.05 (d, J = 9.4 Hz, 1H), 8.22 (d, J = 1.8 Hz, 1H), 8.35 (d, J = 8.5 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.40 (s, 1H), 10.04 (s, 1H), 12.48 (s, 1H). ESI-POS $[M - H]^+$ 437.0.

(*S*)-2-(7-(Methoxycarbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (9b). The title compound was prepared following the synthetic scheme and procedures described in the Supporting Information section. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H), 1.95 (m, 1H), 3.61 (m, 1H), 3.72 (s, 3H), 7.81 (d, J = 8.8 Hz, 1H), 7.91 (dd, J = 8.5, 1.6 Hz, 1H), 8.10 (m, 1H), 8.42 (d, J = 8.8 Hz, 1H), 8.50 (d, J = 8.5 Hz, 1H), 8.52 (d, J = 1.3 Hz, 1H), 9.46 (s, 1H), 12.45 (s, 1H). ESI-POS $[M - H]^+$ 437.0.

(*R*)-2-(7-(Methoxycarbonylamino)dibenzo[*b*,*d*]furan-3-sulfonamido)-3-methylbutanoic Acid (10a). The title compound was obtained as a white solid following the literature procedures.[34] ^{1}H NMR (400 MHz, MeOD) δ 1.13 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 2.17−2.34 (m, 1H), 3.94 (d, J = 5.6 Hz, 1H), 4.01 (s, 3H), 7.57 (dd, J = 8.5, 1.6 Hz, 1H), 8.04 (dd, J = 8.1, 1.5 Hz, 1H), 8.14−8.22 (m, 2H), 8.24 (d, J = 1.5 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 9.85 (s, 1H). HRMS: calcd for $C_{19}H_{20}N_2O_7S + H^+$, 421.10640; found (ESI-FTMS, $[M + H]^+$), 421.10674.

(*S*)-2-(7-(Methoxycarbonylamino)dibenzo[*b*,*d*]furan-3-sulfonamido)-3-methylbutanoic Acid (10b). The title compound was obtained as a white solid following the literature procedures.[34] ^{1}H NMR (400 MHz, MeOD) δ 1.13 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 2.17−2.34 (m, 1H), 3.94 (d, J = 5.6 Hz, 1H), 4.01 (s, 3H), 7.57 (dd, J = 8.5, 1.6 Hz, 1H), 8.04 (dd, J = 8.1, 1.5 Hz, 1H), 8.14−8.22 (m, 2H), 8.24 (d, J = 1.5 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 9.85 (s, 1H). HRMS: calcd for $C_{19}H_{20}N_2O_7S + H^+$, 421.10640; found (ESI-FTMS, $[M + H]^+$), 421.1064. Anal. calcd for $C_{19}H_{20}N_2O_7S$: C 54.28%, H 4.79%, N 6.66%; found: C 53.95%, H 4.72%, N 6.34%.

(*S*)-2-(7-Aminodibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (11). The title compound was prepared by acidic saponification of the intermediate (*S*)-2-(7-amino-dibenzothiophene-3-sulfonylamino)-3-methyl-butyric acid *tert*-butyl ester (step 4 in the preparation of compound **9b**). ^{1}H NMR (400 MHz, MeOD) δ 1.10 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 2.16−2.34 (m, 1H), 3.83 (d, J = 5.3 Hz, 1H), 7.10 (dd, J = 8.6, 2.02 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.3, 1.77 Hz, 1H), 8.20 (d, J = 8.6 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.45 (d, J = 1.0 Hz, 1H). HRMS: calcd for $C_{17}H_{18}N_2O_4S_2 + H^+$, 379.07807; found ESI-FTMS, $[M + H]^+$, 379.0779.

(*R*)-2-(7-(Ethoxycarbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (12a). Following procedures for the preparation of **9b** and using ethyl chloroformate for the *N*-derivatization step, compound **12a** was prepared as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.95 (m, 1H), 3.56 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 7.58 (dd, J = 8.8, 1.9 Hz, 1H), 7.83 (dd, J = 8.8, 1.6 Hz, 1H), 7.99 (s, 1H), 8.22 (d, J = 1.9 Hz, 1H), 8.34 (d, J = 8.8, Hz, 1H), 8.37 (d, J = 7.9 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 10.00 (s, 1H), 12.49 (s, 1H). ESI-POS $[M - H]^+$ 451.01.

(*S*)-2-(7-(Ethoxycarbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (12b). Following procedures for the preparation of **9b** and using ethyl chloroformate for the *N*-derivatization step, compound **12b** was prepared as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.95 (m, 1H), 3.56 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 7.58 (dd, J = 8.8, 1.9 Hz, 1H), 7.83 (dd, J = 8.8, 1.6 Hz, 1H), 7.99 (s, 1H), 8.22 (d, J = 1.9 Hz, 1H), 8.34 (d, J = 8.8 Hz, 1H), 8.37 (d, J = 7.9 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 10.00 (s, 1H), 12.49 (s, 1H). ESI-POS $[M - H]^+$ 450.9.

(*S*)-2-(7-(Isopropoxycarbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (13). Following procedures for the preparation of **9b** and using isopropyl chloroformate for the *N*-derivatization step, compound **13** was prepared as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 1.30 (d, J = 6.2 Hz, 6H), 1.95 (m, 1H), 3.60 (dd, J = 9.5, 6.0 Hz, 1H), 4.95 (dq, J = 6.2, 6.2 Hz, 1H), 7.58 (dd, J = 8.7, 1.9 Hz, 1H), 7.83 (dd, J = 8.3, 1.6 Hz, 1H), 8.05 (d, J = 9.6 Hz, 1H), 8.23 (d, J = 1.8 Hz, 1H), 8.33 (d, J = 8.8 Hz, 1H), 8.38 (d, J = 7.8 Hz, 1H), 8.39 (d, J = 1.8 Hz, 1H), 9.96 (s, 1H), 12.50 (s, 1H). ESI-POS $[M - H]^+$ 465.1.

(*S*)-2-(7-(Isobutoxycarbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (14). Following procedures for the preparation of **9b** and using isobutyl chloroformate for the *N*-derivatization step, compound **14** was prepared as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.6 Hz, 6H), 1.94 (m, 2H), 3.59 (m, 1H), 3.93 (d, J = 6.6 Hz, 2H), 7.58 (dd, J = 8.5, 1.9 Hz, 1H), 7.83 (dd, J = 8.5, 1.6 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 1.9 Hz, 1H), 8.34 (d, J = 8.5 Hz, 1H), 8.38 (d, J = 8.5 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 10.00 (s, 1H), 12.49 (s, 1H). ESI-POS $[M - H]^+$ 479.0.

(*S*)-3-Methyl-2-(7-((2-(methylsulfonyl)ethoxy)carbonylamino)-dibenzo[*b*,*d*]thiophene-3-sulfonamido)butanoic Acid (15). Following procedures for the preparation of **9b** and using 2-methanesulfonyl ethyl chloroformate for the *N*-derivatization step, compound **15** was prepared as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 1.95 (m, 1H), 3.10 (s, 3H), 3.58 (m, 3H), 4.51 (dd, J = 6.0, 6.0 Hz, 2H), 7.60 (dd, J = 8.4, 1.9 Hz, 1H), 7.84 (dd, J = 8.6, 1.9 Hz, 1H), 8.01 (d, J = 9.1 Hz, 1H), 8.24 (d, J = 1.8 Hz, 1H), 8.42−8.34 (m, 3H), 10.16 (s, 1H), 12.52 (s, 1H). ESI-POS $[M - H]^+$ 529.1.

(*S*)-2-(7-((But-3-ynyloxy)carbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (16). Following procedures for the preparation of **9b** and using but-3-ynyl chloroformate for

the *N*-derivatization step, compound **16** was prepared as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 1.95 (m, 1H), 2.60 (dt, J = 6.4, 2.6 Hz, 2H), 2.91 (t, J = 2.6 Hz, 1H), 3.60 (dd, J = 9.1 5.9 Hz, 1H), 4.22 (t, J = 6.4 Hz, 2H), 7.60 (dd, J = 8.7, 1.7 Hz, 1H), 7.84 (dd, J = 8.5, 1.6 Hz, 1H), 8.05 (d, J = 9.4 Hz, 1H), 8.24 (d, J = 1.7 Hz, 1H), 8.35 (d, J = 8.8 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.4 (d, J = 1.9 Hz, 1H), 10.14 (s, 1H), 12.51 (s, 1H). ESI-POS [M − H]$^+$ 475.1.

(*S*)-3-Methyl-2-(7-(phenoxycarbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)butanoic Acid (17). Following procedures for the preparation of **9b** and using phenyl chloroformate for the *N*-derivatization step, compound **17** was prepared as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H), 1.96 (m, 1H), 3.58 (m, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.29 (dd, J = 8.6, 8.6 Hz, 1H), 7.46 (dd, J = 8.6, 8.6 Hz, 2H), 7.66 (dd, J = 8.8, 2.0 Hz, 1H), 7.85 (dd, J = 8.5, 1.5 Hz, 1H), 8.02 (s, 1H), 8.26 (d, J = 1.8 Hz, 1H), 8.41 (m, 3H), 10.62 (s, 1H), 12.48 (s, 1H). ESI-POS [M − H]$^+$ 499.0.

(*S*)-3-Methyl-2-(7-(*p*-tolyloxycarbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)butanoic Acid (18). Following procedures for the preparation of **9b** and using 4-methyl-phenyl chloroformate for the *N*-derivatization step, compound **18** was prepared as a pale-yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 1.96 (m, 1H), 2.33 (s, 3H), 3.57 (m, 1H), 7.14 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 7.65 (dd, J = 9.1, 2.5 Hz, 1H), 7.85 (dd, J = 8.7, 1.7 Hz, 1H), 8.04 (s, 1H), 8.25 (d, J = 1.9 Hz, 1H), 8.41 (m, 3H), 10.57 (s, 1H), 12.52 (s, 1H). ESI-POS [M − H]$^+$ 513.1.

(*S*)-2-(7-((4-Fluorophenoxy)carbonylamino)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (19). Following procedures for the preparation of **9a** and using 4-fluoro-phenyl chloroformate for the *N*-derivatization step, compound **19** was prepared as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 1.95 (m, 1H), 3.6 (m, 1H), 7.37−7.23 (m, 4H), 7.65 (dd, J = 8.7, 1.8 Hz, 1H), 7.85 (dd, J = 8.5, 1.6 Hz, 1H), 8.05 (d, J = 9.5 Hz, 1H), 8.25 (d, J = 1.9 Hz, 1H), 8.41 (m, 3H), 10.63 (s, 1H), 12.51 (s, 1H). ESI-POS [M − H]$^+$ 517.1.

(*S*)-2-(7-(3-Ethylureido)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (20). The title compound was prepared following the scheme and synthetic procedures described at the Supporting Information. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 1.09 (t, J = 5.6 Hz, 3H), 1.95 (m, 1H), 3.15 (dq, J = 7.0, 5.6 Hz, 2H), 3.58 (m, 1H), 6.27 (t, J = 5.5 Hz, 1H), 7.45 (dd, J = 8.6, 2.0 Hz, 1H), 7.81 (dd, J = 8.5, 1.8 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 8.23 (d, J = 1.8 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.34 (d, J = 8.3 Hz, 1H), 8.36 (d, J = 1.8 Hz, 1H), 8.82 (s, 1H), 12.51 (s, 1H). ESI-POS [M − H]$^+$ 450.1.

(*S*)-2-(7-(3-Cyclopentylureido)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (21). Following procedures for the preparation of **20** and using cyclopentyl isocyanate for the *N*-derivatization, compound **21** was prepared as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 1.49−1.32 (m, 2H), 1.74−1.53 (m, 4H), 2.14−1.88 (m, 3H), 3.71 (m, 1H), 4.10 (dt, J = 13.2, 6.6 Hz, 1H), 5.33 (d, J = 10.1 Hz, 1H), 7.29 (dd, J = 8.8, 2.2 Hz, 1H), 7.83 (dd, J = 8.2, 1.6 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 2.2 Hz, 1H), 8.24 (d, J = 1.6 Hz, 1H). ESI-POS [M − H]$^+$ 490.1.

(*S*)-3-Methyl-2-(7-(3-(2-(thiophen-2-yl)ethyl)ureido)dibenzo-[*b*,*d*]thiophene-3-sulfonamido)butanoic Acid (22). Following procedures for the preparation of **20** and using 2-(2-isocyanatoethyl)thiophene for the *N*-derivatization, compound **22** was prepared as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 1.99 (m, 1H), 3.04 (t, J = 6.6 Hz, 2H), 3.45 (dt, J = 6.6, 6.0 Hz, 2H), 3.63 (d, J = 6.0 Hz, 1H), 6.22 (t, J = 6.0 Hz, 1H), 6.93 (m, 1H), 6,98 (dd, J = 5.0, 3.5 Hz, 1H), 7.31 (dd, J = 5.0, 1.3 Hz, 1H), 7.47 (dd, J= 8.8, 1.9 Hz, 1H), 7.84 (dd, J=8.5, 1.9 Hz, 1H), 8.19 (d, J=2.2 Hz, 1H), 8.23 (d, J = 8.8 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.34 (d, J = 1.6 Hz, 1H), 8.67 (s, 1H). ESI-POS [M − H]$^+$ 532.1.

(*S*)-3-Methyl-2-(7-(3-(2-(thiophen-2-yl)ethyl)ureido)dibenzo-[*b*,*d*]furan-3-sulfonamido)butanoic Acid^2 (23). The title compound was prepared as a white solid following the procedures described for the preparation of **20** using 2-(2-isocyanatoethyl)thiophene for the *N*-derivatization step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 1.86−2.02 (m, 1H), 3.00 (t, J = 7.1 Hz, 2H), 3.40 (q, J = 6.8 Hz, 2H), 3.58 (dd, J = 9.4, 6.1 Hz, 1H), 6.39 (t, J = 5.8 Hz, 1H), 6.94 (d, J = 3.5 Hz, 1H), 6.99 (dd, J = 5.1, 3.3 Hz, 1H), 7.27 (dd, J = 8.6, 1.8 Hz, 1H), 7.37 (dd, J = 5.2, 1.1 Hz, 1H), 7.75 (dd, J = 8.1, 1.5 Hz, 1H), 7.97 (d, J = 1.5 Hz, 1H), 8.00−8.12 (m, 3H), 8.15 (d, J = 8.1 Hz, 1H), 9.06 (s, 1H), 12.52 (s, 1H). HRMS: calcd for $C_{24}H_{25}N_3O_6S_2$ + H$^+$, 516.12575; found (ESI-FTMS, [M + H]$^+$), 516.12506.

(*R*)-3-Methyl-2-(7-(3-phenylureido)dibenzo[*b*,*d*]thiophene-3-sulfonamido)butanoic Acid (24a). The title compound was prepared as a white solid following the procedures described for the preparation of **20** using phenyl isocyanate for the *N*-derivatization step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H), 1.89−2.03 (m, 1H), 3.52−3.65 (m, 1H), 7.00 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 8.1 Hz, 3H), 7.50 (d, J = 7.6 Hz, 1H), 7.54 (s, 1H), 7.83 (dd, J = 8.4, 1.6 Hz, 1H), 8.25−8.41 (m, 5H), 8.84 (s, 1H), 9.08 (s, 1H), 12.47 (s, 1H). ESI-POS [M − H]$^+$ 498.1.

(*S*)-3-Methyl-2-(7-(3-phenylureido)dibenzo[*b*,*d*]thiophene-3-sulfonamido)butanoic Acid (24b). The title compound was prepared as a white solid following the procedures described for the preparation of **20** using phenyl isocyanate for the *N*-derivatization step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 1.96 (m, 1H), 3.60 (dd, J = 9.6, 6.4 Hz, 1H), 7.00 (dd, J = 8.0, 8.0 Hz, 1H), 7.31 (dd, J = 8.0, 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.54 (m,1H), 7. 83 (dd, J = 8.5, 1.6 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 8.28 (d, J = 1.8 Hz, 1H), 8.33 (d, J = 8.7 Hz, 1H) 12.47 (s, 1H). ESI-POS [M − H]$^+$ 498.1.

(*S*)-2-(7-(3-Benzylureido)dibenzo[*b*,*d*]thiophene-3-sulfonamido)-3-methylbutanoic Acid (25). The title compound was prepared as a white solid following the procedures described for the preparation of **20** using benzyl isocyanate for the *N*-derivatization step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 1.95 (m, 1H), 3.59 (m, 1H), 4.34 (d, J = 5.6 Hz, 2H), 6.79 (d, J = 5.7 Hz, 1H), 7.22−7.37 (m, 5H), 7.46 (dd, J = 8.7, 2.0 Hz, 1H), 7.81 (dd, J = 8.5, 2.1 Hz, 1H), 8.0 (d, J = 9.5 Hz, 1H), 8.25 (d, J = 1.8 Hz 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.34 (d, J = 8.1 Hz, 1H), 8.35 (s, 1H), 8.96 (s, 1H), 12.49 (s, 1H). ESI-POS [M − H]$^+$ 512.1.

(*S*)-2-(8-(Ethoxycarbonylamino)dibenzo[*b*,*d*]furan-3-sulfonamido)-3-methylbutanoic Acid (26). Following procedures for the preparation of **27** and using ethylchloroformate for the *N*-derivatization step, compound **26** was prepared as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 0.88 (d, J = 6.82 Hz, 3H), 0.95 (d, J = 6.82 Hz, 3H), 1.31 (t, J = 7.07 Hz, 3H), 1.93−2.11 (m, 1H), 3.71 (d, J = 5.56 Hz, 1H), 4.20 (q, J = 7.07 Hz, 2H), 7.44−7.55 (m, 3H), 7.81 (dd, J = 8.34, 1.52 Hz, 1H), 8.01 (d, J = 1.01 Hz, 1H), 8.06 (d, J = 8.59 Hz, 1H), 8.20 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 14.5, 17.7, 18.9, 30.3, 60.2, 61.3, 110.2, 110.6, 112.0, 120.5, 121.3, 122.5, 127.0, 135.4, 140.0, 152.4, 153.8, 154.8, 154.9, 172.0. HRMS: calcd for [$C_{20}H_{22}N_2O_7S$ + H]$^+$, 435.12205; found (ESI-FTMS, [M + H]$^+$), 435.1216. Anal. calcd for $C_{20}H_{22}N_2O_7S$: C 55.29%, H 5.10%, N 6.45%; found: C 55.49%, H 5.03%, N 6.32%.

(*S*)-3-Methyl-2-(8-(2-oxooxazolidin-3-yl)dibenzo[*b*,*d*]furan-3-sulfonamido)butanoic Acid (27, MMP145). The title compound was prepared following the synthetic scheme and procedures described in the Supporting Information section. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 1.88−1.98 (m, 1H), 3.61 (dd, J = 9.6, 6.1 Hz, 1H), 4.12−4.26 (m, 2H), 4.51 (dd, J = 9.1, 6.8 Hz, 2H), 7.76−7.86 (m, 2H), 7.93 (dd, J = 9.1, 2.5 Hz, 1H), 8.06 (d, J = 1.3 Hz, 1H), 8.18

(d, $J = 9.6$ Hz, 1H), 8.30−8.39 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 17.8, 19.0, 30.4, 45.5, 61.3, 61.5, 110.3, 111.6, 112.1, 120.3, 121.5, 121.7, 122.7, 126.9, 134.9, 140.2, 153.0, 155.0, 155.2, 172.0. HRMS: calcd for $C_{20}H_{20}N_2O_7S$ (M + H$^+$) 433.10640, found (ESI-FTMS, [M + H]$^+$) 433.10635; CHN: calcd for $C_{20}H_{20}N_2O_7S$, C 55.55%, H 4.66%, N 6.48%; found C 55.53%, H 4.67%, N 6.75%.

(*S*)-3-Methyl-2-(7-(2-oxooxazolidin-3-yl)dibenzo[*b*,*d*]furan-3-sulfonamido)butanoic Acid (28). The title compound was obtained as a white solid following the procedures described for **27** using the known intermediate (*S*)-methyl 2-(7-aminodibenzo[*b*,*d*]furan-3-sulfonamido)-3-methylbutanoate.[34] ^{1}H NMR (400 MHz, MeOD) δ 1.13 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 2.20−2.33 (m, 1H), 3.94 (d, J = 5.7 Hz, 1H), 4.40−4.51 (m, 2H), 4.73−4.83 (m, 2H), 7.86 (dd, J = 2.0, 8.6 Hz, 1H), 8.07 (dd, J = 1.5, 8.1 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.27 (d, J = 1.5 Hz, 1H), 8.29−8.37 (m, 2H). HRMS: calcd for $C_{20}H_{20}N_2O_7S$ + H$^+$, 433.10640; found (ESI-FTMS, [M + H]$^+$), 433.10635.

(*S*)-3-Methyl-2-(7-(2-oxooxazolidin-3-yl)dibenzo[*b*,*d*]thiophene-3-sulfonamido)butanoic Acid (29). The product was prepared as a white solid using the corresponding aniline intermediate for the preparation of **9b** following the procedures described for **27**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H), 1.90−2.01 (m, 1H), 3.61 (dd, J = 9.4, 5.9 Hz, 1H), 4.19 (t, J = 8.1 Hz, 2H), 4.51 (t, J = 8.1 Hz, 2H), 7.86 (dd, J = 8.5, 1.8 Hz, 1H), 7.90 (dd, J = 8.8, 2.1 Hz, 1H), 8.08 (d, J = 9.4 Hz, 1H), 8.23 (d, J = 2.1 Hz, 1H), 8.41−8.49 (m, 3H), 12.52 (s, 1H). ESI-POS [M − H]$^+$ 449.05.

(*S*)-2-(7-Aminodibenzo[*b*,*d*]furan-3-sulfonamido)-3-methylbutanoic Acid (30). The title compound was prepared by saponification of the known compound, (*S*)-methyl 2-(7-aminodibenzo[*b*,*d*]furan-3-sulfonamido)-3-methylbutanoate[2] under basic conditions (THF/water/LiOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.74 (d, J = 7.1 Hz, 3H). 0.86 (d, J = 7.1 Hz, 3H), 1.93−2.05 (m, 1H), 2.92 (s, 1H), 5.80 (s, 2H), 6.67 (dd, J = 1.8, 8.3 Hz, 1H), 6.76 (d, J = 1.5 Hz, 1H), 6.80 (s, 1H), 7.62 (dd, J = 1.5, 8.1 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 1.0 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H). HRMS: calcd for $C_{17}H_{18}N_2O_5S$ + H$^+$, 363.10092.

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Supporting Information Available: Details of syntheses and assays and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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