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ARTICLE

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Discovery of (1*S*,2*R*,3*R*)-2,3-Dimethyl-2-phenyl-1-sulfamidocyclopropanecarboxylates: Novel and Highly Selective Aggrecanase Inhibitors

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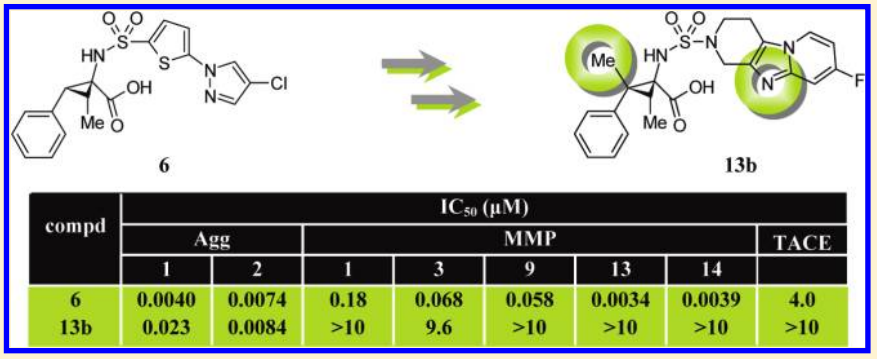
Supporting Information

ABSTRACT:



compd	IC_{50} (μM)							
	Agg		MMP					TACE
	1	2	1	3	9	13	14	
6	0.0040	0.0074	0.18	0.068	0.058	0.0034	0.0039	4.0
13b	0.023	0.0084	>10	9.6	>10	>10	>10	>10

Aggrecanases, particularly aggrecanase-1 (ADAMTS-4) and aggrecanase-2 (ADAMTS-5), are believed to be key enzymes involved in the articular cartilage breakdown that leads to osteoarthritis. Thus, aggrecanases are considered to be viable drug targets for the treatment of this debilitating disease. A series of (1*S*,2*R*,3*R*)-2,3-dimethyl-2-phenyl-1-sulfamidocyclopropanecarboxylates was discovered to be potent, highly selective, and orally bioavailable aggrecanase inhibitors. These compounds have unique P1′ groups comprising novel piperidine- or piperazine-based heterocycles that are connected to a cyclopropane amino acid scaffold via a sulfamido linkage. These P1′ groups are quite effective in imparting selectivity over other MMPs, and this selectivity was further increased by incorporation of a methyl substituent in the 2-position of the cyclopropane ring. In contrast to classical hydroxamate-based inhibitors that tend to lack metabolic stability, our aggrecanase inhibitors bear a carboxylate zinc-binding group and have good oral bioavailability. Lead compound **13b**, characterized by the novel P1′ portion of 1,2,3,4-tetrahydropyrido[3′,4′:4,5]imidazo[1,2-*a*]-pyridine ring, is a potent and selective aggrecanse inhibitor with excellent pharmacokinetic profiles.

INTRODUCTION

Osteoarthritis (OA) is a debilitating disease caused by breakdown of aggrecan and collagen in the articular cartilage, which leads to chronic joint pain and reduced physical function of a large population in the elderly.[1] Current therapeutic options such as treatment with NSAIDs and intra-articular injections of hyaluronic acid only offer temporary symptomatic relief such as pain reduction but rarely halt the progression of the disease. Since OA affects millions of people all over the world and its incidence is increasing with the aging of the population, new therapeutic agents for the treatment of cartilage degradation are of great interest. In 1999, two zinc metalloproteases, aggrecanase-1 (ADAMTS-4) and aggrecanase-2 (ADAMTS-5), were identified as the major enzymes responsible for aggrecan cleavage at the Glu^{373}-Ala^{374} site.[2] These proteases cleave aggrecan at this site 1000-fold more efficiently than any other matrix metalloproteases (MMPs). This finding drew a great deal of interest

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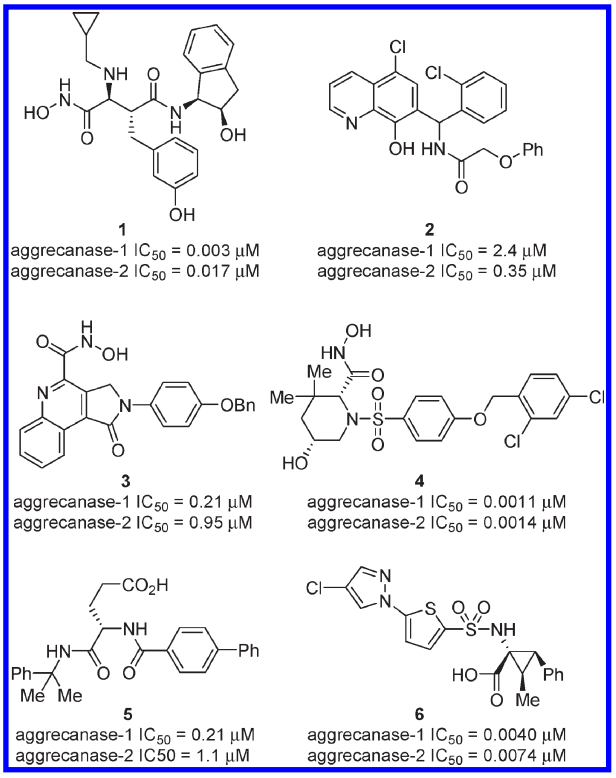

Figure 1. Examples of ADAMTS-5 inhibitors.

because the aggrecan fragments generated from cleavage at this site are found in the synovial fluid of OA patients, which suggests that aggrecanases play a pivotal role in the pathological catabolism of aggrecan.[3] In osteoarthritic cartilage, degradation of aggrecan is initially observed and is followed by substantial and irreversible collagen breakdown, which leads to structural damage of the joints.[4] Thus, blockade of aggrecanases is currently expected to prevent aggrecan degradation and could eventually protect the joints of OA patients.[5] Of the two enzymes, aggrecanase-2 was demonstrated to play a pivotal role in the cleavage of mouse cartilage based on studies using knockout animals,[6] and there have been several reports that suggest that either enzyme could be a major player in the destruction of the cartilage of OA patients.[7] Initially, several general aggrecanase inhibitors as represented by DuPont's hydroxamate-based compound **1**[8a] were reported (Figure 1).[9] The inhibitory activity of compound **1** against each aggrecanase was also reported.[8b] Subsequently, the knockout mouse studies[6] inspired the design of aggrecanase-2 inhibitors.[10] In particular, Wyeth reported a variety of aggrecanase-2 inhibitors exemplified by **2**. Most recently, Cappelli and co-workers reported aggrecanase inhibitors such as **3** that showed submicromolar IC_{50} values for both aggrecanase-1 and -2.[11] Similarly, Pfizer's MMP-13 inhibitor (**4**)[9e] showed strong aggrecanse inhibitory activity, while Wyeth's carboxylate-based compound (**5**)[9g] selectively inhibited aggrecanases.

Recently we have reported aggrecanase-2 inhibitors such as **6** that bear a carboxylate zinc-binding group.[12] While **6** was the most potent compound of these non-hydroxamate inhibitors against aggrecanase-1 and -2, it also inhibited other MMPs such as MMP-3, MMP-9, MMP-13, and MMP-14 in a broad-range selectivity panel. It is widely believed that a variety of unacceptable adverse events, such as musculoskeletal syndrome,[13] that have been clinically observed with the use of broad spectrum MMP inhibitors arose from lack of selectivity. Hence, we undertook the optimization of compound **6** in order to identify highly selective aggrecanase inhibitors, especially inhibitors of aggrecanase-2.

MMP-14 has been implicated as a possible cause of side effects based on knockout mouse studies.[14] Because the inhibitory activity of **6** against MMP-14 was twice as strong as that against aggrecanase-2, an MMP-14 assay was newly employed in addition to the original selectivity assay system which also included MMP-1 and tumor necrosis factor α-converting enzyme (TACE).[15] The earlier gene knockout studies indicated that inhibition of aggrecanase-2 is more important in mice, and thus, the inhibition of aggrecanase-1 was expected to cause no severe side effects based on the phenotype of aggrecanase-1 knockout mice,[6] and its inhibition may even exert some positive effects in vivo. Therefore, in this study we followed only aggrecanase-2 inhibitory activity and did not routinely monitor aggrecanase-1 inhibitory activity.

RESULTS AND DISCUSSION

Initial SAR Exploration of Close Sulfonamide-Based Analogues of Compound 6. Zinc metalloproteases including MMPs contain highly conserved structural features within the catalytic domain, with the exception of the loop region which forms part of the S1′ pocket of each enzyme and imparts substrate specificity. Therefore, generating P1′ moieties that specifically interact with the S1′ pocket of each target MMP may be a key for the development of more selective inhibitors.[16] We therefore initiated an exploration of inhibitor binding to the S1′ pocket starting from compound **6**, whose sulfonyl moiety is accommodated in the S1′ pocket of aggrecanase-2.[12b] First, we examined the effects of substitutions on the two consecutive pyrazole and thiophene rings (Table 1). The compounds were tested in vitro on human recombinant aggrecanase-2, MMPs, and TACE, which used a fluorogenic peptide as the substrate. Introduction of an additional methyl group on the thiophene ring resulted in complete loss of potency (**7a**), while replacement of the terminal chlorine atom with a methoxy or a methyl group led to a slight reduction of selectivity over MMP-14 (**7b**, **7c**). Although these minor modifications on the present ring system had virtually no beneficial effect on aggrecanase-2 selectivity over MMP-14, relatively high selectivity over MMP-1 was observed for **7d**,[12b] a phenyl analogue of compound **6**. This analogue became the focus of additional efforts to impart selectivity over MMP-14.

Discovery of Tricyclic Sulfonamides as P1′ Groups. Among the close analogues of **6** listed in Table 1, only **7a** showed a significant reduction of aggrecanase-2 potency. We considered that the introduction of the methyl group forces the linked heterocycle of **7a** to lose coplanarity, a distortion of the geometry that causes steric congestion in the aggrecanase-2 S1′ pocket and leads to the observed loss of potency. On the basis of this hypothesis, we synthesized **8a**−**c** as analogues of **7d** which bear flat tricyclic structures as the P1′ moiety (Table 2). Analogues **8a**−**c** retained good aggrecanase-2 potency, and moreover, **8c** showed good selectivity over MMP-1. Unfortunately the selectivity over MMP-14 was still unsatisfactory (Table 2). Compounds **8d** and **8e** were subsequently synthesized to evaluate the effect of the terminal chlorine atom, but these compounds offered no improvement in selectivity over MMP-14.

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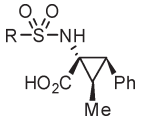
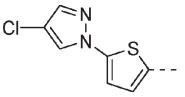
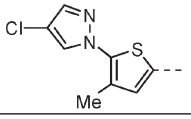
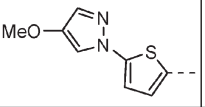
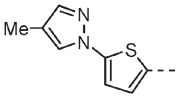
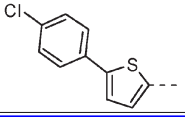
Table 1. SAR of Sulfonamide-Based P1′ Portion of Close Analogues of 6[f]

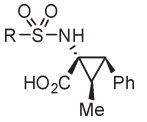


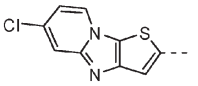
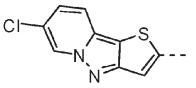
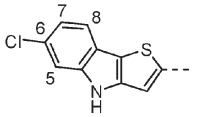
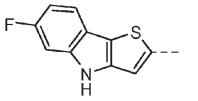
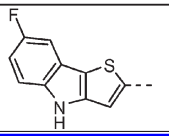
compd	R	IC50 (μM)[a]			
		Agg-2[b]	MMP-14[c]	MMP-1[d]	TACE[e]
6		0.0074	0.0034	0.18	4.0
7a		>1.0	nd	nd	nd
7b		0.017	0.0013	0.033	1.6
7c		0.019	0.0012	<0.3	>10
7d		0.021	0.019	4.0	2.7

[a] See Experimental Section for assay protocols. The IC_{50} values are the average of at least two determinations with a standard deviation of <30%. [b] Reference compound **1** gave mean (±SEM) IC_{50} = 12 (±0.60) nM, n = 30. [c] Reference compound **1** gave IC_{50} > 10 μM, n = 18. [d] Reference compound **1** gave IC_{50} > 10 μM, n = 16. [e] Reference compound **1** gave mean (±SEM) IC_{50} = 430 (±43) nM, n = 13. [f] nd: not determined.

Discovery and Initial Exploration of Sulfamide-Based P1′ Groups. We next evaluated sulfamides as bioisosteric replacements of the sulfonamide group to introduce greater synthetic versatility.[17] We initially synthesized **9a** and **9b**, and although these compounds showed reduced aggrecanase-2 potency compared to the sulfonamide series, their selectivities over MMP-14, MMP-1, and TACE were comparable to that of the most selective sulfonamide **8c**. These results prompted us to modify the piperazine ring of **9a**. Substitution of a methyl group as in **9c** and **9d** provided a 2-fold increase in aggrecanase-2 inhibitory activity and a surprising 10-fold increase in selectivity with respect to MMP-14. These results were in contrast to the loss of potency in compound **7a**, which also has a methyl substituent at the corresponding location of the P1′ site but showed no aggrecanase-2 inhibition. Maity et al. have recently reported a crystal structure of a 2-substituted-1-phenylpiperazine derivative.[18] They reported that in similar systems the piperazine ring was coplanar with the phenyl ring, and this coplanar conformation forced the alkyl substituent at the 2-position of the piperazine into the axial orientation. On the basis of this observation, we postulated that the phenylpiperazine moieties of **9c** and **9d** adopt a similar coplanar conformation so that they can fit in the S1′ pocket of aggrecanase-2 without the steric congestion of **7a** and thus retain their good inhibitory activity. To explain the improved selectivity of the sulfamides, we compared the binding of **9c** and **9d** in the crystal structures of aggrecanase-2[19] and MMP-14.[20] These two protein X-ray structures were superimposed by aligning the Cα atoms, and **9c** and **9d** were docked manually into the resulting protein structures with the carboxylate acting as a zinc-binding group and the phenylpiperazine moiety positioned in the S1′ pocket. As seen in Figure 2, the most striking difference between aggrecanase-2 and MMP-14 is the chemical environment around the piperazine ring of the inhibitors: the backbone carbonyl of Pro259 comes too close to the methyl substituent of **9c** and **9d** in the S1′ pocket of MMP-14, while the corresponding amino acid of aggrecanase-2, Ser441, projects away from the methyl substituent (Figure 2a and Figure 2b). Thus, the available space near the piperazine ring in the S1′ pocket of aggrecanase-2 could account for the aggrecanase-2 selectivity found in **9c** and **9d**. Recently, Wei et al. have reported a similar modulation of selectivity in their MMP-12 inhibitor program.[21] This approach of introducing differences in the S1′ pocket that are more subtle than simply changing the depth represents a novel and attractive strategy for obtaining highly selective MMP inhibitors. To exploit this approach further, we prepared

Table 2. SAR of the P1′ Portion Comprising Novel Tricyclic Heteroaromatics



compd	R	IC_{50} (μM)[a]			
		Agg-2[b]	MMP-14[c]	MMP-1[d]	TACE[e]
8a		0.023	0.10	1.5	>10
8b		0.029	0.10	1.3	>10
8c		0.0029	0.017	1.0	3.8
8d		0.0083	0.0080	0.23	1.1
8e		0.010	0.025	1.3	1.9

[a] See Experimental Section for assay protocols. The IC_{50} values are the average of at least two determinations with a standard deviation of <30%. [b] Reference compound **1** gave mean (±SEM) IC_{50} = 12 (±0.60) nM, n = 30. [c] Reference compound **1** gave IC_{50} > 10 μM, n = 18. [d] Reference compound **1** gave IC_{50} > 10 μM, n = 16. [e] Reference compound **1** gave mean (±SEM) IC_{50} = 430 (±43) nM, n = 13.

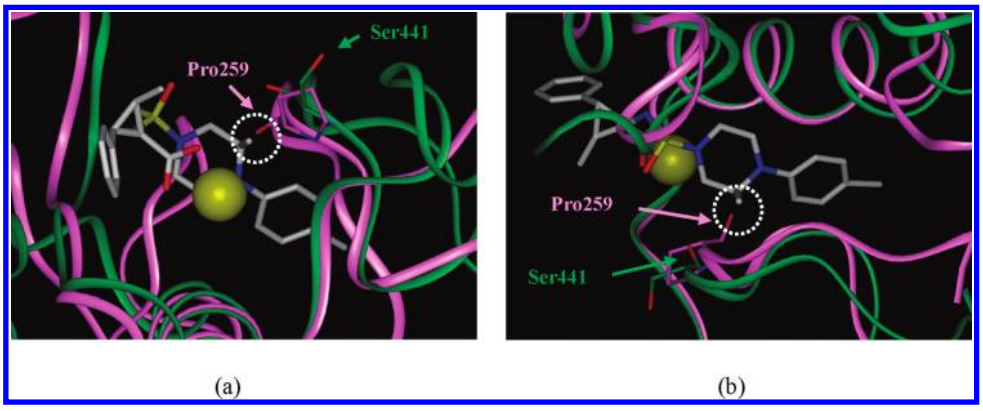


Figure 2. Compounds (a) **9c** and (b) **9d** harbored in the catalytic pockets of aggrecanase-2 and MMP-14. The compounds are depicted in white. Aggrecanase-2 is depicted in green. MMP-14 is depicted in pink, and zinc ion is portrayed as a yellow sphere. The backbone carbonyl of Pro259 (pink arrow) comes too close to the methyl substituent (white dashed circle) of **9c** and **9d** in the S1′ pocket of MMP-14, while the corresponding amino acid of aggrecanase-2, Ser441 (green arrow), projects away from the methyl substituent.

an additional small set of substituted piperazines including a 3-ethyl analogue (**9e**), a 3,3-dimethyl analogue (**9f**), and a 3-hydroxymethyl analogue (**9g**) (Table 3). Unfortunately, these compounds showed neither increased aggrecanase-2 potency nor improved

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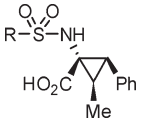
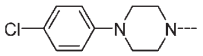
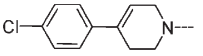
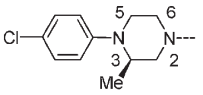
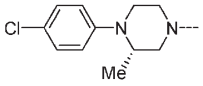
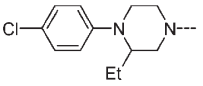
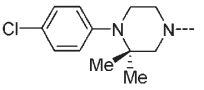
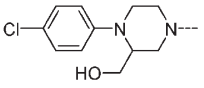
Table 3. SAR of the P1′ Portion Comprising 4-Chlorophenylpiperazines and 4-Chlorophenylpiperidine Sulfamides[f]



compd	R	IC_{50} (μM)[a]			
		Agg-2[b]	MMP-14[c]	MMP-1[d]	TACE[e]
9a		0.087	0.45	>10	>10
9b		0.062	0.30	>10	>10
9c		0.037	2.1	>10	>10
9d		0.047	2.5	>10	>10
9e		0.41	>10	nd	nd
9f		0.33	2.9	nd	nd
9g		0.23	6.1	nd	nd

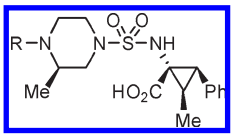
[a] See Experimental Section for assay protocols. The IC_{50} values are the average of at least two determinations with a standard deviation of <30%. [b] Reference compound **1** gave mean (±SEM) IC_{50} = 12 (±0.60) nM, n = 30. [c] Reference compound **1** gave IC_{50} > 10 μM, n = 18. [d] Reference compound **1** gave IC_{50} > 10 μM, n = 16. [e] Reference compound **1** gave mean (±SEM) IC_{50} = 430 (±43) nM, n = 13. [f] nd: not determined.

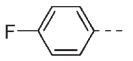
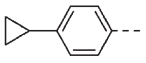
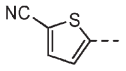
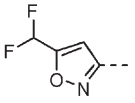
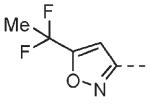
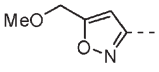
selectivity. Therefore, we concluded that this region of the S1′ pocket is too small to accommodate substituents larger than methyl.

As no further improvement in selectivity was achieved by modification of the piperazine ring, we next focused on the distal benzene portion starting from **9c**. Although simple replacement of the terminal chlorine atom with a smaller fluorine atom (**10a**) or a larger cyclopropane ring (**10b**) resulted in reduction of potency, substitution of phenyl with a five-membered heterocycle (**10c**−**f**) gave some encouraging results. Most notably, **10d** was not only as potent as **9c** but also showed a significantly higher selectivity over MMP-14 (200-fold). This compound also did not inhibit MMP-1 or TACE at >10 μM.

Discovery of Tricyclic Sulfamide P1′ Groups. In the aforementioned SAR investigations of the sulfonamide series, aggrecanase-2 inhibitory activity was significantly improved by incorporating tricycle-based P1′ groups represented by the 4*H*-thieno[3,2-*b*]indole-2-yl core of compound **8c**. These findings encouraged us to prepare compounds that possess P1′ groups comprising tricyclic sulfamides as homologues of **9a** and **9b** (Table 5). Unfortunately, we found no significant improvements in aggrecanase-2 inhibitory activity or selectivity against MMP-14 in the initial small set of tricyclic sulfamides with a fused-piperazine core (**11a**,**b**,**d**), a fused-piperidine core (**11c**), and a fused-pyrrolidine core (**11e**). Thus, we next investigated the

Table 4. SAR of the P1′ Portion Comprising (*R*)-4-Substituted 3-Methylpiperazines[f]



compd	R	IC50 (μM)[a]			
		Agg-2[b]	MMP-14[c]	MMP-1[d]	TACE[e]
10a		0.18	>10	>10	>10
10b		0.27	1.4	>10	nd
10c		0.033	6.0	>10	>10
10d		0.027	5.4	>10	>10
10e		0.13	1.1	2.6	>10
10f		0.067	1.4	>10	>10

[a] See Experimental Section for assay protocols. The IC_{50} values are the average of at least two determinations with a standard deviation of <30%. [b] Reference compound **1** gave mean (±SEM) IC_{50} = 12 (±0.60) nM, n = 30. [c] Reference compound **1** gave IC_{50} > 10 μM, n = 18. [d] Reference compound **1** gave IC_{50} > 10 μM, n = 16. [e] Reference compound **1** gave mean (±SEM) IC_{50} = 430 (±43) nM, n = 13. [f] nd: not determined.

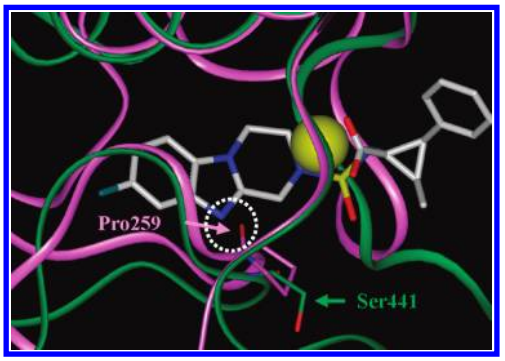


Figure 3. Compound **12b** (in white) is harbored in the catalytic pockets of aggrecanase-2 and MMP-14. Aggrecanase-2 is depicted in green. MMP-14 is depicted in pink, and the zinc ion is portrayed as a yellow sphere. The backbone carbonyl of Pro259 (pink arrow) comes too close to the basic nitrogen atom (white dashed circle) of **12b** in the S1′ pocket of MMP-14, while the corresponding amino acid of aggrecanase-2, Ser441 (green arrow), projects away from the nitrogen atom.

effect of substituents on the terminal ring starting from **11b**, which has a chlorine atom at the 8-position (Table 6). Deletion of the chlorine atom of **11b** resulted in a slight reduction of aggrecanase-2 potency (**12a**), while **12b**, possessing a fluorine atom at this position, retained both the potency against aggrecanase-2 and good selectivity over MMP-14. The regioisomer **12c**, having a fluorine atom at the 7-position, was a nonselective compound with reduced aggrecanase-2 inhibition and increased MMP-14 inhibition compared to the 8-F isomer **12b**. According to our previous SAR investigation,[12b] 6- and 9-substituted regioisomers were unlikely to show good potency. Therefore, only the 8-position of the tricyclic structure was further investigated, and small substituents such as cyano, methyl, and methoxy groups were introduced at this position (**12d**, **12e**, and **12f**, respectively). As listed in Table 6, these compounds are more than 10-fold less potent than **12b** against aggrecanase-2. Thus, the presence of a halogen atom at the 8-position of the tricyclic system appears to be important to boost aggrecanase-2 inhibition. As expected, the other heterotricycles **12g**—**i** with a fluorine

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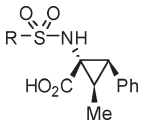
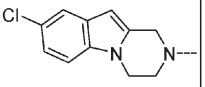
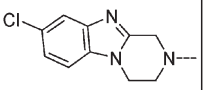
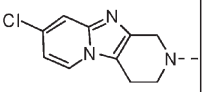
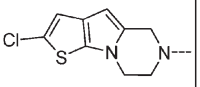
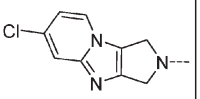
Table 5. Initial SAR of the P1′ Portion Comprised of Heterotricycle-Based Sulfamides



compd	R	IC_{50} (μM)[a]			
		Agg-2[b]	MMP-14[c]	MMP-1[d]	TACE[e]
11a		0.039	0.42	>10	>10
11b		0.060	0.61	>10	>10
11c		0.021	0.27	>10	>10
11d		0.11	2.3	>10	>10
11e		0.066	0.28	3.7	>10

[a] See Experimental Section for assay protocols. The IC_{50} values are the average of at least two determinations with a standard deviation of <30%. [b] Reference compound **1** gave mean (±SEM) IC_{50} = 12 (±0.60) nM, n = 30. [c] Reference compound **1** gave IC_{50} > 10 μM, n = 18. [d] Reference compound **1** gave IC_{50} > 10 μM, n = 16. [e] Reference compound **1** gave mean (±SEM) IC_{50} = 430 (±43) nM, n = 13.

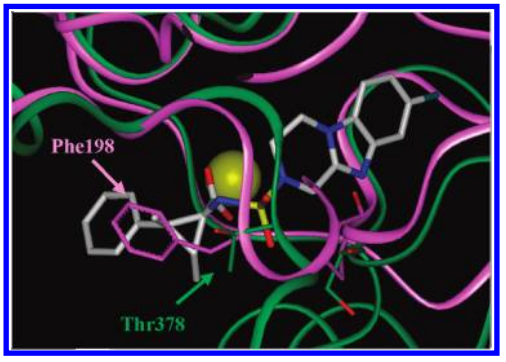
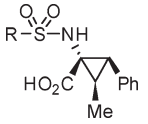


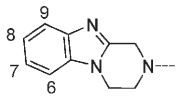
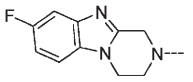
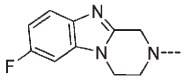
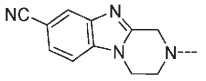
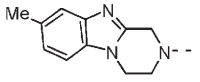
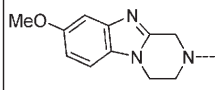
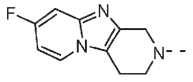
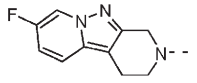
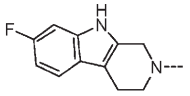
Figure 4. Compound **13a** (in white) in the catalytic pockets of aggrecanase-2 and MMP-14. Aggrecanase-2 is depicted in green. MMP-14 is depicted in pink, and the zinc ion is portrayed as a yellow sphere. The 2-methyl substituent on the cyclopropane ring of **13a** comes too close to Phe198 (pink arrow) of MMP-14, causing a steric repulsion. Meanwhile, the corresponding residue of aggrecanase-2 is Thr378 (green arrow), which allows enough space to accommodate the 2-methyl group.

atom at the corresponding position in **12b** were as potent as **12b**, supporting the importance of a halogen atom at this position. As for the selectivity over MMP-14, positioning a basic nitrogen atom in the middle of the P1′ portion appeared to be a key to reducing MMP-14 inhibition: the IC_{50} values of the two basic imidazole analogues **12b** and **12g** are much higher than those of the less basic pyrazole and pyrrole counterparts **12h** and **12i**. On the basis of the docking studies depicted in Figure 3, perhaps the presence of a basic nitrogen atom in the middle of the P1′ portion of the inhibitor causes electrostatic repulsion with the backbone carbonyl oxygen of Pro259 in MMP-14, resulting in reduced MMP-14 potency. In aggrecanase-2, the corresponding amino acid Ser441 located in this position appears to cause no such repulsion so that all of these compounds showed similar potencies against aggrecanase-2.

Effects of Substitutions on the Cyclopropane Ring. In our earlier paper, we reported 2-methyl-2-phenylcyclopropane as an attractive scaffold although its aggrecanase-2 inhibitory activity was slightly weaker than the corresponding 3-methyl derivatives.[12b] To determine whether there are any combined effects of 2-methyl

Table 6. Effects of Substitutions on the Terminal Ring of P1′ Portion of Heterotricycle-Based Sulfamides



compd	R	IC_{50} (μM)[a]			
		Agg-2[b]	MMP-14[c]	MMP-1[d]	TACE[e]
12a		0.092	2.2	>10	>10
12b		0.020	1.1	>10	>10
12c		0.10	0.24	>10	>10
12d		0.25	4.9	>10	>10
12e		0.32	0.90	>10	>10
12f		0.33	4.3	>10	>10
12g		0.017	2.1	>10	6.3
12h		0.0086	0.14	4.2	>10
12i		0.038	0.098	2.3	>10

[a] See Experimental Section for assay protocols. The IC_{50} values are the average of at least two determinations with a standard deviation of <30%. [b] Reference compound **1** gave mean (±SEM) IC_{50} = 12 (±0.60) nM, n = 30. [c] Reference compound **1** gave IC_{50} > 10 μM, n = 18. [d] Reference compound **1** gave IC_{50} > 10 μM, n = 16. [e] Reference compound **1** gave mean (±SEM) IC_{50} = 430 (±43) nM, n = 13.

and 3-methyl substituents on the cyclopropane ring, **13a** and **13b** were synthesized as 2,3-dimethyl analogues of **12b** and **12g**, respectively. Fortunately, significant improvement of aggrecanase-2 selectivity over MMP-14 was observed and these compounds displayed IC_{50} values of >10 μM against all other zinc metalloproteases in Table 7, including MMP-14, MMP-1, and TACE. The aggrecanase-2 inhibitory activity of **13a** and **13b** exceeded that of **12b** and **12g**, respectively, and a more than 10-fold improvement of selectivity

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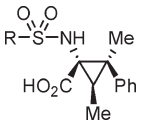
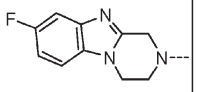
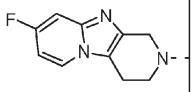
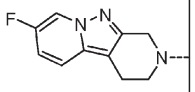
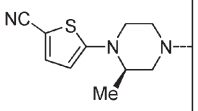
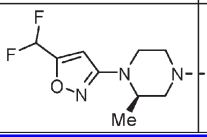
Table 7. SAR of the P1′ Portion of 1-Amino-2,3-dimethyl-2-phenylcycloprapanecarboxylates



compd	R	IC_{50} (μM)[a]			
		Agg-2[b]	MMP-14[c]	MMP-1[d]	TACE[e]
13a		0.014	>10	>10	>10
13b		0.0084	>10	>10	>10
13c		0.010	2.1	>10	>10
13d		0.029	>10	>10	>10
13e		0.017	>10	>10	>10

[a] See Experimental Section for assay protocols. The IC_{50} values are the average of at least two determinations with a standard deviation of <30%. [b] Reference compound **1** gave mean (±SEM) IC_{50} = 12 (±0.60) nM, n = 30. [c] Reference compound **1** gave IC_{50} > 10 μM, n = 18. [d] Reference compound **1** gave IC_{50} > 10 μM, n = 16. [e] Reference compound **1** gave mean (±SEM) IC_{50} = 430 (±43) nM, n = 13.

over MMP-14 was finally achieved. This improvement in selectivity could also be rationalized by means of the docking model as shown in Figure 4. The newly introduced 2-methyl substituent on the cyclopropane ring comes too close to Phe198 of MMP-14, causing a steric repulsion. Meanwhile, the corresponding residue of aggrecanase-2 is Thr378, which allows enough space to accommodate the 2-methyl group. Interestingly, this strong substitution effect on the selectivity was also seen in other P1′ analogues: introduction of a methyl group in the 2-position of **10c**, **10d**, and **12h** afforded **13d**, **13e**, and **13c**, respectively, with a great improvement of aggrecanase-2 selectivity over MMP-14.

Pharmacokinetic (PK) and Selectivity Profiles of Representative Compounds. To assess the PK profile of this series of compounds, we focused on several of the compounds **13** listed in Table 7. Sprague−Dawley rats were used in these experiments, and each compound (10 mg/kg) was administered as a solution in Solutol/ethanol/H_2O = 4:1:5. As shown in Table 8, **13b** showed the best oral bioavailability with an AUC of 421.0 μM·h and having a low clearance of 0.06 μM·h. All the compounds showed no CYP inhibition up to 50 μM (3A4, 2C9, 2D6, 1A2, 2A6, and 2C19). Most strikingly, **13b** showed excellent aggrecanase selectivity over six other members of the Zn metalloproteases (MMP-1, MMP-3, MMP-9, MMP-13, MMP-14, and TACE, Table 9).

Chemistry. Sulfonamide-based aggrecanase-2 inhibitors (Tables 1 and 2) were synthesized as shown in Scheme 1. Amine **14**[12b] was coupled with an appropriate sulfonyl chloride such as **16a**−**c** and **21**, and subsequent acidic cleavage of the *t*-Bu ester gave the targeted compounds **7a**−**c** and **8a**. **16a**−**c** were synthesized from **15a**−**c**,[22] using the procedure described for preparation of **6** and **7d**.[12b] **21** was synthesized by the following steps: coupling of **17** with 2-amino-4-chloropyridine, regioselective bromination of the resultant **18** followed by saponification to **19**, condensation of **19** with ethyl thioglycolate, subsequent saponification to **20**, and decarboxylation in the presence of copper catalyst followed by chlorosulfonylation. In contrast, tricyclic P1′ portions of **8b**−**e** were constructed after sulfonamide bond formation since no examples of chlorosulfonylation of these tricycles were known. Thus, **22** and **24**, obtained by a coupling reaction of **14** with the corresponding sulfonyl chloride, were first coupled with appropriate arylmetal species to give **23** and **25a**−**c**, respectively. The tricyclic systems were constructed

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Table 8. Pharmacokinetics Data for Selected Aggrecanase-2 Inhibitors

compd	iv[a] (mg/kg)	Vd_{ss}(L/kg)	CL((L/h)/kg)	po[b](mg/kg)	$T_{1/2}$(h)	C_{max}(μM)	AUC(μM·h)	F (%)
13a	1	0.70	0.60	10	2.0	17.4	76.9	196
13b	1	0.25	0.06	10	4.0	54.1	421.0	103
13d	1	2.6	0.29	10	4.5	15.9	88.4	119
13e	1	1.9	0.70	10	1.9	4.9	17.8	64

[a] Administered intravenously at 1 mg per 0.5 mL/kg in a solution of Solutol/ethanol/H_2O = 4:1:5. [b] Administered orally by gavage at 10 mg per 5 mL/kg in a solution of Solutol/ethanol/H_2O = 4:1:5.

Table 9. Selectivity Profiles of Compounds 6 and 13b

	IC_{50} (μM)[a]							
	aggrecanase		MMP					
compd	1	2	1	3	9	13	14	TACE
6	0.0040	0.0074	0.18	0.068	0.058	0.0034	0.0039	4.0
13b	0.023	0.0084	>10	9.6	>10	>10	>10	>10

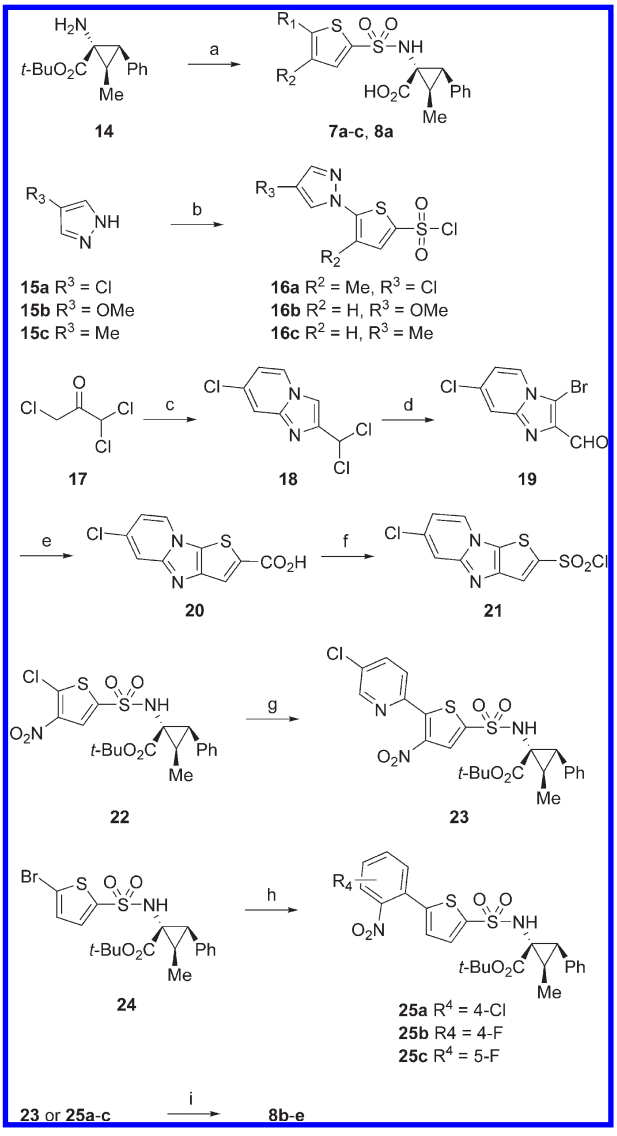
[a] See Experimental Section for assay protocols. The IC_{50} values are the average of at least two determinations with a standard deviation of <30%.

via active nitrene intermediates generated by reduction of **23** and **25a**−**c** with $P(OEt)_3$. The final acidic ester cleavage of the thus obtained products gave **8b**−**e**. There have been few reports of syntheses of these kinds of highly constrained heterocycles, and we found this reductive cyclization through the nitrene intermediate to be one of the best options to synthesize such complex molecules of biological interest.[23]

The sulfamide-based compounds listed in Tables 3 and 4 were synthesized as described in our previous work:[12b] coupling reaction of **26** with appropriate amines[24] and subsequent deprotection gave targeted compounds **9a**−**g** and **10a**−**f**. The novel amines for the synthesis of **9g** and **10b**−**f** were prepared as shown in Scheme 2. *N*-Arylation of **27**[25] with aryl bromides was performed by applying a typical Buchwald protocol to obtain **28a**−**c**. **28c** was further transformed to **28d** by bromination and subsequent Suzuki-coupling. As for isoxazole-substituted piperazines, 3-bromoisoxazole **31a**−**c** were initially prepared by 1,3-dipolar cycloaddition of **29a** or **29b** with 1,1-dibromoformaldoxime and by fluorination of known ketone **30**,[26] respectively. Thus obtained **31a**−**c** were methylated to form quaternary salts by the action of MeOTf to increase their electrophilicity.[27] They were subsequently coupled with **27b** followed by a reductive demethylation[28] to obtain **32a**, **32b**, and **32d**. **32b** was further transformed to **32c** via hydrolysis, oxidation and fluorination. Deprotection of the thus obtained Boc-protected amines with HCl then afforded **33a**−**f**, which were ready for coupling with **26**.

The compounds listed in Tables 5 and 6 were synthesized in an analogous manner. The amines for the synthesis of **11a**, **11b**, **12a**−**f**, and **12i** were prepared following known procedures,[29] while the amines for **11c**−**e**, **12g**, and **12h** were prepared as shown in Scheme 3. The most challenging step in the synthesis of these novel tricyclic amines, including **38a**, **38b**, **43**, **46**, and **51**, was thought to be the construction of the aromatic bicycle; therefore, we planned to prepare the aromatic part prior to the cyclization step that would lead to the aliphatic amine moieties. The imidazo[1,2-*a*]pyridine core for **38** was constructed by the reaction of **34** and 3-bromo-2-oxopentanedioic acid dimethyl

Scheme 1[a]



[a] Reagents and conditions: (a) (i) $ArSO_2Cl$, pyridine; (ii) HCl/1,4-dioxane; (b) (i) 2-bromothiophene or 2-bromo-3-methylthiophene, Cu_2O, salicylaldoxime, Cs_2CO_3, DMA, 150 °C; (ii) $ClSO_3H$, 70 °C; (c) (i) 2-amino-4-chloropyridine, DME; (ii) EtOH, 80 °C; (d) (i) NBS, CH_3CN; (ii) $CaCO_3$, H_2O/CH_3CN, 100 °C; (e) (i) ethyl thioglycolate, NaO-*t*-Bu, EtOH, 100 °C; (ii) 4 M NaOH, 100 °C; (f) (i) Cu_2O, quinoline, 200 °C; (ii) $ClSO_3H$, 80 °C; (g) 5-chloro-2-trimethylstannanylpyridine, $PdClBn(PPh_3)_2$, toluene, 120 °C; (h) 2-(4- or 5- halo-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, $PdCl_2$-(dppf)·CH_2Cl_2, 2 M Na_2CO_3, DME, 100 °C; (i) (i) $P(OEt)_3$, mesitylene, 150 °C; (ii) HCl/1,4-dioxane.

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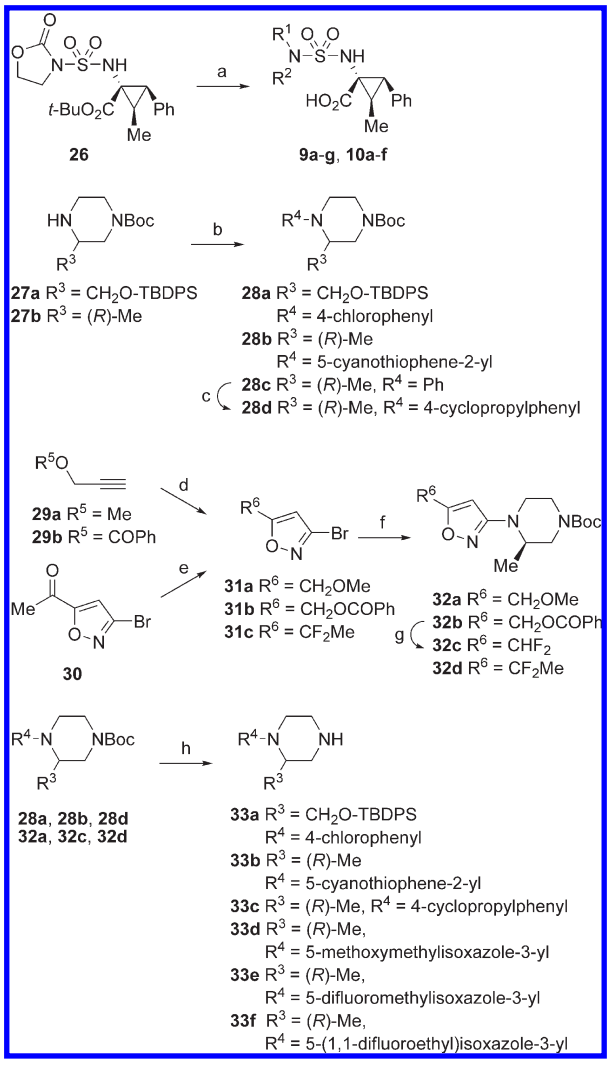
Scheme 2[a]



[a] Reagents and conditions: (a) (i) $R^1R^2NH \cdot n$HCl, NMM, 1,4-dioxane, 100 °C; (ii) HCl/1,4-dioxane or TBAF, THF then HCl/1,4-dioxane; (b) ArBr, NaO-*t*-Bu, $Pd(OAc)_2$, P(*t*-Bu)$_3$, toluene, 110 °C; (c) (i) *n*-$Bu_4N \cdot Br_3$, $CHCl_3$; (ii) cyclopropylboronic acid, $Pd(OAc)_2$, PCy_3, K_3PO_4, toluene/H_2O, 110 °C; (d) 1,1-dibromoformaldoxime, $KHCO_3$, CH_2Cl_2, 40 °C; (e) bis(2-methoxyethyl)aminosulfur trifluoride, CH_2Cl_2, 45 °C; (f) (i) MeOTf, 80 °C; (ii) **27b**, methanol; (iii) Ph_3P, DMF, 130 °C; (g) (i) 1 M NaOH, ethanol, 80 °C; (ii) Dess−Martin periodinane, CH_2Cl_2; (iii) bis(2-methoxyethyl)aminosulfur trifluoride, CH_2Cl_2; (h) HCl/1,4-dioxane.

ester. Thus, the obtained **35** was reduced with excess DIBAL-H to diol **36**, which was directly transformed to **37** by DPPA treatment. Fortunately, compound **37**, obtained by these simple reactions, had a masked nucleophilic nitrogen atom as well as a phosphate leaving group and was ready to cyclize to the piperidine. As expected, reduction of **37** with PPh_3 gave the desired **38** in good yield. Reaction of **34a** with 2-chloro-3-oxosuccinic acid diethyl ester gave the imidazo[1,2-*a*]pyridine core for **43**. One of the two ester groups of the resultant diester **39** was selectively reduced in a chelation-controlled manner to an aldehyde,[30] which was further reduced with $NaBH_4$ to obtain **40**. After THP protection of **40**, the other ester group was reduced by LAH to give **41**, converted to an azide by DPPA treatment,

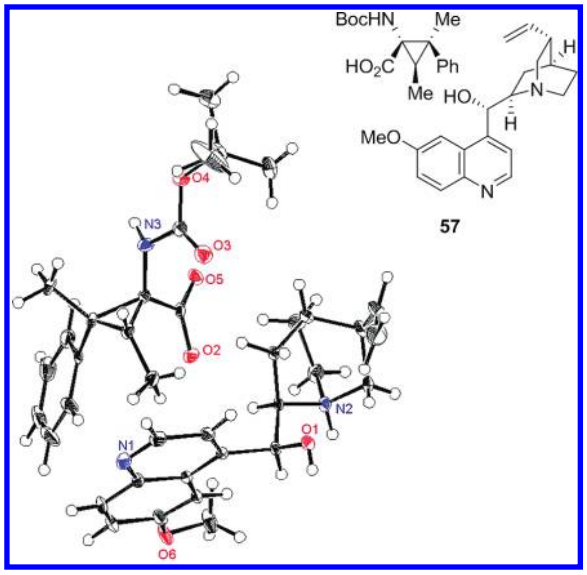


Figure 5. X-ray structure of (1*S*,2*R*,3*R*)-1-*tert*-butoxycarbonylamino-2,3-dimethyl-2-phenylcyclopropanecarboxylic acid quinidine salt **57**. Atomic ellipsoids are drawn at the 50% probability level, and the Flack parameter is refined to −0.2(5). CCDC 810738 contains the supplementary crystallographic data for **57** (available free of charge at The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif).

reduced to an amine with phosphine, and protected with Boc_2O to give **42**. The THP group in **42** was deprotected in hot AcOH, and the resultant hydroxyl group was replaced with a bromine atom. The final pyrrolidine ring formation by the action of NaH and successive Boc deprotection gave **43**. Contrary to other tricycles, the aromatic bicyclic portion of **46** did not have to be constructed because commercially available **44** proved to be a good source of this ring system. Reaction of **44** with *tert*-butyl 2,2-dioxo[1,2,3]oxathiazolidine-3-carboxylate[31] and subsequent acidic Boc deprotection followed by treatment with K_2CO_3 gave intermediate **45**. Finally, this compound was reduced by $BH_3 \cdot$ THF complex to obtain the desired amine **46**. The pyrazolo[1,5-*a*]-pyridine core of **51** was constructed via 1,3-dipolar cycloaddition[32] of 1-aminopyridinium mesitylenesulfonate **47**[33] and 4-(tetrahydropyran-2-yloxy)but-2-ynal.[34] Condensation of the thus obtained **48** with nitromethane followed by LAH reduction gave **49**, which was then converted to **50** by Boc protection and selective THP deprotection. Cyclization of **50** to **51** was conducted via replacement of the hydroxyl group with bromine and successive Boc deprotection. Herein, we have synthesized novel and unique heterocycles as depicted in Scheme 3. These heterocycles and their synthetic procedures are potentially useful for the discovery of other pharmacologically relevant molecules including metalloprotease inhibitors.[23]

The (1*S*,2*R*,3*R*)-1-amino-2,3-dimethyl-2-phenylcyclopropanecarboxylic acid core skeleton was prepared as described in our previous reports.[12b,35] Trans addition of freshly prepared methanesulfenyl chloride to *cis*-2-phenyl-2-butene **52** and subsequent treatment of the adduct with dimethyl malonate gave a mixture of *rac*-**53** and *rac*-**54**. The mixture of these compounds was converted to *rac*-**55** via sulfonium salt formation and subsequent cyclization under basic conditions.[36] Selective hydrolysis of the less hindered ester of *rac*-**55** and successive Curtius rearrangement yielded *rac*-**56**, which was ready for chiral

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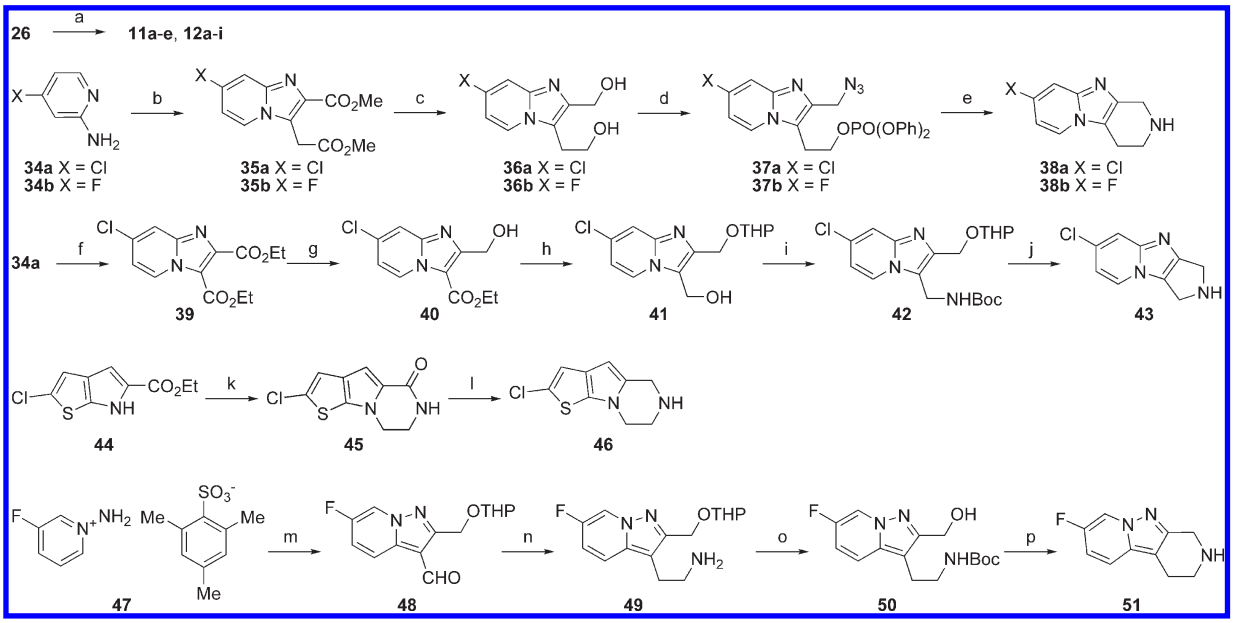
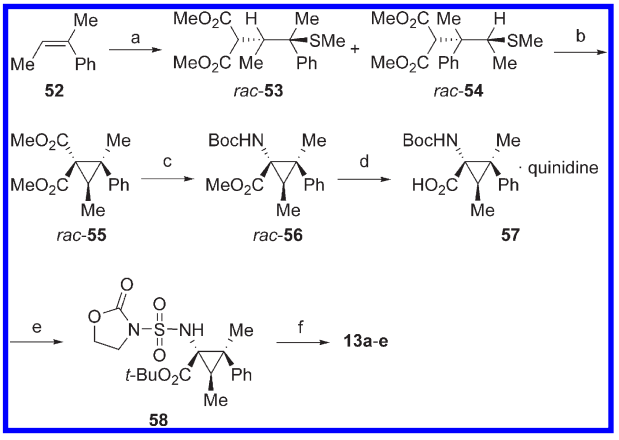
Scheme 3[a]



[a] Reagents and conditions: (a) (i) $R^1R^2NH \cdot n$HCl, NMM, 1,4-dioxane, 100 °C; (ii) HCl/1,4-dioxane; (b) 3-bromo-2-oxopentanedioic acid dimethyl ester, ethanol, 100 °C; (c) DIBAL-H, CH_2Cl_2, 0 °C; (d) DPPA, DBU, THF; (e) (i) PPh_3, THF/H_2O, 60 °C; (ii) Boc_2O, DMAP; (iii) HCl/1,4-dioxane; (f) 2-chloro-3-oxosuccinic acid diethyl ester, ethanol, 100 °C; (g) (i) DIBAL-H, toluene/THF, −78 °C; (ii) $NaBH_4$, methanol; (h) (i) dihydropyrane, $In(OTf)_3$, $CHCl_3$, 80 °C; (ii) LAH, Et_2O, 0 °C; (i) (i) DPPA, DBU, THF; (ii) PPh_3, H_2O, 60 °C; (iii) Boc_2O, DMAP; (j) (i) AcOH, H_2O, 100 °C; (ii) CBr_4, PPh_3, CH_2Cl_2; (iii) NaH, DMSO, 90 °C; (iv) HCl/1,4-dioxane; (k) (i) 3-*tert*-butoxycarbonyl-2,2-dioxo[1,2,3]oxathiazolidine, NaH, DMF; (ii) TFA, $CHCl_3$; (iii) K_2CO_3, THF/methanol; (l) $BH_3 \cdot$THF, THF, 60 °C; (m) 4-(tetrahydropyran-2-yloxy)but-2-ynal, K_2CO_3, DMF; (n) (i) CH_3NO_2, $AcO^-N^+H_4$, 100 °C; (ii) LAH, THF; (o) (i) Boc_2O, THF; (ii) 1 M HCl, 1,4-dioxane; (p) (i) CBr_4, PPh_3, CH_2Cl_2; (ii) NaH, DMF; (iii) HCl/1,4-dioxane.

Scheme 4[a]



[a] Reagents and conditions: (a) (i) $(MeS)_2$, SO_2Cl_2, toluene, −10 °C; (ii) 52, −40 °C; (iii) dimethyl malonate, NaO-*t*-Bu, DME; (b) (i) $(MeO)_2SO_2$, 1,4-dioxane, 50 °C; (ii) NaOMe, methanol, 70 °C; (c) (i) 4 M NaOH, THF/methanol; (ii) DPPA, *t*-BuOH, Et_3N, toluene, 100 °C; (d) (i) 4 M NaOH, THF/methanol, 90 °C; (ii) quinidine, acetone; (e) (i) 10% $KHSO_4$; (ii) $(t\text{-BuO})_2CHNMe_2$, toluene, 100 °C; (iii) *p*-TsOH·H_2O, methanol; (iv) $ClSO_2NCO$, 2-chloroethanol, NMM, CH_3CN, 50 °C; (f) (i) $R^1R^2NH \cdot n$HCl, NMM, 1,4-dioxane, 100 °C; (ii) HCl/1,4-dioxane.

resolution after hydrolysis of another ester group. Among several conditions we examined, recrystallization of the quinidine salt from acetone was finally found to be the best combination to obtain **57** in enantiomerically pure form. The absolute stereochemistry of **57** was determined as (1*S*,2*R*,3*R*) by its X-ray crystallographic analysis, as shown in Figure 5. **57** was converted to sulfamide precursor **58** in the same way described in our earlier paper.[12b] Treatment of **58** with appropriate amines prepared above and subsequent acidic *tert*-butyl ester deprotection provided **13a**−**e** (Scheme 4).

CONCLUSION

Given that broad-spectrum MMP inhibitors have shown serious side effects in clinical trials owing to their lack of specificity, the focus of our aggrecanase inhibitor program has been to develop inhibitors with high selectivity. During the course of our SAR investigation, we discovered that modulation of the P1′ moiety was quite effective in increasing the selectivity for aggrecanase vs other closely related zinc metalloproteases. On the basis of this concept, we have synthesized several novel sulfamide-based compounds and achieved a dramatic enhancement in selectivity. The selectivity was further increased by introduction of a methyl group at the 2-position of the cyclopropane ring. Lead compound **13b** had an IC_{50} of 8.4 nM for aggrecanase-2 and >1000-fold selectivity over the other six zinc metalloproteases tested. Generally, these compounds showed good pharmacokinetic properties, as represented by the data for compound **13b**, and exhibited neither CYP inhibition (IC_{50} > 50 μM against 3A4, 2C9, 2D6, 1A2, 2A6, and 2C19) nor hERG potassium ion channel activity (5.4% inhibition at 30 μM) in the patch clamp assay. Recently, Agg-523, Wyeth's aggrecanase inhibitor, has entered into clinical trials aiming to become the first disease modifying osteoarthritis drug (DMORD).[37] Although its efficacy data are currently unavailable, selective aggrecanase inhibitors, including our compounds such as **13b**,

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have great potential to become DMORDs without the side effects seen previously with nonselective MMP inhibitors.

EXPERIMENTAL SECTION

Chemistry. Unless otherwise specified, materials were purchased from commercial suppliers or prepared using procedures reported elsewhere. Melting points were obtained with a Yanagimoto micromelting point apparatus or a Stanford Research Systems MPA100 and were uncorrected. Combustion analyses were performed with a Perkin-Elmer 2400 series II CHNS/O analyzer, and all values were within ±0.4% of the calculated values. Mass spectra were recorded on an Agilent Technologies 1100 series LC/MS (ESI) spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-A300W, Bruker DPX300, Bruker ARX400, or Varian MERCURYplus-AS400 spectrometer in a solution of $CDCl_3$, methanol-d_4, or DMSO-d_6 using tetramethylsilane as the internal standard. Chemical shifts are expressed as δ (ppm) values for protons relative to the internal standard. Standard abbreviations indicating multiplicity were used as follows: s = singlet, br s = broad singlet, d = doublet, dd = double doublet, ddd = double double doublet, dt = double triplet, dq = double quartet, t = triplet, q = quartet, and m = multiplet. All compounds gave spectra consistent with their assigned structures. Optical rotation was measured at 20 °C with a Rudolph Research Analytical AUTOPOL V spectrometer. Single-crystal X-ray analysis was performed with Rigaku R-AXIS RAPID analysis system. The purity of all of the tested compounds was determined by combustion analyses and was ≥95%.

(1*S*,2*R*,3*R*)-1-[5-(4-Chloropyrazol-1-yl)-4-methylthiophene-2-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (7a). To a stirred solution of (1*S*,2*R*,3*R*)-1-amino-2-methyl-3-phenylcyclopropanecarboxylic acid *tert*-butyl ester **14**[12b] (47 mg, 0.19 mmol) in pyridine (0.5 mL) was added **16a** (56 mg, 0.19 mmol) portionwise at 0 °C. The mixture was stirred at room temperature for 12 h and was then poured into ice−water, and the product was extracted with EtOAc. The organic layer was washed with 0.5 M HCl, 5% solution of $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/EtOAc 4:1) to give the *tert*-butyl ester of **7a** (46 mg, 48% yield), which was successively treated with 4 M HCl in 1,4-dioxane (1 mL) at room temperature for 12 h. After the solvent was removed in vacuo, the crude product was purified by trituration with methanol/H_2O to yield **7a** as a white solid (36 mg, 83% yield): mp 177−181 °C; $[\alpha]^{20}_D$ +104.74° (*c* 0.19, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (d, *J* = 6.8 Hz, 3H), 1.97 (dq, *J* = 10.4, 6.8 Hz, 1H), 2.25 (s, 3H), 2.79 (d, *J* = 10.4 Hz, 1H), 7.16−7.22 (m, 3H), 7.24−7.29 (m, 2H), 7.43 (s, 1H), 7.94 (d, *J* = 0.7 Hz, 1H), 8.53 (d, *J* = 0.5 Hz, 1H), 9.08 (br s, 1H), 12.35 (br s, 1H). Anal. ($C_{19}H_{18}ClN_3O_4S_2 \cdot 0.5H_2O$) calcd C 49.51%, H 4.15%, N 9.11%; found C 49.49%, H 4.26%, N 9.14%.

(1*S*,2*R*,3*R*)-1-[5-(4-Methoxypyrazol-1-yl)thiophene-2-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (7b). **7b** was prepared by coupling of **14** with **16b** following the procedures described for **7a**. The crude product was purified by trituration with methanol/H_2O to yield **7b** as a white solid (41% yield): mp 84−88 °C; $[\alpha]^{20}_D$ +79.23° (*c* 0.13, methanol); ^{1}H NMR (300 MHz, methanol-d_4) δ 1.38 (d, *J* = 6.8 Hz, 3H), 2.15−2.25 (m, 1H), 2.93 (d, *J* = 10.5 Hz, 1H), 3.81 (s, 3H), 7.05(d, *J* = 4.1 Hz, 1H), 7.20−7.24 (m, 5H), 7.47−7.49 (m, 2H), 7.97 (d, *J* = 0.8 Hz, 1H). Anal. ($C_{19}H_{19}N_3O_5S_2 \cdot 0.5H_2O$) calcd C 51.57%, H 4.56%, N 9.50%; found C 51.67%, H 4.66%, N 9.53%.

(1*S*,2*R*,3*R*)-2-Methyl-1-[5-(4-methylpyrazol-1-yl)thiophene-2-sulfonylamino]-3-phenylcyclopropanecarboxylic Acid (7c). **7c** was prepared by coupling of **14** with **16c** following the procedures described for **7a**. The crude product was purified by trituration with methanol/H_2O to yield **7c** as a white solid (34% yield): mp 202−206 °C; $[\alpha]^{20}_D$ +100.00° (*c* 0.14, methanol); ^{1}H NMR (400 MHz, methanol-d_4) δ 1.37 (d, *J* = 6.5 Hz, 3H), 2.14 (s, 3H), 2.16−2.24 (m, 1H), 2.94 (d, *J* = 10.2 Hz, 1H), 7.08 (d, *J* = 4.2 Hz, 1H), 7.16−7.30 (m, 5H), 7.48 (dd, *J* = 4.2, 0.9 Hz, 1H), 7.51 (s, 1H), 7.99 (br s, 1H). Anal. ($C_{19}H_{19}N_3O_4S_2 \cdot 0.5H_2O$) calcd C 53.50%, H 4.73%, N 9.85%; found C 53.85%, H 4.72%, N 9.86%.

(1*S*,2*R*,3*R*)-1-(6-Chlorothieno[3′,2′:4,5]imidazo[1,2-*a*]pyridine-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (8a). **8a** was prepared by coupling of **14** with **21** following the procedures described for **7a**. The crude product was purified by trituration with methanol/H_2O to yield **8a** as a white solid (57% yield): mp 243−248 °C; $[\alpha]^{20}_D$ +52.67° (*c* 0.21, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (d, *J* = 6.6 Hz, 3H), 2.00 (dq, *J* = 10.3, 6.5 Hz, 1H), 2.80 (d, *J* = 10.1 Hz, 1H), 7.12−7.30 (m, 5H), 7.81 (s, 1H), 7.89 (s, 1H), 9.02 (d, *J* = 7.5 Hz, 1H), 9.15 (br s, 1H), 12.22 (br s, 1H). Anal. ($C_{20}H_{16}ClN_3O_4S_2 \cdot H_2O$) calcd C 50.05%, H 3.78%, N 8.75%; found C 50.20%, H 3.59%, N 8.66%.

5-(4-Chloropyrazol-1-yl)-4-methylthiophene-2-sulfonyl Chloride (16a). A mixture of **15a** (500 mg, 3.24 mmol), 2-bromo-3-methylthiophene (689 mg, 3.89 mmol), Cu_2O (46 mg, 0.324 mmol), salicylaldoxime (178 mg, 1.30 mmol), and Cs_2CO_3 (2.11 g, 6.48 mmol) in *N*,*N*-dimethylacetamide (5.0 mL) was heated at 150 °C under an argon atmosphere. After 12 h, the reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated in vacuo, and the residue was purified by flash chromatography (*n*-hexane/EtOAc 8:1) to afford 4-chloro-1-(3-methylthiophen-2-yl)pyrazole as a yellow oil (211 mg, 33% yield). To this product, HSO_3Cl (0.8 mL, 12 mmol) was added, and the mixture was heated at 70 °C for 8 h under argon. After cooling to room temperature, the reaction mixture was poured into ice−water and the resulting precipitate was collected by filtration to give **16a** as a brown solid (214 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 7.62 (s, 1H), 7.70 (s, 1H), 7.82 (s, 1H).

5-(4-Methoxypyrazol-1-yl)thiophene-2-sulfonyl Chloride (16b). **16b** was prepared by coupling of 2-bromothiophene with 4-methoxypyrazole **15b** and subsequent sulfonylation following the procedures described for **16a**. Pale yellow solid (53% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.87 (d, *J* = 4.4 Hz, 1H), 7.48 (s, 1H), 7.51 (s, 1H), 7.74 (d, *J* = 4.4 Hz, 1H).

5-(4-Methylpyrazol-1-yl)thiophene-2-sulfonyl Chloride (16c). **16c** was prepared by coupling of 2-bromothiophene with 4-methylpyrazole **15c** and subsequent sulfonylation following the procedures described for **16a**. Pale yellow solid (13% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.07 (s, 3H), 6.95 (d, *J* = 3.8 Hz, 1H), 6.99 (d, *J* = 3.8 Hz, 1H), 7.49 (s, 1H), 8.14 (s, 1H).

7-Chloro-2-dichloromethylimidazo[1,2-*a*]pyridine (18). A solution of 1,1,3-trichloropropan-2-one **17** (15.1 g, 93.4 mmol) in 1,2-dimethoxyethane (20 mL) was added dropwise to a stirred suspension of 2-amino-4-chloropyridine (8.00 g, 62.3 mmol) in 1,2-dimethoxyethane (80 mL) at 0 °C. The suspension soon turned into a clear solution, and a white precipitate was formed after stirring for 12 h at room temperature. The white solid was collected by filtration and successively heated in ethanol (60 mL) at 80 °C for 4 h. After removal of the solvent under reduced pressure, the mixture was poured into a saturated solution of $NaHCO_3$ at 0 °C and extracted with chloroform. The organic layer was dried over Na_2SO_4 and concentrated. The resultant crude product was purified by trituration with diethyl ether to give **18** as a pale yellow solid (8.22 g, 56% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.58 (s, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 8.18 (s, 1H), 8.59 (d, *J* = 7.3 Hz, 1H).

3-Bromo-7-chloroimidazo[1,2-*a*]pyridine-2-carbaldehyde (19). To a suspension of **18** (8.22 g, 34.9 mmol) in acetonitrile (80 mL) was added *N*-bromosuccinimide (8.06 g, 45.3 mmol) at room temperature, and the mixture was stirred for 4 h under an argon atmosphere.

$CaCO_3$ (10.4 g, 104 mmol) and H_2O (40 mL) were added to the mixture, and the mixture was heated at 100 °C for 4 h. After cooling to room temperature, the reaction mixture was poured into a saturated solution of $NaHCO_3$ at 0 °C and extracted with chloroform. The organic layer was dried over Na_2SO_4 and concentrated, affording a crude product, which was purified by flash chromatography ($CHCl_3$/EtOAc 25:1) to afford **19** as a pale yellow solid (7.69 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, J = 7.4, 2.1 Hz, 1H), 7.71 (dd, J = 2.1, 0.9 Hz, 1H), 8.16 (dd, J = 7.4, 0.9 Hz, 1H), 10.18 (s, 1H).

6-Chlorothieno[3′,2′:4,5]imidazo[1,2-*a*]pyridine-2-carboxylic Acid (20). Ethyl thioglycolate (4.3 mL, 39.2 mmol) was added dropwise to a solution of NaO-*t*-Bu (3.77 g, 39.2 mmol) in ethanol (40 mL), and the mixture was stirred at room temperature for 0.5 h. To this reaction mixture was added a solution of **19** (4.85 g, 18.7 mmol) in ethanol (70 mL). The mixture was heated at 100 °C for 2 h and further heated at this temperature for 1 h after addition of 4 M NaOH (10 mL). After cooling to room temperature, the mixture was concentrated under reduced pressure and neutralized with 2 M HCl at 0 °C to afford a pale yellow solid. The crude product was purified by trituration with ethanol to give **20** as a pale yellow solid (1.33 g, 28% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13 (dd, J = 7.3, 2.2 Hz, 1H), 7.88 (dd, J = 2.2, 0.7 Hz, 1H), 7.95 (s, 1H), 8.97 (dd, J = 7.3, 0.7 Hz, 1H), 13.43 (br s, 1H).

6-Chlorothieno[3′,2′:4,5]imidazo[1,2-*a*]pyridine-2-sulfonyl Chloride (21). A mixture of **20** (411 mg, 1.63 mmol) and Cu_2O (23 mg, 0.16 mmol) in quinoline (4.1 mL) was heated at 200 °C under an argon atmosphere for 1 h. After the mixture was cooled to room temperature, the crude product was purified by flash chromatography (*n*-hexane/EtOAc 5:1) to give 6-chlorothieno[3′,2′:4,5]imidazo[1,2-*a*]pyridine as a brown solid (241 mg, 71% yield). To this brown solid, $ClSO_3H$ (0.5 mL, 7.5 mmol) was added and the mixture was heated at 80 °C for 5 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was poured into ice−water and the resulting precipitate was collected by filtration to give **21** as a pale yellow solid (279 mg, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (dd, J = 7.2, 2.2 Hz, 1H), 7.78 (d, J = 2.2 Hz, 1H), 8.13 (d, J = 7.2 Hz, 1H), 8.18 (s, 1H).

(1*S*,2*R*,3*R*)-1-(5-Chloro-4-nitrothiophene-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid *tert*-Butyl Ester (22). **22** was prepared by coupling of **14** with 5-chloro-4-nitrothiophene-2-sulfonyl chloride following the procedures described for **7a**, but in this case the final acidic hydrolysis was not conducted. Pale yellow solid (50% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.45 (d, J = 6.8 Hz, 3H), 2.40 (dq, J = 10.8, 6.8 Hz, 1H), 3.09 (d, J = 10.8 Hz, 1H), 6.03 (br s, 1H), 7.16−7.34 (m, 5H), 8.03 (s, 1H).

(1*S*,2*R*,3*R*)-1-[5-(5-Chloropyridin-2-yl)-4-nitrothiophene-2-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid *tert*-Butyl Ester (23). A mixture of **22** (352 mg, 0.745 mmol), 5-chloro-2-trimethylstannanylpyridine (300 mg, 0.745 mmol), and $PdClBn(PPh_3)_2$ (56 mg, 0.075 mmol) in toluene (7.0 mL) was heated at 120 °C under argon. After 12 h, the reaction mixture was concentrated and purified by flash chromatography (*n*-hexane/EtOAc 8:1) to afford **23** as a yellow oil (206 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.46 (d, J = 6.6 Hz, 3H), 2.41 (dq, J = 10.6, 6.6 Hz, 1H), 3.09 (d, J = 10.6 Hz, 1H), 6.05 (br s, 1H), 7.19−7.32 (m, 5H), 7.77−7.78 (m, 2H), 8.08 (s, 1H), 8.60−8.61 (m, 1H).

(1*S*,2*R*,3*R*)-1-(5-Bromothiophene-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid *tert*-Butyl Ester (24). **24** was prepared by coupling of **14** with 5-bromothiophene-2-sulfonyl chloride following the procedures described for **7a**, but in this case the final acidic hydrolysis was not conducted. White solid (69% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00 (s, 9H), 1.32 (d, J = 6.7 Hz, 3H), 2.00−2.09 (m, 1H), 2.81 (d, J = 10.4 Hz, 1H), 7.18−7.24 (m, 3H), 7.26−7.30 (m, 2H), 7.31 (d, J = 3.9 Hz, 1H), 7.40 (d, J = 3.9 Hz, 1H), 9.12 (br s, 1H).

(1*S*,2*R*,3*R*)-1-[5-(4-Chloro-2-nitrophenyl)thiophene-2-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid *tert*-Butyl Ester (25a). A mixture of **24** (5.57 g, 11.8 mmol), 2-(4-chloro-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.68 g, 13.0 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (963 mg, 1.18 mmol) in 2 M Na_2CO_3/1,2-dimethoxyethane (70 mL, 2:5) was heated at 100 °C under an argon atmosphere. After 12 h, the reaction mixture was diluted with H_2O and EtOAc. The resultant precipitate was removed by filtration, and the organic layer of the filtrate was separated, washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (*n*-hexane/EtOAc 5:1) to afford **25a** as a brown solid (3.52 g, 54% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (s, 9H), 1.31 (d, J = 7.0 Hz, 3H), 1.96−2.05 (m, 1H), 2.83 (d, J = 10.7 Hz, 1H), 7.17−7.24 (m, 4H), 7.25−7.31 (m, 2H), 7.57 (d, J = 3.9 Hz, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.87 (dd, J = 8.6, 2.3 Hz, 1H), 8.23 (d, J = 2.3 Hz, 1H), 9.14 (br s, 1H).

(1*S*,2*R*,3*R*)-1-[5-(4-Fluoro-2-nitrophenyl)thiophene-2-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid *tert*-Butyl Ester (25b). **25b** was prepared by coupling of **24** with 2-(4-fluoro-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following the procedures described for **25a**. Brown solid (78% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.03 (s, 9H), 1.31 (d, J = 6.7 Hz, 3H), 1.95−2.02 (m, 1H), 2.82 (d, J = 11.6 Hz, 1H), 7.16−7.24 (m, 4H), 7.25−7.32 (m, 2H), 7.51−7.57 (m, 1H), 7.66−7.75 (m, 2H), 8.08 (dd, J = 8.2, 2.4 Hz, 1H), 9.12 (br s, 1H).

(1*S*,2*R*,3*R*)-1-[5-(5-Fluoro-2-nitrophenyl)thiophene-2-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid *tert*-Butyl Ester (25c). **25c** was prepared by coupling of **24** with 2-(5-fluoro-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following the procedures described for **25a**. Brown solid (83% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04 (s, 9H), 1.31 (d, J = 6.7 Hz, 3H), 1.95−2.01 (m, 1H), 2.82 (d, J = 10.4 Hz, 1H), 7.16−7.32 (m, 6H), 7.53−7.62 (m, 3H), 8.14 (dd, J = 8.8, 4.9 Hz, 1H), 9.13 (br s, 1H).

(1*S*,2*R*,3*R*)-1-(7-Chlorothieno[3′,2′:3,4]pyrazolo[1,5-*a*]pyridine-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (8b). To a solution of **23** (200 mg, 0.364 mmol) in mesitylene (4.0 mL) was added $P(OEt)_3$ (362 mg, 2.18 mmol), and the mixture was heated at 150 °C under argon. After 8 h, the reaction mixture was concentrated and the residue was purified by preparative TLC (*n*-hexane/EtOAc 2:1) to afford *tert*-butyl ester of **8b** as a brown oil (22.6 mg, 12% yield), which was successively treated with 4 M HCl in 1,4-dioxane (0.5 mL) at room temperature for 12 h. After the solvent was removed in vacuo, the crude product was purified by trituration with methanol/H_2O to give **8b** as a pale yellow solid (8.2 mg, 40% yield): mp 220−226 °C; $[\alpha]^{20}_D$ +82.50° (*c* 0.20, methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, J = 6.6 Hz, 3H), 1.82−1.87 (m, 1H), 3.09 (d, J = 10.1 Hz, 1H), 6.31 (br s, 1H), 7.14−7.23 (m, 6H), 7.56 (d, J = 9.7 Hz, 1H), 7.76 (s, 1H), 8.58 (s, 1H). Anal. ($C_{20}H_{16}ClN_3O_4S_2\cdot 0.5H_2O$) calcd C 51.00%, H 3.64%, N 8.92%; found C 51.12%, H 3.83%, N 8.95%.

(1*S*,2*R*,3*R*)-1-(6-Chloro-4*H*-thieno[3,2-*b*]indole-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (8c). **8c** was prepared from **25a** following the procedures described for **8b**. The crude product was purified by trituration with methanol/H_2O to yield **8c** as a pale yellow solid (22% yield): mp 136−140 °C; $[\alpha]^{20}_D$ +118.18° (*c* 0.33, THF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26 (d, J = 6.4 Hz, 3H), 1.98 (dq, J = 10.4, 6.6 Hz, 1H), 2.78 (d, J = 10.5 Hz, 1H), 7.10−7.30 (m, 6H), 7.59 (s, 1H), 7.68 (s, 1H), 7.92 (d, J = 8.3 Hz, 1H), 9.02 (s, 1H), 11.72 (s, 1H), 12.23 (s, 1H). Anal. ($C_{21}H_{17}ClN_2O_4S_2$) calcd C 54.72%, H 3.72%, N 6.08%; found C 54.63%, H 3.80%, N 6.16%.

(1*S*,2*R*,3*R*)-1-(6-Fluoro-4*H*-thieno[3,2-*b*]indole-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (8d). **8d** was prepared from **25b** following the procedures described for **8b**. The crude product was purified by trituration with methanol/H_2O

to yield **8d** as a pale yellow solid (57% yield): mp 229−233 °C; $[\alpha]^{20}_D$ +130.80° (*c* 0.10, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (d, *J* = 6.7 Hz, 3H), 1.97 (dd, *J* = 10.2, 6.7 Hz, 1H), 2.77 (d, *J* = 10.2 Hz, 1H), 6.96−7.03 (m, 1H), 7.14−7.21 (m, 3H), 7.22−7.28 (m, 2H), 7.30−7.35 (m, 1H), 7.65 (s, 1H), 7.88−7.93 (m, 1H), 8.97 (br s, 1H), 11.68 (br s, 1H), 12.22 (br s, 1H). Anal. ($C_{21}H_{17}FN_2O_4S_2$) calcd C 56.74%, H 3.85%, N 6.30%; found C 56.95%, H 4.09%, N 6.26%.

(1*S*,2*R*,3*R*)-1-(7-Fluoro-4*H*-thieno[3,2-*b*]indole-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (8e). **8e** was prepared from **25c** following the procedures described for **8b**. The crude product was purified by trituration with methanol/H_2O to yield **8e** as a pale yellow solid (12% yield): mp 129−131 °C; $[\alpha]^{20}_D$ +124.6° (*c* 0.13, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (d, *J* = 6.7 Hz, 3H), 1.97 (dq, *J* = 10.2, 6.7 Hz, 1H), 2.78 (d, *J* = 10.2 Hz, 1H), 7.11−7.22 (m, 4H), 7.22−7.29 (m, 2H), 7.49−7.56 (m, 1H), 7.65 (s, 1H), 7.71−7.78 (m, 1H), 9.01 (br s, 1H), 11.65 (br s, 1H), 12.22 (br s, 1H). Anal. ($C_{21}H_{17}FN_2O_4S_2\cdot 0.5H_2O$) calcd C 55.62%, H 4.00%, N 6.18%; found C 55.69%, H 4.06%, 6.20%.

(1*S*,2*R*,3*R*)-1-[4-(4-Chlorophenyl)piperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid Hydrochloride (9a). To a solution of **26**[12b] (127 mg, 0.32 mmol) in 1,4-dioxane (2.5 mL) were added *N*-methylmorpholine (0.14 mL, 1.27 mmol) and 1-(4-chlorophenyl)piperazine (62 mg, 0.32 mmol) obtained by neutralization of its dihydrochloride. After being stirred at 100 °C under argon atmosphere, the reaction mixture was diluted with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc 5:1) to afford *tert*-butyl ester of **9a** (101 mg, 70% yield), which was successively treated with 4 M HCl in 1,4-dioxane (2.0 mL) at room temperature for 12 h. After the solvent was removed in vacuo, the crude product was purified by trituration with EtOAc to yield **9a** as a white solid (60 mg, 56% yield): mp 107−110 °C; $[\alpha]^{20}_D$ +70.43° (*c* 0.14, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (d, *J* = 6.7 Hz, 3H), 2.00 (dq, *J* = 10.4, 6.7 Hz, 1H), 2.86 (d, *J* = 10.4 Hz, 1H), 3.18 (br s, 8H), 6.97 (d, *J* = 9.3 Hz, 2H), 7.12−7.31 (m, 7H), 8.34 (s, 1H). Anal. ($C_{21}H_{24}ClN_3O_4S\cdot$HCl calcd C 51.86%, H 5.18%, N 8.64%; found C 51.68%, H 5.23%, N 8.72%.

(1*S*,2*R*,3*R*)-1-[4-(4-Chlorophenyl)-1,2,3,6-tetrahydropyridine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (9b). **9b** was prepared by coupling of **26** with 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine following the procedures described for **9a**. The crude product was purified by trituration with methanol/H_2O to yield **9b** as a pale yellow solid (15% yield): mp 94 °C; $[\alpha]^{20}_D$ +45.64° (*c* 0.11, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (d, *J* = 6.8 Hz, 3H), 2.02 (dq, *J* = 10.1, 6.8 Hz, 1H), 2.51−2.58 (m, 2H), 2.88 (d, *J* = 10.1 Hz, 1H), 3.29−3.37 (m, 2H), 3.80 (d, *J* = 3.4 Hz, 2H), 6.24 (t, *J* = 3.4 Hz, 1H), 7.15−7.29 (m, 5H), 7.40 (d, *J* = 11.0 Hz, 2H), 7.46 (d, *J* = 11.0 Hz, 2H), 8.31 (s, 1H), 12.36 (br s, 1H). Anal. ($C_{22}H_{23}ClN_2O_4S\cdot 0.25H_2O$) calcd C 58.53%, H 5.25%, N 6.21%; found C 58.70%, H 5.27%, N 6.18%.

(1*S*,2*R*,3*R*)-1-[(*R*)-4-(4-Chlorophenyl)-3-methylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (9c). **9c** was prepared by coupling of **26** with (*R*)-1-(4-chlorophenyl)-2-methylpiperazine[24a] following the procedures described for **9a**. The crude product was purified by trituration with 1, 4-dioxane/H_2O to yield **9c** as a white solid (70% yield): mp 115−120 °C; $[\alpha]^{20}_D$ +66.70° (*c* 0.40, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (d, *J* = 6.4 Hz, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 2.09 (dq, *J* = 10.5, 6.7 Hz, 1H), 2.74−2.82 (m, 1H), 2.86 (d, *J* = 10.4 Hz, 1H), 2.93−3.04 (m, 2H), 3.32−3.39 (m, 2H), 3.49−3.55 (m, 1H), 4.09 (d, *J* = 6.6 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.15−7.30 (m, 7H), 8.33 (s, 1H). Anal. ($C_{22}H_{26}ClN_3O_4S\cdot$0.75 1,4-dioxane) calcd C 56.65%, H 6.09%, N 7.93%; found C 56.47%, H 5.74%, N 7.72%.

(1*S*,2*R*,3*R*)-1-[(*S*)-4-(4-Chlorophenyl)-3-methylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (9d). **9d** was prepared by coupling of **26** with (*S*)-1-(4-chlorophenyl)-2-methylpiperazine[24a] following the procedures described for **9a**. The crude product was purified by trituration with DMSO/H_2O to yield **9d** as a white solid (75% yield): mp 124−128 °C; $[\alpha]^{20}_D$ +41.42° (*c* 0.45, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.97 (d, *J* = 6.5 Hz, 3H), 1.26 (d, *J* = 6.7 Hz, 3H), 2.01 (dq, *J* = 10.3, 6.8 Hz, 1H), 2.77−2.86 (m, 1H), 2.91 (d, *J* = 10.4 Hz, 1H), 2.95−3.04 (m, 2H), 3.32−3.41 (m, 3H), 4.06−4.14 (m, 1H), 6.90−6.98 (m, 2H), 7.15−7.30 (m, 7H), 8.35 (s, 1H). Anal. ($C_{22}H_{26}ClN_3O_4S\cdot$0.75 DMSO) calcd C 54.01%, H 5.88%, N 8.04%; found C 53.73%, H 5.82%, N 7.99%.

Mixture of (1*S*,2*R*,3*R*)-1-[(*R*)-4-(4-Chlorophenyl)-3-ethylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid Hydrochloride and (1*S*,2*R*,3*R*)-1-[(*S*)-4-(4-Chlorophenyl)-3-ethylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid Hydrochloride (9e). **9e** was prepared by coupling of **26** with 1-(4-chlorophenyl)-2-ethylpiperazine[24b] following the procedures described for **9a**. The crude product was purified by trituration with DMSO/EtOAc to yield **9e** as a white solid (74% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.70−0.91 (m, 3H), 1.21−1.33 (m, 3H), 1.52−1.73 (m, 1H), 1.94−2.14 (m, 1H), 2.67−3.06 (m, 5H), 3.31−3.68 (m, 3H), 3.76−3.94 (m, 1H), 6.83−6.99 (m, 2H), 7.12−7.34 (m, 7H), 8.35 (s, 1H), 11.88−12.55 (m, 1H). Anal. ($C_{23}H_{28}ClN_3O_4S\cdot$HCl$\cdot$0.30DMSO) calcd C 52.70%, H 5.77%, N 7.81%; found C 52.52%, H 5.47%, N 7.52%.

(1*S*,2*R*,3*R*)-1-[4-(4-Chlorophenyl)-3,3-dimethylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (9f). **9f** was prepared by coupling of **26** with 1-(4-chlorophenyl)-2,2-dimethylpiperazine following the procedures described for **9a**. The crude product was purified by trituration with methanol/H_2O to yield **9f** as a white solid (72% yield): mp 131 °C; $[\alpha]^{20}_D$ +74.33° (*c* 0.55, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96 (s, 3H), 0.98 (s, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 2.02 (br s, 1H), 2.78 (br s, 1H), 2.97 (s, 2H), 3.06 (br s, 2H), 3.15 (br s, 2H), 7.07−7.18 (m, 3H), 7.22 (br s, 4H), 7.28−7.31 (m, 2H). Anal. ($C_{23}H_{28}ClN_3O_4S\cdot 0.75H_2O$) calcd C 56.20%, H 6.05%, N 8.55%; found C 56.13%, H 6.02%, N 8.30%.

Mixture of (1*S*,2*R*,3*R*)-1-[(*R*)-4-(4-Chlorophenyl)-3-hydroxymethylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid and (1*S*,2*R*,3*R*)-1-[(*S*)-4-(4-Chlorophenyl)-3-hydroxymethylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (9g). To a solution of **26** (71 mg, 0.181 mmol) in 1,4-dioxane (3.0 mL) were added *N*-methylmorpholine (0.022 mL, 0.200 mmol) and **33a** (vide infra, 84 mg, 0.181 mmol). After being stirred at 100 °C under an argon atmosphere for 12 h, the reaction mixture was diluted with a saturated solution of NH_4Cl, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc 5:1) to give the coupling product as a yellow oil (46 mg, 33% yield). To the solution of this compound in THF (1.0 mL) was added 1 M TBAF in THF (0.10 mL) at room temperature, and the mixture was stirred for 0.5 h. The solvent was removed in vacuo and the residue was purified by preparative TLC ($CHCl_3$/methanol 20:1) to afford the corresponding alcohol (30 mg, 94% yield), which was successively treated with 4 M HCl in 1,4-dioxane (2 mL) at room temperature for 12 h. After concentration in vacuo, the crude product was purified by trituration with DMSO/H_2O to yield **9g** as a pale yellow solid (19 mg, 71% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20−1.28 (m, 3H), 1.88−2.05 (m, 1H), 2.66−3.79 (m, 10H), 6.90 (dd, *J* = 9.3, 2.8 Hz, 2H), 7.11−7.28 (m, 7H), 8.13 (br s, 1H). Anal. ($C_{23}H_{28}ClN_3O_4S\cdot$DMSO) calcd C 53.22%, H 5.63%, N 8.10%; found C 52.86%, H 5.90%, N 7.70%.

(1*S*,2*R*,3*R*)-1-[(*R*)-4-(4-Fluorophenyl)-3-methylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (10a). **10a** was prepared by coupling of **26** with (*R*)-1-(4-fluorophenyl)-2-methylpiperazine[24b] following the procedures described for **9a**. The crude product was purified by trituration with $CHCl_3$/methanol to yield **10a** as a white solid (58% yield): mp 218−222 °C; $[\alpha]^{20}_D$ +174.38° (*c* 0.16, THF); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (d, *J* = 6.3 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.86−1.98 (m, 1H), 2.52−2.62 (m, 1H), 2.91−3.00 (m, 2H), 3.12−3.20 (m, 2H), 3.22−3.28 (m, 1H), 3.45−3.53 (m, 1H), 3.84−3.91 (m, 1H), 6.89−6.95 (m, 2H), 7.01−7.11 (m, 3H), 7.16 (t, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.45 (br s, 1H). Anal. ($C_{22}H_{26}FN_3O_4S\cdot0.75CHCl_3$) calcd C 56.21%, H 5.55%, N 8.64%; found C 56.33%, H 5.49%, 8.80%.

(1*S*,2*R*,3*R*)-1-[(*R*)-4-(4-Cyclopropylphenyl)-3-methylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid Hydrochloride (10b). **10b** was prepared by coupling of **26** with **33c** (vide infra) following the procedures described for **9a**. The crude product was purified by trituration with DMSO/EtOAc to yield **10b** as a pale yellow solid (49% yield): mp 141 °C; $[\alpha]^{20}_D$ +50.89° (*c* 0.45, methanol); ^{1}H NMR (400 MHz, methanol-d_4) δ 0.75 (dt, *J* = 6.5, 4.6 Hz, 2H), 1.03−1.09 (m, 2H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.96−2.04 (m, 1H), 2.24 (dq, *J* = 10.6, 6.8 Hz, 1H), 3.03 (d, *J* = 10.4 Hz, 1H), 3.21 (dd, *J* = 13.6, 10.7 Hz, 1H), 3.43−3.52 (m, 1H), 3.71−3.78 (m, 2H), 3.94−4.04 (m, 2H), 4.08 (d, *J* = 13.8 Hz, 1H), 7.17−7.23 (m, 1H), 7.24−7.33 (m, 6H), 7.48−7.53 (m, 2H). Anal. ($C_{25}H_{31}N_3O_4S\cdot HCl\cdot1.1DMSO$) calcd C 55.18%, H 6.57%, N 7.10%; found C 54.86%, H 6.27%, N 7.42%.

(1*S*,2*R*,3*R*)-1-[(*R*)-4-(5-Cyanothiophen-2-yl)-3-methylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (10c). **10c** was prepared by coupling of **26** with **33b** (vide infra) following the procedures described for **9a**. The crude product was purified by trituration with methanol/H_2O to yield **10c** as a pale yellow solid (74% yield): mp 104 °C; $[\alpha]^{20}_D$ +75.35° (*c* 0.99, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.11 (d, *J* = 6.7 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 2.08 (dq, *J* = 10.4, 6.7 Hz, 1H), 2.70−2.84 (m, 2H), 2.99 (d, *J* = 12.5 Hz, 1H), 3.16−3.22 (m, 1H), 3.38−3.47 (m, 2H), 3.59 (d, *J* = 10.9 Hz, 1H), 3.95−4.02 (m, 1H), 6.20 (d, *J* = 4.4 Hz, 1H), 7.11−7.29 (m, 5H), 7.61 (d, *J* = 4.4 Hz, 1H), 8.38 (br s, 1H). Anal. ($C_{21}H_{24}N_4O_4S_2\cdot$methanol) calcd C 53.64%, H 5.73%, N 11.37%; found C 53.40%, H 5.55%, 11.10%.

(1*S*,2*R*,3*R*)-1-[(*R*)-4-(5-Difluoromethylisoxazol-3-yl)-3-methylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (10d). **10d** was prepared by coupling of **26** with **33e** (vide infra) following the procedures described for **9a**. The crude product was purified by trituration with methanol/H_2O to yield **10d** as a pale yellow solid (68% yield): mp 99 °C; $[\alpha]^{20}_D$ +49.51° (*c* 1.0, methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.6 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 3H), 2.30 (dq, *J* = 10.6, 6.8 Hz, 1H), 2.90 (td, *J* = 11.9, 3.5 Hz, 1H), 3.07 (d, *J* = 10.4 Hz, 1H), 3.12 (dd, *J* = 11.9, 3.5 Hz, 1H), 3.28 (td, *J* = 12.4, 3.4 Hz, 1H), 3.49 (d, *J* = 12.6 Hz, 1H), 3.58 (d, *J* = 11.9 Hz, 1H), 3.70 (d, *J* = 11.9 Hz, 1H), 3.89−3.97 (m, 1H), 5.76 (br s, 1H), 6.20 (s, 1H), 6.59 (t, *J* = 53.8 Hz, 1H), 7.18−7.31 (m, 5H). Anal. ($C_{20}H_{24}F_2N_4O_5S\cdot1.2H_2O$) calcd C 48.81%, H 5.41%, N 11.39%; found C 48.54%, H 5.10%, N 11.17%.

(1*S*,2*R*,3*R*)-1-{(*R*)-4-[5-(1,1-Difluoroethyl)isoxazol-3-yl]-3-methylpiperazine-1-sulfonylamino}-2-methyl-3-phenylcyclopropanecarboxylic Acid (10e). **10e** was prepared by coupling of **26** with **33f** (vide infra) following the procedures described for **9a**. The crude product was purified by trituration with methanol/H_2O to yield **10e** as a pale yellow solid (54% yield): mp 85−90 °C; $[\alpha]^{20}_D$ +47.73° (*c* 0.22, methanol); ^{1}H NMR (400 MHz, methanol-d_4) δ 1.11 (d, *J* = 6.6 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.86 (t, *J* = 18.6 Hz, 3H), 2.15 (dq, *J* = 10.5, 6.7 Hz, 1H), 2.77 (td, *J* = 11.9, 3.5 Hz, 1H), 2.88 (d, *J* = 10.4 Hz, 1H), 3.00 (dd, *J* = 11.8, 3.4 Hz, 1H), 3.11−3.20 (m, 1H), 3.39−3.46 (m, 1H), 3.46−3.52 (m, 1H), 3.59−3.67 (m, 1H), 3.88−3.96 (m, 1H), 6.43 (s, 1H), 7.01−7.19 (m, 5H). Anal. ($C_{21}H_{26}F_2N_4O_5S\cdot0.25H_2O$) calcd C 51.58%, H 5.46%, N 11.46%; found C 51.40%, H 5.57%, 11.43%.

(1*S*,2*R*,3*R*)-1-[(*R*)-4-(5-Methoxymethylisoxazol-3-yl)-3-methylpiperazine-1-sulfonylamino]-2-methyl-3-phenylcyclopropanecarboxylic Acid (10f). **10f** was prepared by coupling of **26** with **33d** (vide infra) following the procedures described for **9a**. The crude product was purified by trituration with methanol/H_2O to yield **10f** as a pale yellow solid (67% yield): mp 71 °C; $[\alpha]^{20}_D$ +61.70° (*c* 0.47, methanol); ^{1}H NMR (400 MHz, methanol-d_4) δ 1.18 (d, *J* = 6.6 Hz, 3H), 1.37 (d, *J* = 6.8 Hz, 3H), 2.24 (dq, *J* = 10.4, 6.8 Hz, 1H), 2.86 (td, *J* = 12.0, 3.6 Hz, 1H), 2.96 (d, *J* = 10.4 Hz, 1H), 3.09 (dd, *J* = 11.7, 3.3 Hz, 1H), 3.23 (td, *J* = 12.5, 3.3 Hz, 1H), 3.38 (s, 3H), 3.47 (d, *J* = 12.6 Hz, 1H), 3.57 (dt, *J* = 11.7, 2.0 Hz, 1H), 3.67−3.74 (m, 1H), 3.93−4.00 (m, 1H), 4.41 (s, 2H), 6.17 (s, 1H), 7.15−7.20 (m, 1H), 7.21−7.29 (m, 4H). Anal. ($C_{21}H_{28}N_4O_6S\cdot0.5H_2O$) calcd C 53.26%, H 6.17%, N 11.83%; found C 53.04%, H 6.13%, N 11.66%.

1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsilanyloxymethyl)-4-(4-chlorophenyl)piperazine (28a). A mixture of **27a**[25] (227 mg, 0.50 mmol), 1-bromo-4-chlorobenzene (115 mg, 0.60 mmol), NaO-*t*-Bu (67 mg, 0.70 mmol), $Pd(OAc)_2$ (2.2 mg, 0.013 mmol), and $P(t\text{-}Bu)_3$ (8.1 mg, 0.040 mmol) in toluene (3.0 mL) was heated at 110 °C under argon. After 12 h, the reaction mixture was diluted with H_2O and then extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (*n*-hexane/EtOAc 9:1) to give **28a** as a yellow oil (152 mg, 54% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94 (s, 9H), 1.40 (s, 9H), 2.88−3.28 (m, 4H), 3.37−3.41 (m, 1H), 3.65−3.92 (m, 3H), 4.26 (d, *J* = 13.0 Hz, 1H), 6.62−6.84 (m, 2H), 7.05−7.17 (m, 2H), 7.35−7.50 (m, 6H), 7.52−7.60 (m, 4H).

(*R*)-1-(*tert*-Butoxycarbonyl)-4-(5-cyanothiophen-2-yl)-3-methylpiperazine (28b). **28b** was prepared by coupling of **27b** with 5-bromothiophene-2-carbonitrile following the procedures described for **28a**. Pale yellow oil (21% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05 (d, *J* = 6.5 Hz, 3H), 1.41 (s, 9H), 2.86−3.22 (m, 3H), 3.31−3.36 (m, 1H), 3.72−4.05 (m, 3H), 6.19 (d, *J* = 4.2 Hz, 1H), 7.61 (d, *J* = 4.2 Hz, 1H).

(*R*)-1-(*tert*-Butoxycarbonyl)-3-methyl-4-phenylpiperazine (28c). **28c** was prepared by coupling of **27b** with bromobenzene following the procedures described for **28a**. Pale yellow oil (73% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.3 Hz, 3H), 1.49 (s, 9H), 3.02−3.29 (m, 3H), 3.38 (dd, *J* = 13.0, 3.6 Hz, 1H), 3.73 (ddd, *J* = 13.0, 3.6, 1.5 Hz, 1H), 3.77−3.85 (m, 1H), 3.85−4.16 (m, 1H), 6.84−6.94 (m, 3H), 7.22−7.30 (m, 2H).

(*R*)-1-(*tert*-Butoxycarbonyl)-4-(4-cyclopropylphenyl)-3-methylpiperazine (28d). To a solution of **28c** (900 mg, 3.25 mmol) in $CHCl_3$ (45 mL) was added tetrabutylammonium tribromide (1.57 g, 3.25 mmol) at 0 °C. After being stirred for 0.5 h at room temperature, the reaction mixture was diluted with a saturated solution of $NaHCO_3$, extracted with $CHCl_3$, and dried over $MgSO_4$. The organic layer was concentrated in vacuo, and the crude product was purified by flash chromatography (*n*-hexane/EtOAc 10:1) to afford (*R*)-1-(4-bromophenyl)-4-(*tert*-butoxycarbonyl)-2-methylpiperazine as a yellow oil (790 mg, 68% yield). To the solution of this product in toluene/H_2O (10.5 mL, 20:1) were added cyclopropylboronic acid (229 mg, 2.66 mmol), K_3PO_4 (1.65 g, 7.77 mmol), $Pd(OAc)_2$ (25 mg, 0.111 mmol), and tricyclohexylphosphine (62 mg, 0.222 mmol). After heating at 110 °C for 4 h, the reaction mixture was diluted with H_2O and then extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified by flash chromatography (*n*-hexane/EtOAc 10:1) to give **28d** as a yellow oil (647 mg, 92% yield). ^{1}H NMR (400 MHz,, $CDCl_3$) δ 0.59−0.64

(m, 2H), 0.86−0.91 (m, 2H), 0.95 (d, J = 6.3 Hz, 3H), 1.48 (s, 9H), 1.79−1.87 (m, 1H), 2.98−3.10 (m, 2H), 3.19−3.37 (m, 1H), 3.37−3.48 (m, 1H), 3.54−3.70 (m, 2H), 3.70−3.99 (m, 1H), 6.83 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H).

3-Bromo-5-methoxymethylisoxazole (31a). To a mixture of **29a** (1 mL, 11.8 mmol) and 1,1-dibromoformaldoxime (2.00 g, 9.86 mmol) in CH_2Cl_2 (20 mL) was added $KHCO_3$ (2.96 g, 29.6 mmol) at 0 °C. After being stirred at 40 °C for 4 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The thus obtained residue was purified by flash chromatography (*n*-hexane/EtOAc 20:1) to give **31a** as a yellow oil (1.59 g, 84% yield based on 1,1-dibromoformaldoxime). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 3H), 4.55 (d, J = 0.7 Hz, 2H), 6.35 (t, J = 0.7 Hz, 1H).

5-Benzoyloxymethyl-3-bromoisoxazol (31b). **31b** was prepared from **29b** following the procedures described for **31a**. Yellow oil (83% yield based on 1,1-dibromoformaldoxime); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (s, 2H), 6.48 (s, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 8.06 (d, J = 7.4 Hz, 2H).

3-Bromo-5-(1,1-difluoroethyl)isoxazole (31c). To a solution of **30** (500 mg, 2.63 mmol) in CH_2Cl_2 (5 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (2.43 mL, 13.2 mmol) at 0 °C. After being stirred at 45 °C for 4 h, the reaction mixture was poured into 1 M NaOH at 0 °C and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The thus obtained residue was purified by flash chromatography (*n*-hexane) to give **31c** as a pale yellow oil (211 mg, 38% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (td, J = 18.5, 1.1 Hz, 3H), 6.58 (t, J = 1.1 Hz, 1H).

(*R*)-1-(*tert*-Butoxycarbonyl)-4-(5-methoxymethylisoxazol-3-yl)-3-methylpiperazine (32a). A mixture of **31a** (1.45 g, 7.55 mmol) and MeOTf (0.897 mL, 7.93 mmol) was heated at 80 °C for 1 h. The resulting methylisoxazolium salt was dissolved in methanol (25 mL) and treated with **27b** (3.18 g, 15.9 mmol) at room temperature for 1 h. After concentration, the residue was treated with PPh_3 (2.97 g, 11.3 mmol) in DMF (20 mL) at 130 °C for 12 h. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ at 0 °C and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained residue was purified by flash chromatography (*n*-hexane/EtOAc 9:1) to give **32a** as a pale yellow oil (507 mg, 22% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 6.6 Hz, 3H), 1.48 (s, 9H), 2.91−3.23 (m, 3H), 3.34−3.45 (m, 1H), 3.43 (s, 3H), 3.76−4.24 (m, 3H), 4.42 (s, 2H), 5.88 (s, 1H).

(*R*)-1-(*tert*-Butoxycarbonyl)-4-(5-benzoyloxymethylisoxazol-3-yl)-3-methylpiperazine (32b). **32b** was prepared from **31b** following the procedures described for **32a**. Pale yellow oil (26% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, J = 6.6 Hz, 3H), 1.47 (s, 9H), 2.85−3.25 (m, 3H), 3.33−3.45 (m, 1H), 3.78−4.23 (m, 3H), 5.31 (s, 2H), 5.99 (s, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 8.06 (d, J = 7.4 Hz, 2H).

(*R*)-1-(*tert*-Butoxycarbonyl)-4-(5-difluoromethylisoxazol-3-yl)-3-methylpiperazine (32c). To a solution of **32b** (100 mg, 0.249 mmol) in ethanol (1 mL) was added 1 M NaOH (0.55 mL), and the mixture was heated at 80 °C for 1 h. After neutralization with 1 M HCl, the mixture was extracted with EtOAc and dried over $MgSO_4$. The organic layer was concentrated under reduced pressure, and the resultant alcohol was oxidized by Dess−Martin periodinane (116 mg, 0.274 mmol) in CH_2Cl_2 (1.5 mL) at room temperature for 1 h. The mixture was diluted with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to give the corresponding aldehyde. The product was dissolved in CH_2Cl_2 (1 mL) and treated with bis(2-methoxyethyl)aminosulfur trifluoride (0.087 mL, 0.479 mmol) at room temperature for 1.5 h. The reaction mixture was poured into saturated $NaHCO_3$ at 0 °C and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. The thus obtained crude product was purified by flash chromatography (*n*-hexane/EtOAc 4:1) to give **32c** as a pale yellow oil (58 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.6 Hz, 3H), 1.48 (s, 9H), 2.87−3.27 (m, 3H), 3.33−3.47 (m, 1H), 3.76−4.26 (m, 3H), 6.19 (s, 1H), 6.60 (t, J = 53.8 Hz, 1H).

(*R*)-1-(*tert*-Butoxycarbonyl)-4-[5-(1,1-difluoroethyl)isoxazol-3-yl]-3-methylpiperazine (32d). **32d** was prepared from **31c** following the procedures described for **32a**. Pale yellow oil (4% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.8 Hz, 3H), 1.47 (s, 9H), 1.97 (t, J = 18.5 Hz, 3H), 2.84−3.28 (m, 3H), 3.32−3.45 (m, 1H), 3.74−4.27 (m, 3H), 6.11 (s, 1H).

2-(*tert*-Butyldiphenylsilanyloxymethyl)-1-(4-chlorophenyl) piperazine (33a). **28a** (152 mg, 0.269 mmol) was treated with 4 M HCl in 1,4-dioxane (3 mL) at room temperature for 12 h. After removal of the solvent in vacuo, the mixture was diluted with EtOAc, washed with saturated solution of $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography ($CHCl_3$/methanol 10:1) to give **33a** as a yellow oil (70 mg, 56% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (s, 9H), 2.59−2.69 (m, 1H), 2.73−2.84 (m, 2H), 2.92 (d, J = 11.6 Hz, 1H), 3.16 (d, J = 10.7 Hz, 1H), 3.24 (d, J = 11.6 Hz, 1H), 3.47 (dd, J = 9.5, 4.9 Hz, 1H), 3.77−3.85 (m, 1H), 4.00 (t, J = 9.5 Hz, 1H), 6.69 (d, J = 9.0 Hz, 2H), 7.06 (d, J = 9.0 Hz, 2H), 7.36−7.50 (m, 6H), 7.52−7.61 (m, 4H).

5-((*R*)-2-Methylpiperazin-1-yl)thiophene-2-carbonitrile (33b). **33b** was prepared from **28b** following the procedures described for **33a**. Pale yellow oil (99% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 (d, J = 6.6 Hz, 3H), 2.60−2.70 (m, 1H), 2.74 (d, J = 12.5 Hz, 1H), 2.84 (dd, J = 12.5, 3.6 Hz, 1H), 2.92 (d, J = 11.9 Hz, 1H), 3.04 (td, J = 11.9, 3.6 Hz, 1H), 3.13−3.21 (m, 1H), 3.65−3.74 (m, 1H), 6.13 (d, J = 4.4 Hz, 1H), 7.58 (d, J = 4.4 Hz, 1H).

(*R*)-1-(4-Cyclopropylphenyl)-2-methylpiperazine (33c). **33c** was prepared from **28d** following the procedures described for **33a**. Pale yellow oil (90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55−0.68 (m, 2H), 0.82−0.93 (m, 2H), 0.98 (d, J = 6.5 Hz, 3H), 1.78−1.90 (m, 1H), 2.72−2.86 (m, 1H), 2.89−3.18 (m, 5H), 3.49−3.63 (m, 1H), 6.86 (d, J = 6.5 Hz, 2H), 6.99 (d, J = 6.6 Hz, 2H).

(*R*)-1-(5-Methoxymethylisoxazol-3-yl)-2-methylpiperazine (33d). **33d** was prepared from **32a** following the procedures described for **33a**. Pale yellow oil (89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 6.8 Hz, 3H), 2.79−2.92 (m, 2H), 2.98−3.20 (m, 3H), 3.31−3.39 (m, 1H), 3.43 (s, 3H), 3.68−3.79 (m, 1H), 4.42 (s, 2H), 5.87 (s, 1H).

(*R*)-1-(5-Difluoromethylisoxazol-3-yl)-2-methylpiperazine (33e). **33e** was prepared from **32c** following the procedures described for **33a**. Pale yellow oil (88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 6.6 Hz, 3H), 2.82−2.92 (m, 2H), 2.98−3.12 (m, 2H), 3.13−3.23 (m, 1H), 3.31−3.40 (m, 1H), 3.70−3.79 (m, 1H), 6.18 (s, 1H), 6.60 (t, J = 53.8 Hz, 1H).

(*R*)-1-[5-(1,1-Difluoroethyl)isoxazol-3-yl]-2-methylpiperazine (33f). **33f** was prepared from **32d** following the procedures described for **33a**. Pale yellow oil (74% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13 (d, J = 6.6 Hz, 3H), 2.00 (t, J = 19.2 Hz, 3H), 2.62 (td, J = 12.1, 3.6 Hz, 1H), 2.70 (d, J = 12.1 Hz, 1H), 2.80−2.91 (m, 2H), 2.98 (td, J = 12.1, 3.6 Hz, 1H), 3.24−3.31 (m, 1H), 3.69−3.77 (m, 1H), 6.77 (s, 1H).

(1*S*,2*R*,3*R*)-1-(8-Chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (11a). **11a** was prepared by coupling of **26** with 8-chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole[29a] following the procedures described for **9a**. The product was purified by trituration with methanol/H_2O to yield **11a** as a pale yellow solid (20% yield): mp 145 °C; $[\alpha]^{20}_D$ +65.14° (*c* 0.21, THF); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (d, J = 6.6 Hz, 3H), 2.03 (dq, J = 10.4, 6.8 Hz, 1H), 2.90 (d, J = 10.4 Hz, 1H), 3.70 (t, J = 5.4 Hz, 2H), 4.15 (t, J = 5.5 Hz, 2H), 4.54 (s, 2H), 6.32 (s, 1H), 7.11 (dd, J = 8.6, 2.2 Hz, 1H), 7.15−7.26 (m, 5H),

7.41 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 2.2 Hz, 1H), 8.59 (br s, 1H). Anal. ($C_{22}H_{22}ClN_3O_4S \cdot 0.5H_2O$) calcd C 56.35%, H 4.94%, N 8.96%; found C 56.05%, H 5.04%, N 8.86%.

(1*S*,2*R*,3*R*)-1-(8-Chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid Hydrochloride (11b). **11b** was prepared by coupling of **26** with 8-chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole[29b] following the procedures described for **9a**. The product was purified by trituration with EtOAc/DMSO to yield **11b** as a white solid (38% yield): mp 188 °C; $[\alpha]^{20}_D$ +76.31° (c 0.13, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (d, J = 6.7 Hz, 3H), 2.04 (dq, J = 10.4, 6.7 Hz, 1H), 2.93 (d, J = 10.4 Hz, 1H), 3.77−3.85 (m, 2H), 4.27−4.34 (m, 2H), 4.70 (br s, 2H), 7.13−7.21 (m, 3H), 7.21−7.33 (m, 2H), 7.42 (dd, J = 8.8, 1.9 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 1.9 Hz, 1H), 8.83 (br s, 1H). Anal. ($C_{21}H_{21}ClN_4O_4S \cdot HCl \cdot 0.75DMSO$) calcd C 48.60%, H 4.80%, N 10.07%; found C 48.43%, H 5.02%, N 10.18%.

(1*S*,2*R*,3*R*)-1-(8-Chloro-1,2,3,4-tetrahydropyrido[3′,4′:4,5]imidazo[1,2-*a*]pyridine-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (11c). **11c** was prepared by coupling of **26** with **38a** (vide infra) following the procedures described for **9a**. The product was purified by trituration with methanol/H_2O to yield **11c** as a white solid (59% yield): mp 193−197 °C; $[\alpha]^{20}_D$ +57.32° (c 0.41, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (d, J = 6.6 Hz, 3H), 2.02 (dq, J = 10.4, 6.6 Hz, 1H), 2.88 (d, J = 10.4 Hz, 1H), 2.96 (t, J = 5.4 Hz, 2H), 3.56−3.69 (m, 2H), 4.37 (s, 2H), 7.00 (dd, J = 7.3, 2.0 Hz, 1H), 7.16−7.28 (m, 5H), 7.68 (d, J = 2.2 Hz, 1H), 8.32 (d, J = 7.3 Hz, 1H), 8.42 (s, 1H), 12.37 (br s, 1H). Anal. ($C_{21}H_{21}ClN_4O_4S$) calcd C 54.72%, H 4.59%, N 12.15%; found C 54.40%, H 4.62%, N 12.22%.

(1*S*,2*R*,3*R*)-1-(2-Chloro-5,6,7,8-tetrahydrothieno[3′,2′:4,5]pyrrolo[1,2-*a*]pyrazine-7-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (11d). **11d** was prepared by coupling of **26** with **46** (vide infra) following the procedures described for **9a**. The product was purified by trituration with methanol/H_2O to yield **11d** as a white solid (75% yield): mp 95 °C; $[\alpha]^{20}_D$ +65.88° (c 0.17, THF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25 (d, J = 6.8 Hz, 3H), 2.02 (dq, J = 10.5, 6.8 Hz, 1H), 2.89 (d, J = 10.2 Hz, 1H), 3.63 (t, J = 5.5 Hz, 2H), 4.01 (t, J = 5.5 Hz, 2H), 4.41 (s, 2H), 6.20 (s, 1H), 7.10 (s, 1H), 7.15−7.28 (m, 6H), 8.57 (br s, 1H). Anal. ($C_{20}H_{20}ClN_3O_4S_2$) calcd C 51.55%, H 4.33%, N 9.02%; found C 51.50%, H 4.63%, N 8.80%.

(1*S*,2*R*,3*R*)-1-(6-Chloro-2,3-dihydro-1*H*-pyrrolo[3′,4′:4,5]imidazo[1,2-*a*]pyridine-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid Hydrochloride (11e). **11e** was prepared by coupling of **26** with **43** (vide infra) following the procedures described for **9a**. The product was purified by trituration with EtOAc/methanol to yield **11e** as a white solid (22% yield): mp 176−181 °C; $[\alpha]^{20}_D$ +65.33° (c 0.15, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (d, J = 6.6 Hz, 3H), 2.03−2.13 (m, 1H), 2.89 (d, J = 10.1 Hz, 1H), 4.49−4.63 (m, 2H), 4.67−4.79 (m, 2H), 7.16−7.23 (m, 4H), 7.23−7.29 (m, 2H), 7.85 (d, J = 1.5 Hz, 1H), 8.55 (s, 1H), 8.61 (d, J = 7.3 Hz, 1H). Anal. ($C_{20}H_{19}ClN_4O_4S \cdot HCl \cdot 1.25$methanol) calcd C 48.76%, H 4.81%, N 10.70%; found C 48.79%, H 4.77%, N 10.45%.

(1*S*,2*R*,3*R*)-2-Methyl-3-phenyl-1-(1,2,3,4-tetrahydropyrazino-[1,2-*a*]benzimidazole-2-sulfonylamino)cyclopropanecarboxylic Acid Hydrochloride (12a). **12a** was prepared by coupling of **26** with 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole[29b] following the procedure described for **9a**. The product was purified by trituration with EtOAc to yield **12a** as a white solid (43% yield): mp 182−186 °C; $[\alpha]^{20}_D$ +64.22° (c 0.18, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (d, J = 6.6 Hz, 3H), 2.08 (dq, J = 10.5, 6.7 Hz, 1H), 2.96 (d, J = 10.4 Hz, 1H), 3.88 (t, J = 5.5 Hz, 2H), 4.36−4.46 (m, 2H), 4.84 (s, 2H), 7.17−7.23 (m, 3H), 7.24−7.30 (m, 2H), 7.51−7.56 (m, 2H), 7.80−7.87 (m, 2H), 8.95 (s, 1H). Anal. ($C_{21}H_{22}N_4O_4S \cdot HCl \cdot 0.5H_2O$) calcd C 53.44%, H 5.13%, N 11.87%; found C 53.62%, H 5.34%, N 11.67%.

(1*S*,2*R*,3*R*)-1-(8-Fluoro-1,2,3,4-tetrahydropyrazino[1,2-*a*]-benzimidazole-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid Hydrochloride (12b). **12b** was prepared by coupling of **26** with 8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole[29b] following the procedures described for **9a**. The product was purified by trituration with EtOAc to yield **12b** as a white solid (67% yield): mp 190−193 °C; $[\alpha]^{20}_D$ +73.33° (c 0.18, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (d, J = 6.8 Hz, 3H), 2.02−2.11 (m, 1H), 2.95 (d, J = 10.4 Hz, 1H), 3.82−3.89 (m, 2H), 4.37 (t, J = 5.2 Hz, 2H), 4.78 (s, 2H), 7.16−7.30 (m, 5H), 7.36 (td, J = 9.4, 2.4 Hz, 1H), 7.65 (dd, J = 9.2, 2.3 Hz, 1H), 7.81 (dd, J = 8.9, 4.5 Hz, 1H), 8.90 (s, 1H). Anal. ($C_{21}H_{21}FN_4O_4S \cdot HCl$) calcd C 52.45%, H 4.61%, N 11.65%; found C 52.21%, H 4.71%, N 11.58%.

(1*S*,2*R*,3*R*)-1-(7-Fluoro-1,2,3,4-tetrahydropyrazino[1,2-*a*]-benzimidazole-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid Hydrochloride (12c). **12c** was prepared by coupling of **26** with 7-fluoro-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole[29b] following the procedures described for **9a**. The product was purified by trituration with EtOAc to yield **12c** as a white solid (62% yield): mp 170 °C; $[\alpha]^{20}_D$ +68.89° (c 0.18, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (d, J = 6.6 Hz, 3H), 2.02−2.11 (m, 1H), 2.95 (d, J = 10.4 Hz, 1H), 3.82−3.88 (m, 2H), 4.30−4.34 (m, 2H), 4.76 (s, 2H), 7.18−7.35 (m, 6H), 7.73 (dd, J = 8.8, 2.4 Hz, 1H), 7.79 (dd, J = 8.9, 4.5 Hz, 1H), 8.90 (s, 1H). Anal. ($C_{21}H_{21}FN_4O_4S \cdot HCl \cdot H_2O$) calcd C 50.55%, H 4.85%, N 11.23%; found C 50.69%, H 5.22%, N 10.89%.

(1*S*,2*R*,3*R*)-1-(8-Cyano-1,2,3,4-tetrahydropyrazino[1,2-*a*]-benzimidazole-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid Hydrochloride (12d). **12d** was prepared by coupling of **26** with 1,2,3,4-tetrahydropyrazino[1,2-*a*]-benzimidazole-8-carbonitrile[29b] following the procedures described for **9a**. The product was purified by trituration with EtOAc/methanol to yield **12d** as a white solid (41% yield): mp 151 °C; $[\alpha]^{20}_D$ +62.22° (c 0.18, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26 (d, J = 6.4 Hz, 3H), 2.05 (dq, J = 10.5, 6.8 Hz, 1H), 2.93 (d, J = 10.2 Hz, 1H), 3.79−3.86 (m, 2H), 4.30 (t, J = 5.3 Hz, 2H), 4.65 (s, 2H), 7.16−7.31 (m, 5H), 7.66 (dd, J = 8.5, 1.3 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H), 8.78 (s, 1H). Anal. ($C_{22}H_{21}N_5O_4S \cdot HCl \cdot 0.75$methanol) calcd C 53.37%, H 4.92%, N 13.68%; found C 53.34%, H 4.63%, N 13.53%.

(1*S*,2*R*,3*R*)-2-Methyl-1-(8-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole-2-sulfonylamino)-3-phenylcyclopropanecarboxylic Acid (12e). **12e** was prepared by coupling of **26** with 8-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole[29b] following the procedures described for **9a**. The product was purified by trituration with DMSO/H_2O to yield **12e** as a white solid (63% yield): mp 185−189 °C; $[\alpha]^{20}_D$ +55.26° (c 0.19, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (d, J = 6.5 Hz, 3H), 2.02−2.12 (m, 1H), 2.49 (s, 3H), 2.95 (d, J = 10.4 Hz, 1H), 3.86 (t, J = 5.3 Hz, 2H), 4.34−4.39 (m, 2H), 4.80 (s, 2H), 7.16−7.37 (m, 6H), 7.61 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 8.94 (s, 1H). Anal. ($C_{22}H_{24}N_4O_4S \cdot 1.25DMSO$) calcd C 54.67%, H 5.90%, N 10.41%; found C 54.23%, H 6.03%, N 10.34%.

(1*S*,2*R*,3*R*)-1-(8-Methoxy-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid Hydrochloride (12f). **12f** was prepared by coupling of **26** with 8-methoxy-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole[29b] following the procedures described for **9a**. The product was purified by trituration with EtOAc to yield **12f** as a white solid (79% yield): mp 170 °C; $[\alpha]^{20}_D$ +66.67° (c 0.18, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (d, J = 6.6 Hz, 3H), 2.02−2.11 (m, 1H), 2.95 (d, J = 9.9 Hz, 1H), 3.82−3.86 (m, 2H), 3.85 (s, 3H),

4.32−4.38 (m, 2H), 4.78 (s, 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.17−7.22 (m, 3H), 7.24−7.31 (m, 3H), 7.68−7.73 (m, 1H), 8.91 (s, 1H). Anal. ($C_{22}H_{24}N_4O_5S\cdot HCl\cdot H_2O$) calcd C 51.71%, H 5.33%, N 10.96%; found C 51.43%, H 5.50%, N 10.65%.

(1*S*,2*R*,3*R*)-1-(8-Fluoro-1,2,3,4-tetrahydropyrido[3′,4′:4,5]imidazo[1,2-*a*]pyridine-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (12g). **12g** was prepared by coupling of **26** with **38b** (vide infra) following the procedures described for **9a**. The product was purified by trituration with methanol/H_2O to yield **12g** as a white solid (65% yield): mp 212−214 °C; $[\alpha]^{20}_D$ +58.53° (*c* 0.095, methanol); ^{1}H NMR (300 MHz, methanol-d_4) δ 1.36 (d, J = 6.8 Hz, 3H), 2.21 (dq, J = 10.5, 6.8 Hz, 1H), 3.02−3.13 (m, 3H), 3.86 (t, J = 5.8 Hz, 2H), 4.62−4.67 (m, 2H), 7.14−7.28 (m, 4H), 7.47 (td, J = 7.5, 2.4 Hz, 1H), 7.50−7.59 (m, 1H), 7.59−7.67 (m, 1H), 7.76 (dd, J = 8.1, 2.4 Hz, 1H), 8.70 (dd, J = 7.3, 5.1 Hz, 1H). Anal. ($C_{21}H_{21}FN_4O_4S$) calcd C 56.75%, H 4.76%, N 12.61%; found C 56.41%, H 4.82%, N 12.46%.

(1*S*,2*R*,3*R*)-1-(7-Fluoro-1,2,3,4-tetrahydropyrido[3′4′:3,4]pyrazolo[1,5-*a*]pyridine-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (12h). **12h** was prepared by coupling of **26** with 7-fluoro-1,2,3,4-tetrahydropyrido[3′4′:3,4]-pyrazolo[1,5-*a*]pyridine **51** following the procedures described for **9a**. The product was purified by trituration with methanol/H_2O to yield **12h** as a white solid (49% yield): mp 205−209 °C; $[\alpha]^{20}_D$ +101.88° (*c* 0.16, THF); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (d, J = 6.8 Hz, 3H), 2.03 (dq, J = 10.3, 6.7 Hz, 1H), 2.84 (t, J = 5.7 Hz, 2H), 2.90 (d, J = 10.4 Hz, 1H), 3.52 (q, J = 5.4 Hz, 2H), 4.43 (s, 2H), 7.16−7.32 (m, 6H), 7.65 (dd, J = 9.8, 5.8 Hz, 1H), 8.43 (s, 1H), 8.89 (dd, J = 5.0, 2.1 Hz, 1H), 12.34 (br s, 1H). Anal. ($C_{21}H_{21}FN_4O_4S$) calcd C 56.75%, H 4.76%, N 12.61%; found C 56.74%, H 4.90%, N 12.41%.

(1*S*,2*R*,3*R*)-1-(7-Fluoro-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-2-sulfonylamino)-2-methyl-3-phenylcyclopropanecarboxylic Acid (12i). **12i** was prepared by coupling of **26** with 7-fluoro-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole[29c] following the procedure described for **9a**. The product was purified by trituration with methanol/H_2O to yield **12i** as a white solid (18% yield): mp 150−152 °C; $[\alpha]^{20}_D$ +73.64° (*c* 0.22, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (d, J = 6.6 Hz, 3H), 1.98−2.08 (m, 1H), 2.72−2.78 (m, 2H), 2.89 (d, J = 10.4 Hz, 1H), 3.49 (t, J = 5.6 Hz, 2H), 4.35 (s, 2H), 6.79−6.84 (m, 1H), 7.10 (dd, J = 10.1, 2.2 Hz, 1H), 7.15−7.28 (m, 5H), 7.37 (dd, J = 8.6, 5.5 Hz, 1H), 8.38 (br s, 1H), 10.96 (s, 1H), 12.37 (br s, 1H). Anal. ($C_{22}H_{22}FN_3O_4S\cdot 0.25H_2O$) calcd C 58.98%, H 5.06%, N 9.38%; found C 58.76%, H 5.24%, N 9.21%.

7-Chloro-3-methoxycarbonylmethylimidazo[1,2-*a*]pyridine-2-carboxylic Acid Methyl Ester (35a). A mixture of **34a** (11.0 g, 85.6 mmol) and 3-bromo-2-oxopentanedioic acid dimethyl ester (30.3 g, 120 mmol) in ethanol (200 mL) was heated at 100 °C for 12 h. After concentration, the crude product was purified by flash chromatography ($CHCl_3$/methanol 20:1) to give **35a** as a yellow oil (11.8 g, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.99 (s, 3H), 4.45 (s, 2H), 6.92 (dd, J = 7.5, 2.1 Hz, 1H), 7.68 (dd, J = 2.1, 0.9 Hz, 1H), 7.96 (dd, J = 7.5, 0.9 Hz, 1H).

7-Fluoro-3-methoxycarbonylmethylimidazo[1,2-*a*]pyridine-2-carboxylic Acid Methyl Ester (35b). **35b** was prepared from **34b** following the procedure described for **35a**. Yellow oil (39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.99 (s, 3H), 4.45 (s, 2H), 6.80−6.86 (m, 1H), 7.27−7.33 (m, 1H), 7.98−8.04 (m, 1H).

2-(7-Chloro-2-hydroxymethylimidazo[1,2-*a*]pyridin-3-yl)ethanol (36a). To a solution of **35a** (4.66 g, 16.5 mmol) in CH_2Cl_2 (100 mL) was added 1 M DIBAL-H in CH_2Cl_2 (99 mL, 99 mmol) dropwise at 0 °C. After being stirred for 2 h, the mixture was diluted with a saturated solution of Rochelle's salt and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained crude product was purified by flash chromatography ($CHCl_3$/methanol 9:1) to give **36a** as a pale yellow oil (2.84 g, 76% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.12 (t, J = 6.2 Hz, 2H), 3.63 (dt, J = 6.2, 5.2 Hz, 2H), 4.55 (d, J = 5.6 Hz, 2H), 4.81 (t, J = 5.2 Hz, 1H), 4.97 (t, J = 5.6 Hz, 1H), 6.93 (dd, J = 7.3, 2.2 Hz, 1H), 7.60 (dd, J = 2.2, 0.7 Hz, 1H), 8.42 (dd, J = 7.3, 0.7 Hz, 1H).

2-(7-Fluoro-2-hydroxymethylimidazo[1,2-*a*]pyridin-3-yl)ethanol (36b). **36b** was prepared from **35b** following the procedures described for **36a**. Yellow oil (76% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.11 (t, J = 6.4 Hz, 2H), 3.58−3.66 (m, 2H), 4.53 (d, J = 5.6 Hz, 2H), 4.80 (t, J = 5.6 Hz, 1H), 4.92 (t, J = 5.6 Hz, 1H), 6.86−6.97 (m, 1H), 7.22−7.33 (m, 1H), 8.39−8.48 (m, 1H).

Phosphoric Acid 2-(2-Azidomethyl-7-chloroimidazo[1,2-*a*]pyridin-3-yl)ethyl Ester Diphenyl Ester (37a). To a mixture of **36a** (500 mg, 2.21 mmol) and DBU (739 mg, 4.86 mmol) in THF (5.0 mL) was added DPPA (1.34 g, 4.86 mmol) at 0 °C. After being stirred at room temperature for 1 h, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained crude product was purified by flash chromatography (*n*-hexane/EtOAc 2:1) to give **37a** as a yellow oil (851 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (t, J = 6.5 Hz, 2H), 4.39−4.47 (m, 4H), 6.71 (dd, J = 7.3, 2.0 Hz, 1H), 7.10 (d, J = 7.9 Hz, 4H), 7.15−7.42 (m, 6H), 7.54 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 7.3 Hz, 1H).

Phosphoric Acid 2-(2-Azidomethyl-7-fluoroimidazo[1,2-*a*]pyridin-3-yl)ethyl Ester Diphenyl Ester (37b). **37b** was prepared from **36b** following the procedures described for **37a**. Yellow oil (70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (t, J = 6.5 Hz, 2H), 4.36−4.50 (m, 4H), 6.59−6.66 (m, 1H), 7.07−7.22 (m, 6H), 7.24−7.37 (m, 5H), 7.92−7.99 (m, 1H).

8-Chloro-1,2,3,4-tetrahydropyrido[3′,4′:4,5]imidazo[1,2-*a*]pyridine (38a). A mixture of **37a** (850 mg, 1.76 mmol) and PPh_3 (600 mg, 2.29 mmol) in THF/H_2O = 10:1 (11 mL) was heated at 60 °C for 4 h. After the mixture was cooled to room temperature, Boc_2O (768 mg, 3.52 mmol) and DMAP (22 mg, 0.176 mmol) were added to the mixture, which was then stirred at room temperature for 12 h. The mixture was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography (*n*-hexane/EtOAc 1:1) to give the corresponding tricycle (352 mg, 65% yield) as a white solid, which was successively treated with 4 M HCl in 1,4-dioxane (4.0 mL) at room temperature for 12 h. The solvent was removed in vacuo, and the crude product was neutralized with NaO-*t*-Bu (219 mg, 2.28 mmol) in THF (4.0 mL). After filtration of the resultant precipitates, the filtrate was concentrated to give **38a** as a white solid (234 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.91 (br s, 2H), 3.24 (br s, 2H), 4.01 (br s, 2H), 7.00 (dd, J = 7.3, 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 8.34 (d, J = 7.3 Hz, 1H).

8-Fluoro-1,2,3,4-tetrahydropyrido[3′,4′:4,5]imidazo[1,2-*a*]pyridine (38b). **38b** was prepared from **37b** following the procedure described for **38a**. Pale yellow solid (70% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.73 (t, J = 5.6 Hz, 2H), 3.05 (t, J = 5.6 Hz, 2H), 3.80 (br s, 2H), 6.89−6.97 (m, 1H), 7.27−7.34 (m, 1H), 8.26−8.32 (m, 1H).

7-Chloroimidazo[1,2-*a*]pyridine-2,3-dicarboxylic Acid Diethyl Ester (39). A mixture of **34a** (1.15 g, 8.98 mmol) and 2-chloro-3-oxosuccinic acid diethyl ester (1.00 g, 4.49 mmol) in ethanol (10 mL) was heated at 100 °C for 12 h. After concentration, the crude product was purified by flash chromatography (*n*-hexane/EtOAc 20:1) to give **39** as a white solid (982 mg, 74% yield based on 2-chloro-3-oxosuccinic acid diethyl ester). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.2 Hz, 3H), 1.44 (t, J = 7.2 Hz, 3H), 4.43 (q, J = 6.5 Hz, 2H), 4.48 (q, J = 6.5 Hz, 2H), 7.08 (dd, J = 7.5, 2.2 Hz, 1H), 7.75 (dd, J = 2.2, 0.9 Hz, 1H), 9.21 (dd, J = 7.5, 0.9 Hz, 1H).

7-Chloro-2-hydroxymethylimidazo[1,2-*a*]pyridine-3-carboxylic Acid Ethyl Ester (40). To a solution of **39** (980 mg, 3.30 mmol) in THF (10 mL) was added 1 M DIBAL-H in toluene (4.0 mL,

4.0 mmol) dropwise at −78 °C. After being stirred for 2 h, the mixture was diluted with saturated solution of Rochelle's salt and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The resultant aldehyde was treated with $NaBH_4$ (62 mg, 1.63 mmol) in methanol (8.2 mL) at room temperature. After being stirred for 2 h, the reaction was neutralized with 2 M H_2SO_4 and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained crude product was purified by trituration with *n*-hexane/EtOAc to give **40** as a white solid (786 mg, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 4.45 (q, J = 7.2 Hz, 2H), 5.05 (s, 2H), 7.03 (dd, J = 7.5, 1.9 Hz, 1H), 7.69 (d, J = 1.9 Hz, 1H), 9.22 (d, J = 7.5 Hz, 1H).

[7-Chloro-2-(tetrahydropyran-2-yloxymethyl)imidazo[1,2-*a*]pyridin-3-yl]methanol (41). A mixture of **40** (786 mg, 3.09 mmol), dihydropyrane (1.41 mL, 15.5 mmol), and $In(OTf)_3$ (84 mg, 0.15 mmol) in $CHCl_3$ (8.0 mL) was heated at 80 °C for 12 h. After the solvent was removed in vacuo, the residue was purified by flash chromatography (*n*-hexane/EtOAc 3:1) to give the corresponding THP-protected ether as a pale yellow solid (868 mg, 83% yield), which was further dissolved in Et_2O (9.0 mL) and transferred to a suspension of $LiAlH_4$ (97 mg, 2.56 mmol) in Et_2O (4.0 mL) dropwise at 0 °C. After the mixture was stirred for 1 h, the reaction was quenched by an addition of 15% NaOH (0.10 mL) and H_2O (0.40 mL), and the resultant precipitate was removed by filtration. The filtrate was concentrated, and the residue was purified by flash chromatography ($CHCl_3$/methanol 20:1) to give **41** as a white solid (632 mg, 83% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.40−1.76 (m, 6H), 3.44−3.54 (m, 1H), 3.78−3.87 (m, 1H), 4.56 (d, J = 11.9 Hz, 1H), 4.71−4.74 (m, 1H), 4.74 (d, J = 11.9 Hz, 1H), 4.84 (d, J = 5.3 Hz, 2H), 5.21 (t, J = 5.3 Hz, 1H), 7.04 (dd, J = 7.3, 2.2 Hz, 1H), 7.70 (dd, J = 2.2, 0.6 Hz, 1H), 8.41 (dd, J = 7.3, 0.6 Hz, 1H).

3-*tert*-Butoxycarbonylaminomethyl-7-chloro-2-(tetrahydropyran-2-yloxymethyl)imidazo[1,2-*a*]pyridine (42). To a solution of **41** (632 mg, 2.12 mmol) in THF (6.3 mL) were added DPPA (762 mg, 2.77 mmol) and DBU (422 mg, 2.77 mmol) at 0 °C. After the mixture was stirred at room temperature for 12 h, PPh_3 (838 mg, 3.20 mmol) and H_2O (1.1 mL) were added to the mixture, which was then heated at 60 °C for 4 h. Boc_2O (929 mg, 4.26 mmol) and DMAP (13 mg, 0.106 mmol) were added to this solution, and the mixture was stirred at room temperature for 12 h. The mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained crude product was purified by flash chromatography (*n*-hexane/EtOAc 1:1) to give **42** as a white solid (498 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.51−1.89 (m, 6H), 3.52−3.61 (m, 1H), 3.85−3.94 (m, 1H), 4.65−4.73 (m, 3H), 4.73 (d, J = 12.4 Hz, 1H), 4.94 (d, J = 12.4 Hz, 1H), 5.17 (br s, 1H), 6.81 (dd, J = 7.3, 2.0 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 8.35 (d, J = 7.3 Hz, 1H).

6-Chloro-2,3-dihydro-1*H*-pyrrolo[3′,4′:4,5]imidazo[1,2-*a*]pyridine (43). A solution of **42** (498 mg, 1.26 mmol) in AcOH/H_2O (1:1, 5.0 mL) was heated at 100 °C for 1 h. The mixture was neutralized with 4 M NaOH and triturated by addition of *n*-hexane/EtOAc to afford the corresponding alcohol as a white solid (282 mg, 72% yield). To a solution of this compound in CH_2Cl_2 (2.8 mL), CBr_4 (360 mg, 1.09 mmol) and PPh_3 (286 mg, 1.09 mmol) were added. The mixture was stirred at room temperature for 1 h. After concentration, the residue was purified by flash chromatography ($CHCl_3$/EtOAc 2:1) to give the corresponding bromide (275 mg, 81% yield), which was further treated with 60% NaH (44 mg, 1.10 mmol) in DMSO (34 mL) at 90 °C for 10 min. The mixture was diluted with ice−water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained residue was purified by preparative TLC ($CHCl_3$/EtOAc 1:1) to give the cyclized product as a white solid (54 mg, 25% yield). This product was treated with 4 M HCl in 1,4-dioxane (1.0 mL) at room temperature for 12 h. The solvent was removed in vacuo, and the crude product was diluted by THF (3.0 mL) and neutralized with NaO-*t*-Bu (35 mg, 0.364 mmol). After filtration of the resultant precipitate, the filtrate was concentrated to give **43** as a white solid (32 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (t, J = 2.6 Hz, 2H), 4.32 (t, J = 2.6 Hz, 2H), 6.81 (dd, J = 7.2, 2.1 Hz, 1H), 7.59 (dd, J = 2.1, 0.7 Hz, 1H), 7.77 (dd, J = 7.2, 0.7 Hz, 1H).

2-Chloro-5,6,7,8-tetrahydrothieno[3′,2′:4,5]pyrrolo[1,2-*a*]pyrazine-5-one (45). To a solution of **44** (800 mg, 3.48 mmol) in DMF (8.0 mL) was added 60% NaH (153 mg, 3.83 mmol) at 0 °C. After the mixture was stirred at the same temperature for 15 min, 3-*tert*-butoxycarbonyl-2,2-dioxo[1,2,3]oxathiazolidine[31] (894 mg, 4.00 mmol) was added to the mixture, which was then stirred at room temperature for 12 h. The mixture was diluted with EtOAc, washed with saturated solution of $NaHCO_3$, and dried over $MgSO_4$. After concentration, the residue was diluted with $CHCl_3$ (14 mL) and treated with TFA (4.0 mL) at room temperature for 2 h. The mixture was concentrated, and the residue was again diluted with THF/methanol (1:1, 54 mL) and treated with K_2CO_3 (3.00 g, 21.7 mmol) at room temperature for 12 h. The mixture was diluted with EtOAc, washed with 5% solution of $KHSO_4$, and dried over $MgSO_4$. After concentration, the crude product was purified by trituration with *n*-hexane to give **45** as a white solid (630 mg, 80% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.52−3.61 (m, 2H), 4.17 (t, J = 5.8 Hz, 2H), 6.85 (s, 1H), 7.20 (s, 1H), 7.90 (br s, 1H).

2-Chloro-5,6,7,8-tetrahydrothieno[3′,2′:4,5]pyrrolo[1,2-*a*]pyrazine (46). To a solution of **45** (630 mg, 2.78 mmol) in THF (6.3 mL) was added 1 M BH_3·THF (22.2 mL, 22.2 mmol). After being stirred at 60 °C for 3 h, the mixture was poured into a saturated solution of $NaHCO_3$ at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The thus obtained crude product was purified by flash chromatography ($CHCl_3$/methanol 10:1) to give **46** as a white solid (37 mg, 6.3% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09 (t, J = 5.7 Hz, 2H), 3.80 (t, J = 5.7 Hz, 2H), 3.90 (d, J = 0.7 Hz, 2H), 5.99 (t, J = 0.7 Hz, 1H), 7.05 (s, 1H).

6-Fluoro-2-(tetrahydropyran-2-yloxymethyl)pyrazolo[1,5-*a*]pyridine-3-carbaldehyde (48). To a solution of **47**[33] (50 g, 160 mmol) in DMF (500 mL) were added 4-(tetrahydropyran-2-yloxy)but-2-ynal[34] (40.4 g, 240 mmol) and K_2CO_3 (28.8 g, 208 mmol) at 0 °C. After being stirred at room temperature for 12 h, the mixture was poured into ice−water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained residue was purified by flash chromatography (*n*-hexane/EtOAc 5:1) to give **48** as a yellow solid (5.59 g, 13% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.90 (m, 6H), 3.56−3.64 (m, 1H), 3.87−3.95 (m, 1H), 4.83 (t, J = 3.3 Hz, 1H), 4.91 (d, J = 12.6 Hz, 1H), 5.18 (d, J = 12.6 Hz, 1H), 7.40−7.46 (m, 1H), 8.32 (ddd, J = 9.7, 5.6, 0.7 Hz, 1H), 8.46 (ddd, J = 3.7, 2.3, 0.7 Hz, 1H), 10.25 (s, 1H).

2-[6-Fluoro-2-(tetrahydropyran-2-yloxymethyl)pyrazolo-[1,5-*a*]pyridin-3-yl]ethylamine (49). A mixture of **48** (5.50 g, 19.8 mmol) and ammonium acetate (762 mg, 9.89 mmol) in CH_3NO_2 (44 mL) was heated at 100 °C for 2 h. The mixture was diluted with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained residue was purified by flash chromatography ($CHCl_3$/EtOAc 10:1) to give the corresponding nitroolefin as a yellow solid (4.55 g, 72% yield). A solution of this compound in THF (140 mL) was added to a suspension of $LiAlH_4$ (2.69 g, 70.8 mmol) in THF (50 mL) dropwise at 0 °C. After being stirred at room temperature for 4 h, the mixture was diluted with a saturated solution of Rochelle's salt and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to give **49** as a yellow oil (4.12 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47−1.90 (m, 6H), 2.87−3.00 (m, 4H), 3.52−3.64 (m, 1H), 3.89−4.00 (m, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.78 (t, J = 3.4 Hz, 1H), 4.96 (d, J = 11.7 Hz, 1H), 6.97−7.06 (m, 1H), 7.42−7.47 (m, 1H), 8.34 (ddd, J = 4.3, 2.2, 0.8 Hz, 1H).

3-(2-*tert*-Butoxycarbonylaminoethyl)-6-fluoro-2-hydroxymethylpyrazolo[1,5-*a*]pyridine (50). To a solution of **49**

(4.12 g, 14.0 mmol) in THF (60 mL) was added Boc_2O (3.71 g, 17.0 mmol), and the mixture was stirred at room temperature for 12 h. The mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained residue was purified by flash chromatography (*n*-hexane/EtOAc 3:1) to give the corresponding Boc-protected amine (1.82 g, 33% yield). The product was further treated with 1 M HCl (18 mL) in 1,4-dioxane (36 mL) at room temperature for 2 h. After neutralization with 1 M NaOH, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The thus obtained residue was purified by flash chromatography (*n*-hexane/EtOAc 1:1) to give **50** as a yellow oil (1.07 g, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 2.95 (t, J = 6.7 Hz, 2H), 3.29−3.39 (m, 2H), 4.84 (s, 2H), 4.97 (br s, 1H), 6.99−7.07 (m, 1H), 7.42 (dd, J = 9.5, 5.5 Hz, 1H), 8.30 (dd, J = 4.3, 2.1 Hz, 1H).

7-Fluoro-1,2,3,4-tetrahydropyrido[3′4′:3,4]pyrazolo[1,5-*a*]pyridine (51). A mixture of **50** (1.07 g, 3.46 mmol), CBr_4 (1.72 g, 5.19 mmol), and PPh_3 (1.18 g, 4.50 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 0.5 h. The mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained residue was purified by flash chromatography (*n*-hexane/EtOAc 4:1) to give the corresponding bromide (1.12 g, 87% yield). To a solution of this product in DMF (22 mL) was added 60% NaH (177 mg, 4.43 mmol). After the mixture was stirred at room temperature for 12 h, the reaction was quenched by an addition of H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The thus obtained residue was purified by flash chromatography (*n*-hexane/EtOAc 6:1) to give the cyclized product as a white solid (673 mg, 78% yield). To a solution of this compound in 1,4-dioxane (14 mL) was added 4 M HCl in 1,4-dioxane (14 mL). After being stirred at room temperature for 12 h, the mixture was concentrated in vacuo, neutralized with saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to give **51** as a yellow solid (437 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (t, J = 5.8 Hz, 2H), 3.18 (t, J = 5.8 Hz, 2H), 4.14 (s, 2H), 6.97−7.04 (m, 1H), 7.32 (dd, J = 9.7, 5.5 Hz, 1H), 8.31 (ddd, J = 4.4, 2.2, 0.7 Hz, 1H).

Mixture of Dimethyl 2-((2*R,3*R**)-3-(Methylthio)-3-phenylbutan-2-yl)malonate (*rac*-53) and Dimethyl 2-((2*R**,3*R**)-3-(Methylthio)-2-phenylbutan-2-yl)malonate (*rac*-54).** To a solution of dimethyl disulfide (36.4 g, 0.387 mol) in toluene (350 mL) was added sulfuric chloride (31.1 mL, 0.387 mol) dropwise at −10 °C, and the mixture was stirred at the same temperature for 5 min. A solution of **52** (102 g, 0.773 mol) in toluene (102 mL) was successively added to the mixture at −40 °C. After being stirred at the same temperature for 1 h, the mixture was concentrated. The thus obtained residual oil in DME (770 mL) was added to a solution of sodiodimethyl malonate prepared from dimethyl malonate (337 g, 2.55 mol) and NaO-*t*-Bu (223 g, 2.32 mol) in DME (1.55 L). After the mixture was stirred at room temperature for 12 h, the reaction was neutralized with 4 M HCl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a mixture of *rac*-**53** and *rac*-**54** as a yellow oil (214 g, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08−1.14 (m, 3H), 1.64−1.74 (m, 3H), 2.00−2.08 (m, 3H), 3.39−3.68 (m, 7H), 3.72−3.77 (m, 1H), 7.11−7.38 (m, 3H), 7.40−7.57 (m, 2H).

(2*R,3*R**)-Dimethyl 2,3-Dimethyl-2-phenylcyclopropane-1,1-dicarboxylate (*rac*-55).** To a mixture of *rac*-**53** and *rac*-**54** (214 g, 0.689 mol) in 1,4-dioxane (214 mL) was added dimethyl sulfate (78.4 mL, 0.827 mol), and the mixture was stirred at 50 °C for 12 h. After the mixture was cooled to room temperature, the precipitates were triturated with EtOAc to give a mixture of the corresponding sulfonium salt (239 g, 79% yield). To a solution of this salt in methanol (1.1 L) was added 28% NaOMe in methanol (123 mL) dropwise at room temperature. After being stirred at 70 °C for 2 h, the mixture was concentrated under reduced pressure and the residue was triturated in H_2O to give *rac*-**55** as a pale yellow solid (134 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3H), 1.35 (s, 3H), 2.10 (q, J = 6.5 Hz, 1H), 3.57 (s, 3H), 3.83 (s, 3H), 7.13−7.38 (m, 5H).

(1*R,2*S**,3*S**)-Methyl 1-(*tert*-Butoxycarbonylamino)-2,3-dimethyl-2-phenylcyclopropanecarboxylate (*rac*-56).** To a solution of *rac*-**55** (7.35 g, 28.0 mmol) in THF/methanol (1:1, 76 mL) was added 4 M NaOH (16.8 mL, 67.2 mmol) at room temperature. After being stirred for 12 h, the mixture was diluted with H_2O and washed with diisopropyl ether. The aqueous layer was acidified with 4 M HCl and extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentration in vacuo. To a mixture of the thus obtained residue and Et_3N (5.4 mL, 38.7 mmol) in *t*-BuOH (77 mL) was added a solution of diphenylphosphorylazide (6.8 mL, 31.6 mmol) in toluene (23 mL) dropwise at 100 °C. After being stirred at the same temperature for 12 h, the reaction mixture was concentrated and purified by flash chromatography (*n*-hexane/EtOAc 4:1) to afford *rac*-**56** as a yellow oil (5.21 g, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 6.0 Hz, 3H), 1.50 (s, 9H), 1.59−1.68 (m, 1H), 2.35 (s, 3H), 3.49 (s, 3H), 5.25 (br s, 1H), 7.08−7.33 (m, 5H).

Quinidine Salt of (1*S*,2*R*,3*R*)-1-(*tert*-Butoxycarbonylamino)-2,3-dimethyl-2-phenylcyclopropanecarboxylic Acid (57). A mixture of *rac*-**56** (5.21 g, 16.3 mmol) and 4 M NaOH (16.3 mL, 65.2 mmol) in THF/methanol (1:1, 66 mL) was stirred at 90 °C for 12 h. The reaction mixture was acidified with a saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The residue was treated with quinidine (5.29 g, 16.3 mmol) in acetone (63 mL) and the resultant precipitates were collected by filtration to give **57** as fine crystals (3.73 g, 36% yield). Their quality was good enough, and they were directly used for a single crystal X-ray diffraction analysis: mp 236−238 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (d, J = 5.1 Hz, 1H), 1.33−1.53 (m, 17H), 1.69 (s, 1H), 1.90 (dd, J = 13.1, 8.3 Hz, 1H), 2.00 (d, J = 4.2 Hz, 1H), 2.19 (q, J = 8.3 Hz, 1H), 2.44−2.74 (m, 3H), 2.95−3.07 (m, 2H), 3.90 (s, 3H), 5.02−5.12 (m, 2H), 5.28 (d, J = 6.8 Hz, 1H), 5.62 (br s, 1H), 6.04−6.14 (m, 1H), 7.10−7.16 (m, 1H), 7.20−7.30 (m, 4H), 7.38 (dd, J = 9.0, 2.9 Hz, 1H), 7.45 (d, J = 2.9 Hz, 1H), 7.49 (d, J = 4.4 Hz, 1H), 7.54 (br s, 1H), 7.92 (d, J = 9.0 Hz, 1H), 8.68 (d, J = 4.4 Hz, 1H). Anal. ($C_{37}H_{47}N_3O_6 \cdot 0.25H_2O$) calcd C 70.06%, H 7.55%, N 6.62%; found 70.16%, H 7.37%, N 6.79%.

(1*S*,2*R*,3*R*)-*tert*-Butyl 2,3-Dimethyl-1-(2-oxooxazolidine-3-sulfonamido)-2-phenylcyclopropanecarboxylate (58). To a suspension of **57** (3.73 g, 5.92 mmol) in EtOAc (50 mL) was added 10% $KHSO_4$ until the mixture turned into a clear solution. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. To a solution of the thus obtained residue in toluene (8.9 mL) was added *N*,*N*-dimethylformamide di-*tert*-butyl acetal (5.69 mL, 23.7 mmol) dropwise at 100 °C and stirred for 2 h. The mixture was diluted with 5% aqueous $NaHCO_3$ solution and extracted with *n*-hexane/EtOAc (2:1). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give the corresponding *t*-Bu ester. To a solution of this ester in methanol (11 mL) was added *p*-TsOH·H_2O (2.25 g, 11.8 mmol), and the mixture was stirred at room temperature for 12 h. After neutralization with 4 M NaOH, the mixture was concentrated under reduced pressure and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to afford the corresponding amine as a yellow oil (1.30 g, 84% yield). This product was then dissolved in acetonitrile (7.0 mL), and the resultant solution was added to a mixture of chlorosulfonyl isocyanate (0.476 mL, 5.47 mmol), 2-chloroethanol (0.400 mL, 5.96 mmol), and *N*-methylmorpholine (2.19 mL, 19.9 mmol) in acetonitrile (7.0 mL). After being stirred at 50 °C for 2 h, the mixture was acidified with 2 M HCl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and

concentrated. The thus obtained crude product was purified by flash chromatography (*n*-hexane/EtOAc 4:1) to give **58** as a pale yellow oil (1.77 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.49 (d, J = 6.8 Hz, 3H), 1.54 (s, 3H), 2.23 (q, J = 6.8 Hz, 1H), 3.92−4.02 (m, 1H), 4.15−4.24 (m, 1H), 4.32−4.46 (m, 2H), 6.27 (br s, 1H), 7.10−7.17 (m, 2H), 7.19−7.33 (m, 3H).

(1*S*,2*R*,3*R*)-2,3-Dimethyl-1-(8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole-2-sulfonylamino)-2-phenylcyclopropanecarboxylic Acid (13a). **13a** was prepared by coupling of **58** with 8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole[29b] following the procedures described for **9a**. The crude product was purified by trituration with methanol/H_2O to yield **13a** as a white solid (41% yield): mp 202−207 °C; $[\alpha]^{20}_D$ +27.85° (*c* 0.53, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, J = 6.8 Hz, 3H), 1.37 (s, 3H), 1.96 (q, J = 6.8 Hz, 1H), 3.73−3.86 (m, 2H), 4.22 (t, J = 5.3 Hz, 2H), 4.57 (d, J = 16.8 Hz, 1H), 4.62 (d, J = 16.8 Hz, 1H), 7.08−7.19 (m, 4H), 7.22−7.29 (m, 2H), 7.40 (dd, J = 9.8, 2.3 Hz, 1H), 7.53 (dd, J = 8.8, 4.6 Hz, 1H), 8.80 (s, 1H), 12.37 (br s, 1H). Anal. ($C_{22}H_{23}FN_4O_4S$) calcd C 57.63%, H 5.06%, N 12.22%; found C 57.55%, H 5.14%, N 12.18%.

(1*S*,2*R*,3*R*)-2.3-Dimethyl-1-(8-fluoro-1,2,3,4-tetrahydropyrido[3′,4′:4,5]imidazo[1,2-*a*]pyridine-2-sulfonylamino)-2-phenylcyclopropanecarboxylic Acid (13b). **13b** was prepared by coupling of **58** with **38b** following the procedures described for **9a**. The crude product was purified by trituration with methanol/H_2O to yield **13b** as a white solid (76% yield): mp 189−193 °C; $[\alpha]^{20}_D$ +41.29° (*c* 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (d, J = 6.6 Hz, 3H), 1.35 (s, 3H), 1.92 (q, J = 6.8 Hz, 1H), 2.95 (t, J = 5.0 Hz, 2H), 3.56−3.69 (m, 2H), 4.33 (d, J = 15.2 Hz, 1H), 4.40 (d, J = 15.2 Hz, 1H), 6.99 (td, J = 7.6, 2.6 Hz, 1H), 7.09−7.20 (m, 3H), 7.24−7.30 (m, 2H), 7.38 (dd, J = 10.1, 2.4 Hz, 1H), 8.35 (t, J = 6.5 Hz, 1H), 8.46 (br s, 1H), 12.21 (br s, 1H). Anal. ($C_{22}H_{23}FN_4O_4S\cdot0.5H_2O$) calcd C 56.52%, H 5.17%, N 11.98%; found C 56.38%, H 5.31%, N 11.86%.

(1*S*,2*R*,3*R*)-2,3-Dimethyl-1-(7-fluoro-1,2,3,4-tetrahydropyrido[3′,4′:3,4]pyrazolo[1,5-*a*]pyridine-2-sulfonylamino)-2-phenylcyclopropanecarboxylic Acid (13c). **13c** was prepared by coupling of **58** with **51** following the procedure described for **9a**. The crude product was purified by trituration with methanol/H_2O to yield **13c** as a white solid (84% yield): mp 194−200 °C; $[\alpha]^{20}_D$ +37.0° (*c* 1.1, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (s, 3H), 1.30 (d, J = 6.6 Hz, 3H), 1.98 (q, J = 6.6 Hz, 1H), 2.75−2.83 (m, 2H), 3.33−3.46 (m, 1H), 3.69−3.78 (m, 1H), 4.49 (d, J = 15.0 Hz, 1H), 4.61 (d, J = 15.0 Hz, 1H), 7.00−7.12 (m, 3H), 7.12−7.20 (m, 2H), 7.23−7.32 (m, 1H), 7.59−7.66 (m, 1H), 8.84−8.91 (m, 1H). Anal. ($C_{22}H_{23}FN_4O_4S\cdot0.5H_2O$) calcd C 56.52%, H 5.17%, N 11.98%; found C 56.59%, H 5.13%, N 12.12%.

(1*S*,2*R*,3*R*)-1-[(*R*)-4-(5-Cyanothiophen-2-yl)-3-methylpiperazine-1-sulfonylamino]-2,3-dimethyl-2-phenylcyclopropanecarboxylic Acid (13d). **13d** was prepared by coupling of **58** with **33b** following the procedures described for **9a**. The crude product was purified by trituration with chloroform to yield **13d** as a pale yellow solid (93% yield): mp 128−132 °C; $[\alpha]^{20}_D$ +34.6° (*c* 1.0, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (d, J = 6.5 Hz, 3H), 1.35 (d, J = 6.7 Hz, 3H), 1.38 (s, 3H), 1.97 (q, J = 6.8 Hz, 1H), 2.78 (td, J = 11.7, 3.1 Hz, 1H), 2.99−3.05 (m, 1H), 3.18 (td, J = 12.1, 3.6 Hz, 1H), 3.38−3.47 (m, 2H), 3.68 (d, J = 11.8 Hz, 1H), 3.95−4.02 (m, 1H), 6.20 (d, J = 4.4 Hz, 1H), 7.12−7.20 (m, 3H), 7.23−7.29 (m, 2H), 7.61 (d, J = 4.4 Hz, 1H), 8.53 (br s, 1H), 12.41 (br s, 1H). Anal. ($C_{22}H_{26}N_4O_4S_2\cdot1.25CHCl_3$) calcd C 51.81%, H 5.10%, N 10.40%; found C 51.62%, H 5.41%, N 10.60%.

(1*S*,2*R*,3*R*)-1-[(*R*)-4-(5-Difluoromethylisoxazol-3-yl)-3-methylpiperazine-1-sulfonylamino]-2,3-dimethyl-2-phenylcyclopropanecarboxylic Acid (13e). **13e** was prepared by coupling of **58** with **33e** following the procedures described for **9a**. The crude product was purified by trituration with methanol/H_2O to yield **13e** as a pale yellow solid (71% yield): mp 174−180 °C; $[\alpha]^{20}_D$ +10.1° (*c* 0.93, methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, J = 6.6 Hz, 3H), 1.43 (d, J = 6.8 Hz, 3H), 1.51 (s, 3H), 2.26 (q, J = 6.7 Hz, 1H), 2.91 (td, J = 11.9, 3.3 Hz, 1H), 3.16 (dd, J = 11.9, 3.3 Hz, 1H), 3.25 (td, J = 12.4, 3.2 Hz, 1H), 3.48 (d, J = 12.6 Hz, 1H), 3.58 (d, J = 11.9 Hz, 1H), 3.75 (d, J = 11.9 Hz, 1H), 3.87−3.95 (m, 1H), 6.18 (br s, 1H), 6.21 (s, 1H), 6.58 (t, J = 53.8 Hz, 1H), 7.06 (d, J = 7.1 Hz, 2H), 7.16−7.27 (m, 3H). Anal. ($C_{21}H_{26}F_2N_4O_5S\cdot0.75H_2O$) calcd C 50.64%, H 5.57%, N 11.25%; found C 50.97%, H 5.46%, N 11.13%.

Binding Model. Molecular modeling and visualization were performed using Insight II/Discover software (Accelrys, Inc.). Crystal structures of aggrecanase-2 and MMP-14 were both available in the Protein Data Bank (PDB codes 2RJQ and 1BQQ, respectively), and their structural information was used to generate the binding models for the inhibitors. Each compound was manually docked into aggrecanase or MMP-14 so that the sulfonylamino portion of the compound was placed in the S1′ pocket of enzymes while the carboxylate oxygens bound the zinc atom in a bidentate fashion.

Biological Assays. Recombinant human enzymes of MMP-1, MMP-3, MMP-9, MMP-13, and TACE were purchased from R&D Systems. Recombinant human enzymes of MMP-14 and aggrecanases (ADAMTS-4, ADAMTS-5) were purchased from Calbiochem and ImmunoDiagnostics, respectively. MMP-1 and MMP-14 assays were performed by incubating 10 μM fluorogenic substrate MOCAc-Lys-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH_2 (Peptide Institute) with 20 ng/mL rh-MMP-1 or rh-MMP-14 along with various concentrations of inhibitor in the buffer (100 mM Tris-HCl, pH 7.5, 150 mM NaCl, 10 mM $CaCl_2$, and 0.05% Brij-35). MMP-3 assay was performed by incubating 10 μM fluorogenic substrate MOCAc-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH_2 (Peptide Institute) with 40 ng/mL rh-MMP-3 along with various concentrations of inhibitor in the buffer (100 mM Tris-HCl, pH 7.5, 150 mM NaCl, 10 mM $CaCl_2$, and 0.05% Brij-35). MMP-9 assay was performed by incubating 10 μM fluorogenic substrate MOCAc-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH_2 (Peptide Institute) with 4 ng/mL rh-MMP-9 along with various concentrations of inhibitor in the buffer (100 mM Tris-HCl, pH 7.5, 150 mM NaCl, 10 mM $CaCl_2$, and 0.05% Brij-35). MMP-13 assay was performed by incubating 5 μM fluorogenic substrate 7-MCA-Pro-CHA-Gly-NVal-His-Ala-DPA (Enzyme Systems Products) with 40 ng/mL rh-MMP-13 along with various concentrations of inhibitor in the buffer (100 mM Tris-HCl, pH 7.5, 150 mM NaCl, 10 mM $CaCl_2$, and 0.05% Brij-35). TACE assay was performed by incubating 10 μM fluorogenic substrate MCA-Pro-Leu-Ala-Gln-Ala-Val-Dpa-Arg-Ser-Ser-Ser-Arg-NH_2 (Calbiochem) with 80 ng/mL rh-TACE along with various concentrations of inhibitor in the buffer (100 mM Tris-HCl, pH 7.5, 150 mM NaCl, 10 mM $CaCl_2$, and 0.05% Brij-35). Aggrecanase assay was performed by incubating 120 μM fluorogenic substrate Abz-Thr-Glu-Gly-Glu-Ala-Arg-Gly-Ser-Val-Ile-Dap(Dnp)-Lys-Lys-NH_2 (AnaSpec) with 1 μg/mL rh-aggrecanase-1 (ADAMTS-4) or rh-aggrecanase-2 (ADAMTS-5) along with various concentrations of inhibitor in the buffer (50 mM Tris-HCl, pH 7.5, 100 mM NaCl, and 10 mM $CaCl_2$). Each enzyme was pretreated with inhibitor at 25 °C for 15 min, and the enzymatic reaction was initiated by an addition of the substrate at 37 °C. The increase in fluorescence (λ_{ex} = 325 nm, λ_{em} = 405 nm) due to cleavage of the substrate was monitored with a BMG FLUOstar fluorescence plate reader after 150 and 60 min for aggrecanases and the others, respectively. IC_{50} of each inhibitor was calculated with Excel software, using three points in the central linear range of fluorescence inhibition.

In Vivo Pharmacokinetics. The pharmacokinetic profile was investigated in SD rats following a single dose given intravenously (iv) and orally (po). Two rats were treated with the compound. Blood samples of each rat were collected at 0.08, 0.17, 0.25, 0.50, 1, 2, 4, 8, 24 h

following oral dosing (10 mg/kg) and at 0.50, 1, 2, 4, 8, 24 h following iv dosing (1 mg/kg). Samples were centrifuged at 10 000 rpm for 5 min and the plasma collected and stored at −20 °C until analysis. Samples were analyzed by LC−MS/MS technique. The pharmacokinetic parameters were derived by noncompartmental analysis.

■ ASSOCIATED CONTENT

Supporting Information. Crystallographic data for compound **57**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

OA, osteoarthritis; ADAMTS-4, a disintegrin and metalloprotease with thrombospondin motifs-4; ADAMTS-5, a disintegrin and metalloprotease with thrombospondin motifs-5; PK, pharmacokinetic; MMP, matrix metalloprotease; TACE, tumor necrosis factor α-converting enzyme; SAR, structure−activity relationship; CYP, cytochrome P450; DMORD, disease modifying osteoarthritis drug

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After this paper was published online March 21, 2011, a misspelling was corrected in the author list for author Takayuki Yamasaki. The revised version was published March 23, 2011.