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Synthesis, SAR, and Biological Evaluation of α-Sulfonylphosphonic Acids as Selective Matrix Metalloproteinase Inhibitors

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*Eleven simple α-sulfonylphosphonates, new analogues of previously reported α-sulfonylaminophosphonates, were prepared and tested as MMP inhibitors. The IC_{50} values of most of these compounds are in the nanomolar range against MMP-2, -8, -13, and -14. Compound **11** proved to be the most effective inhibitor of MMP-2 (IC_{50} = 60 nM), with interesting selectivity versus the antitarget enzymes MMP-3 and MMP-9. The mode of binding of the new phosphonates in the active site of MMP-2 was studied, and variations in inhibition was explained by means of molecular modeling.*

Introduction

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that catalyze the turnover of extracellular matrix (ECM) components. The family of human MMPs includes more than 24 enzymes that can degrade virtually all the constituents of the ECM. These enzymes have been classified by their substrate specificity into collagenases (MMP-1, -8, -13, and -18), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -7, -10, -11, and -26), membrane-type MMPs (MMP-14, -15, -16, -17, -24, and -25), and unclassified MMPs (MMP-12, -19, -20, -23, and -28).[1] Apart from their role in degrading connective tissue, MMPs are also involved in the activation of zymogen (pro) forms of other MMPs and in the mediation of angiogenesis and mitogenesis signaling pathways.[2]

Although they intervene in various physiological processes, chronic overexpression or over-regulation of MMP activity has been implicated in several pathological conditions including inflammatory, vascular and autoimmune disorders, and carcinogenesis. Because of the relevant therapeutic potential, a wide variety of synthetic, low-molecular-weight MMP inhibitors (MMPIs) have been synthesized and tested over the past 20 years, and some of these have entered phase III clinical trials as anticancer drugs, but none have reached clinical utility. Broad-spectrum MMPIs, as well as those that show partial selectivity, failed in advanced clinical trials because no major clinical benefits and/or severe musculoskeletal side effects were observed. To date, the only medically approved MMPI is a tetracycline derivative with inhibition in the micromolar range, used in the treatment of periodontal inflammation.[3]

As a consequence, some efforts have been focused on target validation. Although members of the MMP family have long been suggested as promising cancer targets, only MMP-1, -2, and -7 are currently considered to be sufficiently experimentally validated, whereas MMP-3, -8, and -9, which are involved in normal tissue homeostasis and host resistance in cancer, are defined as antitargets.[4] Selective inhibition seems to be an essential requirement, and successful MMPIs should ideally spare MMP antitargets by ~3 log units difference in K_i over target enzymes.[5]

A general structure for an effective MMP inhibitor includes a zinc binding group (ZBG) capable of binding the catalytic zinc(II) ion, at least one functional group that provides crucial H-bonding interactions with the enzyme backbone, and one or more side chains giving rise to effective van der Waals interactions with the enzyme subsites.

The hydroxamic acid group is by far the most commonly used ZBG in inhibitor design and has generally been found to be the most effective.[6–12] Hydroxamate binds the catalytic zinc(II) ion in a bidentate fashion,[13] blocking substrate access to the active site and rendering the metal incapable of peptide hydrolysis. Recently, Cohen and co-workers identified new bidentate ZBGs that are more potent than hydroxamic acids,[13–15] some of which have been developed into potent inhibitors of MMPs.[15–17] With only a single coordinate bond to the metal

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center, inhibitors with monodentate ZBGs (such as carboxylic acid or phosphonic acid) are generally weaker inhibitors.[11,12]

The failure of hydroxamic acid based MMPIs in vivo may stem from poor pharmacokinetics (low oral bioavailability and short half-life), from the ability to bind other metal ions, and from the lack of specificity due to very strong binding to the catalytic zinc ion. As a consequence, it has been pointed out that the design of selective inhibitors should involve weaker ZBGs to effectively modulate affinity by variation of substituents on the molecule scaffold.[18]

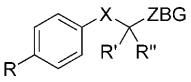
Recently we evaluated the inhibitory activities of (*R*)- and (*S*)-α-biarylsulfonylamino-(2-methyl)propylphosphonates on several MMPs.[19,20] These compounds are currently the most effective inhibitors based on a phosphonic acid group as the ZBG and exhibit highly enantioselective binding; in all cases only the *R* isomers present IC_{50} values in the nanomolar range. The most powerful analogues are characterized by alkoxy substituents at the 4′ position, and IC_{50} values for these are in the range 0.37–1.1 nM toward MMP-2, -8, -9, and -13. The 3′-methyl analogue was used to determine the role of MMP-8 in the development and progression of experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis.[21]

As part of our continuing effort to explore phosphonate-based MMP inhibitors, we report herein the synthesis and evaluation of a series of new compounds in which the α-sulfonylamino group is replaced by a simple α-sulfonyl substituent (Table 1). For comparison purposes, the carboxylate and hydroxamate analogues **2** and **3**, and the phosphonate thioether **4** were also prepared, as well as the β- and γ-arylsulfonylphosphonates **12** and **13**. The α-arylsulfonylphosphonates were designed by using the biphenylsulfonylmethylphosphonic acid **1** as a scaffold in which the following modifications were examined:

- Introduction of substituents with different stereoelectronic properties on the distal phenyl ring of the biaryl moiety (compounds **5**–**8**) or its replacement with 2-thiophene (compound **9**);
- Insertion of an oxygen atom or an ethynyl spacer between the two aromatic rings of the biaryl moiety (compounds **10** and **11**, respectively);
- Introduction of a side chain (methyl, isobutyl, benzyl) in the α position to the phosphonic acid group (compounds **14**–**16**).

All derivatives were evaluated in vitro by a fluorimetric assay for their ability to inhibit MMP-2. The most active compounds from the preliminary tests against MMP-2 were screened on MMP-1, -3, -8, -9, -13, and -14 to assess their selectivity profile. The effect of the P1′ group on the MMP inhibitory activity is also discussed.

Table 1. Compounds used in this study.

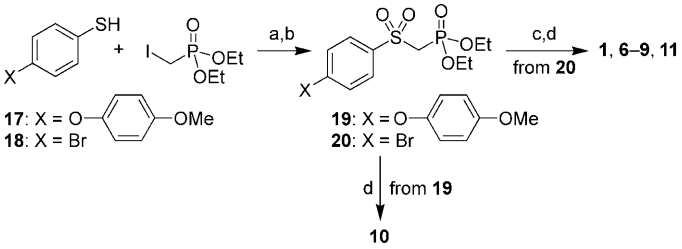


Compd	R	R′	R″	X	ZBG
1	C_6H_5	H	H	SO_2	PO_3H_2
2	C_6H_5	H	H	SO_2	COOH
3	C_6H_5	H	H	SO_2	CONHOH
4	C_6H_5	H	H	S	PO_3H_2
5	(4-CH_3O)-C_6H_4	H	H	SO_2	PO_3H_2
6	(4-Cl)-C_6H_4	H	H	SO_2	PO_3H_2
7	(4-CF_3)-C_6H_4	H	H	SO_2	PO_3H_2
8	(3-Cl)-C_6H_4	H	H	SO_2	PO_3H_2
9	2-thienyl	H	H	SO_2	PO_3H_2
10	(4-CH_3O)-C_6H_4O	H	H	SO_2	PO_3H_2
11	(C_6H_5)C≡C	H	H	SO_2	PO_3H_2
12	C_6H_5	H	H	SO_2CH_2	PO_3H_2
13	C_6H_5	H	H	$SO_2(CH_2)_2$	PO_3H_2
14	C_6H_5	H	$(CH_3)_2CHCH_2$	SO_2	PO_3H_2
15	(4-CH_3O)-C_6H_4	H	(C_6H_5)CH_2	SO_2	PO_3H_2
16	C_6H_5	CH_3	CH_3	SO_2	PO_3H_2

Results and Discussion

Chemistry

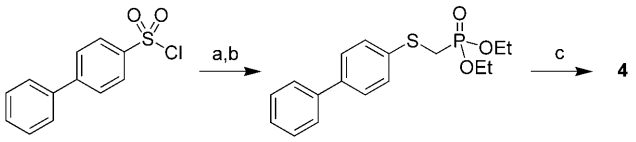
The synthesis of compounds **1** and **6**–**11** (Scheme 1) involved the key intermediates **19** or **20**, which were readily prepared



Scheme 1. a) NaH (95%), DMF (anhyd), room temperature; b) *m*-CPBA, CH_2Cl_2, 0 °C; c) $ArB(OH)_2$, $Pd[P(C_6H_5)_3]_4$, Cs_2CO_3, toluene (anhyd), 100 °C, or PhC≡CH, CuI, Et_3N, $Pd[P(C_6H_5)_3]_2Cl_2$, 80 °C; d) BBr_3, toluene (anhyd), CH_3OH, or dioxane/6 N HCl (2:1), reflux.

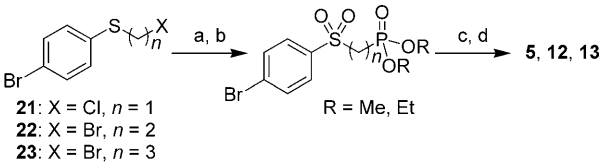
by alkylation of the appropriate 4-substituted thiophenol (**17** or **18**) with diethyliodomethylphosphonate in the presence of NaH, followed by oxidation of the resulting sulfides with *m*-chloroperbenzoic acid (*m*-CPBA). Compounds **1** and **6**–**9** were prepared by Suzuki–Miyaura[22] cross-coupling of **20** with the appropriate commercially available arylboronic acids, followed by deprotection of the corresponding diethylphosphonate esters with BBr_3[23] or HCl hydrolysis. Coupling of **20** with phenylacetylene in the presence of CuI and $Pd[P(C_6H_5)_3]_2Cl_2$, followed by HCl hydrolysis of the ethyl ester intermediate, afforded phosphonate **11**.

Compound **4** was obtained by alkylation of 4-phenylthiophenol, readily prepared by reduction of the commercially available biphenylsulfonyl chloride in the presence of triphenylphosphine, with diethyliodomethylphosphonate as reported above. The subsequent acid hydrolysis of the ethyl ester intermediate afforded the final acid (Scheme 2).



Scheme 2. a) $P(C_6H_5)_3$, dioxane/H_2O; b) diethyl iodomethylphosphonate, NaH (95%), DMF (anhyd), room temperature; c) dioxane/6 N HCl (2:1), reflux.

Compounds **5**, **12**, and **13** were prepared as shown in Scheme 3 following the Arbuzov coupling of the appropriate

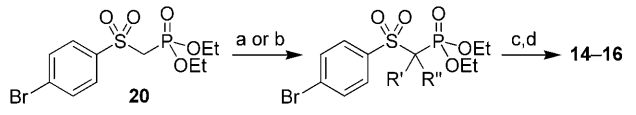


Scheme 3. a) $P(OR)_3$, reflux; b) *m*-CPBA, CH_2Cl_2, 0 °C; c) $ArB(OH)_2$, Pd[$P(C_6H_5)_3]_4$, Cs_2CO_3, toluene (anhyd), 100 °C; d) dioxane/6 N HCl (2:1), reflux.

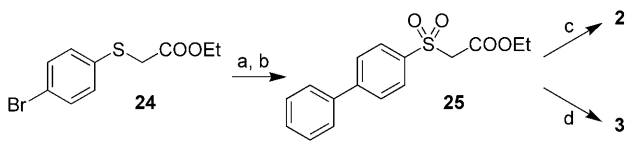
(4-bromophenylthio)-1-chloro- or 1-bromoalkane (**21**–**23**) with trimethyl or triethylphosphite.[24] Oxidation of the resulting sulfides with *m*-CPBA afforded the sulfone intermediates that were coupled with the appropriate commercially available arylboronic acids under Suzuki–Miyaura conditions.[22] Final acid hydrolysis of the esters led to the desired compounds.

Compounds **14**–**16** were obtained by alkylation of **20** with the appropriate alkyl halide in the presence of K_2CO_3 and 18-crown-6[25] for compound **14**, or LDA for compounds **15** and **16**. Subsequent Suzuki–Miyaura coupling with the appropriate arylboronic acids and final acid hydrolysis of the ester intermediates afforded the desired phosphonates (Scheme 4).

Synthesis of the carboxylate and hydroxamate analogues **2** and **3** is shown in Scheme 5. Sulfide **24**, prepared by alkylation of 4-bromothiophenol with α-bromoethyl acetate, was oxidized with *m*-CPBA followed by Suzuki–Miyaura[22] coupling with phenylboronic acid to give ethyl ester **25**. Alkaline hydrolysis of the ester afforded carboxylic acid **2**, whereas treatment with hydroxylamine hydrochloride and $NaOCH_3$ gave hydroxamic acid **3**.[26] The preparation of thiophenol **17** (Scheme 1) and 4-bromophenylthioalkyl halides **21**–**23** (Scheme 3) are reported in the Experimental Section below.



Scheme 4. a) *i*BuBr, K_2CO_3, 18-crown-6, CH_3CN (anhyd), 90 °C, for compound **14**; b) CH_3I or BnBr, LDA, THF (anhyd), −78 °C, for compounds **15** and **16**; c) $ArB(OH)_2$, Pd[$P(C_6H_5)_3]_4$, Cs_2CO_3, toluene (anhyd), 100 °C; d) dioxane/6 N HCl (2:1), reflux.



Scheme 5. a) *m*-CPBA, CH_2Cl_2, 0 °C; b) $C_6H_5B(OH)_2$, Cs_2CO_3, toluene (anhyd), Pd[$P(C_6H_5)_3]_4$, 100 °C; c) 1 N NaOH, THF; d) $NH_2OH{\cdot}HCl$, $NaOCH_3$, CH_3OH.

MMP inhibition

Compounds **1**–**16** were initially evaluated against MMP-2 by a fluorimetric assay. The most active compounds against MMP-2 were tested on a larger set of MMPs (MMP-1, -3, -8, -9, -13, and -14) to obtain a complete selectivity profile. MMP inhibition data are reported in Table 2 as IC_{50} values. All the phosphonic acid derivatives showed moderate to good activity against MMP-2, confirming the phosphonate as a good ZBG when inserted in a suitable structure.[18–21,27]

α-Biphenylsulfonylphosphonate **1** was less active than hydroxamate **3**, but exhibited a better inhibitory profile than the carboxylate analogue **2**, characterized by potency in the five- or six-digit nanomolar range. With the aim to obtain inhibitors with a more favorable pharmacokinetic profile than that of hydroxamate **3**, we focused on the design of phosphonic acid derivatives that were less active but potentially more selective. Moreover, the good potency of compound **1** and its binding features (see docking results below) suggests that the novel α-sulfonylphosphonic acid scaffold provides a good starting point for an optimization process.

The absence of activity of compound **4**, which contains a sulfur atom, confirms the important role of the sulfone group, as recently highlighted,[28] in establishing H-bond interactions with the backbone NH groups of Leu 164 and Ala 165 (MMP-2 numbering) and in directing the biphenyl group into the S1′ site.

The optimization of the P1′ group against MMP-2 was explored in several directions. With the aim to investigate the substitution effect on the distal aromatic ring, we prepared some analogues of **1**, introducing various substituents at the 4′ (compounds **5**–**7**) or 3′ positions (compound **8**). As can be seen in Table 2, substitutions on the terminal phenyl ring increases the potency of MMP-2 inhibition. Nevertheless, MMP-2 inhibitory activity was insensitive to the nature of the substituents; electron-withdrawing groups such as Cl (in **6**) and CF_3 (in **7**) shifted the IC_{50} to lower nanomolar values. Similarly, the electron-donating substituent CH_3O (in **5**) produced a fourfold increase in the inhibition of MMP-2 versus the unsubstituted derivative **1**. This higher inhibitory activity is probably due to more extensive van der Waals interactions provided by the 4′-substitution, and is not affected by the electronic effect on the distal aromatic ring. On the other hand, incorporation of a chlorine atom at the 3′ position (compound **8**) led to a >40-fold decrease in potency toward MMP-2 relative to the 4′-isomer **6**, probably due to an unfit arrangement in the narrow S1′ pocket. Replacement of the distal phenyl ring of the lead **1** with a thienyl ring (compound **9**) caused an approximate fivefold increase in MMP-2 inhibition. The introduction of a linker into the biphenyl system produced different effects. Compound **11**, containing a rigid acetylenic unit between the two aromatic rings, showed about a ninefold increase in inhibitory activity against MMP-2 compared with compound **1**. In con-

Table 2. Inhibition data for compounds **1**–**16** against MMPs.

Compd	IC_{50} [μM] MMP-1	MMP-2	MMP-3	MMP-8	MMP-9	MMP-13	MMP-14
1	9.1 ± 0.8	0.52 ± 0.04	38 ± 5	1.10 ± 0.07	13.2 ± 1.5	13.6 ± 1.6	13 %[a]
2	380 ± 18	12.5 ± 0.9	364 ± 25	14.2 ± 0.6	212 ± 17	101 ± 8	165 ± 11
3	1.8 ± 0.1	0.0060 ± 0.0003	0.20 ± 0.01	0.024 ± 0.001	0.140 ± 0.005	0.0098 ± 0.0004	0.376 ± 0.020
4	ND[b]	2.8 ± 0.3	ND	ND	ND	ND	ND
5	12.3 ± 1.6	0.141 ± 0.007	10.0 ± 0.8	0.273 ± 0.028	4.1 ± 0.4	6.4 ± 0.2	12.4 ± 1.3
6	58 ± 3	0.069 ± 0.007	1.2 ± 0.1	0.137 ± 0.013	1.73 ± 0.07	0.84 ± 0.04	25 %[a]
7	IA[c]	0.135 ± 0.010	IA	0.319 ± 0.027	12 %[a]	32 %[a]	IA
8	ND	2.9 ± 0.3	ND	ND	ND	ND	ND
9	16 %[a]	0.096 ± 0.005	2.5 ± 0.1	0.273 ± 0.013	2.3 ± 0.1	1.05 ± 0.05	0.76 ± 0.05
10	ND	6.7 ± 0.7	ND	ND	ND	ND	ND
11	IA	0.060 ± 0.006	10 ± 2	0.59 ± 0.03	20 %[a]	0.77 ± 0.07	28 %[a]
12	ND	40 ± 4	ND	ND	ND	ND	ND
13	ND	330 ± 30	ND	ND	ND	ND	ND
14	ND	6.5 ± 0.7	ND	ND	ND	ND	ND
15	ND	8.2 ± 0.8	ND	ND	ND	ND	ND
16	ND	70 ± 7	ND	ND	ND	ND	ND

[a] Percent inhibition at 500 nM. [b] Not determined. [c] Inactive at 500 nM.

trast, compound **10**, containing an oxygen linker, is 48-fold less potent against MMP-2 than the corresponding less flexible compound **5**.

These data suggested that a linear, rigid, biaryl group fits well into the hydrophobic tunnel-like S1′ pocket with an open bottom, and this is necessary for MMP-2 inhibitory activity in the nanomolar range. These results are in agreement with the SAR of P1′ substituents of previously reported sulfonylamido MMP inhibitors.[19]

The effects of the distance between the ZBG and sulfonyl group were also investigated. Elongation of the spacer from methylene (compound **1**) to ethylene (compound **12**) and propylene (compound **13**) produced a 77- and 630-fold loss in potency toward MMP-2, respectively.

Our attention was then focused on the effects of substitution in the α position to the ZBG. The inhibition data reported in Table 2 reveal that mono- or disubstitution at the position α to the phosphonic acid group are not well tolerated in the scaffold of lead compound **1**. In fact, compounds **14** and **15**, which respectively contain isobutyl and benzyl groups, exhibited 12- and 60-fold decreases in potency relative to their respective analogues **1** and **5**. A further drop in activity takes place if the α carbon atom is substituted with two methyl groups (compound **16**).

To investigate the selectivity against several MMPs, compounds **1**–**3** and the most promising phosphonate inhibitors (**5**–**7**, **9**, and **11**) of MMP-2 were also tested against MMP-1, -3, -8, -9, -13, and -14. The lack of activity of these phosphonic acids toward MMP-1 is consistent with published examples showing evidence that the shallow S1′ pocket of MMP-1 typically favors a short hydrophobic group. Enlargement of the P1′ group improves selectivity, as expected from the S1′ subsite (selectivity pocket) geometry of various MMPs.[8]

All the α-arylsulfonylmethylphosphonic acids tested proved to be more active toward MMP-2 than toward MMP-3, -9, -13, and -14, while the selectivity against MMP-8 was moderate. In particular, compound **5** showed the best MMP-2 selectivity profile, with 71-, 29-, 45-, and 88-fold decreases in potency against MMP-3, -9, -13, and -14, respectively. All these α-arylsulfonylmethylphosphonic acids are less active toward the MMPs tested with respect to the previously reported α-sulfonylaminophosphonates,[19,20] but are notably more selective for MMP-2 over the antitargets MMP-3 and MMP-9, in particular.

To rationalize the observed activity data, all the synthesized compounds were docked into the MMP-2 active site by applying the Induced Fit[29] protocol available in the Schrödinger suite.[30] The Induced Fit approach is able to predict ligand-induced conformational changes in receptor active sites by merging the predictive power of Prime (homology modeling) with the docking and scoring capabilities of Glide (docking). This methodology was preferred as it performed better in reproducing the crystallographic conformation of sulfonamide phosphonate in complex with MMP-8 (PDB code: 1ZVX).

Enzyme rearrangement allowed by the program was not so relevant; residues showing higher flexibility were part of the ω-loop surrounding the S1′ site (Pro 221–Tyr 228), Leu 163, and Leu 164 (Supporting Information). Other more relevant modifications are discussed below.

As depicted in Figure 1, compounds **1** and **3** show very similar interactions, except for the ZBG: hydroxamate **3** is able to chelate the zinc ion, forming two important H bonds with the carboxylate of Glu 202 and the backbone carbonyl oxygen atom of Ala 165, whereas the phosphonate group of **1** binds just Glu 202 and gives monodentate zinc ion binding, as does carboxylate **2**.[20] The higher potency of phosphonate relative to carboxylate **2** can be ascribed to the difference in geometry between the PO_3H^- function and COO^- which allows the α-CH_2 moiety of phosphonate to moved away from the steric clash with the C=O group of Ala 165, while maintaining contact with the zinc ion and Glu 202 (Figure 1B; the unfavorable contact is depicted as a gray dotted line).

The putative binding mode showed a common interaction profile for most of the phosphonate ligands (Figure 2; for the sake of clarity just the most potent derivative **11** is shown): the

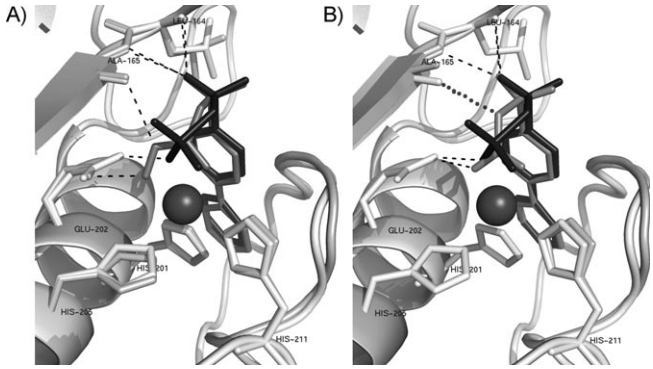


Figure 1. Superimposition of docked poses of phosphonate **1** (black) with A) hydroxamate **3** (dark gray) and B) carboxylate **2** (dark gray). H-bonds are depicted as black dashed lines. Unfavorable contact between α-CH_2 of compound **2** and the C=O group of Ala 165 is shown as a gray dotted line in panel B. MMP-2 structures are shown as a light gray solid ribbon, and the most relevant residues are displayed as sticks. The zinc ion is represented as a dark gray sphere.

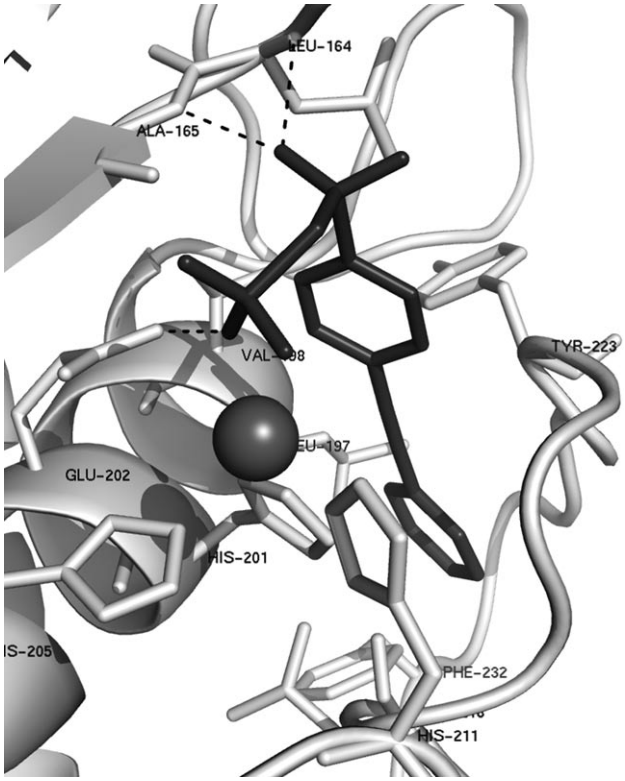


Figure 2. Docked pose of phosphonate **11** (black) into the MMP-2 active site (light gray). H bonds are depicted as black dashed lines. The MMP-2 structure is shown as a solid ribbon, and the most relevant residues are displayed as sticks. The zinc ion is represented as a dark gray sphere.

phosphonate group binds the zinc ion in a monodentate (or asymmetric bidentate) fashion, establishing an H bond with catalytic Glu 202; one sulfone oxygen forms two H bonds with the backbone NH group of Ala 165 and Leu 164; the aromatic portion is inserted in the S1′ subsite, giving a π-staking interaction with His 201 and hydrophobic interactions with surrounding residues such as Leu 164, Val 198, Leu 197, Leu 218, Tyr 223, and Phe 232. The same pattern of interactions was found in the X-ray crystal structure of the (*R*)-α-biarylsulfonylamino-(2-methyl)propylphosphonates mentioned above, in complex with MMP-8 (PDB code: 1ZVX).

As discussed, 4′-substituted compounds show more extensive hydrophobic interactions in the tunnel-like S1′ site of MMP-2, enhancing their potency. The greater activity of compound **11** can be also attributed to the presence of an interesting NH–π interaction between the distal aromatic ring of the ligand and the backbone NH group of Thr 227 (N–aromatic centroid distance: 3.98 Å; angle between N–H and the ring normal: ~180°).[31] To favor this interaction, the enzyme ω-loop surrounding the S1′ site moves more than 1 Å from its crystallographic position to bring the NH group closer to the distal aromatic ring of the ligand (Supporting Information). Unfavorable binding was observed for the 3′-Cl-substituted compound that accommodates its chlorine atom in a region surrounded by the carbonyl oxygen atoms of Ala 220, Ala 217, Leu 218, and Ile 222 (distances in the range of 3.3–3.8 Å).

Docking calculations demonstrated that linker length is relevant for inhibition; compound **13**, with a propylene spacer, does not allow the phosphonate and sulfone groups to bind simultaneously. Ligand **12** has a two-atom linker between these two functions, similar to sulfonamides previously described.[20] The resulting distance between the sulfone and the phosphonate should allow a good arrangement for the inhibitor, as observed for sulfonamides. However, the torsion angles of the ethylene group are eclipsed, and this conformational strain can explain the low activity of compound **12** (Supporting Information).

The docked poses of α-substituted ligands show the hydrophobic substituent in a solvent-exposed orientation. Moreover, their phosphonate groups are located in a position that is different from both the X-ray crystal structure of the phosphonate–MMP-8 complex and all the other sulfone ligands, which explains the non-ideal zinc binding. In addition, the complex of compound **16** docked with MMP-2 shows that the side chain of Leu 163 is moved dramatically from its position in the above-mentioned crystal structure and with respect to all other docked ligand complexes, demonstrating the difficulty in fitting this compound into the MMP-2 active site (Supporting Information).

As already stated, the most interesting aspect concerning these compounds is the selectivity they show with respect to MMP-3 and MMP-9. To get more insight on the observed selectivity profile, all the compounds were docked into the MMP-3 and MMP-9 active sites using the same procedure applied before. The resulting binding mode was compared with that observed in MMP-2. Selectivity can be generally ascribed to the differences in the residues that constitute the bottom of the S1′ site; the binding mode of compound **5** in the MMP-2 active site is very similar to that described above for compound **11**, with favorable hydrophobic interactions between the 4′-OCH_3 group and the side chains of Leu 218 and Thr 227. Analysis of the docked pose of compound **5** shows a steric clash between the 4′-OCH_3 group and the side chains of His 224 in MMP-3 and Arg 424 in MMP-9. Moreover, less effective key H-bond interactions are observed for the sulfone

group with the NH groups of Leu 164 and Ala 165 (corresponding to Leu 188 and Ala 189 in MMP-9) in both MMP-3 and MMP-9 (Supporting Information).

Conclusions

We have prepared a small set of α-arylsulfonylphosphonic acids, characterized by inhibitory activity in the nanomolar range against MMP-2 and fairly good selectivity over MMP-1, -3, -9, -13, -14, and -8. Although these phosphonates do not attain the potency displayed by the previously reported α-sulfonylaminophosphonates,[19,20] they represent an interesting alternative in view of their improved selectivity for MMP-2. In accordance with molecular modeling studies, elongation of the biphenyl moiety of the inhibitor, accommodated in the P1′ pocket of the enzymes, allows a further increase in selectivity toward other MMPs, while the potency against MMP-2 is preserved.

Experimental Section

Biological methods: MMP inhibition assays[32,33]

Recombinant human progelatinase A (pro-MMP-2), B (pro-MMP-9) and MMP-14 catalytic domains were supplied by Professor Gillian Murphy (Department of Oncology, University of Cambridge, UK). Pro-MMP-1, pro-MMP-8, pro-MMP-3, and pro-MMP-13 were purchased from Calbiochem. Proenzymes were activated immediately prior to use with *p*-aminophenylmercuric acetate (APMA; 2 mM for 1 h at 37 °C for MMP-2, MMP-1, and MMP-8; 1 mM for 1 h at 37 °C for MMP-9 and MMP-13). Pro-MMP-3 was activated with trypsin (5 μg mL^{-1}) for 30 min at 37 C° followed by soybean trypsin inhibitor (SBTI; 62 μg mL^{-1}). For assay measurements, inhibitor stock solutions (100 mM in DMSO) were further diluted at seven different concentrations (0.01 nM–300 μM) for each MMP in the fluorimetric assay buffer [FAB: Tris (50 mM pH 7.5), NaCl (150 mM), $CaCl_2$ (10 mM), Brij 35 (0.05%), and DMSO (1%)]. Assays on MMP-3 were performed with a different buffer: [MES (50 mM), $CaCl_2$ (10 mM), Brij 35 (0.05%), pH 6.0]. Activated enzyme (final concentration 2.9 nM for MMP-2, 5 nM for MMP-3, 2.7 nM for MMP-9, 1.5 nM for MMP-8, 0.3 nM for MMP-13, 1 nM for MMP-14 cd and 2.0 nM for MMP-1) and inhibitor solutions were incubated in the assay buffer for 4 h at 25 °C. After the addition of a solution of the fluorigenic substrate (200 μM) Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys-(Dnp)-NH_2 (Sigma) for MMP-3 and Mca-Lys-Pro-Leu-Gly-Leu-Dap-(Dnp)-Ala-Arg-NH_2 (Bachem)[34] in DMSO (for a final concentration of 2 μM), hydrolysis was monitored every 15 s for 20 min, recording the increase in fluorescence (λ_{ex} = 325 nm, λ_{em} = 395 nm) with a Molecular Devices SpectraMax Gemini XS plate reader. The assays were performed in triplicate in a total volume of 200 μL per well in 96-well microtitre plates (Corning, black, NBS); control wells lacked inhibitor. MMP inhibition activity was expressed in relative fluorescence units (RFU). Percent inhibition was calculated from control reactions without inhibitor. IC_{50} values were determined by the formula: $V_i/V_o = 1/(1+[I]/IC_{50})$, for which V_i is the initial velocity of substrate cleavage in the presence of the inhibitor at concentration [I], and V_o is the initial velocity in the absence of inhibitor. Results were analyzed with SoftMax Pro and GraFit software.[35]

Computational methods

All calculations were performed on a Fujitsu Siemens Celsius R550 workstation equipped with two Intel Quad-Core Xeon E5410 2.33 GHz processors. Reproduction of the sulfonamidophosphonate pose in the crystal structure complex with MMP-8 (PDB code: 1ZVX) was used as a test to validate the docking protocol. The Induced Fit procedure produced better results and was applied to all the ligands docked into MMP-2.

All compounds in Table 1 were manually built in Maestro version 8.5111,[36] exploiting the Built facility, and compounds **14** and **15** were processed through LigPrep version 2.2110[37] to generate all possible stereoisomers. To favor zinc ion binding for docking purposes, all compounds were considered completely deprotonated. Ligand structures were minimized to a derivative convergence of 0.001 kJ Å^{-1} mol^{-1} by using the truncated Newton conjugate gradient (TNCG) minimization algorithm, the OPLS2005 force field, and the GB/SA water solvation model implemented in MacroModel version 9.6110.[38]

Conformational searches applying the Mixed torsional/Low-mode sampling and the automatic setup protocol were carried out on all minimized ligand structures in order to obtain the global minimum geometry of each molecule, as the docking program Glide[39] has been demonstrated to perform better using the global minimum conformation as the starting geometry.[40,41]

3D structures of MMP-2, MMP-3, and MMP-9 were downloaded from the Protein Data Bank (PDB codes: 1QIB, 1CIZ, and 1GKC, respectively) and submitted to the Protein Preparation routine in Maestro that allows one to fix up the receptor structure by eliminating water molecules, adding hydrogen atoms, deleting undesired ligands, and minimizing the macromolecular structure to optimize hydrogen atom positioning and to eliminate strains. Lysine, arginine, glutamate, and aspartate residues were ionized, except the catalytic glutamate residue, which was protonated to allow H bonding with the ligand's ZBG. Structures of MMP-2, MMP-3, and MMP-9 prepared in this way were submitted to Receptor Grid Generation, imposing zinc ion binding as a constraint.

Ligand global minimum geometry and MMP-2/MMP-3/MMP-9 grids were used for following Induced Fit Docking (IFD).[29] The IFD procedure combines rigid-receptor docking with protein refinement. The standard procedure from Schrödinger for IFD was followed. Glide SP (standard precision) was used for all docking calculations. During the first step initial softened-potential Glide docking was performed on a van der Waals scaled-down rigid receptor; a van der Waals radii scaling of 0.5 was set for all three MMP-2/MMP-3/MMP-9 and ligands. Sampling of the protein for each of the top 20 ligand poses (ranked by GlideScore) was performed using Prime.[42] Residues within 5 Å of any ligand pose were refined; this consisted of a side chain conformational search and optimization followed by full minimization of the ligand and the residues. A total of 20 receptor conformations were generated for each of the 16 ligands. The next step involved re-docking the ligands into their respective 20 structures that were within 30.0 kcal mol^{-1} of their lowest-energy structure. Finally, the ligand poses were scored by using a combination of Prime and GlideScore scoring functions in which the top-ranked pose for each ligand was chosen as the final result.

Chemistry

Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus and are uncorrected. Mass spectra were recorded on an HP GC–MS 6890-5973 MSD spectrometer, electron impact: 70 eV, equipped with HP chemstation or on an Agilent LC–MS 1100 Series LC–MSD Trap System VL spectrometer,

electrospray ionization (ESI). ^{1}H and ^{13}C NMR spectra were recorded with the appropriate deuterated solvent on a Varian-Mercury 300 spectrometer, operating at 300 and 75 MHz, respectively. Chemical shifts (δ) are expressed as parts per million (ppm), and the coupling constants (J) are given in hertz (Hz). Microanalyses of solid compounds were carried out with a Eurovector Euro EA 3000 model analyzer; the analytical results are within $\pm$0.4% of theoretical values. Flash column chromatography was performed with Geduran silica gel 60 Å (40–63 μm). Chemicals were obtained from Aldrich Chemicals (Milan, Italy) or Lancaster Synthesis (Milan, Italy), and were used without further purification.

Preparation of 17.[43] 95% NaH powder (0.31 g, 12.9 mmol) was carefully added to a solution of 4-(4-methoxyphenoxy)phenol[44] (2.71 g, 12.5 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF; 12 mL) cooled on ice. After stirring for 10 min at 0 °C, a solution of *N*,*N*-dimethylthiocarbamoyl chloride (1.78 g, 14.4 mmol) in anhydrous DMF (5 mL) was added dropwise. The resulting mixture was stirred at 70 °C for 4 h, and the solvent was removed under reduced pressure. The resulting residue was suspended in a saturated solution of NH_4Cl (30 mL) and extracted with $CHCl_3$ (3×30 mL). The combined organic phases were washed with 5% KOH and brine, dried over Na_2SO_4, and evaporated in vacuo to obtain a brown solid residue (3.80 g). The residue was purified by flash chromatography on silica gel using petroleum ether/EtOAc (95:5 and 85:15) as eluents to give a white solid that was crystallized from hexane to afford *O*-[4-(4-methoxyphenoxy)phenyl]-*N*,*N*-dimethylthiocarbamate (2.71 g, 71%); mp: 92–94 °C; ^{1}H NMR ($CDCl_3$): δ = 3.33 (s, 3H, CH_3N), 3.45 (s, 3H, CH_3N), 3.80 (s, 3H, CH_3O), 6.86–7.02 ppm (m, 8H, aromatics); GC–MS *m*/*z* (%): 303 ([*M*]$^+$, 66), 88 (100) $[C_3H_6NS]^+$.

This intermediate was rearranged into *S*-[4-(4-methoxyphenoxy)-phenyl]-*N*,*N*-dimethylthiocarbamate by heating at 250 °C for 3.5 h under N_2 atmosphere. The resulting dark brown oil was purified by flash chromatography on silica gel (petroleum ether/EtOAc 95:5 → 80:20) to give the desired compound as a yellow oil (2.0 g, 74%); ^{1}H NMR ($CDCl_3$): δ = 3.05 (bs, 6H, $2CH_3N$), 3.80 (s, 3H, CH_3O), 6.85–7.04 and 7.36–7.41 ppm (m, 6H, 2H, aromatics); GC–MS *m*/*z* (%): 303 ([*M*]$^+$, 40), 72 (100) $[C_3H_6NO]^+$.

A solution of this compound in CH_3OH (15 mL) and NaOH (10% aq, 7.4 mL) was held at reflux for 5 h, cooled to room temperature, and acidified with 2 N HCl. After evaporation of the organic solvent, the aqueous phase was extracted with $CHCl_3$ (3×30 mL), the organic phase was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting yellow residue was crystallized from $CHCl_3$/hexane to afford 1.45 g (95% yield) of the title compound; mp: 72–74 °C; ^{1}H NMR ($CDCl_3$): δ = 3.39 (s, 1H, SH), 3.80 (s, 3H, CH_3O), 6.80–6.97 and 7.22–7.27 ppm (m, 6H, 2H, aromatics); GC–MS *m*/*z* (%): 232 ([*M*]$^+$, 100).

Preparation of diethyl(arylthio)methylphosphonates: general procedure. A solution of diethyliodomethylphosphonate (6.41 mmol) in anhydrous DMF (6 mL) was added, under N_2 atmosphere, to a solution of sodium 4-substituted thiophenol (**17** or **18**, Scheme 1) or 4-phenylthiophenol[45] (Scheme 2) (7.95 mmol) in anhydrous DMF (17 mL). After stirring overnight, the reaction mixture was concentrated to dryness. The crude product was re-dissolved in EtOAc (50 mL) and washed with 0.5 N NaOH and brine. The organic phase was dried over Na_2SO_4 and evaporated in vacuo to afford a yellowish residue that was purified by flash chromatography on silica gel (80–97% yield).

Diethyl-[4-(4-methoxyphenoxy)phenylthio]methylphosphonate (Scheme 1). Eluent: $CHCl_3$, 97% yield; ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, J = 7.1, 6H, $2CH_3CH_2$), 3.11 (d, J = 13.7, 2H, SCH_2P), 3.80 (s, 3H, CH_3O), 4.10–4.15 (m, 4H, $2CH_3CH_2$), 6.84–6.90, 6.93–6.97 and 7.40–7.45 ppm (m, 4H, 2H, 2H, aromatics); GC–MS *m*/*z* (%): 382 ([*M*]$^+$, 100).

Diethyl-(4-bromophenylthio)methylphosphonate (Scheme 1). Eluent: $CHCl_3$, 82% yield; ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, J = 7.1, 6H, $2CH_3$), 3.13 (d, J = 13.7, 2H, SCH_2P), 4.07–4.16 (m, 4H, $2CH_3CH_2$), 7.26–7.42 ppm (m, 4H, aromatics); GC–MS *m*/*z* (%): 340 ([*M*+2]$^+$, 100), 338 ([*M*]$^+$, 97).

Diethyl(biphenyl-4-thio)methylphosphonate (Scheme 2). Eluent: petroleum ether/Et_2O (1:1), pale-yellow solid, 80% yield; mp: 34–36 °C; ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, 6H, J = 7.1, $2CH_3$), 3.23 (d, J = 13.7, 2H, SCH_2P), 4.13–4.18 (m, 4H, $2CH_3CH_2$), 7.32–7.58 ppm (m, 9H, aromatics); GC–MS *m*/*z* (%): 336 ([*M*]$^+$, 100).

Oxidation of dialkyl(arylthio)alkylphosphonates: general procedure. *m*-CPBA (70%, 105 mmol) was added to a solution of sulfide (17 mmol) in CH_2Cl_2 (250 mL) cooled on ice. After stirring for 2–15 h, the organic phase was washed with 0.5–1 N NaOH and brine, dried over Na_2SO_4, and evaporated to dryness to afford a solid that was purified by crystallization or silica gel chromatography to afford the desired sulfonyl compounds in 50–91% yield.

Diethyl-[4-(4-methoxyphenoxy)phenylsulfonyl)methylphosphonate (**19**, Scheme 1). Eluent: $CHCl_3/CH_2Cl_2$ (1:1), colorless oil, 50% yield; ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, J = 7.1, 6H, $2CH_3CH_2$), 3.74 (d, J = 16.8, 2H, SCH_2P), 3.83 (s, 3H, CH_3O), 4.12–4.22 (m, 4H, $2CH_3CH_2$), 6.91–7.03 and 7.88–7.91 ppm (m, 6H, 2H aromatics); GC–MS *m*/*z* (%): 414 ([*M*]$^+$, 29), 213 (100).

Diethyl-(4-bromophenylsulfonyl)methylphosphonate (**20**, Scheme 1). Colorless crystals, 84% yield; mp: 76–78 °C (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, J = 7.1, 6H, $2CH_3$), 3.74 (d, J = 16.8, 2H, SCH_2P); 4.11–4.21 (m, 4H, $2CH_3CH_2$), 7.69–7.72 and 7.84–7.87 ppm (m, 2H, 2H, aromatics); GC–MS *m*/*z* (%): 373 ([*M*+2]$^+$, 1), 371 ([*M*]$^+$, 1), 280 (99), 278 (100).

Diethyl-2-(4-bromophenylsulfonyl)ethylphosphonate (Scheme 3). Eluent: CH_2Cl_2/EtOAc (4:1), colorless crystals, 76% yield; mp: 88–90 °C; ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, J = 7.1, 6H, $2CH_3$), 2.06–2.18 (m, 2H, CH_2P), 3.23–3.31 (m, 2H, SCH_2), 4.08 (quintet-like, J = 7.1, 4H, $2CH_3CH_2$), 7.71–7.78 ppm (m, 4H, aromatics); GC–MS *m*/*z* (%): 340 ([*M*+2]$^+$, 5), 338 ([*M*]$^+$, 4), 109 (100) $[C_6H_5S]^+$.

Diethyl-3-(4-bromophenylsulfonyl)propylphosphonate (Scheme 3). Eluent: $CHCl_3$/EtOAc (95:5), colorless oil, 76% yield; ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, J = 7.1, 6H, $2CH_3$), 1.79–1.90 (m, 2H, CH_2P), 1.95–2.10 (m, 2H, $CH_2CH_2CH_2$), 3.20–3.25 (m, 2H, SCH_2), 4.00–4.10 (m, 4H, $2CH_3CH_2$), 7.70–7.73 and 7.75–7.79 ppm (m, 2H, 2H, aromatics); GC–MS *m*/*z* (%): 400 ([*M*+2]$^+$, 1), 398 ([*M*]$^+$, 1), 123 (100).

Dimethyl-(4-bromophenylsulfonyl)methylphosphonate (Scheme 3). Eluent: CH_2Cl_2/EtOAc (9:1), colorless oil, 90% yield; ^{1}H NMR ($CDCl_3$): δ = 3.76 (d, J = 16.8, 2H, SCH_2P), 3.81 (d, J = 11.5, 6H, $2CH_3$), 7.70–7.75 and 7.84–7.88 ppm (m, 2H, 2H, aromatics); GC–MS *m*/*z* (%): 171 (96), 169 (100).

Ethyl-(4-bromophenylsulfonyl)acetate (Scheme 5). White solid, 91% yield; mp: 53–54 °C; ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, J = 7.1, 3H, CH_3), 4.10 (s, 2H, SCH_2), 4.15 (q, J = 7.1, 2H, CH_3CH_2), 7.70–7.75 and 7.79–7.83 ppm (m, 2H, 2H, aromatics); GC–MS *m*/*z* (%): 308 ([*M*+2]$^+$, 5), 306 ([*M*]$^+$, 4), 157 (99), 155 (100) $[C_6H_4Br]^+$.

Preparation of dialkyl(biphenylsulfonyl)alkylphosphonates: general procedure. A suspension of sulfone (2.16 mmol), the appropri-

ate arylboronic acid (4.33 mmol), and Cs_2CO_3 (3.27 mmol) in anhydrous toluene (20 mL) was stirred at room temperature under N_2 atmosphere for 25 min. [$Pd(PPh_3)_4$] was added (0.065 mmol), and the resulting mixture was heated at 95 °C for 6 h, cooled to room temperature, diluted with 1 N HCl and EtOAc (1:1, 16 mL), and filtered through a pad of Celite. The organic phase was washed with saturated solutions of $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo to give a residue that was purified by column chromatography on silica gel (32–98% yield).

Diethyl(biphenylsulfonyl)methylphosphonate (Scheme 1). Eluent: CH_2Cl_2 and $CHCl_3/CH_2Cl_2$ (1:1), yellow oil, 98% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.31$ (t, $J = 7.1$, 6H, $2CH_3$), 3.81 (d, $J = 16.8$, 2H, SCH_2P), 4.19 (quintet-like, $J = 7.1$, 4H, $2CH_3CH_2$), 7.43–7.51, 7.59–7.63, 7.75–7.79, 8.04–8.07 ppm (m, 3H, 2H, 2H, 2H, aromatics); GC–MS *m/z* (%): 368 ($[M]^+$, 1), 167 (100).

Diethyl-(4′-chlorobiphenyl-4-sulfonyl)methylphosphonate (Scheme 1). Eluent: EtOAc/petroleum ether (3:2), yellow solid, 98% yield; mp: 100–103 °C; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, $J = 7.1$, 6H, $2CH_3$), 3.82 (d, $J = 16.8$, 2H, SCH_2P), 4.13–4.23 (m, 4H, $2CH_3CH_2$), 7.43–7.47, 7.52–7.56, 7.71–7.75 and 8.03–8.08 (m, 2H, 2H, 2H, 2H, aromatics); GC–MS *m/z* (%): 402 ($[M]^+$, 1), 203 (32), 201 (100).

Diethyl-(4′-trifluoromethylbiphenyl-4-sulfonyl)methylphosphonate (Scheme 1). Eluent: petroleum ether/EtOAc (3:2 and 3:7), yellow solid, 32% yield; mp: 117–118 °C ($CHCl_3$/hexane); ^{1}H NMR ($CDCl_3$): $\delta = 1.31$ (t, $J = 7.1$, 6H, $2CH_3$), 3.80 (d, $J = 17.0$, 2H, SCH_2P), 4.19 (quintet-like, $J = 7.1$, 4H, $2CH_3CH_2$), 7.69–7.80 and 8.07–8.12 (m, 6H, 2H, aromatics); GC–MS *m/z* (%): 436 ($[M]^+$, 1), 344 (100).

Diethyl-(3′-chlorobiphenyl-4-sulfonyl)methylphosphonate (Scheme 1). Eluent: petroleum ether/EtOAc (3:2), colorless oil, 79% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.31$ (t, $J = 6.9$, 6H, $2CH_3$), 3.79 (d, $J = 17.0$, 2H, SCH_2P), 4.16–4.23 (m, 4H, $2CH_3CH_2$), 7.40–7.72, 7.73–7.76 and 8.04–8.08 ppm (m, 4H, 2H, 2H, aromatics); GC–MS *m/z* (%): 152 (100) $[C_5H_{13}O_3P]^+$.

Diethyl-[4-(2-thienyl)phenylsulfonyl]methylphosphonate (Scheme 1). Eluent: Et_2O and Et_2O/*i*PrOH (98:2), yellow oil, 79% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.30$ (t, $J = 7.1$, 6H, $2CH_3$), 3.78 (d, $J = 16.8$, 2H, SCH_2P), 4.17 (quintet-like, $J = 7.1$, 4H, $2CH_3CH_2$), 7.12–7.19, 7.40–7.46, 7.76–7.79 and 7.96–7.99 ppm (m, 1H, 2H, 2H, 2H, aromatics); GC–MS *m/z* (%): 374 ($[M]^+$, 12), 173 (100).

Dimethyl-(4′-methoxybiphenyl-4-sulfonyl)methylphosphonate (Scheme 3). Eluent: petroleum ether/EtOAc (1:1), pale-yellow solid, 50% yield; mp: 119–121 °C; ^{1}H NMR ($CDCl_3$): $\delta = 3.80$ (d, $J = 17.0$, 2H, SCH_2P), 3.82 (d, $J = 11.5$, 6H, $2CH_3$), 3.87 (s, 3H, CH_3O), 6.99–7.03, 7.55–7.59, 7.72–7.76 and 7.99–8.03 ppm (m, 2H, 2H, 2H, 2H, aromatics); MS (ESI) *m/z*: 393 $[M+Na]^+$, MS^2 *m/z* (%): 393 (100).

Diethyl-2-(biphenyl-4-sulfonyl)ethylphosphonate (Scheme 3). Eluent: CH_2Cl_2/EtOAc (9:1), yellow solid, 87% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.30$ (t, $J = 7.1$, 6H, $2CH_3$), 2.11–2.23 (m, 2H, CH_2P), 3.28–3.37 (m, 2H, SCH_2), 4.11 (quintet-like, $J = 7.1$, 4H, $2CH_3CH_2$), 7.41–7.57, 7.59–7.70, 7.76–7.80 and 7.95–7.97 ppm (m, 3H, 2H, 2H, 2H, aromatics); GC–MS *m/z* (%): 382 ($[M]^+$, 1), 180 (100).

Diethyl-3-(biphenyl-4-sulfonyl)propylphosphonate (Scheme 3). Eluent: Et_2O/EtOAc (4:1 and 1:1), yellow oil, 89% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.29$ (t, $J = 7.1$, 6H, $2CH_3$), 1.82–1.93 (m, 2H, $CH_2CH_2CH_2$), 2.01–2.27 (m, 2H, CH_2P), 3.24–3.29 (m, 2H, SCH_2), 4.01–4.13 (m, 4H, $2CH_3CH_2$), 7.41–7.52, 7.58–7.62, 7.74–7.79 and 7.94–7.99 ppm (m, 3H, 2H, 2H, 2H, aromatics); GC–MS *m/z* (%): 396 ($[M]^+$, 1), 152 (100) $[C_5H_{13}O_3P]^+$.

Diethyl-1-(biphenyl-4-sulfonyl)-3-methylbutylphosphonate (Scheme 4). Eluent: $CHCl_3$/EtOAc (95:5), yellow oil, 98% yield; ^{1}H NMR ($CDCl_3$): $\delta = 0.84$ (d, $J = 6.0$, 3H, CH_3CH), 0.92 (d, $J = 6.0$, 3H, CH_3CH), 1.29 (t, $J = 7.1$, 6H, $2CH_3CH_2$), 1.84–2.01 (m, 3H, CH_2CHCH_3), 3.57 (dt, $J = 19.0$, $J = 6.0$, 1H, SCHP), 4.14 (quintet-like, $J = 7.1$, 4H, $2CH_3CH_2$), 7.33–7.54, 7.58–7.63, 7.74–7.78 and 8.01–8.05 ppm (m, 3H, 2H, 2H, 2H, aromatics); GC–MS *m/z* (%): 317 (100).

Diethyl-1-(4′-methoxy-biphenyl-4-sulfonyl)-2-phenylethylphosphonate (Scheme 4). Eluent: $CHCl_3/CH_2Cl_2$ (4:1), yellow oil, 96% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.18$–1.25 (m, 6H, $2CH_3CH_2$), 3.32 (dt, $J = 14.8$, $J = 7.1$, 1H, $1CH_2Ph$), 3.41–3.59 (m, 1H, $1CH_2Ph$), 3.82–3.92 (m, 1H, SCHP), 3.85 (s, 3H, CH_3O), 4.03–4.17 (m, 4H, $2CH_3CH_2$), 6.98–7.01, 7.11–7.21, 7.51–7.55, 7.63–7.66 and 7.91–7.94 (m, 2H, 5H, 2H, 2H, 2H, aromatics); GC–MS *m/z* (%): 488 ($[M]^+$, 4), 241 (100) $[C_{12}H_{18}O_3P]^+$.

Diethyl-1-(biphenyl-4-sulfonyl)-1-methylethylphosphonate (Scheme 4). Eluent: Et_2O/EtOAc (7:3), yellow solid, 82% yield; mp: 69–72 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.29$ (t, $J = 7.1$, 6H, $2CH_3CH_2$), 1.62 (d, $J = 14.8$, 6H, $2CCH_3$), 4.19 (quintet-like, $J = 7.1$, 4H, $2CH_3CH_2$), 7.39–7.51, 7.59–7.63, 7.71–7.76 and 8.02–8.06 (m, 3H, 2H, 2H, 2H, aromatics); GC–MS *m/z* (%): 195 (100).

Ethyl(biphenyl-4-sulfonyl)acetate (Scheme 5). Eluent: petroleum ether/EtOAc (9:1 and 3:2), yellow solid, 93% yield; mp: 113–116 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.21$ (t, $J = 7.1$, 3H, CH_3), 4.15 (s, 2H, SCH_2CO), 4.17 (q, $J = 7.1$, 4H, CH_3CH_2), 7.43–7.52, 7.60–7.64, 7.76–7.80, 7.99–8.03 (m, 3H, 2H, 2H, 2H, aromatics); GC–MS *m/z* (%): 304 ($[M]^+$, 66), 153 (100) $[C_{12}H_9]^+$.

Preparation of diethyl-(4-phenylethynylphenylsulfonyl)methylphosphonate[46] (Scheme 1). Triethylamine (0.3 mL, 2.16 mmol) was added, under Ar atmosphere, to a suspension of phosphonate **20** (0.21 g, 0.56 mmol), phenylacetylene (0.08 mL, 0.73 mmol), CuI (0.01 g, 0.05 mmol), and $[Pd(PPh_3)_2]Cl_2$ (0.01 g, 0.014 mmol) in anhydrous DMF (4 mL). After heating for 9 h at 80 °C the resulting mixture was cooled to room temperature, poured into a saturated solution of NH_4Cl (5 mL), and extracted with EtOAc (3×5 mL). The organic phase was washed with 1 N HCl, 5% $NaHCO_3$, and brine, dried over Na_2SO_4, and evaporated in vacuo to afford a brown oily residue, which was purified by silica gel chromatography (petroleum ether/CH_2Cl_2/*i*PrOH/5:4.8:0.2) to give the title compound (0.17 g, 77% yield). ^{1}H NMR ($CDCl_3$): $\delta = 1.30$ (t, $J = 7.1$, 6H, $2CH_3$), 3.77 (d, $J = 17.1$, 2H, SCH_2P), 4.11–4.21 (m, 4H, $2CH_3CH_2$), 7.36–7.39, 7.52–7.56, 7.67–7.71, 7.94–7.98 ppm (m, 3H, 2H, 2H, 2H, aromatics); GC–MS *m/z* (%): 392 ($[M]^+$, 7), 191 (100).

Chloromethyl-4-bromophenyl sulfide (**21**).[47] Concentrated HCl (51 mL) was carefully added to a stirred solution of paraformaldeyde (1.92 g, 63.9 mmol) in anhydrous toluene (11 mL). The resulting mixture was heated at 60 °C, and a solution of 4-bromothiophenol (10.01 g, 52.9 mmol) in anhydrous toluene (25 mL) was added dropwise over 30 min. After 1 h the organic phase was separated, and the aqueous phase was extracted with toluene (2× 50 mL). The combined organic phases were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated in vacuo to afford a yellow oil that was used without further purification. ^{1}H NMR ($CDCl_3$): $\delta = 4.93$ (s, 2H, CH_2), 7.37–7.40 and 7.48–7.51 ppm (m, 2H, 2H, aromatics); GC–MS *m/z* (%): 240 ($[M+4]^+$, 27), 238 ($[M+2]^+$, 86), 236 ($[M]^+$, 65), 203 (100), 201 (98) $[C_7H_6BrS]^+$.

Bromoethyl and bromopropyl-(4-bromophenyl) sulfides (**22** and **23**). 95% NaH powder (2.9 mmol) was added to a solution of 4-bromothiophenol (2.7 mmol) in anhydrous DMF (3 mL) cooled on

ice under N_2 atmosphere. After stirring for 15 min, a solution of the commercially available 1,2-dibromoethane or 1,3-dibromopropane (8.1 mmol) in anhydrous DMF (3 mL) was added. The resulting mixture was stirred for 20 h, poured into 1 N NaOH (5 mL), and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo to afford a residue that was purified by column chromatography on silica gel (53–60% yield).

2-Bromoethyl-(4-bromophenyl) sulfide (**22**). Eluent: petroleum ether/CH_2Cl_2 (95:5), 60% yield; ^{1}H NMR ($CDCl_3$): $\delta = 3.24$–3.30 (m, 2H, CH_2Br), 3.41–3.47 (m, 2H, SCH_2), 7.23–7.27 and 7.42–7.46 ppm (m, 2H, 2H, aromatics); GC–MS *m/z* (%): 298 ($[M+4]^+$, 52), 296 ($[M+2]^+$, 100), 294 ($[M]^+$, 52).

3-Bromopropyl-(4-bromophenyl) sulfide (**23**). Eluent: petroleum ether/Et_2O (95:5), 53% yield; ^{1}H NMR ($CDCl_3$): $\delta = 2.13$ (q, $J = 6.9$, 2H, $CH_2CH_2CH_2$), 3.05 (t, $J = 6.9$, 2H, CH_2Br), 3.52 (t, $J = 6.3$, 2H, SCH_2), 7.19–7.22 and 7.39–7.43 ppm (m, 2H, 2H aromatics); GC–MS *m/z* (%): 312 ($[M+4]^+$, 55), 310 ($[M+2]^+$, 100), 308 ($[M]^+$, 55).

Preparation of dialkyl-(4-bromophenylthio)alkylphosphonates: general procedure. A mixture of **21**, **22**, or **23** (0.71 mmol) and trimethyl- or triethylphosphite (2.3 mmol) was held at reflux for 5–24 h. After removing the unreacted trialkylphosphite by distillation, the residue was purified by column chromatography on silica gel to afford the title compounds as colorless oils (50–73% yield).

Dimethyl-(4-bromophenylthio)methylphosphonate (Scheme 3). Eluent CH_2Cl_2/EtOAc (9:1), 50% yield; ^{1}H NMR ($CDCl_3$): $\delta = 3.16$ (d, $J = 13.7$, 2H, CH_2), 3.76 (d, $J = 11.0$, 6H, $2CH_3$), 7.29–7.33 and 7.40–7.44 ppm (m, 2H, 2H aromatics); GC–MS *m/z* (%): 312 ($[M+2]^+$, 74), 310 ($[M]^+$, 73), 122 (100).

Diethyl-2-(4-bromophenylthio)ethylphosphonate (Scheme 3). Eluent: $CHCl_3$/CH_2Cl_2 (4:1), 73% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.32$ (t, $J = 7.1$, 6H, $2CH_3$), 1.97–2.09 (m, 2H, CH_2P), 3.05–3.13 (m, 2H, SCH_2), 4.05–4.14 (m, 4H, $2CH_3CH_2$), 7.18–7.22 and 7.40–7.44 ppm (m, 2H, 2H, aromatics); GC–MS *m/z* (%): 354 ($[M+2]^+$, 70), 352 ($[M]^+$, 67), 216 (100), 214 (99) $[C_8H_7BrS]^+$.

Diethyl-3-(4-bromophenylthio)propylphosphonate (Scheme 3). Eluent: $CHCl_3$/CH_2Cl_2 (4:1), 73% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.31$ (t, $J = 7.1$, 6H, $2CH_3$), 1.66–1.80 (m, 2H, CH_2P), 2.08–2.31 (m, 2H, $CH_2CH_2CH_2$), 2.94–3.01 (m, 2H, SCH_2), 4.00–4.16 (m, 4H, $2CH_3CH_2$), 7.17–7.20 and 7.37–7.40 ppm (m, 2H, 2H, aromatics); GC–MS *m/z* (%): 368 ($[M+2]^+$, 21), 366 ($[M]^+$, 22), 125 (100).

Diethyl-1-(4-bromophenylsulfonyl)-3-methylbutylphosphonate (Scheme 4).[25] Compound **20** (1.03 g, 2.78 mmol) was added to a suspension of 1-bromo-2-methylpropane (0.93 mL, 8.55 mmol), 18-crown-6 (0.17 g, 0.64 mmol), anhydrous K_2CO_3 (3.85 g, 27.8 mmol) in anhydrous CH_3CN (33 mL), and the resulting mixture was stirred at 90 °C for 48 h. After cooling to room temperature, the potassium salts were filtered off, and the solvent was removed under reduced pressure. The crude brown oil was purified by column chromatography on silica gel (Et_2O/petroleum ether 4:1) to afford the title compound as a colorless oil (0.79 g, 67% yield). ^{1}H NMR ($CDCl_3$): $\delta = 0.85$ (d, $J = 6.0$, 3H, CH_3CH), 0.90 (d, $J = 6.0$, 3H, CH_3CH), 1.27 (td, $J = 7.1$, $J = 1.9$, 6H, $2CH_3CH_2$), 1.76–1.97 (m, 3H, CH_2CH), 3.49 (dt, $J = 19.2$, $J = 6.3$, 1H, SCHP), 4.07–4.19 (m, 4H, $2CH_3CH_2$), 7.66–7.7 and 7.80–7.85 ppm (m, 2H, 2H, aromatics); GC–MS *m/z* (%): 428 ($[M+2]^+$, 1), 426 ($[M]^+$, 1), 321 (100), 319 (100) $[C_{11}H_{14}BrO_2PS]^+$.

Diethyl-1-(4-bromobenzensulfonyl)-1-methylethylphosphonate (Scheme 4). A solution of **20** (1.02 g, 2.7 mmol) in anhydrous THF (8 mL) was added at −78 °C to a solution of *n*BuLi (6.2 mmol) and diisopropylamine (0.63 g, 6.2 mmol) in anhydrous THF (8 mL) under N_2 atmosphere. After 10 min, a solution of CH_3I (1.54 g, 10.8 mmol) in anhydrous THF (3 mL) was added. The resulting mixture was stirred at −78 °C for 2.5 h, then at room temperature overnight and quenched with 2 N HCl. After evaporating THF under reduced pressure, the acid phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography on silica gel ($CHCl_3$) to afford the title compound as a yellow oil (0.76 g, 70% yield). ^{1}H NMR ($CDCl_3$): $\delta = 1.29$ (t, $J = 7.1$, 6H, $2CH_3CH_2$), 1.57 (d, $J = 14.8$, 6H, $2CCH_3$), 4.17 (m, 4H, $2CH_3CH_2$), 7.66–7.69 and 7.82–7.87 ppm (m, 2H, 2H, aromatics); GC–MS *m/z* (%): 336 ($[M+2]^+$, 25), 334 ($[M]^+$, 25), 123 (100).

Diethyl-1-(4-bromophenylsulfonyl)-2-phenylethylphosphonate (Scheme 4). This compound was obtained following the procedure reported above using benzyl bromide (3.2 mmol) *n*BuLi (3.2 mmol), and diisopropylamine (3.2 mmol). Eluent: petroleum ether/EtOAc (7:3), white solid, 90% yield; mp: 81–84 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.17$–1.27 (m, 6H, $2CH_3$), 3.29 (dt, $J = 14.8$, $J = 6.9$, 1H, CH_2Ph), 3.42–3.55 (m, 1H, CH_2Ph), 3.76–3.86 (m, 1H, SCHP), 3.99–4.16 (m, 4H, $2CH_3CH_2$), 7.13–7.24 (m, 5H, aromatics), 7.62–7.65 and 7.76–7.78 ppm (m, 2H, 2H, aromatics); GC–MS *m/z* (%): 241 (100) $[C_{12}H_{18}O_3P]^+$.

Ethyl-(4-bromophenylthio)acetate (Scheme 5). A solution of ethyl bromoacetate (0.88 g, 5.26 mmol) in EtOH (2 mL) was added dropwise to a solution of sodium 4-bromothiophenate (1.03 g, 4.76 mmol) in EtOH (10.5 mL), under N_2 atmosphere. After stirring for 30 min the reaction mixture was held at reflux for 5 h. The solvent was removed under reduced pressure, and the resulting residue was dissolved in EtOAc and washed with 1 N NaOH, brine, and dried over Na_2SO_4. The organic phase was concentrated in vacuo to afford a yellow oil that was purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2 4:1) to obtain the title compound as a colorless oil (1.23 g, 94% yield). ^{1}H NMR ($CDCl_3$): $\delta = 1.23$ (t, $J = 7.1$, 3H, CH_3), 3.60 (s, 2H, SCH_2), 4.16 (q, $J = 7.1$, 2H, CH_3CH_2), 7.26–7.30 and 7.39–7.43 ppm (m, 2H, 2H, aromatics); GC–MS *m/z* (%): 276 ($M^+ + 2$, 100), 274 ($[M]^+$, 98).

General procedure for hydrolysis. A solution of the appropriate dialkylphosphonates (0.50 mmol) in 6 N HCl/dioxane (1:2, 10 mL) was held at reflux for 4–72 h. After removing the aqueous phase under reduced pressure, the crude phosphonic acids were crystallized or triturated with hexane or Et_2O and filtered to afford the final compounds. The phosphonic acids were obtained as white solids in 52–94% yield.

(Biphenyl-4-sulfonyl)methylphosphonic acid (**1**). 94% yield; mp: 224 °C (dec); ^{1}H NMR ([D$_6$]DMSO): $\delta = 3.92$ (d, $J = 16.0$, 2H, SCH_2P), 7.43–7.56, 7.73–7.75, 7.87–7.90, 7.98–8.01 ppm (m, 3H, 2H, 2H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): $\delta = 55.36$ (d, $J = 128$, SCH_2P), 127.73, 127.84, 129.22, 129.31, 129.84, 139.14, 140.43, 145.56 ppm; MS (ESI) *m/z*: 311 $[M-H]^-$, MS^2 *m/z* (%): 293 (100); anal. calcd for $C_{13}H_{13}O_5PS$: C 50.00%, H 4.20%, found: C 49.77%, H 4.58%.

(3′-Chlorobiphenyl-4-sulfonyl)methylphosphonic acid (**8**). 52% yield; mp: 192–195 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 3.89$ (d, $J = 16.0$, 2H, SCH_2P), 7.46–7.56, 7.69–7.72, 7.80–7.81, 7.87–7.92 and 7.98–8.00 ppm (m, 2H, 1H, 1H, 2H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): $\delta = 55.40$ (d, $J = 127$, SCH_2P), 126.58, 127.58, 127.95, 129.11, 129.25, 131.65, 134.62, 141.08, 141.26, 143.84 ppm; MS (ESI) *m/z*: 347 $[M+2-H]^-$, 345 $[M-H]^-$, MS^2 *m/z* (%): 347 ($[M+2]^+$, 35), 345 ($[M]^+$, 100); anal. calcd for $C_{13}H_{12}ClO_5PS$: C 45.03%, H 3.49%, found: C 45.38%, H 3.79%.

[4-(4-Methoxyphenoxy)phenylsulfonyl]methylphosphonic acid (**10**). 93% yield; mp: 167–168 °C; ^{1}H NMR ([D$_6$]DMSO): δ = 3.75 (s, 3H, CH_3O), 3.83 (d, J = 16.0, 2H, SCH_2P), 6.97–7.03, 7.06–7.10 and 7.83–7.88 ppm (m, 4H, 2H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 55.57 (d, J = 128, SCH_2P), 56.13, 116.05, 116.89, 122.47, 131.16, 134.94, 148.29, 157.20, 162.96 ppm; MS (ESI) *m/z*: 357 $[M-H]^-$, MS^2 *m/z* (%): 357 (100); anal. calcd for $C_{14}H_{15}O_7PS$: C 46.93%, H, 4.22%, found: C 46.59%, H 4.27%.

[4-(Phenylethynyl)phenylsulfonyl]methylphosphonic acid (**11**). 73% yield; mp: 207–209 °C (H_2O); ^{1}H NMR ([D$_6$]DMSO): δ = 3.84 (d, J = 16.0, 2H, SCH_2P), 7.43–7.46, 7.58–7.61, 7.74–7.77 and 7.94–7.97 ppm (m, 3H, 2H, 2H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ 55.19 (d, J = 128, SCH_2P), 88.70, 93.18, 122.24, 128.00, 128.95, 129.54, 130.13, 132.32, 132.34, 141.16 ppm; MS (ESI) *m/z*: 335 $[M-H]^-$, MS^2 *m/z* (%): 193 (100); anal. calcd for $C_{15}H_{13}O_5PS{\cdot}H_2O$: C 50.85%, H 4.27%, found: C 50.85%, H 4.07%.

(Biphenyl-4-thio)methylphosphonic acid (**4**). 70% yield; mp: 187–189 °C (H_2O); ^{1}H NMR ([D$_6$]DMSO): δ = 3.15 (d, J = 14.8, 2H, SCH_2P), 7.29–7.46 and 7.57–7.64 ppm (m, 4H, 5H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 29.34 (d, J = 140, SCH_2P), 127.05, 127.76, 128.1, 128.49, 129.66, 136.95, 138.01, 140.06 ppm; MS (ESI) *m/z*: 279 $[M-H]^-$, MS^2 *m/z* (%): 109 (100) $[C_6H_5S]^+$; anal. calcd for $C_{13}H_{13}O_3PS$: C 55.71%, H 4.68%, found: C 56.09%, H 4.74%.

(4′-Methoxybiphenyl-4-sulfonyl)methylphosphonic acid (**5**). 76% yield; mp: 208–210 °C; ^{1}H NMR ([D$_6$]DMSO): δ = 3.79 (s, 3H, CH_3O), 3.89 (d, J = 16.0, 2H, SCH_2P), 7.03–7.06, 7.69–7.72, 7.82–7.85 and 7.89–7.95 ppm (m, 2H, 2H, 2H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 60.13 (d, J = 128, SCH_2P), 60.71, 120.03, 131.74, 133.81, 133.95, 136.04, 144.34, 149.92, 165.24 ppm; MS (ESI) *m/z*: 341 $[M-H]^-$, MS^2 *m/z* (%): 323 (100); anal. calcd for cyclohexylamine salt $C_{14}H_{15}O_6PS{\cdot}C_6H_{13}N$: C 54.41%, H 6.39%, N 3.17%, found: C 54.06%, H 6.24%, N 3.14%.

2-(Biphenyl-4-sulfonyl)ethylphosphonic acid (**12**). 77% yield; mp: 225 °C (dec); ^{1}H NMR ([D$_6$]DMSO): δ = 1.68–1.80 (m, 2H, CH_2P), 3.30–3.80 (m, 2H, SCH_2), 7.42–7.54, 7.74–7.77, 7.93–7.99 ppm (m, 2H, 2H, 5H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 22.40 (d, J = 135, CH_2P), 50.97, 127.94, 128.44, 129.38, 129.48, 129.88, 137.35, 138.95, 146.22 ppm; MS (ESI) *m/z*: 325 $[M-H]^-$, MS^2 *m/z* (%): 217 (100) $[C_{12}H_9O_2S]^+$; anal. calcd for $C_{14}H_{15}O_5PS$: C 51.53%, H 4.63%, found: C 51.14%, H 4.58%.

3-(Biphenyl-4-sulfonyl)propylphosphonic acid (**13**). 71% yield; mp: 167–170 °C; ^{1}H NMR ([D$_6$]DMSO): δ = 1.54–1.64 (m, 2H, $CH_2CH_2CH_2$), 1.64–1.74 (m, 2H, CH_2P), 3.43 (t, J = 7.9, 2H, SCH_2), 7.44–7.53, 7.74–7.76, 7.91–7.97 ppm (m, 3H, 2H, 4H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 17.74, 26.55 (d, J = 137, CH_2P), 55.67, 127.91, 128.36, 129.05, 129.44, 129.87, 138.29, 139.00, 145.97 ppm; MS (ESI) *m/z*: 339 $[M-H]^-$, MS^2 *m/z* (%): 217 (100) $[C_{12}H_9O_2S]^+$; anal. calcd for $C_{15}H_{17}O_5PS$: C 52.94%, H 5.03%, found: C 52.67%, H 4.95%.

1-(4′-Methoxybiphenyl-4-sulfonyl)-2-phenylethylphosphonic acid (**15**). 74% yield; mp: 200–203 °C; ^{1}H NMR ([D$_6$]DMSO): δ = 3.16–3.39 (m, 2H, CH_2Ph), 3.76–3.86 (m, 1H, $CHCH_2Ph$), 3.82 (s, 3H, CH_3O), 7.04–7.18, 7.63–7.74, 7.83–7.86 ppm (m, 7H, 4H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 31.90, 55.95, 65.66 (d, J = 127, SCH_2P), 115.27, 126.82, 126.91, 128.73, 129.05, 129.16, 129.95, 131.29, 138.26, 139.35, 145.20, 160.49 ppm; MS (ESI) *m/z*: 431 $[M-H]^-$, MS^2 *m/z* (%): 183 (100) $[C_{13}H_{11}O]^+$; anal. calcd for cyclohexylamine salt $C_{21}H_{21}O_6PS{\cdot}C_6H_{13}N$: C 60.99%, H 6.65%, N 2.63%, found: C 60.83%, H 6.40%, N 2.82%.

1-(Biphenyl-4-sulfonyl)-1-methylethylphosphonic acid (**16**). 66% yield; mp: 197–198 °C (dec); ^{1}H NMR ([D$_6$]DMSO): δ = 1.41 (d, J = 13.7, 6H, $2CCH_3$), 7.41–7.53, 7.74–7.76, 7.86–7.89 and 7.93–7.95 ppm (m, 3H, 2H, 2H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 20.29, 62.59 (d, J = 133, SCH_2P), 127.18, 127.85, 129.37, 129.86, 131.97, 136.52, 139.06, 145.58 ppm; MS (ESI) *m/z*: 339 $[M-H]^-$, MS^2 *m/z* (%): 217 (100) $[C_{12}H_9O_2S]^+$; anal. calcd for $C_{15}H_{17}O_5PS$: C 52.94%, H 5.03%, found: C 52.77%, H 5.06%.

Preparation of acids 6, 7, 9, and 14.[23] BBr_3 (1 M CH_2Cl_2 solution, 0.50 mmol) was carefully added dropwise under N_2 atmosphere to a cooled (−30 °C) solution of the appropriate diethylphosphonate (0.54 mmol) in anhydrous toluene (5 mL). After 6 h at 75 °C, CH_3OH (4 mL) was added at room temperature, and the resulting solution was stirred for a further 30 min. The organic solvents were removed under reduced pressure, and the crude solid was triturated with Et_2O and filtered to afford the desired phosphonic acids as a white solid in 69–84% yields.

(4′-Chlorobiphenyl-4-sulfonyl)methylphosphonic acid (**6**). 80% yield; mp: 205 °C (dec); ^{1}H NMR ([D$_6$]DMSO): δ = 3.94 (d, J = 16.0, 2H, SCH_2P), 7.54–7.56, 7.71–7.81, 7.87–7.93 and 7.96–8.05 ppm (m, 2H, 2H, 2H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 55.23 (d, J = 128, SCH_2P), 127.72, 129.30, 129.65, 129.82, 134.30, 137.90, 140.70, 144.18 ppm; MS (ESI) *m/z*: 345 $[M-H]^-$, MS^2 *m/z* (%): 327 (100); anal. calcd for cyclohexylamine salt $C_{13}H_{12}ClO_5PS{\cdot}C_6H_{13}N$: C 51.18%, H 5.65%, N 3.14%, found: C 51.46%, H 6.04%, N 3.42%.

(4′-Trifluoromethylbiphenyl-4-sulfonyl)methylphosphonic acid (**7**). 84% yield; mp: 231–232 °C; ^{1}H NMR ([D$_6$]DMSO): δ = 3.94 (d, J = 16.0, 2H, SCH_2P), 7.82–7.85, 7.93–7.96 and 8.02–8.05 ppm (m, 2H, 4H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 55.12 (d, J = 128, SCH_2P), 123.00, 126.61, 128.21, 128.72, 129.34, 129.76, 141.25, 143.13, 143.96 ppm; MS (ESI) *m/z*: 379 $[M-H]^-$, MS^2 *m/z* (%): 237 (100); anal. calcd for $C_{14}H_{12}F_3O_5PS$: C 44.22%, H 3.18%, found: C 43.88%, H 3.52%.

[4-(2-Thienyl)phenylsulfonyl]methylphosphonic acid (**9**). Yellow solid, 79% yield; mp: 240 °C (dec); ^{1}H NMR ([D$_6$]DMSO): δ = 3.91 (d, J = 16.5, 2H, SCH_2P), 7.18–7.21, 7.68–7.72, 7.81–7.88, 7.91–7.94 ppm (m, 1H, 2H, 2H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 55.28 (d, J = 128, SCH_2P), 126.07, 126.70, 128.58, 129.56, 129.63, 139.01, 139.90, 142.08 ppm; MS (ESI) *m/z*: 317 $[M-H]^-$, MS^2 *m/z* (%): 317 (30), 299 (100); anal. calcd for $C_{11}H_{11}O_5PS_2$: C 41.51%, H 3.48%, found: C 41.90%, H 3.21%.

1-(Biphenyl-4-sulfonyl)-3-methylbutylphosphonic acid (**14**). 69% yield; mp: 212 °C (dec); ^{1}H NMR ([D$_6$]DMSO): δ = 0.70 (d, J = 6.0, 3H, $CHCH_3$), 0.81 (d, J = 6.0, 3H, $CHCH_3$), 1.63–1.83 (m, 3H, CH_2CHCH_3), 3.47 (dt, J = 18.0, J = 5.5, 1H, SCHP), 7.41–7.53, 7.73–7.76, 7.88–7.91 and 7.95–7.99 ppm (m, 3H, 2H, 2H, 2H, aromatics); ^{13}C NMR ([D$_6$]DMSO): δ = 22.17, 22.98, 26.76 (d, J = 4, CH_2CHP), 35.04, 62.38 (d, J = 129, SCHP), 127.57, 127.82, 129.37, 129.87, 130.20, 139.03, 139.05, 145.55 ppm; MS (ESI) *m/z*: 367 $[M-H]^-$; MS^2 *m/z* (%): 217 (100) $[C_{12}H_9O_2S]^+$; anal. calcd for $C_{17}H_{21}O_5PS$: C 55.43%, H 5.75%, found: C 55.59%, H 5.95%.

Preparation of (biphenyl-4-sulfonyl)acetic acid (**2**). A solution of ethyl(biphenyl-4-sulfonyl)acetate **25** (0.13 g, 0.43 mmol) in THF (9 mL) and 1 N NaOH (8.5 mL) was stirred at room temperature for 4 h. The organic solvent was removed under reduced pressure, and the residue was acidified with 6 N HCl and extracted with $CHCl_3$ (3×20 mL). The organic phases were dried over Na_2SO_4 and evaporated to dryness to obtain the title acid as a white solid, which was crystallized from $CHCl_3$/hexane (0.07 g, 56% yield); mp: 147–150 °C; ^{1}H NMR ($CDCl_3$): δ = 4.20 (s, 2H, CH_2), 7.41–7.52, 7.60–

7.63, 7.77–7.79, 8.00–8.03 ppm (m, 3H, 2H, 2H, 2H, aromatics); ^{13}C NMR ($CDCl_3$): δ 60.80, 127.67, 128.20, 129.10, 129.32, 129.36, 137.08, 139.10, 147.78, 166.03 ppm; MS (ESI) *m/z*: 299 $[M+Na]^+$, 231 $[M-CO_2H]^-$; MS^2 *m/z* (%): 231 (100) $[C_{13}H_{11}O_2S]^+$; anal. calcd for $C_{14}H_{12}O_4S$: C 60.86%, H 4.38%, found: C 60.47%, H 4.37%.

Preparation of (biphenyl-4-sulfonyl)acetohydroxamic acid (3).[26] A solution of freshly prepared $NaOCH_3$ (5 mmol) in CH_3OH (2.5 mL) was added to a solution of ethyl(biphenyl-4-sulfonyl)acetate **25** (0.42 g, 1.37 mmol) and hydroxylamine hydrochloride (0.19 g, 2.74 mmol) in CH_3OH (7 mL). After stirring overnight the solvent was evaporated in vacuo. The resulting residue was dissolved in $CHCl_3$ and washed with diluted HCl (pH ~3) and brine. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The resulting colorless residue was crystallized from $CHCl_3$ to give a white solid (0.16 g, 40% yield); mp: 175–178 °C; ^{1}H NMR ([D$_6$]DMSO): δ = 4.17 (s, 2H, CH_2), 7.42–7.54, 7.74–7.76, 7.92 (m, 3H, 2H, 4H aromatics), 9.21 (bs, 1H), 10.76 ppm (bs, 1H); ^{13}C NMR ([D$_6$]DMSO): δ = 59.36, 127.88, 127.97, 129.40, 129.48, 129.86, 138.91, 139.05, 146.00, 158.47 ppm; MS (ESI) *m/z*: 290 $[M-H]^-$, MS^2 *m/z* (%): 217 (100) $[C_{12}H_9O_2S]^+$; anal. calcd for $C_{14}H_{13}NO_4S$: C 57.72%, H 4.50%, N 4.81%, found: C 57.48%, H 4.55%, N 4.87%.

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