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Design and synthesis of potent hydroxamate inhibitors with increased selectivity within the gelatinase family†

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MMP-2 is a validated target for the development of anticancer agents. Herein we describe the synthesis of a new series of potent phenylalanine derived hydroxamates, with increased MMP-2/MMP-9 selectivity compared to analogous hydroxamates described previously. Docking and molecular dynamics experiments have been used to account for this selectivity, and to clarify the role of the triazole ring in the binding process.

Introduction

Proteases are classified into serine proteases, cysteine proteases, aspartate proteases and metalloproteinases, based on differences in the hydrolysis mechanism of peptide bonds.[1] The human degradome (proteases produced by cells) consists of at least 569 proteases and homologues, with metalloproteinases representing the largest class (194 described in humans).[2]

The Metzincin superfamily of metalloproteinases can, in turn, be classified into the following four subfamilies, according to the slight differences in their catalytic site and the presence of additional domains: matrix metalloproteinases (MMPs), adamalysins (ADAM, ADAMTS and class III snake venom proteins), astacins (BMP1/TLL proteins and meprins) and bacterial serralysins.[3] Metzincins are distinguished by a highly conserved HEXXHXXGXXH domain that bears three histidine residues that bind a zinc atom at the active site.[4]

The 26 MMPs described so far in the vertebrate family can be classified into several subfamilies according to their degree of sequence homology and substrate specificity: collagenases, gelatinases, stromelysins, matrilysines and membrane-type MMPs (MT-MMPs).[5]

Basically, all MMPs have been linked to disease development,[6,7] mainly in cardiovascular disorders,[8–10] arthritis,[11] acute lung injury,[12] and cancer.[13–15]

Gelatinase A (MMP-2) and gelatinase B (MMP-9) play an important role in cancer. They are over-expressed or deregulated in a variety of malignant tumors.[16] It has been shown, in an experiment in MMP-2 knockout mice, that angiogenesis and tumour progression can be controlled by inhibiting the activity of this enzyme, suggesting the use of MMP-2 inhibitors for chemotherapy of cancer and other diseases.[17] However, while MMP-2 is a validated target in cancer therapy, MMP-9 has both pro- and anti-tumorigenic effects, and is an anti-target protein in advanced stages of the disease.[18]

A large number of MMP inhibitors (MMPIs) have been reported so far. MMPIs containing a Zinc Binding Group (ZBG) and a lipophilic chain (called the P1′-segment) which interacts with the hydrophobic S1′ pocket are very effective. The latter is considered the "selectivity pocket", as it is the region where MMPs exhibit the largest differences.[19–22]

In our research group we are interested in the design of MMP-2 inhibitors with selectivity over other metalloproteinases, especially over MMP-9. Because the active sites of both enzymes are very similar, it is necessary to carefully select the fragment that has to interact with the S1′ pocket. Our approach is based on the use of Cu(I)-catalyzed azide–alkyne cycloaddition, one of the most effective click reactions, to easily connect the selected ZBG with different non-polar P1′ substituents in order to explore the S1′ pocket. Following this strategy we have obtained inhibitors with high potency and MMP-2/MMP-9 selectivity

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† Electronic supplementary information (ESI) available: Torsional energies of the C_{sp2}–C_{sp2} and C_{sp2}–N_{sp2} scan; and per-residue energy decomposition of the four systems. ^{1}H NMR and ^{13}C NMR spectra of compounds **1a–g**, **7**, **13** and **14**. See DOI: 10.1039/c4ob01516a

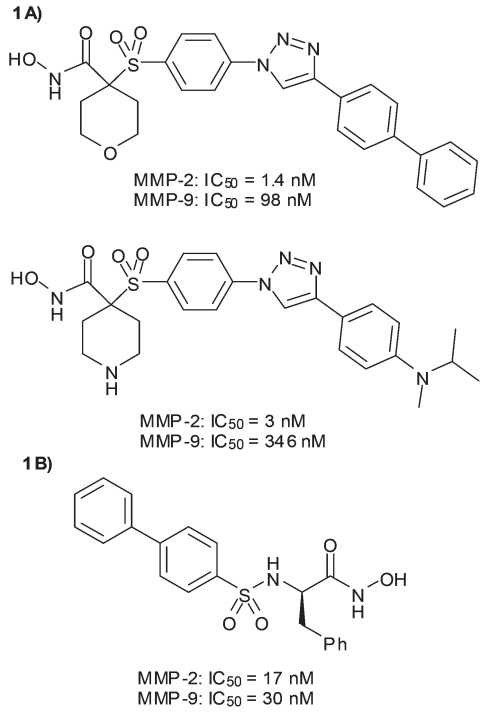


Fig. 1 Structure and inhibitory activity of (A) clicked MMP-2 selective inhibitors and (B) BiPS.

(Fig. 1A).[23–25] The potent but not selective MMPI (2*R*)-[(4-biphenylylsulfonyl)amino]-*N*-hydroxy-3-phenylpropionamide (BiPS)[26] (Fig. 1B) has been the starting point for the design of the new series of inhibitors described herein. With the aim of increasing the selectivity between both gelatinases we have followed the same approach based on click chemistry.

Results and discussion

Chemistry

Hydroxamates **1a–g** were synthesized following the pathway outlined in Scheme 1. Compound **2** was obtained as described previously,[27] starting from phenylalanine and 4-nitrobenzenesulfonyl chloride under basic conditions. The nitro group was reduced by catalytic hydrogenation to give amino acid **3**, which was transformed into azide **4** by reaction with *tert*-butyl nitrite and azidotrimethylsilane. Reaction of the carboxylic acid with *O*-THP protected hydroxylamine, using EDCI as an amide coupling agent, gave hydroxamate **5**. Copper(I) catalyzed Huisgen cycloaddition (CuAAC) between **5** and different alkynes gave compounds **6a–g**, which were deprotected to obtain the final hydroxamates **1a–g**.

(*R*) and (*S*) enantiomers of hydroxamates **1b**, **1c** and **1f** were prepared separately following the same pathway starting from D or L phenylalanine.

In order to study the effect of the triazole ring on the activity, hydroxamate **7** was synthesized. This compound has a different substitution pattern in the triazole ring, with the biphenyl group attached to N1, instead of the C-4 position that is occupied in **1a–g**. The synthetic pathway for **7** (Scheme 2) started from (±) phenylalanine methyl ester hydrochloride, which was transformed into sulphonamide **8** by reaction with pipsyl chloride. Sonogashira cross-coupling reaction with ethynyltrimethylsilane gave **9**, which was deprotected under basic conditions to give **10**, and was subsequently transformed into **11** by coupling with NH_2OTHP. The terminal alkyne was *clicked* with 4-azidobiphenyl[28] to give triazole **12**, which was deprotected to give the desired compound **7**.

With the aim of improving the solubility of this class of compounds, a basic side chain was introduced into the sulphonamide nitrogen atom. We chose a morpholinoethyl moiety, as this fragment was used before to improve the solubility of valine-derived hydroxamates.[29]

Thus, compounds **13** and **14** were synthesized following the synthetic pathway shown in Scheme 3. Carboxylic acid **4** was protected as *tert*-butyl ester **15**, and after alkylation with 4-(2-chloroethyl)morpholine in the presence of K_2CO_3, **16** was obtained. A sequence of *tert*-butyl deprotection to give **17** and coupling of the carboxylic acid with *O*-THP hydroxylamine gave azide **18**. The CuAAC reaction with two different alkynes gave the corresponding triazoles **19–20** which were converted into hydroxamates **13** and **14** by acidic *O*-THP deprotection.

Biological evaluation

The inhibitory activities of hydroxamates **1a–g**, **7**, **13** and **14** against MMP-2 and MMP-9 were determined by the colorimetric method using a thiopeptide as a chromogenic substrate (Enzo Life Science Inc.). The assay conditions were similar to those described before [Fabre, 2013 #34].[24] The results are collected as IC_{50} in Table 1.

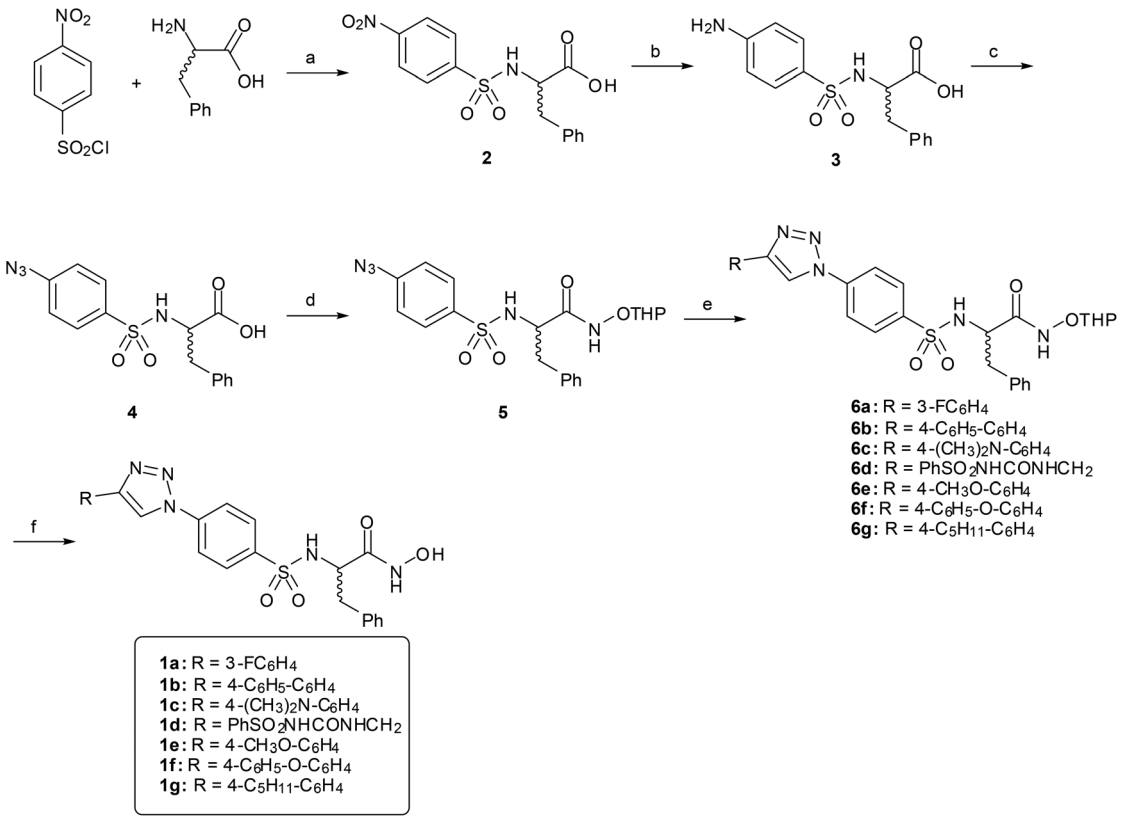
All racemic compounds showed potent inhibitory activity against MMP-2, which was higher than the one reported for BiPS (IC_{50} = 17 nM).[26]

An exception was **1d**, where the P1′ side chain is too polar to interact with the hydrophobic S1′ pocket of the enzyme. This result was expected, as we also found the lack of activity with this P1′ group in our previous studies.[23]

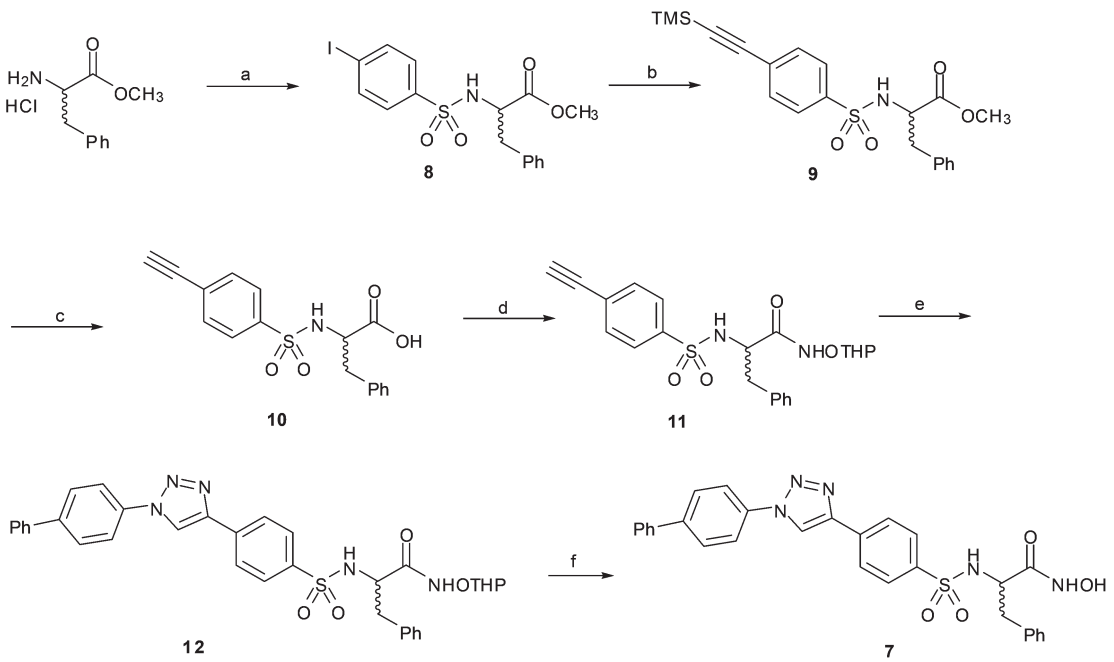
The best result in potency and selectivity was found for **1b**, with an IC_{50} of 1.3 nM for MMP-2 and almost 100-fold less activity against MMP-9. This result shows that our click based strategy is a useful approach to improve the profile of this type of inhibitor, especially in the search for ligands capable of differentiating between the two gelatinases.

In the previously reported activity against MMP-3 of phenylalanine-derived hydroxamates, it was found that the preferred stereochemistry at the stereogenic centre corresponded to the *R*-isomer, which was more potent than the racemate.[30] A similar result was reported for BiPS, which was 28-fold more active in MMP-9 than the *S*-isomer.[26]

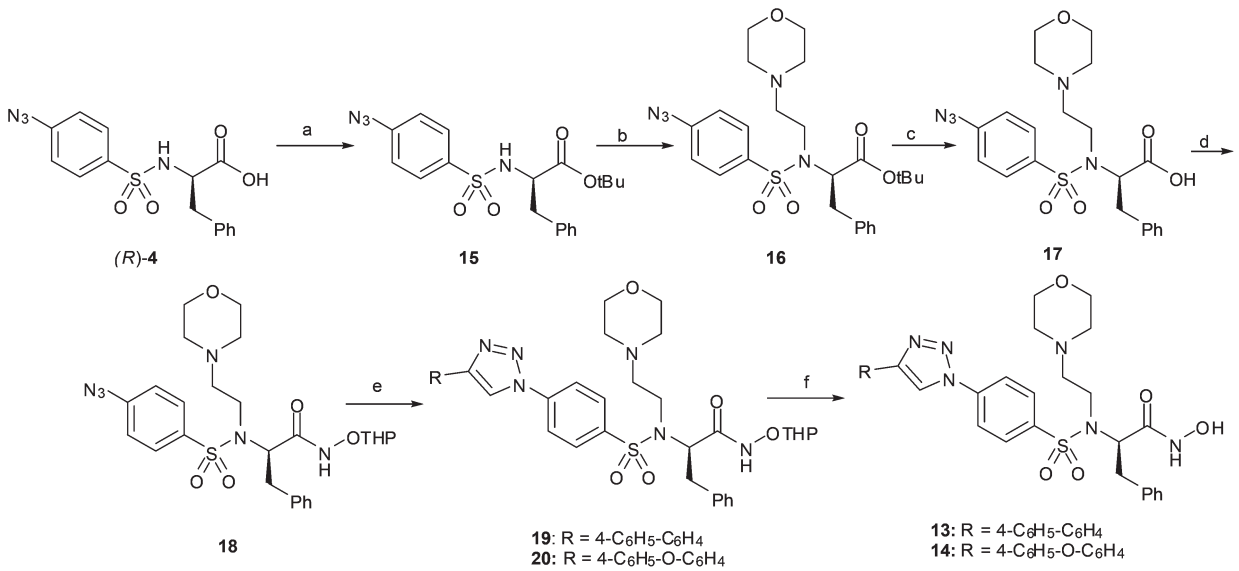
In order to verify if the configuration of the stereogenic centre has an effect also on the inhibitory activity of **1b**, **1c** and **1f**, both enantiomers of these compounds were synthesized and tested against both gelatinases. The results show that (*R*)-**1b** is 293-fold more potent against MMP-2 than (*S*)-**1b**, and



Scheme 1 Synthesis of triazoles **1a–g**. (a) NaOH–H_2O; (b) H_2, Pd/C, MeOH; (c) *t*-BuONO, $TMSiN_3$, acetonitrile, 0 °C; (d) *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine, EDCI, HOBt, NMM, DMF; (e) alkyne, $CuSO_4$, sodium ascorbate, DMF or *t*-BuOH–H_2O; (f) 4 M HCl–dioxane, MeOH.

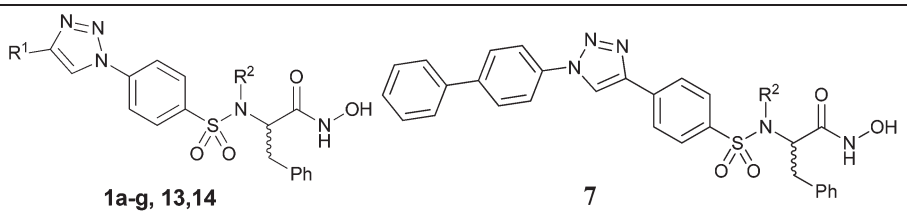


Scheme 2 Synthesis of triazole **7**: (a) pipsyl chloride, NMM, CH_2Cl_2; (b) TMSCCH, CuI, Et_3N, Ph_3P, Pd/C, reflux; (c) 1: KOH, dioxane, rt, 2: citric acid 20%; (d) NH_2OTHP, EDCI, HOBt, NMM, DMF; (e) biphenylazide, $CuSO_4{\cdot}5H_2O$, sodium ascorbate, DMF, (f) 4 M HCl–dioxane, MeOH.



Scheme 3 Synthesis of triazoles **13** and **14**. (a) 2-Methylpropene, H_2SO_4, DCM, 86%; (b) 4-(2-chloroethyl)morpholine, K_2CO_3, DMF, 85%; (c) TFA, thioanisole, DCM, 80%; (d) NH_2OTHP, EDC, HOBt, DMAP, DMF, 91%; (e) alkyne, $CuSO_4$, sodium ascorbate, DMF; (f) HCl, dioxane, 60–75%.

Table 1 MMP inhibition activities for compounds **1a–g**, **7**, **13** and **14**



Compound	R^1	R^2	MMP-2 IC_{50} [a] (nM)	MMP-9 IC_{50} [a] (nM)	Selectivity for MMP-9/MMP-2
Rac.-**1a**	3-FC_6H_4	H	0.27	3.6	13
Rac.-**1b**	4-C_6H_5-C_6H_4	H	1.3	124	95
(*R*)-**1b**	4-C_6H_5-C_6H_4	H	0.75	58.5	78
(*S*)-**1b**	4-C_6H_5-C_6H_4	H	220	>1000	—
Rac.-**1c**	$(CH_3)_2N$-C_6H_4	H	0.88	2.11	2.4
(*R*)-**1c**	$(CH_3)_2N$-C_6H_4	H	0.32	1.06	3.4
(*S*)-**1c**	$(CH_3)_2N$-C_6H_4	H	49	>1000	—
Rac.-**1d**	$PhSO_2NHCONHCH_2$	H	>500	>1000	—
Rac.-**1e**	4-CH_3O-C_6H_4	H	0.42	1.16	2.8
Rac.-**1f**	4-C_6H_5-O-C_6H_4	H	2.2	88	41
(*R*)-**1f**	4-C_6H_5-O-C_6H_4	H	1.08	36.8	34
(*S*)-**1f**	4-C_6H_5-O-C_6H_4	H	>500	>1000	—
Rac.-**1g**	4-C_5H_{11}-C_6H_4	H	8.18	372	46
Rac.-**7**			1.32	5.54	4
(*R*)-**13**	4-C_6H_5-C_6H_4	2-Morpholinoethyl	2.66	6.34	2.4
(*R*)-**14**	4-C_6H_5-O-C_6H_4	2-Morpholinoethyl	1.99	29.9	15

[a] IC_{50} values on the nM scale were determined using a colorimetric assay. Enzymatic data are the main values from three independent experiments. SD are within ±10%.

1.7-fold more potent than the racemic form, showing that the racemate activity is mainly due to the *R*-isomer. However, the MMP-2/MMP-9 selectivity of (*R*)-**1b** is slightly diminished with respect to the racemic mixture because the *S*-isomer was completely inactive in MMP-9 (IC_{50} > 1000). A similar effect was observed for **1c** and **1f**.

Compounds **13** and **14**, where a basic chain was introduced into the sulphonamide nitrogen atom, presented better solubility during sample preparation. However, although the inhibition against MMP-2 was kept at the same level, the inhibitory activities against MMP-9 were increased giving a worse selectivity profile.

Table 2 Inhibitory activity (IC_{50} values) of*Rac*.-**1b**, *Rac*.-**1f** and *Rac*.-**1g** towards a panel of metalloproteinases

	1b[a] (nM)	**1f**[a] (nM)	**1g**[a] (nM)
MMP-1	>10 000	>10 000	>1000
MMP-2	1.3	2.2	8.2
MMP-3	50	33.4	170
MMP-7	>500	>1000	>1000
MMP-8	>500	128.8	450
MMP-9	124	88	372.5
MMP-10	181	103.4	336
MMP-12	3.8	2	14.2
MMP-13	<5	1.5	36.8
MMP-14	555.7	256.6	>200

[a] Enzymatic data are the mean values from two independent experiments. SD are within ±10%.

Interestingly, the same effect was observed for compound 7. This compound was obtained through a click reaction between 4-azidobiphenyl and an alkyne bearing the hydroxamate ZBG. The structure is closely related to **1b**, with the only difference being in the substitution pattern of the triazole ring: the biphenyl group in 7 is attached to the N1 of the triazole, instead of the C-4 position that is occupied in **1b**. While the activity of 7 against MMP-2 was maintained (IC_{50} = 1.32 nM), a high increase in the activity against MMP-9 was observed (IC_{50} = 5.54 nM) compared to the activity of **1b** (*Rac*.-**1b**: IC_{50} = 124 nM; (*R*)-**1b**: 58.5 nM), with the corresponding loss of selectivity.

Compounds **1b**, **1f** and **1g**, showing a promising selectivity profile within gelatinases, were chosen for the analysis of their activity towards other metalloproteinases (Table 2). The obtained profile showed that these compounds are devoid of activity towards MMP-1, whose inhibition is hypothesized to be connected with the musculoskeletal syndrome,[31,32] and have lower activity towards MMP-8, an enzyme whose inhibition could enhance tumourigenesis and metastasis.[33] Moreover, **1b** and **1f** displayed good activity towards MMP-13, an enzyme whose inhibition is targeted in the treatment of osteoarthritis, while having much lower potency towards MMP-14, proposed recently as an anti-target in the treatment of this disease.[34]

In order to explain the difference in selectivity between compounds **1b** and 7 we first studied both separately by means of *ab initio* quantum mechanics (QM) methods. Despite being structurally very similar, the difference in the substitution pattern of the triazole determines the relative orientation of the P1′-segment with the rest of the compound. The main difference arises from the energy profile of the dihedral angle that describes the torsion around C_{sp2}–C_{sp2} and C_{sp2}–N_{sp2}. The first dihedral angle presents energy minima at ±15° and global maxima of 3.3 kcal mol^{-1} at ±90°, whereas the dihedral angle between C_{sp2}–N_{sp2} presents energy minima between ±30–45°, a local maximum of 0.7 kcal mol^{-1} at 0°, and a global maximum of 1.6 kcal mol^{-1} at ±90° (ESI† Fig. 1). This means that compound **1b** will be almost flat from the triazole to the end of the P1′-segment, whereas compound 7 will form an angle of around 45° between the triazole and the P1′-segment.

The docking experiments for compound **1b** were carried out with a deprotonated hydroxamic acid moiety on MMP-2 and MMP-9, and with a protonated side chain of Glu404. The obtained poses were overall similar to those obtained in our previous work,[35] so these complexes were used to build the complexes of 7 with MMP-2 and MMP-9 by changing the atom type in the triazole ring and allowing the geometries to relax in the molecular mechanics force field. During the 10 ns molecular dynamics (MD) simulations we monitored the per-residue protein–ligand interactions, especially those established between the P1′-segment and the S1′ pocket. Compounds **1b** and 7 establish mainly van der Waals interactions in the complexes with both MMP-2 and MMP-9 (ESI† Fig. 2). Both compounds establish strong van der Waals interactions with the amino acids of the first segment of the Ω-loop within both MMPs, especially with Ile424(MMP-2)/Met422(MMP-9) that interacts with the triazole through the backbone; and Tyr425(MMP-2)/Tyr423(MMP-9) and Thr426 (MMP-2)/Arg424(MMP-9) that stack their side chains with the triazole and biphenyl moieties. The slight difference in the interaction energy between both compounds and the side chain of Arg424 in the case of MMP-9 can be explained by the difference in flexibility at the end of the P1′-segment mentioned before. The C_{sp2}–C_{sp2} bond present in the P1′ fragment of **1b** is more rigid than the C_{sp2}–N_{sp2} bond present in 7, which induces fewer fluctuations in the interaction with the highly flexible side chain of Arg424, resulting in a better interaction energy for **1b** compared to 7. The interactions established between compounds **1b** and 7 and the last segment of the Ω-loop can account for the lack of selectivity of compound 7. In our previous work we proposed that the selectivity of this type of molecules, especially the biphenyl derivatives, arises from the presence of the Phe431-Arg432 motif in MMP-2, which is mutated to Pro429-Pro430 in MMP-9. This difference makes the Ω-loop more rigid in MMP-9 than in MMP-2.[25] In the case of MMP-2, both compounds interact with the side chain of Phe431 (Fig. 2). Interestingly, the study of the MD trajectories and the minimized cooled structure obtained after the 10 ns simulations showed that compound 7, having a torsion of around 45° between the triazole and the P1′-segment, due to the C_{sp2}–N_{sp2} bond, is able to adopt more easily the shape of the S1′ pocket, establishing a van der Waals interaction with Pro429 (Fig. 2). This interaction is absent in compound **1b** which is flatter and has less flexibility. This difference could explain the different *in vitro* activity observed for both compounds. Although we have explained the difference in selectivity between compounds **1b** and 7, we were not able to give the rationale of the difference in binding affinity between both enantiomers of compound **1b** as they did not show any significant differences in the dynamic behaviour and interactions with the two proteins in the time span and conditions of our simulations.

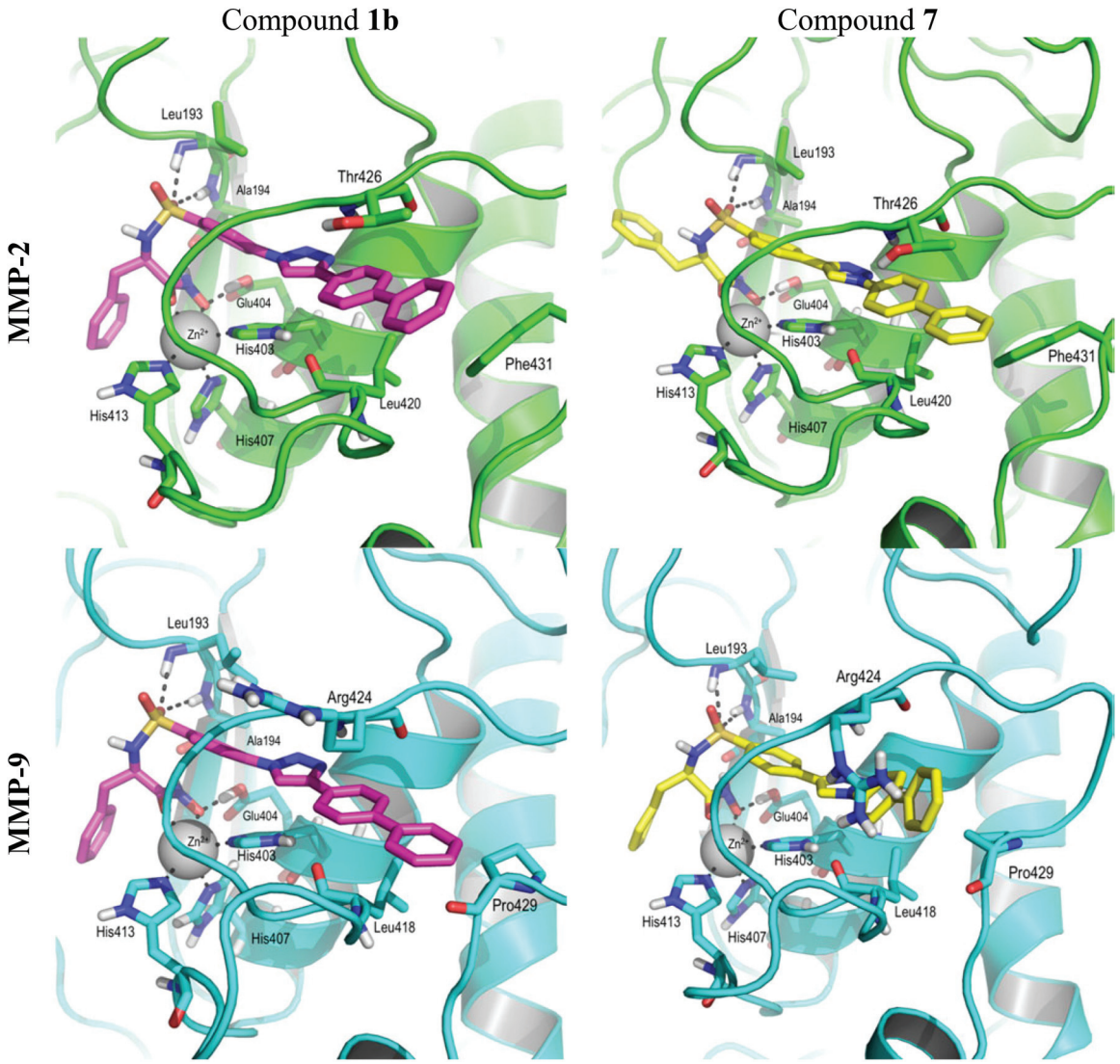


Fig. 2 PyMOL cartoon representation of the complexes between MMP2 (green) and MMP9 (cyan) and compounds **1b** (magenta) and **7** (yellow) respectively. For the sake of clarity, only polar hydrogens are displayed; and only the side chains of the amino acids that stabilize the ZBG-end and those that bring about the most different interactions in the Ω-loop are shown as sticks.

Experimental section

Molecular modeling

The proteins were prepared and the docking experiments were carried out as in the previous work.[25] The ligands (compounds **1b** and **7**) were built using the Maestro LigPrep module (http://www.Schrodinger.com). pK_a of titratable groups were calculated using the Sparc pK_a online calculator,[36] and the non-protonated form of the hydroxamate was used for the docking calculations making use of the Glide module.[37–39] The center of the box was positioned on the catalytic zinc ion present in the active site. The box size was set up to enclose the ligand-binding domain to ensure an adequate exploration of the binding poses. The docking procedure was performed with XP (extra precision) mode, and a van der Waals radii scale factor of 1.0/0.8 for the receptor and the ligand, respectively. The best-obtained result for each ligand in each complex was considered for analysis of the ligand–receptor interactions and subsequent molecular modeling simulations.

For the MD simulations the charge distribution for the ligands was obtained by fitting the quantum mechanically calculated (RHF/6-31G**//RHF/3-21G*) molecular electrostatic potential (MEP) of the geometry-optimized molecules to a point charge model, as implemented in Gaussian 03 (Gaussian, Inc., Wallingford, CT). Consistent bonded and non-bonded AMBER parameters for both molecules were assigned by analogy or through interpolation from those already present in the AMBER database (ff03). Each MMP molecular system was immersed in a truncated octahedron containing ~10 000 TIP3P water molecules[40] and four Na^+ ions[41] to achieve system electroneutrality. The sander and pmemd modules of the AMBER12 suite (http://ambermd.org/) were used for the

restrained and unrestrained MD simulations, respectively. Periodic boundary conditions were applied and electrostatic interactions were treated using the smooth particle mesh Ewald method[42] with a grid spacing of 1 Å. The cutoff distance for the non-bonded interactions was 9 Å, the SHAKE[43] algorithm was applied to all bonds, and an integration step of 2.0 fs was used throughout. After an initial energy minimization of the water molecules and counterions, the system was heated to 300 K in 25 ps, after which the solvent was allowed to redistribute around the positionally restrained solute for 220 ps. After this time, the system was allowed to move freely so as to explore the mutual adaptation between the ligand and the protein. Snapshots from each 10 ns MD trajectory were collected every 20 ps for further analysis carried out with the ptraj module of AMBER to monitor the hydrogen bonding distances between the ligands and the protein. The per-residue energy decomposition of the 10 ns MD trajectory was carried out using the ISM program.[44,45]

Chemistry

General procedures. Melting points (uncorrected) were determined on a Stuart Scientific SMP3 apparatus. Infrared (IR) spectra were recorded with a Perkin-Elmer Spectrum 100 Series infrared spectrophotometer. ^{1}H and ^{13}C NMR data were recorded on a Bruker 300-AC or a Bruker 400-ultrashield instrument. Chemical shifts (δ) are expressed in parts per million relative to internal tetramethylsilane; coupling constants (J) are in hertz. Mass spectra were run on a Bruker Esquire 3000 spectrometer. Elemental analyses (C, H, N, S) were performed on a LECO CHNS-932 apparatus at the Microanalyses Service of the University Complutense of Madrid; unless otherwise stated, all reported values are within ±0.4% of the theoretical compositions. Thin-layer chromatography (TLC) was run on Merck silica gel 60 F-254 plates. Unless stated otherwise, the starting materials used were high-grade commercial products.

2-{[(4-Aminophenyl)sulfonyl]amino}-3-phenylpropanoic acid (3). A solution of **2**[27] (2.2 g, 6.28 mmol) in EtOH (50 mL) and 10% Pd/C (220 mg) were introduced into a Parr shaker apparatus, and maintained under a hydrogen pressure of 60 p.s.i. for 18 h at room temperature. Palladium was filtered off and the solvent was removed. Then, it was evaporated to dryness, and the residue was purified by column chromatography on silica gel (hexane–EtOAc 1 : 4) to afford **3** (1.57 g, 78%) as a white solid, mp 205–206 °C (EtOH). (Found: C, 56.04; H, 5.00; N, 8.82; S, 9.97. $C_{15}H_{16}N_2O_4S$ requires C, 56.24; H, 5.03; N, 8.74; S, 10.01%); ν_{max} (KBr)/cm^{-1} 3372, 3306, 3284, 1719; δ_H (300 MHz, DMSO-d$_6$) 2.68 (1H, dd, J 13.4, 7.9, $\frac{1}{2}$CH$_2$), 2.91 (1H, dd, J 13.4, 6.1, $\frac{1}{2}$CH$_2$), 3.69–3.76 (1H, m, CH), 5.90 (2H, bs, NH$_2$), 6.48 (2H, d, J 8.5, ArH), 7.09–7.12 (2H, m, ArH), 7.17–7.27 (5H, m, ArH), 7.69 (1H, d, J 8.5, SO$_2$NH), 12.64 (1H, bs, COOH); δ_C (75.4 MHz, DMSO-d$_6$) 37.9, 57.1, 112.4, 125.8, 126.4, 128.1, 128.4, 129.2, 136.9, 152.4, 172.4. EM (ESI+) m/z 319.00 $[M - H]^+$.

(2*R*)-2-{[(4-Aminophenyl)sulfonyl]amino}-3-phenylpropanoic acid ((*R*)-3). A solution of (*R*)-**2**[27] (2.42 g, 6.91 mmol) in EtOH (50 mL) and 10% Pd/C (200 mg) were introduced into a Parr shaker apparatus, and maintained under a hydrogen pressure of 60 p.s.i for 5 h at room temperature. Palladium was filtered off and the solvent was removed to afford after recrystallization from EtOH–H_2O (*R*)-**3** (2.17 g, 98%) as a yellowish solid, mp 189–190 °C.

(2*S*)-2-{[(4-Aminophenyl)sulfonyl]amino}-3-phenylpropanoic acid ((*S*)-3). A solution of (*S*)-**2**[27] (2.75 g, 7.84 mmol) in EtOH (50 mL) and 10% Pd/C (225 mg) were introduced into a Parr shaker apparatus, and maintained under a hydrogen pressure of 60 p.s.i. for 5 h at room temperature. Palladium was filtered off and the solvent was removed to afford after recrystallization from EtOH–H_2O (*S*)-**3** (2.49 g, 99%) as a yellowish solid, mp 189–190 °C.

2-{[(4-Azidophenyl)sulfonyl]amino}-3-phenylpropanoic acid (4). Compound **3** (1.45 g, 4.53 mmol) was suspended in anhydrous CH_3CN (30 mL) under argon and cooled to 0 °C in an ice bath. To this suspension was added *t*-BuONO (0.80 mL, 5.45 mmol), followed by $TMSN_3$ (0.72 mL, 5.42 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 min, and at room temperature for 6 h. Then, it was evaporated to dryness, and the residue was purified by column chromatography on silica gel (DCM–MeOH 5% MeOH) to afford **4** (1.4 g, 89%) as a yellowish solid, mp 197.0–198.4 °C. (Found: C, 52.11; H, 4.08; N, 15.87; S, 9.20. $C_{15}H_{14}N_4O_4S$ requires C, 52.02; H, 4.07; N, 16.18; S, 9.26%); ν_{max} (KBr)/cm^{-1} 3276, 2118, 2095, 1719; δ_H (300 MHz, DMSO-d$_6$) 2.71 (1H, dd, J 13.4, 9.2, $\frac{1}{2}$CH$_2$Ar), 2.94 (1H, dd, J 13.4, 5.5, $\frac{1}{2}$CH$_2$Ar), 3.82–3.89 (1H, m, CH), 7.11–7.21 (7H, m, ArH), 7.56 (2H, d, J 8.6, ArH), 8.34 (1H, d, J 9.2, SO$_2$NH), 12.78 (1H, bs, COOH); δ_C (75.4 MHz, DMSO-d$_6$) 37.8, 57.5, 119.4, 126.5, 128.2, 128.3, 129.2, 136.8, 137.3, 143.3, 172.4. EM (ESI+) m/z 328.06 $[M - H_2O]^+$ 369.01 $[M + Na]^+$.

(2*R*)-2-{[(4-Azidophenyl)sulfonyl]amino}-3-phenylpropanoic acid ((*R*)-4). Compound (*R*)-**3** (2.14 g, 6.68 mmol) was suspended into anhydrous CH_3CN (50 mL) under argon and cooled to 0 °C in an ice bath. To this suspension was added *t*-BuONO (1.19 mL, 10.02 mmol), followed by $TMSN_3$ (1.05 mL, 8.02 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 min, and at room temperature for 3 h. Then, it was evaporated to dryness, and the residue was purified by column chromatography on silica gel (DCM–MeOH 2.5% MeOH) to afford (*R*)-**4** (2.16 g, 93%) as a yellowish solid, mp 127–128 °C.

(2*S*)-2-{[(4-Azidophenyl)sulfonyl]amino}-3-phenylpropanoic acid ((*S*)-4). Compound (*S*)-**3** (2.48 g, 7.73 mmol) was suspended in anhydrous CH_3CN (50 mL) under argon and cooled to 0 °C in an ice bath. To this suspension was added *t*-BuONO (1.38 mL, 11.60 mmol), followed by $TMSN_3$ (1.22 mL, 9.28 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 min, and at room temperature for 3 h. Then, it was evaporated to dryness, and the residue was purified by column chromatography on silica gel (DCM–MeOH 2.5% MeOH) to afford (*S*)-**4** (2.25 g, 84%) as a yellowish solid, mp 127–128 °C.

2-{[(4-Azidophenyl)sulfonyl]amino}-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (5). To a solution of **4** (1.3 g, 3.75 mmol) in DMF (30 mL) were added HOBt (1.11 g,

8.25 mmol), *O*-tetrahydro-2*H*-pyran-2-yl-hydroxylamine (0.88 g, 7.50 mmol), EDCI (1.72 g, 9 mmol) and NMM (1.5 mL, 15 mmol). The reaction mixture was stirred overnight at room temperature and then diluted with EtOAc (50 mL) and washed successively with a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried ($MgSO_4$), and evaporated to dryness, and the residue was purified by column chromatography on silica gel (hexane–AcOEt 7 : 3) to afford **5** (1.14 g, 68%) as a yellow solid. This compound is present as a diastereoisomeric mixture (55 : 45), mp 142–144 °C. (Found: C, 53.81; H, 5.14; N, 15.37; S, 7.18. $C_{20}H_{23}N_5O_5S$ requires C, 53.92; H, 5.20; N, 15.72; S, 7.20%); ν_{max} (KBr)/cm^{-1} 3213, 2130, 2097, 1673; δ_H (300 MHz, $CDCl_3$) 1.45–1.65 (4H, m, CH_2), 1.68–1.82 (2H, m, CH_2), 2.87–3.05 (2H, m, CH_2Ph), 3.54–3.58 (1H, m, CHN), 3.81–3.92 (2H, m, OCH_2), 4.72 (0.45H, m, O–CH–O, isomer b), 4.77 (0.55H, m, O–CH–O, isomer a), 5.47, (0.55H, d, *J* 7.8, $\frac{1}{2}SO_2NH$, isomer a), 5.52 (0.45H, d, *J* 7.8, $\frac{1}{2}SO_2NH$, isomer b), 6.96–7.02 (5H, m, ArH), 7.18–7.21 (2H, m, ArH), 7.59 (2H, d, *J* 8.4, ArH), 9.05 (1H, s, CONH, isomer a), 9.17 (1H, s, CONH, isomer b); δ_C (75.4 MHz, $CDCl_3$): 18.4, 18.6, 24.9, 27.9, 38.6, 39.0, 56.6, 62.5, 62.7, 102.5, 119.5, 127.4, 128.9, 129.0, 129.3, 134.9, 135.2, 145.0, 167.5. EM (ESI+) *m*/*z* 468.00 $[M + Na]^+$.

(2*R*)-2-{[(4-Azidophenyl)sulfonyl]amino}-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide ((*R*)-5). To a solution of (*R*)-**4** (0.5 g, 1.44 mmol) in DMF (5 mL) were added HOBt (234 mg, 1.73 mmol), *O*-tetrahydro-2*H*-pyran-2-yl-hydroxylamine (338 mg, 2.89 mmol), EDCI (387 mg, 2.02 mmol) and NMM (0.48 mL, 4.33 mmol). The reaction mixture was stirred overnight at room temperature and then diluted with EtOAc (50 mL) and washed successively with a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried ($MgSO_4$), and evaporated to dryness, and the residue was purified by column chromatography on silica gel (hexane–AcOEt 3 : 2) to afford (*R*)-**5** (594 mg, 92%) as a yellow solid. This compound is present as a diastereoisomeric mixture (55 : 45), mp 137–138 °C.

(2*S*)-2-{[(4-Azidophenyl)sulfonyl]amino}-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide ((*S*)-5). To a solution of (*S*)-**4** (0.5 g, 1.44 mmol) in DMF (5 mL) were added HOBt (234 mg, 1.73 mmol), *O*-tetrahydro-2*H*-pyran-2-yl-hydroxylamine (338 mg, 2.89 mmol), EDCI (387 mg, 2.02 mmol) and NMM (0.48 mL, 4.33 mmol). The reaction mixture was stirred overnight at room temperature and then diluted with EtOAc (50 mL) and washed successively with a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried ($MgSO_4$), evaporated to dryness, and the residue was purified by column chromatography on silica gel (hexane–AcOEt 3 : 2) to afford (*S*)-**5** (589 mg, 92%) as a yellow solid. This compound is present as a diastereoisomeric mixture (55 : 45), mp 137–138 °C.

Preparation of triazoles: general procedure 1

To a suspension of azide **5** (1 equiv.) and the corresponding alkyne (1–1.5 equiv.) in *t*-BuOH–H_2O (1 : 1) or DMF were added sodium ascorbate (2 equiv. of freshly prepared 1 M solution in water) and copper(II) sulfate pentahydrate (0.5 equiv. of a 0.25 M solution in water) under argon. The mixture was stirred vigorously overnight, and then diluted with water (20 mL) and extracted with AcOEt. The organic layer was washed successively with saturated aqueous NH_4Cl and brine. The extract was dried ($MgSO_4$), filtered and evaporated to dryness, and the residue was chromatographed on silica gel.

2-[({4-{4-[(3-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonylamino]-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)-propanamide (6a). From **5** (100 mg, 0.224 mmol), 1-ethynyl-3-fluorobenzene (44 mg, 0.247 mmol), sodium ascorbate (448 μL, 0.448 mmol) and copper(II) sulfate pentahydrate (448 μL, 0.112 mmol) in DMF (3 mL), **6a** (84.8 mg, 67%) was produced as a light yellow solid after chromatography purification (hexane–AcOEt 1 : 1 + 2% MeOH), mp 146–147 °C. (Found: C, 59.06; H, 5.08; N, 12.27; S 5.70. $C_{28}H_{28}FN_5O_5S$ requires C, 59.46; H, 4.99; N, 12.38; S, 5.67%); ν_{max} (KBr)/cm^{-1} 3203, 1665, 1620; δ_H (300 MHz, DMSO-d_6) 1.43–1.59 (6H, m, $3CH_2$), 2.66–2.73 (1H, m, $\frac{1}{2}CH_2Ph$), 2.79–2.89 (1H, m, $\frac{1}{2}CH_2Ph$), 3.38–3.49 (1H, m, CHN), 3.76–3.85 (1H, m, OCH_2, isomer a), 3.93–3.98 (1H, m, OCH_2, isomer b), 4.39 (0.5H, s, O–CH–O, isomer a), 4.57 (0.5H, s, O–CH–O, isomer b), 7.11–7.29 (6H, m, ArH), 7.55–7.62 (1H, m, ArH), 7.76–7.84 (4H, m, ArH), 8.02 (2H, dd, *J* 8.7, 1.4, ArH), 8.54 (1H, bs, SO_2NH), 9.51 (1H, s, triazole), 11.25 (0.5H, bs, CONH, isomer a) 11.32 (0.5H, bs, CONH, isomer b); δ_C (75.4 MHz, DMSO-d_6): 18.2, 24.5, 27.7, 38.5, 55.2, 61.3 (61.4 b), 101.0, 112.0 (d, $^2J_{CF}$ 22.5), 115.17 (d, $^2J_{CF}$ 21.0), 119.9, 120.9 (d, $^2J_{CF}$ 74.2), 126.4, 128.0, 128.1, 129.2 (129.3 b), 131.3 (d, $^3J_{CF}$ 9.0), 132.31 (d, $^3J_{CF}$ 9.0), 136.5, 136.8, 138.6, 140.9, 146.4, 162.6 (d, $^1J_{CF}$ 241.5), 166.6 (166.7 b). EM (ESI+): *m*/*z* 588.26 $[M + Na]^+$.

2-{[(4-{4-[(Biphenyl-4-yl)]-1*H*-1,2,3-triazol-1-yl}phenyl)sulfonyl]-amino}-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (6b). From **5** (100 mg, 0.224 mmol), 4-ethynylbiphenyl (44 mg, 0.247 mmol), sodium ascorbate (448 μL, 0.448 mmol) and copper(II) sulfate pentahydrate (448 μL, 0.112 mmol) in DMF (3 mL), **6b** (89 mg, 64%) was produced as a yellow solid after chromatography purification (DCM–MeOH 0.6% MeOH), mp 189–191 °C. (Found: C, 64.74; H, 5.45; N, 11.13; S, 5.13. $C_{34}H_{33}N_5O_5S{\cdot}0.5H_2O$ requires C, 64.54; H, 5.42; N, 11.07; S, 5.07%); ν_{max} (KBr)/cm^{-1} 3284, 1668; δ_H (300 MHz, $CDCl_3$) 1.44–1.56 (6H, m, $3CH_2$), 2.67–2.74 (1H, m, $\frac{1}{2}CH_2Ph$), 2.80–2.86 (1H, m, $\frac{1}{2}CH_2Ph$), 3.39–3.49 (1H, m, CHN), 3.75–3.85 (1H, m, OCH_2, isomer a), 3.86–3.97 (1H, m, OCH_2, isomer b), 4.38 (0.5H, s, O–CH–O, isomer a), 4.57 (0.5H, s, O–CH–O, isomer b), 7.11–7.22 (5H, m, ArH), 7.37–7.42 (1H, m, ArH), 7.48–7.53 (2H, m, ArH), 7.76 (2H, d, *J* 7.3, ArH), 7.80–7.86 (4H, m, ArH), 8.04–8.09 (4H, m, ArH), 8.53 (1H, m, SO_2NH), 9.5 (1H, s, triazole), 11.25 (0.5H, s, CONH, isomer b), 11.33 (0.5H, s, CONH, isomer a); δ_C (75.4 MHz, $CDCl_3$): 18.1, 24.4, 27.6, 38.6, 55.1, 61.3, 101.0, 119.6, 119.7, 125.8, 126.3, 126.5, 127.21, 127.6, 127.9, 128.1, 128.9, 129.1, 136.5, 136.7, 138.6, 139.3, 139.9, 140.8, 147.2, 166.5. EM (ESI+) *m*/*z* 646.26 $[M + Na]^+$.

(2*R*)-2-{[(4-{4-[(Biphenyl-4-yl)]-1*H*-1,2,3-triazol-1-yl}phenyl)-sulfonyl]amino}-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide ((*R*)-6b). From (*R*)-**5** (150 mg, 0.337 mmol), 4-ethynyl-

biphenyl (90 mg, 0.505 mmol), sodium ascorbate (673 μL, 0.673 mmol) and copper(II) sulfate pentahydrate (673 μL, 0.168 mmol) in *t*-BuOH–H_2O (1 : 1, 5 mL), (*R*)-**6b** (68 mg, 32%) was produced as a white solid after chromatography purification (DCM–MeOH 0.6% MeOH), mp 199–200 °C (hexane–EtOAc).

(2*S*)-2-{[(4-{4-[(Biphenyl-4-yl)]-1*H*-1,2,3-triazol-1-yl}phenyl)sulfonyl]amino}-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide ((*S*)-6b). From (*S*)-**5** (150 mg, 0.337 mmol), 4-ethynylbiphenyl (90 mg, 0.505 mmol), sodium ascorbate (673 μL, 0.673 mmol) and copper(II) sulfate pentahydrate (673 μL, 0.168 mmol) in *t*-BuOH–H_2O (1 : 1, 5 mL), (*S*)-**6b** (105 mg, 50%) was produced as a white solid after chromatography purification (DCM–MeOH 0.6% MeOH), mp 199–200 °C (hexane–EtOAc).

2-{[(4-{4-[(4-Dimethylamino)phenyl]-1*H*-[1,2,3]-triazol-1-yl}-phenyl)sulfonyl]amino}-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (6c). From **5** (100 mg, 0.224 mmol), 4-ethynyl-*N*,*N*-dimethylaniline (36 mg, 0.248 mmol), sodium ascorbate (448 μL, 0.448 mmol) and copper(II) sulfate pentahydrate (448 μL, 0.112 mmol) in DMF (3 mL), **6c** (71.6 mg, 54%) was produced as a yellow solid after chromatography purification (DCM–MeOH 0.75% MeOH), mp 192–194 °C. (Found: C, 59.92; H, 5.91; N, 13.96; S, 5.27. $C_{30}H_{34}N_6O_5S{\cdot}0.5H_2O$ requires: C, 60.08; H, 5.88; N, 14.01; S, 5.35%); ν_{max} (KBr)/cm^{-1} 3276, 1668, 1616. δ_H (300 MHz, DMSO-d_6) 1.43–1.58 (6H, m, $3CH_2$), 2.65–2.73 (1H, m, $\frac{1}{2}CH_2Ph$), 2.79–2.85 (1H, m, $\frac{1}{2}CH_2Ph$), 2.96 (6H, s, $2CH_3$), 3.38–3.49 (1H, m, CH), 3.75–3.85 (1H, m, OCH_2, isomer a), 3.85–3.95 (1H, m, OCH_2, isomer b), 4.36 (0.5H, s, O–CH–O, isomer a), 4.56 (0.5H, s, O–CH–O, isomer b), 6.84 (2H, d, *J* 8.9, ArH), 7.1–7.2 (5H, m, Ar), 7.76–7.81 (4H, m, Ar), 8.02 (2H, d, *J* 8.6, ArH), 8.53 (1H, bs, SO_2NH), 9.2 (1H, s, triazole), 11.23 (0.5H, s, CONH, isomer b), 11.32 (0.5H, s, CONH, isomer a); δ_C (75.4 MHz, DMSO-d_6): 18.1, 24.4, 27.6, 37.2, 39.8, 55.1, 61.3, 100.9, 112.2, 117.3, 117.4, 119.4, 126.2, 127.9, 128.0, 129.1, 136.5, 136.7, 138.7, 140.3, 148.2, 150.2, 166.5. EM (ESI+) *m*/*z* 613.30 $[M + Na]^+$.

(2*R*)-2-{[(4-{4-[(4-Dimethylamino)phenyl]-1*H*-[1,2,3]-triazol-1-yl}phenyl)sulfonyl]amino}-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide ((*R*)-6c). From (*R*)-**5** (150 mg, 0.337 mmol), 4-ethynyl-*N*,*N*-dimethylaniline (73 mg, 0.505 mmol), sodium ascorbate (673 μL, 0.673 mmol) and copper(II) sulfate pentahydrate (673 μL, 0.168 mmol) in *t*-BuOH–H_2O (1 : 1, 5 mL), (*R*)-**6c** (130 mg, 65%) was produced as a yellow solid after chromatography purification (DCM–MeOH 0.75% MeOH), mp 203–204 °C (hexane–EtOAc).

(2*S*)-2-{[(4-{4-[(4-Dimethylamino)phenyl]-1*H*-[1,2,3]-triazol-1-yl}phenyl)sulfonyl]amino}-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide ((*S*)-6c). From (*S*)-**5** (150 mg, 0.337 mmol), 4-ethynyl-*N*,*N*-dimethylaniline (73 mg, 0.505 mmol), sodium ascorbate (673 μL, 0.673 mmol) and copper(II) sulfate pentahydrate (673 μL, 0.168 mmol) in *t*-BuOH–H_2O (1 : 1, 5 mL), (*S*)-**6c** (130 mg, 65%) was produced as a yellow solid after chromatography purification (DCM–MeOH 0.75% MeOH), mp 203–204 °C (hexane–EtOAc).

3-Phenyl-2-[({4-[4-({[(phenylsulfonyl)amino]carbonyl}aminomethyl)-1*H*-1,2,3-triazol-1-yl]-phenyl}sulfonyl)amino]-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (6d). From **5** (100 mg, 0.224 mmol), *N*-[(prop-2-yn-1-yl-amino)carbonyl)]benzenesulfonamide[23] (58.5 mg, 0.247 mmol), sodium ascorbate (448 μL, 0.448 mmol) and copper(II) sulfate pentahydrate (448 μL, 0.112 mmol) in DMF (3 mL), **6d** (87.6 mg, 60%) was produced as a beige solid after chromatography purification (DCM–MeOH, 5% MeOH), mp 165–167 °C. (Found: C, 52.64; H, 4.96; N, 14.10; S, 9.15. $C_{30}H_{33}N_7O_8S_2$ requires: C, 52.70; H, 4.86; N, 14.34; S, 9.38) ν_{max} (KBr)/cm^{-1} 3343, 3284, 1694, 1675 cm^{-1}. δ_H (300 MHz, DMSO-d_6) 1.35–1.58 (6H, m, $3CH_2$), 2.64–2.73 (1H, m, $\frac{1}{2}CH_2Ph$), 2.78–2.84 (1H, m, $\frac{1}{2}CH_2Ph$), 3.37–3.45 (2H, m, OCH_2), 3.75–3.80 (0.5H, m, CHN, isomer a), 3.89–3.94 (0.5H, m, CHN, isomer b), 4.31 (2H, s, $NHCH_2$), 4.33 (0.5H, s, O–CH–O, isomer a), 4.55 (0.5H, s, O–CH–O, isomer b), 7.09–7.2 (7H, m, ArH + NHCONH), 7.54–7.63 (3H, m, Ar), 7.73–7.76 (2H, m, ArH), 7.89–7.93 (4H, m, ArH), 8.47–8.54 (1H, m, SO_2NH), 8.61 (1H, s, triazole), 11.23 (0.5H, s, CONH, isomer b), 11.31 (0.5H, s, CONH, isomer a); δ_C (75.4 MHz, DMSO-d_6) 18.0, 24.4, 27.5, 34.6, 37.2, 55.1 (55.2 b), 61.3, 100.9 (101.1 b), 119.8, 120.9, 126.2, 127.08, 127.9 (127.9 b), 128.8, 129.1 (129.1 b), 133.0, 136.4, 136.7, 138.5, 140.2, 140.7, 145.9, 151.4, 166.6. MS (ESI−) *m*/*z* 682.30 $[M - H]^-$.

2-[({4-[4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (6e). From **5** (100 mg, 0.224 mmol), 4-ethynylanisole (33 mg, 0.25 mmol), sodium ascorbate (448 μL, 0.448 mmol) and copper(II) sulfate pentahydrate (448 μL, 0.112 mmol) in DMF (3 mL), **6e** (98.8 mg, 76%) was produced as a yellow solid after chromatography purification (DCM–MeOH, 5% MeOH), mp 151–153 °C. (Found: C, 59.94; H, 5.46; N, 12.04; S, 5.54; $C_{29}H_{31}N_5O_6S$ requires: C, 60.3; H, 5.41; N, 12.12; S, 5.55%); ν_{max} (KBr)/cm^{-1} 3202, 1668, 1620. δ_H (300 MHz, DMSO-d_6) 1.43–1.58 (6H, m, $3CH_2$), 2.66–2.73 (1H, m, $\frac{1}{2}CH_2Ph$), 2.79–2.85 (1H, m, $\frac{1}{2}CH_2Ph$), 3.35–3.48 (1H, m, CH), 3.76–3.85 (1H, m, OCH_2, isomer a), 3.82 (3H, s, OCH_3), 3.87–3.95 (1H, m, OCH_2, isomer b), 4.37 (0.5H, s, O–CH–O, isomer a), 4.56 (0.5H, s, O–CH–O, isomer b), 6.84 (2H, d, *J* 8.9, ArH), 7.1–7.2 (7H, m, ArH), 7.78–7.81 (2H, dd, *J* 8.7, 2.3, ArH), 7.89 (2H, d, *J* 8.7, ArH), 8.00–8.04 (2H, dd, *J* 8.7, 1.5, ArH), 8.44 (1H, bs, SO_2NH), 9.32 (1H, s, triazole), 11.24 (0.5H, s, CONH, isomer b), 11.32 (0.5H, s, CONH, isomer a); δ_C (75.4 MHz, DMSO-d_6): 18.1, 24.4, 27.5, 38.5, 55.1, 55.2, 61.3, 100.9 (101.1 b), 114.4, 119.6, 122.3, 126.3, 126.7, 127.9, 128.0, 129.1 (129.2 b), 136.5, 136.7, 138.7, 140.6, 147.5, 159.3, 166.5 (166.6 b). MS (ESI+): *m*/*z* 600.27 $[M + Na]^+$.

2-[({4-[4-(4-Phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (6f). From **5** (100 mg, 0.224 mmol), 1-ethynyl-4-phenoxybenzene (48 mg, 0.247 mmol), sodium ascorbate (448 μL, 0.448 mmol) and copper(II) sulfate pentahydrate (448 μL, 0.112 mmol) in DMF (3 mL), **6f** (115 mg, 80%) was produced as a pale yellow solid after chromatography purification (hexane–AcOEt 1 : 1 + 2% MeOH), mp 189–190 °C. (Found: C, 63.70; H, 5.26; N, 10.87; S, 4.95; $C_{34}H_{33}N_5O_6S$

requires: C, 63.83; H, 5.20; N, 10.95; S, 5.01%); ν_{max} (KBr)/cm^{-1} 3166, 1657. δ_H (300 MHz, DMSO-d$_6$): 1.43–1.58 (6H, m, 3CH$_2$), 2.66–2.73 (1H, m, $\frac{1}{2}$CH$_2$Ph), 2.79–2.86 (1H, m, $\frac{1}{2}$CH$_2$Ph), 3.42–3.49 (1H, m, CH), 3.76–3.85 (1H, m, OCH$_2$, isomer a), 3.93–3.98 (1H, m, OCH$_2$, isomer b), 4.38 (0.5H, s, O–CH–O, isomer a), 4.57 (0.5H, s, O–CH–O, isomer b), 7.08–7.21 (10H, m, ArH), 7.41–7.46 (2H, m, ArH), 7.78–7.82 (2H, dd, *J* 8.6, 2,1, ArH), 7.89 (2H, d, *J* 8.6, ArH), 8.03 (2H, d, *J* 7.4, ArH), 8.5 (1H, bs, SO$_2$NH), 9.39 (1H, s, triazole), 11.32 (1H, bs, CONH); δ_C (75.4 MHz, DMSO-d$_6$) 18.2, 24.5, 27.6, 38.5, 55.2, 61.4, 101.1, 118.93, (118.98 b), 119.2, 119.7, 123.7, 125.1, 126.4, 127.2, 128.0, 128.15, 129.2 (129.3 b), 130.1, 136.5, 136.8, 138.7, 140.7, 147.1, 156.3, 156.9, 166.5 (166.7 b). MS (ESI+): *m*/*z* 662.26 [M + Na]$^+$.

(2*R*)-2-[({4-[4-(4-Phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide ((*R*)-6f). From (*R*)-**5** (150 mg, 0.337 mmol), 1-ethynyl-4-phenoxybenzene (98 mg, 0.505 mmol), sodium ascorbate (673 μL, 0.673 mmol) and copper(II) sulfate pentahydrate (673 μL, 0.168 mmol) in *t*-BuOH–H$_2$O (1 : 1, 5 mL), (*R*)-**6f** (170 mg, 79%) was produced as a white solid after chromatography purification (DCM–MeOH 0.6% MeOH), mp 169–170 °C (hexane–EtOAc).

(2*S*)-2-[({4-[4-(4-Phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide ((*S*)-6f). From (*S*)-**5** (150 mg, 0.337 mmol), 1-ethynyl-4-phenoxybenzene (98 mg, 0.505 mmol), sodium ascorbate (673 μL, 0.673 mmol) and copper(II) sulfate pentahydrate (673 μL, 0.168 mmol) in *t*-BuOH–H$_2$O (1 : 1, 5 mL), (*S*)-**6f** (175 mg, 81%) was produced as a white solid after chromatography purification (DCM–MeOH 0.6% MeOH), mp 169–170 °C (hexane–EtOAc).

2-[({4-[4-(4-Pentylphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (6g). From **5** (100 mg, 0.224 mmol), 1-ethynyl-4-pentylbenzene (42.5 mg, 0.247 mmol), sodium ascorbate (448 μL, 0.448 mmol) and copper(II) sulfate pentahydrate (448 μL, 0.112 mmol) in DMF (3 mL), **6g** (107 mg, 77%) was produced as a pale yellow solid after chromatography purification (hexane–AcOEt 1 : 1 + 2% MeOH), mp 189–190 °C. (Found: C, 63.72; H, 6.43; N, 11.32; S, 5.17; C$_{33}$H$_{39}$N$_5$O$_5$S requires: C, 64.16; H, 6.36; N, 11.34; S, 5.19; ν_{max} (KBr)/cm^{-1} 3291, 1690. δ_H (300 MHz, DMSO-d$_6$) 0.87 (3H, t, *J* 6.8, CH$_3$), 1.30–1.63 (12H, m, 6CH$_2$), 2.62–2.73 (3H, t, *J* 7.6, CH$_2$Ar + m, $\frac{1}{2}$CH$_2$Ph), 2.79–2.89 (1H, m, $\frac{1}{2}$CH$_2$Ph), 3.42–3.49 (1H, m, CH), 3.78–3.85 (1H, m, OCH$_2$, isomer a), 3.92–3.99 (1H, m, OCH$_2$, isomer b), 4.37 (0.5H, s, O–CH–O, isomer a), 4.57 (0.5H, s, O–CH–O, isomer b), 7.01–7.21 (5H, m, ArH), 7.34 (2H, d, *J* 8.1, ArH), 7.80 (2H, dd, *J* 8.7, 2.1, ArH), 7.87 (2H, d, *J* 8.0, ArH), 8.03 (2H, dd, *J* 8.6, 1.6, ArH), 8.52 (1H, bs, SO$_2$NH), 9.38 (1H, s, triazole), 11.24 (0.5H, bs, CONH isomer a), 11.32 (0.5H, bs, CONH, isomer b); δ_C (75.4 MHz, DMSO-d$_6$) 13.9, 18.2, 21.9, 24.5, 27.7, 30.5, 30.8, 34.8, 38.5, 55.3, 61.4, 101.0, 119.1 (119.7 b), 125.3, 126.4, 127.4, 128.04, 128.1, 128.9, 129.2 (129.3 b), 136.5, 136.8, 138.7, 140.79, 142.7, 147.7, 166.5 (166.7 b). MS (ESI+): *m*/*z* 640.33 [M + Na]$^+$.

Cleavage of the tetrahydropyrane protecting group: general procedure 2

To a suspension of the corresponding tetrahydro-2*H*-pyranyl derivative in DCM (5 mL) were added 4 M HCl in dioxane (4 equivalents) and MeOH (0.1 mL). After stirring at room temperature for 1 h the reaction mixture was concentrated under vacuum and the obtained solid was washed with DCM–hexane 1 : 1.

2-[({4-[4-(3-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-*N*-hydroxy-3-phenylpropanamide (1a). From **6a** (111 mg, 0.178 mmol), MeOH (0.18 mL) and 4 M HCl–dioxane (0.18 mL, 0.72 mmol), **1a** was produced as a light beige solid (73.2 mg, 76%), mp 210 °C (dec.). (Found: C, 56.67; H, 4.22; N, 14.35; S, 6.54. C$_{23}$H$_{20}$FN$_5$O$_4$S requires: C, 57.37; H, 4.19; N, 14.54; S, 6.66; ν_{max} (KBr)/cm^{-1} 3313, 1675, 1620; δ_H (300 MHz, DMSO-d$_6$) 2.68 (1H, dd, *J* 13.5, 9.1, $\frac{1}{2}$CH$_2$Ph), 2.83 (1H, dd, *J* 13.5, 5.8, $\frac{1}{2}$CH$_2$Ph), 3.84–3.92 (1H, m, CH), 7.09–7.16 (5H, m, ArH), 7.25 (1H, dt, *J* 8.5, 2.1, ArH), 7.54–7.61 (1H, m, ArH), 7.77 (2H, d, *J* 8.7, ArH), 7.83 (1H, d, *J* 7.7, ArH), 7.99 (2H, d, *J* 8.7, ArH), 8.43 (1H, d, *J* 8.9, SO$_2$NH), 8.87 (1H, bs, CONHO*H*), 9.47 (1H, s, CH, triazole), 10.67 (1H, s, CON*H*OH); δ_C (75.4 MHz, DMSO-d$_6$) 38.4, 55.5, 111.8–112.1 (d, $^2J_{CF}$ 22.5), 114.9–115.2 (d, $^2J_{CF}$ 21.0), 119.85, 120.8 (d, $^2J_{CF}$ 74.2), 126.2, 127.9, 129.1, 131.15 (d, $^3J_{CF}$ 9.0), 132.26 (d, $^3J_{CF}$ 9.0), 136.8, 138.4, 141.0, 146.4, 162.5 (d, *J* 241.5, Ar–F), 166.6. MS (ESI): *m*/*z* 504.20 [M + Na]$^+$.

2-[({4-[4-(Biphenyl-4-yl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-*N*-hydroxy-3-phenyl-propanamide (1b). From **6b** (83.8 mg, 0.147 mmol), MeOH (0.14 mL) and 4 M HCl–dioxane (0.14 mL, 0.56 mmol), **1b** was produced as a light yellow solid (54.0 mg, 75%), mp 182–183 °C (Found: C, 62.81; H, 4.72; N, 12.63; S, 5.57. C$_{29}$H$_{25}$N$_5$O$_4$S·H$_2$O requires: C, 62.46; H, 4.88; N, 12.56; S, 5.75%). ν_{max} (KBr)/cm^{-1} 3557, 3284, 1683, 1668. δ_H (300 MHz, DMSO-d$_6$): 2.69 (1H, dd, *J* 13.5, 9.1, $\frac{1}{2}$CH$_2$Ar), 2.84 (1H, dd, *J* 13.5, 5.8, $\frac{1}{2}$CH$_2$Ar), 3.84–3.93 (1H, m, CH), 7.10–7.16 (5H, m, ArH), 7.39 (1H, t, *J* 7.3, ArH), 7.48–7.52 (2H, m, ArH), 7.75–7.86 (6H, m, ArH), 8.02 (2H, d, *J* 8.6, ArH), 8.07 (2H, d, *J* 8.1, ArH), 8.43 (1H, d, *J* 8.9, SO$_2$NH), 8.86 (1H, bs, OH), 9.47 (s, 1H, CH, triazole), 10.68 (s, 1H, CONH); δ_C (75 MHz, DMSO-d$_6$) 38.4, 55.5, 119.6, 119.7, 125.8, 126.2, 126.5, 127.2, 127.5, 127.9, 127.9, 128.9, 128.9, 129.1, 136.8, 138.5, 139.4, 139.9, 140.8, 147.2, 166.6. MS (ESI+): *m*/*z* 562.27 [M + Na]$^+$.

(2*R*)-2-[({4-[4-(Biphenyl-4-yl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-*N*-hydroxy-3-phenyl-propanamide ((*R*)-1b). From (*R*)-**6b** (48 mg, 0.077 mmol), MeOH (1 mL) and 4 M HCl–dioxane (1 mL, 4 mmol), (*R*)-**1b** was produced as a white solid (34.1 mg, 82%), mp 240 °C (dec.) (EtOH) (Found: C, 63.91; H, 4.70; N, 12.93; S, 5.99. C$_{29}$H$_{25}$N$_5$O$_4$S·H$_2$O requires: C, 64.01; H, 4.72; N, 12.87; S, 5.89%). $[\alpha]_D^{25}$ − 8.3 (*c* 0.0012 g cm^{-3} in DMSO).

(2*S*)-2-[({4-[4-(Biphenyl-4-yl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-*N*-hydroxy-3-phenyl-propanamide ((*S*)-1b). From (*S*)-**6b** (78 mg, 0.125 mmol), MeOH (1 mL) and 4 M HCl–dioxane (3 mL, 12 mmol), (*S*)-**1b** was produced as a white solid (58 mg, 86%), mp 240 °C (dec.) (EtOH) (Found: C, 64.32; H, 4.68; N, 12.89; S, 5.92. C$_{29}$H$_{25}$N$_5$O$_4$S requires: C, 64.55;

H, 4.67; N, 12.98; S, 5.94%). $[\alpha]_D^{25}$ + 7.9 (*c* 0.007 g cm^{-3} in DMSO).

2-{[(4-{[4-(4-Dimethylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}-phenyl)sulfonyl]amino}-*N*-hydroxy-3-phenylpropanamide hydrochloride (1c). From **6c** (79.8 mg, 0.135 mmol), MeOH (0.14 mL) and 4 M HCl–dioxane (0.14 mL, 0.56 mmol), **1c** was produced as a light orange solid (62.9 mg, 92%), mp 223 °C (dec.) (Found: C, 54.71; H, 4.97; N, 15.40; S, 5.83; $C_{25}H_{26}N_6O_4S{\cdot}HCl{\cdot}1/3H_2O$ requires: C, 54.69; H, 5.08; N, 15.31; S, 5.84%); ν_{max} (KBr)/cm^{-1} 3431, 3188, 2428, 1679. δ_H (300 MHz, DMSO-d_6) 2.68 (1H, dd, *J* 13.5, 9.1, $\frac{1}{2}CH_2Ph$), 2.83 (1H, dd, *J* 13.5, 5.8, $\frac{1}{2}CH_2Ph$), 3.07 (6H, s, $2CH_3$) 3.84–3.92 (1H, m, CH), 7.09–7.16 (5H, m, ArH), 7.42 (1H, bs, ArH), 7.75 (2H, d, *J* 8.6, ArH), 7.95–8.01 (4H, m, ArH), 8.42 (1H, d, *J* 8.9, SO_2NH), 9.38 (1H, s, CH, triazole), 10.72 (1H, s, CONH); δ_C (75.4 MHz, DMSO-d_6) 38.4, 42.6, 55.5, 116.9, 118.9, 119.6, 126.2, 126.4, 127.9, 127.9, 129.1, 136.8, 138.5, 140.7, 147.1, 166.6. MS (ESI−): *m*/*z* 505.19 $[M - H]^-$.

(2*R*)-2-{[(4-{[4-(4-Dimethylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}phenyl)sulfonyl]amino}-*N*-hydroxy-3-phenylpropanamide hydrochloride ((*R*)-1c). From (*R*)-**6c** (74 mg, 0.125 mmol), MeOH (1 mL) and 4 M HCl–dioxane (3 mL, 12 mmol), (*R*)-**1c** was produced as a yellow solid (53.6 mg, 79%), mp 210 °C (dec.) (EtOH) (Found: C, 58.66; H, 5.20; N, 16.39; S, 6.26; $C_{25}H_{26}N_6O_4S{\cdot}1/3H_2O$ requires: C, 58.58; H, 5.24; N, 16.40; S, 6.26%). $[\alpha]_D^{25}$ – 0.81 (*c* 0.005 g cm^{-3} in DMSO).

(2*S*)-2-{[(4-{[4-(4-Dimethylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}phenyl)sulfonyl]amino}-*N*-hydroxy-3-phenylpropanamide hydrochloride ((*S*)-1c). From (*S*)-**6c** (80 mg, 0.135 mmol), MeOH (1 mL) and 4 M HCl–dioxane (3 mL, 12 mmol), (*S*)-**1c** was produced as a yellow solid (61.4 mg, 83%), mp 210 °C (dec.) (EtOH) (Found: C, 58.11; H, 5.11; N, 16.24; S, 6.18; $C_{25}H_{26}N_6O_4S{\cdot}1/2H_2O$ requires: C, 58.24; H, 5.28; N, 16.30; S, 6.22%). $[\alpha]_D^{25}$ + 0.99 (*c* 0.006 g cm^{-3} in DMSO).

***N*-Hydroxy-3-phenyl-2-{[(4-{4-[({[(phenylsulfonyl)amino]carbonyl}amino)methyl]-1*H*-1,2,3-triazol-1-yl}phenyl)sulfonyl]-amino}propanamide (1d).** From **6d** (117 mg, 0.17 mmol), MeOH (0.17 mL) and 4 M HCl–dioxane (0.17 mL, 0.68 mmol), **1d** was produced as a white solid (93 mg, 90%), mp 179–180 °C (Found: C, 49.53; H, 4.25; N, 16.08; S, 10.52. $C_{25}H_{25}N_7O_7S_2{\cdot}1/3H_2O$ requires: C, 49.58; H, 4.27; N, 16.19; S, 10.59%); ν_{max} (KBr)/cm^{-1} 3579, 1690, 1642. δ_H (300 MHz, DMSO-d_6) 2.66 (1H, dd, *J* 13.6, 9.1, $\frac{1}{2}CH_2Ph$), 2.81 (1H, dd, *J* 13.6, 5,9, $\frac{1}{2}CH_2Ph$), 3.81–3.89 (1H, m, CH), 4.33 (2H, d, *J* 5.5, C*H*$_2$NHCO), 7.04–7.16 (7H, m, NHCONH + ArH), 7.56–7.72 (5H, m, ArH), 7.88–7.93 (4H, m, ArH), 8.41 (1H, d, *J* 8.9, SO_2NH), 8.59 (1H, s, CH, triazole), 10.65 (1H, s, CON*H*OH), 10.79 (1H, s, CONHO*H*); δ_C (75.4 MHz, DMSO-d_6) 34.6, 38.3, 55.5, 119.8, 121.0, 126.20, 127.1, 127.8, 127.9, 128.9, 129.0, 133.1, 136.7, 138.4, 140.0, 140.7, 145.8, 151.3, 166.6. MS (ESI−) *m*/*z* 598.09 $[M - H]^-$.

***N*-Hydroxy-2-[({4-[4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-phenyl}sulfonyl)amino]-3-phenylpropanamide (1e).** From **6e** (112 mg, 0.194 mmol), MeOH (0.20 mL) and 4 M HCl–dioxane (0.20 mL, 0.80 mmol), **1e** was produced as a yellow solid (93 mg, 90%), mp 160 °C (dec.) (Found: C, 57.49; H, 4.70; N, 13.96; S, 6.35. $C_{24}H_{23}N_5O_5S{\cdot}1/3H_2O$ requires: C, 57.70; H, 4.78; N, 14.02; S, 6.42%); ν_{max} (KBr)/cm^{-1} 3571, 3298, 1668, 1635. δ_H (300 MHz, DMSO-d_6) 2.67(1H, dd, *J* 13.5, 9.0, $\frac{1}{2}CH_2Ph$), 2.83 (1H, dd, *J* 13.5, 5,6 $\frac{1}{2}CH_2Ph$), 3.82 (3H, s, OCH_3), 3.85–3.91 (1H, m, CH), 7.07–7.16 (8H, m, ArH), 7.75 (2H, d, *J* 8.7, ArH), 7.89 (2H, d, *J* 8.7, ArH), 7.98 (2H, d, *J* 8.7, ArH), 8.42 (1H, d, *J* 8.9, SO_2NH), 9.28 (s, 1H, CH, triazole), 10.67 (s, 1H, CON*H*OH); δ_C (75.4 MHz, DMSO-d_6) 38.4, 55.2, 55.6, 114.4, 118.6, 119.7, 122.5, 126.3, 126.8, 127.9, 128.0, 129.1, 136.8, 138.7, 140.8, 147.5, 159.4, 166.7. MS (ESI+) *m*/*z* 516.22 $[M + Na]^+$.

***N*-Hydroxy-2-{[(4-[4-(4-phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-phenyl)sulfonyl]amino}-3-phenylpropanamide (1f).** From **6f** (94 mg, 0.147 mmol), MeOH (0.15 mL) and 4 M HCl–dioxane (0.15 mL, 0.60 mmol), **1f** was produced as a pale yellow solid (64 mg, 78%), mp 229 °C (dec.) (Found: C, 61.59; H, 4.54; N, 12.32; S, 5.66; $C_{29}H_{25}N_5O_5S{\cdot}1/2H_2O$ requires: C, 61.69; H, 4.64; N, 12.40; S, 5.68%); ν_{max} (KBr)/cm^{-1} 3564, 3306, 1675. δ_H (300 MHz, DMSO-d_6) 2.67 (1H, dd, *J* 13.6, 9.0, $\frac{1}{2}CH_2Ph$), 2.82 (1H, dd, *J* 13.6, 5.8, $\frac{1}{2}CH_2Ph$), 3.83–3.91 (1H, m, CH), 7.08–7.21 (10H, m, ArH), 7.41–7.46 (2H, m, ArH), 7.76 (2H, d, *J* 8.7, ArH), 7.96–8.01 (4H, m, ArH), 8.42 (1H, d, *J* 8.9, SO_2NH), 8.85 (1H, s, CONHO*H*), 9.35 (s, 1H, CH, triazole), 10.66 (s, 1H, CON*H*OH); δ_C (75.4 MHz, DMSO-d_6) 38.4, 55.5, 118.8, 118.9, 119.1, 119.7, 123.6, 125.1, 126.2, 127.1, 127.9, 127.9, 129.1, 130.0, 136.8, 138.5, 140.8, 147.0, 156.2, 156.8, 166.6. MS (ESI−) *m*/*z* 554.27 $[M - H]^-$.

(2*R*)-*N*-Hydroxy-2-{[(4-[4-(4-phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl)sulfonyl]amino}-3-phenylpropanamide ((*R*)-1f). From (*R*)-**6f** (130 mg, 0.203 mmol), MeOH (1 mL) and 4 M HCl–dioxane (3 mL, 12 mmol), (*R*)-**1f** was produced as a white solid (87.5 mg, 78%), mp 199–200 °C (EtOH). (Found: C, 62.59; H, 4.52; N, 12.52; S, 5.68; $C_{29}H_{25}N_5O_5S$ requires: C, 62.69; H, 4.54; N, 12.60; S, 5.77%). $[\alpha]_D^{25}$ – 2.06 (*c* 0.004 g cm^{-3} in DMSO).

(2*S*)-*N*-Hydroxy-2-{[(4-[4-(4-phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl)sulfonyl]amino}-3-phenylpropanamide ((*S*)-1f). From (*S*)-**6f** (125 mg, 0.195 mmol), MeOH (1 mL) and 4 M HCl–dioxane (3 mL, 12 mmol), (*S*)-**1f** was produced as a white solid (100.9 mg, 93%), mp 199–200 °C (EtOH). (Found: C, 62.56; H, 4.51; N, 12.63; S, 5.75; $C_{29}H_{25}N_5O_5S$ requires: C, 62.69; H, 4.54; N, 12.60; S, 5.77%). $[\alpha]_D^{25}$ + 1.97 (*c* 0.010 g cm^{-3} in DMSO).

***N*-Hydroxy-2-[({4-[4-(4-pentylphenyl)-1*H*-1,2,3-triazol-1-yl]-phenyl}sulfonyl)amino]-3-phenylpropanamide (1g).** From **6g** (83.8 mg, 0.147 mmol), MeOH (0.15 mL) and 4 M HCl–dioxane (0.15 mL, 0.60 mmol), **1g** was produced as a yellow solid (54 mg, 75%), mp 196 °C (dec.) (Found: C, 68.11; H, 6.53; N, 14.12; S, 6.47; $C_{28}H_{31}N_5O_4S$ requires: C, 63.02; H, 5.86; N, 13.12; S, 6.01%); ν_{max} (KBr)/cm^{-1} 3549, 3291, 2450, 1664, 1635. δ_H (300 MHz, DMSO-d_6) 0.87 (3H, t, *J* 6.8, CH_3), 1.29–1.32 (4H, m, $2CH_2$), 1.59–1.63 (2H, m, CH_2), 2.60–2.71 (3H, t, *J* 7.6, ArC*H*$_2$CH$_2$ + m, $\frac{1}{2}CH_2$ Ph), 2.79–2.86 (1H, dd, *J* 13.66, 5.8, $\frac{1}{2}CH_2Ar$), 3.84–3.92 (1H, m, CH), 7.09–7.16 (5H, m, ArH), 7.33 (2H, d, *J* 8.1, ArH), 7.76 (2H, d, *J* 8.6, ArH), 7.87 (2H, d, *J* 8.0, ArH), 8.00 (2H, d, *J* 8.7, ArH), 8.42 (1H, d, *J* 8.9, SO_2NH), 9.35 (s, 1H, CH, triazole), 10.68 (s, 1H, CON*H*OH); δ_C (75.4 MHz, DMSO-d_6) 13.8, 21.9, 30.4, 30.8, 34.8, 38.4, 55.6, 119.2, 119.7,

125.4, 126.3, 127.4, 127.9, 128.0, 128.9, 129.1, 136.8, 138.6, 140.8, 142.7, 147.7, 166.7. MS (ESI+) m/z 556.31 $[M + Na]^+$.

Methyl 2-{[(4-iodophenyl)sulfonyl]amino}-3-phenylpropanoate (8). To a stirred mixture of the L-alanine methyl ester (1 g, 4.63 mmol) and NMM (1.3 mL, 11.6 mmol) in CH_2Cl_2 (5 mL) was slowly added a solution of 4-iodobenzenesulfonyl chloride (1.54 g, 5.1 mmol) in CH_2Cl_2 (5 mL) under a N_2 atmosphere, and the reaction mixture was stirred for 30 min at 0 °C and 24 h at RT. The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate, and the solution was washed with HCl aqueous solution and brine. The extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was crystallized from EtOH to obtain **8** as colorless crystals (1.89 g, 92%), mp 117–118 °C. (Found C, 43.15; H, 3.67; N, 3.38; S, 7.19; $C_{16}H_{16}INO_4S$ requires: C, 43.16; H, 3.62; N, 3.15; S, 7.20%). ν_{max} (KBr)/cm^{-1} 3291, 1731, 1569. δ_H (300 MHz, $CDCl_3$) 2.95–3.11 (2H, m, CH_2Ar), 3.56 (3H, s, CH_3), 4.15–4.23 (1H, m, CH), 5.18 (1H, d, J 9.2, SO_2NH), 7.04–7.07 (2H, m, ArH), 7.24–7.25 (3H, m, ArH), 7.41 (2H, d, J 8.7, ArH), 7.77 (2H, d, J 8.7, ArH); δ_C (75.4 MHz, $CDCl_3$) 39.2, 52.5, 56.7, 100.1, 127.3, 128.4, 128.6, 129.2, 134.7, 138.1, 139.1, 171.1. MS (ESI+) m/z 467.88 $[M + Na]^+$.

Methyl 3-phenyl-2-{[(4-trimethylsilanylethynyl)phenylsulfonyl]amino}propanoate (9). To a mixture of **8** (1 g, 2.24 mmol), triphenylphosphine (94 mg, 359 μmol), bis(triphenylphosphine)palladium(II) dichloride (120 mg, 170 μmol), and copper(I) iodide (20 mg, 110 μmol) in degassed acetonitrile–NEt_3 (5 mL/3.5 mL) was added (trimethylsilyl)acetylene (0.38 mL, 2.70 mmol) under a nitrogen atmosphere. The reaction mixture was refluxed for 20 h. After cooling to room temperature, methanol was added and the mixture was filtered over Celite and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane, and the solution was washed with an HCl aqueous solution. The extracts were dried using anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel with ethyl hexane–EtOAc (4 : 1) to give **9** (0.69 g, 74%) as a white solid, mp. 118–119 °C (DCM–hexane). (C, 60.74; H, 5.96; N, 3.50; S, 7.66; $C_{21}H_{25}NO_4SSi$ requires: C, 60.69; H, 6.06; N, 3.37; S, 7.72%). $]^+$. ν_{max} (KBr)/cm^{-1} 3239, 2154, 1745, 1587. δ_H (300 MHz, $CDCl_3$) 0.27 (9H, s, $(CH_3)_3Si$), 2.97–3.09 (2H, m, CH_2Ar), 3.52 (3H, s, OCH_3), 4.17–4.24 (1H, m, CH), 5.29 (1H, d, J 9.2, SO_2NH), 7.05–7.23 (2H, m, ArH), 7.24–7.26 (3H, m, ArH), 7.49 (2H, d, J 8.3 Hz, ArH), 7.66 (2H, d, J 8.3, ArH); δ_C (75.4 MHz, $CDCl_3$) −0.3, 39.1, 52.4, 56.6, 98.4, 102.9, 126.8, 127.2, 127.7, 129.3, 132.2, 134.7, 138.9, 171.0. MS (ESI+) m/z 438.10 $[M + Na]^+$.

2-{[(4-Ethynylphenyl)sulfonyl]amino}-3-phenylpropanoic acid (10). To a solution of **9** (0.25 g, 0.6 mmol) in dioxane (3 mL) was added KOH (1 M in water, 3 mL), and the mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The residue was diluted in water (50 mL), acidified to pH 3 with 20% solution of citric acid, and extracted with EtOAc (2 × 50 mL). The collected organic phase was washed with saturated solution of NH_4Cl (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 2 : 8, 1 : 9) to give **10** as a white solid (0.165 g, 83%), mp 136–137 °C. ν_{max} (KBr)/cm^{-1} 3335, 3261, 2108, 1705, 1590. δ_H (300 MHz, $CDCl_3$) 2.98 (1H, dd, J 13.9, 7.3, $\frac{1}{2}CH_2Ar$), 3.15 (1H, dd, J 13.9, 4.8, $\frac{1}{2}CH_2Ar$), 3.26 (1H, s, ArCCH), 4.19–4.27 (1H, m, CH), 5.28 (1H, d, J 8.3, SO_2NH), 7.08–7.09 (2H, m, ArH), 7.24–7.27 (3H, m, ArH), 7.48 (2H, d, J 8.3, ArH), 7.67 (2H, d, J 8.3, ArH); δ_C (75.4 MHz, $CDCl_3$) 38.7, 56.5, 80.8, 81.9, 126.8, 126.9, 127.4, 128.7, 129.3, 132.5, 134.5, 139.5, 176.0. MS (ESI+) m/z 352.04 $[M + Na]^+$.

2-{[(4-Ethynyl)phenyl]sulfonyl}amino-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (11). To a solution of **10** (0.15 g, 0.45 mmol) in DMF (5 mL) were added HOBt (0.135 g, 1 mmol), *O*-tetrahydro-2*H*-pyran-2-yl-hydroxylamine (0.107 g, 0.9 mmol), EDCI (0.2 g, 1.09 mmol) and NMM (0.15 mL, 1.37 mmol). The reaction mixture was stirred overnight at room temperature and then diluted with EtOAc (50 mL) and washed successively with a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried ($MgSO_4$), evaporated to dryness, and the residue was purified by column chromatography on silica gel (hexane–AcOEt 7 : 3) to afford **11** (0.135 g, 69%) as a white solid. This compound is present as a diastereoisomeric mixture (55 : 45), mp 148–149 °C. (C, 61.86; H, 5.69; N, 6.61; S, 7.34; $C_{22}H_{24}N_2O_5S$ requires: C, 61.67; H, 5.65; N, 6.54; S, 7.48%). ν_{max} (KBr)/cm^{-1} 3276, 3202, 2110, 1660. δ_H (300 MHz, $CDCl_3$) 1.57–1.77 (6H, m, 3 × CH_2), 2.88–3.07 (2H, m, CH_2Ar), 3.27 (1H, s, ArCCH), 3.55–3.59 (1H, m, CH), 3.80–3.89 (2H, m, CH_2O), 4.7 (0.55H, s, O–CH–O, isomer a), 4.79 (0.45H, s, O–CH–O, isomer b), 5.43 (1H, bs, SO_2NH), 6.99 (2H, d, J 7.32, ArH), 7.18–7.22 (3H, m, ArH), 7.48 (2H dd, J 8.3, 2.8, ArH) 7.58 (2H dd, J 8.3, 2.8, ArH), 8.79 (0.55H, s, CONH, isomer a), 9.09 (0.45H, s, CONH, isomer b); δ_C (75.4 MHz, $CDCl_3$) 18.4, 24.8, 27.8, 38.9, 56.4, 62.4, 80.9, 82.2, 102.5, 126.8, 126.9, 127.3, 128.8, 128.9, 129.1, 132.7, 134.9, 162.7. MS (ESI+) m/z = 451.14 $[M + Na]^+$.

2-{[4-(1-Biphenyl-4-yl-1*H*-1,2,3-triazol-4-yl)phenyl]sulfonyl}-amino-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (12). *General procedure 1*: from **11** (50 mg, 0.117 mmol), 4-azidobiphenyl[28] (23 mg, 0.117 mmol), sodium ascorbate (234 μL, 0.234 mmol) and copper(II) sulfate pentahydrate (234 μL, 0.06 mmol) in DMF (3 mL), **12** (84.8 mg, 67%) was produced. The reaction mixture was diluted in EtOAc and washed with 30% aqueous NH_3, 6 M HCl and brine. The organic layer was dried ($MgSO_4$), evaporated to dryness, and the residue was suspended in $CHCl_3$ and filtered off to obtain a white solid (47 mg, 64%), mp 203–204 °C. (C, 65.26; H, 5.27; N, 11.26; S, 5.13; $C_{34}H_{33}N_5O_5S$ requires: C, 65.47; H, 5.33; N, 11.23; S, 5.14%); found: ν_{max} (KBr)/cm^{-1} 3210, 1664, 1602. δ_H (300 MHz, DMSO-d_6) 1.36–1.60 (6H, m, 3 × CH_2), 2.64–2.72 (1H, m, $\frac{1}{2}CH_2Ar$), 2.79–2.85 (1H, m, $\frac{1}{2}CH_2Ar$), 3.39–3.51 (1H, m, CH), 3.81–3.85 (1H, m, OCH_2, isomer a), 3.91–3.96 (1H, m, OCH_2, isomer b), 4.38 (0.55H, s, O–CH–O, isomer a), 4.56 (0.45H, s, O–CH–O, isomer b), 7.10–7.13 (1H, m, ArH), 7.16–7.23 (4H, m, ArH), 7.43–7.45 (1H, m, ArH), 7.50–7.55 (2H, m, ArH), 7.70–7.74 (2H, m, ArH), 7.79 (2H, d, J 8.6, ArH), 7.95–8.09 (6H, m, ArH), 8.34–8.42 (1H, m, SO_2NH), 9.54 (1H, s,

triazole), 11.23 (0.55H, s, CONH, isomer b), 11.33 (0.45H, s, CONH, isomer a); δ_C (75.4 MHz, DMSO-d_6) 18.6, 24.9, 28.0, 38.8, 55.5 (55.6 b), 61.3, 101.4, (101.6 b), 120.8, 121.1, 125.8, 126.8, 127.1, 127.4, 128.4 (128.4 b), 129.4, 129.5, 129.6, 133.9, 136.0, 136.9, 137.2, 139.0, 140.8 (140.8 b), 140.9, 146.4, 167.0 (167.1 b). MS (ESI+) m/z 646.24 $[M + Na]^+$.

2-{[4-(1-Biphenyl-4-yl-1*H*-1,2,3-triazol-4-yl)phenyl]sulfonyl}-amino-*N*-hydroxy-3-phenylpropanamide (7). *General procedure 2*: from **12** (54.2 mg, 0.073 mmol), MeOH (0.1 mL) and 4 M HCl–dioxane (0.1 mL, 0.4 mmol), **7** was produced as a white solid (30.0 mg, 77%), mp 223 °C (dec.); (C, 63.66; H, 4.77; N, 12.71; S, 5.85, $C_{29}H_{25}N_5O_4S{\cdot}1/3H_2O$ requires: C, 63.84; H, 4.74; N, 12.84; S, 5.88%) ν_{max} (KBr)/cm^{-1} 3254, 1649, 1605. δ_H (300 MHz, DMSO-d_6) 2.65 (1H, dd, J 13.5, 8.7, $\frac{1}{2}CH_2Ar$), 2.83 (1H, dd, J 13.5, 6.1, $\frac{1}{2}CH_2$), 3.82–3.90 (1H, m, CH), 7.09–7.18 (6H, m, ArH), 7.40–7.45 (1H, m, ArH), 7.50–7.55 (2H, m, ArH), 7.69 (2H, d, J 8.4, ArH), 7.78 (2H, d, J 7.4, ArH), 7.94–8.01 (4H, m, ArH), 8.08 (2H, d, J 8.6, ArH), 8.28 (1H, d, J 8.8, SO_2NH), 8.86 (1H, s, CONHO*H*), 9.50 (1H, s, triazole), 10.65 (1H, s, CON*H*OH); δ_C (75.4 MHz, DMSO-d_6) 38.4, 55.4, 120.4, 120.6, 125.3, 126.2, 126.6, 126.8, 127.9, 128.0, 128.9, 129.1, 133.4, 135.6, 136.8, 138.6, 140.4, 140.5, 146.0, 166.0. MS (ESI+): m/z = 562.25 $[M + Na]^+$.

***tert*-Butyl (2*R*)-2-{[(4-azidophenyl)sulfonyl]amino}-3-phenylpropanoate (15).** To a solution of (*R*)-**4** (4.08 g, 11.77 mmol) in DCM (100 mL) was added concentrated H_2SO_4 (0.2 mL) and the solvent was saturated with 2-methylpropene. After 24 h, water was added, neutralized with $NaHCO_3$ and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness, and the residue was chromatographed on silica gel (hexane–AcOEt 4 : 1) to give **15** (4.05 g, 86%) as a yellowish solid, mp 75.5–77.4 °C. ν_{max} (KBr)/cm^{-1} 3271, 2135, 2106, 1730, 1589. δ_H (400 MHz, DMSO-d_6) 1.15 (9H, s, $(CH_3)_3$), 2.91 (1H, dd, J 6.4, 1.3, CH_2Ar), 3.94–4.04 (1H, m, CH), 5.43 (1H, d, J 9.3 NH), 6.93 (2H, d, J 8.7 ArH), 7.01–7.08 (2H, m, ArH), 7.09–7.20 (3H, m, ArH), 7.64 (2H, d, J 8.7, ArH); δ_C (100.6 MHz, DMSO-d_6) 27.7, 39.5, 57.1, 82.7, 119.3, 127.1, 128.4, 129.2, 129.6, 135.4, 136.2, 144.6, 170.0. MS (ESI+): m/z = 401.2 $[M - H]^+$.

***tert*-Butyl (2*R*)-2-{[(4-azidophenyl)sulfonyl][2-(morpholin-4-yl)ethyl]amino}-3-phenylpropanoate (16).** To a solution of **15** (0.8 g, 1.99 mmol) in DMF (10 mL) were added K_2CO_3 (0.69 g, 4.97 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (0.44 g, 2.39 mmol). The reaction was heated for 24 h at 80 °C and, after cooling, was diluted with ethyl acetate and washed successively with saturated aqueous NH_4Cl and brine. The extract was dried ($MgSO_4$), filtered off and evaporated to dryness, and the residue was chromatographed on silica gel (hexane–AcOEt 3 : 2) to give **16** (872 mg, 85%) as a yellow oil. ν_{max} (KBr)/cm^{-1} 2971, 2853, 2806, 2129, 2106, 2106, 1730, 1589. δ_H (400 MHz, DMSO-d_6) 1.25 (9H, s), 2.38–2.56 (5H, m), 2.57–2.65 (1H, m), 2.97 (1H, dd, J = 14.0, 7.2), 2.97 (1H, dd, J = 14.0, 8.2), 3.34–3.53 (2H, m), 3.68 (4H, t, J 4.6), 4.67 (1H, t, J 7.7), 7.04 (2H, d, J 8.7 ArH), 7.18–7.31 (5H, m, ArH), 7.73 (2H, d, J 8.7, ArH); δ_C (100.6 MHz, DMSO-d_6) 27.7, 37.3, 42.7, 53.9, 58.8, 61.7, 66.9, 82.2, 119.2, 126.9, 128.5, 129.2, 129.4, 136.3, 136.6, 144.6, 169.4. MS (ESI+): m/z = 516.1 $[M + H]^+$.

(2*R*)-2-{[(4-Azidophenyl)sulfonyl][2-(morpholin-4-yl)ethyl]-amino}-3-phenylpropanoic acid (17). To a mixture of **16** (0.82 g, 1.58 mmol) and thioanisole (3.34 mL, 28.45 mmol) in DCM (4 mL) at 0 °C was added TFA (3.65 mL, 47.4 mmol). The reaction was stirred at room temperature overnight and evaporated to dryness. The residue was purified by column chromatography on silica gel (DCM–MeOH 9 : 1) to afford **17** (580 mg, 80%) as a white foam, mp 160.2 °C (dec.). ν_{max} (KBr)/cm^{-1} 3430, 2926, 2131, 2101, 1617, 1591. δ_H (400 MHz, DMSO-d_6) 2.70–3.05 (7H, m), 3.45–3.60 (3H, m), 3.60–3.80 (4H, m), 4.79 (1H, dd, J = 9.7, 3.9), 6.94 (2H, d, J 8.4 ArH), 7.12–7.23 (5H, m, ArH), 7.60 (2H, d, J 8.4, ArH); δ_C (100.6 MHz, DMSO-d_6) 36.9, 41.0, 52.4, 56.9, 62.9, 64.5, 119.1, 126.6, 128.5, 128.9, 129.3, 135.6, 137.8, 144.5, 174.7. MS (ESI+): m/z = 460.1 $[M + H]^+$.

(2*R*)-2-{[(4-Azidophenyl)sulfonyl][2-(morpholin-4-yl)ethyl]-amino}-*N*-(tetrahydro-2*H*-pyran-2-yl)-3-phenylpropanamide (18). To a solution of **17** (543 mg, 1.18 mmol) in DMF (5 mL) were added HOBt (192 mg, 1.42 mmol), NMM (0.39 mL, 3.55 mmol), *O*-tetrahydro-2*H*-pyran-2-yl-hydroxylamine (277 mg, 2.36 mmol) and EDCI (317 mg, 1.65 mmol). The reaction mixture was stirred overnight at room temperature and then diluted with AcOEt and washed successively with a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried ($MgSO_4$), evaporated to dryness and the solid obtained was purified by column chromatography on silica gel (hexane–AcOEt 2 : 3) to afford **18** (600 mg, 91%). This compound is present as a diastereoisomeric a : b mixture (60 : 40), mp 59.8–61.5 °C. ν_{max} (KBr)/cm^{-1} 3206, 2126, 2101, 1693, 1592; δ_H (400 MHz, $CDCl_3$) 1.50–1.65 (3H, m), 1.68–1.85 (3H, m), 2.35–2.47 (2H, m), 2.50–2.65 (4H, m), 2.65–2.85 (1H, m), 3.25–3.52 (2H, m), 3.54–3.82 (6H, m), 3.94–4.02 (0.6H, m, isomer a), 4.05–4.13 (0.4H, m, isomer b), 4.42–4.49 (0.4H, m, isomer b), 4.50–4.55 (0.6H, m, isomer a), 4.84 (0.6H, d, J 2.6, isomer a), 4.97 (0.4H, s, isomer b), 6.90–7.03 (4H, m, ArH), 7.08–7.18 (3H, m, ArH), 7.58 (1.2H, d, J 8.6, ArH, isomer a), 7.64 (0.8H, d, J 8.5, ArH, isomer b), 11.01 (0.4H, bs, CONH, isomer b), 11.13 (0.6H, bs, CONH, isomer a); δ_C (100.6 MHz, $CDCl_3$): 18.9 (isomer b), 19.5 (isomer a), 25.0, 28.1 (isomer b), 28.3 (isomer a), 34.4 (isomer a), 34.7 (isomer b), 41.6 (isomer a), 42.0 (isomer b), 53.5, 57.0 (isomer b), 57.2 (isomer a), 59.9 (isomer a), 60.0 (isomer b), 62.9 (isomer b), 63.4 (isomer a), 66.4 (isomer a), 66.5 (isomer b), 102.5 (isomer b), 103.3 (isomer a), 119.4, 126.7, 128.6, 128.8, 128.9, 135.4 (isomer a), 135.6 (isomer b), 136.7 (isomer a), 137.0 (isomer b), 144.7, 167.9 (isomer a), 168.1 (isomer b). MS (ESI) m/z 559.1 $[M + H]^+$.

(2*R*)-2-[({4-[4-(Biphenyl-4-yl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)(2-[morpholin-4-yl]ethyl)amino]-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (19). The product was prepared by General procedure 1 (preparation of triazoles), using **18** (150 mg, 0.269 mmol), 4-ethynylbiphenyl (57.4 mg, 0.322 mmol), sodium ascorbate (106 mg, 0.537 mmol) and copper(II) sulfate pentahydrate (33.5 mg, 0.134 mmol) in DMF (5 mL); **19** (145 mg, 73%) was produced as a white solid after chromatography purification (DCM–MeOH 1% MeOH). This

compound is present as a diastereoisomeric a : b mixture (60 : 40), mp 196.1 °C (dec.). ν_{max} (KBr)/cm^{-1} 3374, 2951, 2854, 2814, 1704, 1597; δ_H (400 MHz, $CDCl_3$) 1.50–1.65 (3H, m), 1.70–1.88 (3H, m), 2.40–2.54 (2H, m), 2.56–2.70 (4H, m), 2.75–2.85 (1H, m), 3.35–3.85 (8H, m), 3.94–4.02 (0.6H, m, isomer a), 4.05–4.13 (0.4H, m, isomer b), 4.50–4.59 (1H, m), 4.89 (0.6H, d, *J* 2.7, isomer a), 5.01 (0.4H, s, isomer b), 6.92–7.00 (2H, m, ArH), 7.04–7.08 (3H, m, ArH), 7.36 (1H, t, *J* 7.3, ArH), 7.45 (2H, t, *J* 7.5, ArH), 7.63 (2H, d, *J* 7.5, ArH), 7.62–7.78 (6H, m, ArH), 7.99 (2H, d, *J* 8.2, ArH), 8.34 (1H, s, triazole), 11.12 (0.4H, bs, CONH, isomer b), 11.24 (0.6H, bs, CONH, isomer a); δ_C (100.6 MHz, $CDCl_3$): 19.0 (isomer b), 19.6 (isomer a), 25.0, 28.2 (isomer b), 28.4 (isomer a), 34.4, 41.8 (isomer a), 42.2 (isomer b), 53.4, 57.0 (isomer b), 57.2 (isomer a), 60.4 (isomer a), 60.5 (isomer b), 63.0 (isomer b), 63.6 (isomer a), 66.5 (isomer a), 66.6 (isomer b), 102.8 (isomer b), 103.5 (isomer a), 114.1, 117.3 (isomer a), 117.4 (isomer b), 120.3, 123.6, 126.4, 126.9, 127.0, 127.7, 128.6, 128.7, 128.8, 128.9, 128.9, 129.0, 136.6 (isomer a), 136.9 (isomer b), 139.2, 139.3, 139.3, 139.7, 140.3, 140.5, 141.5, 148.7, 168.0 (isomer a), 168.2 (isomer b). MS (ESI) *m*/*z* 737.1 $[M + H]^+$.

(2*R*)-2-[(2-[Morpholin-4-yl]ethyl)({4-[4-(4-phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-3-phenyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)propanamide (20). The product was prepared by General procedure 1 (preparation of triazoles), using **18** (150 mg, 0.269 mmol), 4-ethynylbiphenyl (57.4 mg, 0.322 mmol), sodium ascorbate (106 mg, 0.537 mmol) and copper(II) sulfate pentahydrate (33.5 mg, 0.134 mmol) in DMF (5 mL); **20** (150 mg, 74%) was produced as a gray solid after chromatography purification (DCM–MeOH 1% MeOH). This compound is present as a diastereoisomeric a : b mixture (60 : 40), mp 81.5–82.9 °C. ν_{max} (KBr)/cm^{-1} 2956, 1693, 1597; δ_H (400 MHz, $CDCl_3$) 1.50–1.65 (3H, m), 1.70–1.85 (3H, m), 2.44–2.52 (2H, m), 2.56–2.72 (4H, m), 2.75–2.86 (1H, m), 3.38–3.85 (8H, m), 3.97–4.03 (0.6H, m, isomer a), 4.10–4.15 (0.4H, m, isomer b), 4.47–4.59 (1H, m), 4.89 (0.6H, d, *J* 2.7, isomer a), 5.01 (0.4H, s, isomer b), 6.94–7.00 (2H, m, ArH), 7.04–7.11 (7H, m, ArH), 7.15 (1H, t, *J* 7.4, ArH), 7.33–7.40 (2H, m, ArH), 7.71–7.80 (4H, m, ArH), 7.89 (2H, d, *J* 8.5, ArH), 8.27 (1H, s, triazole), 11.12 (0.4H, bs, CONH, isomer b), 11.25 (0.6H, bs, CONH, isomer a); δ_C (100.6 MHz, $CDCl_3$): 19.0 (isomer b), 19.6 (isomer a), 25.0, 28.2 (isomer b), 28.4 (isomer a), 34.4 (isomer a), 34.6 (isomer b), 41.7 (isomer a), 42.2 (isomer b), 53.4, 57.0 (isomer b), 57.1 (isomer a), 60.4 (isomer a), 60.5 (isomer b), 63.1 (isomer b), 63.6 (isomer a), 66.5 (isomer a), 66.6 (isomer b), 102.8 (isomer b), 103.5 (isomer a), 114.1, 116.8 (isomer a), 116.9 (isomer b), 119.0, 119.3, 120.3, 123.8, 124.6, 126.9, 127.5, 128.7, 128.8, 128.8, 128.9, 128.9, 129.0, 136.5 (isomer a), 136.8 (isomer b), 139.1, 139.3, 139.7, 148.6, 156.6, 158.0 168.0 (isomer a), 168.2 (isomer b). MS (ESI) *m*/*z* 753.1 $[M + H]^+$.

(2*R*)-2-[({4-[4-(Biphenyl-4-yl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)(2-[morpholin-4-yl]ethyl)amino]-*N*-hydroxy-3-phenylpropanamide (13). The product was prepared by General procedure 2 (cleavage of tetrahydropyrane protecting group) using **19** (125 mg, 0.17 mmol), MeOH (0.5 mL) and 4 M HCl–dioxane (2 mL). The crude was purified by chromatography (DCM–MeOH 4% MeOH) to obtain **13** (66.0 mg, 60%) as a white solid, mp 208 °C (dec.). (Found: C, 64.31; H, 5.68; N, 12.51; S, 4.67. $C_{29}H_{25}N_5O_4S{\cdot}H_2O$ requires: C, 64.40; H, 5.56; N, 12.87; S, 4.91%). ν_{max} (KBr)/cm^{-1} 3470, 3129, 1668, 1622, 1597. δ_H (400 MHz, DMSO-d_6): 2.38–2.59 (6H, m, 3 × NCH_2), 2.80 (1H, dd, *J* = 13.9, 7.1, $\frac{1}{2}CH_2Ph$), 2.97 (1H, dd, *J* = 14.0, 8.1, $\frac{1}{2}CH_2Ph$), 3.40–3.46 (1H, m, $\frac{1}{2}SO_2NCH_2$), 3.58 (4H, t, *J* 4.5, 2 × OCH_2), 3.63–3.74 (1H, m, $\frac{1}{2}SO_2NCH_2$), 4.48 (1H, t, *J* 7.5, CH), 7.14–7.24 (5H, m, ArH), 7.41 (1H, t, *J* 7.3, ArH), 7.51 (2H, t, *J* 7.6, ArH), 7.76 (2H, d, *J* 7.5, ArH), 7.85 (2H, d, *J* 8.3, ArH), 8.03 (2H, d, *J* 8.8, ArH), 8.08 (2H, d, *J* 8.3, ArH), 8.14 (2H, d, *J* 8.7, ArH), 8.93 (1H, bs, OH), 9.54 (s, 1H, CH triazole), 10.96 (s, 1H, CONH); δ_C (100.6 MHz, DMSO-d_6) 36.0, 41.7, 53.33, 58.0, 58.3, 66.1, 119.8, 120.1, 125.9, 126.5, 126.6, 127.2, 127.7, 128.3, 129.0, 136.6, 139.0, 139.3, 139.4, 140.0, 147.3, 165.5. MS (ESI+): *m*/*z* 653.1 $[M + H]^+$. $[\alpha]_D^{25}$ + 12.2 (*c* 0.0018 g cm^{-3} in DMSO).

(2*R*)-*N*-Hydroxy-2-[(2-[morpholin-4-yl]ethyl)({4-[4-(4-phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl]phenyl}sulfonyl)amino]-3-phenylpropanamide (14). The product was prepared by General procedure 2 (cleavage of tetrahydropyrane protecting group) using **20** (130 mg, 0.17 mmol), MeOH (0.5 mL) and 4 M HCl–dioxane (2 mL). The crude was purified by chromatography (DCM–MeOH 4% MeOH) to obtain **14** (64.0 mg, 56%) as a gray solid, mp 131–133 °C. (Found: C, 64.31; H, 5.68; N, 12.51; S, 4.67. $C_{29}H_{25}N_5O_4S{\cdot}H_2O$ requires: C, 64.40; H, 5.56; N, 12.87; S, 4.91%). ν_{max} (KBr)/cm^{-1} 3368, 3140, 1673, 1597. δ_H (400 MHz, DMSO-d_6): 2.33–2.60 (6H, m, 3 × NCH_2), 2.79 (1H, dd, *J* = 13.8, 7.1, $\frac{1}{2}CH_2Ph$), 3.18 (1H, dd, *J* = 13.8, 7.8, $\frac{1}{2}CH_2Ph$), 3.37–3.48 (1H, m, $\frac{1}{2}SO_2NCH_2$), 3.58 (4H, t, *J* 4.5, 2 × OCH_2), 3.63–3.74 (1H, m, $\frac{1}{2}SO_2NCH_2$), 4.47 (1H, t, *J* 7.5, CH), 7.09–7.24 (10H, m, ArH), 7.44 (1H, t, *J* 8.0, ArH), 7.97–8.02 (4H, m, ArH), 8.12 (2H, d, *J* 8.7, ArH), 8.93 (1H, bs, OH), 9.43 (s, 1H, CH triazole), 10.96 (s, 1H, CONH); δ_C (100.6 MHz, DMSO-d_6) 36.0, 41.7, 53.3, 58.0, 58.3, 66.1, 118.9, 119.0, 119.3, 120.1, 123.8, 125.1, 126.5, 127.2, 128.3, 128.9, 129.0, 130.1, 136.6, 139.0, 139.3, 147.2, 156.3, 156.9, 165.5. MS (ESI+): *m*/*z* 669.1 $[M + H]^+$. $[\alpha]_D^{25}$ + 4.0 (*c* 0.0005 g cm^{-3} in DMSO).

Conclusions

We have used a *click* chemistry approach to synthesize a series of phenylalanine derived hydroxamates. The substitution pattern in the resulting triazole seems to be crucial to obtain a high degree of selectivity between both gelatinases. The best compound **1b** displayed subnanomolar IC_{50} against MMP-2 and was 95-fold less potent against MMP-9, while the closely structurally related compound **7** was devoid of selectivity. We have used docking and molecular dynamics tools to shed light on the reason for this difference in selectivity between **1b** and **7**. The difference in the energetic profile of the dihedral angle that describes the torsion around C_{sp2}–C_{sp2} and C_{sp2}–N_{sp2} induces a change in the dynamic behaviour of the P1′-segment that allows **7** to establish good interactions with both MMP-2 and MMP-9.

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