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Fast and selective synthesis of novel cyclic sulfamide HIV-1 protease inhibitors under controlled microwave heating

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Abstract—A novel and highly selective silver-promoted monobenzylation method was developed to promote synthesis of nonsymmetrical sulfamide-based HIV-1 inhibitors. Microwave-accelerated palladium-catalyzed *N*-amide arylation- and aminocarbonylation reactions were employed for rapid and reliable compound generation. With this class of inhibitory agents, six active inhibitors were identified, the most potent inhibitor possessing a K_i-value of 20 nM.

1. Introduction

Since the mid-1980s, a large number of studies have demonstrated that an acceleration of chemical rates can be achieved by employing high-density microwave irradiation instead of traditional sources of heat.[1–4] Although high yields and clean reactions are commonly obtained with microwave heating, reduced selectivities have been reported at high temperatures.[5,6] Hence, development of fast and highly selective reaction protocols, remains a challenge.

The recent development of palladium-catalyzed gas-free aminocarbonylations[7] and *N*-amide arylations[8] has enabled direct attachment of amide functionalities to sp^2-carbons that were previously difficult to accomplish. However, the commonly tedious fine-tuning of the appropriate reaction parameters, and the requirement for inert conditions and long reaction times, has limited the usage of these direct transformations in medicinal chemistry.

A large number of very potent urea-based cyclic HIV-1 protease inhibitors carrying four-side chains has been prepared and evaluated following the pioneering work by Lam and coworkers.[9] Interestingly, by switching the water-mimicking group from urea to sulfamide, an unanticipated flipped binding mode was obtained according to X-ray crystal structures of inhibitors in complex with the HIV-1 protease.[10,11] The preparative route to these inhibitors was complex and the inhibitors were lipophilic and of high-molecular weight. To investigate if properly functionalized benzylic side-chains could span from *P*2/*P*2′ to *P*1/*P*1′ and thus simplify the otherwise cumbersome synthetic pathway, a set of C_2-symmetric *ortho*-functionalized sulfamide derivatives were synthesized and evaluated. The most potent inhibitor from this series (K_i=0.53 μM), substituted with two benzofuran moieties, was identified as a lead structure for further optimization (Fig. 1).[12] Thus, based on isosteric replacement and modeling, it was hypothesized that an amide function (–CONH) might be of interest to incorporate in the two *ortho*-positions (R-) of the dibenzylated cyclic sulfamide **5** to act as a mimic for the furan ring (Fig. 1, Scheme 1). In addition, we decided to investigate the inverted amides (–NHCO). Reactants were selected in order to vary flexibility and size of the *ortho*-substituents. With the aim to reduce

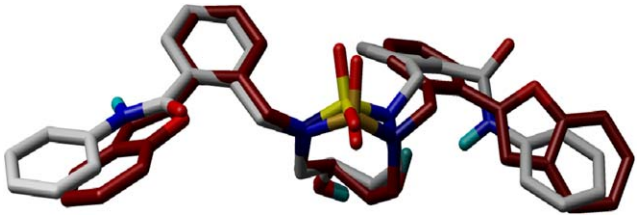

Figure 1. Superposition of benzofuran and anilide (**5a**) *o*-substituted *N*,*N*′-dibenzylic seven-membered sulfamide structures. The molecular graphics image was produced using the UCSF program Chimera.[13]

Keywords: Microwave; Aminocarbonylation; Goldberg; HIV-1 protease inhibitor.
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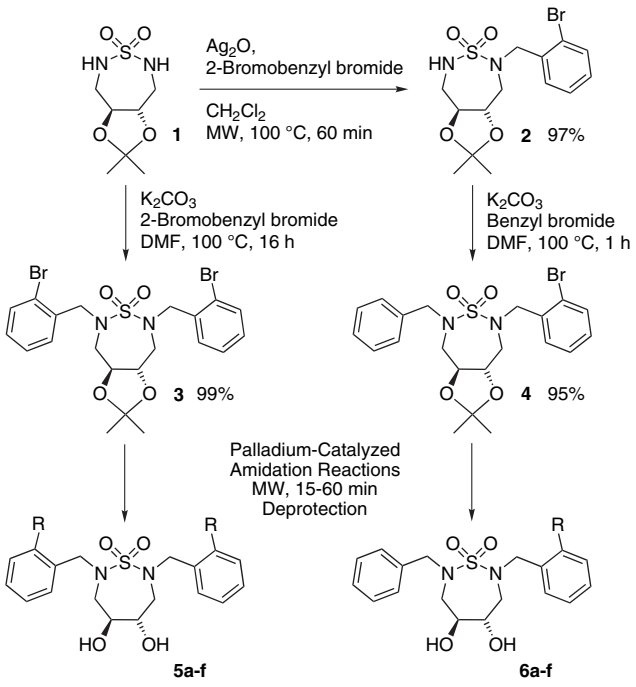


Scheme 1.

the size of the inhibitors and to produce nonsymmetrically decorated dibenzyl sulfamides, precursor **2** was much desired.

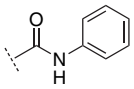
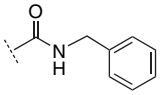
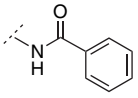
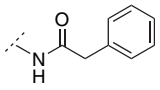
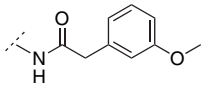
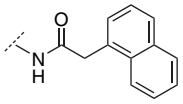
In this communication, a microwave promoted and chemoselective procedure for monoalkylation of the sulfamide scaffold **1** is reported (Scheme 1). Furthermore, a number of direct palladium-catalyzed *ortho*-amidations of the *P*2/*P*2′ benzyl groups have been conducted, delivering 12 new HIV-1 protease inhibitors.

2. Results and discussion

2.1. Synthetic strategies

The core structure **1** served as the precursor to provide the symmetric and nonsymmetric aryl bromide derivatives **3** and **4**, respectively (Scheme 1). Compound **3** was obtained, as previously reported, in 99% yield after N,N-dibenzylation with 2-bromobenzyl bromide in the presence of K_2CO_3.[10] Double *ortho*-amidations of **3** by palladium-catalyzed coupling reactions and deprotection, provided the symmetrical inhibitors in good yields (Table 1). More specifically, the aminocarbonylation products **5a**,**b** were obtained in 59 and 80% yield after 60 min of heating at 150 °C, respectively.[14] The corresponding *N*-amide arylations delivered the inverted amides **5c–f** in 53–72% yields after only 15 min of irradiation (160 °C). Early attempts to prepare unsymmetrical **4** from **1** showed an increased reactivity of the monoalkylated product **2** towards concomitant dialkylation, resulting in unwanted **3**. Fortunately, by initial addition of 1.5 equiv Ag_2O, subsequent microwave-assisted benzylation afforded pure aryl bromide **2** with excellent selectivity (**2**/**3**=99:1, Scheme 1). The yield of **2** was 97% despite the high-reaction temperature (100 °C). Related monoalkylations of symmetrical diols have been performed in presence of Ag_2O.[15]

Table 1. Microwave-heated palladium-catalyzed coupling reactions on symmetric and nonsymmetric cyclic sulfamides **3** and **4**

Reactant[a], route[b]	R-group	Symmetric (yield)[c], K_i (nM)	Nonsymmetric (yield)[c], K_i (nM)
a, A		**5a** (59%), >20,000	**6a** (77%), >20,000
b, A		**5b** (80%), 8600	**6b** (74%), >20,000
c, B		**5c** (72%), >20,000	**6c** (77%), >20,000
d, B		**5d** (53%), 1200	**6d** (51%), >20,000
e, B		**5e** (54%), 1300	**6e** (68%), 7700
f, B		**5f** (57%), 20	**6f** (66%), 140

[a] a: Aniline, b: Benzylamine, c: Benzamide, d: 2-Phenylacetamide, e: 2-(3-Methoxyphenyl)acetamide, f: 2-(2-Naphthyl)acetamide.
[b] A: Aminocarbonylation, B: *N*-amide arylation.
[c] Isolated yields after deprotection.

Aminocarbonylations of parent **4** with $Mo(CO)_6$ as the CO-source smoothly produced the monofunctionalized products **6a**,**b** (74 and 77%, Table 1). Similarly, **6c–f** were prepared as reported for the symmetric analogs **5c–f** in 51–77% yields after deprotection. The K_i-values for the synthesized compounds were determined as previously described.[16,17]

2.2. Discussion

Six active inhibitors were identified. Apparently, incorporation of the amide function alone was not sufficient, and an extra methylene spacer was required in order to yield active symmetrical compounds (**5b**, **5d–f**). The most potent compound **5f** possessed low nanomolar activity with a K_i-value of 20 nM. The high activity of **5f** was obtained by steric replacement of phenylacetamide for 1-naphthylacetamide. To our satisfaction, the smaller nonsymmetric compounds, occupying only three subsites, also proved to be active (**6e**, **6f**). With these structures, both the extra methylene spacer and further enlargement of the R-group was essential for activity.

3. Conclusion

In conclusion, the concept of *ortho*-extension from benzylic *P*2/*P*2′ side-chains to reach the *P*1/*P*1′ binding sites provided highly active HIV-1 protease inhibitors. With regard to inhibition potency, improved K_i-values were achieved using mono- and di-*ortho*-elongated structures with flexible three-atom spacers between the aromatic moieties.

Furthermore, single-mode microwave heating at 100 °C for 60 min was exploited without compromising the selectivity in the key monobenzylation step.

4. Experimental

4.1. General

The microwave-assisted reactions were performed in a single-mode microwave cavity (Smith Synthesizer, Biotage AB, Uppsala, Sweden) producing controlled irradiation at 2450 MHz. Reaction temperatures were determined and controlled via the built-in, on-line IR-sensor. Flash column chromatography was performed using Merck Silica gel 60 (0.040–0.063 mm). Analytical HPLC–MS analyses were performed using a Gilson HPLC system with a Chromolith SpeedROD RP-18e column (50×4.6 mm) and a Finnigan AQA quadropole mass spectrometer using a 4 mL/min CH_3CN/H_2O gradient (0.05% HCOOH), employing UV-detection (214 and 254 nm) and mass selective detector (ESI+). ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-400 spectrometer at 399.8 and 100.6 MHz, respectively. All starting materials and reagents were commercially available and used as received. Xantphos, (4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene) was purchased from Aldrich. Herrmann's palladacycle, *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium (II) was purchased from Strem and $Mo(CO)_6$ was obtained from Acros.

4.2. Method for monobenzylation of cyclic sulfamides

Cyclic sulfamide **1** (0.45 mmol, 100 mg) and Ag_2O (0.67 mmol, 156 mg) were mixed in a Smith process vial for 5 min in 2 mL of CH_2Cl_2. After addition of *o*-bromobenzyl bromide (0.47 mmol, 117 mg) and another 3 mL of CH_2Cl_2, the vial was capped with a septum. The microwave synthesizer was set to 100 °C for 1 h. After cooling, the reaction mixture was filtered through a plug of Celite and immediately transferred to a short flash column and **2** was easily purified using 9:1 *iso*-hexane/EtOAc as the eluent (>95% purity by ^1H NMR and GC–MS). In a subsequent benzylation, **2** (0.68 mmol, 266 mg), benzyl bromide (1.36 mmol, 232 mg) and K_2CO_3 (3.33 mmol, 460 mg) were mixed in a process vial with 5 mL DMF. Reaction was heated in a heating block at 60 °C overnight. The reaction mixture was concentrated in vacuo and purified over silica, using 2:1–1:1 *iso*-hexane/CH_2Cl_2 as the eluent.

4.2.1. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(2-bromobenzyl)-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (2). White solid. LC–MS, m/z=392 [M+H$^+$]. ^1H NMR (400 MHz, acetone-d_6): δ=7.62 (dd, 1H, J=1.2, 8.0 Hz), 7.56 (dd, 1H, J=1.7, 7.8 Hz), 7.44 (ddd, 1H, J=1.2, 7.4, 7.8 Hz), 7.26 (ddd, 1H, J=1.7, 7.4, 8.0 Hz), 6.72 (br m, 1H), 4.51 (d, 1H, J=16.0 Hz), 4.46 (d, 1H, J=16.0 Hz), 4.32–4.22 (m, 2H), 3.59 (ddd, 1H, J=3.9, 4.7, 12.8 Hz), 3.50 (dd, 1H, J=4.2, 13.6 Hz), 3.15 (ddd, 1H, J=0.6, 9.4, 13.6 Hz), 3.08 (ddd, 1H, J=7.0, 9.5, 12.8 Hz), 1.37 (m, 3H), 1.36 (m, 3H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=136.5, 132.9, 1230.0, 129.6, 128.3, 128.2, 109.2, 78.7, 77.8, 54.0, 49.4, 43.5, 26.6, 26.5. Anal. Calcd (%) for $C_{14}H_{19}BrN_2O_4S$: C, 42.98; H, 4.89; N, 7.16. Found: C, 43.30; H, 5.04; N, 7.19.

4.2.2. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(2-bromobenzyl)-7-benzyl-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (4). White solid. LC–MS, m/z=482 [M+H$^+$]. ^1H NMR (400 MHz, $CDCl_3$): δ=7.57 (m, 1H), 7.54 (m, 1H), 7.40–7.29 (m, 6H), 7.18 (m, 1H), 4.58 (d, 1H, J=15.4 Hz), 4.50 (d, 1H, J=15.4 Hz), 4.49 (d, 1H, J=14.6 Hz), 4.36 (d, 1H, J=14.6 Hz), 4.31–4.18 (m, 2H), 3.50 (dd, 1H, J=4.5, 13.0 Hz), 3.46 (dd, 1H, J=4.6, 12.8 Hz), 3.11 (dd, 1H, J=9.2, 13.0 Hz), 3.02 (dd, 1H, J=9.3, 12.8 Hz), 1.38 (d, 1H, J=0.6 Hz), 1.37 (d, 1H, J=0.6 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=136.1, 135.5, 133.2, 130.3, 129.7, 129.0, 128.7, 128.4, 128.2, 123.8, 110.1, 77.9, 77.7, 55.4, 54.8, 49.3, 48.6, 27.1. Anal. Calcd (%) for $C_{21}H_{25}N_2O_4S$: C, 52.39; H, 5.23; N, 5.82. Found: C, 52.46; H, 5.29; N, 5.79.

4.3. General method for aminocarbonylation of both symmetrical (3) and nonsymmetrical (4) sulfamide scaffolds

Cyclic sulfamide (0.083 mmol), Herrmann's catalyst (8.3 μmol, 7.8 mg), $Mo(CO)_6$ (0.017 mmol, 47 mg), DBU (0.83 mmol, 136 mg) and amine (2.5 mmol) were put in a 2–5 mL Smith process vial. THF (2.5 mL) was added and the reaction was run at 150 °C for 60 min. After cooling the reaction mixture was filtered through a plug of Celite and the organic solvent was evaporated under reduced pressure. Flash column chromatography and removal of the protective group using 1 mL 2.2 M HCl/ether and 2 mL methanol at rt for 45 min, followed by a second rapid flash column chromatography yielded pure products in all cases.

4.3.1. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis(*N*-phenyl-2-amido-benzyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5a). White solid. LC–MS, m/z=601 [M+H$^+$]. ^1H NMR (400 MHz, $CDCl_3$): δ=8.09 (s, 2H), 7.62–7.54 (m, 6H), 7.46–7.40 (m, 4H), 7.36–7.24 (m, 6H), 7.15 (tt, 2H, J=7.4, 1.2 Hz), 4.64 (d, 2H, J=15.8 Hz), 4.58 (d, 2H, J=15.8 Hz), 3.61–3.56 (m, 2H), 3.35 (d, 1H, J=15.4 Hz), 3.34 (d, 1H, J=15.4 Hz), 3.22 (d, 1H, J=15.4 Hz), 3.20 (d, 1H, J=15.4 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=168.3, 137.9, 136.2, 136.0, 131.3, 130.2, 129.4, 128.2, 127.1, 125.2, 120.5, 72.4, 50.6, 48.9.

4.3.2. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis(*N*-benzyl-2-amido-benzyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5b). White solid. LC–MS, m/z=629 [M+H$^+$]. ^1H NMR (400 MHz, $CDCl_3$): δ=7.68 (ddd, 2H, J=7.8, 1.2, 0.6 Hz), 7.49 (ddd, 2H, J=7.8, 7.3, 1.5 Hz), 7.42–7.27 (m, 14H), 6.34 (br t, 2H, J=5.8 Hz), 4.78 (d, 2H, J=15.4 Hz), 4.73 (d, 2H, J=15.4 Hz), 4.64 (dd, 2H, J=14.7, 5.8 Hz), 4.59 (dd, 2H, J=14.7, 5.8 Hz), 3.76–3.72 (m, 2H), 3.58–3.54 (m, 2H), 3.53–3.47 (m, 2H), 327–3.20 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=169.9, 137.8, 136.2, 135.8, 131.3, 130.9, 129.2, 128.22, 128.18, 128.1, 126.9, 72.5, 49.9, 47.2, 44.5.

4.3.3. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(*N*-phenyl-2-amido-benzyl)-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6a). White solid. LC–MS, m/z=482 [M+H$^+$]. ^1H NMR (400 MHz, acetone-d_6): δ=9.57 (br s, 1H),

7.87–7.82 (m, 2H), 7.70 (m, 1H), 7.62 (m, 1H), 7.55 (m, 1H), 7.46–7.27 (m, 8H), 7.13 (m, 1H), 4.97 (d, 1H, J=16.8 Hz), 4.82 (d, 1H, J=16.8 Hz), 4.68 (d, 1H, J=15.8 Hz), 4.55 (d, 1H, J=15.8 Hz), 4.26 (d, 1H, J=3.9 Hz), 4.22 (d, 1H, J=4.3 Hz), 3.42–3.23 (m, 3H), 3.15 (dd, 1H, J=15.2, 3.2 Hz). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=168.2, 140.3, 138.5, 137.3, 137.3, 131.2, 129.6, 129.4, 129.2, 128.8, 128.34, 128.30, 128.0, 124.7, 120.8, 73.1, 73.0, 53.2, 50.9, 49.3, 48.5. Anal. Calcd (%) for $C_{25}H_{27}N_3O_5S$: C, 62.35; H, 5.65; N, 8.73. Found: C, 62.21; H, 5.80; N, 8.61.

4.3.4. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(*N*-benzyl-2-amidobenzyl)-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6b). White solid. LC–MS, m/z=496 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.13 (br t, 1H), 7.67 (ddd, 1H, J=7.8, 1.2, 0.6 Hz), 7.57–7.22 (m, 13H), 4.89 (d, 1H, J=16.6 Hz), 4.78 (d, 1H, J=16.6 Hz), 4.70 (d, 1H, J=15.8 Hz), 4.61 (d, 2H, J=6.0 Hz), 4.56 (d, 1H, J=15.8 Hz), 4.29 (d, 1H, J=3.8 Hz), 4.26 (d, 1H, J=4.2 Hz), 3.67–3.56 (m, 2H), 3.40–3.12 (m, 4H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=169.7, 140.3, 138.6, 137.2, 137.1, 131.0, 129.42, 129.40, 129.3, 128.9, 128.4, 128.3, 128.1, 128.1, 127.8, 73.1, 73.0, 53.2, 50.6, 49.0, 48.5, 43.9. Anal. Calcd (%) for $C_{26}H_{29}N_3O_5S$: C, 63.01; H, 5.90; N, 8.48. Found: C, 62.89; H, 6.06; N, 8.43.

4.4. General method for *N*-amide arylation of both symmetrical (3) and nonsymmetrical (4) sulfamide scaffolds

Cyclic sulfamide (0.083 mmol), Pd(dba)$_2$ (4 μmol, 2.4 mg), Xantphos (6.2 μmol, 3.6 mg), Cs_2CO_3 (0.4 mmol, 135 mg) and amide (0.8 mmol) were put in a Smith process vial, with 2.5 mL 10% NMP in dioxane as the solvent. The reaction mixture was heated in the microwave at 160 °C for 15 min. After cooling the reaction mixture was filtered through a plug of Celite and the organic solvent was evaporated under reduced pressure. Flash column chromatography and removal of the protecting group using 1 mL of 2.2 M HCl/ether and 2 mL methanol at rt for 45 min followed by a second rapid flash column chromatography yielded pure products in all cases.

4.4.1. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis(2-benzamidobenzyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5c). White solid. LC–MS, m/z=601 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=9.31 (br s, 2H), 8.05 (dd, 4H, J=1.4, 8.4 Hz), 7.80 (dd, 2H, J=1.4, 8.0 Hz), 7.61–7.56 (m, 2H), 7.55–7.47 (m, 6H), 7.38 (ddd, 2H, J=1.6, 7.5, 7.7 Hz), 7.26 (ddd, 2H, J=1.4, 7.5, 7.5 Hz), 4.72 (d, 2H, J=16.2 Hz), 4.68 (d, 2H, J=16.2 Hz), 4.32 (br d, 2H, J=4.1 Hz), 3.54–3.45 (m, 2H), 3.30 (dd, 2H, J=9.2, 15.1 Hz), 3.18 (dd, 2H, J=2.9, 15.1 Hz). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=166.15, 137.0, 135.0, 131.9, 130.6, 129.7, 128.6, 128.5, 127.9, 125.9, 125.7, 72.6, 49.5, 48.3.

4.4.2. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis[2-(2-phenylacetamido)-benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5d). White solid. LC–MS, m/z=629 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.92 (s, 2H), 7.94 (dm, 2H, J=8.1 Hz), 7.49 (dm, 2H, J=7.5 Hz), 7.42 (dm, 4H, J=7.5 Hz), 7.37–7.26 (m, 6H), 7.25–7.15 (m, 4H), 4.68 (d, 2H, J=15.5 Hz), 4.52 (d, 2H, J=15.5 Hz), 4.23 (br s, 2H), 3.76 (s, 4H), 3.30–3.17 (m, 4H), 3.16–3.02 (m, 2H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=169.6, 137.5, 136.2, 130.1, 129.5, 128.9, 128.6, 128.0, 126.9, 124.9, 123.7, 72.5, 49.5, 48.5, 43.9.

4.4.3. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis{2-[2-(3-methoxy-phenyl)-acetamido]-benzyl}-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5e). White solid. LC–MS, m/z=689 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.88 (s, 2H), 7.93 (dm, 2H, J=8.1 Hz), 7.48 (dd, 2H, J=1.6, 7.6 Hz), 7.34 (ddd, 2H, J=1.6, 7.6, 7.6 Hz), 7.23–7.15 (m, 4H), 7.02 (m, 2H), 6.99 (dm, 2H, J=7.6 Hz), 6.80 (ddd, 2H, J=1.0, 2.6, 8.2 Hz), 4.68 (d, 2H, J=15.5 Hz), 4.52 (d, 2H, J=15.5 Hz), 4.21 (br s, 2H), 3.77 (s, 6H), 3.73 (s, 4H), 3.32–3.18 (m, 4H), 3.17–3.08 (m, 2H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=167.8, 146.2, 138.7, 138.2, 137.9, 130.1, 129.8, 129.7, 129.3, 128.8, 126.9, 73.1, 50.9, 49.0, 46.2, 44.1.

4.4.4. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2,7-bis{2-[2-(2-naphthyl)-acetamido]-benzyl}-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (5f). White solid. LC–MS, m/z=729 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.91 (s, 2H), 8.25 (ddd, 2H, J=0.9, 2.1, 8.5 Hz), 7.90 (dm, 2H, J=8.2 Hz), 7.83 (dd, 2H, J=1.2, 8.0 Hz), 7.82 (dm, 2H, J=8.2 Hz), 7.60–7.39 (m, 10H), 7.31 (ddd, 2H, J=1.6, 7.5, 7.7 Hz), 7.16 (ddd, 2H, J=1.3, 7.5, 7.5 Hz), 4.63 (d, 2H, J=15.6 Hz), 4.51 (d, 2H, J=15.6 Hz), 4.27 (s, 4H), 4.22 (br s, 2H), 3.32–3.22 (m, 4H), 3.20–3.08 (m, 2H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=170.2, 138.0, 134.9, 133.4, 133.1, 130.6, 129.43, 129.39, 129.3, 129.0, 128.5, 127.1, 126.6, 126.4, 125.8, 125.3, 124.9, 73.2, 50.1, 49.2, 42.1. Anal. Calcd (%) for $C_{42}H_{40}N_4O_6S$: C, 69.2; H, 5.53; N, 7.69. Found: C, 68.95; H, 5.66; N, 7.50.

4.4.5. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(2-benzamidobenzyl)-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6c). White solid. LC–MS, m/z=482 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.73 (br s, 1H), 7.93 (dd, 2H, J=1.3, 8.4 Hz), 7.86 (dm, 1H, J=8.1 Hz), 7.55 (m, 2H), 7.49–7.42 (m, 2H), 7.39–7.23 (m, 7H), 7.20 (m, 1H), 4.60 (d, 1H, J=14.8 Hz), 4.58 (d, 1H, J=15.5 Hz), 4.34 (d, 1H, J=14.8 Hz), 4.30 (d, 1H, J=15.5 Hz), 3.42 (m, 1H), 3.30 (dd, 1H, J=9.2, 14.6 Hz), 3.26–3.08 (m, 4H), 3.03 (dd, 1H, J=3.9, 15.2 Hz), 2.84 (br s, 1H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=167.7, 136.5, 136.2, 134.0, 132.5, 131.1, 129.7, 129.1, 128.9, 128.44, 128.43, 128.2, 127.9, 126.4, 125.7, 73.2, 72.4, 53.2, 50.0, 48.7, 47.9. Anal. Calcd (%) for $C_{25}H_{27}N_3O_5S$: C, 62.35; H, 5.65; N, 8.73. Found: C, 62.51; H, 5.79; N, 8.64.

4.4.6. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(2-phenylacetamidobenzyl)-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6d). White solid. LC–MS, m/z=496 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.93 (s, 1H), 8.06 (dd, 1H, J=1.2, 8.1 Hz), 7.51–7.39 (m, 7H), 7.37–7.30 (m, 2H), 7.29–7.18 (m, 3H), 7.14 (ddd, 1H, J=1.3, 7.5, 7.5 Hz), 4.78 (d, 1H, J=15.7 Hz), 4.70 (d, 1H, J=15.3 Hz), 4.54 (d, 1H, J=15.7 Hz), 4.42 (d, 1H, J=15.3 Hz), 4.21–4.19 (m, 2H), 3.74 (s, 1H), 3.57 (m, 1H), 3.44–3.04 (m, 5H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=169.5, 137.7, 137.5, 136.2, 130.5, 129.5, 128.9,

128.6, 128.3, 127.9, 127.4, 126.9, 125.4, 124.5, 123.0, 73.1, 71.9, 52.4, 49.6, 48.8, 48.1, 43.9. Anal. Calcd (%) for $C_{26}H_{29}N_3O_5S$: C, 63.01; H, 5.90; N, 8.48. Found: C, 63.23; H, 6.23; N, 8.13.

4.4.7. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-[2-(3-methoxyphenyl-acetamido)-benzyl]-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6e). White solid. LC–MS, m/z=526 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.90 (br s, 1H), 8.02 (dd, 1H, J=1.3, 8.2 Hz), 7.50–7.29 (m, 7H), 7.20–7.12 (m, 2H), 7.03 (m, 1H), 6.98 (dm, 1H, J=7.5 Hz), 6.97 (ddd, 1H, J=1.0, 2.6, 8.3 Hz), 4.76 (d, 1H, J=15.7 Hz), 4.68 (d, 1H, J=15.3 Hz), 4.55 (d, 1H, J=15.7 Hz), 4.43 (d, 1H, J=15.3 Hz), 4.22–4.19 (m, 2H), 3.76 (s, 3H), 3.71 (s, 2H), 3.58 (m, 1H), 3.40–3.06 (m, 5H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=170.1, 160.7, 138.3, 138.2, 138.1, 131.1, 130.2, 129.6, 129.5, 128.9, 128.6, 125.3, 123.9, 122.4, 115.7, 113.1, 73.7, 72.6, 55.4, 53.1, 50.3, 49.4, 48.8, 44.7.

4.4.8. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-{2-[2-(2-naphthyl)-acetamido]-benzyl}-7-benzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (6f). White solid. LC–MS, m/z=546 [M+H$^+$]. ^{1}H NMR (400 MHz, acetone-d_6): δ=8.98 (s, 1H), 8.27 (dm, 1H, J=8.4 Hz), 7.90 (m, 2H), 7.82 (dm, 1H, J=8.2 Hz), 7.61–7.27 (m, 11H), 7.15 (ddd, 1H, J=1.2, 7.5, 7.5 Hz), 4.75 (d, 1H, J=15.8 Hz), 4.66 (d, 1H, J=15.4 Hz), 4.55 (d, 1H, J=15.8 Hz), 4.46 (d, 1H, J=15.4 Hz), 4.27 (s, 1H), 4.26 (d, 1H, J=4.4 Hz), 4.24 (d, 1H, J=4.2 Hz), 3.60 (m, 1H), 3.40–3.10 (m, 5H). ^{13}C NMR (100.5 MHz, acetone-d_6): δ=169.5, 137.6, 137.5, 134.2, 132.8, 132.5, 130.2, 128.9, 128.74, 128.73, 128.4, 128.2, 127.9, 127.8, 126.4, 125.9, 125.8, 124.8, 124.7, 123.7, 72.9, 72.0, 52.5, 49.5, 48.7, 48.1, 41.4. Anal. Calcd (%) for $C_{30}H_{31}N_3O_5S$: C, 66.04; H, 5.73; N, 7.70. Found: C, 66.05; H, 5.85; N, 7.68.

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