Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 13 (2005) 755–764
Bioorganic & Medicinal Chemistry

Cyclic sulfamide HIV-1 protease inhibitors, with sidechains spanning from P2/P2′ to P1/P1′

Anna Ax,[a] Wesley Schaal,[a] Lotta Vrang,[b] Bertil Samuelsson,[b] Anders Hallberg[a] and Anders Karlén[a,*]

[a]*Department of Medicinal Chemistry, Uppsala University, BMC, Box 574, SE-751 23 Uppsala, Sweden*
[b]*Medivir AB, Lunastigen 7, SE-141 44 Huddinge, Sweden*

Received 16 July 2004; revised 14 October 2004; accepted 19 October 2004

Abstract—Previous studies of HIV protease inhibitors have shown that it is possible to elongate the P1/P1′ sidechains to reach the S3/S3′ binding sites. By analogy, we expected that it would be possible to design inhibitors reaching between the S1/S1′ and S2/S2′ binding sites. Molecular modeling suggested that this could be achieved with appropriate *ortho*-substitution of the P2/P2′ benzyl groups in our cyclic sulfamide inhibitors. Four different spacer groups were investigated. The compounds were smoothly prepared from tartaric acid in five steps and exhibit low to moderate activity, the most potent inhibitor possessing a K_i value of 0.53 μM.

1. Introduction

The number of people living with HIV/AIDS is estimated to 38 million and approximately 3 million AIDS deaths were reported in 2003.[1] The inhibitors of HIV protease, which entered the market in 1995, have proven to be valuable therapeutics in combination with nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTI's and NNRTI's, respectively) in the treatment of AIDS. This effective drug combination therapy is known as highly active antiretroviral therapy (HAART).[2,3] Unfortunately this therapy is often attributed to problems with adherence and to the emergence of HIV drug resistance.[4] As a result, intensive research efforts have been devoted to the search for new chemical entities such as potent HIV protease inhibitors exhibiting a minimum of cross-resistance and that are anticipated to be structurally distinct from those used in therapy today.

Inspired by the elegant design of cyclic ureas as HIV protease inhibitors that was reported by Lam et al. in 1994,[5] we embarked on a study of related cyclic sulfamides, where carbohydrates were employed as precursors and chiral pools.[6] These cyclic sulfamides, for example, the lead compound **2**, prepared from L-mannonic-γ-lactone in nine steps and with a K_i value of 23 nM, was found to bind to HIV protease in an non-symmetric binding mode.[6,7] Specifically, the P1′ and P2′ sidechains were transposed relative to the expected binding mode observed for the corresponding cyclic urea-based inhibitor (**1**).[8] All cyclic sulfamide—HIV protease X-ray complexes to date have presented this same binding mode (PDB codes: ajv1, 1gk2, and 1g35).[7–9]

Previous studies of HIV protease inhibitors have shown that it is possible to elongate the P1/P1′ sidechains to reach the S3/S3′ binding sites.[10] By analogy, inspection of the X-ray structure of our cyclic sulfamide inhibitors in complex with HIV-1 protease,[7–9] predicted that it could also be possible to reach between the S1/S1′ and S2/S2′ binding sites. Molecular modeling suggested that this design could be achieved with appropriate *ortho*-substitution of the P2/P2′ benzyl groups. We herein report compounds with the generic structure **3** (Fig. 1) that exhibited low to moderate activity and that could easily be prepared via a short synthetic route that includes bisbenzylation and cross-couplings as key reactions.

Keywords: AIDS; HIV-1 protease inhibitors; Cyclic sulfamide; Molecular modeling.
* Corresponding author. Tel.: +46 18 471 4293; fax: +46 18 471 4474; e-mail: anders.karlen@orgfarm.uu.se

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.10.042

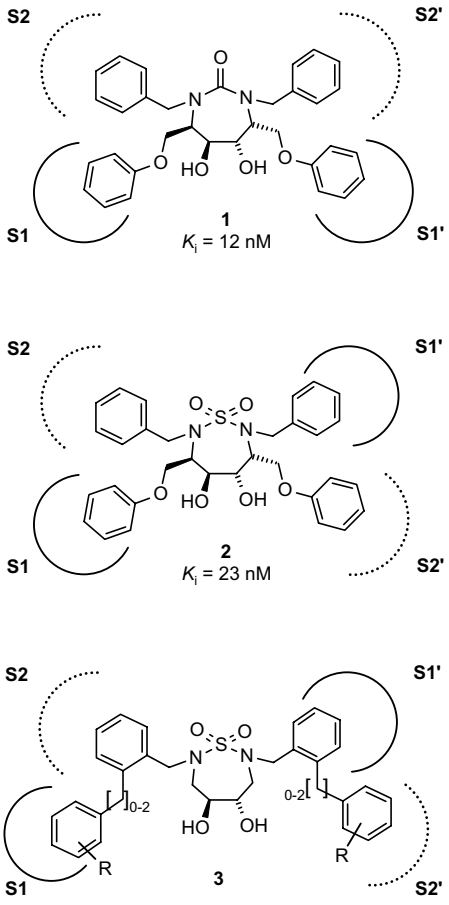


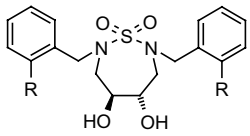
Figure 1. Structure of a cyclic urea inhibitor **1** with symmetric binding to HIV-1 protease and a cyclic sulfamide inhibitor **2** with nonsymmetric binding. The generic structure **3** and the proposed nonsymmetric binding to HIV-1 protease.

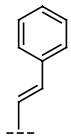
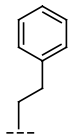
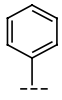
2. Results

2.1. Modeling

Compounds **9**–**13** (Table 1) were subjected to a conformational search in the active site of the HIV-1 protease. The results from the docking are depicted in Figure 2 with the X-ray structure of **2** (yellow) for comparison. The unsubstituted compound **9** (gray), stilbene analog **10** (green), ethylene analog **11** (cyan), and methylene analog **12** (orange) all adopted binding modes, which were quite similar to that observed for **2**, except that **10** and **11** appeared to be touching the edge of S3. In contrast, the biphenyl **13** (magenta) seemed to prefer a significantly different mode of binding. The bulk of the phenyl ring in the *ortho*-position could simply not be accommodated. As a result, the prime side benzyl group of **13** got positioned in between S1′ and S2′ and the terminal phenyl group on the opposite side was positioned between the S2 and S3 binding sites. Therefore, **13** as well as the unsubstituted **9** were predicted to occupy only two out of the four possible binding sites and would likely result in poor activity. The promising results for the docking of **10**–**12** encouraged us to proceed with their synthesis. Compounds **9** and **13** were included as negative controls.

Table 1. Inhibitory activity of biaryl analogs



Compd	R	Yield (%)	K_i (μM)
9		37	>20
10		53	2.0
11		28	3.0
12		51	2.5
13		53	2.5

2.2. Enzyme inhibition

The inhibitory activities for compounds **9**–**13** are summarized in Table 1. Consistent with the predictions from modeling, compound **9** was found to be inactive.

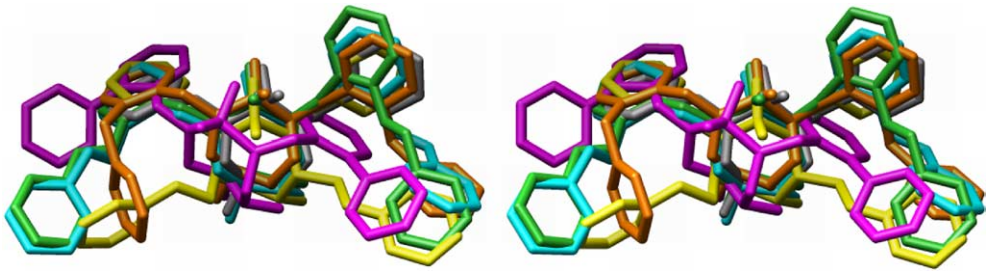
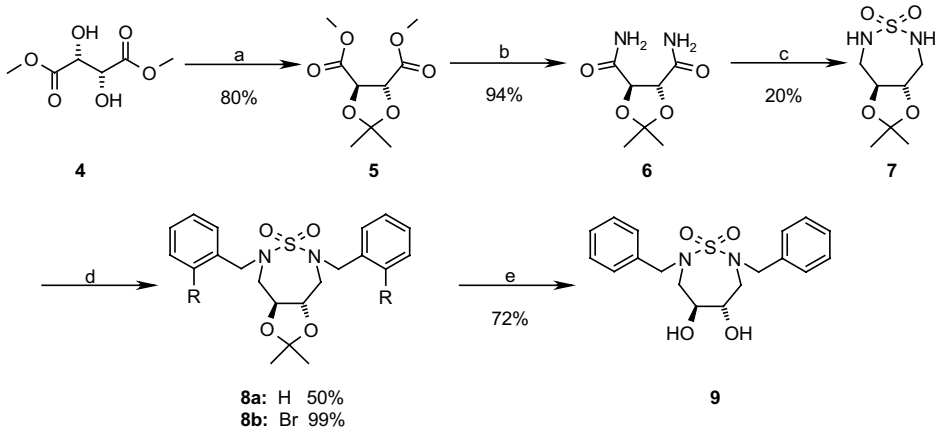


Figure 2. Results from the Monte Carlo conformational search. Depicted are the low energy conformations of **9** (gray), **10** (green), **11** (cyan), **12** (orange), and **13** (magenta), the X-ray crystal structure of **2** (yellow) is included for comparison. The molecular graphics image was produced using the UCSF Chimera.[32]



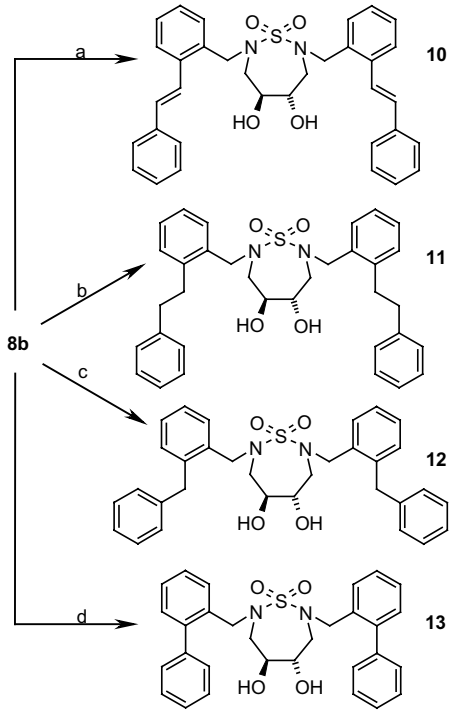
Scheme 1. Reagents and conditions: (a) 2,2-dimethoxypropane and DL-10-camphorsulfonic acid in acetone; (b) NH_3/methanol; (c) i. $LiAlH_4$ in THF, 80 °C, ii. $NH_2SO_2NH_2$, Et_3N, toluene, 120 °C; (d) for **8a** benzyl bromide, DMF, K_2CO_3 and for **8b** 2-bromobenzyl bromide, DMF, K_2CO_3; (e) HCl/ether and methanol.

Compounds **10**–**12** were found to have reasonably good inhibitory potency but unfortunately did not attain the potency of the lead compound **2**. Compound **13**, which according to the modeling studies should only interact with two binding sites, turned out to be as potent as **10**–**12**.

To explore this unexpected result, we decided to focus our further research efforts on the derivatives of **13**. Small groups in the *para*- or *meta*-position of the attached aryl were anticipated by modeling to be favorably accommodated in the protein by reaching further into or filling, the S1 and S2′. A large variety of building blocks were commercially available.

2.3. Chemistry

Dimethyl L-tartrate (**4**) served as the chiral starting material for the target molecules (Schemes 1 and 2). The protection of the two hydroxyl groups of the tartrate and the transformation of the ester groups to amides were performed essentially as described in the literature.[11–13] Reduction of the amides with $LiAlH_4$[14,15] and subsequent cyclization with sulfamide with either diisopropylamine or triethylamine delivered the seven-membered cyclic scaffold. The scaffold was thereafter alkylated using either benzyl bromide or 2-bromobenzyl bromide to obtain compounds **8a** and **8b**, respectively. Deprotection of **8a**, using HCl/ether in methanol, delivered compound **9**. Compound **8b** served as the precursor for the subsequent palladium catalyzed cross-coupling reactions.



Scheme 2. Reagents and conditions: (a) i. styrene, DIEA, $Pd(OAc)_2$, PPh_3, DMF, H_2O, microwaves 150 °C, 20 min, ii. HCl/ether and methanol; (b) i. styrene, DIEA, $Pd(OAc)_2$, PPh_3, DMF, H_2O, microwaves 150 °C, 20 min, ii. H_2, Pd/C, ethyl acetate, iii. HCl/ether and methanol; (c) i. benzyl zinc, $PdCl_2$, DPPF, THF under N_2, 80 °C, 88 h, ii. HCl/ether and methanol; (d) i. phenyl boronic acid, $Pd(OAc)_2$, PPh_3, Na_2CO_3, DME, ethanol, microwaves 150 °C, 5 min, ii. HCl/ether and methanol.

Compounds **10** and **11** were prepared using a microwave mediated Heck coupling (150 °C, 5 min) with styrene and triethylamine as base.[16,17] The double bond of **11** was reduced using palladium on charcoal and hydrogen gas. Finally, deprotection was achieved with HCl/ether in methanol to deliver **10** and **11** in 53% and 28% yield, respectively. Compound **12** was prepared using a Nigishi coupling[18] with benzyl zinc bromide (6 equiv), palladium chloride, and DPPF in a heating block at 80 °C. After 24 h, an additional 2 equiv of benzyl zinc bromide was added and heating continued for another 64 h. After deprotection, 51% of **12** was isolated. Compound **13** was prepared using a Suzuki–Miyaura coupling[19,20] with palladium acetate, triphenylphosphine, 5 equiv of phenylboronic acid, and sodium carbonate as the base. Microwave irradiation for 5 min at 150 °C[17] followed by deprotection afforded compound **13** in 53% yield.

A series of 15 substituted biaryl compounds were prepared from **8b**. A representative set of aryl boronic acids and esters with desirable properties were selected. The Suzuki–Miyaura reaction conditions were identical to those described for the synthesis of compound **13** except for compounds **25** and **26** where a slight modification of the reaction times and temperature were required (140 °C, 20 min). All of the products from the Suzuki–Miyaura couplings were purified only by extraction and, in all but one case, provided pure compounds according to NMR and elemental analysis.

3. Discussion

To investigate whether it would be possible to fill all four binding sites using only two substituents on the scaffold, by attaching the P1/P1′ substituents to the P2/P2′ sidechains, we designed four target compounds with different spacer groups. All four compounds **10**–**13** turned out to be about equally potent, with K_i values of 2.0–3.0 μM. A compound lacking *ortho*-substituents (**9**) was also synthesized and tested for comparison. As anticipated, it was found to be inactive. The most interesting result from this series of compounds was the activity and proposed binding mode for compound **13**. This biphenyl compound was modeled to adopt the least optimal interaction with the enzyme but was shown to have similar activity. This unanticipated finding certainly called into question the validity of the modeling results. On the other hand, if the modeling could be trusted and the activity of **13** has been achieved by only filling two sites, we anticipated that adding groups, which could reach the other two binding sites (S2 to S1 and S1′ to S2′), would result in an improved inhibitory potency.

A series of 15 biaryl derivatives of **13** were prepared using Suzuki–Miyaura coupling. The aryl boronic acids that were used in the coupling reactions were selected based on those that were available in house. We aimed for moderately lipophilic building blocks that would produce inhibitors with a molecular weight below 700 g/mol. To insure that the chosen reactants well represented the desired region of the chemical space, we searched the Available Chemicals Directory (ACD)[21] for boronic acids and esters. Seven physicochemical descriptors were calculated for each reactant and a principal component analysis was performed. A two-component model representing 71% of the variance was produced (Fig. 3). Inspection of the score and loading plots shows that the selected boronic acids were spread throughout the desired chemical space. We were therefore satisfied with our selection.

The K_i values of **14**–**28** ranged between 0.53 and 9.7 μM (Table 2). Compounds **14** and **16**, with lipophilic substituents in the *para*-position, were more potent than the parent biphenyl compound **13**. When other groups were introduced into the *para*-position (**18**, **20**, **21**, **22**, and **24**) the activity dropped. Compounds with a *meta*-substituent (**15**, **17**, **19**, **23**, and **24**) have a similar or slightly poorer activity compared to **13**. It was difficult to draw

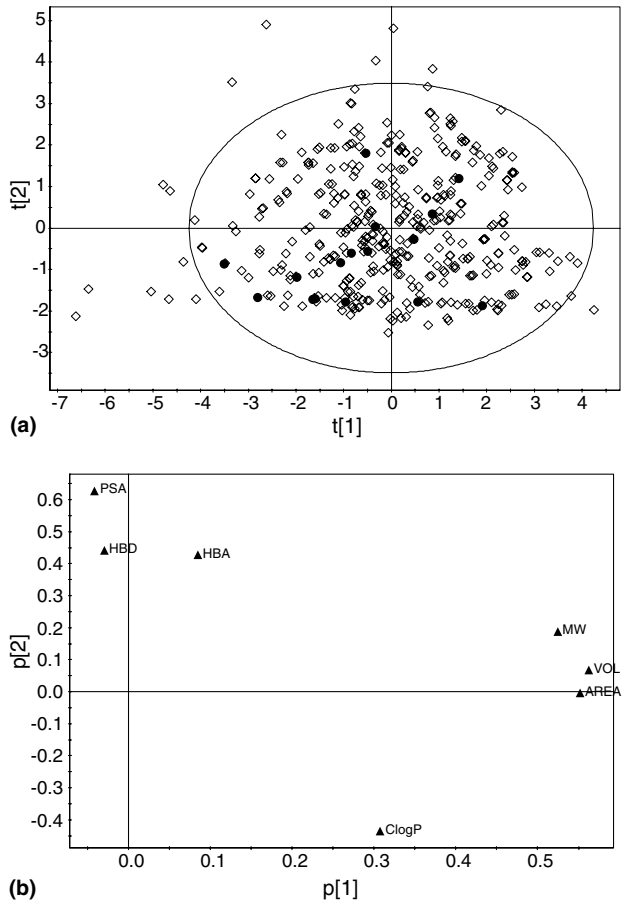


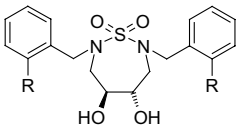
Figure 3. Results from the principal component analysis (PCA) for the selected boronic acids and esters. In score plot (a), the building blocks used are depicted (black dots) among the commercially available building blocks (open diamond). Analyzing the loading plot (b), a preference for lipophilic compounds with low molecular weight can be seen, which corresponds to our design criterion.

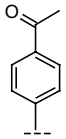
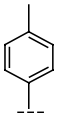
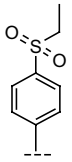
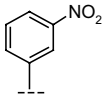
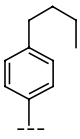
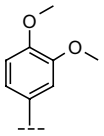
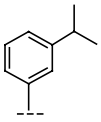
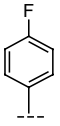
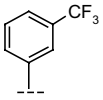
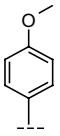
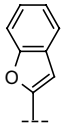
any conclusions regarding compounds with an *ortho*-substituent (**25** and **26**) since one compound was a somewhat poorer inhibitor than **13** and the other, with a thiomethyl group, exhibited the second best activity. The thiophene derivative **27** was equipotent to phenyl derivative **13**, which could be expected by bioisosterism.[22] Notably, the benzofurane derivative **28** was seen to be the most potent inhibitor. Modeling suggested that the benzofurane oxygen might favorably interact with backbone NH of Gly 48 and the S3 subsite would be better filled.

4. Conclusion

A series of HIV protease inhibitors utilizing an unusual design has been synthesized. The P2/P2′ substituents are elongated and substituted with the P1/P1′ sidechain in an attempt to reach between the binding sites. The synthesized inhibitors possess moderate activity with K_i values of 0.53–9.7 μM. The concept has proven promising though the potency of the parent, tetra-substituted compound **2** has not yet been attained. The reason for this may be that the binding mode of the investigated

Table 2. Inhibitory activity of the biphenyl analogs[a]



Compd	R	Yield (%)	K_i (μM)	Compd	R	Yield (%)	K_i (μM)
13		53	2.5	**21**		65	5.3
14		60	1.5	**22**		26	5.2
15		63	2.7	**23**		60	7.4
16		60	1.9	**24**		57	9.4
17		56	3.2	**25**		54	5.1
18		62	5.3	**26**		68	1.1
19		52	2.4	**27**		45	2.7
20		50	9.7	**28**		31	0.53

[a] Compounds **14**–**28** were prepared as described for **13** (Scheme 2), except for **25** and **26** where a slight modification of time and temperature were necessary (140 °C, 20 min).

inhibitors are different from the ones suggested by the modeling; this will be addressed in future investigations. Considering the modeled differences in the occupation of the S1 versus S1′ subsites, we are also investigating nonsymmetric derivatives, which may have improved activity.

5. Experimental

5.1. Modeling

The compounds were built in Maestro[23] starting from the crystal structure of **2** in complex with HIV-1 protease (PDB code 1ajv). The enzyme–ligand complex was prepared using the protein preparation feature in Maestro. Both of the catalytic aspartic acids were protonated, as has been suggested for the cyclic ureas;[24] this protonation pattern seems to be suitable for the sulfamide class as well (unpublished results).

Each compound was first minimized (MacroModel 8.5[25]) in the active site using the OPLS-AA force field[26] and GB/SA[27] solvation model. The torsions and bond angles of the sulfamide ring were constrained to preserve the conformation observed in all available X-ray complexes for the tetra-substituted inhibitors. Inhibitors were allowed to reposition and relax in a 6 Å shell from

the **2**–enzyme complex (extended to full residues), which was restrained with a force constant of 100 kJ/mol Å^2. Debug switch 17 was set to include constrained-atom mutual interactions in the calculations. Additionally, distance constraints were applied between the hydroxyl groups and the carbonyl oxygen in Asp25/25′ (±1.0 Å, force constant 100 kJ/mol Å^2) in order to focus our docking efforts to the active site.

The conformational preferences of compounds **9**–**13** were explored in the environment described above with a 5000-step Monte Carlo search (MCMM) and a 2000-step minimization at each step. Excluding the constrained seven-membered ring, the rotatable bonds were varied. The lowest energy conformer of each of the four compounds was subjected to a final (2000-step) minimization in the fully unrestrained enzyme; the sulfamide ring conformation was maintained as described above (Fig. 2).

5.2. Descriptor calculation and analysis

The ACD (Version 2003.3)[21] was used to search for boronic acids and esters to be used in the syntheses of **14**–**28**. In total 986 were found. Logic filtration was used to select boronic acids compatible with the chemistry to be used. Thus, only activated boronic acids, that is, aryl, benzyl, or vinyl, which did not contain halogens (besides F), carboxyl, ester, or formyl groups, were used. Compounds with more than one boronic acid function as well as resin bound boronic acids were also excluded. The boronic esters were 'hydrolyzed' and duplicates were removed to yield a total of 583 unique boronic acids. Gasteiger–Hückel charges were applied and physicochemical descriptors were calculated using in-house and standard SPL scripts (Sybyl 6.9[28]). Size descriptors (molecular weight, surface area, and volume), as well as Clog *P*, polar surface area (PSA), and H-bonding (acceptors and donors) descriptors were used. Finally, boronic acids that would result in an inhibitor with molecular weight above 700 g/mol were excluded to result in 416 suitable reagents. Simca-P+ (version 10)[29] was used to generate the principle component analysis (PCA) with all settings kept at default. The generated model consisted of two principal components with a cumulative r^2 of 0.71.

5.3. HIV protease inhibition

The HIV-1 protease was cloned and heterologously expressed in *Escherichia coli* and purified as described elsewhere.[30] The K_i values for the synthesized compounds were determined by fluorometric assay[31] (Tables 1 and 2).

5.4. Synthesis

5.4.1. General information. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM-EX270 spectrometer at 270.2 and 67.8 MHz, respectively. Chemical shifts are reported as δ values (ppm) indirectly referred to TMS by the solvent residual signal. Elemental analyses were preformed by Analytische Laboratorium Lindlar, Germany and were within ±0.4% of calculated values. Column chromatography was preformed on silica gel 60, 0.040–0.063 mm (E. Merck). Thin-layer chromatography was preformed on precoated silica gel F-254 plates, 0.25 mm (E. Merck) plates and visualized with UV light, phosphomolybdic acid, or ninhydrin. Analytical RP-LC/MS was performed on a Gilson HPLC system with a Chromolith Performance RP-18e, 4.6 × 100 mm column, with a Finnigan AQA quadropole mass spectrometer at a flow rate of 4 mL/min (H_2O/CH_3CN/0.05% HCOOH). All microwave reactions were carried out in heavy-walled glass Smith process vials sealed with aluminum crimp caps fitted with a silicon septum. The microwave heating was performed in a Smith Synthesizer™ single-mode cavity producing continuous irradiation at 2450 MHz (Biotage AB, Uppsala, Sweden). Reaction mixtures were stirred during irradiation. The temperature, pressure, and irradiation power were monitored during the course of the reaction. After the irradiation was completed, the reaction tube was cooled with high-pressure air until the temperature was below 39 °C. A Reacto-Station™ (STEM Electrothermal) was used for conventional heating. Centrifugation was performed using a Centra EC-4 (International Equipment Company). Vacuum centrifugation was performed using a SpeedVac Plus SC250DDA (Savant).

5.4.2. General procedure for the Suzuki–Miyaura cross-coupling reactions. A Smith-vial was charged with **8b** (0.088 mmol, 1 equiv), $Pd(OAc)_2$ (8.8 μmol, 0,1 equiv), PPh_3 (0.026 mmol, 0.3 equiv), boronic acid (0.44 mmol, 5 equiv), DME (480 μL), ethanol (120 μL), and 1 M Na_2CO_3 (300 μL) and heated to 150 °C for 5 min (except for compound **25** and **26**, which were heated to 140 °C for 20 min) using microwave irradiation. The reaction mixture was diluted with petroleum ether (2 mL) and 50% acetonitrile/water (1 mL) and transferred to a centrifuge tube, equipped with a filter. The phases were separated, the petroleum ether phase was washed with 50% acetonitrile/water (1 mL) and concentrated in vacuo. (In some cases, the product precipitates as a red-brown oil, which was then collected and washed together with the petroleum ether phase.) The crude product was dissolved in methanol (1 mL) and then HCl in ether (1 mL) was added. The reaction mixture was stirred for 2 h before the solvent was removed in vacuo. The product was dissolved in acetonitrile (1 mL), washed with petroleum ether (2 × 1 mL), dried by filtration through $MgSO_4$, and concentrated in vacuo. In some cases, white crystals (salt) precipitate during extraction or when the sample was dissolved for NMR. These were then filtered off.

5.4.3. (4*S*,5*S*)-*O*-Isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (7). Compound **6** (2.1 g, 0.011 mol) was placed in a Soxhlet thimble and extracted down to a refluxing suspension of $LiAlH_4$ (1.0 g, 0.26 mmol) in dry THF (350 mL). Refluxing was continued overnight and the reaction mixture was then stirred at room temperature for another 16 h. Water (3 mL) was added dropwise to the reaction mixture followed by 15% NaOH (3 mL) and water (10 mL). The solution was filtered through Celite and K_2CO_3, the solid was washed with THF

and the combined filtrates were concentrated to afford the crude diamine as a pale brown oil (1.34 g, 77%). The crude amine (1.34 g, 7.6 mmol) and an equimolar quantity of sulfamide (0.73 g, 7.62 mmol) were dissolved in toluene (100 mL) and triethylamine (3 mL). The reaction mixture was refluxed at 120 °C overnight. The reaction mixture was concentrated in vacuo and purified using dry-flash, followed by column chromatography, for a total yield of 20% (0.49 g) of white solid: $[\alpha]_D^{24}$ +72.19 (*c* 0.525, CH_3OH, 23 °C); IR (cm^{-1}): 3300 (NH); ^1H NMR (270 MHz, acetone-d_6): 1.31 (s, 6H), 3.01 (m, 2H), 3.48 (m, 2H), 4.12 (m, 2H), 6.16 (s, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 27.1, 44.3, 80.0, 109.5. Anal. ($C_7H_{14}N_2O_4S$) C, H, N.

5.4.4. (4*S*,5*S*)-2,7-Bisbenzyl-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (8a). To a solution of **7** (50.0 mg, 0.22 mmol) in DMF (10 mL), benzyl bromide (192.4 mg, 1.1 mmol, 5 equiv) and potassium carbonate (310 mg, 2.2 mmol, 10 equiv) were added. The reaction mixture was left to stir overnight at room temperature. The reaction mixture was concentrated in vacuo and the product was purified using flash chromatography to yield 51% (45.8 mg) of white solid: ^1H NMR (270 MHz, $CDCl_3$): 1.28 (s, 6H), 2.92 (m, 2H), 3.37 (m, 2H), 4.11 (m, 2H), 4.28 (d, $J = 14.52$, 2H), 4.40 (d, $J = 14.52$, 2H), 7.17–7.23 (m, 10H); ^{13}C NMR (270 MHz, acetone-d_6): 29.7, 49.0, 55.3, 78.1, 110.1, 128.6, 129.1, 129.5, 137.7. Anal. ($C_{21}H_{26}N_2O_4S$) C, H, N.

5.4.5. (4*S*,5*S*)-2,7-Bis(2-bromobenzyl)-4,5-*O*-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (8b). To a solution of **7** (1.6 g, 7.5 mmol) in DMF (100 mL), 2-bromobenzylbromide (5.6 g, 0.023 mol, 3 equiv) and potassium carbonate (5.2 g, 0.037 mol, 5 equiv) were added. The reaction mixture was left to stir overnight at room temperature. The reaction mixture was concentrated in vacuo and the product was purified using flash chromatography to yield 99% (4.2 g) of white solid: $[\alpha]_D^{24}$ 51.35 (*c* 0.534, $CHCl_3$, 22 °C); ^1H NMR (270 MHz, $CDCl_3$): 1.31 (s, 6H), 3.05 (m, 2H), 3.42 (m, 2H), 4.23 (m, 2H), 4.39 (d, $J = 15.51$, 2H), 4.55 (d, $J = 15.51$, 2H), 7.10 (m, 2H), 7.27 (m, 2H), 7.43 (m, 2H), 7.49 (m, 2H); ^{13}C NMR (270 MHz, $CDCl_3$): 27.2, 49.3, 54.9, 77.7, 110.1, 123.8, 128.1, 129.7, 130.4, 133.2, 135.3. Anal. ($C_{21}H_{24}Br_2N_2O_4S$) C, H, N.

5.4.6. (4*S*,5*S*)-2,7-Bisbenzyl-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (9). To a solution of **8a** (35.6 mg, 0.088 mmol) in methanol (5 mL) was added 2 M HCl in ether (2 mL) and then the reaction mixture was stirred for 3 h. The reaction mixture was concentrated and the product was purified by flash chromatography to yield 72% (23.1 mg) of light-yellow solid: ^1H NMR (270 MHz, acetone-d_6): 3.13 (m, 2H), 3.32 (m, 2H), 3.58 (m, 2H), 4.28 (br s, 2H), 4.53 (d, $J = 15.84$, 2H), 4.70 (d, $J = 15.84$, 2H), 7.26–7.49 (m, 10H); ^{13}C NMR (270 MHz, CD_3OD): 49.1, 53.6, 73.1, 129.0, 129.3, 129.9, 138.5. Anal. ($C_{18}H_{22}N_2O_4S$) C, H, N.

5.4.7. (4*S*,5*S*)-2,7-Bis(2-styrylbenzyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (10). Two Smith-vials were each charged with **8b** (51 mg, 0.091 mmol, 1 equiv), styrene (86 μL, 0.91 mmol, 10 equiv), DIEA (57 μL, 0.055 mmol, 6 equiv), $Pd(OAc)_2$ (2 mg, 9.1 μmol, 0.1 equiv), PPh_3 (7.2 mg, 0.027 mmol, 0.3 equiv), DMF (1 mL), and water (200 μL). The reaction was heated to 150 °C for 20 min using microwave irradiation. The two reactions were combined, transferred to a centrifuge tube, equipped with a filter, centrifuged to remove palladium, and were then concentrated in vacuo. The crude product was purified using column chromatography to yield >98% (115 mg) of white solid. This intermediate was used for the synthesis of **10** and **11**.

The intermediate (53.2 mg, 0.086 mmol, 1 equiv) was deprotected using HCl/ether in methanol. The reaction mixture was concentrated in vacuo and the crude product was purified using column chromatography to yield 53% (26.2 mg) of white solid: ^1H NMR (270 MHz, acetone-d_6): 2.97 (m, 2H), 3.37 (m, 4H), 4.12 (br s, 2H), 4.67 (d, $J = 15.1$, 2H), 4.89 (d, $J = 15.1$, 2H), 7.15–7.43 (m, 14H), 7.49 (m, 2H), 7.72 (m, 4H), 7.81 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 48.5, 51.1, 73.1, 125.9, 126.4, 127.8, 128.5, 128.5, 129.1, 129.4, 130.8, 131.6, 134.6, 137.7, 138.4. Anal. ($C_{34}H_{34}N_2O_4S$) C, H, N.

5.4.8. (4*S*,5*S*)-2,7-Bis[2-(2-phenylethyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (11). Compound **11** was prepared using the intermediate described in the synthesis of **10**. The intermediate (61.9 mg, 0.10 mmol, 1 equiv) was hydrogenated to remove the double bond using H_2 and palladium on charcoal suspended in ethyl acetate. The reaction mixture was stirred overnight. The reaction mixture was filtered and concentrated in vacuo. The protecting group was cleaved using HCl/ether and methanol and the crude product was purified using column chromatography to yield 28% (16.4 mg) of white solid: ^1H NMR (270 MHz, acetone-d_6): 2.01 (m, 2H), 2.74–3.20 (m, 10H), 3.23 (m, 2H), 3.36 (m, 2H), 4.31 (d, $J = 15.18$, 2H), 4.48 (d, $J = 15.18$, 2H), 7.07–7.25 (m, 16H), 7.31 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 34.1, 37.6, 47.6, 50.3, 72.7, 126.1, 126.8, 128.4, 128.5, 128.8, 129.2, 130.1, 133.6, 140.5, 141.5. Anal. ($C_{34}H_{38}N_2O_4S$) C, H, N.

5.4.9. (4*S*,5*S*)-2,7-Bis[2-(phenylmethyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (12). Compound **8b** (50.0 mg, 0.089 mmol, 1 equiv), palladium chloride (1.1 mg, 6.20 μmol, 0.07 equiv), DPPF (1.5 mg, 2.7 μmol, 0.03 equiv), and THF (2 mL) were placed in a dry vial and flushed with nitrogen gas. After a few minutes, benzyl zinc bromide (1.1 mL, 0.053 mmol, 6 equiv) was added to the reaction mixture and the vial was placed in an 80 °C heating block and stirred overnight. Another 2 equiv of benzyl zinc was added and the reaction mixture was heated an additional 64 h. The reaction mixture was diluted with petroleum ether (2 mL) and 50% acetonitrile/water (1 mL) and then transferred to a centrifuge tube, equipped with a filter and the phases were separated. The acetonitrile/water phase was extracted two times with dichloromethane and the organic phase was concentrated in vacuo. The crude product was dissolved in methanol (2.5 mL) and 2 M HCl in ether (1 mL) was added. The reaction mixture was left to stir at room

temperature overnight. The reaction mixture was concentrated in vacuo and the product was purified using column chromatography to yield 51% (24.7 mg): ^{1}H NMR (270 MHz, acetone-d_6): 3.07 (m, 2H), 3.31 (m, 2H), 3.54 (m, 2H), 4.14 (s, 4H), 4.25 (m, 2H), 4.57 (d, J = 15.84, 2H), 4.69 (d, J = 15.84, 2H), 7.14–7.22 (m, 8H), 7.22–7.31 (m, 8H), 7.51 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 38.6, 48.5, 50.6, 73.0, 126.8, 127.4, 128.5, 129.2, 129.5, 129.7, 131.4, 135.7, 140.3, 141.3; Anal. ($C_{32}H_{34}N_2O_4S$) C, H, N.

5.4.10. (4*S*,5*S*)-2,7-Bis(2-phenylbenzyl)-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (13). A Smith-vial was charged with **8b** (49.3 mg, 0.088 mmol, 1 equiv), $Pd(OAc)_2$ (2.0 mg, 8.8 μmol, 0.1 equiv), PPh_3 (8.0 mg, 0.026 mmol, 0.3 equiv), phenyl boronic acid (53.7 mg, 0.44 mmol, 5 equiv), DME (480 μL), ethanol (120 μL), and 1 M Na_2CO_3 (300 μL) and heated to 150 °C for 5 min. The reaction mixture was transferred to a centrifuge tube, equipped with a filter. Solids were filtered off and the reaction mixture was concentrated in vacuo. The crude product was purified using column chromatography to yield 53% (24 mg) of white solid. The compound was later remade using the general procedure for Suzuki–Miyaura cross-coupling described above (81% yield (36.7 mg) the product was >90% pure): ^{1}H NMR (270 MHz, acetone-d_6): 2.86 (m, 2H), 3.14 (m, 2H), 3.29 (m, 2H), 4.15 (m, 2H), 4.43 (d, J = 16.50, 2H), 4.67 (d, J = 16.50, 2H), 7.22 (m, 2H), 7.27–7.49 (m, 14H), 7.64 (m, 2H); ^{13}C NMR (270 MHz, $CDCl_3$): 47.5, 49.7, 71.7, 127.3, 127.4, 128.0, 128.2, 128.2, 128.3, 129.1, 130.0, 133.5, 140.3, 141.7. Anal. ($C_{30}H_{30}N_2O_4S$) C, H, N.

5.4.11. (4*S*,5*S*)-2,7-Bis[2-(4-methylphenyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (14). Compound **14** was prepared according to the general procedure (Section 5.4.2) in 60% yield (28.6 mg): ^{1}H NMR (270 MHz, acetone-d_6): 2.87 (m, 2H), 3.11 (m, 2H), 3.26 (m, 2H), 4.43 (d, J = 16.50, 2H), 4.68 (d, J = 16.50, 2H), 7.15 (m, 4H), 7.20 (m, 6H), 7.29 (m, 2H), 7.36 (m, 2H), 7.59 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 21.1, 48.7, 50.7, 72.7, 127.9, 128.4, 128.4, 129.8, 129.8, 130.8, 135.4, 137.6, 138.4, 142.5. Anal. ($C_{32}H_{34}N_2O_4S$) C, H, N.

5.4.12. (4*S*,5*S*)-2,7-Bis[2-(3-methylphenyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (15). Compound **15** was prepared according to the general procedure (Section 5.4.2) in 63% yield (30.1 mg): ^{1}H NMR (270 MHz, acetone-d_6): 2.36 (s, 6H), 2.89 (m, 2H), 3.17 (m, 2H), 3.29 (m, 2H), 4.1 (br s, 2H), 4.40 (d, J = 16.4, 2H), 4.61 (d, J = 16.4, 2H), 7.19 (m, 8H), 7.38 (m, 6H), 7.64 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 20.2, 48.6, 50.6, 72.8, 126.9, 127.9, 128.5, 128.6, 128.7, 129.0, 129.4, 130.6, 130.7, 135.3, 138.7, 141.4, 142.8. Anal. ($C_{32}H_{34}N_2O_4S$) C, H, N.

5.4.13. (4*S*,5*S*)-2,7-Bis[2-(4-*n*-butylphenyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (16). Compound **16** was prepared according to the general procedure (Section 5.4.2) to a yield of 60% (33.3 mg): ^{1}H NMR (270 MHz, acetone-d_6): 0.89 (t, J = 7.26, 6H), 1.33 (m, 4H), 1.60 (m, 4H), 2.62 (m, 4H), 2.84 (m, 2H), 3.10 (m, 2H), 3.26 (m, 2H), 4.07 (br s, 2H), 4.41 (d, J = 16.50, 2H), 4.63 (d, J = 16.50, 2H), 7.2 (m, 8H), 3.32 (m, 6H), 7.59 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 14.2, 23.0, 34.4, 35.8, 48.7, 50.8, 72.8, 128.0, 128.4, 128.6, 129.2, 129.8, 130.8, 135.4, 138.7, 142.6. Anal. ($C_{38}H_{36}N_2O_4S$) C, H, N.

5.4.14. (4*S*,5*S*)-2,7-Bis[2-(3-isopropylphenyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (17). Compound **17** was prepared according to the general procedure (Section 5.4.2) in 56% yield (29.7 mg): ^{1}H NMR (270 MHz, acetone-d_6): 1.22 (d, J = 6.93, 12H), 2.83 (m, 2H), 2.92 (m, J = 6.93, 2H), 3.08 (m, 2H), 3.23 (m, 2H), 4.08 (br s, 2H), 4.40 (d, J = 16.17, 2H), 4.59 (d, J = 16.17, 2H), 7.08 (m, 2H), 7.11–7.4 (m, 12H) 7.59 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 24.2, 30.1, 34.7, 48.8, 50.7, 72.9, 126.9, 127.4, 128.0, 128.1, 128.5, 128.8, 129.2, 130.7, 135.5, 141.4, 143.0, 149. Anal. ($C_{36}H_{42}N_2O_4S$) C, H, N.

5.4.15. (4*S*,5*S*)-2,7-Bis[2-(4-fluorophenyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (18). Compound **18** was prepared according to the general procedure (Section 5.4.2) in 62% yield (30.0 mg): ^{1}H NMR (270 MHz, acetone-d_6): 2.90 (m, 2H), 1.13 (m, 2H), 3.33 (m, 2H), 4.26 (s, 2H), 4.44 (d, J = 16.50, 2H), 4.66 (d, J = 16.50, 2H), 7.15–7.28 (m, 6H), 7.28–7.47 (m, 8H), 7.63 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 48.5, 50.8, 72.6, 115.9 (d, J = 21.97), 128.1, 128.7, 128.8, 130.9, 131.9 (d, J = 8.54), 135.6, 137.6 (d, J = 3.66), 141.5, 161.5 (d, J = 244.14). Anal. ($C_{30}H_{28}F_2N_2O_4S$) C, H, N.

5.4.16. (4*S*,5*S*)-2,7-Bis{2-[(3-trifluoromethyl)phenyl]benzyl}-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (19). Compound **19** was prepared according to the general procedure (Section 5.4.2) in 52% yield (29.5 mg): ^{1}H NMR (270 MHz, acetone-d_6): 2.99 (m, 2H), 3.12 (m, 2H), 2.36 (m, 2H), 4.26 (s, 2H), 4.39 (d, J = 16.50, 2H), 4.55 (d, J = 16.50, 2H), 7.29 (m, 2H), 7.44 (m, 4H), 7.70 (m, 10H); ^{13}C NMR (270 MHz, $CDCl_3$): 48.5, 50.9, 72.8, 124.8 (q, J = 3.66), 126.5 (q, J = 3.66), 128.2, 129.0, 129.2, 130.1, 130.9, 130.9 (q, J = 32), 133.9, 135.6, 141.0, 142.5. Anal. ($C_{32}H_{28}F_6N_2O_4S$) C, H, N.

5.4.17. (4*S*,5*S*)-2,7-Bis[2-(4-methoxyphenyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (20). Compound **20** was prepared according to the general procedure (Section 5.4.2) in 50% yield (25.3 mg): ^{1}H NMR (270 MHz, acetone-d_6): 2.68 (m, 2H), 3.13 (m, 2H), 3.76–3.90 (m, 10H), 4.28 (d, J = 15.01, 2H), 4.41 (d, J = 15.01, 2H), 7.02 (m, 4H), 7.23 (m, 6H), 7.32–7.43 (m, 4H), 7.52 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 49.1, 52.3, 55.5, 77.8, 114.6, 128.27, 128.29, 129.5, 131.0, 131.2, 133.5, 134.8, 142.6, 159.9. Anal. ($C_{32}H_{34}N_2O_6S$) C, H, N.

5.4.18. (4*S*,5*S*)-2,7-Bis[2-(4-acetylphenyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (21). Compound **21** was prepared according to the general procedure (Section 5.4.2) in 65% yield (34.3 mg): ^{1}H NMR

(270 MHz, acetone-d_6): 2.91 (m, 2H), 3.10 (m, 2H), 3.32 (m, 2H), 4.30 (br s, 2H), 4.30 (d, $J = 16.50$, 2H), 4.69 (d, $J = 16.50$, 2H), 7.25 (m, 2H), 7.30–7.51 (m, 8H), 7.66 (m, 2H), 8.07 (m, 4H); ^{13}C NMR (270 MHz, acetone-d_6): 26.9, 48.6, 50.9, 72.7, 128.3, 128.9, 129.2, 129.5, 130.4, 130.7, 135.6, 137.0, 141.7, 146.2, 197.8. Anal. ($C_{34}H_{34}N_2O_6S$) C, H, N.

5.4.19. (4*S*,5*S*)-2,7-Bis{2-[(4-ethylsulfonyl)phenyl]benzyl}-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (22). Compound **22** was prepared according to the general procedure (Section 5.4.2) in 26% yield (16.1 mg): ^{1}H NMR (270 MHz, acetone-d_6): 1.14 (t, $J = 7.26$, 6H), 2.79 (m, 2H), 3.98 (m, 2H), 3.15 (q, $J = 7.26$, 4H), 2.14 (m, 2H), 4.09 (s, 2H), 4.38 (d, $J = 16.17$, 2H), 4.58 (d, $J = 16.17$, 2H), 7.2 (m, 2H), 7.34 (m, 2H), 7.40 (m, 2H), 7.55 (m, 4H), 7.89 (m, 4H); ^{13}C NMR (270 MHz, acetone-d_6): 7.7, 48.3, 50.8, 72.7, 128.4, 129.0, 129.4, 129.5, 130.7, 130.9, 135.4, 138.9, 141.0, 146.8. Anal. ($C_{34}H_{38}N_2O_8S_3$) C, H, N.

5.4.20. (4*S*,5*S*)-2,7-Bis[2-(3-nitrophenyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (23). Compound **23** was prepared according to the general procedure (Section 5.4.2) in 60% yield (31.9 mg): ^{1}H NMR (270 MHz, acetone-d_6): 2.28 (m, 4H), 3.34 (m, 2H), 4.48 (d, $J = 16.17$, 2H), 4.67 (d, $J = 16.17$, 2H), 4.24 (s, 2H), 7.30 (m, 2H), 7.35–7.51 (m, 4H), 7.56–7.88 (m, 6H), 8.11–8.29 (m, 4H); ^{13}C NMR (270 MHz, acetone-d_6): 48.3, 50.9, 72.7, 122.9, 124.0, 124.6, 128.4, 129.4, 129.5, 130.3, 130.8, 135.6, 136.4, 140.3, 143.0, 149.0. Anal. ($C_{30}H_{28}N_4O_8S$) C, H, N.

5.4.21. (4*S*,5*S*)-2,7-Bis[2-(3,4-dimethoxyphenyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (24). Compound **24** was prepared according to the general procedure (Section 5.4.2) in 57% yield (31.9 mg): ^{1}H NMR (270 MHz, acetone-d_6): 2.87 (m, 2H), 3.15 (m, 2H), 3.31 (m, 2H), 4.24 (s, 2H), 4.47 (d, $J = 16.50$, 2H), 4.69 (d, $J = 16.50$, 2H), 6.82 (m, 2H), 6.9 (s, 2H), 7.00 (m, 2H), 7.21 (m, 2H), 7.35 (m, 4H), 7.61 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 48.8, 50.8, 56.1, 56.2, 72.8, 112.5, 113.8, 122.2, 127.9, 128.3, 128.7, 131.0, 134.1, 135.8, 142.8, 149.7, 150.1. Anal. ($C_{34}H_{38}N_2O_8S$) C, H, N.

5.4.22. (4*S*,5*S*)-2,7-Bis[2-(2-methoxyphenyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (25). Compound **25** was prepared according to the general procedure (Section 5.4.2) in 54% yield (27.5 mg) the product was >80% pure after extraction but was further purified by column chromatography before being sent to elemental analysis: ^{1}H NMR (270 MHz, acetone-d_6): 2.76–38 (m, 8H), 3.77 (m, 4H), 4.11 (m, 2H), 4.37 (br s, 2H), 6.98–7.20 (m, 8H), 7.29–7.47 (m, 6H), 7.61 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): (isomers in the spectra, major peaks reported) 48.6, 50.6, 55.6, 72.7, 111.6, 121.4, 127.7, 127.9, 128.4, 130.0, 131.1, 131.1, 131.4, 131.7, 136.6, 139.1. Anal. ($C_{32}H_{34}N_2O_6S{\cdot}2H_2O$) C, H, N.

5.4.23. (4*S*,5*S*)-2,7-Bis{2-[2-(methylthio)phenyl]benzyl}-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (26). Compound **26** was prepared according to the general procedure (Section 5.4.2) in 68% yield (34.1 mg): ^{1}H NMR (270 MHz, $CDCl_3$): 2.25 (m, 6H), 2.26–3.29 (m, 6H), 3.68–4.49 (m, 4H), 6.93–7.62 (m, 16H) OH-peak not visible; ^{13}C NMR (270 MHz, $CDCl_3$): (isomers in spectra; major peaks indicated when possible) 15.0 (major), 15.6, 47.2, 47.7 (major), 48.2, 49.5, 51.5, 51.7 (major), 52.1, 71.5, 71.8 (major), 72.1, 109.1, 123.8, 123.9 (major), 124.4 (major), 124.8, 126.5, 127.6 (major), 127.8, 128.6 (major), 128.4 (major), 128.7 (major), 129.1, 129.5, 129.7, 130.0 (major), 134.2 (major) 134.3, 134.8 (major), 138.1 (major), 139.2, 139.5 (major). Anal. ($C_{32}H_{34}N_2O_4S_3$) C, H, N.

5.4.24. (4*S*,5*S*)-2,7-Bis[2-(3-thienyl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (27). Compound **27** was prepared according to the general procedure (Section 5.4.2) in 45% yield (20.9 mg): ^{1}H NMR (270 MHz, acetone-d_6): 2.90 (m, 2H), 3.21 (m, 2H), 3.40 (m, 2H), 4.26 (br s, 2H), 4.55 (d, $J = 16.50$, 2H), 4.77 (d, $J = 16.50$, 2H), 7.21 (m, 2H), 7.25–7.52 (m, 8H), 7.57 (m, 2H), 7.65 (m, 2H); ^{13}C NMR (270 MHz, acetone-d_6): 48.7, 50.9, 72.8, 124.1, 126.6, 127.1, 128.0, 128.6, 128.6, 129.7, 130.8, 135.9, 137.2, 141.5. Anal. ($C_{28}H_{26}N_2O_4S_3$) C, H, N.

5.4.25. (4*S*,5*S*)-2,7-Bis[2-(benzo[*b*]furan-2-yl)benzyl]-4,5-dihydroxy-1,2,7-thiadiazepine 1,1-dioxide (28). Compound **28** was prepared according to the general procedure (Section 5.4.2) in 31% yield (16.1 mg); ^{1}H NMR (270 MHz, acetone-d_6): 3.19 (m, 2H), 3.43 (m, 2H), 3.67 (m, 2H), 4.22 (m, 2H), 4.94 (d, $J = 16.99$, 2H), 5.17 (d, $J = 16.99$, 2H), 7.17 (m, 2H), 7.24–7.40 (m, 4H), 7.40–7.58 (m, 4H), 7.58–7.75 (m, 4H), 7.75–7.90 (m, 4H); ^{13}C NMR (270 MHz, acetone-d_6): 48.7, 51.7, 72.8, 106.8, 112.0, 122.0, 124.0, 125.4, 128.4, 128.9, 129.8, 129.9, 130.1, 130.2, 136.3, 155.5, 155.6. Anal. ($C_{34}H_{30}N_2O_6S$) C, H, N.

Acknowledgements

We thank the Swedish Foundation for Strategic Research (SSF) and the Swedish Research Council (VR) for financial support. We also thank Biotage AB for providing a Smith Synthesizer. Dr. Johan Hultén is acknowledged for early work in this project.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2004.10.042.

References and notes

1. UNAIDS. 2004 Report on the Global AIDS Epidemic, 4th Global Report; Joint United Nations Programme on HIV/AIDS, World Health Organization; Geneva, 2004.
2. Jacobson, M. A.; French, M. *AIDS* **1998**, *12 Suppl A*, S157.
3. Collier, A. C.; Coombs, R. W.; Schoenfeld, D. A.; Bassett, R.; Baruch, A.; Corey, L. *Antiviral Res.* **1996**, *29*, 99.

4. Clavel, F.; Hance, A. J. *New Engl. J. Med.* **2004**, *350*, 1023.
5. Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, O. M. J.; Rayner, M. M. *Science* **1994**, *263*, 380.
6. Hultén, J.; Bonham, N. M.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Åqvist, J.; Classon, B.; Danielson, U. H.; Karlén, A.; Kvarnström, I.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 885.
7. Hultén, J.; Andersson, H. O.; Schaal, W.; Danielson, H. U.; Classon, B.; Kvarnström, I.; Karlén, A.; Unge, T.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 4054.
8. Bäckbro, K.; Löwgren, S.; Österlund, K.; Atepo, J.; Unge, T.; Hultén, J.; Bonham, N. M.; Schaal, W.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 898.
9. Schaal, W.; Karlsson, A.; Ahlsén, G.; Lindberg, J.; Andersson, H. O.; Danielson, U. H.; Classon, B.; Unge, T.; Samuelsson, B.; Hultén, J.; Hallberg, A.; Karlén, A. *J. Med. Chem.* **2001**, *44*, 155.
10. Kaldor, S. W.; Appelt, K.; Fritz, J.; Hammond, M.; Crowell, T. A.; Baxter, A. J.; Hatch, S. D.; Wiskerchen, M. A.; Muesing, M. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 715.
11. Carroll, F. I. *J. Org. Chem.* **1966**, *31*, 366.
12. Carmack, M.; Kelley, C. J. *J. Org. Chem.* **1968**, *33*, 2171.
13. Briggs, M. A.; Haines, A. H.; Jones, H. F. *J. Chem. Soc. Perkin Trans. 1* **1985**, 795.
14. Shainyan, B. A.; Ustinov, M. V.; Bel'skii, V. K.; Nindakova, L. O. *Russ. J. Org. Chem.* **2002**, *38*, 104.
15. Haines, A. H.; Morley, C.; Murrer, B. A. *J. Med. Chem.* **1989**, *32*, 742.
16. Hallberg, A.; Larhed, M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Bäckvall, J. E., Cacci, S., Hayashi, T., et al., Eds.; Wiley-Interscience: New York, 2002; Vol. I, pp 1133–1178.
17. Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582.
18. Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Bäckvall, T., Cacci, S., Hayashi, T. et al., Eds.; Wiley-Interscience: New York, 2002; Vol. I, pp 229–248.
19. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
20. Suzuki, A. In *Handbook of Organopalladium for Organic Synthesis*; Negishi, E., de Meijere, A., Bäckvall, J. E., Cacci, S., Hayashi, T. et al., Eds.; Wiley-Interscience: New York, 2002; Vol. I, pp 249–262.
21. Available Chemicals Directory; MDL Information Systems Inc., 14600 Catalina St., San Leandro, CA 94577, USA, www.mdli.com.
22. Wermuth, C. G. In *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed.; Academic Press: London, 2000; pp 203–237.
23. Maestro, 6.0 ed.; Schrödinger: 1500 S.W. First Avenue, Suite 1180 Portland, OR 97201, USA; www.schrodinger.com.
24. Yamazaki, T.; Nicholson, L. K.; Wingfield, P.; Stahl, S. J.; Kaufman, J. D.; Eyermann, C. J.; Hodge, C. N.; Lam, P. Y. S.; Torchia, D. A., et al. *J. Am. Chem. Soc.* **1994**, *116*, 10791.
25. MacroModel, 8.5 ed.; Schrödinger: 1500 S.W. First Avenue, Suite 1180 Portland, OR 97201, USA; www.schrodinger.com.
26. Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225.
27. Qui, D.; Shenkin, P. S.; Hollinger, F. P.; Still, W. C. *J. Phys. Chem.* **1997**, *101*, 3005.
28. Sybyl, 6.9 ed.; Tripos Inc.: 1699 South Hanley Rd., St. Louis, MO 63144, USA, www.tripos.com.
29. Simca-P+, 10.0.2.0, Sept 30, 2002 ed.; Umetrics: Box 7960, SE-907 19 Umeå, Sweden, www.umetrics.com.
30. Danielson, U. H.; Lindgren, M. T.; Markgren, P.-O.; Nillroth, U. *Adv. Exp. Med. Biol.* **1998**, *463*, 99.
31. Nillroth, U.; Vrang, L.; Markgren, P.-O.; Hulten, J.; Hallberg, A.; Danielson, U. H. *Antimicrob. Agents Chemother.* **1997**, *41*, 2383.
32. Pettersen, E. F.; Goddard, T. D.; Huang, C. C.; Couch, G. S.; Greenblatt, D. M.; Meng, E. C.; Ferrin, T. E. *J. Comput. Chem.* **2004**, *25*, 1605, www.cgl.ucsf.edu/chimera.