

Polymer-Supported Stereoselective Synthesis of Tetrahydrobenzopyrazino-thiadiazinone Dioxides via *N*-Sulfonyl Iminiums

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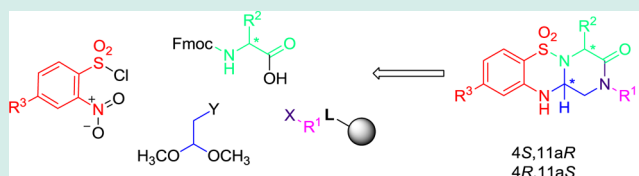
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S Supporting Information

ABSTRACT: The stereoselective synthesis of 1,2,11,11a-tetrahydrobenzo[*e*]pyrazino[1,2-*b*][1,2,4]thiadiazin-3(4*H*)-one 6,6-dioxides on a solid support via tandem *N*-sulfonyl iminium ion cyclization, followed by nucleophilic addition is reported. The synthesis proceeded with full control of stereoselectivity at the newly formed asymmetric carbon, under mild conditions, and using commercially available building blocks. The synthetic route provided high-purity crude products.

KEYWORDS: *N*-sulfonyl iminiums, polymer-supported, stereoselective, tetrahydrobenzopyrazinothiadiazinone, sp³ carbon



INTRODUCTION

Recent structural analyses of drugs and compound libraries used in high-throughput screening have revealed significant differences in the chemical space covered by individual groups of compounds.¹ Compared to drugs and natural products, the existing compound collections typically exhibit a low frequency of sp³-hybridized carbons and chiral centers.² The incorporation of a greater proportion of chiral compounds with higher degrees of saturation has been suggested to possibly improve clinical outcomes.^{3,4} Moreover, the hybridization of carbon atoms can influence the biological and physicochemical properties of the compounds.^{2–4} The fraction of sp³-hybridized carbon atoms out of the total carbon count, which is known as the Fsp³ value,² influences the “flatness” of the molecule.^{3,4} Larger Fsp³ values indicate that the molecule is more likely to have a nonplanar, three-dimensional architecture.^{1,2,5} Furthermore, it was suggested and supported by computational analysis that space coverage originated primarily from the 3D-geometry correlated with broad biological activity.^{6–8}

Our ongoing research is focused on the design and synthesis of compound collections with structural features that are largely missing from traditional compound decks. We have already developed efficient synthetic routes that lead to fused and bridged ring systems with 3D architectures as well as to the formation of asymmetric carbons, with full control over the stereochemistry.^{9–12} These synthetic routes have involved the formation of *N*-acyl-*N*-(2,2-dimethoxyethyl)alkylamides, which were transformed into the target compounds via tandem iminium-ion cyclization–nucleophilic addition. In this communication, we have extended the iminium-based chemistry and have focused on the solid-phase synthesis of 2,4,9,11-

tetrasubstituted 1,2,11,11a-tetrahydrobenzo[*e*]pyrazino[1,2-*b*][1,2,4]thiadiazin-3(4*H*)-one 6,6-dioxides (hereafter referred to as “tetrahydrobenzopyrazino-thiadiazinone dioxides”) via *N*-sulfonyl iminiums. Although *N*-acyl iminium chemistry has been documented in numerous examples,^{13–17} *N*-sulfonyl iminiums have been used only sporadically.^{18–24} To our knowledge, the use of *N*-sulfonyl iminiums in the formation of fused-ring heterocycles has been reported only recently.²⁵

Until now, the synthesis of tetrahydrobenzopyrazino-thiadiazinone dioxides **Ia** (Figure 1) had not been described. The closest related compounds, 1,2,3,4,11,11a-hexahydrobenzo[*e*]pyrazino[1,2-*b*][1,2,4]thiadiazine 6,6-dioxides **Ib**, were patented almost half a century ago, in 1967.²⁶ Since then, little attention has been paid to these compounds, despite their demonstrated use as central nervous system depressants and analgesics.²⁶ Other related compounds, **II**, contain a cyclic guanidine moiety²⁷ and have exhibited interesting biological properties, including antitumor, broncholytic,²⁸ antihypertensive,²⁹ and immunosuppressive activities.³⁰ Moreover, the 1,2,4-benzothiadiazine-1,1-dioxide core induced antagonistic activity toward the chemokine CXCR2 receptor³¹ and adrenergic system,^{32,33} as well as activation of potassium channels.³⁴

The synthesis of 2,3,10,10a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*b*][1,2,4]thiadiazine 5,5-dioxides **III** (Figure 1) via reductive cyclization of appropriate iminium ions has been reported previously.³⁵ Similarly, the chemical route leading to compound **IV** (Figure 1) and its stereoisomer has been shown

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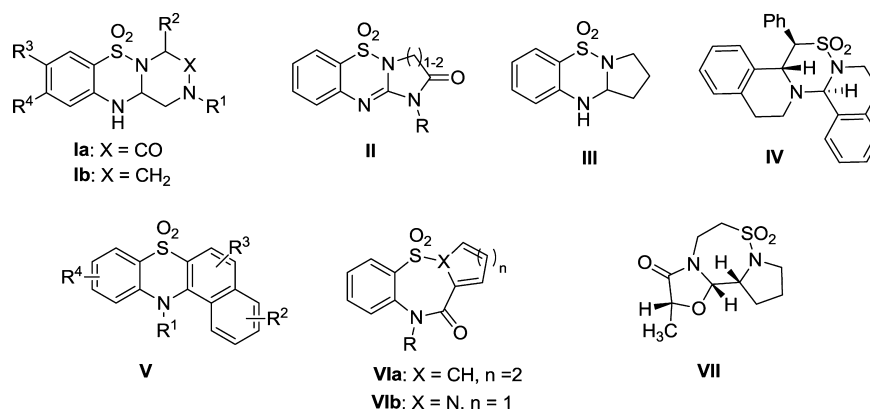


Figure 1. Reported related heterocycles.

to involve iminium ions as the key intermediates.³⁶ 12*H*-Benzo[*a*]phenothiazine 7,7-dioxides **V** (Figure 1) were found to be useful in the treatment of allergy, asthma, cardiovascular disorders, inflammation, and pain, and they can serve as cytoprotective agents.^{37,38} Compounds **VIa** (Figure 1) have been reported to be non-nucleoside reverse transcriptase inhibitors (NNRTIs).³⁹ Benzo[*f*]pyrrolo[1,2-*b*][1,2,5]-thiadiazepin-11(10*H*)-one 5,5-dioxides **VIb** have been synthesized, and their antiviral activity has been evaluated.⁴⁰ The effects of the presence of pyrrole and carbonyl moieties have been investigated. The pyrrole ring was found to be a determinant for anti-HIV-1 activity, and its replacement with a saturated pyrrolidine eliminates that activity. Similarly, the reduction of the carbonyl to a methylene inactivates the compounds. Sulfonamide **VII** (Figure 1) has also been described, and its conformation has been studied in detail.⁴¹

Marketed drugs diazoxide (Eudemine, Hyperstat IV, Proglycem) **VIII** (Figure 2) and hydrochlorothiazide (Cidrex,

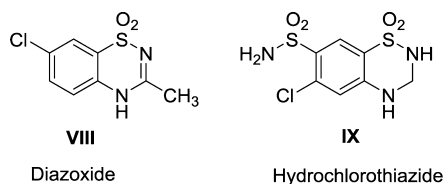


Figure 2. Marketed drugs containing the 1,2,4-benzothiadiazine-1,1-dioxide core.

Disalunil, Hydrodiuril, Microzide) **IX** (Figure 2) contain the 1,2,4-benzothiadiazine-1,1-dioxide core and are used as antihypertensives (diazoxide and hydrochlorothiazide in combination with other drugs), as diuretics (hydrochlorothiazide), and for the treatment of hypoglycemia (diazoxide).^{42–44}

Here, we describe the solid-phase synthesis of tetrahydrobenzopyrazino-thiadiazinone dioxides with three diversity positions and three *sp*³-hybridized carbon atoms on the skeleton, two of which are chiral.

RESULTS AND DISCUSSION

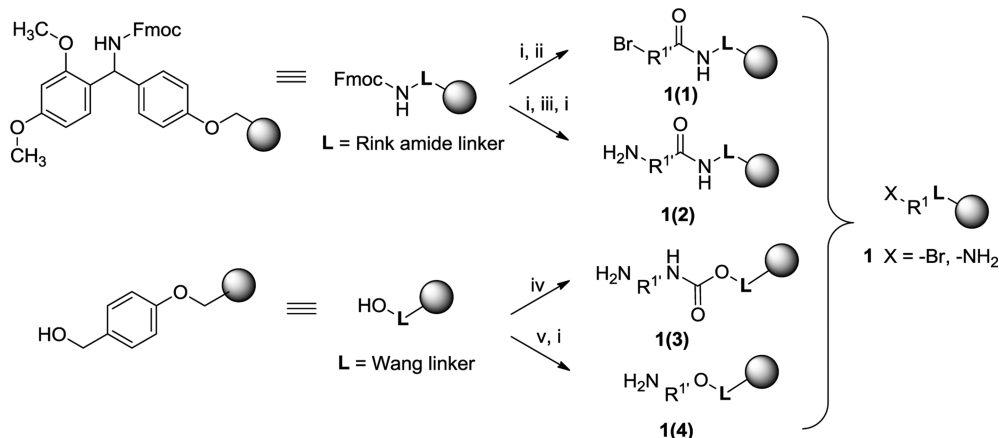
The key step in our synthetic route was the tandem *N*-sulfonyl iminium-ion cyclization–nucleophilic addition reaction. Cyclic *N*-sulfonyl iminium intermediates were formed from an aldehyde and sulfonamide. The aldehyde functionality was incorporated in protected form as a dimethyl acetal and was linked via a two-carbon spacer to the amide nitrogen. Dimethyl acetals were unmasked using 50% trifluoroacetic acid (TFA) in

dichloromethane (DCM) to afford the cyclic *N*-sulfonyl iminium ion. Subsequent intramolecular attack by the aniline nitrogen closed the fused rings, and the target structures were simultaneously released from the resin.

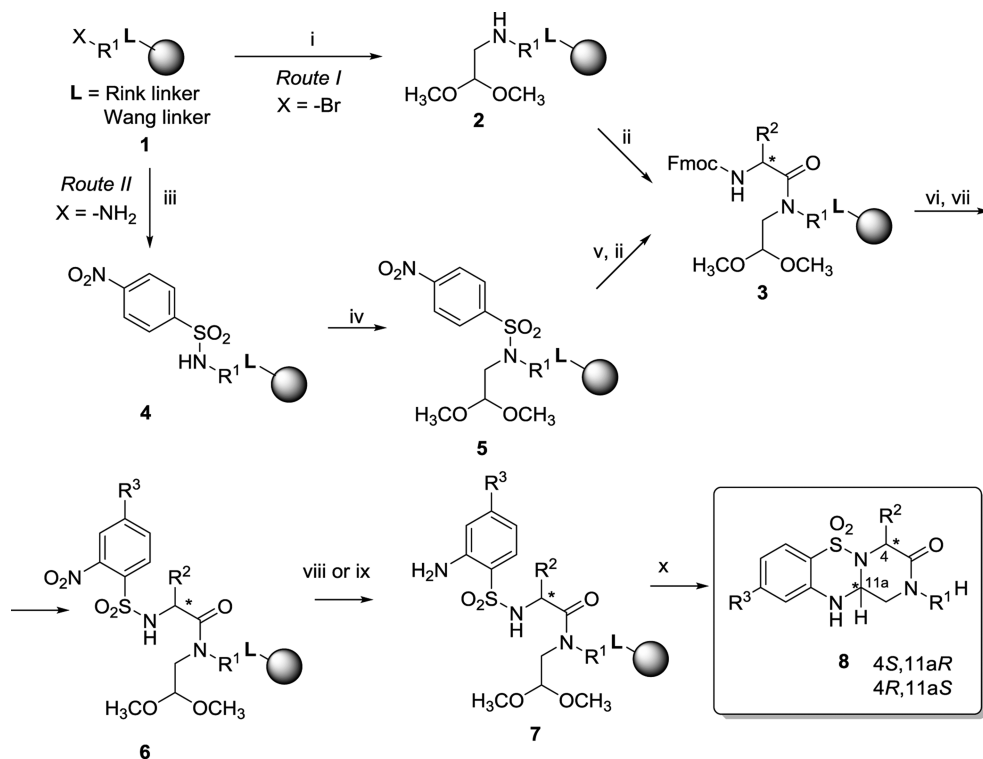
Our strategy closely followed the recently reported stereoselective synthesis of benzimidazolinopiperazinones on a polymer support.⁹ To achieve diversity at the *R*¹ side chain, we chose to immobilize the first building blocks on Wang and Rink amide resins. Rink amide resin was used to attach two carboxylic acids with carbon chains of different lengths and a terminal functional group (bromide or amino), specifically, bromoacetic acid and Fmoc-β-Ala-OH (Scheme 1, structures **1**(1) and **1**(2)). The target compounds released from the resin contained an amide. To expand the diversity of the final compounds at the *R*¹ position, a diamine (ethylenediamine) and an Fmoc-amino alcohol were immobilized on the Wang resin (Scheme 1, structures **1**(3) and **1**(4)) and yielded amines and alcohols, respectively.

The key intermediates, *N*-acyl-*N*-(2,2-dimethoxyethyl)-amines **3** (Scheme 2), were prepared according to two different published routes.⁹ Briefly, route I started with Rink-supported bromoacetic acid **1** (*R*¹ = –CH₂–; X = –Br). The bromine was substituted with aminoacetaldehyde dimethyl acetal in the presence of DIEA in DMF to yield the resin-bound *N*-((2,2-dimethoxyethyl)amino)amine **2**. Acylation of this intermediate with various Fmoc-amino acids, i.e., Fmoc-Gly-OH, Fmoc-Ala-OH, Fmoc-Leu-OH, Fmoc-Ile-OH, Fmoc-Ser(*t*Bu)-OH, Fmoc-Tyr(*t*Bu)-OH, and Fmoc-D-Ala-OH afforded the key intermediates, *N*-acyl-*N*-(2,2-dimethoxyethyl)amines **3**.

The second route, route II, enabled access to a greater diversity of compounds; the side chain *R*¹ represents amides **1**(2), amines **1**(3), or alcohols **1**(4) (Scheme 1). Resins **1** (Scheme 2; X = –NH₂) were treated with 4-nitrobenzenesulfonyl chloride (4-Nos-Cl) to afford the corresponding 4-nitrobenzenesulfonamides **4**. These intermediates, each bearing an activated nitrogen atom, underwent Mitsunobu alkylation and yielded alkylated sulfonamides **5**. These reactions were conducted in a solution containing 0.1 M glycolaldehyde dimethyl acetal, 0.1 M PPh₃, and 0.1 M DIAD in anhydrous tetrahydrofuran (THF) at 50 °C for 16 h.⁹ Deprotection of the 4-Nos-group followed by acylation with various Fmoc-α-amino acids (Figure 3, BB2) yielded the *N*-acyl-*N*-(2,2-dimethoxyethyl)amines **3** in high purity. The Fmoc protecting group was replaced by three 2-nitrobenzenesulfonyl chlorides that differ in their substitution at the para position. Unsubstituted 2-Nos-Cl and derivatives substituted with

Scheme 1. Immobilization of the First Building Blocks on a Polymer Support^a

^aReagents and conditions: (i) 50% piperidine in DMF, rt, 15 min; (ii) bromoacetic acid (2 equiv), *N,N'*-diisopropylcarbodiimide (DIC, 1 equiv), DCM, 5 min, then *N,N'*-diisopropylethylamine (DIEA, 1 equiv), rt, 2 h; (iii) Fmoc-amino acid (1 equiv), 1-hydroxybenzotriazole hydrate (HOBt, 1 equiv), DIC (1 equiv), DCM/DMF (1:1), rt, 16 h; (iv) 1,1'-carbonyldiimidazole (CDI), pyridine, DCM, rt, 2 h, then ethylenediamine, DCM, rt, 2 h; (v) CCl_3CN , DBU, DCM, rt, 2 h, then 3-(Fmoc-amino)propanol, $\text{BF}_3\cdot\text{Et}_2\text{O}$, anhydrous THF, rt, 1 h, then Fmoc- β -Ala-OH (1 equiv), 1-hydroxybenzotriazole hydrate (HOBt, 1 equiv), DIC (1 equiv), DCM/DMF (1:1), rt, 16 h.

Scheme 2. Solid-Phase Stereoselective Synthesis of Tetrahydrobenzopyrazino-thiadiazinone Dioxides 8^a

^aReagents and conditions: (i) aminoacetaldehyde dimethyl acetal, DIEA, DMF, rt, 2 h; (ii) Fmoc- α -amino acid (1 equiv), HOBt (1 equiv), DIC (1 equiv), DCM/DMF (1:1), rt, 16 h; (iii) 4-Nos-Cl, 2,6-lutidine, DCM, rt, 4 h; (iv) glycolaldehyde dimethyl acetal, PPh_3 , diisopropyl azodicarboxylate (DIAD), anhydrous THF, 0–50 °C, 16 h, repetition; (v) 2-mercaptoethanol, DBU, DMF, rt, 5 min; (vi) 50% piperidine in DMF, rt, 15 min; (vii) unsubstituted/4-substituted 2-Nos-Cl, 2,6-lutidine, DCM, rt, 4 h; (viii) $\text{SnCl}_2\cdot 2\text{H}_2\text{O}$, DIEA, DMF (saturated with N_2), 50 °C, see Table 1 for reaction times; (ix) $\text{Na}_2\text{S}_2\text{O}_4$, tetrabutylammonium hydrogen sulfate (TBAHS), K_2CO_3 , DCM/water (1:1), rt, 2 h; (x) 50% TFA in DCM, rt, 90 min.

electron-withdrawing groups were evaluated (Figure 3, BB3). This series provided access to the appropriate 2-nitrobenzenesulfonamides 6. A list of the synthetic building blocks is shown in Figure 3.

The last step on solid support involved reduction of the nitro group. The polymer-supported nitroarenes were typically

reduced by tin(II) chloride dihydrate.⁴⁵ The reduction, however, was reportedly problematic on several occasions, with incomplete reduction⁴⁶ and tin salt contamination⁹ being the most severe. We observed both of these problems during the reduction of intermediates 6. Several derivatives were incompletely reduced, and LC/MS analysis revealed the

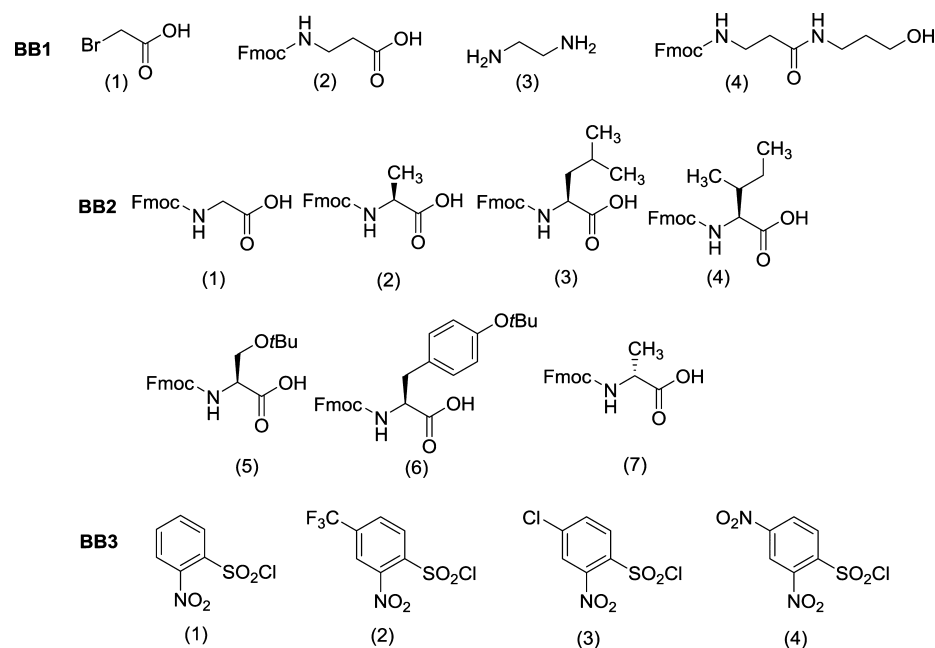


Figure 3. Building blocks used for the synthesis of tetrahydrobenzopyrazino-thiadiazinone dioxides 8.

Table 1. Synthesized Derivatives of Tetrahydrobenzopyrazino-thiadiazinone Dioxide 8

8 4*S*,11*aR*
4*R*,11*aS*

compound	R ¹ -H	R ²	R ³	reduction ^a	purity ^b (%)	yield ^c (%)
8(1,1,1)	-CH ₂ -CONH ₂	-H	-H	A: rt, 2 days	93	63
8(1,1,2)	-CH ₂ -CONH ₂	-H	-CF ₃	A: rt, 2 days	97	25
8(1,2,1)	-CH ₂ -CONH ₂	-(<i>S</i>)-CH ₃	-H	A: rt, 2 days	98	46
8(1,2,2)	-CH ₂ -CONH ₂	-(<i>S</i>)-CH ₃	-CF ₃	A: rt, 2 days	96	33
8(1,3,1)	-CH ₂ -CONH ₂	-(<i>S</i>)- <i>i</i> Bu	-H	A: 50 °C, on	74 ^d	73
8(1,4,1)	-CH ₂ -CONH ₂	-(<i>S</i>)- <i>sec</i> Bu	-H	A: 60 °C, on	49 ^d	20
9(1,4,1)	-CH ₂ -CONH ₂	-(<i>S</i>)- <i>sec</i> Bu	-H	A: 60 °C, on	42	13
8(1,5,1)	-CH ₂ -CONH ₂	-(<i>S</i>)-CH ₂ OH	-H	A: 50 °C, on	79 ^d	48
8(1,5,2)	-CH ₂ -CONH ₂	-(<i>S</i>)-CH ₂ OH	-CF ₃	A: rt, 2 days	94	36
8(1,6,1)	-CH ₂ -CONH ₂	-(<i>S</i>)- <i>p</i> -OH-Bn	-H	A: rt, 2 days	98	65
8(2,2,1)	-(CH ₂) ₂ -CONH ₂	-(<i>S</i>)-CH ₃	-H	B: rt, 2 h	93	60
8(2,2,2)	-(CH ₂) ₂ -CONH ₂	-(<i>S</i>)-CH ₃	-CF ₃	B: rt, 2 h	91	53
8(2,7,1)	-(CH ₂) ₂ -CONH ₂	-(<i>R</i>)-CH ₃	-H	B: rt, 2 h	95	57
8(2,7,2)	-(CH ₂) ₂ -CONH ₂	-(<i>R</i>)-CH ₃	-CF ₃	B: rt, 2 h	95	58
8(3,5,2)	-(CH ₂) ₂ -NH ₂	-(<i>S</i>)-CH ₂ OH	-CF ₃	A: rt, 2 days	74	27
8(3,6,2)	-(CH ₂) ₂ -NH ₂	-(<i>S</i>)- <i>p</i> -OH-Bn	-CF ₃	A: rt, 2 days	99	23
8(4,2,2)	-(CH ₂) ₂ -CONH-(CH ₂) ₃ -OH	-(<i>S</i>)-CH ₃	-CF ₃	B: rt, 2 h	83	63
8(4,2,3)	-(CH ₂) ₂ -CONH-(CH ₂) ₃ -OH	-(<i>S</i>)-CH ₃	-Cl	B: rt, 2 h	80	74

^aA: Tin(II) chloride method. B: Dithionite method. ^bPurity of the crude product. ^cTotal yield after purification by reverse-phase HPLC. ^dIncompletely reduced; contained *N*-hydroxy derivative 9.

presence of *N*-hydroxy derivatives of target compound 8 (referred to as compound 9). In the case of incomplete reduction, the reaction was repeated overnight (see Table 1). The reduction of derivative 6(1,4,1), however, did not proceed quantitatively, even when the temperature was increased to 80 °C. Therefore, we isolated, purified, and fully characterized the *N*-hydroxy derivative 9(1,4,1). Moreover, the crude products were contaminated by tin salts despite thorough washing of the

resin. The tin salts were liberated upon acid cleavage of the product, thus making the final purification substantially more complex. Therefore, the crude product solution was passed through an octadecyl silica plug as a prepurification step (see Experimental Procedures).

To overcome the problems with tin chloride reduction, we searched for an alternative reducing agent and obtained superior results by reducing the nitro group with sodium

dithionite in DCM–water and TBAHS as a phase-transfer catalyst.⁴⁷ Application of this method proceeded with complete conversion and afforded good yields of the desired products **8** after simple and fast purification.

The target tetrahydrobenzopyrazino-thiadiazinone dioxides **8** were obtained from resin-bound intermediates **7** by acid-mediated deprotection of acetal with concurrent TFA cleavage from the acid-labile linkers. With the exception of compounds suffering from incomplete reduction by tin(II) chloride, the crude products were obtained in high purity, where the purity ranged from 74% to 99% (Table 1).

Compounds **8**(1,1,1) and **8**(1,1,2), which were synthesized with Fmoc-Gly-OH (BB2 = (1)), formed a racemic mixture. The absence of a stereogenic center in the ring-forming acyclic precursor failed to induce stereospecific nucleophilic addition. In contrast, the synthesis of target tetrahydrobenzopyrazino-thiadiazinone dioxides **8**, which were prepared with chiral amino acids, proceeded with full stereochemical control. L-Amino acids in the (S)-configuration yielded tetrahydrobenzopyrazino-thiadiazinone dioxides with an (R)-configuration on the newly formed stereogenic center (carbon 11a). Only one diastereoisomer was detected in the LC/MS traces, and the ¹H and ¹³C NMR spectra of the purified compounds confirmed their optical purity. These results are consistent with those from the stereoselective synthesis of related bicyclic tetrahydro-1H-pyrazino[1,2-*a*]pyrimidine-4,7(6H,8H)-diones. The configuration was confirmed by ROESY 2D NMR and X-ray crystallography.⁴⁸ Furthermore, we have recently described a related stereoselective, solid-phase synthesis of 1,2,10,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-3(4H)-ones.⁹

To demonstrate the stereochemical diversity provided by this reaction,^{49,50} we also prepared target compounds with Fmoc-D-Ala-OH. As predicted, its (R)-configuration produced an (S)-configuration on carbon 11a of the products (**8**(2,7,1) and **8**(2,7,2)). These enantiomers differ in their 3D spatial arrangements while having 2D structures identical to those of their analogues **8**(2,2,1) and **8**(2,2,2).

CONCLUSION

We described the stereoselective, solid-phase synthesis of tetrahydrobenzopyrazino-thiadiazinone dioxides via *N*-sulfonyl iminium ion cyclization–nucleophilic addition. The target compounds have three diversity positions and were prepared from simple, commercially available building blocks, including L- and D-amino acids, to generate stereochemical diversity. These chiral amino acids controlled the configuration of the newly formed chiral center and afforded optically pure products. Given their favorable structural properties, which include a nonplanar scaffold, chiral carbons, and a sulfonamide moiety, as well as the biological activity observed for several of their analogues, tetrahydrobenzopyrazino-thiadiazinone dioxides represent heterocycles with potential therapeutic activity.

EXPERIMENTAL PROCEDURES

The solid-phase syntheses were carried out in plastic reaction vessels (syringes, each equipped with a porous disc) using a manually operated synthesizer.⁵¹ The volume of the wash solvent was 10 mL per 1 g of resin. For washing, the resin slurry was shaken with fresh solvent for at least 1 min before changing the solvent. All reactions were carried out at ambient temperature unless stated otherwise. Commercially available Rink resin (100–200 mesh, 0.66 mmol/g) and Wang resin

(100–200 mesh, 1.0 mmol/g) were used. Individual synthetic steps for the synthesis of resins **3** were described in our recent publications.⁹

Cleavage of the Fmoc-Protecting Group and Reaction with Unsubstituted/4-Substituted 2-Nos-Cl (Resins 6). Resins **3** (1 g), which were prepared according to a reported protocol,⁹ were washed with DCM 3× and DMF 3× and treated with 50% piperidine in DMF for 15 min. After the resins were washed with DMF 3× and DCM 3×, a solution of 2-Nos-Cl (3 mmol) and 2,6-lutidine (3.3 mmol, 382 μL) in 10 mL of DCM was added to the resin, and the resulting slurry was shaken at rt for 16 h. The resin was subsequently washed with DCM 3×.

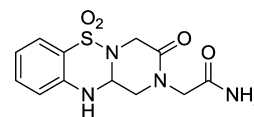
Reduction of the Nitro Group with Tin(II) Chloride Dihydrate (Resins 7). Resins **6** (0.25 g) were swollen in DCM and washed with N₂-saturated DMF 3×. A solution containing tin(II) chloride dihydrate (2.5 mmol, 564 mg) and DIEA (2.5 mmol, 433 μL) in 2.5 mL of N₂-saturated DMF was then added to the resin. The temperatures and reaction times for individual compounds are listed in Table 1. The resins were washed thoroughly with DMF 7× and DCM 5×.

Cleavage, Cyclization, and Isolation of the Products (8). Resins **7** (0.25 g) were treated with 3 mL of 50% TFA in DCM at rt for 90 min. The cleavage products were collected, and the resins were washed with 50% TFA in DCM 3×. All washes were combined and evaporated by a stream of nitrogen.

Isolation after Tin(II) Chloride Reduction. The oily residue was dissolved in 1 mL of MeCN and was diluted with 15 mL of water. Depending on the compound used, a solution or an opalescent solution, occasionally with precipitation, was formed. A 3 mL of octadecyl cartridge (Applied Separations) was wetted with 3 mL of MeCN and washed with 3 mL of distilled water. Half the volume of the solution of the target compound was passed through the column, and the column was washed with 3 mL of distilled water. The target compound was eluted with 3–5 mL of MeCN. The MeCN was evaporated, and the oily residue was concentrated on a freeze drier for 16 h; the residue was then weighed and dissolved in 0.7 mL of DMSO-*d*₆ for NMR analysis. The solution was purified by semipreparative reversed-phase HPLC.

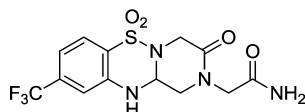
Isolation after Dithionite Reduction. The oily residue was dissolved in 1 mL of MeCN and purified by semipreparative reversed-phase HPLC.

2-(6,6-Dioxido-3-oxo-3,4,11,11a-tetrahydrobenzo[*e*]pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1H)-yl)acetamide 8-(1,1,1).



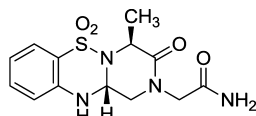
Yield: 18.6 mg (63%) of amorphous solid. ¹H NMR (600 MHz, DMSO-*d*₆): δ 7.60–7.53 (m, 2 H), 7.47 (s, 1 H), 7.40 (ddd, *J* = 1.5, 7.8 Hz, 1 H), 7.22 (br. s., 1 H), 6.89–6.81 (m, 2 H), 5.47–5.41 (m, 1 H), 4.32 (d, *J* = 16.4 Hz, 1 H), 3.95 (dd, *J* = 3.4, 13.4 Hz, 1 H), 3.74 (d, *J* = 16.4 Hz, 1 H), 3.65 (d, *J* = 16.4 Hz, 1 H), 3.51 (dd, *J* = 1.8, 13.4 Hz, 1 H), 3.09 (d, *J* = 16.4 Hz, 1 H). ¹³C NMR (151 MHz, DMSO-*d*₆): δ 169.6, 163.1, 142.6, 133.9, 125.6, 117.9, 116.2, 116.1, 62.5, 50.6, 48.6, 44.9. HRMS (ESI-TOF): *m/z* calcd for C₁₂H₁₅N₄O₄S [M + H]⁺ 311.0809, found 311.0893.

2-(6,6-Dioxido-3-oxo-9-(trifluoromethyl)-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-b][1,2,4]thiadiazin-2(1H)-yl)acetamide 8(1,1,2).



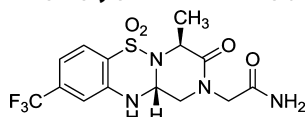
Yield: 12.5 mg (25%) of amorphous solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 7.96 (s, 1 H), 7.81 (d, J = 8.2 Hz, 1 H), 7.56 (br. s., 1 H), 7.23 (br. s., 1 H), 7.17 (s, 1 H), 7.11 (d, J = 8.2 Hz, 1 H), 5.56–5.46 (m, 1 H), 4.32 (d, J = 16.4 Hz, 1 H), 3.98 (dd, J = 3.4, 13.6 Hz, 1 H), 3.77 (d, J = 16.4 Hz, 1 H), 3.66 (d, J = 16.4 Hz, 1 H), 3.53 (d, J = 13.6 Hz, 1 H), 3.18 (d, J = 16.4 Hz, 1 H). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 169.5, 162.8, 143.2, 133.6 (q, J = 31.5 Hz), 127.5, 123.3 (q, J = 271.5 Hz), 119.1, 113.5, 113.0, 62.5, 50.5, 48.6, 44.8. HRMS (ESI-TOF): m/z calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{N}_4\text{O}_4\text{S}$ [$\text{M} + \text{H}$] $^+$ 379.0682, found 379.0684.

2-((4S,11aR)-4-Methyl-6,6-dioxido-3-oxo-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-b][1,2,4]thiadiazin-2(1H)-yl)acetamide 8(1,2,1).



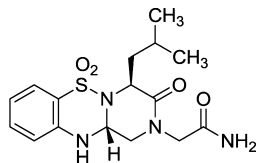
Yield: 38.6 mg (46%) of amorphous solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 7.73 (br. s., 1 H), 7.69 (d, J = 1.8 Hz, 1 H), 7.55 (dd, J = 1.5, 7.9 Hz, 1 H), 7.43–7.33 (m, 2 H), 6.85–6.74 (m, 2 H), 5.44–5.38 (m, 1 H), 4.10–3.94 (m, 3 H), 3.63 (dd, J = 2.6, 13.8 Hz, 1 H), 3.33 (q, J = 6.9 Hz, 1 H), 1.49 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 170.9, 168.0, 143.1, 133.9, 125.3, 117.4, 116.1, 116.0, 63.4, 53.5, 49.6, 48.3, 22.4. HRMS (ESI-TOF): m/z calcd for $\text{C}_{13}\text{H}_{17}\text{N}_4\text{O}_4\text{S}$ [$\text{M} + \text{H}$] $^+$ 325.0965, found 325.0992.

2-((4S,11aR)-4-Methyl-6,6-dioxido-3-oxo-9-(trifluoromethyl)-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-b][1,2,4]thiadiazin-2(1H)-yl)acetamide 8(1,2,2).



Yield: 19.6 mg (33%) of amorphous solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 8.16 (d, J = 1.8 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 1 H), 7.73 (br. s., 1 H), 7.41 (br. s., 1 H), 7.09 (dd, J = 1.3, 8.3 Hz, 1 H), 7.05 (s, 1 H), 5.51–5.46 (m, 1 H), 4.15–4.05 (m, 2 H), 4.00–3.91 (m, 1 H), 3.66 (dd, J = 2.8, 14.2 Hz, 1 H), 3.43–3.36 (m, 1 H), 1.50 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 170.9, 167.6, 143.5, 133.7 (q, J = 31.5 Hz), 127.2, 123.3 (q, J = 273.0 Hz), 118.9, 113.1, 112.7, 63.5, 53.5, 49.4, 48.4, 22.3. HRMS (ESI-TOF): m/z calcd for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{N}_4\text{O}_4\text{S}$ [$\text{M} + \text{H}$] $^+$ 393.0839, found 393.0864.

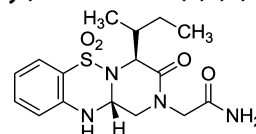
2-((4S,11aR)-4-Isobutyl-6,6-dioxido-3-oxo-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-b][1,2,4]thiadiazin-2(1H)-yl)acetamide 8(1,3,1).



Yield: 20.0 mg (73%) of amorphous solid. ^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ 7.78 (d, J = 2.3 Hz, 1 H), 7.75 (br. s., 1 H), 7.53 (dd, J = 1.8, 8.0 Hz, 1 H), 7.39–7.32 (m, 2 H), 6.79 (ddd, J =

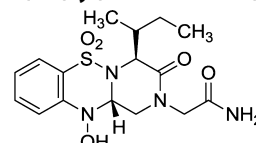
1.0, 7.1, 8.0 Hz, 1 H), 6.75 (dd, J = 1.0, 8.5 Hz, 1 H), 5.47–5.36 (m, 1 H), 4.07–3.97 (m, 3 H), 3.66 (dd, J = 2.8, 14.2 Hz, 1 H), 3.45–3.39 (m, 1 H), 1.84–1.74 (m, 2 H), 1.74–1.66 (m, 1 H), 0.87 (d, J = 6.5 Hz, 3 H), 0.83 (d, J = 6.5 Hz, 3 H). ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$): δ 171.2, 167.5, 143.2, 133.8, 125.0, 117.2, 116.4, 116.2, 63.9, 56.3, 49.5, 48.2, 44.9, 23.6, 23.4, 22.0. HRMS (ESI-TOF): m/z calcd for $\text{C}_{16}\text{H}_{23}\text{N}_4\text{O}_4\text{S}$ [$\text{M} + \text{H}$] $^+$ 367.1435, found 367.1431.

2-((4S,11aR)-4-((R)-sec-Butyl)-6,6-dioxido-3-oxo-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-b][1,2,4]thiadiazin-2(1H)-yl)acetamide 8(1,4,1).



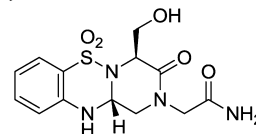
Yield: 5.6 mg (20%) of amorphous solid. ^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ 7.76–7.69 (m, 2 H), 7.54 (dd, J = 1.5, 7.9 Hz, 1 H), 7.37 (ddd, J = 1.5, 7.2, 8.5 Hz, 1 H), 7.33 (br. s., 1 H), 6.80 (ddd, J = 1.0, 7.2, 7.9 Hz, 1 H), 6.75 (dd, J = 1.0, 8.5 Hz, 1 H), 5.49–5.43 (m, 1 H), 4.05–3.98 (m, 2 H), 3.98 (dd, J = 2.1, 14.1 Hz, 1 H), 3.61 (dd, J = 2.8, 14.1 Hz, 1 H), 3.37 (d, J = 3.2 Hz, 1 H), 2.12–1.98 (m, 1 H), 1.47–1.38 (m, 1 H), 1.27–1.18 (m, 1 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.81 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$): δ 171.1, 165.4, 143.1, 133.9, 125.2, 117.3, 116.1, 116.0, 63.8, 60.7, 49.9, 48.2, 41.4, 26.3, 13.3, 11.9. HRMS (ESI-TOF): m/z calcd for $\text{C}_{16}\text{H}_{23}\text{N}_4\text{O}_4\text{S}$ [$\text{M} + \text{H}$] $^+$ 367.1435, found 367.1429.

2-((4S,11aR)-4-((R)-sec-Butyl)-11-hydroxy-6,6-dioxido-3-oxo-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-b][1,2,4]thiadiazin-2(1H)-yl)acetamide 9(1,4,1).



Yield: 3.6 mg (13%) of amorphous solid. ^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ 10.59 (s, 1 H), 7.96 (br. s., 1 H), 7.59 (dd, J = 1.5, 7.9 Hz, 1 H), 7.57–7.53 (m, 2 H), 7.30 (dd, J = 0.6, 8.5 Hz, 1 H), 7.05–7.01 (m, 1 H), 5.52–5.49 (m, 1 H), 4.05 (d, J = 16.1 Hz, 1 H), 4.02–3.96 (m, 2 H), 3.84 (dd, J = 1.5, 14.4 Hz, 1 H), 3.76 (d, J = 3.2 Hz, 1 H), 2.14–2.08 (m, 1 H), 1.53–1.47 (m, 1 H), 1.32–1.25 (m, 1 H), 0.92 (d, J = 7.0 Hz, 3 H), 0.84 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$): δ 172.0, 165.2, 145.6, 134.1, 124.9, 121.0, 120.3, 116.0, 71.4, 61.4, 48.9, 48.5, 41.5, 26.3, 13.3, 11.9. HRMS (ESI-TOF): m/z calcd for $\text{C}_{16}\text{H}_{23}\text{N}_4\text{O}_5\text{S}$ [$\text{M} + \text{H}$] $^+$ 383.1384, found 383.1394.

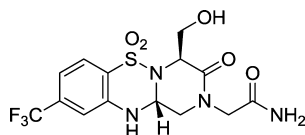
2-((4S,11aR)-4-(Hydroxymethyl)-6,6-dioxido-3-oxo-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-b][1,2,4]thiadiazin-2(1H)-yl)acetamide 8(1,5,1).



Yield: 12.3 mg (48%) of amorphous solid. ^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ 7.77 (br. s., 1 H), 7.64 (br. s., 1 H), 7.53 (dd, J = 1.5, 7.9 Hz, 1 H), 7.46 (br. s., 1 H), 7.37 (ddd, J = 1.5, 7.0, 8.5 Hz, 1 H), 6.82–6.75 (m, 2 H), 5.51–5.47 (m, 1 H), 4.08 (d, J = 17.0 Hz, 1 H), 4.01–3.93 (m, 2 H), 3.87 (dd, J = 2.5, 11.0 Hz, 1 H), 3.77 (dd, J = 2.1, 11.0 Hz, 1 H), 3.63 (dd, J = 2.9, 13.5 Hz, 1 H), 3.34 (t, J = 2.1 Hz, 1 H). ^{13}C NMR (151 MHz,

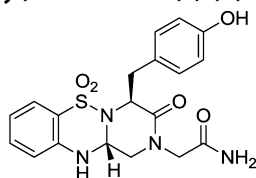
DMSO- d_6): δ 171.1, 166.4, 143.2, 133.9, 125.1, 117.2, 116.2, 116.0, 65.1, 63.5, 59.9, 49.5, 48.8. HRMS (ESI-TOF): m/z calcd for $C_{13}H_{17}N_4O_5S$ $[M + H]^+$ 341.0914, found 341.0920.

2-((4*S*,11*aR*)-4-(Hydroxymethyl)-6,6-dioxido-3-oxo-9-(trifluoromethyl)-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1*H*)-yl)acetamide 8-(1,5,2).



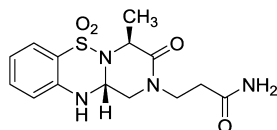
Yield: 19.3 mg (36%) of amorphous solid. 1H NMR (300 MHz, DMSO- d_6): δ 8.21 (br. s, 1 H), 7.79 (d, J = 8.2 Hz, 1 H), 7.64 (br. s, 1 H), 7.53 (br. s, 1 H), 7.08 (d, J = 8.2 Hz, 1 H), 7.04 (s, 1 H), 5.60–5.52 (m, 2 H), 4.11 (d, J = 17.0 Hz, 1 H), 4.01 (dd, J = 1.5, 13.5 Hz, 1 H), 3.98 (d, J = 17.0 Hz, 2 H), 3.84 (dd, J = 2.1, 5.6 Hz, 1 H), 3.79 (dd, J = 1.8, 6.2 Hz, 1 H), 3.66 (dd, J = 2.5, 13.5 Hz, 1 H), 3.43–3.38 (m, 1 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 171.2, 166.1, 143.6, 133.7 (q, J = 31.5 Hz), 127.1, 123.3 (q, J = 271.5 Hz), 119.1 (d, J = 1.5 Hz), 112.8 (q, J = 4.5 Hz), 65.1, 63.7, 59.9, 49.4, 48.8, 40.4. HRMS (ESI-TOF): m/z calcd for $C_{14}H_{16}F_3N_4O_5S$ $[M + H]^+$ 409.0788, found 409.0816.

2-((4*S*,11*aR*)-4-(4-Hydroxybenzyl)-6,6-dioxido-3-oxo-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-*b*][1,2,4]-thiadiazin-2(1*H*)-yl)acetamide 8(1,6,1).



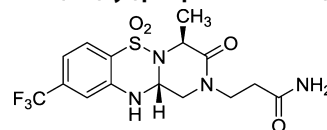
Yield: 35.0 mg (65%) of amorphous solid. 1H NMR (300 MHz, DMSO- d_6): δ 9.36 (br. s, 1 H), 7.70 (br. s, 1 H), 7.63–7.56 (m, 2 H), 7.44 (br. s, 1 H), 7.42–7.32 (m, 1 H), 6.93 (d, J = 8.5 Hz, 2 H), 6.83 (t, J = 7.5 Hz, 1 H), 6.75–6.64 (m, 3 H), 5.32–5.23 (m, 1 H), 4.19 (d, J = 16.7 Hz, 1 H), 3.62–3.47 (m, 2 H), 3.35 (dd, J = 2.6, 13.8 Hz, 1 H), 3.10 (dd, J = 5.6, 13.8 Hz, 1 H), 3.00 (dd, J = 2.6, 13.5 Hz, 1 H), 2.72–2.61 (m, 1 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 171.4, 166.6, 156.4, 143.1, 133.9, 131.3, 125.2, 125.2, 117.6, 116.4, 116.3, 114.8, 63.4, 58.6, 48.7, 47.3. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}N_4O_5S$ $[M + H]^+$ 417.1227, found 417.1239.

3-((4*S*,11*aR*)-4-Methyl-6,6-dioxido-3-oxo-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1*H*)-yl)propanamide 8(2,2,1).



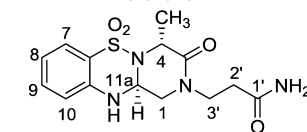
Yield: 13.9 mg (60%) of amorphous solid. 1H NMR (500 MHz, DMSO- d_6): δ 7.51 (dd, J = 1.4, 7.9 Hz, 1 H), 7.48 (br. s, 1 H), 7.35 (ddd, J = 1.4, 7.1, 8.4 Hz, 1 H), 7.33 (s, 1 H), 6.97 (br. s, 1 H), 6.82–6.74 (m, 2 H), 5.46–5.40 (m, 1 H), 3.90 (dd, J = 2.2, 13.8 Hz, 1 H), 3.74 (dt, J = 7.1, 13.5 Hz, 1 H), 3.57 (dd, J = 2.6, 13.8 Hz, 1 H), 3.37–3.27 (m, 2 H), 2.37 (t, J = 7.1 Hz, 2 H), 1.47 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO- d_6): δ 172.8, 167.0, 143.3, 133.8, 125.1, 117.1, 115.7, 115.7, 63.0, 53.3, 49.3, 44.1, 33.0, 22.5. HRMS (ESI-TOF): m/z calcd for $C_{14}H_{19}N_4O_4S$ $[M + H]^+$ 339.1122, found 339.1142.

3-((4*S*,11*aR*)-4-Methyl-6,6-dioxido-3-oxo-9-(trifluoromethyl)-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1*H*)-yl)propanamide 8(2,2,2).



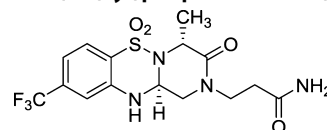
Yield: 14.8 mg (53%) of amorphous solid. 1H NMR (500 MHz, DMSO- d_6): δ 8.43 (br. s, 1 H), 7.75 (d, J = 8.6 Hz, 1 H), 7.58 (br. s, 1 H), 7.21 (s, 1 H), 7.03 (d, J = 8.6 Hz, 1 H), 6.94 (br. s, 1 H), 5.53–5.42 (m, 1 H), 3.92 (dd, J = 2.1, 13.8 Hz, 1 H), 3.74–3.70 (m, 1 H), 3.68 (dd, J = 2.8, 13.8 Hz, 1 H), 3.41–3.33 (m, 2 H), 2.38 (t, J = 7.0 Hz, 2 H), 1.48 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO- d_6): δ 172.7, 166.7, 143.6, 133.6 (q, J = 32 Hz), 127.0, 123.3 (q, J = 273 Hz), 118.7, 112.8 (q, J = 3 Hz), 112.4 (q, J = 4 Hz), 63.1, 53.3, 49.0, 44.1, 33.0, 22.4. HRMS (ESI-TOF): m/z calcd for $C_{15}H_{18}F_3N_4O_4S$ $[M + H]^+$ 407.0995, found 407.0979.

3-((4*R*,11*aS*)-4-Methyl-6,6-dioxido-3-oxo-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1*H*)-yl)propanamide 8(2,7,1).



Yield: 13.1 mg (57%) of amorphous solid. 1H NMR (500 MHz, DMSO- d_6): δ 7.51 (d, J = 7.9 Hz, 1 H, H_7), 7.49 (br. s, 1 H, –CONH₂), 7.38–7.35 (m, 1H, H_{10}), 7.34 (s, 1 H, –NH₁₀–), 6.98 (br. s, 1 H, –CONH₂), 6.84–6.73 (m, 2 H, H_8 and H_9), 5.46–5.37 (m, 1 H, H_{11a}), 3.90 (dd, J = 1.8, 13.5 Hz, 1 H, $\cdots H_1$), 3.74 (dt, J = 13.5, 6.8 Hz, 1 H, H_3), 3.57 (dd, J = 2.1, 13.5 Hz, 1 H, – H_1), 3.36–3.28 (m, 2 H, H_4 , H_3'), 2.37 (t, J = 6.9 Hz, 2 H, H_2), 1.47 (d, J = 6.7 Hz, 3 H, C_4 –CH₃). ^{13}C NMR (101 MHz, DMSO- d_6): δ 172.8 (CONH₂), 167.0 (C_3), 143.3 (C_{6a}), 133.8 (C_{10}), 125.1 (C_7), 117.1 (C_8 or C_9), 115.7 (C_8 or C_9 and C_{10a}), 63.0 (C_{11a}), 53.3 (C_4), 49.3 (C_1), 44.1 (C_3'), 33.0 (C_2'), 22.5 (C_4 –CH₃). NOESY 1D spectra: NOE interactions between protons from methyl group with H_{11a} and $\cdots H_1$. HRMS (ESI-TOF): m/z calcd for $C_{14}H_{19}N_4O_4S$ $[M + H]^+$ 339.1122, found 339.1145.

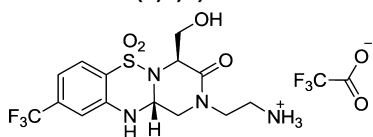
3-((4*R*,11*aS*)-4-Methyl-6,6-dioxido-3-oxo-9-(trifluoromethyl)-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1*H*)-yl)propanamide 8(2,7,2).



Yield: 16.2 mg (58%) of amorphous solid. 1H NMR (500 MHz, DMSO- d_6): δ 8.10 (s, 1 H), 7.76 (d, J = 8.6 Hz, 1 H), 7.53 (br. s, 1 H), 7.17 (s, 1 H), 7.04 (d, J = 8.6 Hz, 1 H), 6.97 (br. s, 1 H), 5.56–5.39 (m, 1 H), 4.00–3.88 (m, 1 H), 3.74 (dd, J = 7.0, 13.6 Hz, 1 H), 3.63 (dt, J = 2.4, 14.1 Hz, 1 H), 3.41–3.30 (m, 2 H), 2.38 (t, J = 7.0 Hz, 2 H), 1.48 (d, J = 7.3 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO- d_6): δ 172.7, 166.7, 143.6, 133.6 (q, J = 32 Hz), 127.0, 123.3 (q, J = 273 Hz), 118.8, 112.8 (q, J = 3 Hz), 112.4 (q, J = 4 Hz), 63.1, 53.3, 49.0, 44.1, 33.0, 22.4. HRMS (ESI-TOF): m/z calcd for $C_{15}H_{18}F_3N_4O_4S$ $[M + H]^+$ 407.0995, found 407.1010.

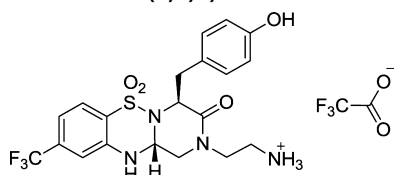
2-((4*S*,11*aR*)-4-(Hydroxymethyl)-6,6-dioxido-3-oxo-9-(trifluoromethyl)-3,4,11,11a-tetrahydrobenzo[e]pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1*H*)-yl)acetamide 8(1,5,2).

pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1*H*)-yl)ethanaminium 2,2,2-trifluoroacetate 8(3,5,2).



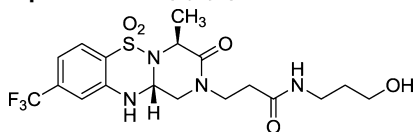
Yield: 28.6 mg (27%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 7.73 (d, J = 8.2 Hz, 1 H), 7.22 (s, 1 H), 7.01 (d, J = 8.2 Hz, 1 H), 5.61–5.49 (m, 1 H), 3.95 (d, J = 13.4 Hz, 1 H), 3.83 (dd, J = 2.4, 11.2 Hz, 1 H), 3.78 (dd, J = 2.4, 11.2 Hz, 1 H), 3.68 (dd, J = 1.9, 13.4 Hz, 1 H), 3.54 (dd, J = 6.0, 13.4 Hz, 1 H), 3.46–3.32 (m, 2 H), 2.91–2.76 (m, 2 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 173.4, 165.9, 144.1, 133.7 (q, J = 31.5 Hz), 126.7, 123.4 (q, J = 271.5 Hz), 118.7, 112.5 (q, J = 3.8 Hz), 64.8, 63.7, 60.1, 48.9, 47.4, 38.2. HRMS (ESI-TOF): m/z calcd for $\text{C}_{14}\text{H}_{18}\text{F}_3\text{N}_4\text{O}_4\text{S}$ [$\text{M} + \text{H}$] $^+$ 395.0995, found 395.1016.

2-((4*S*,11*aR*)-4-(4-Hydroxybenzyl)-6,6-dioxido-3-oxo-9-(trifluoromethyl)-3,4,11,11*a*-tetrahydrobenzo[*e*]pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1*H*)-yl)ethanaminium 2,2,2-trifluoroacetate 8(3,6,2).



Yield: 28.5 mg (23%) of amorphous solid. ^1H NMR (300 MHz, DMSO- d_6): δ 7.78 (d, J = 8.2 Hz, 1 H), 7.19 (s, 1 H), 7.04 (d, J = 8.2 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 2 H), 6.70 (d, J = 8.4 Hz, 2 H), 5.38–5.32 (m, 1 H), 3.67 (t, J = 3.6 Hz, 1 H), 3.38 (dd, J = 2.2, 13.5 Hz, 1 H), 3.33–3.27 (m, 1 H), 3.22–3.06 (m, 3 H), 3.02 (dd, J = 2.7, 13.5 Hz, 1 H), 2.73–2.61 (m, 2 H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 173.0, 165.8, 156.6, 143.9, 133.6 (q, J = 32.3 Hz), 131.3, 126.7, 124.9, 123.4 (q, J = 271.5 Hz), 118.8, 114.8, 112.6 (q, J = 4.5 Hz), 63.4, 58.5, 48.4, 47.8, 39.6, 38.4. HRMS (ESI-TOF): m/z calcd for $\text{C}_{20}\text{H}_{22}\text{F}_3\text{N}_4\text{O}_4\text{S}$ [$\text{M} + \text{H}$] $^+$ 471.1308, found 471.1334.

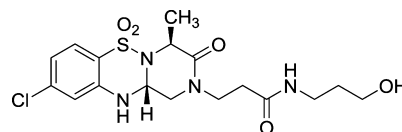
***N*-(3-Hydroxypropyl)-3-((4*S*,11*aR*)-4-methyl-6,6-dioxido-3-oxo-9-(trifluoromethyl)-3,4,11,11*a*-tetrahydrobenzo[*e*]pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1*H*)-yl)propanamide 8(4,2,3).**



Yield: 20.6 mg (63%) of amorphous solid. ^1H NMR (500 MHz, DMSO- d_6): δ 8.04 (t, J = 5.4 Hz, 1 H), 7.88 (s, 1 H), 7.76 (d, J = 8.0 Hz, 1 H), 7.13 (d, J = 1.4 Hz, 1 H), 7.07–7.04 (m, 2 H), 5.49 (s, 1 H), 3.93 (dd, J = 2.0, 14.0 Hz, 1 H), 3.80 (dt, J = 6.7, 13.6 Hz, 1 H), 3.73 (t, J = 6.7 Hz, 2 H), 3.57 (dd, J = 2.3, 14.3 Hz, 1 H), 3.40–3.34 (m, 2 H), 3.15–3.04 (m, 2 H), 2.42–2.31 (m, 2 H), 1.65 (quin, J = 6.7 Hz, 2 H), 1.47 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO- d_6): δ 170.3, 166.7, 143.7, 133.6 (q, J = 32.2 Hz), 127.0, 123.3 (q, J = 273.8 Hz), 118.7, 112.7 (q, J = 3.4 Hz), 112.4 (q, J = 4.2 Hz), 63.1, 58.4, 53.3, 49.0, 44.3, 35.8, 33.4, 32.3, 22.4. HRMS (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{24}\text{F}_3\text{N}_4\text{O}_5\text{S}$ [$\text{M} + \text{H}$] $^+$ 465.1414, found 465.1425.

3-((4*S*,11*aR*)-9-chloro-4-methyl-6,6-dioxido-3-oxo-3,4,11,11*a*-tetrahydrobenzo[*e*]pyrazino[1,2-*b*][1,2,4]thiadiazin-2(1*H*)-yl)propanamide 8(4,2,3).

thiadiazin-2(1*H*)-yl)-*N*-(3-hydroxypropyl)propanamide 8(4,2,3).



Yield: 22.4 mg (74%) of amorphous solid. ^1H NMR (500 MHz, DMSO- d_6): δ 8.03 (t, J = 5.4 Hz, 1 H), 7.67 (s, 1 H), 7.55 (d, J = 8.6 Hz, 1 H), 6.84 (d, J = 2.0 Hz, 1 H), 6.80 (dd, J = 2.0, 8.6 Hz, 1 H), 5.46–5.43 (m, 1 H), 3.90 (dd, J = 2.3, 13.7 Hz, 1 H), 3.78 (dt, J = 6.9, 13.7 Hz, 1 H), 3.73 (t, J = 6.7 Hz, 2 H), 3.54 (dd, J = 2.6, 13.8 Hz, 1 H), 3.31–3.26 (m, 2 H), 3.15–3.05 (m, 2 H), 2.41–2.30 (m, 2 H), 1.65 (quin, J = 6.7 Hz, 2 H), 1.46 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO- d_6): δ 170.3, 166.7, 144.4, 138.3, 127.3, 117.0, 114.6, 114.5, 63.1, 58.4, 53.3, 49.1, 44.3, 35.8, 33.3, 32.3, 22.4. HRMS (ESI-TOF): m/z calcd for $\text{C}_{17}\text{H}_{23}\text{ClN}_4\text{NaO}_5\text{S}$ [$\text{M} + \text{Na}$] $^+$ 453.0970, found 453.0947.

■ ASSOCIATED CONTENT

Supporting Information

Details of the experimental procedures and the NMR spectra associated with this article. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

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