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Solid-Phase Synthesis of Trisubstituted 2,5-Dihydrobenzo[*f*]-[1,2,5]thiadiazepine 1,1-Dioxide Derivatives

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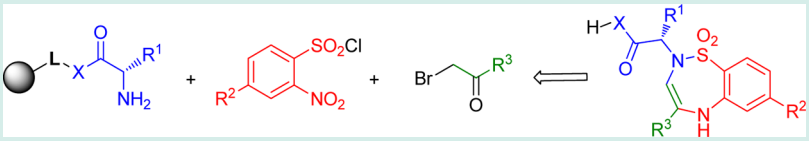
Supporting Information



ABSTRACT: The solid-phase synthesis of trisubstituted 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxides is reported. Acyclic polymer-supported intermediates were prepared using commercially available building blocks: Fmoc-protected amino acids, 2-nitrobenzenesulfonyl chlorides, and bromoketones. The acyclic precursors underwent acid-mediated release from the resin and the cyclization was completed in solution.

KEYWORDS: *amino acids, benzothiadiazepines, bromoketones, cyclative cleavage, nitrobenzenesulfonyl chlorides, solid-phase synthesis*

INTRODUCTION

Compounds derived from 1*H*-benzo[*e*][1,4]diazepines **I** (see Figure 1) have been well studied. They are pharmacologically

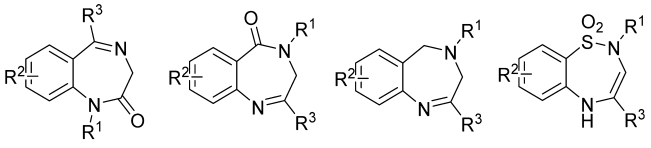


Figure 1. Benzodiazepine scaffolds.

relevant substances with various effects on the central nervous system (CNS), including sedative, hypnotic, muscle relaxant, amnesic, anxiolytic, and anticonvulsant effects.[1−3] In addition, some of them exhibit antitumor or cholecystokinin (CCK-A) agonistic activity.[4,5] In recent years, attention has also been focused on the preparation and biological screening of the structurally isomeric 3*H*-benzo[*e*][1,4]diazepines **II**. However, the analogous derivatives **III** and **IV** have seldom been studied, and only a few reports have described their synthesis or properties.

Structurally analogous benzodiazepines containing fused five-membered heterocyclic rings have exhibited significant biological effects. Compounds **II** with a fused pyrrole are 4,5-dihydro-6*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-6-ones **V**, which enhance effect on CNS.[6] The introduction of an imidazole ring to scaffolds **III** and **IV** affords **VI** and **VII**, which inhibit HIV-1 replication.[7,8] In this Research Article, we focused on preparation of the benzothiadiazepine 1,1-dioxides **IV**, as sulfur analogues of privileged benzodiazepines.

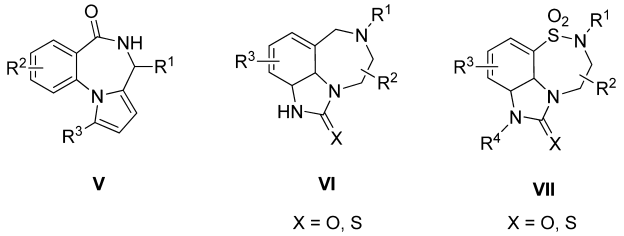


Figure 2. Structures of known biologically active compounds.

Two different routes were developed for the synthesis of benzodiazepines **II** and **III** in solution. The first route is based on the intramolecular azide cycloaddition of 2-azido-*N*-alkyl-*N*-(2-propenyl)benzamide intermediates to provide derivatives **II**.[9,10] The second synthesis involves cycloaddition of the nucleophilic amine to the carbonyl group. In this case, the precursors of both Schiff bases **II** and **III** were obtained by Ugi multicomponent reactions utilizing isocyanide solution chemistry.[11,12] To prepare the 2-nitro-*N*,*N*-disubstituted benzamide precursor of compound **III**, polymer-supported chemistry was also used.[13] The last compound **IV**, was also synthesized via Schiff base formation. Sternbach and co-workers[14] have described the rearrangement of benzothiadiazine 1,1-dioxide with sodium methoxide to form a tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide intermediate, which was then transformed to benzothiadiazepine 1,1-dioxide by heating in benzene. A subsequently developed method involved the catalytic opening of a suitable

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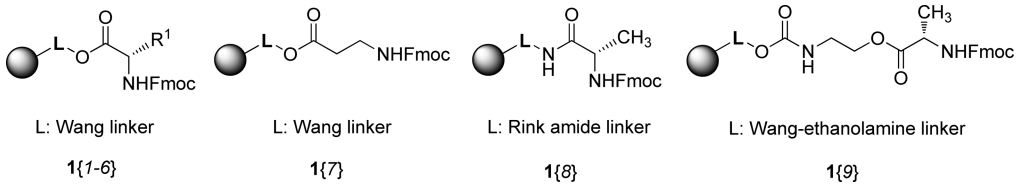
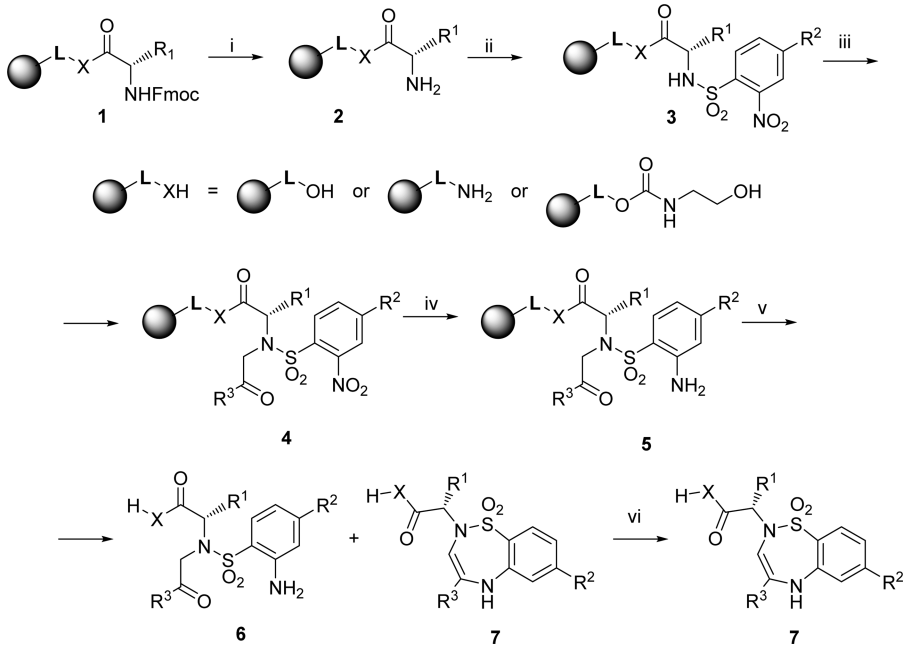


Figure 3. Amino acids immobilized on various linkers.

Scheme 1. Solid-Phase Synthesis of the Target Compounds[a]



[a]Reagents: (i) 50% piperidine in DMF, rt, 30 min; (ii) 2-nitrobenzensulfonyl chlorides, 2,6-lutidine, dichloromethane (DCM), rt, overnight; (iii) bromoketone, DIEA, DMF, rt, overnight; (iv) $Na_2S_2O_4$, K_2CO_3, tetrabutylammonium hydrogen sulfate (TBAHS), 50% H_2O/DCM, rt, overnight; (v) 50% TFA in DCM, rt, 1 h; (vi) DMSO-d_6, rt, see Table 1 for the reaction time.

(isoxazolyl)benzenesulfonamide followed by intramolecular nucleophilic addition.[15]

We have recently reported the solid-phase synthesis of trisubstituted benzo[1,4]diazepin-5-ones **II**.[13] This synthesis was based on conversion of immobilized primary amines to the corresponding 4-nitrobenzenesulfonamides followed by alkylation with bromoketones. Cleavage of the 4-nitrobenzenesulfonyl group (4-Nos) and subsequent acylation provided the 2-nitro-*N*,*N*-disubstituted benzamide intermediates, which were then converted to the final benzodiazepinones by reduction of the nitro group. Here, we extend the original synthetic route to the polymer-supported synthesis of thiadiazepinedioxide derivatives. The principal modification is the use of the 2-nitrobenzenesulfonyl (2-Nos) group as a building block rather than as a protecting/activating group. We have already exploited the 2-Nos group in our previous syntheses of nitrogenous heterocycles.[16−22]

RESULTS AND DISCUSSION

Solid-Phase Synthesis. The solid-phase synthesis of 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxides was performed on resin-bound amines **1**, which were prepared by immobilization of Fmoc-protected alpha or beta amino acids (see Figure 4 for the structures and numbering of the building blocks) on commercially available Wang **1**{*1*−*7*} and Rink amide **1**{*8*} resins (Figure 3). To increase the diversity of the target compounds and to study the effect of ester group, the Fmoc-Ala-OH was also attached to the Wang resin via an acidic/basic-labile ethanolamine linker **1**{*9*}.

The Fmoc group was cleaved with piperidine, and the deprotected primary amines **2** were transformed to the corresponding 2-nitrobenzenesulfonamides (2-Nos) (Scheme 1) with an excellent rate of conversion (more than 93%, LC traces at 205−450 nm). The activating 2-Nos group of intermediates **3** enabled Fukuyama alkylation[23] using aromatic bromoketones with both electron-withdrawing and electron-donating groups (Figure 4). This step afforded compounds **4** with good crude purity (from 73% to 93%, LC traces at 205−450 nm). Alkylation was not quantitative despite attempts to alkylate valine **3**{*4,1,1*} three times and lysine **3**{*5,1,1*} twice.

Resins **4** were exposed to a phase-transfer catalyzed nitro group reduction developed for polymer-supported synthesis.[24] The acyclic resin-bound precursors **5** were treated with a TFA cleavage cocktail to release the products from the resin.

Structure Determination. The LC/MS analysis of the crude products revealed the presence of two major components, the mass spectra showed the appropriate positive and negative molecular ions corresponding to the acyclic compounds **6** and cyclized products **7**. To confirm their structures, the crude products were purified by reverse-phase semipreparative HPLC using mobile phases consisting of MeCN and 0.1% aqueous TFA. The acyclic compounds **6**

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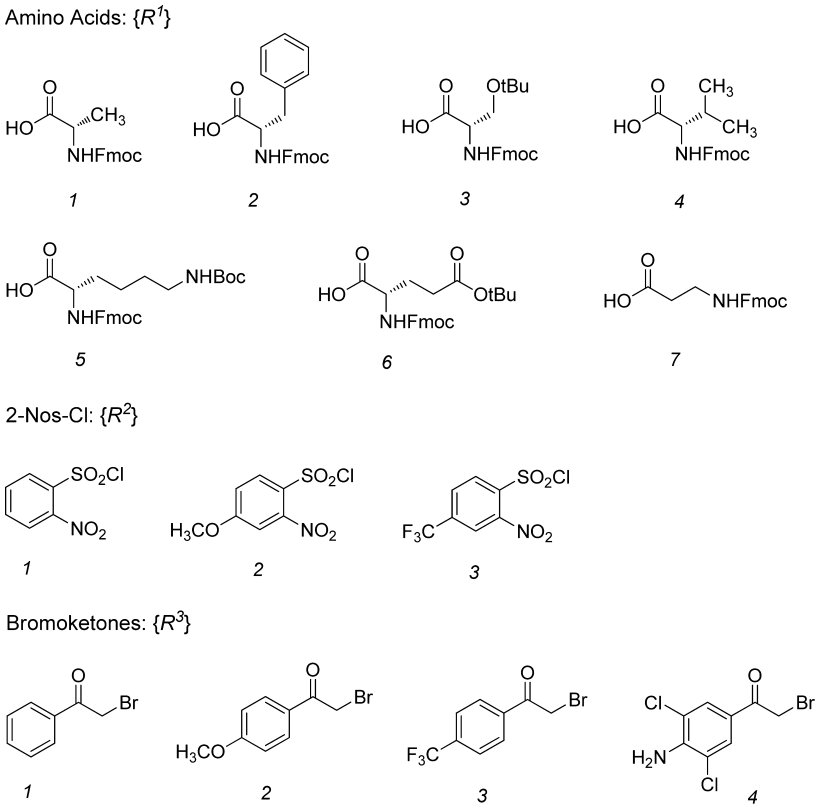

Figure 4. Structures and numbering of the tested building blocks.

spontaneously cyclized and formed **7**, however majority of compounds did not cyclized completely and the rate of cyclization depended on the linker and substituents R. The ^{1}H NMR spectra indicated complete cyclization to target products **7**{*1,1,2*}, **7**{*2,1,1*}, and **7**{*4,1,1*}. On the other hand, compound **6**{*9,1,2*} contained only 5% of cyclic form **7**{*9,1,2*}.

Analysis of the ^{1}H NMR spectrum of **6**{*9,1,2*} enabled identification of diagnostic resonances of acyclic compound **6**: methylene protons as two doublets at 4.78−5.00 and 4.98−5.18 ppm with a *J* value of 19.0−19.3 Hz. The carbon with the chemical shift at 193.1−195.7 ppm corresponded to the carbonyl carbon of the linear ketones **6**. LC/MS analysis showed the appropriate positive and negative molecular ions, and HRMS analysis confirmed the molecular formula.

Two tautomeric forms, **7** and **8**, are possible for the cyclic derivatives (Figure 5). In our previous work, we investigated

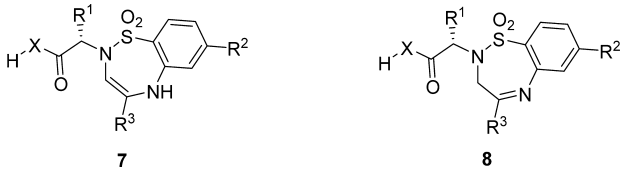

Figure 5. Two possible tautomeric forms.

the tautomeric forms of cyclic benzodiazepinone derivatives **II**.[13] The broad singlet at 4.20 ppm in the proton spectra corresponded to the methylene group and confirmed the structure of **II**. In contrast to benzodiazepinone, we observed diagnostic resonances for the aniline proton at 8.32−9.03 ppm and for the olefinic proton at 5.25−5.38 ppm, confirming the tautomer **7**. The olefinic proton appeared as a singlet or a doublet with a very small *J* value (0.4−0.8 Hz), but long distance coupling of the corresponding proton was not observed. The olefinic carbon signal was present at 101.3−105.5 ppm in the ^{13}C NMR spectrum and was confirmed by an HSQC experiment. Previously reported synthesis identified the same tautomer.[14] A potential cause for the presence of tautomer **7** could be the extended conjugation involving two sp^2 carbons, whereas the sulfonamide is not planar. The presence of **7** could also be a result of the electron-withdrawing effect of the sulfonyl group, which is stronger than the effect of the carbonyl in structure **II**. The tautomer **8** has never been observed in our case.

Cyclization. A subset of the compounds was not completely cyclized, and a mixture of linear **6** and cyclic **7** compounds was obtained (Figures 6 and 7). We utilized the NMR diagnostic

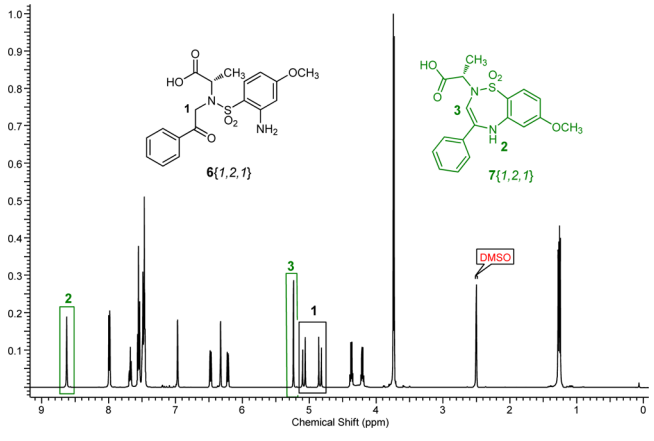

Figure 6. ^{1}H NMR spectrum of a mixture of **6**{*1,2,1*} and **7**{*1,2,1*}.

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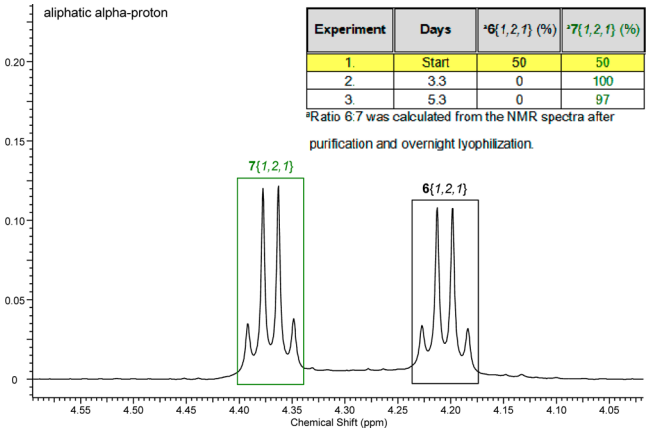


Figure 7. Expansion of the ^{1}H NMR aliphatic region.

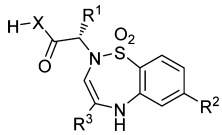
signals to calculate the **6**/**7** ratio and to study the progress of cyclization as a function of time. The cyclization time depended on substituents R^2 and R^3 and the linker (Table 1). To accelerate the cyclization by using different solvents and elevated temperature resulted in transformation of the target compounds **7** and deterioration the overall purity. Thus, we used spontaneous cyclization in the DMSO solution at room temperature to prepare products **7**. Only compounds **6**{*9,1,2*} did not cyclized completely and attempts to force the cyclization (elevated temperature) resulted in decomposition.

Scope and Limitation. The NMR spectra and LC/MS data were used to evaluate the effects of the linker and the R groups on the transformation and to establish the scope and limitation of the benzothiadiazepine synthesis. In addition to the cyclization rate, we analyzed the crude reaction products to determine the presence of side-products. During the N-alkylation of compound **3** by bromoketones in the presence of DIEA, the presence of the Nos group is known to cause intramolecular *C*-arylation followed by the formation of indazole oxide (Scheme 2). Base-mediated C-arylation and exploitation of this carbon−carbon bond formation for the synthesis of 2*H*-indazole-1-oxides via C-aryl intermediates have already been reported.[25] We analyzed all crude reaction products by LC/MS and found that the derivatives with strongly electron-withdrawing CF_3 groups underwent partial C-arylation; in addition to the main products **4**, the *C*-aryl derivatives **10** and indazole oxide **11** were also present. As a result of the presence of the C-arylated compound, after reduction of the nitro group, *C*-aryl **10** was converted to the indole derivative **12**. The indazole oxide **11**, also present on the resin, was reduced to indazole **13** (for the yield of the individual side-products, see the Experimental Procedures). In addition, nitro reduction of compound **4**{*9,1,3*} afforded dealkylated product **14**{*9,1*} (16%, LC traces at 205−250 nm) and the indole derivative **12**{*9,1,3*} (32%, LC traces at 205−450 nm). No linear **6**{*9,1,3*} or cyclic **7**{*9,1,3*} compounds were observed.

We also evaluated the effects of the carboxy terminal functional groups of acids, amides, and esters. In the case of *α*-amino acids attached to the Wang resin, the indole-side products **12** were detected in the preparations, except for the Ala-derived compound. To confirm the structures, four indoles **12** and one indazole **13**{*1,3,1*} were isolated and fully characterized.

To address the effect of the amides, the Ala-derived, resin-bound acyclic intermediate was synthesized on a Rink amide resin. We observed substantial dealkylation during nitro reduction of compound **4**{*8,1,1*}, and the dealkylated substance **14**{*8,1*} was isolated as a main product (45%, LC traces at 205−450 nm). We also detected the formation of indole **12**{*8,1,1*}; however, the target amide **7**{*8,1,1*} was only obtained in a minute amount.

Table 1. Synthesized Compounds



cmpd	XH	R^1	R^2	R^3	ratio **6**/**7**[a] (%)	cycle time (days)	purity[c] (%)
7{*1,1,1*}	OH	CH_3	H	Ph	13:87	1.3	53
7{*1,1,2*}	OH	CH_3	H	4-CH_3O-Ph	<1:>99	*b*	71
7{*1,1,3*}	OH	CH_3	H	4-CF_3-Ph	14:86	1.3	77
7{*1,1,4*}	OH	CH_3	H	3,5-diCl-4-NH_2-Ph	51:49	1.3	69
7{*1,2,1*}	OH	CH_3	OCH_3	Ph	50:50	3.3	67
7{*1,3,1*}	OH	CH_3	CF_3	Ph	21:79	6.3	33
7{*2,1,1*}	OH	Bn	H	Ph	<1:>99	*b*	65
7{*3,1,1*}	OH	CH_2OH	H	Ph	NI	NI	NI
7{*4,1,1*}	OH	$CH(CH_3)_2$	H	Ph	<1:>99	*b*	67
7{*5,1,1*}	OH	$(CH_2)_4NH_2$	H	Ph	67:33	1.0	72
7{*6,1,1*}	OH	$(CH_2)_2COOH$	H	Ph	27:73	3.3	74
7{*7,1,1*}	OH	NA	H	Ph	9:91	*b*	71
7{*8,1,1*}	NH_2	CH_3	H	Ph	NI	NI	NI
7{*9,1,1*}	O-$(CH_2)_2$-NH_2	CH_3	H	Ph	67:27	6.3	65
7{*9,1,2*}	O-$(CH_2)_2$-NH_2	CH_3	H	4-CH_3O-Ph	97:3	NI	NI
7{*9,1,3*}	O-$(CH_2)_2$-NH_2	CH_3	H	4-CF_3−Ph	NI	NI	NI

[a]The ratio was calculated from the NMR spectra obtained after purification and overnight lyophilization. [b]NMR spectra indicated >90% of cyclic product **7** after purification and overnight lyophilization. [c]Crude purity of **6** + **7** estimated from LC traces at 205−450 nm; NA = not applicable and NI = not isolated (see the text).

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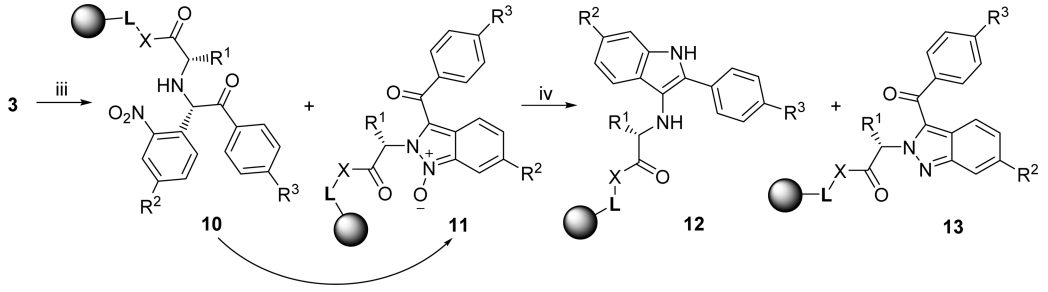
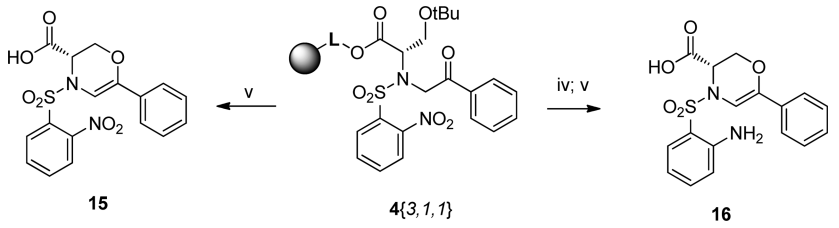
Scheme 2. Side-Product Formation during the Alkylation and Reduction Steps[a]



[a]Reagents: (iii) bromoketone, DIEA, DMF, rt, overnight; (iv) $Na_2S_2O_4$, K_2CO_3, TBAHS, 50% H_2O/DCM, rt, overnight.

Scheme 3. Morpholine Derivative Formation during Acidic Cleavage[a]



[a]Reagents: (iv) $Na_2S_2O_4$, K_2CO_3, TBAHS, 50% H_2O/DCM, rt, overnight; (v) 50% TFA in DCM, rt, 60 min.

Substitutions on the two aromatic rings (R groups) did not have a remarkable effect; notably, only the electron donating OMe group in the R^2 position accelerated cyclization of the compound synthesized on the Wang linker. However, NMR monitoring revealed significant effects of the ethanolamine linker (amino acids 2-aminoethyl esters). The acyclic compounds **6**{*9*,R^2,R^3} were present at a substantially higher ratio, and their conversion was significantly slower than those of other substances. In addition, cyclic products **7**{*9*,R^2,R^3} underwent spontaneous O−N shifts after HPLC repurification in MeCN−ammonium acetate aqueous buffer.

To show that the benzothiadiazepine synthesis was also compatible with a general primary amino group, we also performed the synthesis on polymer-supported *β*-Ala-OH. As expected, there was no difference compared with *α*-amino acids, and the final product **7**{*7*,*1*,*1*} was isolated.

The compound prepared using Ser(*t*Bu) yielded morpholine derivatives. The *tert*-butyl group of **4**{*3*,*1*,*1*} was cleaved using a TFA-based cleavage cocktail, and the morpholine derivative **15** was formed (Scheme 3). After nitro reduction and subsequent cleavage from the resin benzodiazepine ring, **7**{*3*,*1*,*1*} was not formed, and morpholine **16** was isolated in 43% yield.

CONCLUSION

We have developed an efficient solid-phase synthesis for 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxides using three types of commercially available building blocks: Fmoc-protected amino acids, 2-nitrobenzenesulfonyl chlorides, and bromoketones. Cyclic products **7**, except for the CF_3 derivatives, were obtained with good crude purities (53−77%), and their structures were confirmed by 1D and 2D NMR spectra. Substantial C-arylation during the alkylation step was observed for the CF_3 compounds. The carboxy-terminal functional group exhibited a significant effect on the reaction outcome. Whereas the free acids provided the expected products, the amides did not afford products, and conversion of the linear compounds to the target thiadiazepine-1,1-dioxides was remarkably slower for the compounds synthesized using an ester-type linker. The serine-containing compound yielded morpholine scaffold **16**.

EXPERIMENTAL PROCEDURES

The solid-phase syntheses were performed in plastic reaction vessels (syringes, each equipped with a porous disc) using a manually operated synthesizer.[26] 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 performed at ambient temperature unless stated otherwise. Commercially available Wang resin (100−200 mesh, 1.0 mmol/g) and Rink amide resin (100−200 mesh, 0.57 mmol/g) were used. The yields of the crude products were calculated with respect to the loading of the first building block.

Cleavage of Fmoc Group. Resin **1** (or Rink amide resin) (1 g) was washed 3× with DMF. A solution of piperidine in DMF (50%, 10 mL) was then added to the resin, and the slurry was shaken at ambient temperature for 30 min. The resin was washed 3× with DMF and 3× with DCM.

Immobilization of Ethanolamine Linker. Wang resin (1 g) was washed 3× with DCM. A solution of 1,1′-carbonyldiimidazole (800 mg, 5 mmol) and pyridine (400 μL, 5 mmol) in DCM (10 mL) was added to the resin, and the slurry was shaken at ambient temperature for 2 h. The resin was washed 3× with DCM, and a solution of ethanolamine (300 μL, 5 mmol) in DCM (10 mL) was then added to the resin. The slurry was shaken at ambient temperature for 3 h, and the resin was washed 5× with DCM.

Reaction with Fmoc-Amino Acids. Wang or Rink amide resin (1 g) was washed 3× with DCM. A solution of Fmoc-amino acid (2 mmol), HOBt (306 mg, 2 mmol), DMAP (61 mg, 0.5 mmol, not used for the Rink amide resin), and DIC (312 μL, 2 mmol) in DMF/DCM (50%, 10 mL) was added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 3× in DMF and 3× in DCM.

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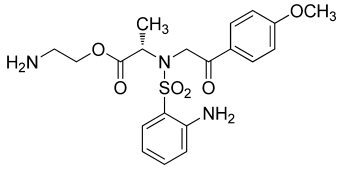
Reaction with Nos-Cl. Resin **2** (1 g) was washed 3× with DCM. A solution of Nos-Cl (3 mmol) and 2,6-lutidine (381 μL, 3 mmol) in DCM (10 mL) was added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 5× with DCM.

Reaction with Bromoacetophenone. Resin **3** (250 mg) was washed 3× with DMF. A solution of bromoacetophenone (0.5 mmol) and DIEA (218 μL, 0.5 mmol) in DMF (2.5 mL) was then added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 3× with DMF and 3× with DCM.

Reduction of Nitro Group. Resin **4** (250 mg) was washed 3× with DCM. A solution of $Na_2S_2O_4$ (525 mg, 3 mmol), K_2CO_3 (480 mg, 3.5 mmol), and TBAHS (85 mg, 0.25 mmol) in H_2O/DCM (50%, 5 mL) was then added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 3× with H_2O/DCM (50%), 3× with MeOH/DCM (50%), and 3× with DCM.

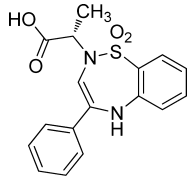
Cleavage and Isolation. Resins **5** (250 mg, resins **5**{*5,1,1*}, **5**{*6,1,1*}, **5**{*7,1,1*}, **5**{*9,1,1*}, 500 mg) were treated with TFA/DCM (50%) for 1 h. The TFA solution was collected and concentrated using a stream of nitrogen. The oily product was dissolved in MeOH (2.5 mL) and purified by semi-preparative reverse phase HPLC in a MeCN−0.1% aqueous TFA mobile phase. After lyophilization, the amorphous powder was dissolved in 750 μL of DMSO-d_6, and the NMR spectra were obtained. Compounds that contained the acyclic precursor were cyclized in the DMSO solution at room temperature (for the cyclization times, see Table 1). Cyclized compounds were purified in MeCN−10 mM ammonium acetate buffer.

Analytical Data of Individual Compounds. *(S)-2-Aminoethyl 2-(2-amino-N-(2-(4-methoxyphenyl)-2-oxoethyl)phenylsulfonamido)propanoate* ***6****{9,1,2}.*



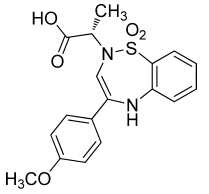
Yield: 10.5 mg (37%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.95−8.00 (m, 4 H), 7.56 (dd, J = 8.1, 1.5 Hz, 1 H), 7.29 (ddd, J = 8.3, 7.0, 1.5 Hz, 1 H), 7.05−7.09 (m, 2 H), 6.83 (dd, J = 8.3, 1.0 Hz, 1 H), 6.63 (ddd, J = 8.1, 7.0, 1.0 Hz, 1 H), 5.03 (d, J = 19.0 Hz, 1 H), 4.86 (d, J = 19.0 Hz, 1 H), 4.47 (q, J = 7.2 Hz, 1 H), 4.01−4.13 (m, 2 H), 3.86 (s, 3 H), 3.00−3.07 (m, 2 H), 1.29 (d, J = 7.2 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 193.1, 170.4, 163.5, 147.1, 134.2, 130.4, 129.9, 127.5, 118.4, 117.3, 115.3, 114.0, 61.2, 55.6, 54.4, 50.0, 37.7, 15.5. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{25}N_3O_6S$ $[M + H]^+$ 436.1537, found 436.1520.

(S)-2-(1,1-Dioxido-4-phenylbenzo[f][1,2,5]thiadiazepin-2(5H)-yl)propanoic Acid ***7****{1,1,1}.*



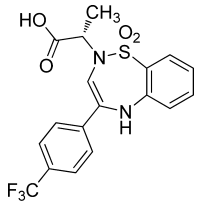
Yield: 36.5 mg (74%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.72 (s, 1 H), 7.63 (dd, J = 8.0, 1.1 Hz, 1 H), 7.45−7.51 (m, 5 H), 7.37−7.39 (m, 2 H), 6.87 (ddd, J = 8.0, 6.0, 2.2 Hz, 1 H), 5.25 (d, J = 0.7 Hz, 1 H), 4.40 (q, J = 7.3 Hz, 1 H), 1.26 (d, J = 7.3 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 172.1, 141.9, 140.0, 136.2, 133.0, 129.3, 128.5, 127.7, 127.7, 126.5, 120.1, 118.4, 101.7, 56.2, 15.3. LC/MS (ESI): m/z 345.2 $[M + H]^+$, 345.2.

(S)-2-(4-(4-Methoxyphenyl)-1,1-dioxidobenzo[f][1,2,5]-thiadiazepin-2(5H)-yl)propanoic Acid ***7****{1,1,2}.*



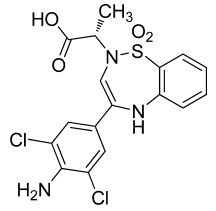
Yield: 35.0 mg (66%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.65 (s, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.41−7.45 (m, 2 H), 7.36−7.38 (m, 2 H), 7.00−7.03 (m, 2 H), 6.87 (ddd, J = 8.1, 4.8, 3.4 Hz, 1 H), 5.20 (d, J = 0.4, 1 H), 4.4 (q, J = 7.3 Hz, 1 H), 3.79 (s, 3 H), 1.25 (d, J = 7.3 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.3, 160.3, 142.1, 140.0, 133.0, 129.6, 129.1, 128.4, 126.7, 120.2, 118.4, 113.9, 100.7, 56.3, 55.4, 15.3. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}N_2O_5S$ $[M + H]^+$ 375.1009, found 375.1030.

(S)-2-(1,1-Dioxido-4-(4-(trifluoromethyl)phenyl)benzo[f]-[1,2,5]thiadiazepin-2(5H)-yl)propanoic Acid ***7****{1,1,3}.*



Yield: 8.0 mg (19%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.76 (s, 1 H), 7.81−7.84 (m, 2 H), 7.71−7.74 (m, 2 H), 7.63 (dd, J = 8.0, 1.6 Hz, 1 H), 7.40 (ddd, J = 8.4, 7.1, 1.6 Hz, 1 H), 7.32 (dd, J = 8.4, 0.9 Hz, 1 H), 6.89 (ddd, J = 8.0, 7.1, 0.9 Hz, 1 H), 5.35 (d, J = 0.5 Hz, 1 H), 4.42 (q, J = 7.3 Hz, 1 H), 1.28 (d, J = 7.3 Hz, 3 H). HRMS (ESI-TOF): m/z calcd for $C_{18}H_{15}F_3N_2O_4S$ $[M + H]^+$ 413.0777, found 413.0781.

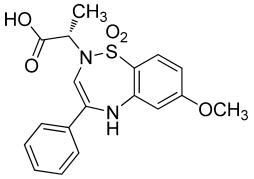
(S)-2-(4-(4-Amino-3,5-dichlorophenyl)-1,1-dioxidobenzo-[f][1,2,5]thiadiazepin-2(5H)-yl)propanoic Acid ***7****{1,1,4}.*



Yield: 22.3 mg (46%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.56 (s, 1 H), 7.60 (dd, J = 8.0, 1.4 Hz, 1 H), 7.36 (ddd, J = 8.3, 6.9, 1.4 Hz, 1 H), 7.31−7.34 (m, 3 H), 6.86 (ddd, J = 8.0, 6.9, 1.4 Hz, 1 H), 5.85 (s, 2 H), 5.25 (s, 1 H), 4.31 (q, J = 7.2 Hz, 1 H), 1.21 (d, J = 7.3 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.3, 142.1, 139.9, 139.8, 132.9, 129.8, 127.1, 126.5, 124.5, 120.1, 118.4, 117.6, 101.5, 56.8, 15.5. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{16}Cl_2N_2O_4S$ $[M + H]^+$ 428.0233, found 428.0239.

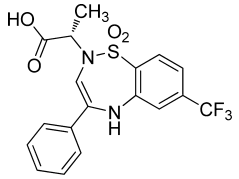
dx.doi.org/10.1021/co500084k | ACS Comb. Sci. 2014, 16, 412−420

*(S)-2-(7-Methoxy-1,1-dioxido-4-phenylbenzo[f][1,2,5]-thiadiazepin-2(5H)-yl)propanoic Acid **7**{1,2,1}.*



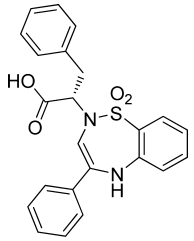
Yield: 35.2 mg (74%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.61 (s, 1 H), 7.54 (d, J = 8.9 Hz, 1 H), 7.45−7.51 (m, 5 H), 6.97 (d, J = 2.4 Hz, 1 H), 6.47 (dd, J = 8.9, 2.4 Hz, 1 H), 5.24 (s, 1 H), 4.37 (q, J = 7.3 Hz, 1 H), 3.75 (s, 3 H), 1.25 (d, J = 7.3 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 172.1, 162.6, 141.5, 141.4, 136.3, 129.2, 128.5, 128.4, 127.6, 122.7, 105.5, 103.8, 101.6, 56.2, 55.3, 15.3. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}N_2O_5S$ $[M + H]^+$ 375.1009, found 375.1033.

*(S)-2-(1,1-Dioxido-4-phenyl-7-(trifluoromethyl)benzo[f]-[1,2,5]thiadiazepin-2(5H)-yl)propanoic Acid **7**{1,3,1}.*



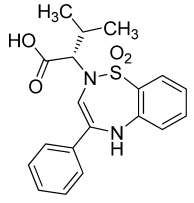
Yield: 17.3 mg (20%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.03 (s, 1 H), 7.83 (d, J = 8.3 Hz, 1 H), 7.80 (s, 1 H), 7.44−7.56 (m, 5 H), 7.16 (dd, J = 8.3, 1.0 Hz, 1 H), 5.38 (s, 1 H), 4.48 (q, J = 7.2 Hz, 1 H), 1.34 (d, J = 7.3 Hz, 3 H). HRMS (ESI-TOF): m/z calcd for $C_{18}H_{15}F_3N_2O_4S$ $[M + H]^+$ 413.0777, found 413.0770.

*(S)-2-(1,1-Dioxido-4-phenylbenzo[f][1,2,5]thiadiazepin-2(5H)-yl)-3-phenylpropanoic Acid **7**{2,1,1}.*



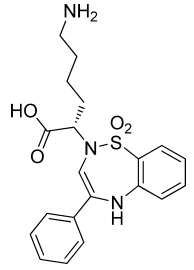
Yield: 47.3 mg (76%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.33 (s, 1 H), 7.43−7.52 (m, 5 H), 7.37 (dd, J = 7.9, 1.5 Hz, 1 H), 7.19 (ddd, J = 8.6, 7.2, 1.5 Hz, 1 H), 7.06−7.11 (m, 3 H), 6.94−7.03 (m, 3 H), 6.68 (ddd, J = 7.9, 7.2, 1.0 Hz, 1 H), 5.31 (s, 1 H), 4.63 (dd, J = 10.4, 5.1 Hz, 1 H), 3.22 (dd, J = 14.3, 5.1 Hz, 1 H), 3.01 (dd, J = 14.3, 10.4 Hz, 1 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.5, 140.1, 139.7, 137.4, 132.4, 129.8, 128.6, 128.5, 127.8, 127.6, 126.1, 125.3, 119.9, 117.6, 102.5, 62.1, 35.9. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{20}N_2O_4S$ $[M + H]^+$ 421.1217, found 421.1231.

*(S)-2-(1,1-Dioxido-4-phenylbenzo[f][1,2,5]thiadiazepin-2(5H)-yl)-3-methylbutanoic Acid **7**{4,1,1}.*



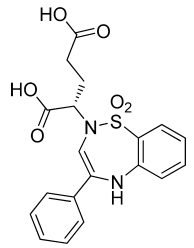
Yield: 5.0 mg (13%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.56 (s, 1 H), 7.56−7.59 (m, 1 H), 7.42−7.48 (m, 5 H), 7.30−7.33 (m, 2 H), 6.81 (ddd, J = 8.0, 5.8, 2.4 Hz, 1 H), 5.44 (s, 1 H), 3.95 (d, J = 9.3 Hz, 1 H), 2.16−2.26 (m, 1 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 171.3, 140.5, 139.5, 136.5, 132.8, 129.7, 129.1, 128.5, 127.5, 125.8, 119.7, 103.5, 66.4, 28.4, 19.2, 19.2. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{20}N_2O_4S$ $[M + H]^+$ 373.1217, found 373.1248.

*(S)-6-Amino-2-(1,1-dioxido-4-phenylbenzo[f][1,2,5]-thiadiazepin-2(5H)-yl)hexanoic Acid **7**{5,1,1}.*



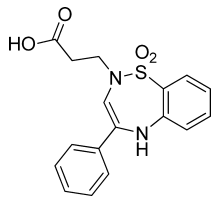
Yield: 110.0 mg (71%).^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.64 (s, 1 H), 7.57−7.63 (m, 1 H), 7.42−7.53 (m, 5 H), 7.32−7.37 (m, 2 H), 6.84 (ddd, J = 8.1, 4.9, 3.3 Hz, 1 H), 5.27 (s, 1 H), 4.33 (dd, J = 9.9, 5.5 Hz, 1 H), 2.52−2.71 (m, 2 H), 1.75−1.92 (m, 2 H), 1.46 (quin, J = 7.5 Hz, 2 H), 1.17−1.40 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.3, 140.7, 138.9, 136.9, 132.4, 130.8, 128.8, 128.4, 127.3, 125.7, 119.5, 117.6, 104.9, 62.3, 38.3, 30.2, 26.6, 22.9. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{23}N_3O_4S$ $[M + H]^+$ 402.1482, found 402.1515.

*(S)-2-(1,1-Dioxido-4-phenylbenzo[f][1,2,5]thiadiazepin-2(5H)-yl)pentanedioic Acid **7**{6,1,1}.*



Yield: 21.0 mg (24%).^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.48 (s, 1 H), 7.53−7.58 (m, 1 H), 7.41−7.49 (m, 5 H), 7.28−7.32 (m, 2 H), 6.79 (ddd, J = 8.0, 4.8, 3.4 Hz, 1 H), 5.55 (s, 1 H), 4.18 (t, J = 7.8 Hz, 1 H), 2.16−2.26 (m, 1 H), 1.99−2.11 (m, 2 H), 1.63−1.74 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 174.4, 172.6, 140.5, 139.7, 136.7, 132.6, 130.6, 129.0, 128.5, 127.4, 125.9, 119.7, 117.8, 104.7, 61.6, 32.2, 26.7. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{18}N_2O_6S$ $[M + H]^+$ 403.0958, found 403.0986.

*3-(1,1-Dioxido-4-phenylbenzo[f][1,2,5]thiadiazepin-2(5H)-yl)propanoic Acid **7**{7,1,1}.*

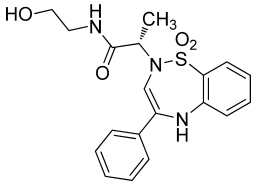


Yield: 109.0 mg (77%).^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.84 (s, 1 H), 7.71 (dd, J = 8.1, 1.3 Hz, 1 H), 7.50−7.54 (m, 2 H), 7.42−7.48 (m, 5 H), 6.94 (ddd, J = 8.1, 6.4, 1.7 Hz, 1 H), 5.39 (d, J = 0.8 Hz, 1 H), 3.29 (t, J = 7.0 Hz, 2 H), 2.57 (t, J = 7.0 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 172.5, 141.3, 139.5, 136.0, 133.2, 129.4, 128.5, 128.0, 127.9,

dx.doi.org/10.1021/co500084k | ACS Comb. Sci. 2014, 16, 412−420

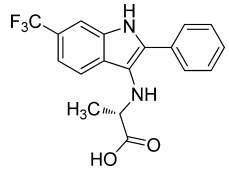
127.6, 120.4, 118.8, 105.5, 46.8, 33.0. HRMS (ESI-TOF): m/z calcd for $C_{17}H_{16}N_2O_4S$ $[M + H]^+$ 345.0904, found 345.0916.

(S)-2-(1,1-Dioxido-4-phenylbenzo[f][1,2,5]thiadiazepin-2(5H)-yl)-N-(2-hydroxyethyl)propanamide ***7****{9,1,1}.*



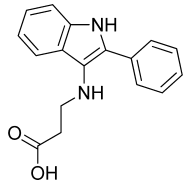
Yield: 55.0 mg (75%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.72 (s, 1 H), 7.87 (t, J = 5.6 Hz, 1 H), 7.63−7.67 (m, 1 H), 7.45−7.51 (m, 5 H), 7.38−7.41 (m, 2 H), 6.89 (ddd, J = 8.1, 5.9, 2.3 Hz, 1 H), 5.35 (d, J = 0.7 Hz, 1 H), 4.25 (q, J = 7.1 Hz, 1 H), 3.35−3.40 (m, 2 H), 3.06−3.16 (m, 2 H), 1.17 (d, J = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.1, 141.7, 139.9, 136.3, 133.2, 129.3, 129.1, 128.5, 127.7, 127.0, 120.2, 118.4, 102.5, 59.6, 57.4, 41.5, 15.4. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}N_3O_4S$ $[M + H]^+$ 388.1326, found 388.1346.

(S)-2-((2-Phenyl-6-(trifluoromethyl)-1H-indol-3-yl)amino)-propanoic Acid ***12****{1,3,1}.*



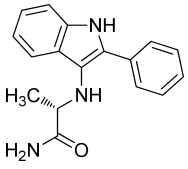
Yield: 27.2 mg (37%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.50 (s, 1 H), 7.94−7.99 (m, 2 H), 7.90 (d, J = 8.5 Hz, 1 H), 7.58 (s, 1 H), 7.48−7.54 (m, 3 H), 7.33−7.38 (m, 1 H), 7.24 (d, J = 8.5 Hz, 1 H), 3.70 (q, J = 6.9 Hz, 1 H), 1.31 (d, J = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 175.7, 133.0, 131.9, 128.8, 128.8, 128.1, 127.5, 125.4 (q, J = 267.7 Hz), 126.4, 121.9 (q, J = 31.1 Hz), 121.2, 119.7, 114.3−114.5 (m), 108.1−108.4 (m), 56.3, 18.5. LC/MS (ESI): m/z 349.2 $[M + H]^+$ 349.2.

3-((2-Phenyl-1H-indol-3-yl)amino)propanoic Acid ***12****{7,1,1}.*



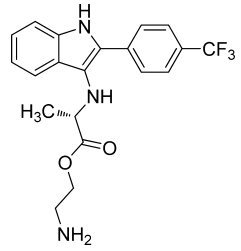
Yield: 9.0 mg (8%).^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.61 (br. s., 1 H), 7.79−7.83 (m, 2 H), 7.75 (d, J = 8.0 Hz, 1 H), 7.52−7.59 (m, 3 H), 7.40−7.48 (m, 2 H), 7.18−7.23 (m, 1 H), 7.09−7.14 (m, 1 H), 3.47 (t, J = 6.3 Hz, 2 H), 2.62 (t, J = 6.6 Hz, 2 H). LC/MS (ESI): m/z 281.2 $[M + H]^+$ 281.3

(S)-2-((2-Phenyl-1H-indol-3-yl)amino)propanamide ***12****{8,1,1}.*



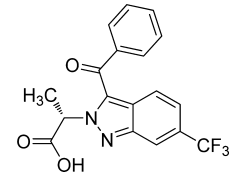
Yield: 0.9 mg (3%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.22 (br. s., 1 H), 7.88 (m, J = 7.5 Hz, 2 H), 7.70 (d, J = 8.1 Hz, 1 H), 7.46−7.52 (m, 3 H), 7.30−7.37 (m, 2 H), 7.08−7.12 (m, 1 H), 7.00 (t, J = 7.4 Hz, 1 H), 3.74−3.79 (m, 1 H), 1.27 (d, J = 6.5 Hz, 3 H). LC/MS (ESI): m/z 280.2 $[M + H]^+$, 280.3.

(S)-2-Aminoethyl 2-((2-(4-(Trifluoromethyl)phenyl)-1H-indol-3-yl)amino)propanoate ***12****{9,1,3}.*



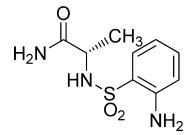
Yield: 4.0 mg (10%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.13 (s, 1 H), 8.18−8.23 (m, 2 H), 7.93 (s, 1 H), 7.78−7.85 (m, 4 H), 7.70 (d, J = 8.0 Hz, 1 H), 7.31 (d, J = 8.1 Hz, 1 H), 7.09−7.14 (m, 1 H), 6.96−7.01 (m, 1 H), 3.94−4.08 (m, 2 H), 3.68−3.76 (m, 1 H), 2.93−2.99 (m, 2 H), 1.40 (d, J = 7.0 Hz, 3 H). LC/MS (ESI): m/z 392.2 $[M + H]^+$, 392.4.

(S)-2-(3-Benzoyl-6-(trifluoromethyl)-2H-indazol-2-yl)-propanoic Acid ***13****{1,3,1}.*



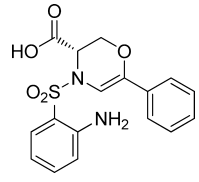
Yield: 14.3 mg (19%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.37 (s, 1 H), 7.75−7.83 (m, 3 H), 7.60−7.67 (m, 2 H), 7.42 (d, J = 8.9 Hz, 1 H), 7.12 (d, J = 8.9 Hz, 1 H), 6.02 (q, J = 7.1 Hz, 1 H), 1.93 (d, J = 7.2 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 185.5, 170.8, 144.9, 137.8, 133.7, 132.1, 129.5, 128.9, 126.9 (q, J = 31.8 Hz), 124.2 (q, J = 272.0 Hz), 123.7, 122.2, 120.1 (m), 117.0 (q, J = 4.9), 60.5, 16.8. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{13}F_3N_2O_3$ $[M + H]^+$ 363.0951, found 363.0986.

(S)-2-(2-Aminophenylsulfonamido)propanamide ***14****{8,1}.*



Yield: 7.0 mg (26%).^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.73 (d, J = 8.2 Hz, 1 H), 7.47 (dd, J = 8.0, 1.5 Hz, 1 H), 7.24 (ddd, J = 8.3, 7.0, 1.5 Hz, 1 H), 7.20 (br. s., 1 H), 7.02 (br. s., 1 H), 6.77 (dd, J = 8.3, 1.0 Hz, 1 H), 6.58 (ddd, J = 8.0, 7.0, 1.0 Hz, 1 H), 5.95 (br. s, 2 H), 3.51−3.58 (m, 1 H), 1.02 (d, J = 7.1 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 173.3, 146.2, 133.5, 129.0, 120.2, 116.8, 114.9, 51.1, 19.0. HRMS (ESI-TOF): m/z calcd for $C_9H_{13}N_3O_3S$ $[M + H]^+$ 244.0750, found 244.0751.

(S)-4-((2-Aminophenyl)sulfonyl)-6-phenyl-3,4-dihydro-2H-1,4-oxazine-3-carboxylic Acid ***16****{3,1,1}.*



Yield: 27.2 mg (43%, acidic purification). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.54 (dd, J = 8.2, 1.5 Hz, 1 H), 7.45−7.48 (m, 2 H), 7.23−7.34 (m, 4 H), 6.81−6.84 (m, 2 H), 6.61

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(ddd, J = 8.2, 7.1, 1.1 Hz, 1 H), 4.96 (dt, J = 2.9, 1.5 Hz, 1 H), 4.64 (dd, J = 10.9, 1.5 Hz, 1 H), 3.27 (dd, J = 10.9, 2.9 Hz, 1 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 168.9, 147.2, 138.7, 134.7, 133.1, 129.5, 128.4, 127.8, 123.2, 117.6, 116.5, 115.6, 101.6, 64.8, 54.6. HRMS (ESI-TOF): m/z calcd for $C_{17}H_{16}N_2O_5S$ $[M + H]^+$ 361.0853, found 361.0858.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental synthetic and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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