JOURNAL OF combinatorial CHEMISTRY

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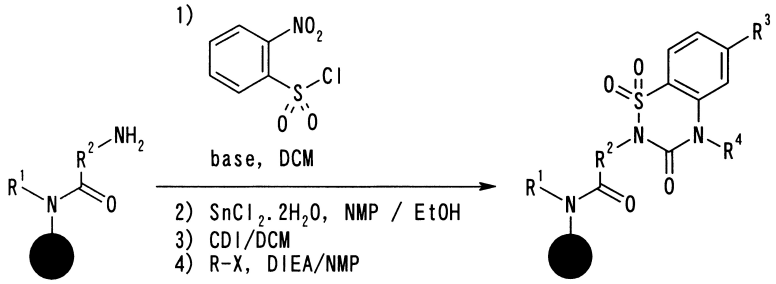
J. Comb. Chem., **2003**, 5 (1), 73-78• DOI: 10.1021/cc020056k • Publication Date (Web): 09 November 2002



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Efficient Synthesis of 2,4-Disubstituted 1,2,4-Benzothiadiazin-3-one 1,1-Dioxides on Solid Support

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Received July 31, 2002

The first solid-phase synthesis of 1,2,4-benzothiadiazin-3-one 1,1-dioxides has been developed. Synthesis of the title compounds was achieved by the reduction of 2-nitrobenzenesulfonamides, followed by cyclization with carbonyldiimidazole. Because 1,2,4-benzothiadiazin-3-one 1,1-dioxides have been known to possess various bioactivities, this method is useful from the viewpoint of new drug discovery. In addition to the excellent purity of the title compounds, a large number of compounds can be synthesized with this method, because this synthesis includes four diversity points.

Introduction

Combinatorial chemistry for the synthesis of nonpeptide organic compounds has emerged as an important tool for drug discovery.[1] Solid-phase synthesis of substituted heterocyclic compounds, in particular, has been a focus of recent investigations with application toward a variety of drug targets.[2] As a part of our project to develop efficient synthetic methods for heterocyclic compounds,[3] the solid-phase synthesis of 1,2,4-benzothiadiazin-3-one 1,1-dioxides was investigated. In addition to their interesting bioactivities, such as bone regeneration,[4a] prolylendopeptidase inhibition,[4b] the structural similarity of 1,2,4-benzothiadiazin-3-one 1,1-dioxide to other important pharmacophores such as quinazoline-2, 4-diones,[3d,5] 4-quinazolinones,[3b,6] 2-thioxoquinazolin-4-ones,[3a, 3c] benzimidazole,[7] hydantoin,[8] 2-piperazinone,[9] and pyrrole[10] is fascinating from the viewpoint of new drug discovery. Since these heterocycles have been prepared from solid-supported primary amines using the nitrogen atoms of the amines as part of the heterocycles, the bioactivities of 1,2,4-benzothiadiazin-3-one 1,1-dioxides can be compared easily with them by developing the solid-phase synthesis of 1,2,4-benzothiadiazin-3-one 1,1-dioxides. (Figure 1)

Result and Discussion

First, **1** was prepared by reductive amination of 4-(4-formyl-3-methoxyphenoxy)butyryl AM resin[11] with 1-aminomethylnaphthalene. Although the derivatized resin **1** was used for all the compounds, various amines can be used for this reductive amination to offer the first diversity point.[12] The solid-supported arylamine **3** was obtained by acylation of **1** with 4-nitrophenylacetic acid **2** and subsequent reduction of the nitro group. Various solid-supported amines can be prepared using other building blocks instead of **2** as the second diversity point as described later. Next, sulfonylation of **3** using 2-nitrobenzenesulfonyl chlorides **4** was examined.

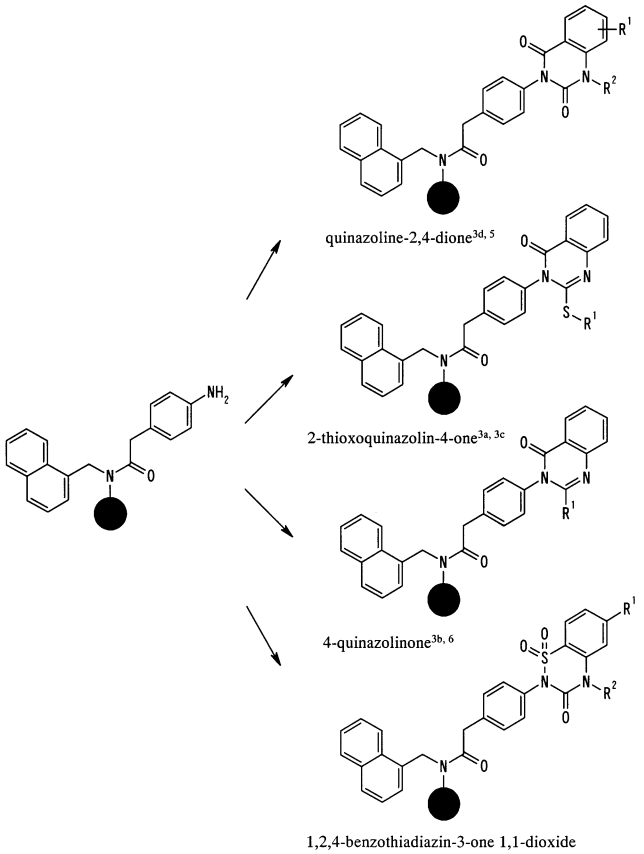

Figure 1. Examples of heterocycles that have been synthesized on solid-support. Although these heterocycles were synthesized using different reactants in the previous reports, we confirmed that the same solid-phase synthesis worked with this reactant.

Although there have been numerous reports of the preparation of 2-nitrobenzenesulfonamides for the solid-phase Fukuyama-Mitsunobu alkylations,[13] the reaction of **3** with **4** did not give **5** with high purity because of insufficient sulfonylation at 4 °C or disulfonylation (formation of sulfonimides) and other unknown byproduct formations at 25 °C. After testing various bases (diisopropylethylamine {DIEA}, py-

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10.1021/cc020056k CCC: $25.00
Published on Web 11/09/2002

Table 1. Synthesis of 1,2,4-Benzothiadiazin-3-one 1,1-Dioxides with Three 2-Nitrobenzenesulfonyl Chlorides

		9	
entry	R^1	purity[a] (%)	yield[b] (%)
a	H	>95	85
b	MeO	91	94
c	CF_3	>95	96

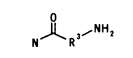
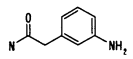
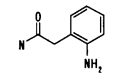
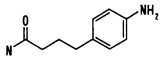
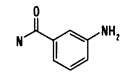
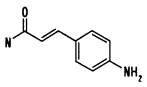
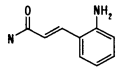
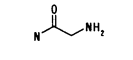
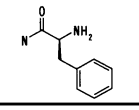
[a] Reverse-phase HPLC was carried out using water/acetonitrile (0.04% TFA) linear gradients from 5 to 98% organic component over 5 min. Flow rate: 2 mL/min. Column: Waters Symmetry C_{18} (3.5 μm) 4.6 × 50 mm. HPLC purities were determined by summation of integrated HPLC peak areas at 214 nm. [b] Crude yields based on the theoretical loading weight of target molecules.

Table 2. Synthesis of 1,2,4-Benzothiadiazin-3-one 1,1-Dioxides with Various Substitutions at the 4N Position

			12	
entry	**10**	R^1	purity (%)	yield (%)
d	2-bromoacetylnaphthalene	H	>95	87
e	2-bromoacetylnaphthalene	MeO	93	86
f	2-bromoacetylnaphthalene	CF_3	92	95
g	methyl bromoacetate	H	>95	89
h	bromoacetonitrile	H	>95	90
i	propargylbromide	H	93	82
j	2-bromomethylnaphthalene	H	>95	79
k	benzylbromide	H	93	82
l	allylbromide	H	87	78
m	cinnamylbromide	H	>95	79
n	iodomethane	H	92	71
o	phenoxypropylbromide	H	0	−
p	2,4-dinitrofluorobenzene	H	86	84

ridine, 2,6-lutidine, 2,4,6-collidine, 2,6-*tert*-butylpyridine,[14] and 2,6-di-*tert*-butyl-4-methylpyridine[15]), solvents (NMP, dichloromethane {DCM}), and reaction temperatures (4−25 °C), the sulfonylation with 2,6-di-*tert*-butyl-4-methylpyridine/DCM at 25 °C was found to give **5** with excellent purity. The bulky 2,6-*tert*-butyl group successfully suppressed the sulfonimidation. Then, **5** was treated with $SnCl_2 \cdot 2H_2O$/EtOH/NMP[16] to reduce the nitro group. To our surprise, even after 3 days at 25 °C, the reduction of the nitro group was not complete to give a mixture of the nitroso intermediate and **6**. The nitroso intermediate disappeared with higher reaction temperature (70 °C) to give **6** with high purity. The cyclization of **6** proceeded smoothly with carbonyldiimidazole **7** at 25 °C to give **8**, probably owing to the high acidity of sulfonamides. Although the variety of 2-nitrobenzenesulfonyl chlorides as the third diversity point is restricted because of the limited commercial availability, 1,2,4-benzothiadiazin-3-one 1,1-dioxides **9** were obtained with excellent purities and yields, as shown in Table 1. As the fourth diversity point, N-alkylation of **8** was attempted. After examining various reaction conditions, it was found that the best purities were achieved with alkyl halide **10**/DIEA/NMP at 45 °C for 16 h. As shown in Table 2, **12** was obtained with high purities and yields using the following alkyl halides: alkyl bromides with an electron-withdrawing group at the α position (entries d−i), benzyl bromide type (entries j, k), allylbromide type (entries l, m), and iodomethane (entry n). Alkylation did not proceed at all with the simple alkyl halide, even at 95 °C (entry o). Arylation also proceeded smoothly using the Sanger reagent (entry p).

Table 3. Synthesis of 1,2,4-benzothiadiazin-3-one 1,1-dioxides from Various Solid-supported Amines, and Their Derivatization with 2-bromoacetylnaphthalene

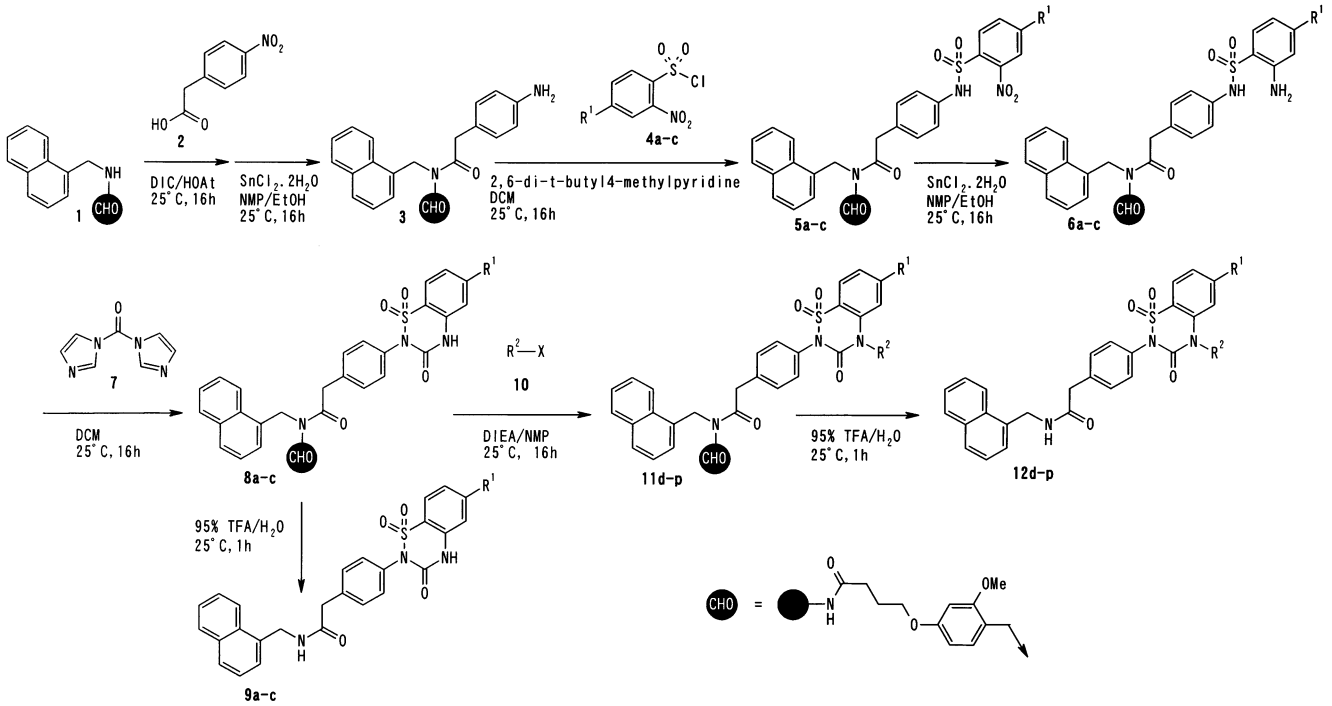
	13	**15**		**17**	
Entry		purity (%)	yield (%)	purity (%)	yield (%)
q		86	81	83	67
r		92	90	89	78
s		> 95	76	90	51
t		> 95	56	89	55
u		> 95	51	> 95	53
v		83	82	85	75
w		74	85	76	65
x		89	99	87	91

The benzene derivatives at the 4N position can be prepared only when S_NAr reactions proceed. As the second diversity point, various solid-supported amines **13** were prepared by reaction of **1** with nitrobenzene derivatives followed by treatment with $SnCl_2 \cdot 2H_2O$/EtOH/NMP (entries q−v), or with Fmoc-amino acids followed by treatment with 20% piperidine/NMP (entries w, x), as shown in Scheme 2. 1,2,4-Benzothiadiazin-3-one 1,1-dioxides (**15**, **17**) were obtained with excellent purity using both the solid-supported arylamines (entries q−v) and alkylamines (entries w, x), showing that the procedure is quite general and is suitable for the preparation of an array of compounds. All of the product structures in this manuscript were confirmed by ^{1}H NMR and LC/MS (ESI mass spectrometer).

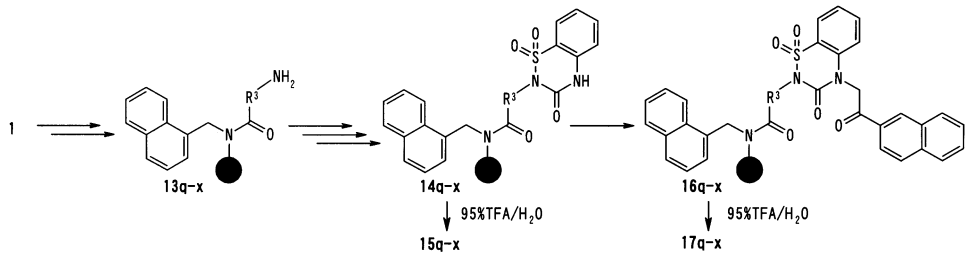
Conclusion

The solid-phase chemistry for the synthesis of 1,2,4-benzothiadiazin-3-one 1,1-dioxides was achieved for the first time with excellent purities and yields. Although the variety of sulfonyl chlorides is limited (the third diversity point), a number of reagents are commercially available for amines (the first diversity point), nitrobenzene derivatives with carboxylic acids or Fmoc-amino acids (the second diversity point), and alkyl halides (the fourth diversity point). Therefore, a large number of 1,2,4-benzothiadiazin-3-one 1,1-dioxides can be synthesized using this solid-phase synthesis. Furthermore, the bioactivities of 1,2,4-benzothiadiazin-3-one 1,1-dioxides can be compared with those of numerous

Scheme 1



Scheme 2



heterocylcles, because the same solid-supported amines can be derivatized into various heterocycles as described above.

Experimental Section

General. Commercial reagents were used without further purification. ^{1}H NMR spectra were recorded on Varian VXR-300S (300 MHz) spectrometers using tetramethylsilane as an internal standard. Liquid chromatography was performed using a symmetry C_{18} column with ESI/PDA detection on a Micromass platform.

General Procedure for Preparation of 2-[4-(1,1-Dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)-phenyl]-*N*-(1-naphthylmethyl)acetamide (9a). 4-(4-Formyl-3-methoxyphenoxy)butyryl AM resin (NOVAbiochem, 100−200 mesh, loading 0.53 mmol/g, 60 mg) was put into a 2.5-mL syringe fitted with polyethylene filter. 1-Aminomethylnaphthalene/$NaCNBH_3$/NMP/AcOH (150 μL/32 mg/1.0 mL/10 μL) was added to the syringe, and the syringe was shaken for 16 h at 25 °C, then for 6 h at 50 °C.[17] The resin was washed with MeOH (2 mL × 3), DMF (2 mL × 3) and DCM (2 mL × 3), and dried under vacuum for 3 h. After 4-nitrophenylacetic acid (73 mg) was preactivated with *N*,*N*′-diisopropylcarbodiimide (DIC)/1-hydroxy-7-azabenzotriazole (HOAt)/NMP (29 μL/55 mg/1.2 mL) at 25 °C for 1 h, this solution was added to the syringe, and the syringe was shaken for 16 h. The resin was washed with DMF (2 mL × 3) and DCM (2 mL × 3), and dried under vacuum for 3 h. The resin was treated with $SnCl_2$·$2H_2O$/NMP/EtOH (1.0 g/2.0 mL/0.1 mL) at 25 °C for 16 h and was washed with DMF (2 mL × 3) and DCM (2 mL × 3) and dried under vacuum for 3 h. 2-Nitrophenylsulfonyl chloride/2,6-*tert*-butyl-4-methylpyridine/DCM (100 mg/300 μL/1 mL) was added to the syringe, and the syringe was shaken for 16 h at 25 °C. The resin was washed with DMF (2 mL × 3) and DCM (2 mL × 3) and dried under vacuum for 3 h. Then, $SnCl_2$·$2H_2O$/NMP/EtOH (1.0 g/2.0 mL/0.1 mL) was added to the syringe, and it was shaken at 70 °C for 16 h. After the resin was washed with DMF (2 mL × 3) and DCM (2 mL × 3), CDI/DCM (100 mg/1 mL) was added to the syringe, and the syringe was shaken for 16 h. The resin was washed with DMF (2 mL × 3) and DCM (2 mL × 3), then dried under vacuum for 3 h. Finally, the resin was treated with 95% TFA/H_2O for 1 h, and the solution was concentrated.[18] The residue was dissolved with 50% CH_3CN/H_2O and lyophilized to give the crude product **9a** (12.7 mg, 85%). ^{1}H NMR (Varian VXR-300S, 300 MHz, DMSO-d_6) δ 11.58 (s, 1H), 8.69 (t, J = 5.4 Hz, 1H), 8.04−7.99 (m, 1H), 7.96−7.88 (m, 2H), 7.84 (dd, J = 6.9, 2.1 Hz, 1H), 7.75 (dt, J = 1.5, 8.7 Hz, 1H), 7.49−7.39 (m, 6H), 7.37−7.31 (m, 4H), 4.74 (d, J = 5.1 Hz, 2H), 3.57 (s, 2H). ESIMS *m*/*z* 472 $[MH]^+$.

2-[4-(6-Methoxy-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)phenyl]-*N*-(1-naphthylmethyl)acetamide (9b). Prepared as described above using 2-nitro-4-methoxybenzenesulfonyl chloride (14.9 mg, 94%). ^{1}H NMR (DMSO-d_6) δ 11.45 (s, 1H), 8.69 (t, J = 5.3 Hz, 1H), 8.02−7.99 (m, 1H), 7.95−7.91 (m, 1H), 7.85−7.79 (m, 2H), 7.55−7.50 (m, 2H), 7.47−7.40 (m, 4H), 7.30 (d, J = 8.1 Hz, 2H), 6.91 (dd, J = 9.1, 2.3 Hz, 1H), 4.74 (d, J = 5.7 Hz, 2H), 3.85 (s, 3H), 3.57 (s, 2H). ESIMS m/z 502 $[MH]^+$.

2-{4-[1,1-Dioxido-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl]phenyl}-*N*-(1-naphthylmethyl)acetamide (9c). Prepared as described above using 2-nitro-4-trifluoromethylbenzenesulfonyl chloride. (16.5 mg, 96%) ^{1}H NMR (DMSO-d_6) δ 11.86 (s, 1H), 8.68 (t, J = 6.9 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.02−7.99 (m, 1H), 7.95−7.92 (m, 2H), 7.84 (d, J = 7.2 Hz, 1H), 7.70−7.65 (m, 1H), 7.54−7.50 (m, 2H), 7.47−7.42 (m, 4H), 7.34 (d, J = 8.1 Hz, 2H), 4.74 (d, J = 5.7 Hz, 2H), 3.58 (s, 2H). ESIMS m/z 540 $[MH]^+$.

***N*-(1-Naphthylmethyl)-2-(4-{4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}phenyl)acetamide (12d).** The derivatized resin **8a** was prepared as the intermediate for the synthesis of **9a**. Compound **8a** was treated with 2-bromoacetylnaphthalene/DIEA/NMP (100 mg/200 μL/1 mL) at 45 °C for 16 h with gentle shaking, then washed with DMF (2 mL × 3) and DCM (2 mL × 3) and dried under vacuum for 3 h. The target compound **12d** was cleaved from the derivatized resin as described above (17.7 mg, 87%). ^{1}H NMR (DMSO-d_6) δ 8.89 (s, 1H), 8.67 (t, J = 5.4 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 8.10−7.90 (m, 6H), 7.84−7.76 (m, 2H), 7.73−7.63 (m, 2H), 7.53−7.40 (m, 8H), 7.33 (d, J = 9.0 Hz, 2H), 5.87 (s, 2H), 4.73 (d, J = 5.7 Hz, 2H), 3.57 (s, 2H). ESIMS m/z 640 $[MH]^+$.

2-(4-{6-Methoxy-4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}-phenyl)-*N*-(1-naphthylmethyl)acetamide (12e). Prepared as described above using 2-bromoacetylnaphthalene and **8b** (18.4 mg, 86%). ^{1}H NMR (DMSO-d_6) δ 8.87 (s, 1H), 8.67 (t, J = 5.4 Hz, 1H), 8.15 (d, J = 7.5 Hz, 1H), 8.09−7.89 (m, 7H), 7.81 (dd, J = 7.0, 2.2 Hz, 1H), 7.72−7.62 (m, 2H), 7.53−7.47 (m, 2H), 7.46−7.39 (m, 4H), 7.32−7.29 (m, 2H), 7.04 (dd, J = 8.7 Hz, 2.1, 1H), 6.94 (d, J = 2.1 Hz, 1H), 5.85 (s, 2H), 4.72 (d, J = 5.7 Hz, 2H), 3.82 (s, 3H), 3.56 (s, 2H). ESIMS m/z 670 $[MH]^+$.

***N*-(1-Naphthylmethyl)-2-{4-[4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl]phenyl}acetamide (12f).** Prepared as described above using 2-bromoacetylnaphthalene and **8c** (21.3 mg, 95%). ^{1}H NMR (DMSO-d_6) δ 8.87 (s, 1H), 8.66 (t, J = 5.4 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.10−7.88 (m, 6H), 7.85−7.80 (m, 2H), 7.73−7.64 (m, 2H), 7.53−7.39 (m, 6H), 7.34−7.31 (m, 2H), 5.97 (s, 2H), 4.72 (d, J = 5.4 Hz, 2H), 3.56 (s, 2H). ESIMS m/z 708 $[MH]^+$.

Methyl [2-(4-{2-[(1-naphthylmethyl)amino]-2-oxoethyl}-phenyl)-1,1-dioxido-3-oxo-2,3-dihydro-4H-1,2,4-benzothiadiazin-4-yl]acetate (12g). Prepared as described above using methyl bromoacetate and **8a** (15.4 mg, 89%). ^{1}H NMR (DMSO-d_6) δ 8.68 (t, J = 5.4 Hz, 1H), 8.02−7.98 (m, 2H), 7.95−7.90 (m, 1H), 7.87−7.81 (m, 2H), 7.57−7.42 (m, 8H), 7.28 (d, J = 8.1 Hz, 2H), 4.91 (s, 2H), 4.74 (d, J = 5.4 Hz, 2H), 3.71 (s, 3H), 3.57 (s, 2H). ESIMS m/z 544 $[MH]^+$.

2-{4-[4-(Cyanomethyl)-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl]phenyl}-*N*-(1-naphthylmethyl)acetamide (12h). Prepared as described above using bromoacetonitrile and **8a** (14.6 mg, 90%). ^{1}H NMR (DMSO-d_6) δ 8.69 (t, J = 5.3 Hz, 1H), 8.05−7.90 (m, 4H), 7.84 (dd, J = 6.9, 2.1 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.67−7.43 (m, 7H), 7.35 (d, J = 8.4 Hz, 2H), 5.29 (s, 2H), 4.74 (d, J = 5.1 Hz, 2H), 3.58 (s, 2H). ESIMS m/z 511 $[MH]^+$.

2-{4-[1,1-Dioxido-3-oxo-4-(2-propynyl)-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl]phenyl}-*N*-(1-naphthylmethyl)-acetamide (12i). Prepared as described above using propagylbromide and **8a**. ^{1}H NMR (DMSO-d_6) δ 8.68 (t, J = 5.4 Hz, 1H), 8.02−7.98 (m, 2H), 7.95−7.89 (m, 2H), 7.84 (dd, J = 7.2, 1.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.54−7.41 (m, 7H), 7.32 (d, J = 8.4 Hz, 2H), 4.93 (d, J = 2.1 Hz, 2H), 4.74 (d, J = 5.1 Hz, 2H), 3.58 (s, 2H), 3.41 (s, 1H). ESIMS m/z 510 $[MH]^+$. (82%)

2-[4-(4-Benzyl-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)phenyl]-*N*-(1-naphthylmethyl)acetamide (12j). Prepared as described above using 2-bromomethylnaphthalene and **8a** (13.2 mg, 79%). ^{1}H NMR (DMSO-d_6) δ 8.69 (t, J = 5.4 Hz, 1H), 8.02−7.82 (m, 8H), 7.74−7.68 (m, 1H), 7.55−7.37 (m, 13H), 5.58 (s, 2H), 4.74 (d, J = 5.4 Hz, 2H). ESIMS m/z 612 $[MH]^+$.

2-[4-(4-Benzyl-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)phenyl]-*N*-(1-naphthylmethyl)acetamide (12k). Prepared as described above using benzylbromide and **8a** (14.6 mg, 82%). ^{1}H NMR (DMSO-d_6) δ 8.69 (t, J = 5.4 Hz, 1H), 8.03−7.91 (m, 3H), 7.84 (dd, J = 6.7, 2.3 Hz, 1H), 7.73 (dt, J = 1.5, 7.8 Hz, 1H), 7.58−7.21 (m, 15H), 5.54 (s, 2H), 4.74 (d, J = 5.4 Hz, 2H), 3.58 (s, 2H). ESIMS m/z 562 $[MH]^+$.

2-[4-(4-Allyl-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)phenyl]-*N*-(1-naphthylmethyl)acetamide (12l). Prepared as described above using allylbromide and **8a** (12.7 mg, 78%). ^{1}H NMR (DMSO-d_6) δ 8.68 (t, J = 5.4 Hz, 1H), 8.21−7.92 (m, 3H), 7.86−7.80 (m, 2H), 7.59−7.41 (m, 8H), 7.32 (d, J = 8.7 Hz, 2H), 5.99−5.89 (m, 1H), 5.24 (d, J = 1.2 Hz, 1H), 5.19 (dd, J = 3.6, 1.2 Hz, 1H), 4.77−4.73 (m, 4H), 3.57 (s, 2H). ESIMS m/z 512 $[MH]^+$.

2-(4-{1,1-Dioxido-3-oxo-4-[(2E)-3-phenyl-2-propenyl]-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}phenyl)-*N*-(1-naphthylmethyl)acetamide (12m). Prepared as described above using cinnamylbromide and **8a** (14.7 mg, 78%). ^{1}H NMR (DMSO-d_6) δ 8.68 (t, J = 5.5 Hz, 1H), 8.02−7.91 (m, 3H), 7.87−7.81 (m, 2H), 7.68 (d, J = 8.1 Hz, 1H), 7.55−7.20 (m, 14H), 6.65 (d, J = 16.2 Hz, 1H), 6.40 (dt, J = 16.2 Hz, 5.1, 5.1, 1H), 4.91 (d, J = 4.8 Hz, 2H), 4.74 (d, J = 5.7 Hz, 2H), 3.57 (s, 2H). ESIMS m/z 588 $[MH]^+$.

2-[4-(4-Methyl-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)phenyl]-*N*-(1-naphthylmethyl)acetamide (12n). Prepared as described above using iodomethane and **8a** (10.9 mg, 70%). ^{1}H NMR (DMSO-d_6) δ 8.68 (t, J = 5.3 Hz, 1H), 8.03−8.00 (m, 1H), 7.97−7.89 (m, 2H), 7.87−7.83 (m, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.55−7.40 (m, 7H),

7.29 (d, J = 8.4 Hz, 2H), 4.74 (d, J = 5.1 Hz, 2H), 3.57 (s, 2H), 3.52 (s, 2H). ESIMS m/z 486 $[MH]^+$.

***N*1,*N*3-Dihydroxy-4-[2-(4-{2-[(1-naphthylmethyl)amino]-2-oxoethyl}phenyl)-1,1-dioxido-3-oxo-2,3-dihydro-4H-1,2,4-benzothiadiazin-4-yl]-*N*1,*N*3-dioxo-1,3-benzenediaminium (12p).** Prepared as described above using 2,4-dinitrofluorobenzene and **8a** (17.0 mg, 84%). ^{1}H NMR (DMSO-d_6) δ 9.01 (d, J = 2.1 Hz, 1H), 8.76 (dd, J = 8.7, 2.7 Hz, 1H), 8.68 (t, J = 5.4 Hz, 1H), 8.14−8.10 (m, 2H), 8.01−7.91 (m, 2H), 7.83 (dd, J = 7.0, 2.2 Hz, 1H), 7.74 (dt, J = 1.2, 7.8 Hz, 1H), 7.57−7.40 (m, 7H), 7.33 (d, J = 8.1 Hz, 2H), 6.94 (d, J = 8.4 Hz, 1H), 4.73 (d, J = 5.7 Hz, 2H), 3.57 (s, 2H). ESIMS m/z 638 $[MH]^+$.

2-[3-(1,1-Dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)phenyl]-*N*-(1-naphthylmethyl)acetamide (15q). Prepared as described above using 3-nitrophenylacetic acid (12.1 mg, 81%). ^{1}H NMR (DMSO-d_6) δ 11.62 (s, 1H), 8.68 (t, J = 5.4 Hz, 1H), 8.02−7.99 (m, 1H), 7.91−7.88 (m, 2H), 7.83−7.74 (m, 2H), 7.52−7.27 (m, 10H), 4.73 (d, J = 5.4 Hz, 2H), 3.56 (s, 2H). ESIMS m/z 472 $[MH]^+$.

2-[2-(1,1-Dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)phenyl]-*N*-(1-naphthylmethyl)acetamide (15r). Prepared as described above using 2-nitrophenylacetic acid (13.5 mg, 90%). ^{1}H NMR (DMSO-d_6) δ 11.56 (s, 1H), 8.31 (t, J = 5.5 Hz, 1H), 7.95−7.72 (m, 5H), 7.53−7.28 (m, 10H), 4.52 (d, J = 5.2 Hz, 2H), 3.42 (d, J = 3.6 Hz, 2H). ESIMS m/z 472 $[MH]^+$.

4-[4-(1,1-Dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)phenyl]-*N*-(1-naphthylmethyl)butanamide (15s). Prepared as described above using 4-nitrophenylbutyric acid (12.1 mg, 76%). ^{1}H NMR (DMSO-d_6) δ 11.56 (s, 1H), 8.39 (t, J = 5.6 Hz, 1H), 8.09−8.05 (m, 1H), 7.94−7.91 (m, 1H), 7.88−7.85 (m, 1H), 7.84−7.81 (m, 1H), 7.74 (dt, J = 1.5, 8.7 Hz, 1H), 7.57−7.42 (m, 4H), 7.36−7.28 (m, 6H), 4.72 (d, J = 5.7 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H), 2.21 (t, J = 7.3 Hz, 2H), 1.87 (q, J = 7.2 Hz, 2H). ESIMS m/z 500 $[MH]^+$.

3-(1,1-Dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)-*N*-(1-naphthylmethyl)benzamide (15t). Prepared as described above using 3-nitrobenzoic acid (8.2 mg, 56%). ^{1}H NMR (DMSO-d_6) δ 11.65 (s, 1H), 9.21 (t, J = 5.7 Hz, 1H), 8.16 (dd, J = 7.5, 1.5 Hz, 1H), 8.08 (dt, J = 7.2, 1.7 Hz, 1H), 7.96−7.88 (m, 2H), 7.84 (dd, J = 6.4, 2.9 Hz, 1H), 7.76 (dt, J = 1.5, 7.8 Hz, 1H), 7.67−7.43 (m, 7H), 7.37−7.32 (m, 2H), 4.95 (d, J = 5.4 Hz, 2H). ESIMS m/z 458 $[MH]^+$.

(2E)-3-[4-(1,1-Dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)phenyl]-*N*-(1-naphthylmethyl)-2-propenamide (15u). Prepared as described above using 4-nitrocinnamic acid (7.8 mg, 51%). ^{1}H NMR (DMSO-d_6) δ 11.61 (s, 1H), 8.71 (t, J = 5.6 Hz, 1H), 8.10 (d, J = 7.5 Hz, 1H), 7.96−7.93 (m, 1H), 7.91−7.84 (m, 2H), 7.78−7.67 (m, 1H), 7.59−7.42 (m, 8H), 7.37−7.33 (m, 3H), 4.87 (d, J = 5,4 Hz, 2H). ESIMS m/z 484 $[MH]^+$.

(2E)-3-[2-(1,1-Dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)phenyl]-*N*-(1-naphthylmethyl)-2-propenamide (15v). Prepared as described above using 2-nitrocinnamic acid (12.6 mg, 82%). ^{1}H NMR (DMSO-d_6) δ 11.69 (s, 1H), 8.66 (t, J = 5.6 Hz, 1H), 8.03−8.00 (m, 1H), 7.94−7.90 (m, 2H), 7.85−7.77 (m, 3H), 7.58−7.38 (m, 10H), 6.73 (d, J = 15.6 Hz, 1H), 4.77 (d, J = 5.7 Hz, 2H). ESIMS m/z 484 $[MH]^+$.

2-(1,1-Dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)-*N*-(1-naphthylmethyl)acetamide (15w). After adding Fmoc-Gly-OH/HOAt/DIC/NMP (198 mg/91 mg/49 μL/2 mL) to the derivatized resin **1** in the syringe, the syringe was shaken at 25 °C for 16 h. After washing the resin with DMF (2 mL × 3) and DCM (2 mL × 3), the resin was treated with 20% piperidine/NMP (2 mL) for 20 min and washed with DMF (2 mL × 3) and DCM (2 mL × 3). After drying the resin under vacuum for 3 h, cleavage was performed as described above to give **15w** (10.7 mg, 85%). ^{1}H NMR (DMSO-d_6) δ 11.46 (s, 1H), 8.70 (t, J = 5.4, 1H), 8.03−7.98 (m, 1H), 7.94−7.90 (m, 2H), 7.85−7.69 (m, 2H), 7.57−7.50 (m, 2H), 7.48−7.43 (m, 2H), 7.35−7.29 (m, 2H), 4.71 (d, J = 5.7, 2H), 4.44 (s, 2H). ESIMS m/z 396 $[MH]^+$.

(2S)-2-(1,1-Dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl)-*N*-(1-naphthylmethyl)-3-phenylpropanamide (15x). Prepared as described above using Fmoc-L-Phe-OH (15.2 mg, 99%). ^{1}H NMR (DMSO-d_6) δ 11.23 (s, 1H), 8.43 (t, J = 5.3 Hz, 1H), 8.03 (dt, J = 9.9, 3.6 Hz, 1H), 7.92 (dt, J = 9.6, 3.6 Hz, 2H), 7.82 (d, J = 6.6 Hz, 1H), 7.67−7.40 (m, 6H), 7.23−6.70 (m, 7H), 5.16 (dd, J = 9.9, 5.7 Hz, 1H), 4.77 (d, J = 5.4 Hz, 2H), 3.33 (dd, J = 13.5, 10.2 Hz, 2H). ESIMS m/z 486 $[MH]^+$.

***N*-(1-Naphthylmethyl)-2-(3-{4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}phenyl)acetamide (17q).** Prepared as described above using 2-bromoacetylnaphthalene and **14q** (13.6 mg, 67%). ^{1}H NMR (DMSO-d_6) δ 8.90 (s, 1H), 8.68 (t, J = 5.6 Hz, 1H), 8.17 (d, J = 7.2 Hz, 1H), 8.12−8.00 (m, 5H), 7.92−7.66 (m, 5H), 7.55−7.34 (m, 9H), 7.30 (dt, J = 6.9, 2.1 Hz, 1H), 5.87 (s, 2H), 4.72 (d, J = 5.7 Hz, 2H), 3.57 (s, 2H). ESIMS m/z 640 $[MH]^+$.

***N*-(1-Naphthylmethyl)-2-(2-{4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}phenyl)acetamide (17r).** Prepared as described above using 2-bromoacetylnaphthalene and **14r** (15.8 mg, 78%) .^{1}H NMR (DMSO-d_6) δ 8.87 (s, 1H), 8.26 (t, J = 5.5 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H), 8.08−7.96 (m, 5H), 7.92−7.89 (m, 2H), 7.82−7.77 (m, 2H), 7.73−7.62 (m, 2H), 7.54−7.36 (m, 9H), 5.95 (d, J = 18.6 Hz, 1H), 5.80 (d, J = 18.6 Hz, 1H), 4.57 (ddd, J = 24.9, 15.0, 5.7 Hz, 2H), 3.42 (d, J = 3.0 Hz, 2H). ESIMS m/z 640 $[MH]^+$.

***N*-(1-Naphthylmethyl)-4-(4-{4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}phenyl)butanamide (17s).** Prepared as described above using 2-bromoacetylnaphthalene and **14s** (10.8 mg, 51%). ^{1}H NMR (DMSO-d_6) δ 8.88 (s, 1H), 8.37 (t, J = 5.7 Hz, 1H), 8.16−7.25 (m, 21H), 5.84 (s, 2H), 4.72 (d, J = 5.4 Hz, 2H), 2.61 (t, J = 7.4 Hz, 2H), 2.19 (t, J = 7.4 Hz, 2H), 1.86 (dd, J = 14.6, 7.4 Hz, 2H). ESIMS m/z 668 $[MH]^+$.

***N*-(1-Naphthylmethyl)-3-{4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}benzamide (17t).** Prepared as described above using 2-bromoacetylnaphthalene and **14t** (10.9 mg, 55%). ^{1}H NMR (DMSO-d_6) δ 9.24 (t, J = 5.7 Hz, 1H), 8.87 (s, 1H), 8.16−

7.45 (m, 21H), 5.86 (s, 2H), 4.94 (d, $J = 5.7$ Hz, 2H). ESIMS *m*/*z* 626 $[MH]^+$.

(2E)-*N*-(1-Naphthylmethyl)-3-(4-{4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}phenyl)-2-propenamide (17u). Prepared as described above using 2-bromoacetylnaphthalene and **14u** (11.1 mg, 53%) .^{1}H NMR (DMSO-d_6) δ 8.88 (s, 1H), 8.70 (t, $J = 5.7$ Hz, 1H), 8.16−7.40 (m, 22H), 6.77 (d, $J = 15.9$ Hz, 1H), 5.86 (s, 2H), 4.86 (d, $J = 5.7$ Hz, 2H). ESIMS *m*/*z* 652 $[MH]^+$.

(2E)-*N*-(1-Naphthylmethyl)-3-(2-{4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}phenyl)-2-propenamide (17v). Prepared as described above using 2-bromoacetylnaphthalene and **14v** (15.5 mg, 75%). ^{1}H NMR (DMSO-d_6) δ 8.88 (s, 1H), 8.61 (t, $J = 5.6$ Hz, 1H), 8.15−7.42 (m, 22H), 6.74 (d, $J = 15.6$ Hz, 1H), 5.88 (d, $J = 7.2$ Hz, 2H), 4.81 (d, $J = 5.7$ Hz, 2H). ESIMS *m*/*z* 652 $[MH]^+$.

***N*-(1-Naphthylmethyl)-2-{4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}acetamide (17w).** Prepared as described above using 2-bromoacetylnaphthalene and **14w** (11.6 mg, 65%). ^{1}H NMR (DMSO-d_6) δ 8.90 (s, 1H), 8.68 (t, $J = 5.6$ Hz, 1H), 8.16 (d, $J = 7.5$ Hz, 1H), 8.12−7.89 (m, 4H), 7.85−7.81 (m, 2H), 7.77−7.65 (m, 4H), 7.54−7.41 (m, 6H), 5.81 (s, 2H), 4.73 (d, $J = 5.4$ Hz, 2H), 4.46 (s, 2H). ESIMS *m*/*z* 564 $[MH]^+$.

(2S)-*N*-(1-Naphthylmethyl)-2-{4-[2-(2-naphthyl)-2-oxoethyl]-1,1-dioxido-3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazin-2-yl}-3-phenylpropanamide (17x). Prepared as described above using 2-bromoacetylnaphthalene and **14x** (18.9 mg, 91%). ^{1}H NMR (DMSO-d_6) δ 8.94 (s, 1H), 8.35 (t, $J = 5.5$ Hz, 1H), 8.19 (d, $J = 7.8$ Hz, 1H), 8.12 (s, 1H), 8.07 (d, $J = 7.8$ Hz, 1H), 7.91 (d, $J = 9.3$ Hz, 1H), 7.81−7.16 (m, 15H), 6.93−6.91 (m, 2H), 5.82 (d, $J = 18.2$ Hz, 1H), 5.64 (d, $J = 18.2$ Hz, 1H), 5.06 (dd, $J = 11.1$, 4.5 Hz, 1H), 4.80 (d, $J = 5.4$ Hz, 2H), 3.13 (t, $J = 12.2$ Hz, 2H). ESIMS *m*/*z* 654 $[MH]^+$.

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CC020056K