

Supporting Information

Synthesis and Biological Characterization of B-Ring Amino Analogs of Potent Benzothiadiazine Hepatitis C Virus Polymerase Inhibitors.

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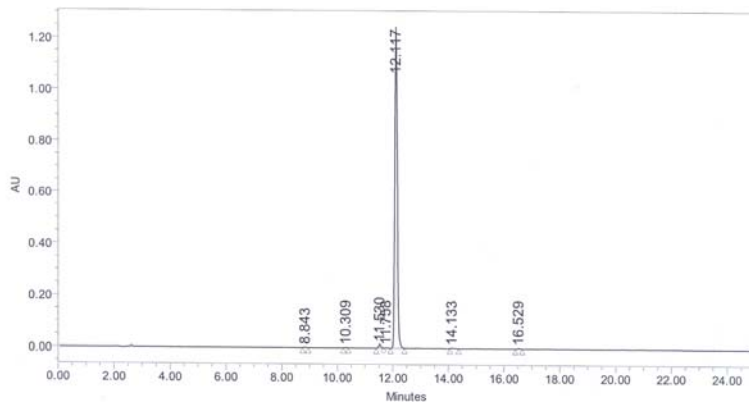
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C-18 reverse-phase HPLC conditions: Column = YMC ODS-A (4.6 x 120 mm, 5.5 μ M particle size); Solvent gradient = 10 - 100% CH₃CN in H₂O (0.1% TFA) over 20 min; Flow rate = 1 mL/min; UV detection at 254 nM.

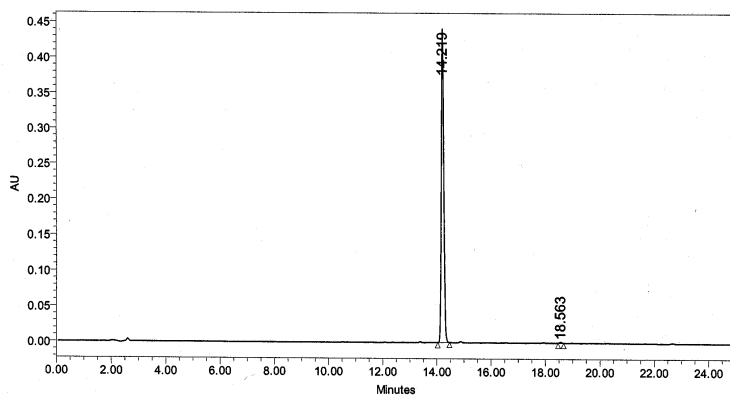
Results:

Compound **33** (purity = 98.04%)



	RT	Area	% Area	Height
1	8.843	11735	0.15	2062
2	10.309	8527	0.11	1480
3	11.530	86326	1.12	14133
4	11.758	12373	0.16	1804
5	12.117	7548612	98.04	1234576
6	14.133	10040	0.13	1271
7	16.529	21794	0.28	3565

Compound **30** (purity = 99.66%)

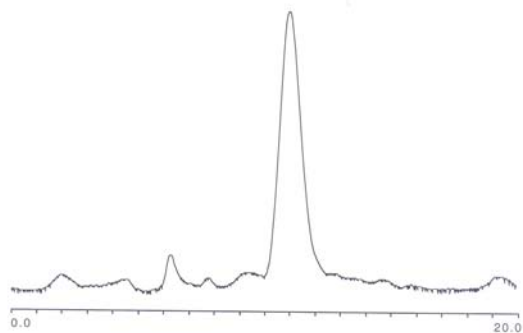


	RT	Area	% Area	Height
1	14.219	2755149	99.66	438242
2	18.563	9342	0.34	1607

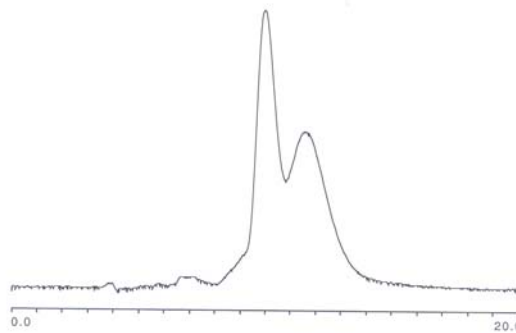
Chiral HPLC conditions: Column = Daicel Chem. Ind. Chiralpak AD-H (4.6 x 250 mm); Eluent = 10:10:80 MeOH:EtOH:hexane(0.1% TFA) for **33** and 15:85 2-PrOH:hexanes(0.1% TFA) for **30**; Flowrate = 0.8 mL/min; UV detection at 254 nM.

Results:

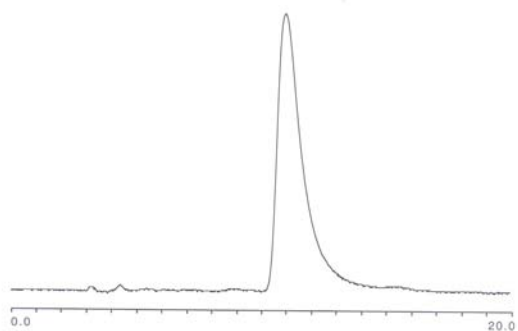
Compound **33**



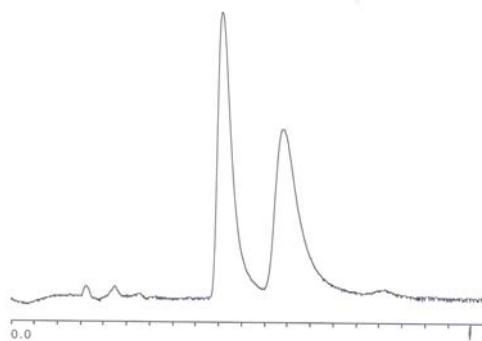
racemic mixture



Compound **30**



racemic mixture



C-18 reverse-phase HPLC conditions and results for compounds in Tables 1-5:

Method A: Column = YMC ODS-A (4.6 x 150 mm, 5.5 μ M particle size); Solvent gradient = 10-100% CH₃CN in H₂O (0.1% TFA) over 20 min; Flow rate = 1 mL/min; UV detection at 254 nM.

Method B: Column = Xterra RP18 (4.6 x 150 mm, 5 μ M particle size); Solvent gradient = 20-100% MeOH in H₂O (0.1% TFA) over 16 min; Flow rate = 0.7 mL/min; UV detection at 254 nM.

	Method A		Method B			Method A		Method B	
	rt ^a	% ^b	rt	%		rt	%	rt	%
14	17.05	97.21	16.16	100.00	26j	12.00	95.21	13.81	97.32
16	9.96	94.51	12.53	95.77	26k	12.68	98.83	14.35	99.31
17a	15.05	99.24	15.15	99.80	26l	14.25	96.24	15.16	97.85
17b	16.02	94.94	15.62	94.25	26m	14.76	98.44	15.62	98.82
17c	14.89	94.70	14.85	99.27	26n	14.20	99.14	15.47	99.67
17d	12.89	95.68	14.70	99.40	26o	12.23	96.14	13.80	97.60
17e	14.19	99.00	14.58	99.83	26p	10.27	98.97	12.49	97.31
17f	12.12	95.27	13.98	95.71	26q	12.10	98.83	13.52	99.45
17g	12.22	98.11	14.08	98.10	26r	10.01	95.22	11.96	98.23
26a	16.56	99.80	15.97	100.00	26s	12.05	97.25	13.67	97.84
26b	12.53	98.24	13.78	98.14	26t	11.83	98.12	12.02	98.91
26c	12.71	97.12	13.93	96.64	26u	13.48	96.64	14.97	98.73
26d	12.66	97.29	13.84	96.38	26v	13.64	98.82	14.95	99.00
26e	12.44	97.05	13.78	96.61	30	14.22	99.66	15.09	100.00
26f	13.29	99.21	14.01	99.68	31	17.06	99.16	16.21	99.10
26g	11.56	95.19	13.95	95.52	32	10.01	99.54	12.69	100.00
26h	14.23	98.90	15.49	100.00	33	12.12	98.04	13.94	98.47
26i	17.07	96.01	15.28	95.70	34	14.23	96.60	14.66	98.01

^a rt = retention time in minutes; ^b percent purity.

Experimental procedures for the synthesis of isoamyl analogs 14, 16 and 17a-17g.

(E)-3-Hydroxy-4-(methoxyimino)naphthalen-1(4H)-one (5). To a solution of 2-hydroxy-1,4-naphthoquinone (**4**) (3.0 g, 17.2 mmol) in abs. EtOH (30 mL) was added 1N aq. NaOH (51 mL, 51 mmol), followed by methoxyamine hydrochloride (2.86 g, 34.2 mmol). The resulting mixture was stirred at 80 °C for 5 h. The mixture was cooled to rt, solvents were removed *in vacuo*, and the residue was acidified using 10% aq. HCl (20 mL). The resulting solid was filtered, rinsed with H₂O, and dried in vacuo to give **5** as a yellowish tan solid (3.26 g, 93%): ¹H NMR (DMSO-*d*₆) δ 11.10 (br s, 1H), 8.76 (d, *J* = 8.1 Hz, 1H), 8.00-8.11 (m, 1H), 7.60-7.77 (m, 2H), 5.93 (s, 1H), 4.25 (s, 3H).

4-Allyl-3-hydroxy-4-(methoxyamino)naphthalen-1(4H)-one (6). To a suspension of indium powder (0.68 g, 5.9 mmol) in DMF (2 mL) at 0 °C was added allylbromide (0.76 mL, 8.8 mmol) dropwise over 5 min. The cooling bath was removed and the resulting exothermic reaction was allowed to stir for several minutes, during which time the indium metal dissolved. The resulting solution was cooled to 0 °C, and a solution of **5** (1.0 g, 4.9 mmol) in DMF (8 mL) was added. The resulting solution was allowed to warm to rt and was stirred for 1 h. The reaction mixture was partitioned between H₂O (50 mL) and ethyl acetate (3 x 50 mL), and the combined organic layers were dried over Na₂SO₄. The solution was filtered and concentrated, and the product was precipitated from diethyl ether to provide **6** as a light tan powder (0.99 g, 82%): ¹H NMR (DMSO-*d*₆) δ 11.84 (br s, 1H), 7.78 - 7.92 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.37-7.47 (m, 1H), 7.14 (s, 1H), 5.61-5.74 (m, 1H), 4.99-5.21 (m, 1H), 4.66-4.85 (m, 2H), 3.11 (s, 3H), 2.20-2.45 (m, 2H).

9b-Allyl-2-isopropyl-1-methoxy-1,2-dihydronaphtho[1,2-*d*]oxazol-5(9bH)-one (7). To a solution **6** (0.80g, 3.3mmol) in anhydrous dichloroethane (25 mL), was added isobutyraldehyde (1.8mL, 19.6 mmol), AcOH (0.37 mL, 6.5 mmol), and MgSO₄ (2.5 g), and the resulting mixture was stirred at rt for 18 h. The mixture was filtered and concentrated, and the crude product was purified by column chromatography on silica gel using 4:1 hexanes:ethyl acetate to give **7** as a colorless, waxy solid (0.71 g, 73%): ¹H NMR (DMSO-*d*₆) δ 7.92 (d, *J* = 7.7 Hz, 1H), 7.62-7.75 (m, 2H), 7.43-7.52 (m, 1H), 5.76 (s, 1H), 5.59 (d, *J* = 9.2 Hz, 1H), 5.03-5.21 (m, 1H), 4.71-4.92 (m, 2H), 3.48 (s, 3H), 2.65-2.77 (m, 1H), 2.53-2.64 (m, 1H), 2.35 (dd, *J* = 9.0, 6.4 Hz, 1H), 1.11-1.23 (m, 6H).

2-Isopropyl-1-methoxy-9b-(3-methylbut-2-enyl)-1,2-dihydronaphtho[1,2-*d*]oxazol-5(9bH)-one (8). To a solution of **7** (1.0 g, 3.3 mmol) in anhydrous CH₂Cl₂ (40 mL, degassed by bubbling with Ar for 10 min) was added 2-methyl-2-butene (20 mL) and Hoveyda-Grubbs catalyst, 2nd generation [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(*o*-isopropoxyphenylmethylene)ruthenium (31 mg, 0.16 mmol). The mixture was placed under N₂ in a sealed tube and heated at 60 °C for 16 h. Solvent was evaporated and the crude product was purified by column chromatography on silica gel using 9:1 hexanes:ethyl acetate to give **8** as a colorless gum (0.62g, 57%): ¹H NMR (DMSO-*d*₆) δ 7.90 (d, *J* = 7.4 Hz, 1 H), 7.68-7.74 (m, 1 H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 5.64 (d, *J* = 9.2 Hz, 1H), 4.48 (t, *J* = 7.2 Hz, 1H), 3.50 (s, 3H), 3.32 (s, 6H), 2.53-2.63 (m, 2H), 2.28-2.43 (m, 1H), 1.13-1.24 (m, 6H).

3-Hydroxy-4-isopentyl-4-(methoxyamino)naphthalen-1(4H)-one hydrochloride (9). To a solution of **8** (0.32 g, 0.98 mmol) in ethyl acetate (10 mL) was added Adam's catalyst (PtO₂·H₂O, 22 mg), and the resulting mixture was placed under 1 atm H₂ and

stirred for 2 h. The catalyst was filtered off, and the solvent was evaporated to give an oil, which was dissolved in 2:1 THF:2N aq. HCl (6 mL). The resulting solution was stirred at rt for 2 h, and concentrated *in vacuo*. The crude product was triturated with ethyl acetate:hexanes to give a precipitate that was collected by filtration and dried to provide **9** as a light tan amorphous solid (0.31 g, quant.): ¹H NMR (DMSO-*d*₆) δ 7.83 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.27-7.35 (m, 1H), 7.20 (t, *J* = 7.0 Hz, 1H), 6.82 (s, 1H), 3.06 (s, 3H), 1.37-1.51 (m, 1H), 1.23-1.37 (m, 1H), 1.08-1.23 (m, 1H), 0.77-0.92 (m, 1H), 0.27-0.67 (m, 7H).

tert-Butyl 4-amino-3-sulfamoylphenylcarbamate (11). To a mixture of 2,5-diaminobenzenesulfonamide (Goldfarb et al. *J. Am. Chem. Soc.* **1943**, 65, 738-739) (0.168 g, 0.896 mmol) and di-*tert*-butyl dicarbonate (0.196 g, 0.896 mmol) in anhydrous THF (10 mL) was stirred at rt for 16 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with 3:2 hexane/ethyl acetate, to give **11** as a beige powder (0.202 g, 78% yield): ¹H NMR (DMSO-*d*₆) δ 9.06 (s, 1H), 7.77 (s, 1H), 7.45-7.10 (m, 3H), 6.70 (d, *J* = 8.5 Hz, 1H), 5.53 (s, 2H), 1.45 (s, 9H).

2-Amino-5-(methylsulfonamido)benzenesulfonamide (12). To a solution of 2,5-diaminobenzenesulfonamide (Goldfarb et al. *J. Am. Chem. Soc.* **1943**, 65, 738-739) (0.29 g, 1.55 mmol) in anhydrous CH₂Cl₂ (5 mL) and pyridine (5 mL) at 0 °C was added methanesulfonyl chloride (0.12 mL, 1.55 mmol) dropwise over 3 min. The resulting mixture was allowed to warm to rt and stirred for 18 h. The solvent was removed *in vacuo*, and the crude product was purified by column chromatography on silica gel using 9:1 CH₂Cl₂:MeOH to give **12** as an off-white solid (0.28 g, 68%): ¹H NMR (DMSO-*d*₆) δ 9.21 (br s, 1H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.29 (br s, 2H), 7.13 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 5.80 (s, 2H), 2.87 (s, 3H).

tert-Butyl *N*-{3-[1-hydroxy-4-(methoxyamino)-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}carbamate (13). To a solution of **9** (0.31 g, 0.99 mmol) in anhydrous 1,4-dioxane (10 mL) was added pyridine (0.80 mL, 9.9 mmol) and tris(methylthio)methyl methylsulfate (1.05 g, 4.0 mmol), and the solution was heated at 60 °C for 2 h. More tris(methylthio)methyl methylsulfate (0.20 g, 0.76 mmol) was added, and heating was continued for 30 min. The cooled solution was concentrated *in vacuo*, and the crude product was purified by column chromatography on silica gel eluting with 20% ethyl acetate in hexane to give **10**, which was dissolved in anhydrous 1,4-dioxane (10 mL). Compound **11** (0.29 g, 0.99 mmol) was added, and the resulting solution was refluxed for 2 h, and then cooled to rt and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 10% ethyl acetate in hexane to give **13** as a solid (211 mg, 37%): ¹H NMR (DMSO-*d*₆) δ 13.55 (s, 1H), 9.87 (s, 1H), 8.09-8.17 (m, 2H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.73-7.81 (m, 1H), 7.53-7.70 (m, 3H), 3.14 (s, 3H), 1.77-1.90 (m, 1H), 1.60-1.73 (m, 1H), 1.51 (s, 9H), 1.20-1.32 (m, 1H), 0.79-0.94 (m, 1H), 0.42-0.78 (m, 7H).

***N*-{3-[(1-Hydroxy-4-(methoxyamino)-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (14).** To a solution of **9** (82 mg, 0.30 mmol) in anhydrous 1,4-dioxane (3 mL) was added pyridine (0.16 mL, 2.0 mmol) and tris(methylthio)methyl methylsulfate (0.40 g, 1.51 mmol), and the resulting solution was heated at 60 °C for 4 h. The solution was cooled and concentrated *in vacuo*, and the crude product was purified

by column chromatography on silica gel eluting with 20% ethyl acetate in hexane to give **10**, which was dissolved in anhydrous 1,4-dioxane (3 mL). Compound **12** (80 mg, 0.30 mmol) was added, and the resulting solution was heated at 80 °C for 16 h. The cooled solution was concentrated *in vacuo*, and the crude product was purified by column chromatography on silica gel, eluting with 3% CH₃OH in CHCl₃ to give **14** as a lt yellow solid (0.123 g, 75%): ¹H NMR (DMSO-*d*₆) δ 13.83 (s, 1H), 10.16 (s, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.46-7.62 (m, 4H), 3.16 (s, 3H), 3.06 (s, 3H), 1.72-1.89 (m, 1H), 1.53-1.72 (m, 1H), 1.13-1.33 (m, 1H), 0.77-0.95 (m, 1H), 0.56-0.73 (m, 6H), 0.37-0.56 (m, 1H); MS (ESI) *m/z* 549 (M+H)⁺.

***tert*-Butyl *N*-{3-[4-amino-1-hydroxy-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}carbamate (**15**).**

To a solution of **13** (205 mg, 0.36 mmol) in CH₃CN (16 mL) and H₂O (1.1 mL) was added molybdenum hexacarbonyl (66 mg, 0.25 mmol) and the solution was refluxed for 2 h. The cooled mixture was concentrated *in vacuo*, and the crude product was purified by column chromatography on silica gel, eluting with 3% CH₃OH in CHCl₃ to give **15** as a solid (163 mg, 81%): ¹H NMR (DMSO-*d*₆) δ 14.34 (s, 1H), 9.64 (s, 1H), 8.59 (s, 2H), 8.12 (d, *J* = 7.0 Hz, 1H), 7.94 (s, 1H), 7.48-7.73 (m, 4H), 7.25 (d, *J* = 8.8 Hz, 1H), 1.94-2.10 (m, 1H), 1.85 (s, 1H), 1.50 (s, 9H), 1.19-1.39 (m, 1H), 1.01-1.18 (m, 1H), 0.58-0.76 (m, 7H).

***N*-{3-[4-Amino-1-hydroxy-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (**16**).**

To a solution of **14** (210 mg, 0.38 mmol) in CH₃CN (16 mL) and H₂O (1.1 mL) was added molybdenum hexacarbonyl (69 mg, 0.26 mmol) and the solution was refluxed for 2 h, and then cooled to rt and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel, eluting with 5% CH₃OH in CHCl₃ to give **16** as a solid (153 mg, 77%): ¹H NMR (DMSO-*d*₆) δ 14.58 (s, 1H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.32-7.70 (m, 6H), 3.01 (s, 3H), 1.90-2.05 (m, 1H), 1.74-1.89 (m, 1H), 1.25-1.38 (m, 1H), 0.96-1.11 (m, 1H), 0.64-0.82 (m, 7H); MS (ESI) *m/z* 519 (M+H)⁺.

***N*-(4-hydroxy-1-(3-methylbutyl)-3-{7-[(methylsulfonyl)amino]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl}-2-oxo-1,2-dihydronaphthalen-1-yl)methoxyacetamide (**17a**).**

To a solution of **13** (23 mg, 0.04 mmol) in pyridine (0.5 mL) was added acetic anhydride (38 μL, 0.4 mmol). The resulting mixture was stirred at rt for 18 h and then concentrated *in vacuo*. The residue was dissolved in 4N HCl in 1,4-dioxane (0.26 mL) and the solution was stirred at rt for 4 h and then concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (1 mL) and triethylamine (36 μL, 0.3 mmol) and methanesulfonyl chloride (10 μL, 0.13 mmol) were added. The resulting solution was stirred at rt for 2 h and concentrated *in vacuo*. The residue was dissolved in MeOH (1 mL) and treated with K₂CO₃ (10 mg), and the resulting mixture was stirred at rt for 0.5 h. The mixture was partitioned between ethyl acetate (3 mL) and 1 N aq. HCl (2 x 1 mL), and the organic layer was dried over Na₂SO₄. The drying agent was filtered off, and solvent was removed *in vacuo* to give a crude product that was purified by column chromatography on silica, eluting with 5% MeOH in CH₂Cl₂ to **17a** as a lt yellow solid (8 mg, 53%): ¹H NMR (DMSO-*d*₆) δ 14.46 (s, 1H), 10.05 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.32-7.62 (m, 6H), 4.05 (s, 3H), 3.03 (s, 3H), 2.11-2.32 (m, 1H), 2.01 (s, 3H), 1.17-1.39 (m, 2H), 0.91-1.09 (m, 1H), 0.60-0.73 (m, 6H), 0.38-0.56 (m, 1H); MS (ESI) *m/z* 591 (M+H)⁺.

***N*-(4-hydroxy-1-(3-methylbutyl)-3-{7-[(methylsulfonyl)amino]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl}-2-oxo-1,2-dihydronaphthalen-1-yl)benzamide (17b).** To a solution of **15** (30 mg, 0.055 mmol) in CH₂Cl₂ (0.5 mL) was added triethylamine (0.15 mL, 0.11 mmol) and benzoyl chloride (8.6 μL, 0.07 mmol), and the resulting mixture was stirred at rt for 16 h. Solvent was removed *in vacuo*, the residue was dissolved in CH₂Cl₂ (0.5 mL) and trifluoroacetic acid (0.5 mL), and the mixture was stirred at rt for 2 h. Solvent was removed *in vacuo*, and the residue was dissolved in CH₂Cl₂ (0.5 mL) and triethylamine (0.15 mL, 0.11 mmol) and methanesulfonyl chloride (10 μL, 0.11 mmol) were added. The mixture was stirred at rt for 1.5 h, and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (0.5 mL), 1N NaOH (0.5 mL) was added, and the mixture was stirred at rt for 16 h. The pH was made acidic by the dropwise addition of 1N aq. HCl, the mixture was extracted with ethyl acetate (3 x 5 mL), and the combined organic extracts were dried over MgSO₄. The drying agent was filtered off, and the solvent was removed *in vacuo* to give a crude product that was purified by column chromatography on silica gel, eluting with 5% MeOH in CHCl₃ to give **17b** as a solid (19 mg, 56%): ¹H NMR (DMSO-*d*₆) δ 13.69 (s, 1H), 10.26 (s, 1H), 9.52 (s, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 7.0 Hz, 2H), 7.77-7.44 (m, 9H), 3.08 (s, 3H), 2.21-2.01 (m, 2H), 1.37-0.94 (m, 3H), 0.75-0.65 (m, 6H); MS (ESI) *m/z* 623 (M+H)⁺.

Methyl (4-hydroxy-1-(3-methylbutyl)-3-{7-[(methylsulfonyl)amino]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl}-2-oxo-1,2-dihydronaphthalen-1-yl)carbamate (17c).

Compound **15** (30 mg, 0.055 mmol) was subjected to the procedures described for the synthesis of **17b**, substituting methylchloroformate for benzoyl chloride, to give **17c** as a solid (17 mg, 53%): ¹H NMR (DMSO-*d*₆) δ 13.79 (s, 1H), 10.21 (s, 1H), 8.45 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.74-7.45 (m, 6H), 3.43 (s, 3H), 3.07 (s, 3H), 2.01-1.90 (m, 1H), 1.84-1.73 (m, 1H), 1.31-1.15 (m, 2H), 0.99-0.86 (m, 1H), 0.70-0.60 (m, 6H); MS (ESI) *m/z* 577 (M+H)⁺.

***N*-(3-[4-[(aminocarbonyl)amino]-1-hydroxy-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (17d).** To a suspension of **16** (10 mg, 0.018 mmol) in CH₂Cl₂ was added triethylamine (8 μL, 0.054 mmol) and *tert*-butyl isocyanate (3 μL, 0.027 mmol), and the resulting mixture was stirred at rt for 18 h. The solution was diluted with CH₂Cl₂ (1 mL), washed with 1N aq. HCl (2 x 0.5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Column chromatography on silica gel, eluting with 10% MeOH in CH₂Cl₂ afforded a lt yellow solid. The solid was dissolved in CH₂Cl₂ (0.3 mL) and trifluoroacetic acid (0.3 mL), and the resulting solution was stirred at rt for 18 h and then concentrated *in vacuo*. Column chromatography on silica gel, eluting with 5% MeOH in CH₂Cl₂ afforded **17d** as an off-white solid (7mg, 65%): ¹H NMR (DMSO-*d*₆) δ 15.47 (s, 1H), 9.86 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.34-7.43 (m, 3H), 7.23-7.33 (m, 2H), 6.51 (s, 1H), 5.40 (s, 2H), 2.99 (s, 3H), 1.66-1.83 (m, 1H), 1.46-1.62 (m, 1H), 1.17-1.31 (m, 1H), 0.83-1.07 (m, 2H), 0.60-0.76 (m, 6H); MS (ESI) *m/z* 562 (M+H)⁺.

***N*-(4-Hydroxy-1-(3-methylbutyl)-3-{7-[(methylsulfonyl)amino]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl}-2-oxo-1,2-dihydronaphthalen-1-yl)methanesulfonamide (17e).** Compound **15** (30 mg, 0.055 mmol) was subjected to the procedures described for the

synthesis of **17b**, substituting methanesulfonyl chloride for benzoyl chloride, to give **17e** as a solid (21 mg, 65%): $^1\text{H NMR}$ (DMSO- d_6) δ 15.25 (s, 1H), 9.89 (s, 1H), 8.00 (d, $J = 7.7$ Hz, 1H), 7.67-7.29 (m, 6H), 2.99 (s, 3H), 2.88 (s, 3H), 2.02-1.90 (m, 1H), 1.71-1.57 (m, 1H), 1.33-1.13 (m, 2H), 1.01-0.72 (m, 2H), 0.70-0.45 (m, 7H); MS (ESI) m/z 597 (M+H) $^+$.

***N*-{3-[4-(Benzylamino)-1-hydroxy-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (17f)**. To a suspension of **16** (10 mg, 0.018 mmol) in CH_2Cl_2 (0.2 mL) was added *N,N*-diisopropylethylamine (6 μL , 0.036 mmol), and the resulting mixture was stirred at rt until homogenous (approx. 5 min). Benzaldehyde (2 μL , 0.02 mmol) was added, and the mixture was stirred at rt for 18 h. To the mixture was added sodium triacetoxyborohydride (7 mg, 0.029 mmol) and AcOH (3 μL , 0.045 mmol), and stirring was continued at rt for 18 h. The mixture was diluted with ethyl acetate (1 mL), washed with H_2O (2 x 2 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. Column chromatography on silica, eluting with 5% MeOH in CH_2Cl_2 afforded **17f** as a colorless solid (8 mg, 73%): $^1\text{H NMR}$ (DMSO- d_6) δ 14.00 (s, 1H), 9.98 (s, 1H), 9.60 (s, 1H), 8.20 (d, $J = 8.1$ Hz, 1H), 7.88-7.99 (m, 1H), 7.68-7.77 (m, 1H), 7.57-7.67 (m, 1H), 7.27-7.56 (m, 8H), 3.59-3.76 (m, 1H), 3.40-3.50 (m, 1H), 3.02 (s, 3H), 2.17-2.37 (m, 1H), 1.89-2.06 (m, 1H), 1.21-1.38 (m, 1H), 0.96-1.13 (m, 1H), 0.59-0.74 (m, 6H), 0.40-0.59 (m, 1H); MS (ESI) m/z 609 (M+H) $^+$.

***N*-{3-[1-hydroxy-4-[(3-methoxybenzyl)amino]-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (17g)**. Compound **16** (10 mg, 0.018 mmol) was subjected to the conditions described for the synthesis of **17f**, substituting 3-methoxybenzaldehyde (2 μL , 0.02 mmol) for benzaldehyde, to give **17g** as a colorless solid (6 mg, 50%): $^1\text{H NMR}$ (DMSO- d_6) δ 13.98 (s, 1H), 9.97 (s, 1H), 9.57 (s, 1H), 8.19 (d, $J = 7.4$ Hz, 1H), 7.91 (d, $J = 7.4$ Hz, 1H), 7.66-7.76 (m, 1H), 7.56-7.66 (m, 1H), 7.42-7.56 (m, 2H), 7.34-7.41 (m, 1H), 7.29 (t, $J = 7.7$ Hz, 1H), 6.81-6.99 (m, 3H), 3.76 (s, 3H), 3.60-3.73 (m, 1H), 3.02 (s, 3H), 2.15-2.37 (m, 1H), 1.86-2.10 (m, 1H), 1.19-1.36 (m, 1H), 0.96-1.16 (m, 1H), 0.60-0.76 (m, 6H), 0.41-0.59 (m, 1H); MS (ESI) m/z 639 (M+H) $^+$.

Synthesis of chiral isoamyl analogs **31** – **34**.

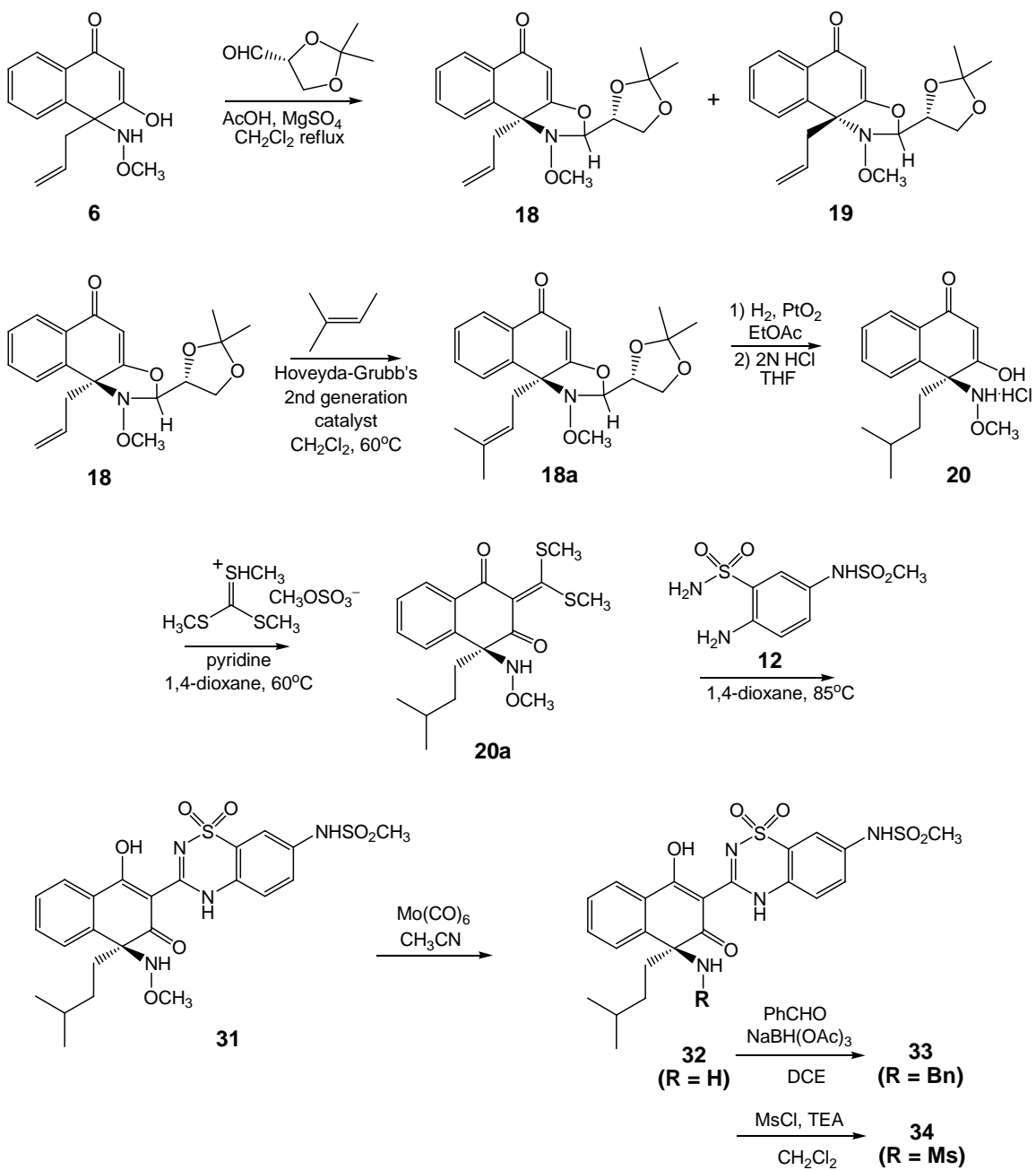
Reaction of allyl methoxyamine intermediate **6** with D-glyceraldehyde acetonide gave a mixture of two stereoisomeric oxazolidine analogs **18** and **19**, which were readily separated by chromatography on silica gel. Crystallization gave each of these compounds in high configurational purity as determined by ¹H NMR analysis. Single crystal x-ray analysis allowed us to determine the isomer having the desired *S*-configuration at the tertiary carbon center. The ORTEP plot for the crystal structure of **18** is shown below. The allyl side-chain of **18** was elaborated via prenyl intermediate **18a** to give chiral isoamyl-substituted AB ring fragment **20**. Polarimetry revealed *S*-isomer **20** to be the (-)-enantiomer $\{[\alpha]_D = -169^\circ (c = 1.0, \text{MeOH})\}$. The *R*-enantiomer **21** $\{[\alpha]_D = +152^\circ (c = 1.4, \text{MeOH})\}$ was obtained in like manner from compound **19**.

Chromatographic separation of stereoisomers **18** and **19** revealed that **18** eluted after **19** using normal-phase silica gel conditions. As a consequence of this order of elution, it was necessary to sacrifice a substantial amount of the desired isomer **18** in order to obtain material with high optical purity. This problem was avoided by reacting **6** with L-glyceraldehyde acetonide, giving a mixture of stereoisomers in which the order of elution was reversed. As expected, the least polar isomer from this mixture was found to be the opposite enantiomer of **19**, thus having the desired *S*-configuration at the tertiary carbon center. In this way, the desired *S*-enantiomer **20** could be obtained in high optical purity and better yield from **6**.

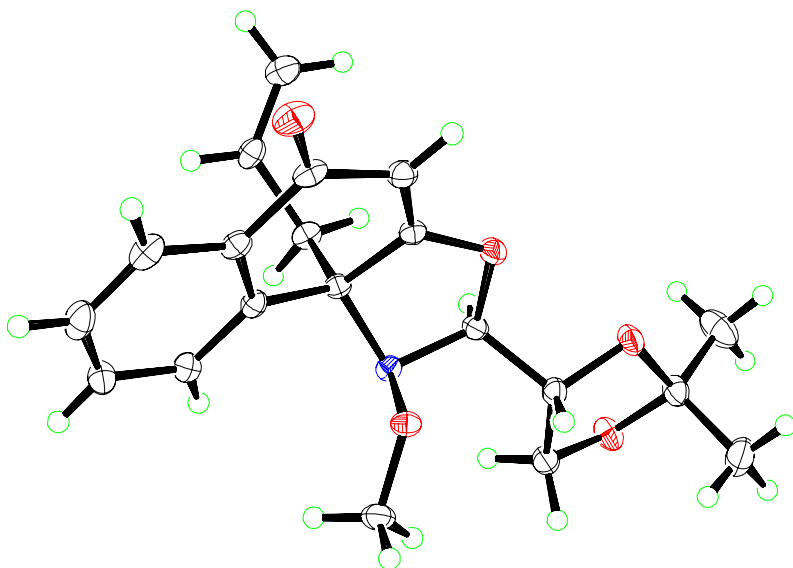
S-Methoxyamine **20** reacted with tris(methylthio)methyl methylsulfate to give dithioketeneacetal intermediate **20a**, which reacted with aminosulfonamide **12** to give benzothiadiazine **31**. Enantiomeric benzothiadiazine **32** was obtained in like-manner from *R*-methoxyamine **21**. Further conversion of *S*-methoxyamino analog **31** to *S*-amino analog **33** was accomplished using molybdenumhexacarbonyl. Compound **33** was converted to benzyl derivative **34** by reductive alkylation with benzaldehyde, and to methanesulfonamide **35** by reaction with methanesulfonyl chloride. Like the *S*-methoxyamine precursor **20**, tetracyclic thiadiazines **31**, **33**, **34**, and **35** each were found to be the (-)-enantiomer by polarimetry.

Enantiomeric purity for these compounds was further established using chiral HPLC. Due to the poor solubility of compounds in this series in typical solvents used for chiral HPLC (mixtures of hexanes and alcohol), only benzylamine derivative **34** could be separated to an extent useful for analysis. Indeed, our initial efforts to make chiral B-ring amino benzothiadiazine inhibitors relied on chiral chromatography to separate the racemic mixtures. This approach proved nonviable, resulting in our need to develop asymmetric synthetic approaches. Chiral analytical HPLC revealed that **26**, obtained using the chiral methods for synthesis described, contained less than 3% of the *R*-enantiomer. It was not possible to determine the amount of the minor isomer to any greater accuracy using this approach due to incomplete separation of enantiomers. However, this result confirmed our previous NMR analyses of **18** and **19**, which showed both of these compounds to be of high optical purity.

Synthesis of chiral isoamyl AB ring fragments.



ORTEP plot of crystal structure for **18** (available through the Cambridge Database using deposition code CCDC 707824).



Experimental procedures:

(2S, 9bS)-9b-Allyl-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-methoxy-1,2-dihydronaphtho[1,2-d]oxazol-5(9bH)-one (18). To a solution of **6** (1.00 g, 4.1 mmol) in CH₂Cl₂ (20 mL) was added isopropylidene-D-glyceraldehyde (1.0 g, 7.7 mmol), AcOH (0.25 mL, 4.1 mmol) and MgSO₄ (~2 g), and the resulting mixture was stirred at rt 16 h. The mixture was filtered, and the filtrate was partitioned between saturated aq. NaHCO₃ (10 mL) and CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give a crude mixture of diastereomers, which were separated by column chromatography on silica gel using a solvent gradient of 10-25% EtOAc in hexanes. Compound **18** eluted as the more polar component (0.24 g, 33% of theoretical): ¹H NMR (DMSO-*d*₆) δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.64-7.73 (m, 2H), 7.45-7.53 (m, 1H), 5.86 (s, 1H), 5.74 (d, *J* = 7.4 Hz, 1H), 5.00-5.18 (m, 1H), 4.87 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.82-4.72 (m, 1H), 4.49-4.61 (m, 1H), 4.27-4.37 (m, 1H), 4.09 (dd, *J* = 8.6, 5.7 Hz, 1H), 3.38 (s, 3H), 2.59-2.76 (m, 2H), 1.47 (s, 3H), 1.35 (s, 3H); MS (ESI) *m/z* 358 (M+H)⁺.

(2R,9bR)-9b-Allyl-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-methoxy-1,2-dihydronaphtho[1,2-d]oxazol-5(9bH)-one (19). Following the procedure described above for the synthesis of **18**, compound **19** eluted as the least polar product (0.54 g, 74% of theoretical): ¹H NMR (DMSO-*d*₆) δ 7.92 (d, *J* = 8.1 Hz, 1H), 7.62-7.78 (m, 2H), 7.42-7.54 (m, 1H), 5.95 (d, *J* = 6.3 Hz, 1H), 5.83 (s, 1H), 4.99-5.21 (m, 1H), 4.88 (dd, *J* = 9.9, 2.2 Hz, 1H), 4.79 (dd, *J* = 16.7, 2.0 Hz, 1H), 4.58-4.67 (m, 1H), 4.10-4.20 (m, 1H), 4.01-4.10 (m, 1H); 3.51 (s, 3H); 2.60-2.81 (m, 2H); 1.46 (s, 3H); 1.37 (s, 3H); MS (ESI) *m/z* 358 (M+H)⁺.

(2S,9bS)-9b-Allyl-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-methoxy-1,2-dihydronaphtho[1,2-d]oxazol-5(9bH)-one (opposite enantiomer of 19). To a solution of **6** (3.0 g, 12.2 mmol) in CH₂Cl₂ (60 mL) was added isopropylidene-L-glyceraldehyde (3.0 g, 23.0 mmol), AcOH (0.75 mL, 13.1 mmol) and MgSO₄ (~5 g), and the resulting mixture was stirred at reflux for 16 h. The mixture was filtered, and the filtrate was partitioned between saturated aq. NaHCO₃ (50 mL) and CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give a mixture of diastereomers that was separated by column chromatography on silica gel using a solvent gradient of 10-25% EtOAc in hexanes. The desired compound eluted as the least polar component (1.92 g, 88% of theoretical): ¹H NMR (DMSO-*d*₆) identical to that reported above for **19**.

(S)-3-Hydroxy-4-isopentyl-4-(methoxyamino)naphthalen-1(4H)-one hydrochloride (20). A solution of **18** (0.20 g, 0.56 mmol) and Hoveyda Grubbs 2nd generation catalyst (20 mg, 0.03 mmol) in a mixture of anhydrous CH₂Cl₂ (20 mL) and 2-methyl-2-butene (2 mL) was degassed by bubbling with Ar for 15 min. The reaction vessel was sealed and heated at 60 °C for 24 h. The mixture was cooled to rt, solvent was evaporated, and the residue was flashed on silica gel using 1:4 EtOAc:hexanes to give **18a** as a colorless solid (147 mg, 68%). To a solution of **18a** (145 mg, 0.38 mmol) in EtOAc (5 mL) was added PtO₂ (10 mg), and the resulting mixture was stirred at rt under 1 atm H₂ for 3 h. The mixture was filtered and concentrated in vacuo, and the residue was dissolved in THF (2 mL). 2N aq. HCl (1 mL) was added, and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated in vacuo and the crude product was purified by column chromatography on silica gel using 2:1 EtOAc:hexanes to give **20** as a colorless solid (58 mg, 50%): ¹H NMR (DMSO-*d*₆) δ 7.84 (m, *J* = 10.8, 7.9 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 5.73 (s, 1H), 3.09 (s, 3H), 1.75-1.90 (m, 1H), 1.48-1.62 (m, 1H), 1.15-1.33 (m, 1H), 0.80-0.92 (m, 1H), 0.57-0.72 (m, 6H), 0.30-0.50 (m, 1H); [α]_D = -169° (c 1.0, MeOH).

(R)-3-Hydroxy-4-isopentyl-4-(methoxyamino)naphthalen-1(4H)-one hydrochloride (21). The procedures described above for the synthesis of **20** from **18** were used to convert **19** (0.10 g, 0.28 mmol) to **21**, which was obtained as a colorless solid (42 mg, 48%): [α]_D = +152° (c 1.4, MeOH).

N-{3-[(4S)-1-Hydroxy-4-(methoxyamino)-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (31). To a solution of **20** (58 mg, 0.19 mmol) in anhydrous 1,4-dioxane (2 mL) was added tris(methylthio)methyl methylsulfate (0.26 g, 1.0 mmol) and pyridine (81 μL, 1.0 mmol). The resulting mixture was stirred at 60 °C for 4 h, and then concentrated in vacuo and flashed on silica gel using 2:1 EtOAc:hexanes to give dithioketeneacetal **20a** as a yellow oil (66 mg, 93%). To a solution of **20a** (65 mg, 0.17 mmol) in anhydrous 1,4-dioxane (2 mL) was added 2-amino-5-(methylsulfonamido)benzenesulfonamide (**12**) (46 mg, 0.17 mmol). The resulting mixture was stirred at 80 °C for 16 h and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 19:1 CHCl₃:MeOH to give **31** as a lt yellow solid (72 mg, 77%): ¹H NMR (DMSO-*d*₆) δ 13.80 (br s, 1H), 10.17 (s, 1H), 8.12 (d, *J* = 7.0 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.73 (t, *J* = 7.0 Hz, 1H), 7.50-7.64 (m, 4H), 3.16 (s, 3H), 3.06 (s, 3H), 1.73-1.88 (m, 1H), 1.57-1.70 (m, 1H), 1.15-1.32 (m, 1H), 0.79-0.94 (m, 1H), 0.60-0.71 (m, 6H), 0.39-0.53 (m, 1H); MS (ESI) *m/z* 549 (M+H)⁺; [α]_D = -109° (c 1.0, MeOH).

***N*-{3-[(4*R*)-1-Hydroxy-4-(methoxyamino)-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (enantiomer of **31**)**. Compound **21** (39 mg, 0.13 mmol) was subjected to the procedures described above for the synthesis of **31** to give a lt yellow solid (33 mg, 48%): ¹H NMR and MS identical to **31**; [α]_D = +98° (c 0.7, MeOH).

***N*-{3-[(4*S*)-4-Amino-1-hydroxy-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (**32**)**. To a solution of **31** (0.24 g, 0.44 mmol) in a mixture of CH₃CN (10 mL) and H₂O (1 mL) was added Mo(CO)₆ (82 mg, 0.31 mmol). The resulting mixture was stirred at reflux for 2 h, and then concentrated in vacuo. The crude product was purified on a C-18 reverse-phase column using 3:2 MeOH:0.1% aq. TFA as eluent to give the TFA salt of **32** as a tan solid (0.18 g, 79%): ¹H NMR (DMSO-*d*₆) δ 14.46 (br s, 1H), 9.95 (s, 1H), 8.60 (br s, 2H), 8.12 (d, *J* = 7.0 Hz, 1H), 7.59-7.70 (m, 2H), 7.41-7.58 (m, 3H), 7.36 (d, *J* = 8.8 Hz, 1H), 3.01 (s, 3H), 1.95-2.08 (m, 1H), 1.80-1.93 (m, 1H), 1.25-1.40 (m, 1H), 1.02-1.15 (m, 1H), 0.65-0.82 (m, 7H); MS (ESI) *m/z* 519 (M+H)⁺; [α]_D = -65° (c 1.0, MeOH).

***N*-{3-[(4*S*)-4-Benzylamino-1-hydroxy-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (**33**)**. A mixture of the TFA salt of **32** (100 mg, 0.16 mmol), benzaldehyde (24 μL, 0.24 mmol), and *N,N*-diisopropylethylamine (56 μL, 0.32 mmol) in 1,2-dichloroethane (2 mL) was stirred at rt overnight. To the mixture was added NaBH(OAc)₃ (68 mg, 0.32 mmol) and AcOH (23 μL, 0.40 mmol), and the resulting mixture was stirred at rt for 24 h. The mixture was poured into EtOAc (10 mL), washed with H₂O (10 mL), and dried over Na₂SO₄. The drying agent was filtered off, solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel using 3% MeOH in CH₂Cl₂ to give **33** as a lt yellow solid (80 mg, 83%): ¹H NMR (DMSO-*d*₆) δ 14.00 (br s, 1H), 9.97 (s, 1H), 9.59 (br s, 1H), 8.13-8.25 (m, 1H), 7.88-7.98 (m, 1H), 7.66-7.77 (m, 1H), 7.57-7.68 (m, 1H), 7.25-7.54 (m, 8H), 3.61-3.78 (m, 1H), 3.51-3.30 (m, 1H), 3.02 (s, 3H), 2.17-2.35 (m, 1H), 1.86-2.05 (m, 1H), 1.20-1.37 (m, 2H), 0.96-1.13 (m, 1H), 0.59-0.74 (m, 6H), 0.45-0.59 (m, 1H); MS (ESI) *m/z* 609 (M+H)⁺; [α]_D = -53° (c 1.0, MeOH).

***N*-{3-[(4*S*)-4-Methanesulfonylamino-1-hydroxy-4-(3-methylbutyl)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (**34**)**. To a solution of **32** (0.18 g, 0.35 mmol) in anhydrous CH₂Cl₂ (4 mL) was added methanesulfonyl chloride (0.082 mL, 1.06 mmol) and triethylamine (0.2 mL, 1.48 mmol). The resulting mixture was stirred at rt for 2 h. Volatiles were removed in vacuo, the residue was dissolved in MeOH (4 mL), and K₂CO₃ (~ 2 equivalents) was added. The resulting mixture was stirred at rt for 16 h, and was poured into 0.5 N aq. HCl (20 mL), extracted with 3:1 mixture of CH₂Cl₂:2-PrOH (3 x 20 mL), and the combined organic layers were dried over Na₂SO₄. The drying agent was filtered off, and the crude product was purified by column chromatography on silica gel using 5% MeOH:CHCl₃ to give **34** as a lt yellow solid (0.154 g, 74%): ¹H NMR (DMSO-*d*₆) δ 13.93 (s, 1H), 10.17 (s, 1H), 8.23 (s, 1H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.46-7.77 (m, 5H), 3.06 (s, 3H), 2.80 (s, 3H), 1.98-2.12 (m, 1H), 1.73-1.86 (m, 1H), 1.19-1.33 (m, 1H), 0.84-1.00 (m, 1H), 0.59-0.73 (m, 6H), 0.44-0.59 (m, 1H); MS (ESI) *m/z* 597 (M+H)⁺; [α]_D = -82° (c 0.9, MeOH).

Experimental procedures for synthesis of 26b – 26v.

***N*-{3-[4-(Benzylamino)-4-(3,3-dimethylbutyl)-1-hydroxy-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (26b).** To a suspension of **25** (0.12 g, 0.21 mmol) in dichloroethane (2 mL) was added *N,N*-diisopropylethylamine (73 μ L, 0.42 mmol). The mixture was stirred at rt until homogenous (approx. 5 min), and then benzaldehyde (38 μ L, 3.2 mmol) and MgSO₄ (25 mg) were added. The reaction mixture was heated at 50 °C for 18 h. The mixture was cooled to rt and filtered, and the filtrate was treated with sodium triacetoxyborohydride (72 mg, 0.34 mmol) and AcOH (36 μ L, 0.63 mmol). The mixture was stirred at rt for 18 h, diluted with CH₂Cl₂ (2 mL), washed with H₂O (2 x 2 mL) and dried over Na₂SO₄. The drying agent was filtered off, and the filtrate was concentrated *in vacuo* to give a crude product that was purified by column chromatography on silica gel, eluting with 5% MeOH in CH₂Cl₂ to give **26b** as a lt yellow solid (84 mg, 60%): ¹H NMR (DMSO-*d*₆) δ 13.99 (s, 1H), 9.98 (s, 1H), 9.61 (s, 1H), 8.18-8.24 (m, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.68-7.77 (m, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.45-7.56 (m, 2H), 7.28-7.43 (m, 6H), 3.43 (d, *J* = 12.9 Hz, 2H), 3.02 (s, 3H), 2.20-2.36 (m, 1H), 1.90-2.05 (m, 1H), 0.98-1.14 (m, 1H), 0.67 (s, 9H), 0.39-0.55 (m, 1H); MS (ESI) *m/z* 623 (M+H)⁺.

***N*-{3-[4-(3,3-dimethylbutyl)-1-hydroxy-4-[(2-methoxybenzyl)amino]-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (26c).** Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 2-methoxybenzaldehyde for benzaldehyde, to give **26c** as a lt yellow solid (16 mg, 56%): ¹H NMR (DMSO-*d*₆) δ 14.08 (s, 1H), 9.97 (s, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 2H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.43-7.55 (m, 2H), 7.30-7.41 (m, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 6.87-7.02 (m, 2H), 3.72 (s, 3H), 3.57-3.69 (m, 1H), 3.43-3.54 (m, 1H), 3.02 (s, 3H), 2.20-2.36 (m, 1H), 1.95-2.12 (m, 1H), 0.94-1.10 (m, 1H), 0.66 (s, 9H), 0.33-0.50 (m, 1H); MS (ESI) *m/z* 653 (M+H)⁺.

***N*-{3-[4-(3,3-Dimethylbutyl)-1-hydroxy-4-[(3-methoxybenzyl)amino]-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (26d).** Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 3-methoxybenzaldehyde for benzaldehyde, to give **26d** as a lt yellow solid (17 mg, 59%): ¹H NMR (DMSO-*d*₆) δ 13.96 (s, 1H), 9.98 (s, 1H), 9.58 (s, 1H), 8.17-8.23 (m, 1H), 7.92 (d, *J* = 7.72 Hz, 1H), 7.72 (t, *J* = 6.8 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.45-7.54 (m, 2H), 7.34-7.40 (m, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 6.89-6.97 (m, 2H), 6.85 (d, *J* = 7.7 Hz, 1H), 3.76 (s, 3H), 3.41 (d, *J* = 12.9 Hz, 2H), 3.02 (s, 3H), 2.20-2.36 (m, 1H), 1.89-2.06 (m, 1H), 0.97-1.14 (m, 1H), 0.67 (s, 9H), 0.39-0.53 (m, 1H); MS (ESI) *m/z* 653 (M+H)⁺.

***N*-{3-[4-(3,3-Dimethylbutyl)-1-hydroxy-4-[(4-methoxybenzyl)amino]-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (26e).** Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 4-methoxybenzaldehyde for benzaldehyde, to give **26e** as a lt yellow solid (13 mg, 45%): ¹H NMR (DMSO-*d*₆) δ 13.99 (s, 1H), 9.98 (s, 1H), 9.52 (s, 1H), 8.20 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 7.7 Hz,

1H), 7.72 (t, $J = 6.8$ Hz, 1H), 7.62 (t, $J = 7.7$ Hz, 1H), 7.44-7.54 (m, 2H), 7.34-7.38 (m, 1H), 7.20 (d, $J = 8.8$ Hz, 2H), 6.92 (d, $J = 8.5$ Hz, 2H), 3.73 (s, 3H), 3.38 (d, $J = 12.5$ Hz, 2H), 3.02 (s, 3H), 2.17-2.34 (m, 1H), 1.89-2.04 (m, 1H), 0.96-1.13 (m, 1H), 0.66 (s, 9H), 0.37-0.53 (m, 1H); MS (ESI) m/z 653 (M+H)⁺.

***N*-{3-[4-[(4-Cyanobenzyl)amino]-4-(3,3-dimethylbutyl)-1-hydroxy-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (26f)**. Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 4-cyanobenzaldehyde for benzaldehyde, to give **26f** as a lt yellow solid (9 mg, 32%): ¹H NMR (DMSO- d_6) δ 13.94 (s, 1H), 9.97 (s, 1H), 9.75 (s, 1H), 8.18 (d, $J = 7.4$ Hz, 1H), 7.9 (d, $J = 7.4$ Hz, 3H), 7.55-7.74 (m, 2H), 7.44-7.55 (m, 4H), 7.33-7.39 (m, 1H), 3.67-3.85 (m, 1H), 3.49-3.66 (m, 1H), 3.02 (s, 3H), 2.14-2.35 (m, 1H), 1.83-2.04 (m, 1H), 0.97-1.11 (m, 1H), 0.67 (s, 9H), 0.39-0.55 (m, 1H); MS (ESI) m/z 648 (M+H)⁺.

***N*-{3-[4-(3,3-Dimethylbutyl)-1-hydroxy-4-[(4-hydroxybenzyl)amino]-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (26g)**. A mixture of **26h** (13mg, 0.018 mmol) and 10% Pd/C (3 mg) in MeOH (1 mL) was stirred at rt under 1 atm H₂ for 6 h. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give a crude product that was purified by column chromatography on silica gel, eluting with 5% MeOH in CH₂Cl₂, to give **26g** as a lt yellow solid (8 mg, 73%): ¹H NMR (DMSO- d_6) δ 14.58 (s, 1H), 8.86 (s, 1H), 8.15 (d, $J = 7.3$ Hz, 1H), 7.80 (d, $J = 7.9$ Hz, 1H), 7.52-7.60 (m, 2H), 7.40-7.48 (m, 2H), 7.24 (d, $J = 8.5$ Hz, 1H), 7.05 (d, $J = 8.5$ Hz, 2H), 6.69 (d, $J = 7.9$ Hz, 2H), 3.41 (d, $J = 12.2$ Hz, 1H), 3.18 (d, $J = 12.2$ Hz, 1H), 2.98 (s, 3H), 2.00-2.11 (m, 1H), 1.78-1.90 (m, 1H), 0.97-1.07 (m, 1H), 0.59-0.69 (m, 10H); MS (ESI) m/z 639 (M+H)⁺.

***N*-{3-[4-[[4-(Benzyloxy)benzyl]amino]-4-(3,3-dimethylbutyl)-1-hydroxy-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (26h)**. Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 4-benzyloxybenzaldehyde for benzaldehyde, to give **26h** as a lt orange solid (17 mg, 53%): ¹H NMR (DMSO- d_6) δ 14.00 (s, 1H), 9.97 (s, 1H), 9.50 (s, 1H), 8.19 (d, $J = 7.4$ Hz, 1H), 7.91 (d, $J = 7.4$ Hz, 1H), 7.71 (t, $J = 7.7$ Hz, 1H), 7.57-7.66 (m, 1H), 7.27-7.55 (m, 8H), 7.19 (d, $J = 8.8$ Hz, 2H), 7.00 (d, $J = 8.5$ Hz, 2H), 5.10 (s, 2H), 3.55-3.67 (m, 1H), 3.01 (s, 3H), 2.14-2.33 (m, 1H), 1.86-2.04 (m, 1H), 0.96-1.12 (m, 1H), 0.66 (s, 9H), 0.36-0.54 (m, 1H); MS (ESI) m/z 729 (M+H)⁺.

***N*-[3-(4-(3,3-Dimethylbutyl)-1-hydroxy-3-oxo-4-[[2-(trifluoromethyl)benzyl]amino]-3,4-dihydronaphthalen-2-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]methanesulfonamide (26i)**. Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 2-trifluoromethylbenzaldehyde for benzaldehyde, to give **26i** as a lt yellow solid (13 mg, 43%): ¹H NMR (DMSO- d_6) δ 13.87 (s, 1H), 9.98 (s, 1H), 8.19 (d, $J = 6.3$ Hz, 1H), 7.56-7.92 (m, 7H), 7.44-7.55 (m, 2H), 7.37 (d, $J = 8.8$ Hz, 1H), 3.87 (d, $J = 10.7$ Hz, 1H), 3.54 (d, $J = 12.1$ Hz, 1H), 3.02 (s, 3H), 2.25-2.43 (m, 1H), 1.87-2.11 (m, 1H), 0.97-1.12 (m, 1H), 0.68 (s, 9H), 0.35-0.54 (m, 1H); MS (ESI) m/z 691 (M+H)⁺.

***N*-{3-[4-[(2-Aminobenzyl)amino]-4-(3,3-dimethylbutyl)-1-hydroxy-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (26j)**. Compound **25** (25 mg, 44 μ mol) was subjected to the

conditions described for the synthesis of **26b**, substituting 2-nitrobenzaldehyde for benzaldehyde, to give a lt yellow solid (13 mg, 43%). To a solution of this solid (7 mg, 0.01 mmol) in EtOAc (0.5 mL) was added 10% Pd/C (2 mg). The mixture was stirred under 1 atm H₂ for 1 h, filtered, and the filtrate was concentrated *in vacuo*. Column chromatography on silica gel, eluting with 3% MeOH in CH₂Cl₂ afforded **26j** as a yellow solid (4 mg, 57%): ¹H NMR (DMSO-*d*₆) δ 13.90 (s, 1H), 9.97 (s, 1H), 8.20 (d, *J* = 6.6 Hz, 1H), 7.90-8.01 (m, 1H), 7.00-7.77 (m, 6H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.55 (t, *J* = 6.3 Hz, 1H), 3.45-3.57 (m, 1H), 3.02 (s, 3H), 2.17-2.37 (m, 1H), 1.86-2.03 (m, 1H), 0.99-1.14 (m, 1H), 0.66 (s, 9H), 0.38-0.55 (m, 1H); MS (ESI) *m/z* 638 (M+H)⁺.

N-(3-{4-(3,3-Dimethylbutyl)-1-hydroxy-4-[(2,5-dimethoxybenzyl)amino]-3-oxo-3,4-dihydronaphthalen-2-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26k). Compound **25** (25 mg, 44 μmol) was subjected to the conditions described for the synthesis of **26b**, substituting 2,5-dimethoxybenzaldehyde for benzaldehyde, to give **26k** as a lt yellow solid (16 mg, 53%): ¹H NMR (DMSO-*d*₆) δ 14.06 (s, 1H), 9.97 (s, 1H), 9.55 (br s, 1H), 9.12 (br s, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.4 Hz, 1H), 7.70-7.81 (m, 1H), 7.57-7.65 (m, 1H), 7.43-7.56 (m, 2H), 7.31-7.40 (m, 1H), 6.89 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H), 3.41-3.60 (m, 2H), 3.02 (s, 3H), 2.18-2.35 (m, 1H), 1.96-2.11 (m, 1H), 0.94-1.10 (m, 1H), 0.66 (s, 9H), 0.32-0.48 (m, 1H); MS (ESI) *m/z* 683 (M+H)⁺.

N-{3-[4-[(2,6-Dimethylbenzyl)amino]-4-(3,3-dimethylbutyl)-1-hydroxy-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide (26l). Compound **25** (25 mg, 44 μmol) was subjected to the conditions described for the synthesis of **26b**, substituting 2,6-dimethylbenzaldehyde for benzaldehyde, to give **26l** as a lt yellow solid (11 mg, 39%): ¹H NMR (DMSO-*d*₆) δ 13.96 (s, 1H), 9.99 (s, 1H), 9.25 (br s, 1H), 8.93 (s, 1H), 8.23 (d, *J* = 7.4 Hz, 1H), 8.03 (d, *J* = 7.4 Hz, 1H), 7.74 (t, *J* = 6.8 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.42-7.58 (m, 2H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.13-7.23 (m, 1H), 7.03-7.11 (m, 2H), 3.63-3.79 (m, 1H), 3.02 (m, 3H), 2.31-2.40 (m, 1H), 2.26 (s, 6H), 1.96-2.13 (m, 1H), 0.97-1.13 (m, 1H), 0.67 (s, 9H), 0.31-0.50 (m, 1H); MS (ESI) *m/z* 651 (M+H)⁺.

N-(3-{4-(3,3-Dimethylbutyl)-1-hydroxy-4-[(mesitylmethyl)amino]-3-oxo-3,4-dihydronaphthalen-2-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26m). Compound **25** (25 mg, 44 μmol) was subjected to the conditions described for the synthesis of **26b**, substituting mesitaldehyde for benzaldehyde, to give **26m** as a lt yellow solid (8 mg, 27%): ¹H NMR (DMSO-*d*₆) δ 13.95 (s, 1H), 9.98 (s, 1H), 9.21 (s, 1H), 8.87 (s, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.69-7.79 (m, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.42-7.56 (m, 2H), 7.36 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 2H), 3.58-3.76 (m, 1H), 3.20 (s, 3H), 2.27-2.45 (m, 1H), 2.21 (s, 9H), 1.96-2.13 (m, 1H), 0.95-1.13 (m, 1H), 0.67 (s, 9H), 0.32-0.50 (m, 1H); MS (ESI) *m/z* 665 (M+H)⁺.

N-{3-[4-[(1,1'-Biphenyl-4-ylmethyl)amino]-4-(3,3-dimethylbutyl)-1-hydroxy-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26n). Compound **25** (25 mg, 44 μmol) was subjected to the conditions described for the synthesis of **26b**, substituting 4-biphenylcaboxaldehyde for benzaldehyde, to give **26n** as a lt yellow solid (16 mg, 52%): ¹H NMR (DMSO-*d*₆) δ 14.01 (s, 1H), 9.97 (s, 1H), 9.64 (s, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 7.94 (d, *J* = 6.6 Hz,

1H), 7.32 - 7.78 (m, 14H), 3.74 (d, $J = 13.2$ Hz, 1H), 3.49 (d, $J = 14.0$ Hz, 1H), 3.02 (s, 3H), 2.19-2.36 (m, 1H), 1.89-2.06 (m, 1H), 0.98-1.16 (m, 1H), 0.67 (s, 9H), 0.39-0.55 (m, 1H); MS (ESI) m/z 699 (M+H)⁺.

***N*-(3-{4-(3,3-Dimethylbutyl)-4-[(2-furylmethyl)amino]-1-hydroxy-3-oxo-3,4-dihydronaphthalen-2-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26o).** Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 2-furaldehyde for benzaldehyde, to give **26o** as a lt yellow solid (14 mg, 52%): ¹H NMR (DMSO-*d*₆) δ 13.98 (s, 1H), 9.98 (s, 1H), 9.75 (br s, 1H), 8.18 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.89 (d, $J = 7.7$ Hz, 1H), 7.65-7.72 (m, 2H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.44-7.54 (m, 2H), 7.33-7.40 (m, 1H), 6.42 (d, $J = 1.5$ Hz, 2H), 3.74-3.83 (m, 1H), 3.50 (d, $J = 14.3$ Hz, 1H), 3.02 (s, 3H), 2.16-2.31 (m, 1H), 1.89-2.04 (m, 1H), 0.96-1.12 (m, 1H), 0.66 (s, 9H), 0.36-0.51 (m, 1H); MS (ESI) m/z 613 (M+H)⁺.

***N*-(3-{4-(3,3-Dimethylbutyl)-1-hydroxy-3-oxo-4-[(pyridin-3-ylmethyl)amino]-3,4,5-dihydronaphthalen-2-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26p).** Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 3-pyridinecarboxaldehyde for benzaldehyde, to give **26p** as a lt yellow solid (6.5 mg, 24%): ¹H NMR (DMSO-*d*₆) δ 9.96 (s, 1H), 8.52 (s, 1H), 8.45 (s, 1H), 8.17 (d, $J = 8.1$ Hz, 1H), 7.81-7.93 (m, 1H), 7.29-7.79 (m, 7H), 3.25-3.85 (m, 1H), 3.02 (s, 1H), 2.05-2.31 (m, 1H), 1.79-2.03 (m, 1H), 0.94-1.12 (m, 1H), 0.66 (s, 9H), 0.41-0.58 (m, 1H); MS (ESI) m/z 624 (M+H)⁺.

***N*-[3-(4-(3,3-Dimethylbutyl)-1-hydroxy-4-[(6-methylpyridin-2-yl)methyl]amino)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26q).** Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 6-methylpyridine-2-carboxaldehyde for benzaldehyde, to give **26q** as a lt yellow solid (19 mg, 68%): ¹H NMR (DMSO-*d*₆) δ 15.33 (s, 1H), 9.89 (s, 1H), 8.06 (d, $J = 7.4$ Hz, 1H), 7.69 (d, $J = 7.0$ Hz, 1H), 7.46-7.61 (m, 3H), 7.29-7.45 (m, 3H), 7.00-7.14 (m, 2H), 3.13-3.25 (m, 1H), 3.03-3.11 (m, 1H), 2.99 (s, 3H), 2.41 (s, 3H), 1.80-1.98 (m, 1H), 1.57-1.74 (m, 1H), 0.83-0.98 (m, 1H), 0.65 (s, 9H), 0.45-0.60 (m, 1H); MS (ESI) m/z 638 (M+H)⁺.

***N*-[3-(4-(3,3-Dimethylbutyl)-1-hydroxy-4-[(6-methylpyridin-3-yl)methyl]amino)-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26r).** Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 6-methylpyridine-3-carboxaldehyde for benzaldehyde, to give **26r** as a lt yellow solid (15 mg, 58%): ¹H NMR (DMSO-*d*₆) δ 15.29 (s, 1H), 8.27 (d, $J = 2.2$ Hz, 1H), 8.06 (d, $J = 6.6$ Hz, 1H), 7.75 (d, $J = 8.1$ Hz, 1H), 7.48-7.60 (m, 2H), 7.31-7.47 (m, 3H), 7.28 (d, $J = 8.8$ Hz, 1H), 7.14 (d, $J = 7.7$ Hz, 1H), 3.60-3.30 (m, 2H), 3.01 (s, 3H), 2.42 (s, 3H), 1.76-1.87 (m, 1H), 1.54-1.70 (m, 1H), 0.79-0.93 (m, 1H), 0.48-0.67 (m, 10H); MS (ESI) m/z 638 (M+H)⁺.

***N*-(3-{4-(3,3-Dimethylbutyl)-4-[(2,5-dimethyl-2H-pyrazol-3-ylmethyl)amino]-1-hydroxy-3-oxo-3,4-dihydronaphthalen-2-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26s).** Compound **25** (152 mg, 0.28 mmol) was subjected to the conditions described for the synthesis of **26b**, substituting 1,3-dimethyl-1-pyrazol-5-carboxaldehyde for benzaldehyde, to give **26s** as an off-white solid (50 mg, 29%): ¹H NMR (DMSO-*d*₆) δ 15.30 (s, 1H), 9.90 (s, 1H), 8.07 (d, $J = 7.7$ Hz, 1H), 7.70 (d, $J = 7.4$

Hz, 1H), 7.29-7.59 (m, 5H), 5.85 (s, 1H), 3.57 (s, 3H), 3.27 (d, $J = 4.4$ Hz, 1H), 3.17 (d, $J = 5.2$ Hz, 1H), 2.97-3.04 (m, 3H), 2.05 (s, 3H), 1.72-1.88 (m, 1H), 1.50-1.70 (m, 1H), 0.80-0.98 (m, 1H), 0.45-0.74 (m, 10H); MS (ESI) m/z 641 (M+H)⁺.

***N*-(3-{4-(3,3-Dimethylbutyl)-4-[(1-methylimidazol-2-yl)methyl]amino}-1-hydroxy-3-oxo-3,4-dihydronaphthalen-2-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26t).** Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 1-methyl-imidazole-2-carboxaldehyde for benzaldehyde, to give **26t** as an off-white solid (3 mg, 11%): ¹H NMR (DMSO-*d*₆) δ 15.27 (s, 1H), 9.90 (s, 1H), 8.07 (d, $J = 7.0$ Hz, 1H), 7.72 (d, $J = 7.4$ Hz, 1H), 7.51-7.59 (m, 1H), 7.46-7.51 (m, 1H), 7.31-7.45 (m, 2H), 6.97-7.01 (m, 1H), 6.71-6.74 (m, 1H), 3.48 (s, 3H), 3.22 (d, $J = 12.1$ Hz, 1H), 2.96-3.08 (m, 4H), 1.77-1.91 (m, 1H), 1.56-1.71 (m, 2H), 0.81-0.96 (m, 1H), 0.63 (s, 9H), 0.44-0.59 (m, 1H); MS (ESI) m/z 627 (M+H)⁺.

***N*-(3-{4-(3,3-Dimethylbutyl)-1-hydroxy-4-[(2-naphthylmethyl)amino]-3-oxo-3,4-dihydronaphthalen-2-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26u).** Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 2-naphthaldehyde for benzaldehyde, to give **26u** as a lt yellow solid (11 mg, 38%): ¹H NMR (DMSO-*d*₆) δ 14.00 (s, 1H), 9.98 (s, 1H), 9.72 (s, 1H), 8.22 (d, $J = 8.5$ Hz, 1H), 7.83-8.02 (m, 5H), 7.74 (t, $J = 5.9$ Hz, 1H), 7.59-7.68 (m, 1H), 7.41-7.59 (m, 5H), 7.33-7.40 (m, 1H), 3.84 (d, $J = 11.4$ Hz, 1H), 3.63 (d, $J = 12.1$ Hz, 1H), 3.03 (s, 3H), 2.19-2.39 (m, 1H), 1.91-2.07 (m, 1H), 0.97-1.17 (m, 1H), 0.67 (s, 9H), 0.42-0.57 (m, 1H); MS (ESI) m/z 673 (M+H)⁺.

***N*-(3-[4-[(1-Benzothien-3-ylmethyl)amino]-4-(3,3-dimethylbutyl)-1-hydroxy-3-oxo-3,4-dihydronaphthalen-2-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide (26v).** Compound **25** (25 mg, 44 μ mol) was subjected to the conditions described for the synthesis of **26b**, substituting 1-benzothiophene-3-carboxyaldehyde for benzaldehyde, to give **26v** as a lt yellow solid (11 mg, 37%): ¹H NMR (DMSO-*d*₆) δ 13.93 (s, 1H), 9.99 (s, 1H), 9.69 (s, 1H), 8.23 (d, $J = 7.7$ Hz, 1H), 7.95-8.05 (m, 2H), 7.84 (s, 1H), 7.60-7.79 (m, 3H), 7.34-7.57 (m, 5H), 3.65-3.98 (m, 2H), 3.03 (s, 3H), 2.21-2.40 (m, 1H), 1.89-2.05 (m, 1H), 0.98-1.13 (m, 1H), 0.66 (s, 9H), 0.37-0.53 (m, 1H); MS (ESI) m/z 679 (M+H)⁺.