Synthesis, Conformation and Antiproliferative Activity of Isothiazoloisoxazole 1,1-dioxides

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ELECTRONIC SUPPLEMENTARY INFORMATION FILE 1:

Part 1: Synthesis and full spectroscopic data for known compounds **5a**, **6a**, **8a**, **9a**, **9e**, **10a**, **10e**, **11a**, **11e**, **13a**, **13e**, **15a**, **16a**, **22a**, **22d** and **22e**.

Part 2: Synthesis and full spectroscopic data for previously unreported compounds **9c, d & f, 10c, d & f, 11c, d and f, 13c, d and f, 22c and 22k – t.**

(references are to the reference list in the main article)

Part 1 (previously reported compounds)

2-Diethylamino-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (8a)

Dry ethanol (6.5 mL) was added to 2,3-dibromo-1-(4-methoxyphenyl)-3-phenylpropan-1-one (**7a**) (6.51 g, 20.52 mmol) to form a damp solid mixture. Diethylamine (4.2 mL, 2.98 g, 40.78 mmol) was rapidly added to the mixture at room temperature, which, after 10 minutes, turned to a dark red solution. The whole was stirred under nitrogen for 26 hours (monitored by TLC). After 26 hours, a solution of sodium ethoxide (0.47 g, 20.52 mmol) in ethanol (10 mL) was added to the mixture. The reaction mixture was stirred for a further 18 hours (monitored by TLC). The solvent was removed *in vacuo* to give the crude product as a dark red oil (8.56 g) which was purified by gravity silica chromatography (PE/ethyl acetate: 10/1) to give the product as a pure orange oil (5.12 g, 81%) that was noted (TLC) to degrade rapidly after isolation and so was used immediately in the next step.
^{1}H NMR δ (500 MHz, $CDCl_3$) 8.06 (2H, d, *J* = 8.8 Hz, ArH), 7.05 (4H, m, ArH), 6.93 (1H, m, ArH), 6.89 (2H, d, *J* = 8.8 Hz, ArH), 5.60 (1H, s, **CH**), 3.85 (3H, s, ArO**CH$_3$**), 3.15 (4H, q, *J* = 7.0 Hz, N**CH$_2$**CH_3), 1.16 (6H, t, *J* = 7.0 Hz, NCH_2**CH$_3$**).
^{13}C NMR δ (125 MHz, $CDCl_3$) 195.70 (C=O), 163.86 (C), 145.57 (C), 137.35 (C), 131.96 (CH, Ar), 129.70 (C), 127.98 (CH, Ar), 127.09 (CH, Ar), 124.28 (CH, Ar), 113.74 (CH, Ar), 102.16 (**C**H=C), 55.48 ($ArOCH_3$), 43.51 (N**C**H_2CH_3), 12.39 (NCH_2**C**H_3).
IR υ_{max} (cm^{-1}) 2976, 2839, 1708, 1657, 1594, 1509, 1454, 1378, 1307, 1250, 1167, 1025, 838.

Reported previously, but without detailed spectroscopic data.[27]

N-Methanesulfonylamidine (9a)

A solution of freshly prepared methanesulfonyl azide (0.83 g, 6.81 mmol) in dry ethanol (7 mL) was added to a solution of 2-diethylamino-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (**8a**) (2.11 g, 6.81 mmol) in dry ethanol (14 mL) under nitrogen. The whole was heated at reflux for 22 hours. The solvent was evaporated under reduced pressure to give the crude product as a dark orange oil. It was crystallised from dry diethyl ether (20 mL) to give the product as a yellow solid (1.75 g, 82%, m.p. = 123 – 125 °C, lit.: m.p. = 116 °C[27]).
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.87 (2H, bd, *J* = 8.8 Hz, ArH), 7.00 (2H, d, *J* = 8.8 Hz, ArH), 3.89 (3H, s, ArO**CH$_3$**), 3.73 (1H, dq, *J* = 13.5 and 7.1 Hz, N**CH$_2$**CH_3), 3.53 (1H, dq, *J* = 13.5 and 7.1 Hz, N**CH$_2$**CH_3), 3.20 (1H, dq, *J* = 14.2 and 7.1 Hz, N**CH$_2$**CH_3), 3.17 (1H, dq, *J* = 14.2 and 7.1 Hz, N**CH$_2$**CH_3), 2.98 (3H, s, **CH$_3$**SO_2), 1.33 (3H, t, *J* = 7.1 Hz, NCH_2**CH$_3$**), 1.10 (3H, t, *J* = 7.1 Hz, NCH_2**CH$_3$**).
^{13}C NMR δ (100 MHz, $CDCl_3$) 190.58 (C=O), 164.88 (**C**-OMe), 162.24 (C=N), 131.40 (CH, Ar), 127.68 (C, Ar), 114.54 (CH, Ar), 55.63 (ArO**C**H_3), 44.12 (N**C**H_2CH_3), 42.57 (**C**H_3SO_2), 42.46 (N**C**H_2CH_3), 13.71 (NCH_2**C**H_3), 11.90 (NCH_2**C**H_3).
IR υ_{max} (cm^{-1}) 2979, 2938, 1674, 1596, 1544, 1512, 1457, 1288, 1264, 1243, 1214, 1170, 1154, 1129, 1020, 981, 881, 831, 786, 728.
MS (*m/z*): 313.1 ([M + H]$^+$), 335.1 ([M + Na]$^+$), 647.2 ([2M + Na]$^+$).
HRMS (*m/z*): [M + Na]$^+$ for $C_{14}H_{20}N_2NaO_4S$ calculated 335.1036 measured 335.1033.

Reported previously, but without detailed spectroscopic data.[27]

3-Diethylamino-4-hydroxy-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide (10a)

N-Methanesulfonyl amidine (**9a**) (1.67 g, 5.36 mmol) was dissolved in dry THF (10 mL) under nitrogen. Potassium *tert*-butoxide (3 mL of a 20% solution in THF, 5.36 mmol) was added to the mixture which turned very milky. The whole was stirred for 2 hours. The reaction mixture was neutralised with 1M aqueous HCl. The aqueous layer was extracted with DCM (2 × 5 mL). The combined organic layers were washed with water (2 × 10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* to yield the product as a yellow solid (1.49 g, 89%, m.p. = 169 – 170 °C, lit.: m.p. = 177 °C[27]).
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.45 (2H, d, *J* = 8.8 Hz, ArH), 6.94 (2H, d, *J* = 8.8 Hz, ArH), 5.54 (1H, bs, **OH**), 3.93 (1H, d, *J* = 14.0 Hz, **CH$_2$**SO_2), 3.83 (3H, s, ArO**CH$_3$**), 3.65 (1H, d, *J* = 14.0 Hz, **CH$_2$**SO_2), 3.54 (1H, dq, *J* = 13.5 and 7.0 Hz, N**CH$_2$**CH_3), 3.45 (1H, dq, *J* = 13.5 and 7.0 Hz, N**CH$_2$**CH_3), 3.32 (1H, q, *J* = 7.0 Hz, N**CH$_2$**CH_3), 3.31 (1H, q, *J* = 7.0 Hz, N**CH$_2$**CH_3), 1.25 (3H, t, *J* = 7.0 Hz, NCH_2**CH$_3$**), 0.81 (3H, t, *J* = 7.0 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (100 MHz, $CDCl_3$) 168.84 (**C**=N), 159.47 (**C**-OMe), 133.03 (**C**, Ar), 125.27 (**CH**, Ar), 114.31 (**CH**, Ar), 83.47 (**C**), 64.68 (**C**$\mathbf{H_2}$$SO_2$), 55.31 (ArO**C**$\mathbf{H_3}$), 44.88 (N**C**$\mathbf{H_2}$$CH_3$), 43.36 (N**C**$\mathbf{H_2}$$CH_3$), 12.73 ($NCH_2$**C**$\mathbf{H_3}$), 11.33 ($NCH_2$**C**$\mathbf{H_3}$).
IR υ_{max} (cm^{-1}) 3384, 2976, 1582, 1513, 1442, 1297, 1252, 1228, 1179, 1148, 1125, 1080, 1031, 969, 949, 914, 854, 834, 783, 732.
MS (*m/z*): 335.1 ($[M + Na]^+$), 647.2 ($[2M + Na]^+$), 959.3 ($[3M + Na]^+$), 1271.4 ($[4M + Na]^+$).
HRMS (*m/z*): $[M + Na]^+$ for $C_{14}H_{20}N_2NaO_4S$ calculated 335.1036 measured 335.1028.

Reported previously, but without detailed spectroscopic data.[27]

4-Chloro-3-diethylamino-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide (11a)

3-Diethylamino-4-hydroxy-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide (**10a**) (1.22 g, 3.91 mmol) was heated in thionyl chloride (2 mL, 3.26 g, 27.42 mmol) at reflux temperature for 2 hours. Excess thionyl chloride was evaporated under reduced pressure. The residue was dissolved in DCM (10 mL) and neutralised with a 10% aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (2 × 10 mL), and the combined organic layers were washed with water (2 × 10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product as an oily yellow solid. Purification by gravity silica chromatography (PE/ethyl acetate: 2/1) gave the desired product as a yellow solid (1.23 g, 95%, m.p. = 103 – 105 °C, lit.: m.p. = 102 °C[27]). Also isolated was the previously unreported compound (**12a**, 225 mg, 4% - see main text). Data for compound (**11a**):
^{1}H NMR δ (500 MHz, $CDCl_3$) 7.42 (2H, d, *J* = 8.9 Hz, ArH), 6.93 (2H, d, *J* = 8.9 Hz, ArH), 4.17 (1H, d, *J* = 14.5 Hz, **C**$\mathbf{H_2}$$SO_2$), 3.85 (3H, s, ArO**C**$\mathbf{H_3}$), 3.82, (1H, d, *J* = 14.5 Hz, **C**$\mathbf{H_2}$$SO_2$), 3.67 (1H, dq, *J* = 13.5 and 7.0 Hz, N**C**$\mathbf{H_2}$$CH_3$), 3.51 (1H, dq, *J* = 13.5 and 7.0 Hz, N**C**$\mathbf{H_2}$$CH_3$), 3.21 (1H, dq, *J* = 14.4 and 7.1 Hz, N**C**$\mathbf{H_2}$$CH_3$), 3.08 (1H, dq, *J* = 14.4 and 7.1 Hz, N**C**$\mathbf{H_2}$$CH_3$), 1.30 (3H, t, *J* = 7.1 Hz, NCH_2**C**$\mathbf{H_3}$), 0.90 (3H, t, *J* = 7.0 Hz, NCH_2**C**$\mathbf{H_3}$).
^{13}C NMR δ (125 MHz, $CDCl_3$) 164.59 (**C=N**), 160.09 (**C**-OMe), 130.35 (**C**, Ar), 126.08 (**CH**, Ar), 114.74 (CH, Ar), 71.03 (**C**), 67.81 (**C**$\mathbf{H_2}$$SO_2$), 55.43 (ArO**C**$\mathbf{H_3}$), 44.97 (N**C**$\mathbf{H_2}$$CH_3$), 43.98 (N**C**$\mathbf{H_2}$$CH_3$), 12.30 ($NCH_2$**C**$\mathbf{H_3}$), 11.06 ($NCH_2$**C**$\mathbf{H_3}$).
IR υ_{max} (cm^{-1}) 2974, 1578, 1509, 1439, 1310, 1237, 1207, 1183, 1137, 1053, 1028, 971, 906, 826, 783.
MS (*m/z*) (^{35}Cl): 353.1 ($[M + Na]^+$), 683.2 ($[2M + Na]^+$).
HRMS (*m/z*)(^{35}Cl): $[M + Na]^+$ for $C_{14}H_{19}ClN_2NaO_3S$ calculated 353.0697 measured 353.0690.

Reported previously, but without detailed spectroscopic data.[27]

3-Diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide (13a)

4-Chloro-3-diethylamino-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide (**11a**) (1.00 g, 3.02 mmol) was dissolved in dry acetone (6 mL) and potassium carbonate (0.42 g, 3.02 mmol) was added to the solution in one portion. The whole was heated at reflux under nitrogen for 5 days. The solvent was evaporated under reduced pressure, and the residue was re-dissolved in DCM (10 mL), and neutralised with a 10% aqueous solution of hydrochloric acid (2.5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 5 mL). The combined organic layers were washed with water (2 × 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield the product as a yellow solid (0.76 g, 86%, m.p. = 133 – 135 °C, lit.: m.p. = 134 °C[27]). The product was pure enough to be used in the next step without further purification.
^{1}H NMR δ (400 MHz,$CDCl_3$) 7.24 (2H, d, *J* = 8.8 Hz, ArH), 7.17 (1H, s, **CH**), 6.97 (2H, d, *J* = 8.8 Hz, ArH), 3.86 (3H, s, ArO**Me**), 3.64 (2H, bd, *J* = 6.3 Hz, N**C**$\mathbf{H_2}$$CH_3$), 3.14 (2H, bd, *J* = 6.3 Hz, N**C**$\mathbf{H_2}$$CH_3$), 1.31 (3H, bs, NCH_2**C**$\mathbf{H_3}$), 0.93 (3H, bs, NCH_2**C**$\mathbf{H_3}$).
^{13}C NMR δ (100 MHz, $CDCl_3$) 161.09 (**C**=N), 160.61 (**C**-OMe), 142.94 (C=**CH**), 139.67 (**C**=CH), 128.71 (**CH**, Ar), 123.82 (**C**, Ar), 114.56 (**CH**, Ar), 55.45 (ArO**C**$\mathbf{H_3}$), 46.67 (N**C**$\mathbf{H_2}$$CH_3$), 43.90 (N**C**$\mathbf{H_2}$$CH_3$), 14.12 ($NCH_2$**C**$\mathbf{H_3}$), 11.93 ($NCH_2$**C**$\mathbf{H_3}$).
IR υ_{max} (cm^{-1}) 3075, 2975, 2839, 1603, 1556, 1506, 1443, 1408, 1358, 1288, 1245, 1189, 1159, 1122, 1083, 1028, 970, 945, 914, 826, 790, 776, 743, 683.
MS (*m/z*): 295.1 ($[M + H]^+$), 317.1 ($[M + Na]^+$), 611.2 ($[2M + Na]^+$), 905.3 ($[3M + Na]^+$).
HRMS (*m/z*): $[M + Na]^+$ for $C_{14}H_{18}N_2NaO_3S$ calculated 317.0930 measured 317.0931.

Reported previously, but without detailed spectroscopic data.[27]

5-Bromo-3-diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide (15a)

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**13a**) (0.94 g, 3.20 mmol) was dissolved in carbon tetrachloride (9.4 mL) and dichloromethane (4.7 mL), and a solution of bromine (164 μL, 0.51 g, 3.20 mmol) in carbon tetrachloride (1.9 mL) was added drop-wise to the mixture at room temperature under nitrogen. After 2 hours, the starting material had disappeared on TLC, and triethylamine (446 μL, 0.32 g, 3.20 mmol) was added to the reaction mixture, which was stirred for a further 5 hours. The reaction mixture was washed with a saturated aqueous solution of sodium metabisulfite ($Na_2S_2O_5$) (30 mL), the organic layer was separated, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to yield the product as a yellow solid (1.11 g, 93%, m.p. = 144 – 145 °C, lit.: m.p. = 163 – 164 °C[47]). The product was pure enough to be used in the next step without further purification.
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.14 (2H, d, *J* = 8.8 Hz, ArH), 6.98 (2H, d, *J* = 8.8 Hz, ArH), 3.81 (3H, s, ArO**Me**), 3.58 (2H, q, *J* = 7.1 Hz, N**C**$\mathbf{H_2}$$CH_3$), 3.09 (2H, q, *J* = 7.0 Hz, N**C**$\mathbf{H_2}$$CH_3$), 1.24 (3H, t, *J* = 7.1 Hz, NCH_2**C**$\mathbf{H_3}$), 0.86 (3H, t, *J* = 7.0 Hz, NCH_2**C**$\mathbf{H_3}$).
^{13}C NMR δ (100 MHz, $CDCl_3$) 160.92 (**C**=N), 160.36 (**C**-OMe), 137.90 (C=**C**-Br), 135.87 (**C**=CBr), 128.77 (**C**H, Ar), 122.62 (**C**, Ar), 114.67 (**C**H, Ar), 55.17 (ArO**C**$\mathbf{H_3}$), 46.31 (N**C**$\mathbf{H_2}$$CH_3$), 43.77 (N**C**$\mathbf{H_2}$$CH_3$), 13.84 ($NCH_2$**C**$\mathbf{H_3}$), 11.62 ($NCH_2$**C**$\mathbf{H_3}$).
IR υ_{max} (cm^{-1}) 2939, 1619, 1603, 1562, 1506, 1439, 1306, 1291, 1251, 1150, 1110, 1096, 1017, 1004, 972, 868, 827, 797, 774, 748, 705.
MS (*m/z*): 395.0 (^{79}Br) ($[M + Na]^+$), 397.0 (^{81}Br) ($[M + Na]^+$), 769.0 ($[2M + Na]^+$), 1143.0 ($[3M + Na]^+$).
HRMS (^{79}Br) (*m/z*): $[M + Na]^+$ for $C_{14}H_{17}BrN_2NaO_3S$ calculated 395.0035 measured 395.0038.

Reported previously,[47] but full data is given above due to the differing melting points.

3-Diethylamino-5-methanesulfanyl-4-(4-methoxyphenyl)isothiazol-1,1-dioxide (16a)

5-Bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**15a**) (0.71 g, 1.89 mmol) was dissolved in dichloromethane (15 mL). Sodium thiomethoxide (0.13 g, 1.89 mmol), and triethylamine (270 μL, 0.20 g, 1.93 mmol) were added to the mixture at room temperature with stirring. The reaction was stirred under nitrogen for 5 hours. The mixture was neutralised with a 10% aqueous solution of hydrochloric acid, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was evaporated *in vacuo* to yield the product as a yellow solid (0.63 g, 97%, m.p. = 170 – 171 °C, lit.: m.p. = 174 °C[28]).
^{1}H NMR δ (500 MHz, $CDCl_3$) 7.19 (2H, d, *J* = 8.7 Hz, ArH), 7.01 (2H, d, *J* = 8.7 Hz, ArH), 3.87 (3H, s, ArO**C**$\mathbf{H_3}$), 3.61 (2H, q, *J* = 7.0 Hz, N**C**$\mathbf{H_2}$$CH_3$), 3.11 (2H, q, *J* = 7.0 Hz, N**C**$\mathbf{H_2}$$CH_3$), 2.79 (3H, s, S**Me**), 1.30 (3H, t, *J* = 7.0 Hz, NCH_2**C**$\mathbf{H_3}$), 0.89 (3H, t, *J* = 7.0 Hz, NCH_2**C**$\mathbf{H_3}$).
^{13}C NMR δ (125 MHz, $CDCl_3$) 160.97 (N=**C**), 160.26 (**C**-OMe), 157.02 (**C**-SMe), 129.55 (**C**H, Ar)), 125.73 (C, **C**=C-SMe), 124.17 (**C**, Ar), 114.95 (**C**H, Ar), 55.32 (O**C**$\mathbf{H_3}$), 46.39 (N**C**$\mathbf{H_2}$$CH_3$), 43.30 (N**C**$\mathbf{H_2}$$CH_3$), 14.09 ($NCH_2$**C**$\mathbf{H_3}$), 12.92 (S**C**$\mathbf{H_3}$), 12.15 ($NCH_2$**C**$\mathbf{H_3}$).
IR υ_{max} (cm^{-1}) 2935, 1608, 1583, 1550, 1505, 1393, 1286, 1245, 1145, 1109, 1096, 1081, 1025, 886, 828, 801, 777, 731, 694.
MS (*m/z*) 341.1 ($[M + H]^+$), 703.2 ($[2M + Na]^+$).
HRMS (*m/z*): $[M + H]^+$ for $C_{15}H_{21}N_2O_3S_2$ calculated 341.0988 measured 341.0992.

Reported previously, but without detailed spectroscopic data.[28]

3-Diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)isothiazol-1,1-dioxide (6a)

3-Diethylamino-5-methanesulfanyl-4-(4-methoxyphenyl)-isothiazole-1,1-dioxide (**16a**) (2.65 g, 7.78 mmol) was dissolved in dry DCM (60 mL), and *m*-CPBA (2.69 g, 15.59 mmol) was added in one portion. The solution was stirred under nitrogen at room temperature, and the reaction was monitored by thin layer chromatography (TLC). More *m*-CPBA was added to the mixture until disappearance of the starting material on TLC (1.35 g after 5 hours; 0.68 g after 24 hours; 0.27 g after 29 hours). The whole was stirred for 31 hours overall. Then, the *m*-chlorobenzoic acid precipitate was filtered off and the filtrate was washed with a 20% sodium bicarbonate solution (20 mL), and then with water (2 × 20 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and the solvent was evaporated to dryness affording the crude product as a yellow solid (3.23 g) which was crystallised from DCM (10 mL)/diethyl ether (5 mL) to give the product as a yellow solid (1.47 g, 51%, m.p. = 171 – 173 °C, lit.: m.p. = 159 – 161 °C[26]).
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.33 (2H, d, *J* = 8.8 Hz, ArH), 7.03 (2H, d, *J* = 8.8 Hz, ArH), 3.87 (3H, s, O**C**$\mathbf{H_3}$), 3.64 (2H, q, *J* = 7.1 Hz, N**C**$\mathbf{H_2}$$CH_3$), 3.17 (3H, s, **C**$\mathbf{H_3}$$SO_2$), 3.08 (2H, q, *J* = 7.1 Hz, N**C**$\mathbf{H_2}$$CH_3$), 1.32 (3H, t, *J* = 7.1 Hz, NCH_2**C**$\mathbf{H_3}$), 0.91 (3H, t, *J* = 7.1 Hz, NCH_2**C**$\mathbf{H_3}$).

^{13}C NMR δ (100 MHz, $CDCl_3$) 161.23 (**C**-OCH_3 (Ar)), 158.24 (**C**=N), 152.63 (ArC=**C**SO_2Me), 142.15 (Ar**C**=CSO_2Me), 129.08 (**CH**, Ar), 119.84 (C, Ar), 114.57 (**CH**, Ar), 55.37 (O**C**$\mathbf{H_3}$), 47.86 (N**C**$\mathbf{H_2}CH_3$), 44.05 (N**C**$\mathbf{H_2}CH_3$), 43.93 (SO_2**C**$\mathbf{H_3}$), 14.19 (NCH_2**C**$\mathbf{H_3}$), 11.65 (NCH_2**C**$\mathbf{H_3}$).
IR υ_{max} (cm^{-1}) 2980, 1605, 1568, 1509, 1405, 1332, 1316, 1292, 1249, 1204, 1162, 1153, 1141, 1099, 1073, 1047, 1021, 968, 921, 880, 841, 810, 779, 766, 743, 714.
MS (*m/z*): 395.1 ($[M + Na]^+$), 767.2 ($[2M + Na]^+$).
HRMS (*m/z*): $[M + Na]^+$ for $C_{15}H_{20}N_2NaO_5S_2$ calculated 395.0706 measured 395.0710.

Reported previously,[26] but full data is given above due to the differing melting points.

4-Cyano-3-diethylamino-4-(4-methoxy-phenyl)-1,2-thiazetin-1,1-dioxide (5a)

3-Diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**6a**) (360 mg, 0.97 mmol) was dissolved in dry acetonitrile (18 mL). Sodium azide (63 mg, 0.97 mmol) was added to the mixture, and the reaction was stirred under nitrogen at room temperature until disappearance of the starting material on TLC (after 5 hours). The solvent was evaporated *in vacuo*, and the residue was taken up with DCM (70 mL), and washed with water (2 × 35 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product as an orange oil (330 mg) which was purified by flash silica chromatography (PE/ethyl acetate: gradient elution 5/2 to 1/1) to give the product as a white solid (170 mg, 57%, m.p.= 104 – 105 °C, lit.: m.p. = 121 °C[26]).
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.40 (2H, d, *J* = 8.9 Hz, ArH), 7.00 (2H, d, *J* = 8.9 Hz, ArH), 3.81 (3H, s, O**C**$\mathbf{H_3}$), 3.61 (1H, dq, *J* = 13.9 and 7.2 Hz, N**C**$\mathbf{H_2}CH_3$), 3.43 (1H, dq, *J* = 13.9 and 7.2 Hz, N**C**$\mathbf{H_2}CH_3$), 3.12 (1H, dq, *J* = 14.4 and 7.2 Hz, N**C**$\mathbf{H_2}CH_3$), 3.09 (1H, dq, *J* = 14.4 and 7.2 Hz, N**C**$\mathbf{H_2}CH_3$). 1.28 (3H, t, *J* = 7.2 Hz, NCH_2**C**$\mathbf{H_3}$), 1.06 (3H, t, *J* = 7.2 Hz, NCH_2**C**$\mathbf{H_3}$).
^{13}C NMR δ (100 MHz, $CDCl_3$) 161.68 (**C**-OMe), 160.58 (**C**=N), 128.37 (**CH**, Ar), 116.45 (**C**, Ar), 115.08 (**CH**, Ar), 111.14 (**CN**), 86.23 (**C**), 55.38 (O**C**$\mathbf{H_3}$), 45.31 (N**C**$\mathbf{H_2}CH_3$), 42.19 (N**C**$\mathbf{H_2}CH_3$), 12.63 (NCH_2**C**$\mathbf{H_3}$), 11.32 (NCH_2**C**$\mathbf{H_3}$).
IR υ_{max} (cm^{-1}) 2981, 2246, 1641, 1608, 1513, 1336, 1308, 1262, 1173, 1158, 1030, 814, 788.
MS (*m/z*): 330.1 ($[M + Na]^+$), 637.2 ($[2M + Na]^+$).
HRMS (*m/z*): $[M + Na]^+$ for $C_{14}H_{17}N_3NaO_3S$ calculated 330.0883 measured 330.0888.

Reported previously,[26] but full data is given above due to the differing melting points and the key importance of this compound.

***N*,*N*-Diethyl-*N*'-methylsulfonyl-2-oxo-2-(p-tolyl)acetamidine (9e)**

Under an atmosphere of nitrogen, a solution of the 2-(diethylamino)-3-phenyl-1-(p-tolyl)prop-2-en-1-one **(8e** – see main text for general procedure**)** crude reaction mass (11.83 mmol based upon **7e**, 4.5 g) in ethanol (40 mL) was added to a solution of methanesulfonyl azide (2.06 g, 17.04 mmol) in ethanol (40 mL). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity silica column chromatography (1:1 PE:EtOAc) to yield the pure product as a dark yellow solid (1.01 g, 29%), m.p. 118 – 121 °C (lit.: 123 °C[27]).
^{1}H NMR δ (400 MHz, $CDCl_3$): 1.08 (3H, t, *J* = 7.0 Hz, $NCH_2C\mathbf{H_3}$); 1.33 (3H, t, *J* = 7.01 Hz, $NCH_2C\mathbf{H_3}$); 2.43 (3H, s, Ar**C**$\mathbf{H_3}$); 2.95 (3H, s, $SO_2C\mathbf{H_3}$); 3.15 (2H, sept, *J* = 6.7 Hz, N**C**$\mathbf{H_2}CH_3$); 3.45 – 3.57 (1H, m, N**C**$\mathbf{H_2}CH_3$); 3.68 – 3.79 (1H, m, N**C**$\mathbf{H_2}CH_3$); 7.33 (2H, d, *J* = 8.1 Hz, Ar**H**); 7.78 (2H, d, *J* = 8.1 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.90 ($NCH_2\mathbf{C}H_3$), 13.69 ($NCH_2\mathbf{C}H_3$), 21.92 (Ar**C**H_3), 42.58 (SO_2**C**H_3), 42.60 (N**C**H_2CH_3), 44.23 (N**C**H_2CH_3), 128.94 (Ar), 129.96 (Ar), 131.99 (Ar), 146.17 (Ar), 162.03 (N=**C**-N), 191.94 (**C**=O).
IR (cm^{-1}): 938.6, 950.3, 964.9, 1131.3, 1117.0, 1236.5, 1290.9, 1315.6, 1441.1, 1553.6.
micrOTOF-Q MS m/z $C_{14}H_{20}N_2O_3S$+Na, calculated 319.1087, observed 319.1077.

Reported previously, but without detailed spectroscopic data.[27]

3-(Diethylamino)-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-4-ol (10e)

To a solution of *N*,*N*-diethyl-*N*'-methylsulfonyl-2-oxo-2-(p-tolyl)acetamidine **(9e)** (1.07 g, 3.41 mmol) in dry tetrahydrofuran (7 mL) under an atmosphere of nitrogen, a 20% w/v solution of potassium *t*-butoxide in tetrahydrofuran (2.29 mL, 4.09 mmol) was added rapidly at room temperature and the mixture set to stir for 24 hours. After this time, the

reaction mixture was neutralised with 1M aqueous hydrochloric acid. The aqueous mixture was extracted with dichloromethane (3 × 25 mL) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a yellow solid (780 mg, 77%), m.p.: 179 – 180 °C (lit.: 174 °C[27]).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.78 (3H, t, *J* = 7.0 Hz, $NCH_2C\mathbf{H}_3$); 1.23 (3H, t, *J* = 7.0 Hz, $NCH_2C\mathbf{H}_3$); 2.35 (3H, s, $ArC\mathbf{H}_3$); 3.28 (2H, q, *J* = 8.2 Hz, $NC\mathbf{H}_2CH_3$); 3.49 – 3.48 (2H, m, $NC\mathbf{H}_2CH_3$); 3.63 (1H, d, *J* = 14.0 Hz, $SO_2C\mathbf{H}_2$); 3.93 (1H, d, *J* = 14.0 Hz, $SO_2C\mathbf{H}_2$); 5.57 (1H, s, O**H**); 7.20 (2H, d, *J* = 8.0 Hz, Ar**H**); 7.41 (2H, d, *J* = 8.0 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.33 ($\mathbf{C}H_3$), 12.71 ($\mathbf{C}H_3$), 21.09 ($Ar\mathbf{C}H_3$), 43.45 ($N\mathbf{C}H_2$), 44.87 ($N\mathbf{C}H_2$), 64.44 ($SO_2\mathbf{C}H_2$), 83.64 (**C**OH), 123.85 (Ar), 129.66 (Ar), 138.13 (Ar), 138.20 (Ar), 168.85 (N=**C**-N).
IR (cm^{-1}): 820.6, 854.8, 916.1, 964.6, 1076.6, 1128.5, 1144.9, 1228.2, 1297.8, 1585.7, 3395.2.
micrOTOF-Q MS m/z $C_{14}H_{20}N_2O_3S$+Na, calculated 319.1087, observed 319.1086.

Reported previously, but without detailed spectroscopic data.[27]

4-Chloro-*N*,*N*-diethyl-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-3-amine (11e)

Under an atmosphere of nitrogen, thionyl chloride (5.75 mL, 78.90 mmol) was added to 3-(diethylamino)-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-4-ol **(10e)** (780 mg, 2.63 mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layer was removed and extracted with dichloromethane (3 × 25 mL) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity column chromatography (2:1 PE:EtOAc) to yield the pure product as a yellow oil (545 mg, 66%).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.87 (3H, t, *J* = 7.0 Hz, $NCH_2C\mathbf{H}_3$); 1.29 (3H, t, *J* = 7.1 Hz, $NCH_2C\mathbf{H}_3$); 2.38 (3H, s, $ArC\mathbf{H}_3$); 3.02 – 3.24 (2H, m, $NC\mathbf{H}_2CH_3$); 3.45 – 3.57 (1H, m, $NC\mathbf{H}_2CH_3$); 3.60 – 3.71 (1H, m, $NC\mathbf{H}_2CH_3$); 3.79 (1H, d, *J* = 14.6 Hz, $SO_2\mathbf{C}H_2$); 4.14 (1H, d, *J* = 14.6 Hz, $SO_2\mathbf{C}H_2$); 7.27 (2H, d, *J* = 8.3 Hz, Ar**H**); 7.38 (2H, d, *J* = 8.3 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.05 ($\mathbf{C}H_3$), 12.20 ($\mathbf{C}H_3$), 20.99 ($Ar\mathbf{C}H_3$), 44.11 ($N\mathbf{C}H_2$), 44.97 ($N\mathbf{C}H_2$), 67.86 ($SO_2\mathbf{C}H_2$), 71.18 (**C**Cl), 124.52 (Ar), 130.19 (Ar), 135.53 (Ar), 139.48 (Ar), 164.54 (N=**C**-N).
IR (cm^{-1}): 781.9, 822.5, 905.4, 971.8, 1141.9, 1189.1, 1201.3, 1235.8, 1312.5, 1587.9.
micrOTOF-Q MS m/z $C_{14}H_{19}N_2ClO_2S$+Na, calculated 337.0745, observed 337.0747.

Reported previously, but without detailed spectroscopic data.[27]

***N*,*N*-Diethyl-1,1-dioxo-4-(p-tolyl)isothiazol-3-amine (13e)**

To 4-chloro-N,N-diethyl-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-3-amine **(11e)** (545 mg, 1.73 mmol) in dry acetone (40 mL) under an atmosphere of nitrogen, anhydrous potassium carbonate (287 mg, 2.08 mmol) was added and the reaction mixture set to stir at reflux for 24 hours. After this time the mixture was filtered to remove excess potassium carbonate and the solvents were removed under reduced pressure. The residues were dissolved in dichloromethane and neutralised with 1M aqueous hydrochloric acid. The aqueous layer was removed and extracted with dichloromethane (3 × 25 mL) and the organic layers combined and washed with water. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a pale yellow solid (146 mg, 30%), m.p.: 142 – 144 °C (lit.: 140 °C[27]).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.92 (3H, t, *J* = 7.0 Hz, $NCH_2C\mathbf{H}_3$); 1.31 (3H, t, *J* = 6.8 Hz, $NCH_2C\mathbf{H}_3$); 2.41 (3H, s, $ArC\mathbf{H}_3$); 3.07 – 3.17 (2H, m, $NC\mathbf{H}_2CH_3$); 3.58 – 3.70 (2H, m, $NC\mathbf{H}_2CH_3$); 7.17 (1H, s, $SO_2C\mathbf{H}$); 7.18 – 7.22 (2H, m, Ar**H**); 7.24 – 7.29 (2H, m, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.89 ($\mathbf{C}H_3$), 14.08 ($\mathbf{C}H_3$), 21.35 ($Ar\mathbf{C}H_3$), 43.86 ($N\mathbf{C}H_2$), 46.66 ($N\mathbf{C}H_2$), 127.19 (Ar), 128.91 (Ar), 129.78 (Ar), 139.88 (Ar), 139.97 (Ar), 142.96 (Ar), 160.90 (N=**C**-N).
IR (cm^{-1}): 739.8, 775.7, 791.1, 826.9, 913.4, 940.5, 1122.2, 1187.6, 1284.8, 1572.8, 3008.1.
micrOTOF-Q MS m/z $C_{14}H_{18}N_2O_2S$+Na, calculated 301.0981, observed 301.0981.

Reported previously, but without detailed spectroscopic data.[27]

3-Diethylamino-6-ethoxycarbonyl-3a-(4-methoxyphenyl)-isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide (22a)

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**13a**) (100 mg, 0.34 mmol) and ethyl chlorooximidoacetate (51 mg, 0.34 mmol) were dissolved in dry diethyl ether (5 mL) under nitrogen. Triethylamine (47 µL, 34 mg, 0.34 mmol) in dry diethyl ether (10 mL) was added drop-wise to the mixture over 20 hours, and the mixture was stirred overnight. Filtration and evaporation under reduced pressure gave the crude product as a yellow oil (214 mg) which was purified by flash silica chromatography (PE 40-60 °C/EtOAc: 2/1) to afford the product as a colourless oil (120 mg; 86 %) which crystallised upon standing m.p.: 123 – 125 °C (lit.: 129 °C[30]).
^{1}H NMR δ (500 MHz, $CDCl_3$) 7.28 (2H, d, *J* = 8.8 Hz, ArH), 6.98 (2H, d, *J* = 8.8 Hz, ArH), 4.97 (1H, s, **CH**), 4.42 (2H, q, *J* = 7.1 Hz, O**CH$_2$**CH$_3$) 3.84 (3H, s, O**CH$_3$**), 3.66 (1H, dq, *J* = 13.6 and 7.0 Hz, N**CH$_2$**CH$_3$), 3.42 (1H, dq, *J* = 13.6 and 7.0 Hz, N**CH$_2$**CH$_3$), 3.28 (1H, dq, *J* = 14.4 and 7.0 Hz, N**CH$_2$**CH$_3$), 3.19 (1H, dq, *J* = 14.4 and 7.0 Hz, N**CH$_2$**CH$_3$), 1.38 (3H, t, *J* = 7.1 Hz, OCH$_2$**CH$_3$**), 1.26 (3H, t, *J* = 7.0 Hz, NCH$_2$**CH$_3$**), 0.88 (3H, t, *J* = 7.0 Hz, NCH$_2$**CH$_3$**).
^{13}C NMR δ (125 MHz, $CDCl_3$) 162.50 (N=**C**), 160.55 (**C**-OMe), 157.97 (**C**=O), 147.65 (N=**C**-CO_2Et), 127.19 (**C**, Ar), 124.96 (**CH**, Ar), 115.09 (**CH**, Ar), 100.40 (**C** (ring junction)), 77.26 (**CH** (ring junction)), 62.92 (O**CH$_2$**CH$_3$), 55.38 (O**CH$_3$**), 45.09 (N**CH$_2$**CH$_3$), 44.10 (N**CH$_2$**CH$_3$), 13.85 (OCH$_2$**CH$_3$**), 12.64 (NCH$_2$**CH$_3$**), 11.19 (NCH$_2$**CH$_3$**).
IR υ_{max} (cm^{-1}) 2980, 1742, 1597, 1514, 1443, 1328, 1254, 1211, 1179, 1135, 1092, 948, 907, 835.
MS (*m/z*): 432.1 ([M + Na]$^+$), 841.3 ([2M + Na]$^+$).
HRMS (*m/z*): [M + Na]$^+$ for $C_{18}H_{23}N_3NaO_6S$ calculated 432.1200 measured 432.1209.

The structure of this compound was confirmed for the first time by X-ray crystallographic analysis.[31]

This compound has been reported in the literature[30] but with incomplete data.

3-Diethylamino-3a-(4-methoxyphenyl)-6-(4-nitrophenyl)-isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide (22d)

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**13a**) (100 mg, 0.34 mmol) and 4-nitrobenzohydroximoyl chloride (102 mg, 0.51 mmol) were suspended in dry diethyl ether (5 mL). Triethylamine (71 µL, 51 mg, 0.51 mmol) in dry diethyl ether (15 mL) was added drop-wise to the mixture over 10 hours. The mixture was stirred for 3 days under nitrogen, filtered, and the solvent evaporated under reduced pressure to give the crude product as an orange solid which was purified by gravity silica chromatography (PE/EtOAc: gradient elution 3/1 to 2/1) to give the pure product as a yellow solid (65 mg; 42%), m.p.: 262 – 264 °C (lit.: 265 – 266 °C[30]).
^{1}H NMR δ (400 MHz, $CDCl_3$) 8.28 (2H, d, *J* = 8.9 Hz, ArNO_2), 7.96 (2H, d, *J* = 8.9 Hz, ArNO_2), 7.35 (2H, d, *J* = 8.9 Hz, ArOMe), 7.00 (2H, d, *J* = 8.9 Hz, ArOMe), 5.12 (1H, s, **CH**), 3.84 (3H, s, OMe), 3.70 (1H, dq, *J* = 13.6 and 7.0 Hz, N**CH$_2$**CH$_3$), 3.43 (1H, dq, *J* = 13.6 and 7.0 Hz, N**CH$_2$**CH$_3$), 3.32 (1H, dq, *J* = 14.3 and 7.3 Hz, N**CH$_2$**CH$_3$), 3.25 (1H, dq, *J* = 14.3 and 7.3 Hz, N**CH$_2$**CH$_3$), 1.29 (3H, t, *J* = 7.1 Hz, NCH$_2$**CH$_3$**), 0.90 (3H, t, *J* = 7.1 Hz, NCH$_2$**CH$_3$**).
^{13}C NMR δ (400 MHz, $CDCl_3$) 163.26 (-**C**=N), 160.59 (**C**-OMe), 151.28 (-**C**=N-O), 148.89 (**C**-NO_2), 132.95 (**C**, ArNO_2), 128.43 (**CH**, ArNO_2), 128.03 (**C**, ArOMe), 125.04 (**CH**, ArOMe), 124.04 (**CH**, ArNO_2), 115.18 (**CH**, ArOMe), 100.16 (**C** (ring junction)), 78.25 (**CH** (ring junction)), 55.46 (O**Me**), 45.24 (N**CH$_2$**CH$_3$), 44.28 (N**CH$_2$**CH$_3$), 12.75 (NCH$_2$**CH$_3$**), 11.32 (NCH$_2$**CH$_3$**).
IR υ_{max} (cm^{-1}) 2980, 1597, 1514, 1443, 1342, 1321, 1253, 1178, 1137, 969, 852, 833.
MS (*m/z*): 459.1 [M + H]$^+$, 934.3 [2M + NH_4]$^+$, 1392.4 [3M + NH_4]$^+$.
HRMS (*m/z*): for $C_{21}H_{23}N_4O_6S$ calculated 459.1333 measured 459.1322.

This compound has been reported in the literature[30] but with incomplete data.

3-Diethylamino-3a,6-di(4-methoxyphenyl)isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide (22e)

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**13a**) (100 mg, 0.34 mmol) and 4-methoxybenzohydroximoyl chloride (63 mg, 0.34 mmol) were suspended in dry diethyl ether (5 mL). Triethylamine (47 µL, 34 mg, 0.34 mmol) in dry diethyl ether (10 mL) was added drop-wise to the mixture over 4 – 5 hours. The mixture was stirred overnight (20 hours) under nitrogen, filtered, and the solvent evaporated under reduced pressure to give the crude product as a yellow solid (185 mg) which was purified by gravity silica chromatography (PE/ EtOAc: gradient elution 3/1 to 2/1) to give the product as a white solid (108 mg; 71%; m.p.= 183 – 185 °C, lit:[30] 169 – 170 °C).
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* = 8.9 Hz, ArH), 7.37 (2H, d, *J* = 8.9 Hz, ArH), 6.98 (2H, d, *J* = 8.9 Hz, ArH), 6.94 (2H, d, *J* = 8.9 Hz, ArH), 5.09 (1H, s, **CH**), 3.84 (3H, s, O**CH$_3$**), 3.83 (3H, s, O**CH$_3$**), 3.69 (1H, dq, *J* = 13.6 and 7.1 Hz, N**CH$_2$**CH$_3$), 3.42 (1H, dq, *J* = 13.6 and 7.1 Hz, N**CH$_2$**CH$_3$), 3.26 (2H, m, N**CH$_2$**CH$_3$), 1.28 (3H, t, *J* = 7.1 Hz, NCH$_2$**CH$_3$**), 0.86 (3H, t, *J* = 7.1 Hz, NCH$_2$**CH$_3$**).
^{13}C NMR δ (400 MHz, $CDCl_3$) 163.69 (**C**=N), 161.76 (**C**-OMe), 160.34 (**C**-OMe), 151.97 (Ar-**C**=N-O), 129.23 (**CH**, Ar), 129.03 (**C**, Ar), 125.12 (**CH**, Ar), 119.22 (**C**, Ar), 115.00 (**CH**, Ar), 114.34 (**CH**, Ar), 98.86 (**C** (ring junction)), 79.57 (**CH**

(ring junction)), 55.43 (O**C**H_3), 55.38 (O**C**H_3), 44.99 (N**C**$H_2$$CH_3$), 44.17 (N**C**$H_2$$CH_3$), 12.74 ($NCH_2$**C**$H_3$), 11.37 ($NCH_2$**C**$H_3$).
IR υ_{max} (cm^{-1}) 2978, 1594, 1514, 1443, 1353, 1320, 1253, 1178, 1137, 1096, 1030, 968, 948, 920, 890, 833.
MS (*m/z*): 466.1 ($[M + Na]^+$), 909.3 ($[2M + Na]^+$), 1352.4 ($[3M + Na]^+$).
HRMS (*m/z*): $[M + Na]^+$ for $C_{22}H_{25}N_3NaO_5S$ calculated 466.1407 measured 466.1409.

This compound has been reported in the literature[30] but with incomplete data.

Part 2 (previously unreported compounds)

2-(4-Chlorophenyl)-*N,N*-diethyl-*N'*-methylsulfonyl-2-oxo-acetamidine (9c)

Using the procedure for compound (**9b**) [see main article], 1-(4-chlorophenyl)-2-(diethylamino)-3-phenyl-prop-2-en-1-one **(8c)** crude reaction mass (11.43 mmol based upon **7c**, 4.6 g) and methanesulfonyl azide (1.74 g, 14.34 mmol) gave a crude product which was purified by gravity silica column chromatography (1:1 PE:EtOAc) to yield the pure product as a red oil (1.92 g, 53%) which solidified upon standing, m.p.: 177 – 179 °C.
^{1}H NMR δ (400 MHz, $CDCl_3$): 1.09 (3H, t, *J* = 7.1 Hz, NCH_2C**H**$_3$); 1.33 (3H, t, *J* = 7.1 Hz, NCH_2C**H**$_3$); 2.97 (3H, s, SO_2C**H**$_3$); 3.14 (2H, q, *J* = 7.1 Hz, N**C**H_2CH_3); 3.46 – 3.60 (1H, m, N**C**H_2CH_3); 3.66 – 3.81 (1H, m, N**C**H_2CH_3); 7.51 (2H, d, *J* = 8.7 Hz, Ar**H**); 7.84 (2H, d, *J* = 8.7 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.90 (NCH_2**C**H_3), 13.73 (NCH_2**C**H_3), 42.59 (SO_2**C**H_3), 42.75 (N**C**H_2CH_3), 44.26 (N**C**H_2CH_3), 124.65 (Ar), 130.11 (Ar), 132.78 (Ar), 141.36 (Ar), 161.32 (N=**C**-N), 191.35 (**C**=O).
IR (cm^{-1}): 781.6, 823.1, 950.9, 1132.2, 1239.1, 1291.0, 1439.4, 1558.8, 1681.7, 2980.8.
micrOTOF-Q MS m/z $C_{13}H_{17}ClN_2O_3S$+Na, calculated 339.0541, observed 339.0535.

2-(4-Chlorophenyl)-*N'*-methylsulfonyl-2-oxo-*N,N*-dipropyl-acetamidine (9d)

Using the procedure for compound (**9b**) [see main article], a solution of the 1-(4-chlorophenyl)-2-(dipropylamino)-3-phenyl-prop-2-en-1-one **(8d)** crude reaction mass (12.42 mmol based upon **7d**, 5.0 g) and methanesulfonyl azide (1.77 g, 14.63 mmol) gave a crude product which was purified by gravity silica column chromatography (2:1 PE:EtOAc) to yield the pure product as an orange oil (3.21 g, 75%) which solidified upon standing, m.p.: 174 – 176 °C.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.73 (3H, t, *J* = 7.4 Hz, NCH_2CH_2C**H**$_3$); 1.01 (3H, t, *J* = 7.4 Hz, NCH_2CH_2C**H**$_3$); 1.42 – 1.66 (2H, m, NCH_2C**H**$_2CH_3$); 1.70 – 1.87 (2H, m, NCH_2C**H**$_2CH_3$); 2.97 (3H, s, SO_2C**H**$_3$); 3.00 (2H, t, *J* = 7.8 Hz, N**C**$H_2CH_2CH_3$); 3.31 – 3.46 (1H, m, N**C**$H_2CH_2CH_3$); 3.60 – 3.72 (1H, m, N**C**$H_2CH_2CH_3$); 7.51 (2H, d, *J* = 8.7 Hz, Ar**H**); 7.84 (2H, d, *J* = 8.7 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 10.88 (NCH_2CH_2**C**H_3), 11.43 (NCH_2CH_2**C**H_3), 19.87 (NCH_2**C**H_2CH_3), 21.72 (NCH_2**C**H_2CH_3), 42.59 (SO_2**C**H_3), 49.71 (N**C**$H_2CH_2CH_3$), 51.40 (N**C**$H_2CH_2CH_3$), 129.66 (Ar), 130.10 (Ar), 132.87 (Ar), 141.36 (Ar), 161.82 (N=**C**-N), 191.46 (**C**=O).
IR (cm^{-1}): 837.9, 956.7, 1008.8, 1083.5, 1110.6, 1126.2, 1222.4, 1285.2, 1551.3, 1684.1.
micrOTOF-Q MS m/z $C_{15}H_{21}ClN_2O_3S$+Na, calculated 367.0854, observed 367.0849.

***N*-[2-Oxo-1-(1-piperidyl)-2-(p-tolyl)ethylidene]methanesulfonamide (9f)**

Using the procedure for compound (**9b**) [see main article], a solution of the 3-phenyl-2-(1-piperidyl)-1-(p-tolyl)prop-2-en-1-one **(8f)** crude reaction mass (12.51 mmol based upon **7f**, 4.78 g) and methanesulfonyl azide (1.98 g, 16.37 mmol) gave a crude product which was purified by gravity silica column chromatography (1:1 PE:EtOAc) to yield the pure product as a dark red oil (2.09 g, 54%).
^{1}H NMR δ (400 MHz, $CDCl_3$): 1.36 – 1.60 (2H, m, $N(CH_2)_2C$**H**$_2$); 1.64 – 1.79 (4H, m, NCH_2C**H**$_2$ × 2); 2.43 (3H, s, Ar**C**H_3); 2.97 (3H, s, SO_2C**H**$_3$); 3.11 – 3.29 (2H, m, N**C**H_2); 3.74 – 3.93 (2H, m, N**C**H_2); 7.33 (2H, d, *J* = 7.9 Hz, Ar**H**); 7.81 (2H, d, *J* = 7.8 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 21.93 (Ar**C**H_3), 23.85 (**C**H_2), 25.28 (**C**H_2), 26.06 (**C**H_2), 42.63 (SO_2C**H**$_3$), 45.83 (N**C**H_2), 48.83 (N**C**H), 128.98 (Ar), 130.00 (Ar), 132.04 (Ar), 146.29 (Ar), 161.45 (N=**C**-N), 192.54 (**C**=O).
IR (cm^{-1}): 804.8, 860.9, 968.0, 1114.5, 1132.4, 1227.5, 1294.0, 1449.3, 1546.9, 1673.0.
micrOTOF-Q MS m/z $C_{15}H_{20}N_2O_3S$+Na, calculated 331.1087, observed 331.1083.

4-(4-Chlorophenyl)-3-(diethylamino)-1,1-dioxo-5H-isothiazol-4-ol (10c)

Using the procedure for compound (**10b**) [see main article], 2-(4-chlorophenyl)-*N,N*-diethyl-*N′*-methylsulfonyl-2-oxo-acetamidine **(9c)** (1.92 g, 6.06 mmol) and a 20% w/v solution of potassium *t*-butoxide in tetrahydrofuran (4.08 mL, 7.27 mmol) gave the title product as an off-white solid (1.60 g, 83%) which was used directly in the next step, m.p.: 162 – 164 °C.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.81 (3H, t, *J* = 7.0 Hz, $NCH_2C\mathbf{H}_3$); 1.22 (3H, t, *J* = 7.1 Hz, $NCH_2C\mathbf{H}_3$); 3.25 (2H, m, $NC\mathbf{H}_2CH_3$); 3.48 – 3.51 (2H, m, $NC\mathbf{H}_2CH_3$); 3.62 (1H, d, *J* = 14.2 Hz, $SO_2C\mathbf{H}_2$); 3.91 (1H, d, *J* = 14.2 Hz, $SO_2C\mathbf{H}_2$); 5.70 – 5.94 (1H, broad, O**H**); 7.39 (2H, d, *J* = 8.7 Hz, Ar**H**); 7.48 (2H, d, *J* = 8.6 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.32 ($NCH_2\mathbf{C}H_3$), 12.80 ($NCH_2\mathbf{C}H_3$), 43.43 ($N\mathbf{C}H_2$), 44.99 ($N\mathbf{C}H_2$), 64.24 ($SO_2\mathbf{C}H_2$), 83.30 (**C**OH), 125.53 (Ar), 129.30 (Ar), 134.49 (Ar), 139.61 (Ar), 168.27 (N=**C**-N).
IR (cm^{-1}): 838.6, 916.0, 967.9, 1078.0, 1141.9, 1124.1, 1207.8, 1220.9, 1286.7, 1585.4.
micrOTOF-Q MS m/z $C_{13}H_{17}ClN_2O_3S$+Na, calculated 339.0541, observed 339.0533.

4-(4-Chlorophenyl)-3-(dipropylamino)-1,1-dioxo-5H-isothiazol-4-ol (10d)

Using the procedure for compound (**10b**) [see main article], 2-(4-chlorophenyl)-*N′*-methylsulfonyl-2-oxo-*N,N*-dipropyl-acetamidine **(9d)** (3.21 g, 9.31 mmol) and a 20% w/v solution of potassium *t*-butoxide in tetrahydrofuran (6.27 mL, 11.17 mmol) gave the title product as a red oil (2.45 g, 76%), which was used directly in the next step.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.62 (3H, t, *J* = 7.3 Hz, $NCH_2CH_2C\mathbf{H}_3$); 0.91 (3H, t, *J* = 7.4 Hz, $NCH_2CH_2C\mathbf{H}_3$); 0.94 – 1.03 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); 1.48 – 1.53 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); 1.54 – 1.67 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); 1.68 – 1.78 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); 3.03 – 3.20 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); 3.23 – 3.33 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); 3.39 – 3.48 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); 3.60 (1H, d, *J* = 14.1 Hz, $SO_2C\mathbf{H}_2$); 3.90 (1H, d, *J* = 14.2 Hz, $SO_2C\mathbf{H}_2$); 5.51 – 5.81 (1H, broad, O**H**); 7.39 (2H, d, *J* = 8.7 Hz, Ar**H**); 7.49 (2H, d, *J* = 8.6 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 10.84 (**C**H_3), 11.27 (**C**H_3), 19.27 (**C**H_2), 21.07 (**C**H_2), 50.66 ($N\mathbf{C}H_2$), 52.18 ($N\mathbf{C}H_2$), 64.24 ($SO_2\mathbf{C}H_2$), 83.37 (**C**OH), 125.54 (Ar), 129.25 (Ar), 134.46 (Ar), 139.69 (Ar), 168.56 (N=**C**-N).
IR (cm^{-1}): 815.7, 856.1, 912.2, 1081.0, 1129.2, 1143.1, 1226.0, 1276.2, 1578.6.
micrOTOF-Q MS m/z $C_{15}H_{21}ClN_2O_3S$+Na, calculated 367.0854, observed 367.0852.

3-(1-Piperidyl)-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-4-ol (10f)

Using the procedure for compound (**10b**) [see main article], *N*-[2-oxo-1-(1-piperidyl)-2-(p-tolyl)ethylidene] methanesulfonamide **(9f)** (2.09 g, 6.78 mmol) and a 20% w/v solution of potassium *t*-butoxide in tetrahydrofuran (4.57 mL, 8.14 mmol) gave a crude product which was purified by gravity silica column chromatography (2:1 PE:EtOAc) to yield the pure product as a dark brown solid (830 mg, 42%), m.p.: 238 – 240 °C.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.95 – 1.05 (1H, m, $N(CH_2)_2C\mathbf{H}_2$); 1.38 – 1.53 (2H, m, $N(CH_2)_2C\mathbf{H}_2$ + $NCH_2C\mathbf{H}_2$); 1.54 – 1.63 (2H, m, $NCH_2C\mathbf{H}_2$); 1.64 – 1.75 (1H, m, $NCH_2C\mathbf{H}_2$); 2.35 (3H, s, Ar$C\mathbf{H}_3$); 3.17 – 3.26 (1H, m, $NC\mathbf{H}_2$); 3.45 – 3.54 (1H, m, $NC\mathbf{H}_2$); 3.63 – 3.70 (1H, m, $NC\mathbf{H}_2$); 3.65 (1H, d, *J* = 14.1 Hz, $SO_2C\mathbf{H}_2$); 3.72 – 3.81 (1H, m, $NC\mathbf{H}_2$); 3.96 (1H, d, *J* = 14.1 Hz, $SO_2C\mathbf{H}_2$); 5.56 (1H, s, O**H**); 7.20 (2H, d, *J* = 7.7 Hz, Ar**H**); 7.40 (2H, d, *J* = 7.7 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 21.10 (Ar**C**H_3), 23.76 (**C**H_2), 25.25 (**C**H_2), 25.39 (**C**H_2), 48.34 ($N\mathbf{C}H_2$), 49.27 ($N\mathbf{C}H_2$), 64.68 ($SO_2C\mathbf{H}_2$), 83.54 (**C**OH), 123.80 (Ar), 129.66 (Ar), 138.09 (Ar), 138.18 (Ar), 168.21 (N=**C**-N).
IR (cm^{-1}): 803.3, 859.7, 942.4, 1073.5, 1138.1, 1217.0, 1289.3, 1442.3, 1594.9, 3348.5.
micrOTOF-Q MS m/z $C_{15}H_{20}N_2O_3S$+Na, calculated 331.1087, observed 331.1085.

4-Chloro-4-(4-chlorophenyl)-*N,N*-diethyl-1,1-dioxo-5H-isothiazol-3-amine (11c)

Using the procedure for compound (**11b**) [see main article], thionyl chloride (10.99 mL, 151.50 mmol) and 4-(4-chlorophenyl)-3-(diethylamino)-1,1-dioxo-5H-isothiazol-4-ol **(10c)** (1.60 g, 5.05 mmol) gave the title product as pale yellow oil (1.39 g, 82%) which was not purified further and was used directly in the next step.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.91 (3H, t, *J* = 7.0 Hz, $NCH_2C\mathbf{H}_3$); 1.29 (3H, t, *J* = 7.1 Hz, $NCH_2C\mathbf{H}_3$); 2.97 – 3.22 (2H, m, $NC\mathbf{H}_2CH_3$); 3.45 – 3.56 (1H, m, $NC\mathbf{H}_2CH_3$); 3.61 – 3.72 (1H, m, $NC\mathbf{H}_2CH_3$); 3.79 (1H, d, *J* = 14.6 Hz, $SO_2C\mathbf{H}_2$); 4.17 (1H, d, *J* = 14.6 Hz, $SO_2C\mathbf{H}_2$); 7.42 – 7.48 (4H, m, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.08 (**C**H_3), 12.37 (**C**H_3), 44.07 ($N\mathbf{C}H_2$), 45.11 ($N\mathbf{C}H_2$), 67.59 ($SO_2\mathbf{C}H_2$), 70.64 (**C**Cl), 126.21 (Ar), 129.84 (Ar), 135.68 (Ar), 137.17 (Ar), 163.93 (N=**C**-N).

4-Chloro-4-(4-chlorophenyl)-1,1-dioxo-*N,N*-dipropyl-5H-isothiazol-3-amine (11d)

Using the procedure for compound (**11b**) [see main article], thionyl chloride (15.45 mL, 213.00 mmol) and 4-(4-chlorophenyl)-3-(dipropylamino)-1,1-dioxo-5H-isothiazol-4-ol **(10d)** (2.45 g, 7.10 mmol) gave the title product as a dark red oil (2.18 g, 85%) which was not purified further and was used directly in the next step.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.58 (3H, t, *J* = 7.4 Hz, $NCH_2CH_2C\mathbf{H}_3$); 0.95 (3H, t, *J* = 7.4 Hz, $NCH_2CH_2C\mathbf{H}_3$); 1.02 – 1.16 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); 1.48 – 1.84 (3H, m, $NCH_2C\mathbf{H}_2CH_3$); 2.84 – 3.04 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); 3.35 – 3.45 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); 3.49 – 3.56 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); 3.79 (1H, d, *J* = 14.6 Hz, $SO_2C\mathbf{H}_2$); 4.17 (1H, d, *J* = 14.6 Hz, $SO_2C\mathbf{H}_2$); 7.42 – 7.50 (4H, m, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 10.80 (**C**H_3), 11.21 (**C**H_3), 19.10 (**C**H_2), 20.72 (**C**H_2), 51.26 (N**C**H_2), 52.26 (N**C**$H_2CH_2CH_3$), 67.72 (SO_2**C**H_2), 70.78 (**C**Cl), 126.24 (Ar), 129.79 (Ar), 135.66 (Ar), 137.18 (Ar), 164.16 (N=**C**-N).

4-Chloro-1,1-dioxo-*N*-piperidyl-4-(p-tolyl)-5H-isothiazol-3-amine (11f)

Using the procedure for compound (**11b**) [see main article], thionyl chloride (5.85 mL, 80.70 mmol) and 3-(1-piperidyl)-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-4-ol **(10f)** (830 mg, 2.69 mmol) gave a crude product which was purified by gravity silica column chromatography (2:1 PE:EtOAc) to yield the pure product as a pale brown oil (627 mg, 71%).
^{1}H NMR δ (400 MHz, $CDCl_3$): 1.01 – 1.20 (1H, m, $N(CH_2)_2C\mathbf{H}_2$); 1.36 – 1.48 (1H, m, $N(CH_2)_2C\mathbf{H}_2$); 1.50 – 1.79 (4H, m, $NCH_2C\mathbf{H}_2$); 2.38 (3H, s, Ar$C\mathbf{H}_3$); 2.99 – 3.07 (1H, m, $NC\mathbf{H}_2$); 3.22 – 3.30 (1H, m, $NC\mathbf{H}_2$); 3.74 – 3.82 (1H, m, $NC\mathbf{H}_2$); 3.79 (1H, d, *J* = 14.6 Hz, $SO_2C\mathbf{H}_2$); 3.83 – 3.91 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); 4.16 (1H, d, *J* = 14.6 Hz, $SO_2C\mathbf{H}_2$); 7.26 (2H, d, *J* = 8.3 Hz, Ar**H**); 7.39 (2H, d, *J* = 8.3 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 21.05 (Ar**C**H_3), 23.45 (**C**H_2), 24.99 (CH_2), 25.27 (**C**H_2), 49.08 (N**C**H_2), 49.62 (N**C**H_2), 67.90 ($SO_2C\mathbf{H}_2$), 71.07 (**C**Cl), 124.44 (Ar), 130.24 (Ar), 135.64 (Ar), 139.51 (Ar), 164.24 (N=**C**-N).
IR (cm^{-1}): 797.3, 805.4, 857.9, 930.9, 1120.9, 1143.6, 1201.4, 1234.9, 1310.4, 1593.3.
micrOTOF-Q MS m/z $C_{15}H_{19}N_2ClO_2S$+Na, calculated 349.0748, observed 349.0748.

4-(4-Chlorophenyl)-*N,N*-diethyl-1,1-dioxo-isothiazol-3-amine (13c)

Using the procedure for compound (**13b**) [see main article], 4-chloro-4-(4-chlorophenyl)-*N,N*-diethyl-1,1-dioxo-5H-isothiazol-3-amine **(11c)** (650 mg, 1.93 mmol) and anhydrous potassium carbonate (290 mg, 2.28 mmol) gave the title product as a brown, highly viscous oil (500 mg, 79%) which was a single spot by TLC and did not need to be purified further.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.94 (3H, t, J = 6.5 Hz, $NCH_2C\mathbf{H}_3$); 1.31 (3H, t, *J* = 6.5 Hz, ($NCH_2C\mathbf{H}_3$); 3.06 – 3.17 (2H, m, $NC\mathbf{H}_2CH_3$); 3.59 – 3.71 (2H, m, $NC\mathbf{H}_2CH_3$); 7.24 (1H, s, $SO_2C\mathbf{H}$); 7.30 (2H, d, *J* = 8.5 Hz, Ar**H**); 7.46 (2H, d, *J* = 8.5 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.85 (**C**H_3), 14.05 (**C**H_3), 43.95 (N**C**H_2), 46.77 (N**C**H_2), 128.78 (Ar), 129.47 (Ar), 130.39 (Ar), 136.05 (Ar), 138.58 (Ar), 143.87 (Ar), 160.39 (N=**C**-N).
IR (cm^{-1}): 741.2, 824.8, 913.6, 942.7, 1087.8, 1122.4, 1188.3, 1293.6, 1557.0, 1590.9, 2950.4.
micrOTOF-Q MS m/z $C_{13}H_{15}ClN_2O_2S$+Na, calculated 321.0435, observed 321.0437.

4-(4-Chlorophenyl)-1,1-dioxo-*N,N*-dipropyl-isothiazol-3-amine (13d)

Using the procedure for compound (**13b**) [see main article], 4-chloro-4-(4-chlorophenyl)-1,1-dioxo-*N,N*-dipropyl-5H-isothiazol-3-amine **(11d)** (2.18 g, 6.00 mmol) and anhydrous potassium carbonate (995 mg, 7.20 mmol) gave the title product as a brown oil (2.07 g, 97%) which was a single spot by TLC and did not need to be purified further.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.43 (3H, t, *J* = 7.2 Hz, $NCH_2CH_2C\mathbf{H}_3$); 0.96 (3H, t, *J* = 7.2 Hz, $NCH_2CH_2C\mathbf{H}_3$); 1.32 – 1.45 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); 1.70 – 1.83 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); 2.89 – 2.98 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); 3.49 – 3.56 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); 7.23 (1H, s, $SO_2C\mathbf{H}$); 7.25 – 7.30 (2H, d, *J* = 8.0 Hz, Ar**H**); 7.46 (2H, d, *J* = 8.0 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 10.42 (**C**H_3), 11.35 (**C**H_3), 19.96 (**C**H_2), 22.63 (**C**H_2), 51.47 (N**C**H_2), 54.39 (N**C**H_2), 128.75 (Ar), 129.49 (Ar), 130.48 (Ar), 136.03 (Ar), 138.50 (Ar), 144.05 (Ar), 160.58 (N=**C**-N).
IR (cm^{-1}): 747.8, 834.0, 908.2, 1088.5, 1186.5, 1123.9, 1295.2, 1556.4, 1590.4, 2964.3.
micrOTOF-Q MS m/z $C_{15}H_{19}N_2ClO_2S$+Na, calculated 349.0748, observed 349.0745.

3-(1-Piperidyl)-4-(p-tolyl)isothiazole-1,1-dioxide (13f)

Using the procedure for compound (**13b**) [see main article], 4-chloro-1,1-dioxo-*N,N*-dipropyl-4-(p-tolyl)-5H-isothiazol-3-amine **(11f)** (500 mg, 1.52 mmol) and anhydrous potassium carbonate (250 mg) gave a crude product was purified by gravity silica column chromatography (2:1 PE:EtOAc) to yield the pure product as a brown solid (277 mg, 62%), m.p.: 178 – 180 °C.
^{1}H NMR δ (400 MHz, $CDCl_3$): 1.33 – 1.45 (2H, m, $N(CH_2)_2C\mathbf{H}_2$); 1.59 – 1.67 (2H, m, $NCH_2C\mathbf{H}_2$); 1.71 – 1.84 (2H, m, $NCH_2C\mathbf{H}_2$); 2.41 (3H, s, Ar$C\mathbf{H}_3$); 3.06 – 3.21 (2H, m, $NC\mathbf{H}_2$); 3.74 – 3.88 (2H, m, $NC\mathbf{H}_2$); 7.18 – 7.23 (3H, m, Ar**H**, $SO_2C\mathbf{H}$); 7.25 – 7.29 (2H, m, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 21.37 (Ar$\mathbf{C}H_3$), 23.75 ($\mathbf{C}H_2$), 25.20 ($\mathbf{C}H_2$), 26.09 ($\mathbf{C}H_2$), 49.54 ($N\mathbf{C}H_2$), 50.38 ($N\mathbf{C}H_2$), 127.00 (Ar), 128.82 (Ar), 130.01 (Ar), 139.98 (Ar), 140.21 (Ar), 142.49 (Ar), 161.71 (N=**C**-N).
IR (cm^{-1}): 744.2, 800.7, 855.6, 941.9, 1114.1, 1127.7, 1179.3, 1191.7, 1296.7, 1548.0, 2986.0.
micrOTOF-Q MS m/z $C_{15}H_{18}N_2O_2S$+Na, calculated 313.0981, observed 313.0982.

6-(2-Azidophenyl)-3-diethylamino-3a-(4-methoxyphenyl)-isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide (22c)

Using the procedure for compound (**22b**) [see main article], 3-diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**13a**) (100 mg; 0.34 mmol), 2-azidobenzohydroximoyl chloride (100 mg; 0.51 mmol) and triethylamine (71 µL; 51 mg; 0.51 mmol) gave the crude product as a pale brown solid which was purified by gravity silica chromatography (PE/EtOAc: gradient elution 4/1 to 1/1) to give the product as a pale brown solid (95 mg; 62%; m.p.= 159 – 160 °C).
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.92 (1H, dd, *J* = 7.9 and 1.4 Hz, ArN_3), 7.46 – 7.48 (1H, m, ArN_3), 7.37 (2H, d, *J* = 8.9 Hz, ArOMe), 7.19 – 7.21 (1H, m, ArN_3), 7.16 – 7.18 (1H, m, ArN_3), 7.00 (2H, d, *J* = 8.9 Hz, ArOMe), 5.70 (1H, s, **CH**), 3.84 (3H, s, O$\mathbf{CH_3}$), 3.69 (1H, dq, *J* = 13.6 and 7.1 Hz, $N\mathbf{CH_2}CH_3$). 3.39 (1H, dq, *J* = 13.6 and 7.1 Hz, $N\mathbf{CH_2}CH_3$), 3.29 (1H, dq, *J* = 14.4 and 7.1 Hz, $N\mathbf{CH_2}CH_3$), 3.21 (1H, dq, *J* = 14.4 and 7.1 Hz, $N\mathbf{CH_2}CH_3$), 1.26 (3H, t, *J* = 7.1 Hz, $NCH_2\mathbf{CH_3}$), 0.90 (3H, t, *J* = 7.1 Hz, $NCH_2\mathbf{CH_3}$).
^{13}C NMR δ (100 MHz, $CDCl_3$) 163.58 (**C**=N), 160.32 (**C**-OMe), 151.00 (N=**C**-ArN_3), 138.01 (**C**, ArN_3), 132.00 (**CH**, ArN_3), 129.94 (**CH**, ArN_3), 128.61 (**C**, ArOMe), 125.21 (**CH**, ArOMe), 124.99 (**CH**, ArN_3), 118.94 (**CH**, ArN_3), 118.67 (**C**-N_3), 114.96 (**CH**, ArOMe), 98.47 (**C** (ring junction)), 79.35 (**CH** (ring junction)), 55.37 (O$\mathbf{CH_3}$), 44.73 ($N\mathbf{CH_2}CH_3$), 43.91 ($N\mathbf{CH_2}CH_3$), 12.78 ($NCH_2\mathbf{CH_3}$), 11.28 ($NCH_2\mathbf{CH_3}$).
IR υ_{max} (cm^{-1}) 2980, 2132, 1595, 1513, 1447, 1346, 1323, 1253, 1176, 1134, 1033, 907, 893.
MS (*m/z*): 477.1 ($[M + Na]^+$), 931.3 ($[2M + Na]^+$), 1385.4 ($[3M + Na]^+$).
HRMS (*m/z*): $[M + Na]^+$ for $C_{21}H_{22}N_6NaO_4S$ calculated 477.1315 measured 477.1316.
HRMS (*m/z*): $[M + H]^+$ for $C_{21}H_{23}N_6O_4S$ calculated 454.1418 measured 454.1418.

3,6a-*bis*(4-Methoxyphenyl)-4,4-dioxo-*N,N*-dipropyl-3aH-isothiazolo[5,4-d]isoxazol-6-amine (22k)

To a mixture of 4-(4-methoxyphenyl)-1,1-dioxo-*N,N*-dipropyl-isothiazol-3-amine **(13b)** (100 mg, 0.31 mmol) and 4-methoxy-*N*-hydroxybenzimidoyl chloride (58 mg, 0.31 mmol) in dry chloroform (10 mL) under an atmosphere of nitrogen, triethylamine (50 µl, 0.34 mmol) in dry chloroform (100 mL) was added drop-wise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity silica column chromatography (7:1 PE:EtOAc) to yield the pure product as a white crystalline solid (43 mg, 29%, m.p. = 92 – 94 °C).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.66 (3H, t, *J* = 7.1 Hz, $NCH_2CH_2C\mathbf{H}_3$), 0.93 (3H, t, *J* = 7.4 Hz, $NCH_2CH_2C\mathbf{H}_3$), 0.98 – 1.11 (1H, m, $NCH_2C\mathbf{H}_2CH_3$), 1.49 – 1.86 (3H, m, $NCH_2C\mathbf{H}_2CH_3$), 3.00 – 3.20 (2H, m, $NC\mathbf{H}_2CH_2CH_3$), 3.21 – 3.31 (1H, m, $NC\mathbf{H}_2CH_2CH_3$), 3.56 – 3.65 (1H, m, $NC\mathbf{H}_2CH_2CH_3$), 3.827 (3H, s, ArO$C\mathbf{H}_3$), 3.831 (3H, s, ArO$C\mathbf{H}_3$), 5.07 (1H, s, $SO_2C\mathbf{H}$), 6.92 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.97 (2H, d, *J* = 9.0 Hz, Ar**H**), 7.37 (2H, dd, *J* = 8.9 Hz, 1.9 Hz, Ar**H**), 7.72 (2H, dd, *J* = 9.0 Hz, 1.9 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 10.87 ($\mathbf{C}H_3$), 11.24 ($\mathbf{C}H_3$), 19.40 ($\mathbf{C}H_2$), 21.10 ($\mathbf{C}H_2$), 51.40 ($N\mathbf{C}H_2$), 52.15 ($N\mathbf{C}H_2$), 55.40 (ArO$\mathbf{C}H_3$), 55.47 (ArO$\mathbf{C}H_3$), 79.71 ($SO_2\mathbf{C}H$), 98.98 (**C**q), 114.37 (Ar), 115.00 (Ar), 119.28 (Ar), 125.12 (Ar), 129.23 (Ar), 129.25 (Ar), 152.00 (Ar), 160.38 (Ar), 161.79 (**C**=N), 164.05 (**C**=N).
IR (cm^{-1}): 833.2, 888.7, 915.8, 1026.7, 1135.1, 1175.3, 1251.8, 1319.8, 1513.2, 1589.1.
micrOTOF-Q MS m/z $C_{24}H_{29}N_3O_5S$+Na, calculated 494.1720, observed 494.1717.

3-(4-Chlorophenyl)-6a-(4-methoxyphenyl)-4,4-dioxo-*N,N*-dipropyl-3aH-isothiazolo[5,4-d]isoxazol-6-amine (22l)

Using the procedure above for compound (**22k**), 4-(4-methoxyphenyl)-1,1-dioxo-*N,N*-dipropyl-isothiazol-3-amine **(13b)** (100 mg, 0.31 mmol), 4-chloro-*N*-hydroxybenzimidoyl chloride (59 mg, 0.31 mmol) and triethylamine (50 µl, 0.34 mmol)

gave a crude product which was purified by gravity silica column chromatography (7:1 PE:EtOAc) to yield the pure product as a pale yellow oil (44 mg, 30%).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.67 (3H, t, *J* = 7.3 Hz, $NCH_2CH_2C\mathbf{H}_3$), 0.93 (3H, t, *J* = 7.4 Hz, $NCH_2CH_2C\mathbf{H}_3$), 0.99 – 1.12 (1H, m, $NCH_2C\mathbf{H}_2CH_3$), 1.49 – 1.86 (3H, m, $NCH_2C\mathbf{H}_2CH_3$), 3.00 – 3.30 (3H, m, $NC\mathbf{H}_2CH_2CH_3$), 3.56 – 3.66 (1H, m, $NC\mathbf{H}_2CH_2CH_3$), 3.83 (3H, s, $ArOC\mathbf{H}_3$), 5.06 (1H, s, $SO_2C\mathbf{H}$), 6.98 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.36 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.40 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.72 (2H, d, *J* = 8.6 Hz, 2.4 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 10.86 (**C**H_3), 11.22 (**C**H_3), 19.40 (**C**H_2), 21.11 (**C**H_2), 51.41 (**C**H_2), 52.23 (**C**H_2), 55.49 (ArO**C**H_3), 79.08 (SO_2**C**H), 99.54 (**C**q), 115.09 (Ar), 125.08 (Ar), 125.42 (Ar), 128.79 (Ar), 128.81 (Ar), 129.22 (Ar), 137.23 (Ar), 151.76 (Ar), 160.50 (**C**=N), 163.86 (**C**=N).
IR (cm^{-1}): 729.3, 832.3, 923.0, 1091.3, 1134.6, 1174.9, 1250.9, 1320.1, 1511.8, 1589.4.
micrOTOF-Q MS m/z $C_{23}H_{26}ClN_3O_4S$+Na, calculated 498.1225, observed 498.1222.

3,6a-*bis*(4-Chlorophenyl)-*N,N*-diethyl-4,4-dioxo-3aH-isothiazolo[5,4-d]isoxazol-6-amine (22m)

Using the procedure above for compound (**22k**), 4-(4-chlorophenyl)-*N,N*-diethyl-1,1-dioxo-isothiazol-3-amine **(13c)** (125 mg, 0.42 mmol), 4-chloro-*N*-hydroxybenzimidoyl chloride (87 mg, 0.47 mmol) and triethylamine (71 µl, 0.51 mmol) gave a crude product which was purified by gravity silica column chromatography (6:1 hexane:EtOAc) to yield the pure product as a pale yellow oil (94 mg, 51%).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.89 (3H, t, *J* = 7.1 Hz, $NCH_2C\mathbf{H}_3$), 1.27 (3H, t, *J* = 7.1 Hz, $NCH_2C\mathbf{H}_3$), 3.15 – 3.32 (2H, m, $NC\mathbf{H}_2CH_3$), 3.42 (1H, *appt.* sxt, *J* = 7.1 Hz, $NC\mathbf{H}_2CH_3$), 3.69 (1H, *appt.* sxt, *J* = 7.1 Hz, $NC\mathbf{H}_2CH_3$), 5.08 (1H, s, $SO_2C\mathbf{H}$), 7.38 – 7.44 (4H, m, Ar**H**), 7.47 (2H, d, *J* = 8.7 Hz, Ar**H**), 7.71 (2H, d, *J* = 8.7 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.36 (**C**H_3), 12.82 (**C**H_3), 44.29 (**C**H_2), 45.23 (**C**H_2), 79.04 (SO_2**C**H), 98.95 (**C**q), 125.10 (Ar), 125.25 (Ar), 128.88 (Ar), 129.31 (Ar), 130.16 (Ar), 135.37 (Ar), 136.01 (Ar), 137.49 (Ar), 151.91 (**C**=N), 162.94 (**C**=N).
IR (cm^{-1}): 728.0, 828.8, 890.0, 906.0, 1013.0, 1091.2, 1135.5, 1175.2, 1321.2, 1593.1.
micrOTOF-Q MS m/z $C_{20}H_{19}Cl_2N_3O_3S$+Na, calculated 474.0416, observed 474.0414.

6a-(4-Chlorophenyl)-*N,N*-diethyl-3-(4-methoxyphenyl)-4,4-dioxo-3aH-isothiazolo[5,4-d]isoxazol-6-amine (22n)

Using the procedure above for compound (**22k**), 4-(4-chlorophenyl)-*N,N*-diethyl-1,1-dioxo-isothiazol-3-amine **(13c)** (100 mg, 0.34 mmol), 4-methoxy-*N*-hydroxybenzimidoyl chloride (57 mg, 0.31 mmol) and triethylamine (47 µl, 0.34 mmol) gave a crude product which was purified by gravity silica column chromatography (7:1 PE:EtOAc) to yield the pure product as a white crystalline solid (57 mg, 45%, m.p. = 126 – 128 °C).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.87 (3H, t, *J* = 7.0 Hz, $NCH_2C\mathbf{H}_3$), 1.27 (3H, t, *J* = 7.1 Hz, $NCH_2C\mathbf{H}_3$), 3.22 (2H, non, *J* = 7.3 Hz, $NC\mathbf{H}_2CH_3$), 3.42 (1H, *appt.* sxt, *J* = 7.1 Hz, $NC\mathbf{H}_2CH_3$), 3.68 (1H, *appt.* sxt, *J* = 7.1 Hz, $NC\mathbf{H}_2CH_3$), 3.83 (3H, s, $ArOC\mathbf{H}_3$), 5.09 (1H, s, $SO_2C\mathbf{H}$), 6.93 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.41 (2H, d, *J* = 8.8 Hz, Ar**H**), 7.46 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.71 (2H, d, *J* = 8.8 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.38 (**C**H_3), 12.81 (**C**H_3), 44.27 (N**C**H_2), 45.11 (N**C**H_2), 55.44 (ArO**C**H_3), 79.66 (SO_2**C**H), 98.41 (**C**q), 114.45 (Ar), 118.94 (Ar), 125.31 (Ar), 129.34 (Ar), 130.06 (Ar), 135.77 (Ar), 135.79 (Ar), 152.15 (Ar), 161.96 (**C**=N), 163.13 (**C**=N).
IR (cm^{-1}): 828.2, 915.9, 966.7, 1092.1, 1135.1, 1174.7, 1254.9, 1320.7, 1350.9, 1591.2.
micrOTOF-Q MS m/z $C_{21}H_{22}ClN_3O_4S$+Na, calculated 470.0912, observed 470.0909.

6a-(4-Chlorophenyl)-3-(4-methoxyphenyl)-4,4-dioxo-*N,N*-dipropyl-3aH-isothiazolo[5,4-d]isoxazol-6-amine (22o)

Using the procedure above for compound (**22k**), 4-(4-chlorophenyl)-1,1-dioxo-*N,N*-dipropyl-isothiazol-3-amine **(13d)** (100 mg, 0.31 mmol), 4-methoxy-*N*-hydroxybenzimidoyl chloride (58 mg, 0.31 mmol) and triethylamine (50 µl, 0.34 mmol) gave a crude product which was purified by gravity silica column chromatography (7:1 PE:EtOAc) to yield the pure product as a white waxy solid (37 mg, 25%, m.p. = 117 – 121 °C).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.68 (3H, t, *J* = 7.4 Hz, $NCH_2CH_2C\mathbf{H}_3$), 0.93 (3H, t, *J* = 7.4 Hz, $NCH_2CH_2C\mathbf{H}_3$), 0.99 – 1.12 (1H, m, $NCH_2C\mathbf{H}_2CH_3$), 1.50 – 1.83 (3H, m, $NCH_2C\mathbf{H}_2CH_3$), 2.97 – 3.16 (2H, m, $NC\mathbf{H}_2CH_2CH_3$), 3.22 – 3.31 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); 3.57 – 3.66 (1H, m, $NC\mathbf{H}_2CH_2CH_3$), 3.84 (3H, s, $ArOC\mathbf{H}_3$), 5.09 (1H, s, $SO_2C\mathbf{H}$), 6.93 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.40 – 7.48 (4H, m, Ar**H**), 7.72 (2H, d, *J* = 8.9 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 10.83 (C**C**H_3), 11.21 (C**C**H_3), 19.39 ($NCH_2\mathbf{C}H_2CH_3$), 21.15 ($NCH_2\mathbf{C}H_2CH_3$), 51.43 (N**C**$H_2CH_2CH_3$), 52.16 (N**C**$H_2CH_2CH_3$), 55.41 (ArO**C**H_3), 79.73 (SO_2**C**H), 98.46 (**C**q), 114.43 (Ar), 118.93 (Ar), 125.26 (Ar), 129.32 (Ar), 130.00 (Ar), 135.76 (Ar), 135.93 (Ar), 152.13 (Ar), 161.94 (**C**=N), 163.45 (**C**=N).

IR (cm^{-1}): 729.3, 832.1, 887.8, 917.0, 1092.3, 1135.5, 1175.2, 1255.2, 1321.3, 1589.3.
micrOTOF-Q MS m/z $C_{23}H_{26}ClN_3O_4S$+Na, calculated 498.1225, observed 498.1241.

3,6a-*bis*(4-Chlorophenyl)-4,4-dioxo-*N,N*-dipropyl-3aH-isothiazolo[5,4-d]isoxazol-6-amine (22p)

Using the procedure above for compound (**22k**), 4-(4-chlorophenyl)-1,1-dioxo-*N,N*-dipropyl-isothiazol-3-amine **(13d)** (100 mg, 0.31 mmol), 4-chloro-*N*-hydroxybenzimidoyl chloride (59 mg, 0.31 mmol) and triethylamine (50 µl, 0.34 mmol) gave a crude product which was purified by gravity silica column chromatography (7:1 PE:EtOAc) to yield the pure product as a pale yellow oil (43 mg, 29%).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.69 (3H, t, *J* = 7.3 Hz, $NCH_2CH_2C\mathbf{H}_3$), 0.93 (3H, t, *J* = 7.4 Hz, $NCH_2CH_2C\mathbf{H}_3$), 0.9- 1.13 (1H, m, $NCH_2C\mathbf{H}_2CH_3$), 1.50 – 1.83 (3H, m, $NCH_2C\mathbf{H}_2CH_3$), 2.96 – 3.18 (2H, m, $NC\mathbf{H}_2CH_2CH_3$), 3.22 – 3.31 (1H, m, $NC\mathbf{H}_2CH_2CH_3$), 3.59 – 3.66 (1H, m, $NC\mathbf{H}_2CH_2CH_3$), 5.08 (1H, s, $SO_2C\mathbf{H}$), 7.38 – 7.43 (4H, m, Ar**H**), 7.47 (2H, d, *J* = 8.8 Hz, Ar**H**), 7.71 (2H, d, *J* = 8.6 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 10.82 (**C**H_3), 11.20 (**C**H_3), 19.38 (**C**H_2), 21.16 (**C**H_2), 51.45 (N**C**H_2), 52.45 (N**C**H_2), 79.09 (SO_2**C**H), 99.00 (**C**q), 125.09 (Ar), 125.21 (Ar), 128.86 (Ar), 129.28 (Ar), 130.09 (Ar), 130.35 (Ar), 135.49 (Ar), 135.97 (Ar), 137.46 (Ar), 151.89 (**C**=N), 163.25 (**C**=N).
IR (cm^{-1}): 730.1, 830.9, 889.1, 922.5, 1013.6, 1090.5, 1135.2, 1174.4, 1321.5, 1590.0.
micrOTOF-Q MS m/z $C_{22}H_{23}N_3Cl_2O_3S$+Na, calculated 502.0729, observed 502.0729.

***N,N*-Diethyl-3-(4-methoxyphenyl)-4,4-dioxo-6a-(p-tolyl)-3aH-isothiazolo[5,4-d]isoxazol-6-amine (22q)**

Using the procedure above for compound (**22k**), *N,N*-diethyl-1,1-dioxo-4-(p-tolyl)isothiazol-3-amine **(13e)** (75 mg, 0.27 mmol), 4-methoxy-*N*-hydroxybenzimidoyl chloride (50 mg, 0.27 mmol) and triethylamine (42 µl, 0.30 mmol) gave a crude product which was purified by gravity silica column chromatography (7:1 PE:EtOAc) to yield the pure product as a white crystalline solid (45 mg, 39%, m.p. = 89 – 90 °C).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.84 (3H, t, *J* = 7.0 Hz, $NCH_2C\mathbf{H}_3$), 1.27 (3H, t, *J* = 7.1 Hz, $NCH_2C\mathbf{H}_3$), 2.38 (3H, s, Ar$C\mathbf{H}_3$), 3.24 (2H, *appt.* non, *J* = 7.3 Hz, $NC\mathbf{H}_2CH_3$), 3.41 (1H, *appt.* sxt, *J* = 7.1 Hz, $NC\mathbf{H}_2CH_3$), 3.69 (1H, *appt.* sxt, *J* = 7.1 Hz, $NC\mathbf{H}_2CH_3$), 3.83 (3H, s, Ar$OC\mathbf{H}_3$), 5.08 (1H, s, $SO_2C\mathbf{H}$), 6.93 (2H, d, *J* = 8.8 Hz, Ar**H**), 7.26 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.33 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.72 (2H, d, *J* = 8.8 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.39 (**C**H_3), 12.71 (**C**H_3), 21.20 (Ar**C**H_3), 44.26 (**C**H_2), 45.00 (**C**H_2), 55.42 (Ar**O**CH_3), 79.77 (SO_2**C**H), 99.03 (**C**q), 115.40 (Ar), 119.29 (Ar), 123.63 (Ar), 129.27 (Ar), 130.38 (Ar), 134.35 (Ar), 139.69 (Ar), 152.00 (Ar), 161.82 (**C**=N), 163.66 (**C**=N).
IR (cm^{-1}): 728.2, 822.5, 889.4, 916.1, 967.3, 1135.4, 1175.8, 1255.0, 1320.1, 1591.6.
micrOTOF-Q MS m/z $C_{22}H_{25}N_3O_4S$+Na, calculated 450.1458, observed 450.1455.

3-(4-Chlorophenyl)-*N,N*-diethyl-4,4-dioxo-6a-(p-tolyl)-3aH-isothiazolo[5,4-d]isoxazol-6-amine (22r)

Using the procedure above for compound (**22k**), *N,N*-diethyl-1,1-dioxo-4-(p-tolyl)isothiazol-3-amine **(13e)** (100 mg, 0.36 mmol), 4-chloro-*N*-hydroxybenzimidoyl chloride (103 mg, 0.55 mmol) and triethylamine (84 µl, 0.60 mmol) gave a crude product which was purified by gravity silica column chromatography (7:1 PE:EtOAc) to yield the pure product as an orange oil (60 mg, 41%).
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.85 (3H, t, *J* = 7.1 Hz, $NCH_2C\mathbf{H}_3$), 1.27 (3H, t, *J* = 7.1 Hz, $NCH_2C\mathbf{H}_3$), 2.38 (3H, s, Ar$C\mathbf{H}_3$), 3.15 – 3.33 (2H, m, $NC\mathbf{H}_2CH_3$), 3.42 (1H, *appt.* sxt, *J* = 7.1 Hz, $NC\mathbf{H}_2CH_3$), 3.69 (1H, *appt.* sxt, *J* = 7.1 Hz, $NC\mathbf{H}_2CH_3$), 5.07 (1H, s, $SO_2C\mathbf{H}$), 7.26 – 7.34 (4H, m, Ar**H**), 7.40 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.72 (2H, d, *J* = 8.6 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 11.37 (**C**H_3), 12.72 (**C**H_3), 21.21 (Ar**C**H_3), 44.30 (N**C**H_2), 45.12 (N**C**H_2), 79.15 (SO_2**C**H), 99.58 (**C**q), 123.58 (Ar), 125.42 (Ar), 128.83 (Ar), 129.25 (Ar), 130.47 (Ar), 133.94 (Ar), 137.26 (Ar), 139.91 (Ar), 151.74 (**C**=N), 163.46 (**C**=N).
IR (cm^{-1}): 729.7, 822.0, 906.9, 967.4, 1091.3, 1135.5, 1175.7, 1322.1, 1593.7, 2922.5.
micrOTOF-Q MS m/z $C_{21}H_{22}N_3ClO_3S$+Na, calculated 454.0963, observed 454.0976.

3-(4-Methoxyphenyl)-6-(1-piperidyl)-6a-(p-tolyl)-3aH-isothiazolo[5,4-d]isoxazole 4,4-dioxide (22s)

Using the procedure above for compound (**22k**), 3-(1-piperidyl)-4-(p-tolyl)isothiazole-1,1-dioxide **(13f)** (50 mg, 0.17 mmol), 4-methoxy-*N*-hydroxybenzimidoyl chloride (32 mg, 0.17 mmol) and triethylamine (27 µl, 0.19 mmol) gave a crude

product which was purified by gravity silica column chromatography (7:1 PE:EtOAc) to yield the pure product as a colourless oil (40 mg, 54%).
^{1}H NMR δ (400 MHz, $CDCl_3$): 1.05 – 1.16 (1H, m, $NCH_2CH_2C\mathbf{H}_2$), 1.39 – 1.49 (1H, m, $NCH_2CH_2C\mathbf{H}_2$), 1.50 – 1.79 (4H, m, $NCH_2C\mathbf{H_2}$ × 2), 2.37 (3H, s, $ArC\mathbf{H}_3$), 3.14 – 3.23 (1H, m, $NC\mathbf{H}_2$), 3.31 – 3.40 (1H, m, $NC\mathbf{H}_2$), 3.78 (2H, t, *J* = 5.2 Hz, $NC\mathbf{H_2}$), 3.83 (3H, s, $ArOC\mathbf{H}_3$), 5.08 (1H, s, $SO_2C\mathbf{H}$), 6.93 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.26 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.32 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.72 (2H, d, *J* = 8.9 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 21.21 ($Ar\mathbf{C}H_3$), 23.55 ($\mathbf{C}H_2$), 25.23 ($\mathbf{C}H_2$), 25.36 ($\mathbf{C}H_2$), 48.99 ($N\mathbf{C}H_2$), 49.41 ($N\mathbf{C}H_2$), 55.43 ($ArO\mathbf{C}H_3$), 79.87 ($SO_2\mathbf{C}H$), 98.92 (**C**q), 114.41 (Ar), 119.35 (Ar), 123.59 (Ar), 129.27 (Ar), 130.36 (Ar), 134.30 (Ar), 139.67 (Ar), 151.94 (Ar), 161.83 (**C**=N), 163.09 (**C**=N).
IR (cm^{-1}): 880.0, 910.2, 936.4, 1020.2, 1134.9, 1175.9, 1255.0, 1319.3, 1514.7, 1593.5.
micrOTOF-Q MS m/z $C_{23}H_{25}N_3O_4S$+Na, calculated 462.1458, observed 462.1458.

3-(4-Chlorophenyl)-6-(1-piperidyl)-6a-(p-tolyl)-3aH-isothiazolo[5,4-d]isoxazole 4,4-dioxide (22t)

Using the procedure above for compound (**22k**), 3-(1-piperidyl)-4-(p-tolyl)isothiazole-1,1-dioxide **(13f)** (50 mg, 0.17 mmol), 4-chloro-*N*-hydroxybenzimidoyl chloride (32 mg, 0.17 mmol) and triethylamine (27 µl, 0.19 mmol) gave a crude product which was purified by gravity silica column chromatography (7:1 PE:EtOAc) to yield the pure product as a white crystalline solid (21 mg, 28%, m.p. = 111 – 113 °C).
^{1}H NMR δ (400 MHz, $CDCl_3$): 1.07 - 1.17 (1H, m, $NCH_2CH_2C\mathbf{H}_2$), 1.39 – 1.49 (1H, m, $NCH_2CH_2C\mathbf{H}_2$), 1.51 – 1.80 (4H, m, $NCH_2C\mathbf{H_2}$ × 2), 2.38 (3H, s, $ArC\mathbf{H}_3$), 3.15 – 3.24 (1H, m, $NC\mathbf{H}_2$), 3.32 – 3.41 (1H, m, $NC\mathbf{H}_2$), 3.78 (2H, t, *J* = 5.2 Hz, $NC\mathbf{H_2}$), 5.07 (1H, s, $SO_2C\mathbf{H}$), 7.25 – 7.33 (4H, m, Ar**H**), 7.39 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.72 (2H, d, *J* = 8.6 Hz, Ar**H**).
^{13}C NMR δ (100 MHz, $CDCl_3$): 21.21 ($Ar\mathbf{C}H_3$), 23.53 ($\mathbf{C}H_2$), 25.23 ($\mathbf{C}H_2$), 25.37 ($\mathbf{C}H_2$), 49.02 ($N\mathbf{C}H_2$), 49.52 ($N\mathbf{C}H_2$), 79.25 ($SO_2\mathbf{C}H$), 99.48 (**C**q), 123.54 (Ar), 125.44 (Ar), 128.83 (Ar), 129.26 (Ar), 130.45 (Ar), 133.90 (Ar), 137.27 (Ar), 139.88 (Ar), 151.68 (**C**=N), 162.89 (**C**=N).
IR (cm^{-1}): 814.0, 889.1, 936.8, 1012.5, 1092.5, 1135.5, 1176.1, 1258.9, 1321.6, 1595.6.
micrOTOF-Q MS m/z $C_{22}H_{22}N_3ClO_3S$+Na, calculated 466.0963, observed 466.0960.