SAR, Pharmacokinetics, Safety, and Efficacy of Glucokinase Activating, 2-(4-Sulfonylphenyl)-*N*-thiazol-2-ylacetamides: Discovery of PSN-GK1

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SUPPORTING INFORMATION

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Further Experimental Details

General. Solvents and reagents for synthesis were obtained from commercial sources and used as received. Column chromatography was carried out on SiO_2 (40–63 mesh). The ^1H NMR spectra of all compounds were acquired on either a Varian Mercury 400 MHz or a Bruker AMX2 500 MHz instrument, using the chemical shifts of residual deuterated solvents as the internal standard. Chemical shift (δ) data are reported in parts per million (ppm) downfield relative to the internal standard. Mass spectra were acquired using an Atlantis LC-MS instrument fitted with a C_{18} column (3 μm, 3.0 × 20.0 mm, flow rate = 0.85 mL/min), which was eluted with a H_2O–CH_3CN solution containing 0.1% HCO_2H. Recombinant human GK (liver form) was expressed as its glutathione *S*-transferase fusion protein in *E. coli* and purified by glutathione affinity chromatography to >98% purity and stored at –80 °C in 50 mM Tris/HCl pH7.4, 1 mM DTT, 50 mM NaCl, 10% glycerol.

Abbreviations. Ac: Acetyl; *i*-Bu: Isobutyl; *t*-Bu: *tert*-Butyl; CDI: 1,1'-Carbonyldiimidazole; DMF: Dimethylformamide; EDCI: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Et: Ethyl; HBTU: *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HOBt: 1-Hydroxybenzotriazole; h: hour(s); IH: Isohexane; LDA: Lithium diisopropylamide; LHMDS: Lithium bis(trimethylsilyl)amide; Me: Methyl; *m*CPBA: 3-chloroperbenzoic acid; min: minutes; nbd: norbornadiene; NBS: *N*-Bromosuccinimide; Ph: Phenyl; PS: Polymer-supported; THF: Tetrahydrofuran; TLC: Thin Layer chromatography.

(*E*)-2-Phenyl-*N*-pyrazin-2-yl-3-thiophen-2-ylacrylamide (3). NBS (210 mg, 1.2 mmol) was added slowly over 5 min to a stirred solution of PPh_3 (391 mg, 1.5 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C. After 10 min, (*E*)-2-phenyl-3-thiophen-2-ylacrylic acid[1] was added portionwise over 10 min. The reaction was stirred at 0 °C for 20 min, then at 20 °C for 30 min, before being cooled back down again to 0 °C. Aminopyrazine (98 mg, 1.0 mmol) and pyridine (169 μL, 2.1 mmol) were added, then the reaction was allowed to warm to ambient temperature over 16 h, before being diluted with CH_2Cl_2 (50 mL). The solution was washed with 5% aqueous citric acid (3 × 20 mL) and brine (50 mL), before being dried ($MgSO_4$).

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(1) Karminski–Zamola, G.; Bajic, M. Synthesis of (5-styryl-2-thienyl)phenylacrylic Acids. *Heterocycles* **1985**, *23*, 1497–1501.

Filtration, solvent removal, and column chromatography (IH–EtOAc, 19:1 to 17:3) furnished the title compound as a white solid (21 mg, 7%): ^{1}H NMR ($CDCl_3$) δ 6.97–7.02 (m, 1H), 7.18–7.25 (m, 2H), 7.41–7.46 (m, 2H), 7.61–7.67 (m, 3H), 7.75 (br s, 1H), 8.18–8.20 (m, 1H), 8.28 (s, 1H), 8.36 (d, J = 3 Hz, 1H), 9.75 (s, 1H); m/z (ES$^+$) = 308 [M + H]$^+$; Anal. Calcd for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67; S, 10.43; Found: C, 66.24; H, 4.36; N, 13.51; S, 10.29.

(*E*)-2-Phenyl-*N*-thiazol-2-yl-3-thiophen-2-yl-acrylamide (4). HBTU (284 mg, 749 μmol) and NEt_3 (105 μL, 749 μmol) were added to a stirred solution of (*E*)-2-phenyl-3-thiophen-2-ylacrylic acid[1] (115 mg, 500 μmol) in DMF (2 mL). 2-Aminothiazole (74.1 mg, 749 μmol) was added and the resulting solution was stirred at ambient temperature for 72 h. The DMF was removed *in vacuo*, then the remainder was dissolved in EtOAc (50 mL) and washed with saturated aqueous Na_2CO_3 solution, H_2O, 1M HCl and brine, before being dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (IH–EtOAc, 9:1 to 17:3) furnished the title compound as a white solid (80 mg, 51%). ^{1}H NMR ($CDCl_3$) δ 6.98–7.05 (m, 2H), 7.23–7.26 (m, 1H), 7.29–7.33 (m, 1H), 7.38–7.46 (m, 3H), 7.60–7.65 (m, 3H), 8.32 (s, 1H), 8.57 (br s, 1H); m/z (ES$^+$) = 313 [M + H]$^+$.

(*E*)-2-(4-Methanesulfonylphenyl)-3-thiophen-2-ylacrylic acid (30). A mixture of 2-thiophenecarboxaldehyde (1.40 mL, 15.0 mmol), (4-methanesulfonylphenyl)-acetic acid (3.21 g, 15.0 mmol), and piperidine (0.44 mL, 4.4 mmol) in PhMe (21 mL) was heated under reflux with stirring for 15 h. On cooling, the PhMe was decanted off from the oily solid that had settled at the bottom of the reaction vessel. This solid was partitioned between 1 M HCl (60 mL) and EtOAc (250 mL), then the aqueous phase was extracted further with EtOAc (60 mL). The combined organic layers were washed with H_2O (60 mL), before being extracted with saturated aqueous Na_2CO_3 (3 × 100 mL). The combined aqueous extracts were washed with Et_2O (60 mL), before being filtered through Celite and carefully acidified with AcOH to adjust the pH to 4. The cream precipitate formed was collected, washed thoroughly with H_2O, and air-dried to furnished the title compound as a cream solid (1.26 g, 27%): ^{1}H NMR ($(CD_3)_2SO$) δ 3.24 (s, 3H), 7.00–7.08 (dd, J = 3, 5 Hz, 1H), 7.41 (d, J = 3 Hz, 1H), 7.50 (d, J = 8 Hz, 2H), 7.55 (d, J = 5 Hz, 1H), 7.99 (d, J = 8 Hz, 2H), 8.04 (s, 1H); m/z (ES$^+$)

= 634 $[2M + NH_4]^+$; Anal. Calcd for $C_{14}H_{12}O_4S_2$: C, 54.53; H, 3.92; S, 20.80; Found: C, 54.62; H, 3.91; S, 20.64.

(*E*)-2-(4-Methanesulfonylphenyl)-*N*-thiazol-2-yl-3-thiophen-2-ylacrylamide (5). A suspension of PS-carbodiimide (688 mg, loading 1.34 μmol/mg, 922 μmol), (*E*)-2-(4-methanesulfonylphenyl)-3-thiophen-2-ylacrylic acid (**30**, 139 mg, 450 μmol), and HOBt (82 mg, 607 μmol) in anhydrous DMF (10 mL) was stirred for 15 min at 20 °C. 2-Aminothiazole (32 mg, 320 μmol) was added, then the mixture was stirred for 16 h at 20 °C, before being filtered through Celite. The filter cake was washed with DMF (8 mL) and EtOAc (20 mL). The combined solvents were removed under reduced pressure, then the residue was dissolved in EtOAc (40 mL). The solution was washed with saturated aqueous Na_2CO_3 (2 × 20 mL), H_2O (20 mL), and brine (20 mL), before being dried ($MgSO_4$). Filtration, solvent evaporation, and flash chromatography (IH–EtOAc, 7:3 to 1:1) gave the title compound as a pale yellow solid (91 mg, 73%): ^{1}H NMR ($CDCl_3$) δ 3.20 (s, 3H), 6.97–7.02 (m, 2H), 7.22 (m, 1H), 7.33 (m, 1H), 7.40 (d, J = 4 Hz, 1H), 7.61 (d, J = 9 Hz, 2H), 8.18 (d, J = 9 Hz, 2H), 8.32 (s, 1H); m/z (ES^+) = 391 $[M + H]^+$; Anal. Calcd for $C_{17}H_{14}N_2O_3S_3$: C, 52.29; H, 3.61; N, 7.17; S, 24.63; Found: C, 52.02; H, 3.54; N, 6.79; S, 24.44.

(*E*)-2-(4-Methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic acid (7). Hexyllithium (2.3 M in hexane, 261 mL, 0.60 mol) was added over 30 min to a suspension of triphenyl(tetrahydropyran-4-ylmethyl)phosphonium iodide (**31**, 293 g, 0.60 mol) in anhydrous THF (1.2 L) at –5 to 0 °C under argon. The resulting mixture was stirred at 0 °C for 15 min, then at 20–25 °C for 2 h, before being recooled to 0 °C. A solution of (4-methylsulfanylphenyl)oxoacetic acid ethyl ester[2] (**6**, 112 g, 0.50 mol) in anhydrous THF (800 mL) was then added dropwise, the temperature being maintained at 0–5 °C. The reaction was stirred for 16 h at 20–25 °C, before being quenched with H_2O (500 mL). The phases were separated and the organic phase was concentrated under reduced pressure. The residue was dissolved in Et_2O (500 mL) and added back to the aqueous phase, before acidifying with 2M HCl. The aqueous layer was extracted with Et_2O (2 × 1 L) and the combined organic extracts were washed with brine (1 L), dried ($MgSO_4$) and concentrated under reduced pressure to

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(2) Creary, X. Reaction of organometallic reagents with ethyl trifluoroacetate and diethyl oxalate. Formation of trifluoromethyl ketones and α-keto esters via stable tetrahedral adducts. *J. Org. Chem.* **1987**, *52*, 5026–5030.

afford ethyl 2-(4-methylsulfanylphenyl)-3-(tetrahydropyran-4-yl)acrylate as a mixture of isomers: ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7 Hz, 1.71H), 1.27 (t, J = 7 Hz, 1.29H), 1.39–1.71 (m, 5H), 2.41 (s, 1.29H), 2.44 (s, 1.71H), 3.17–3.27 (m, 1.14H), 3.37–3.46 (m, 0.86H), 3.81–3.89 (m, 1.14H), 3.90–3.98 (m, 0.86H), 4.15 (q, J = 7 Hz, 1.14H), 4.26 (q, J = 7 Hz, 0.86 H), 5.90 (d, J = 10 Hz, 0.43H), 6.79 (d, J = 10 Hz, 0.57H), 7.03–7.08 (m, 1.14H), 7.13–7.24 (m, 2.86H); m/z (ES$^+$) = 307 [M + H]$^+$. To this crude product in CH_2Cl_2 (1.3 L) at 0 °C was added *m*CPBA (160 g, 0.92 mol) and the resulting mixture was stirred at 20–25 °C overnight. TLC indicated that the reaction had not gone to completion, so further *m*CPBA (70 g, 0.83 mol) was added portionwise until TLC showed that the reaction was complete. The reaction mixture was washed with saturated aqueous Na_2CO_3 solution (2 × 1 L) and brine (500 mL), then the solvent was removed under reduced pressure to afford ethyl 2-(4-methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylate as a mixture of isomers: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 1.71H), 1.30 (t, J = 7 Hz, 1.29H), 1.42–1.75 (m, 5H), 3.03 (s, 1.29H), 3.08 (s, 1.71H), 3.21–3.31 (m, 1.14H), 3.41–3.50 (m, 0.86H), 3.85–3.92 (m, 1.14H), 3.94–4.02 (m, 0.86H), 4.20 (q, J = 7 Hz, 1.14H), 4.30 (q, J = 7 Hz, 0.86 H), 6.08 (d, J = 10 Hz, 0.43H), 6.91 (d, J = 10 Hz, 0.57H), 7.37 (d, J = 8 Hz, 1.14H), 7.50 (d, J = 8 Hz, 0.86H), 7.88 (d, J = 8 Hz, 0.86H), 7.95 (d, J = 8 Hz, 1.14H); m/z (ES$^+$) = 339 [M + H]$^+$. To this crude product in MeOH (1.35 L), was added 2M NaOH (445 mL, 0.89 mol) and the resulting mixture was heated at 64–66 °C for 4 h. The MeOH was removed under reduced pressure, then the remainder was diluted with H_2O (600 mL), washed with EtOAc (2 × 1 L) and acidified with 5M HCl. The aqueous phase was extracted with EtOAc (8 × 500 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Recrystallisation from MeOH (1.2 L) afforded the title compound (71 g, 46%): ^{1}H NMR ($CDCl_3$) δ 1.48–1.57 (m, 2H), 1.60–1.71 (m, 2H), 2.29–2.41 (m, 1H), 3.14 (s, 3H), 3.25–3.37 (m, 2H), 3.92–3.99 (m, 2H), 7.09 (d, J = 11 Hz, 1H), 7.42 (d, J = 8 Hz, 2H), 8.01 (d, J = 8 Hz, 2H); m/z (ES$^+$) = 621 [2M + H]$^+$; Anal. Calcd for $C_{15}H_{18}O_5S$: C, 58.05; H, 5.85; S, 10.33; Found: C, 58.10; H, 5.75; S, 10.41.

2-(4-Methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (8). A mixture of (*E*)-2-(4-methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic acid (**7**, 1.46 g, 4.7 mmol) and 10% Pd on C (0.10 g, 0.94 mmol) in EtOAc (100 mL) was stirred under a H_2 atmosphere.

After 16 h, the reaction was filtered through Celite, washing with EtOAc. The combined filtrate and washings were concentrated to furnish the title compound (1.46 g, 100%): ^{1}H NMR ($(CD_3)_2SO$) δ 1.12–1.23 (m, 2H), 1.27–1.41 (br, 1H), 1.53–1.72 (m, 3H), 1.93–2.02 (m, 1H), 3.15–3.25 (m, 5H), 3.77–3.86 (m, 3H), 7.61 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H); m/z (ES$^+$) = 642.3 $[2M + NH_4]^+$; Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45; S, 10.26; Found: C, 57.45; H, 6.35; S, 9.99.

(*R*)-2-(4-Methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (9). NEt_3 (15.4 mL, 110 mmol) was added to a stirred suspension of 2-(4-methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propanoic acid (**8**, 30.0 g, 96.0 mmol) in anhydrous THF (300 mL) at 0 ºC. After 10 min, pivaloyl chloride (13.6 mL, 110 mmol) was added dropwise over 20 min and the mixture was stirred at 0 °C for 2 h. Meanwhile, *n*-BuLi (45.3 mL of a 2.5 M solution in hexanes, 115 mmol) was added to a solution of (*R*)-(+)-4-benzyl-2-oxazolidinone (20.4 g, 115 mmol) in anhydrous THF (300 mL) at –78 °C. The mixture was stirred at –78 °C to 20 °C over 2 h. The solution thus obtained was added dropwise to the abovementioned mixed anhydride solution at –78 °C. The reaction was stirred at –78 ºC for 1 h and then at 20 °C for 4 h, before being treated with H_2O (300 mL). The THF was removed *in vacuo*, then the remainder was extracted with EtOAc (3 × 300mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. (4*R*)-4-Benzyl-3-[(2*R*)-2-[4-(methylsulfonyl)phenyl]-3-(tetrahydro-2*H*-pyran-4-yl)propanoyl]-1,3-oxazolidin-2-one was obtained, along with the corresponding (4*R*,2*S*) diastereoisomer, following chromatographic separation (EtOAc–*n*-C_6H_{14}, 1:2 to 1:1): M.p. 139–141 °C (from Et_2O–THF); m/z (APCI$^+$) = 472 $[M + H]^+$. A solution of LiOH (1.5 g, 64 mmol) and 35% aqueous H_2O_2 (14.5 g, 128 mmol) in H_2O (400 mL) was added dropwise over 40 min to a stirred solution of (4*R*)-4-benzyl-3-[(2*R*)-2-[4-(methylsulfonyl)phenyl]-3-(tetrahydro-2*H*-pyran-4-yl)propanoyl]-1,3-oxazolidin-2-one (15.1 g, 10.9 mmol) in THF–H_2O (3:1, 1.6 L) at 0 ºC. The reaction was stirred at 0 °C for 1.5 h, then the remaining oxidant was destroyed with 10% aqueous Na_2SO_3. The mixture was washed with Et_2O (4 × 300 mL), acidified with 10% aqueous HCl, and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Trituration with Et_2O–hexanes gave the title compound: ^{1}H NMR ($CDCl_3$) δ 1.26–1.50 (m, 3H), 1.56–1.66 (m, 2H), 1.73–1.82 (m, 1H), 2.04–2.14 (m, 1H), 3.07 (s, 3H), 3.26–3.36 (m, 2H), 3.82 (t, $J = 8$ Hz, 1H), 3.90–3.99 (m, 2H), 7.54 (d, $J = 8$ Hz, 2H), 7.93 (d, $J = 8$ Hz, 2H); M.p. 217 °C; m/z (ES$^-$) = 267 $[M - \mathrm{H} - \mathrm{CO_2}]^-$; $[\alpha]_D^{20}$ –66.2 (c = 0.70, Me_2CO); Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45; S, 10.26; Found: C, 57.56; H, 6.35; S, 10.27.

2-(4-Methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)-*N*-thiazol-2-ylpropionamide (12). EDCI (80 mg, 420 μmol) and HOBt (57 mg, 420 μmol) were added to a stirred solution of 2-(4-methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (**8**, 100 mg, 320 μmol) in anhydrous DMF (5 mL). After 15 min, the solution was treated with 2-aminothiazole (38 mg, 380 μmol). The mixture was stirred at 20 °C for 16 h, before being concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and saturated aqueous Na_2CO_3. The organic layer was washed with 1 M HCl and dried ($MgSO_4$). Filtration and solvent evaporation yielded the title compound (80 mg, 63%): ^{1}H NMR ($CDCl_3$) δ 1.32–1.52 (m, 3H), 1.59–1.68 (m, 2H), 1.80–1.90 (m, 1H), 2.23–2.32 (m, 1H), 3.07 (s, 3H), 3.29–3.38 (m, 2H), 3.84–3.99 (m, 3H), 7.10 (d, $J = 4$ Hz, 1H), 7.51–7.54 (m, 3H), 7.90 (d, $J = 9$ Hz, 2H), 10.78 (br s, 1H); m/z (ES$^+$) = 436 [M + MeCN + H]$^+$; Anal. Calcd for $C_{18}H_{22}N_2O_4S_2$: C, 54.80; H, 5.62; N, 7.10; S, 16.25; Found: C, 54.56; H, 5.19; N, 6.60; S, 16.36.

(*E*)-2-(4-Methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)-*N*-thiazol-2-ylacrylamide (11). Prepared from (*E*)-2-(4-methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic acid (**7**) and 2-aminothiazole in 40% yield employing the procedure described above for **12**: ^{1}H NMR ($CDCl_3$) δ 1.41–1.53 (m, 2H), 1.58–1.73 (m, 2H), 2.12–2.27 (m, 1H), 3.19 (s, 3H), 3.22–3.34 (m, 2H), 3.88–3.98 (m, 2H), 7.03 (d, $J = 4$ Hz, 1H), 7.12 (d, $J = 11$ Hz, 1H), 7.41(d, $J = 4$ Hz, 1H), 7.50 (d, $J = 8$ Hz, 2H), 8.10 (d, $J = 8$ Hz, 2H), 8.54 (br s, 1H); m/z (ES$^+$) = 393 $[M + \mathrm{H}]^+$; Anal. Calcd for $C_{18}H_{20}N_2O_4S_2$: C, 55.08; H, 5.14; N, 7.14; S, 16.35; Found: C, 55.41; H, 5.03; N, 6.68; S, 16.58.

(2*R*)-3-(Tetrahydropyran-4-yl)-2-(4-methanesulfonylphenyl)-*N*-thiazol-2-ylpropionamide (13). Prepared by condensing (*R*)-2-(4-methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (**9**) with 2-aminothiazole hydrochloride in 65% yield employing the procedure described below for **26**: ^{1}H NMR ($CDCl_3$) δ 1.32–1.52 (m, 3H), 1.59–1.68 (m, 2H), 1.80–1.90 (m, 1H), 2.23–2.32 (m, 1H), 3.07 (s, 3H), 3.29–3.38 (m, 2H), 3.84–3.99 (m, 3H), 7.10 (d, $J = 4$ Hz, 1H), 7.51–7.54 (m, 3H), 7.90 (d, $J = 9$ Hz, 2H), 10.78 (br s, 1H); m/z (ES$^+$) = 436 [M + MeCN + H]$^+$; $[\alpha]_D^{23}$ –51.5 (c = 1.00, $CHCl_3$); Anal. Calcd for $C_{18}H_{22}N_2O_4S_2$: C, 54.80; H, 5.62; N, 7.10; S, 16.25; Found: C, 54.99; H, 5.59; N, 6.68; S, 16.56.

(*R*)-*N*-(5-Fluorothiazol-2-yl)-2-(4-methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionamide (15). NBS (5.42 g, 30.5 mmol) was added to a solution of PPh_3 (7.05 g, 26.9 mmol) in CH_2Cl_2 (180 mL) at –5 °C. After stirring at 0 °C for 5 min, (*R*)-2-(4-methanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (**9**, 5.60 g, 17.8 mmol) was added. The resulting solution was then stirred at 0 °C for 30 min, before being warmed to ambient temperature and stirred for a further 30 min. 2-Amino-5-fluorothiazole hydrochloride[3] (3.60 g, 23.3 mmol) and pyridine (3.69 g, 46.6 mmol) were added, then stirring was continued for 16 h at ambient temperature. The reaction mixture was diluted with Et_2O (500 mL), before being washed with H_2O (2 × 180 mL), 5% aqueous citric acid (3 × 150 mL), 2M Na_2CO_3 (150 mL, 50 mL) and brine (50 mL). After drying ($MgSO_4$), the organic extracts were filtered and concentrated in vacuo. The remainder was triturated with EtOAc, then the resulting white precipitate was removed by filtration. The filtrate was concentrated in vacuo, then the residue was purified by column chromatography (EtOAc) to afford the title compound (2.05 g, 28%): ^{1}H NMR ($CDCl_3$) δ 1.29–1.51 (m, 3H); 1.54–1.65 (m, 2H), 1.77–1.87 (m, 1H), 2.15–2.27 (m, 1H), 3.07 (s, 3H), 3.25–3.36 (m, 2H), 3.75–3.84 (m, 1H), 3.89–3.99 (m, 2H), 7.00–7.05 (m, 1H), 7.50 (d, $J = 8$ Hz, 2H), 7.91 (d, $J = 8$ Hz, 2H), 9.82 (br s, 1H); m/z (ES$^+$) = 454 [M + MeCN + H]$^+$; $[\alpha]_D^{25}$ –67.1 (c = 0.82, $CHCl_3$); Anal. Calcd for $C_{18}H_{21}FN_2O_4S_2$: C, 52.41; H, 5.13; N, 6.79; S, 15.55; Found: C, 52.73; H, 5.16; N, 6.42; S, 15.88.

Ethyl (4-cyclobutanesulfonylphenyl)oxoacetate (33). This compound was synthesized from cyclobutyl phenyl sulfide[4] in 22% overall yield using a procedure similar to that outlined for the corresponding cyclopropyl compound: ^{1}H NMR ($CDCl_3$) δ 1.37 (t, $J = 7$ Hz, 3H),

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(3) Briner, P. H.; Fyfe, M. C. T.; Martin, P.; Murray, P. J.; Naud, F.; Procter, M. J. Practical synthesis of 2-amino-5-fluorothiazole hydrochloride. *Org. Process Res. Dev.* **2006**, *10*, 346–348.

(4) Fyfe, M. C. T.; Rasamison, C. M. Reductive thiolation approach to pure cyclobutyl phenyl sulfide. *Org. Prep. Proced. Int.* **2005**, *37*, 194–197.

1.90–2.00 (m, 2H), 2.08–2.19 (m, 2H), 2.47–2.57 (m, 2H), 3.70–3.82 (m, 1H), 4.41 (q, *J* = 7 Hz, 2H), 7.94 (d, *J* = 7 Hz, 2H), 8.14 (d, *J* = 7 Hz, 2H); *m*/*z* (ES^+) = 314 [$M + NH_4$]$^+$.

(*E*)-2-(4-Cyclobutanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic acid (17). Prepared in 33% overall yield from triphenyl(tetrahydropyran-4-ylmethyl)phosphonium iodide (**31**) and ethyl (4-cyclobutanesulfonylphenyl)-oxoacetate (**33**) employing the procedure used for **16**: ^{1}H NMR (($CD_3)_2SO$) δ 1.35–1.50 (m, 4H), 1.84–2.01 (m, 2H), 2.08–2.23 (m, 3H), 2.28–2.44 (m, 2H), 3.10–3.21 (m, 2H), 3.70–3.80 (m, 2H), 4.14 (m, 1H), 6.82 (d, *J* = 10 Hz, 1H), 7.43 (d, *J* = 8 Hz, 2H), 7.83 (d, *J* = 8 Hz, 2H), 12.70–12.80 (br s, 1H).

(2*R*)-2-(4-Cyclobutanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (19). Prepared from (*E*)-2-(4-cyclobutanesulfonylphenyl)-3-(tetrahydropyran-4-yl)acrylic acid (**17**) in 64% yield (95.0% ee) using a procedure similar to that outlined for the corresponding cyclopropyl compound: ^{1}H NMR (($CD_3)_2SO$) δ 1.10–1.40 (m, 3H), 1.50–1.75 (m, 3H), 1.82–2.01 (m, 3H), 2.05–2.20 (m, 2H), 2.30–2.50 (m, 2H), 3.15–3.24 (m, 2H), 3.75–3.86 (m, 3H), 4.05–4.15 (m, 1H), 7.61 (d, *J* = 8 Hz, 2H), 7.82 (d, *J* = 8 Hz, 2H), 12.62 (s, 1H); *m*/*z* (ES^+) = 370.2 [$M + NH_4$]$^+$; $[\alpha]_D^{20}$ –50.6 (c = 0.53, Me_2CO); Anal. Calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86; S, 9.10; Found: C, 61.77; H, 6.83; S, 8.89.

(2*R*)-2-(4-Cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)-*N*-thiazol-2-ylpropionamide (24). Prepared by condensing (2*R*)-2-(4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (**18**) with 2-aminothiazole in 76% yield employing the procedure described above for **26**: ^{1}H NMR ($CDCl_3$) δ 1.02–1.08 (m, 2H), 1.27–1.66 (m, 7H), 1.80–1.90 (m, 1H), 2.23–2.32 (m, 1H), 2.44–2.52 (m, 1H), 3.23–3.35 (m, 2H), 3.89–3.99 (m, 3H), 7.13 (d, *J* = 4 Hz, 1H), 7.52–7.56 (m, 3H), 7.87 (d, *J* = 9 Hz, 2H); *m*/*z* (ES^+) = 421 [M + H]$^+$; $[\alpha]_D^{23}$ –53.7 (c = 1.03, $CHCl_3$); Anal. Calcd for $C_{20}H_{24}N_2O_4S_2$: C, 57.12; H, 5.75; N, 6.66; S, 15.25; Found: C, 56.89; H, 5.62; N, 6.59; S, 14.86.

(2*R*)-2-(4-Cyclopropanesulfonylphenyl)-*N*-(5-methylthiazol-2-yl)-3-(tetrahydropyran-4-yl)propionamide (25). Prepared by condensing (2*R*)-2-(4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (**18**) with 2-amino-5-methylthiazole in 62% yield employing the procedure described above for **26**: ^{1}H NMR ($CDCl_3$) δ 0.90–1.00 (m, 2H), 1.18–1.40 (m, 5H), 1.50–1.60 (br, 2H), 1.70–1.80 (m, 1H), 2.10–2.22 (m, 1H), 2.30–2.40 (m, 4H), 3.18–3.27 (m, 2H), 3.79–3.88 (m, 3H), 7.05 (d, *J* = 1 Hz, 1H), 7.40 (d, *J* = 7 Hz, 2H), 7.74 (d, $J = 7$ Hz, 2H); m/z (ES^+) = 435 $[M + H]^+$; Anal. Calcd for $C_{21}H_{26}N_2O_4S_2$: C, 58.04; H, 6.03; N, 6.45; S, 14.76; Found: C, 57.71; H, 6.01; N, 6.29; S, 14.20.

(2*R*)-2-(4-Cyclobutanesulfonylphenyl)-*N*-(5-fluorothiazol-2-yl)-3-(tetrahydropyran-4-yl)propionamide (27). Prepared by condensing (2*R*)-2-(4-cyclobutanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (**19**) with 2-amino-5-fluorothiazole hydrochloride[3] in 87% yield employing the procedure described above for **26**: ^{1}H NMR ($CDCl_3$) δ 0.80–0.90 (m, 2H), 1.25–1.45 (m, 3H), 1.50–1.65 (m, 2H), 1.75–1.85 (m, 1H) 1.95–2.05 (m, 2H), 2.15–2.25 (m, 1H), 2.50–2.62 (m, 2H), 3.23–3.32 (m, 2H), 3.75–3.95 (m, 4H), 7.00 (d, $J = 3$ Hz, 1H), 7.45 (d, $J = 8$ Hz, 2H), 7.81 (d, $J = 8$ Hz, 2H), 9.73 (br s, 1H); m/z (ES^+) = 494 $[M + MeCN + H]^+$; Anal. Calcd for $C_{21}H_{25}FN_2O_4S_2$: C, 55.73; H, 5.57; N, 6.19; S, 14.17; Found: C, 55.40; H, 5.91; N, 5.61; S, 13.96.

Ethyl (4-cyclopentylsulfanylphenyl)acetate (34). 2M NaOH (100 mL, 0.200 mol) was added over 30 min to a stirred solution of ethyl (4-mercaptophenyl)acetate[5] (**21**, 25.5 g, 0.130 mol) and bromocyclopentane (22.4 g, 0.149 mol) in EtOH (150 mL). After 16 h at 20 °C, the reaction was diluted with H_2O (200 mL), before being extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to afford a yellow oil that was purified by column chromatography (n-C_7H_{16}/EtOAc, 9:1) to afford the title compound (28.6 g, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, $J = 7$ Hz, 3H), 1.52–1.70 (m, 4H), 1.72–1.88 (m, 2H), 1.96–2.13 (m, 2H), 3.53–3.62 (m, 3H), 4.15 (q, $J = 7$ Hz, 2H), 7.19 (d, $J = 8$ Hz, 2H), 7.31 (d, $J = 8$ Hz, 2H).

(4-Cyclopentylsulfanylphenyl)acetic acid (35). A solution of ethyl (4-cyclopentylsulfanylphenyl)acetate (**34**, 27.5 g, 0.104 mol) in EtOH (200 mL) was treated with 2M NaOH (200 mL, 0.400 mol) to afford an emulsion that was stirred overnight at room temperature. The EtOH was distilled off *in vacuo* (120 mbar, 50 °C), then the resulting turbid solution was acidified with 6M HCl to afford an oil. This oil was triturated to give a crystalline material that was collected by filtration, washed with H_2O and dried (125 mbar, 40 °C) to afford the title compound (23.4 g, 95%) as colorless crystals: ^{1}H NMR ($CDCl_3$) δ

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(5) Gadient, F. Verfahren zur herstellung neuer heterocyclischer verbindungen. *Ger. Offen.* 2,442,979 (*Chem. Abstr.* **1975**, *83*, 43212).

1.51–1.69 (m, 4H), 1.71–1.86 (m, 2H), 1.93–2.10 (m, 2H), 3.52–3.61 (m, 3H), 7.18 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H); *m*/*z* (ES^-) = 235 $[M - H]^-$.

2-(4-Cyclopentylsulfanylphenyl)-*N*-((1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylacetamide (22). A mixture of (4-cyclopentylsulfanylphenyl)-acetic acid (**35**, 13.16 g, 0.050 mol) in THF (130 mL) and CDI (10.0 g, 0.060 mol) was stirred at ambient temperature until the liberation of gas ceased. Then, (1*R*,2*R*)-(–)-pseudoephedrine (8.26 g, 0.050 mol) was added, and the mixture was stirred overnight at 20 °C. The solvents were removed under reduced pressure, then the residue was dissolved in EtOAc. The solution was washed with dilute aqueous citric acid, H_2O and aqueous $NaHCO_3$, before being dried ($MgSO_4$), filtered, and concentrated to afford the title compound (15.2 g, 0.040 mol, 80% yield) as colourless crystals: ^{1}H NMR ($CDCl_3$, 27 °C) δ 0.82 (d, *J* = 7 Hz, 0.8H), 1.12 (d, *J* = 7 Hz, 2.2H), 1.55–1.70 (m, 4H), 1.75–1.90 (m, 2H), 1.95–2.15 (m, 2H), 2.81 (s, 2.2H), 2.94 (s, 0.8H), 3.50–4.10 (m, 4H), 4.40–4.65 (m, 2H), 7.07 (d, *J* = 7 Hz, 1.5H), 7.15 (d, *J* = 7 Hz, 0.5H), 7.20–7.40 (m, 7H); *m*/*z* (ES^+) = 384 $[M + H]^+$.

(*R*)-2-(4-Cyclopentanesulfonylphenyl)-*N*-((1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-3-(tetrahydropyran-4-yl)propionamide (23). LDA (57 mL of a 2M solution in *n*-C_7H_{16}/THF/PhEt, 0.114 mol) was added over 10 min to a stirred solution of 2-(4-cyclopentylsulfanylphenyl)-*N*-((1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylacetamide (**22**, 14.6 g, 0.038 mol) in anhydrous THF (150 mL) at –60 °C. After 15 min at –60°C, a solution of 4-iodomethyltetrahydropyran (8.6 g, 0.038 mol) in THF (15 mL) was added dropwise, then the stirred reaction mixture was allowed to warm to ambient temperature overnight. The reaction was concentrated under reduced pressure, before being diluted with aqueous citric acid and extracted with *t*-BuOMe (2 × 250 mL). The organic extracts were washed with H_2O (2 × 50 mL) and brine, before being dried ($MgSO_4$), filtered and concentrated. A portion of this crude thioether (11.0 g, 0.019 mol) was dissolved in EtOH (100 mL), then H_2O (65 mL) and magnesium monoperoxyphthalate hexahydrate (80%, 15.4 g, 0.025 mol) were added. The resulting fine suspension was stirred for 30 min at ambient temperature, before being heated up to 80 °C. After 1 h, the reaction was cooled down to room temperature and concentrated under reduced pressure to ca. 50 mL, before being diluted with H_2O (50 mL) and saturated aqueous $NaHCO_3$ (25 mL). The mixture was extracted with *t*-BuOMe (3 × 100 mL), then the combined organic extracts were washed with H_2O (2 × 50 mL) and brine (25 mL), before being dried ($MgSO_4$). Filtration, solvent evaporation, and column chromatography (CH_2Cl_2–EtOAc, 2:1) yielded the title compound (8.7 g, 89%) as a colorless foam: ^1H NMR ($CDCl_3$, 27 °C) δ 0.55 (d, $J = 7$ Hz, 1.2H), 1.14 (d, $J = 7$ Hz, 1.8H), 1.18–2.25 (m, 15H), 2.75 (s, 1.8H), 2.92 (s, 1.2H), 3.20–3.52 (m, 3H), 3.75–3.95 (m, 3H), 4.00–4.63 (m, 3H), 7.18–7.44 (m, 7H), 7.75–7.83 (m, 2H); *m*/*z* (ES^+) = 514 $[M + H]^+$.

(2*R*)-2-(4-Cyclopentanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (20). 12M HCl (100 mL) was added to a stirred solution of (*R*)-2-(4-cyclopentanesulfonylphenyl)-*N*-((1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-3-(tetrahydropyran-4-yl)propionamide (**23**, 4.3 g, 8.3 mmol) in dioxane (25 mL) at 100 °C. After 3.5 h at 100 °C, the reaction was allowed to cool to ambient temperature, then the dioxane was removed under reduced pressure. The precipitate was collected, washed with H_2O (2 × 50 mL), and dried (40 °C, 100 mbar) to furnish the product as white powder (2.7 g, 90.0% e.e.). This material was recrystallized five times from *i*-BuOAc to furnish the title compound (1.7 g, 57% yield, 95.0% e.e.): ^1H NMR ($CDCl_3$) δ 1.20–2.15 (m, 15H), 3.25–3.39 (m, 2H), 3.42–3.56 (m, 1H), 3.82 (t, $J = 8$ Hz, 1H), 3.90–4.00 (m, 2H), 7.51 (d, $J = 8$ Hz, 2H), 7.87 (d, $J = 8$ Hz, 2H); *m*/*z* (ES^-) = 731 $[2M - H]^-$; $[\alpha]_D^{20}$ –57.1 (c = 0.64, Me_2CO, 20 °C); Anal. Calcd for $C_{19}H_{26}O_5S$: C, 62.27; H, 7.15; S, 8.75; Found: C, 62.39; H, 7.09; S, 9.01.

(2*R*)-2-(4-Cyclopentanesulfonylphenyl)-*N*-(5-fluorothiazol-2-yl)-3-(tetrahydropyran-4-yl)propionamide (28). Prepared by condensing (2*R*)-2-(4-cyclopentanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (**20**) with 2-amino-5-fluorothiazole hydrochloride[3] in 56% yield employing the procedure described above for **26**: ^1H NMR ($CDCl_3$) δ 1.20–1.47 (m, 3H), 1.52–1.70 (m, 4H), 1.70–1.95 (m, 5H), 1.99–2.09 (m, 2H), 2.15–2.25 (m, 1H), 3.20–3.31 (m, 2H), 3.43–3.57 (m, 1H), 3.80–3.98 (m, 3H), 7.01 (d, $J = 3$ Hz, 1H), 7.51 (d, $J = 8$ Hz, 2H), 7.84 (d, $J = 8$ Hz, 2H); *m*/*z* (ES^+) = 508 $[M + MeCN + H]^+$; Anal. Calcd for $C_{22}H_{27}FN_2O_4S_2$: C, 56.63; H, 5.83; N, 6.00; S, 13.74; Found: C, 56.62; H, 5.83; N, 5.68; S, 13.41.

Enzyme assay. GK activity was measured in a coupled reaction with glucose-6-phosphate dehydrogenase (G6PDH) by monitoring NADPH production at A_{340} in a Molecular Device SpectraMax 190 plate reader after 15 min incubation at 24 °C, in a final volume of 100 μL containing 25 mM Hepes pH7.1, 25 mM KCl, 5 mM glucose, 1 mM ATP, 2 mM $MgCl_2$, 1 mM DTT, 1 mM NADP, 2.5 U/mL G6PDH, and 0.4 μg GST-GK. 10 dilutions of test article from 0.004 to 100 μM were tested and fold changes in activity versus controls calculated and fitted to sigmoidal curves using a 4-parameter logistic model.

Plasma compound concentrations. Compounds were dosed orally in 10% aqueous Gelucire 44/14 to three C57Bl/6 mice. Following terminal anesthesia, blood (500–600 μL) was collected, via the abdominal aorta, from the animals 30 min after dosing into heparin/Li containing tubes and kept on ice (<30 min), before centrifugation (2800 × *g*, 10 min, 4 °C), and storage at –20 °C for subsequent compound measurement. For intravenous administration to cannulated, male Sprague–Dawley rats (*n* = 3), **26** was administered at 1 mg/1 mL/kg in 40% DMSO–60% saline. Blood samples (200–500 μL) were collected from the jugular vein catheter into heparin/Li containing tubes at the following timepoints: 0, 5, 15, 30, 60, 120, 240, 360, and 1440 min. The samples were mixed gently, then kept on ice and centrifuged at 2000 × *g* for 10 min at 4 °C within 30 min of collection. The plasma was then harvested and kept frozen at –20 °C until further processing. Orally administered **26** was given to cannulated, male Sprague–Dawley rats (*n* = 3) at 5 mg/10 mL/kg, then plasma was isolated, as described above, at the following timepoints: 0, 15, 30, 60, 120, 240, 360, 480 and 1440 min.

Aliquots (50 μL) of plasma calibration standards, quality controls, unknown samples and blanks were placed into a 96-well protein precipitation plate (Argonaut Technologies, Hengoed, Mid-Glamorgan, UK). The plate was placed on a vacuum manifold over a 96 well, 1 mL collection plate and MeCN (200 μL) added to each well. The plate was left for precipitation to occur and supernatants to drip through under gravity for 10 min. Vacuum was applied and the block removed and centrifuged (3000 *g*, 10 min) prior to injection onto an LC/MS/MS system, comprising a HIRPB (Hichrom, Theale, Berkshire, UK), 50 × 2.1 mm column and mobile phase of MeCN/10mM ammonium formate, flow rate 0.25 mL/min. The Micromass Quattro Micro spectrometer was fitted with an electrospray ionization interface. Compounds were detected by selected reaction monitoring (SRM) of daughter ions in negative ion mode.

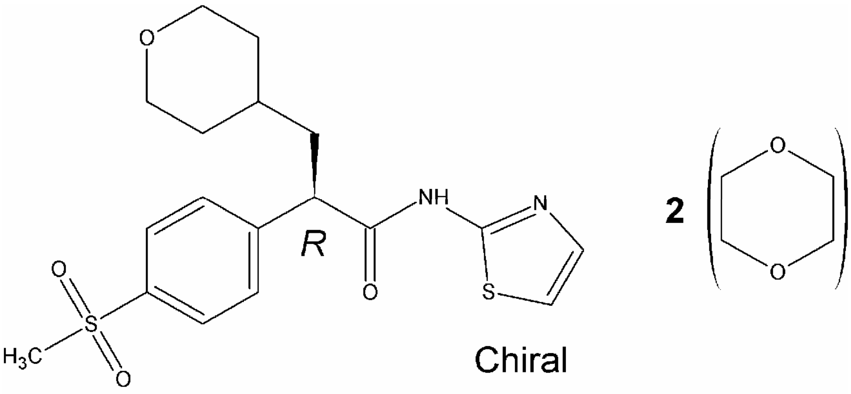
Blood glucose lowering in rats. Male Sprague–Dawley rats were mildly fasted by granting them access to only 50% of their daily energy requirements during the 16 h before the experiment began. A blood sample was taken from the tail tip under local anesthetic for glucose and insulin measurement. Thereafter, rats (*n* = 8/group) were weighed and dosed orally with **26** (10 mg/5 mL/kg) or vehicle (10% aqueous Gelucire 44/14). Blood samples were taken into heparin tubes 15, 30, 60, 120, 180, and 360 min after dosing. Plasma glucose levels were measured on an automated analyzer (Vitros 250, Johnson and Johnson), while plasma insulin was measured using an ultra-sensitive ELISA method (Diamyd diagnostics, Sweden). A satellite PK study was also carried out, where blood samples from three rats (ca. 350 μL) were taken at the same timepoints and were processed as described above.

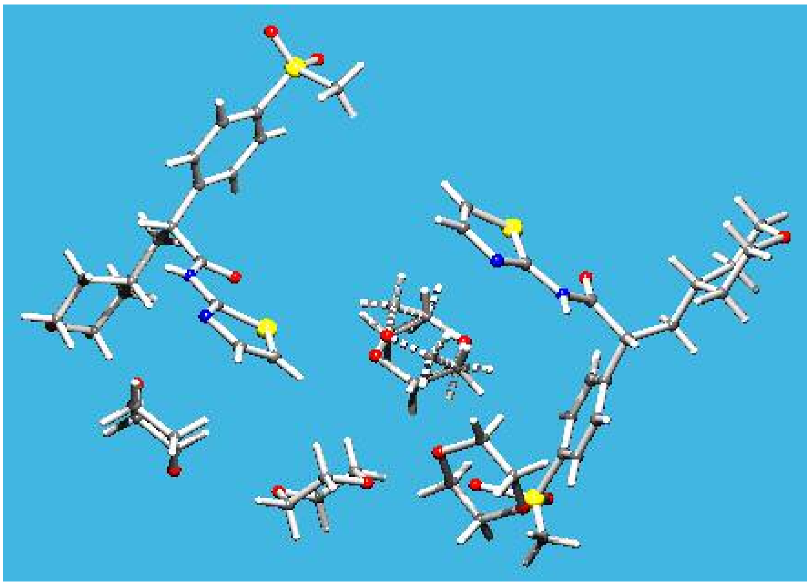
Catalogue of Combustion Analysis Data for Glucokinase Activators

		Calculated				Found			
Cmpd	**Formula**	**C**	**H**	**N**	**S**	**C**	**H**	**N**	**S**
3	$C_{17}H_{13}N_3OS$	66.43	4.26	13.67	10.43	66.24	4.36	13.51	10.29
5	$C_{17}H_{14}N_2O_3S_3$	52.29	3.61	7.17	24.63	52.02	3.54	6.79	24.44
11	$C_{18}H_{20}N_2O_4S_2$	55.08	5.14	7.14	16.35	55.41	5.03	6.68	16.58
12	$C_{18}H_{22}N_2O_4S_2$	54.80	5.62	7.10	16.25	54.56	5.19	6.60	16.36
13	$C_{18}H_{22}N_2O_4S_2$	54.80	5.62	7.10	16.25	54.99	5.59	6.68	16.56
15	$C_{18}H_{21}FN_2O_4S_2$	52.41	5.13	6.79	15.55	52.73	5.16	6.42	15.88
24	$C_{20}H_{24}N_2O_4S_2$	57.12	5.75	6.66	15.25	56.89	5.62	6.59	14.86
25	$C_{21}H_{26}N_2O_4S_2$	58.04	6.03	6.45	14.76	57.71	6.01	6.29	14.20
26	$C_{20}H_{23}FN_2O_4S_2$	54.78	5.29	6.39	14.62	54.21	5.41	5.99	14.60
27	$C_{21}H_{25}FN_2O_4S_2$	55.73	5.57	6.19	14.17	55.40	5.91	5.61	13.96
28	$C_{22}H_{27}FN_2O_4S_2$	56.63	5.83	6.00	13.74	56.62	5.83	5.68	13.41

Crystal Structure and Absolute Stereochemistry Determination of 13 bis-1,4-dioxanate

2-D ISIS Draw and 3-D ball and stick representations





Structural features

- Crystals of **13** suitable for single crystal X-ray diffraction (SXRD) were prepared by the following procedure: 20 mg of **13** was dissolved in up to 1 mL of solvent for each of the 8 solvents listed in Table S1. Upon full dissolution, the solvent was allowed to evaporate to induce precipitation. Maturation experiments were carried out in two further solvents, aiming to induce crystallisation of amorphous **13**. The maturation method was heat cycling (4 h at 50 °C, 4 h at ambient conditions) of an excess of **13** in solvent with continuous stirring (Table S1).

- **13** precipitated from 1,4-dioxane as spherulites of large lath shaped crystals, which were suitable for SXRD (Figure S1). The other nine crystallisations produced amorphous precipitate.
- The crystal structure of **13** is that of the bis-1,4-dioxane solvate of the **13** free base (see 2D diagram above).
- The asymmetric unit contains two independent fully ordered molecules of **13**, henceforth referred to as molecule **A** (Figure S2) and molecule **B** (Figure S3), and four molecules of 1,4-dioxane, one of which is disordered, with the remaining three solvate molecules fully ordered.
- Final R1 $[I>2\sigma(I)] = 6.25\%$.
- The Flack parameter for the structure has been determined as 0.00(10), and 1.14(10) for the inverted structure. On the basis of the former determination the absolute stereochemistry has been assigned as the *R*-enantiomer for both molecules **A** and **B**.
- The determination of the absolute structure using Bayesian statistics on Bijvoet differences reveals that the probability of the absolute structure being correct is 1.000, while the probability of the absolute structure being false or a racemic twin is 0.000. The Flack equivalent and its uncertainty are calculated through this program to be –0.03(3). See Figure S4b.
- The mean plane for the amide group in molecule **A**, O1A N2A C3A C4A C5A, was calculated giving a root mean square deviation (RMSD) from planarity of 0.0280 Å. Atom N2A deviated most from the plane, by –0.036(3) Å. The corresponding functional group in molecule **B**, O1B N2B C3B C4B C5B, gave an RMSD of 0.0310 Å with a maximum deviation of –0.040(3) Å for N2B.
- The mean plane of the 5-membered thiazolyl ring, S1 N1 C1 C2 C3, was calculated for both molecules. Molecule **A** gave an RMSD of 0.0014 Å with maximum deviation for C3A of –0.002(3) Å. Molecule **B** gave an RMSD of 0.0051 Å with maximum deviation for N1B of 0.008(3) Å. The angle between the amide plane and the thiazolyl

ring plane is very similar in both molecules: 3.1(1) ° for molecule **A** and 3.74(4) ° for molecule **B.**

- The mean plane of the phenyl ring, C6 C7 C8 C9 C10 C11, was calculated for both molecules. Molecule **A** gave an RMSD of 0.0040 Å with a maximum deviation of 0.006(4) Å for C9A. Molecule **B** gave an RMSD of 0.0103 Å with a maximum deviation of –0.017(4) Å for C6B.
- The pyranose ring in both molecules **A** and **B** adopt the chair conformation, and all four symmetry-independent 1,4-dioxane molecules also adopt the chair conformation.
- The root mean square deviation overlay of the non-hydrogen atoms (excluding C12, O2 and O3) in the two **13** molecules **A** and **B** gives a value of 0.273 Å, showing that there is no gross difference in the conformations of the two molecules (Figure S5). The orientation of the methane sulfonate groups in molecules **A** and **B** differ significantly, as exemplified by the equivalent torsion angles C12A–S2A–C9A–C10A = –19.7(5) ° and C12B–S2B–C9B–C8B = 78.9(5) °, which have a 99 ° difference. The angle of the phenyl ring with respect to the rest of the molecule varies by 22 ° between molecules **A** and **B**, calculated from the equivalent torsion angles C4A-C5A-C6A-C7A = 62.3 (5) ° and C4B-C5B-C6B-C11B = 84.6(5) °.
- Three of the 1,4-dioxane molecules are fully ordered and adopt chair conformations. The fourth 1,4-dioxane molecule shows disorder in one half of the chair. Three of the atoms, C1F, O1F, C4F, are ordered, while C2F, O2F, C3F are split over two sites (Figure S4). While atoms C1F and C4F are not disordered their hydrogen positions are modelled over two sites to reflect the differing geometry at these atoms due to the disorder in the adjacent carbon atom. The disorder ratio between the two sites is 0.476(7) (Table S10). The disorder is well modelled using this two-site model, with no significant residual electron density peaks.
- There are no further unusual structural features.
- Figure S6 shows the two N–H···N hydrogen bonds that occur in the crystal structure forming a $R^{2}_{2}(8)$ hydrogen bonded ring between molecule **A** and molecule **B** in the

asymmetric unit. These discrete dimer units then pack to give the overall crystal structure, with the voids in the structure filled with the 1,4-dioxane molecules. There are no other strong hydrogen bonds in the crystal structure

- Figure S7 shows the roles that the four symmetry-independent 1,4-dioxane molecules fulfil within the crystal structure. The two **13** molecules are shown in green (**A**) and blue (**B**). 1,4-Dioxane molecule **C** (dark grey) packs in a channel parallel to the crystallographic *a*-axis; 1,4-dioxane molecule **D** (yellow) packs between the pyranose rings of molecule **A**; 1,4-dioxane molecule **E** (purple) packs between the phenyl rings of molecule **A** and 1,4-dioxane molecule **F** (black) packs between the phenyl rings of molecule **B**. Consequently 1,4-dioxane molecules **D, E** and **F** are located on isolated sites, and molecule **C** is located in a channel.
- Figure S8 shows the observed and calculated XRPD patterns. The patterns from the material as crystallised and calculated from the single crystal X-ray structure are shown in the red and black traces respectively. The two diffractograms match well, with no peaks present in the bulk experimental XRPD diffractogram that does not have a corresponding peak in the XRPD diffractogram simulated from the single crystal structure. It should be noted that there is a small temperature shift owing to the fact that the experimental XRPD data were collected at room temperature and the calculated pattern is on a structure at 180K, which has been corrected for in the pattern derived from the single crystal X-ray structure.

Supplementary Figures and Tables

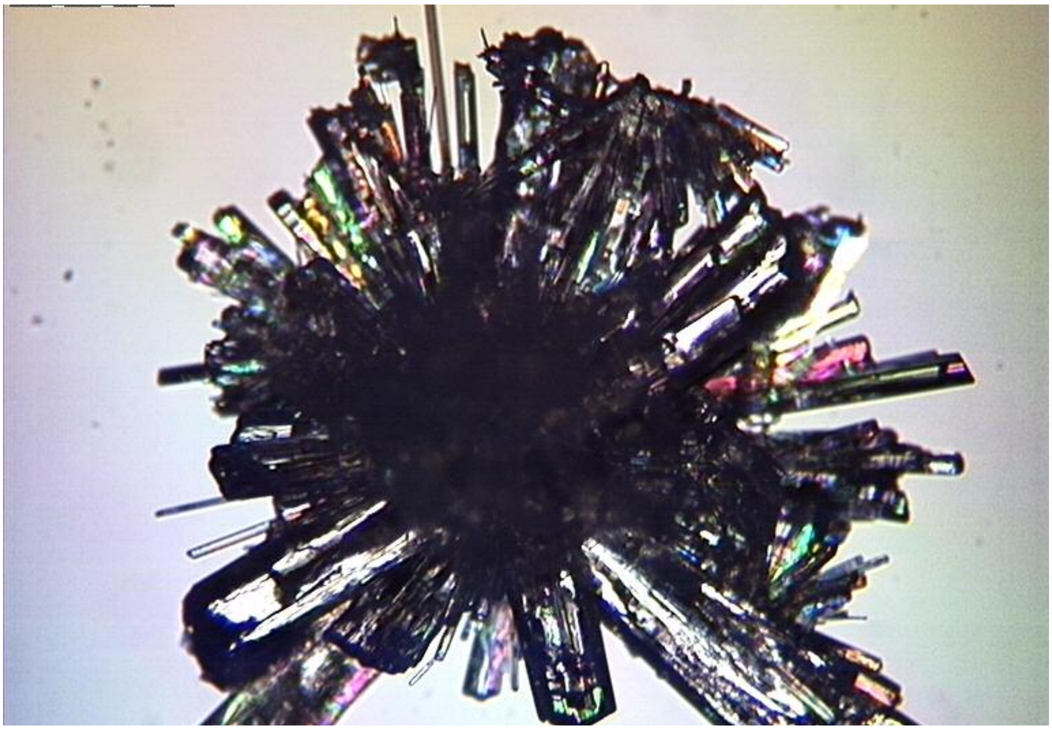


Figure S1. Optical photomicrograph of a spherulite of crystals of **13**·(dioxane)$_2$ viewed with crossed polarisers. The individual crystals exhibit lath morphology

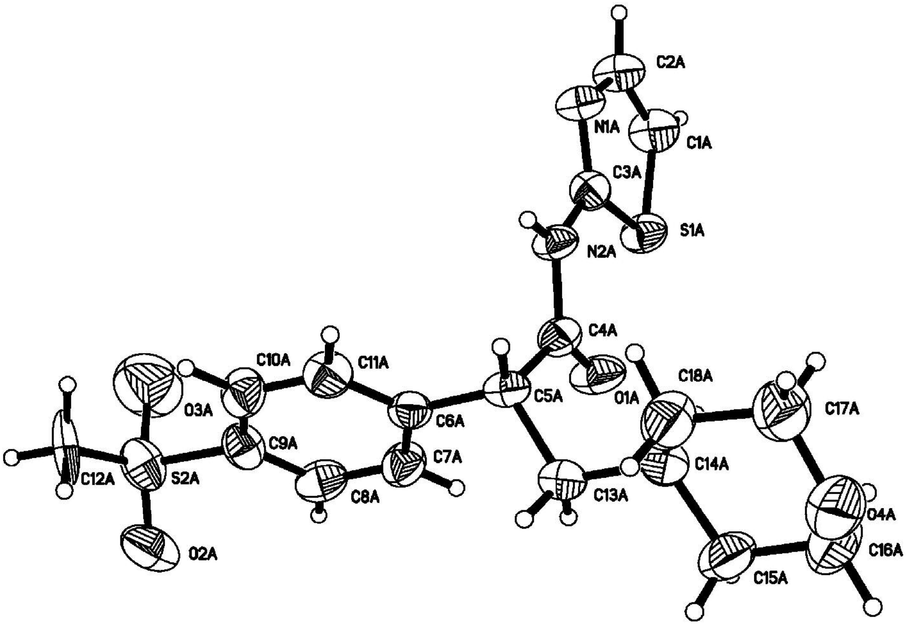


Figure S2. A view of molecule **A** of **13** from the crystal structure showing the numbering scheme employed. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed as spheres with an arbitrarily small radius.

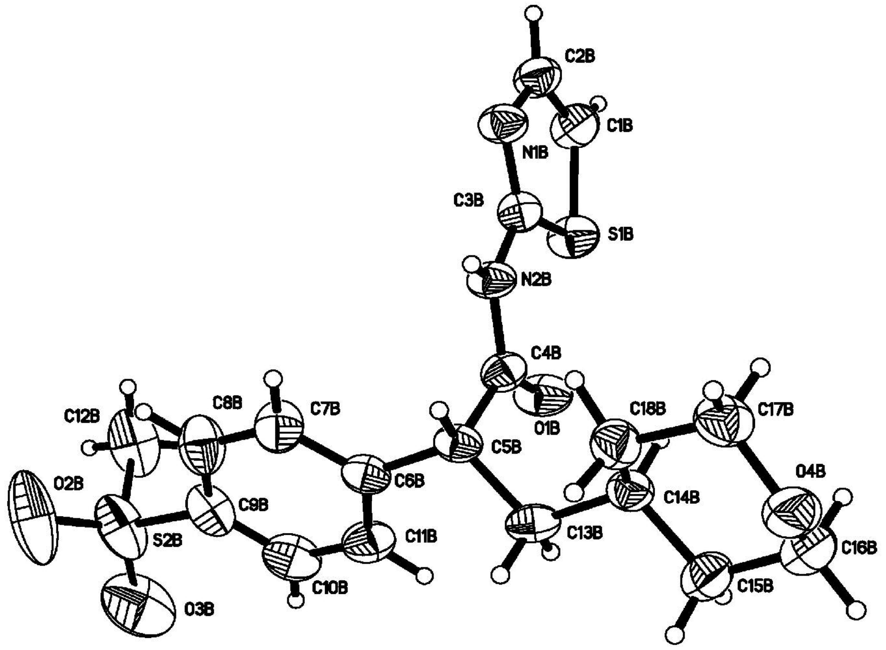


Figure S3. A view of molecule **B** of **13** from the crystal structure showing the numbering scheme employed. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed as spheres with an arbitrarily small radius.

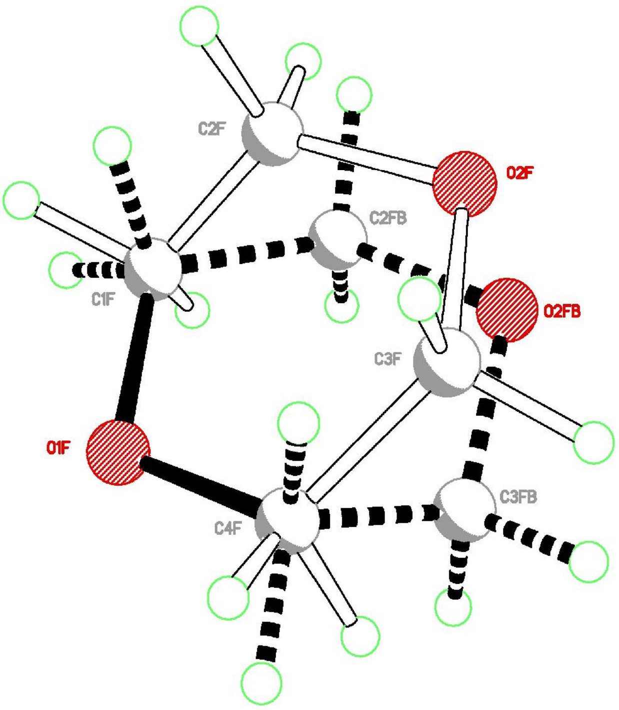
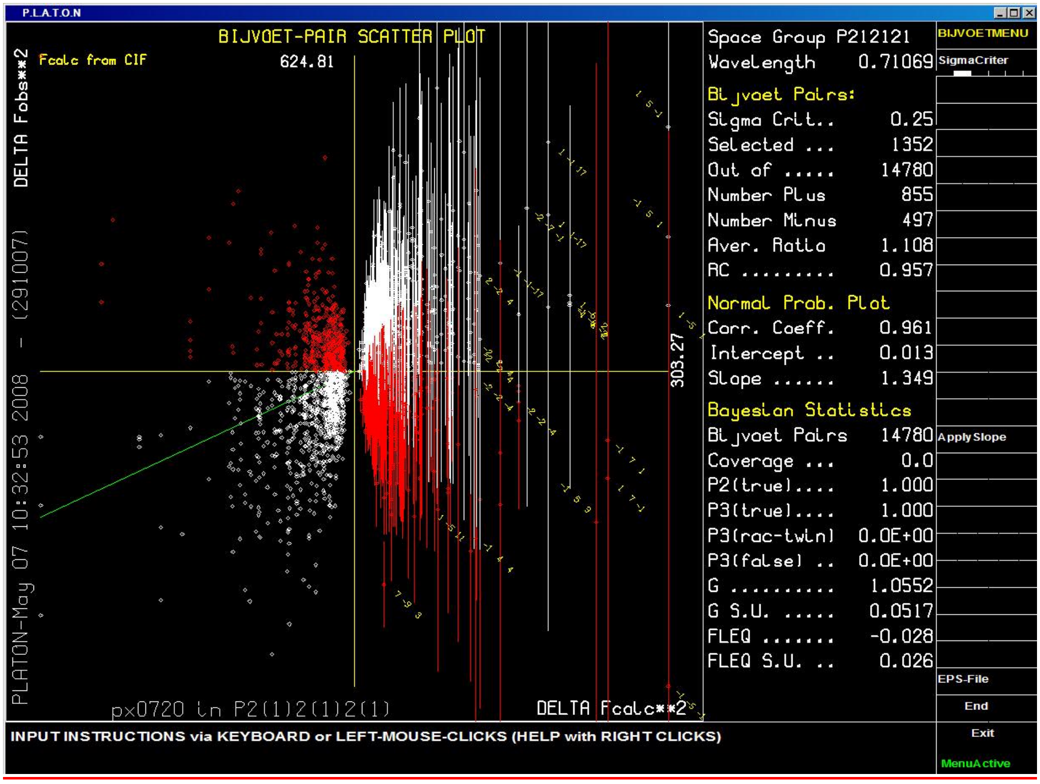


Figure S4. A view of the disordered 1,4-dioxane molecule. Atoms C2F/C2FB, O2F/O2FB, C3F/C3FB are disordered. Atoms C1F and C4F are not disordered, but their hydrogen positions are modelled as disordered.



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Wavelength     0.71069
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Sigma Crit..      0.25
Selected ...      1352
Out of .....     14780
Number Plus        855
Number Minus       497
Aver. Ratio      1.108
RC .........     0.957
Normal Prob. Plot
Corr. Coeff.     0.961
Intercept ..     0.013
Slope ......     1.349
Bayesian Statistics
Bijvoet Pairs    14780
Coverage ...       0.0
P2(true)....     1.000
P3(true)....     1.000
P3(rac-twin)  0.0E+00
P3(false) ..  0.0E+00
G ..........    1.0552
G S.U. .....    0.0517
FLEQ .......    -0.028
FLEQ S.U. ..     0.026
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Figure S4b. Results from the determination of the absolute structure using Bayesian statistics on Bijvoet differences

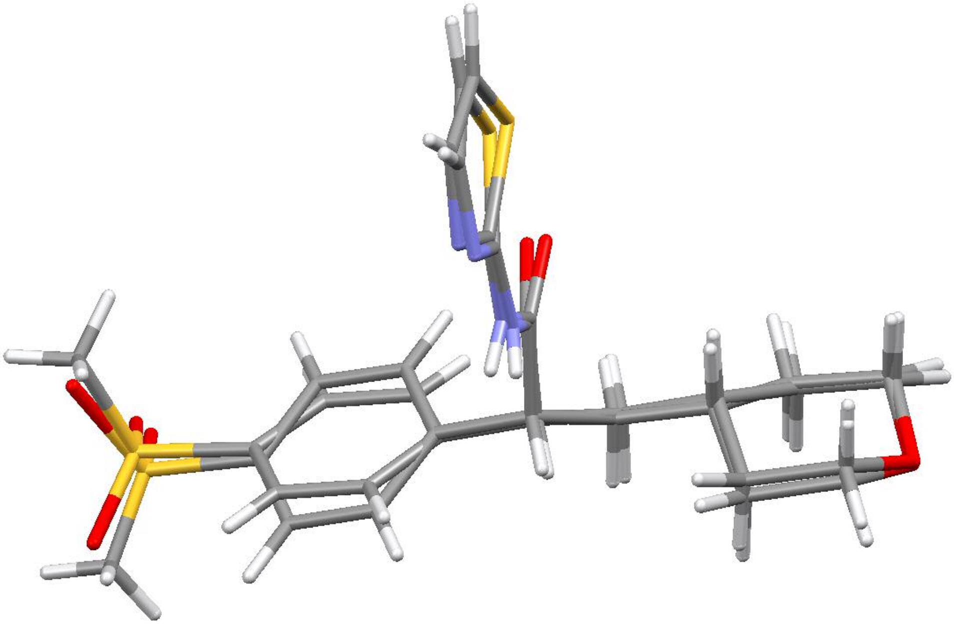

Figure S5. RMSD overlay of the two symmetry independent molecules in the **13** crystal structure. Significant variation is evident in the phenyl ring angle and the orientation of the methane sulfonate group.

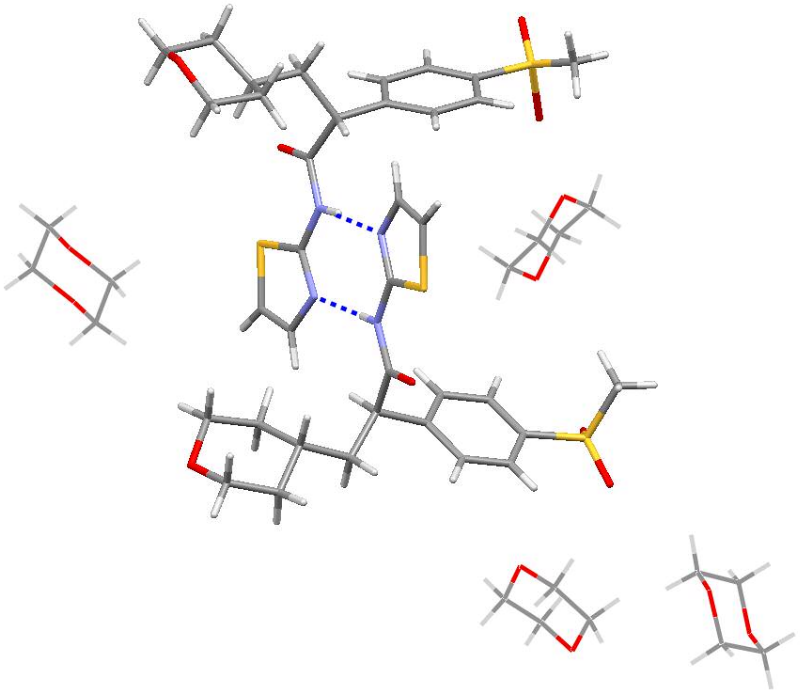

Figure S6. Hydrogen bonded dimer formed between the two symmetry-independent **13** molecules in the asymmetric unit. 1,4-Dioxane disorder not shown.

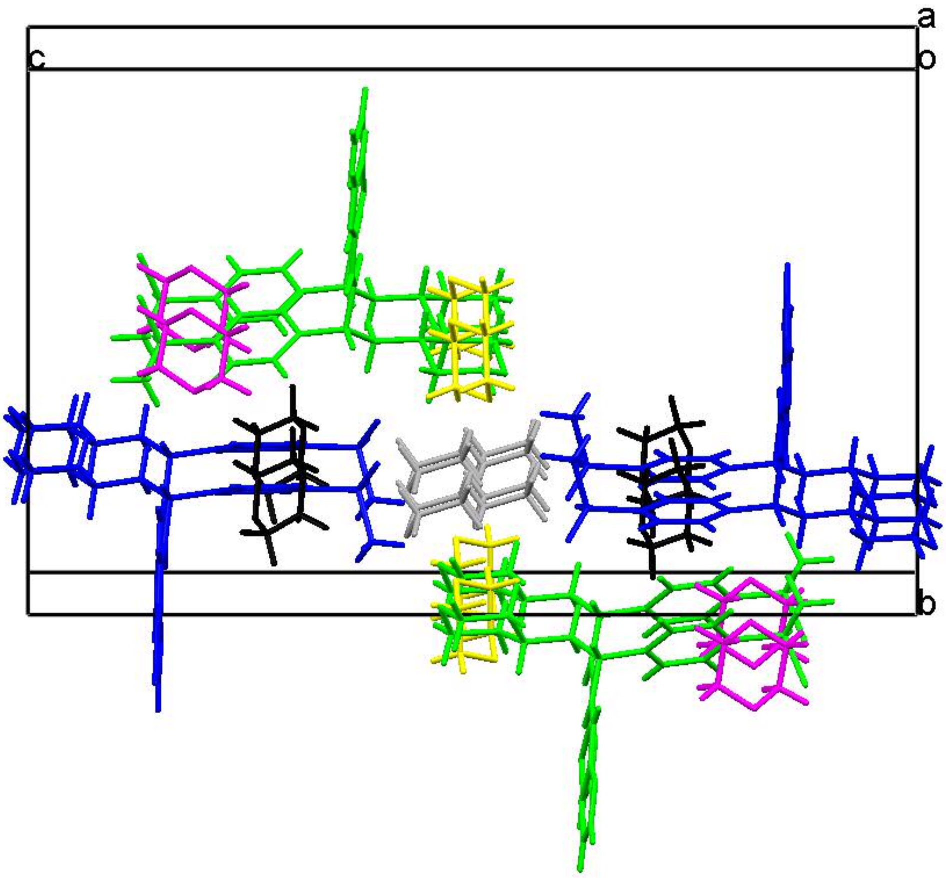

Figure S7. Packing of solvent in the crystal structure. **13** molecule A (green); **13** molecule B (blue); 1,4-dioxane molecule C (dark grey); 1,4-dioxane molecule D (yellow); 1,4-dioxane molecule E (purple); 1,4-dioxane molecule F (black)

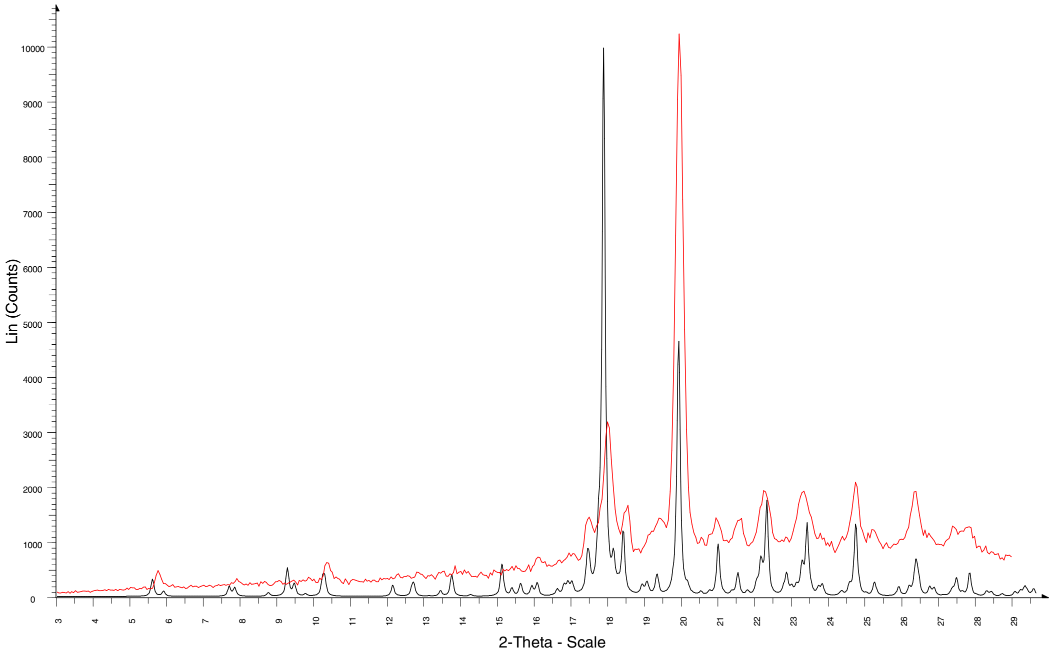

Figure S8. Observed and calculated XRPD patterns. The calculated XRPD diffractogram from the single crystal structure reported is shown in black and the experimental XRPD diffractogram in red.

Table S1. Summary of crystallisations attempted on **13**, detailing solvents, solvent volumes, and precipitate identity.

Entry	**Solvent**	**Solvent Vol. (μL)**	**Technique**	**Precipitate**
1	Me_2CO	200	Solvent evaporation	Amorphous
2	MeCN	200	Solvent evaporation	Amorphous
3	$CHCl_3$	200	Solvent evaporation	Amorphous
4	1,4-dioxane	200	Solvent evaporation	Solvate
5	EtOH	200	Solvent evaporation	Amorphous
6	EtOAc	200	Solvent evaporation	Amorphous
7	MeOH	200	Solvent evaporation	Amorphous
8	*t*-BuOMe	1000	Maturation	Amorphous
9	PhMe	600	Solvent evaporation	Amorphous – small amount of crystalline material
10	H_2O	1000	Maturation	Amorphous

Table S2. Sample and crystal data.

Crystallization solvents	1,4-dioxane	
Crystallization method	Solvent evaporation	
Empirical formula	$C_{26}H_{38}N_2O_8S_2$	
Formula weight	570.70	
Temperature	180(2) K	
Wavelength	0.71069 Å	
Crystal size	0.23 x 0.16 x 0.12 mm	
Crystal habit	Lath colourless	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 11.70410(10) Å	α= 90°
	b = 17.5168(2) Å	β= 90°
	c = 28.3738(5) Å	γ = 90°
Volume	5817.15(13) $Å^3$	
Z	8	
Density (calculated)	1.303 Mg/m^3	
Absorption coefficient	0.232 mm^{-1}	
F(000)	2432	

Table S3. Data collection and structure refinement.

Diffractometer	Nonius Kappa CCD
Radiation source	fine-focus sealed tube, MoKα
Data collection method	Thin slice φ and ω scans
Theta range for data collection	2.09 to 25.03°
Index ranges	$-13 \leq h \leq 13$, $-20 \leq k \leq 20$, $-33 \leq l \leq 33$
Reflections collected	28441
Independent reflections	10078 [R(int) = 0.0529]
Coverage of independent reflections	99.6 %
Variation in check reflections	N/A
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.966 and 0.892
Structure solution technique	Direct methods
Structure solution program	SHELXS-97 (Sheldrick, 1997)
Refinement technique	Full-matrix least-squares on F^2
Refinement program	SHELXL-97 (Sheldrick, 1997)
Function minimized	$\Sigma w(F_o^2-F_c^2)^2$
Data / restraints / parameters	10078 / 0 / 703
Goodness-of-fit on F^2	1.127
Δ/σ_{max}	0.002
Final R indices	
7767 data; I>2σ(I)	R1 = 0.0625, wR2 = 0.1546
all data	R1 = 0.0926, wR2 = 0.1893
Weighting scheme	$w=1 / [\sigma^2 (F_o^2)+(0.0946P)^2+3.3432P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.00(10)
Largest diff. peak and hole	0.414 and -0.460 eÅ^{-3}

Refinement summary:

Ordered Non-H atoms, XYZ	Freely refining
Ordered Non-H atoms, U	Anisotropic
H atoms (on carbon), XYZ	Idealized positions riding on attached atoms
H atoms (on carbon), U	Appropriate multiple of U(eq) for bonded atom
H atoms (on heteroatoms), XYZ	Freely refining
H atoms (on heteroatoms), U	Isotropic
Disordered atoms, OCC	Disorder ratio 0.476(6)
Disordered Non-H atoms, XYZ	Freely refining
Disordered Non-H atoms, U	Anisotropic, ADPs of equivalent components constrained to be equal

Table S4. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å^2). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
S1A	0.67145(10)	0.78984(7)	0.12236(5)	0.0446(3)
S2A	0.50314(12)	0.49848(7)	0.35056(5)	0.0535(3)
O1A	0.5480(3)	0.6608(2)	0.12630(15)	0.0545(9)
O2A	0.3812(3)	0.5001(3)	0.35675(14)	0.0704(12)
O3A	0.5579(6)	0.5852(4)	0.3739(2)	0.116(2)
O4A	0.5367(4)	0.4448(3)	-0.03625(14)	0.0720(12)
N1A	0.8742(3)	0.7383(2)	0.13760(14)	0.0401(9)
N2A	0.7365(3)	0.6416(2)	0.13604(14)	0.0375(9)
C1A	0.7843(4)	0.8529(3)	0.1247(2)	0.0503(13)
C2A	0.8814(4)	0.8164(3)	0.13276(19)	0.0471(12)
C3A	0.7673(4)	0.7175(3)	0.13262(16)	0.0360(10)
C4A	0.6257(4)	0.6164(3)	0.13337(17)	0.0402(11)
C5A	0.6072(4)	0.5320(3)	0.14269(17)	0.0387(11)
C6A	0.5809(4)	0.5208(3)	0.19461(17)	0.0375(10)
C7A	0.4837(4)	0.5541(3)	0.21347(18)	0.0474(12)
C8A	0.4595(4)	0.5458(3)	0.2610(2)	0.0508(13)
C9A	0.5320(4)	0.5047(3)	0.28916(18)	0.0446(11)
C10A	0.6287(4)	0.4702(3)	0.27080(19)	0.0485(12)
C11A	0.6517(4)	0.4788(3)	0.22379(18)	0.0459(12)
C12A	0.5650(5)	0.4368(3)	0.36994(16)	0.0568(16)
C13A	0.5111(4)	0.5022(3)	0.11089(17)	0.0442(11)
C14A	0.5354(4)	0.5084(3)	0.05814(17)	0.0452(12)
C15A	0.4278(5)	0.4973(4)	0.0290(2)	0.0632(16)
C16A	0.4532(6)	0.4997(5)	-0.0239(2)	0.0743(19)
C17A	0.6411(5)	0.4594(4)	-0.0124(2)	0.0650(16)
C18A	0.6269(5)	0.4532(4)	0.0409(2)	0.0601(15)
S1B	0.13317(10)	0.47952(7)	0.14924(5)	0.0474(3)
S2B	0.26197(16)	0.74754(9)	0.37140(5)	0.0686(5)
O1B	0.2529(3)	0.60708(19)	0.15458(14)	0.0513(9)
O2B	0.1852(6)	0.8007(3)	0.39268(16)	0.103(2)
O3B	0.3814(5)	0.7539(3)	0.38184(18)	0.1017(18)
O4B	0.2459(3)	0.8182(2)	-0.01930(13)	0.0569(10)
N1B	-0.0732(3)	0.5302(2)	0.14545(15)	0.0418(9)
N2B	0.0645(3)	0.6285(2)	0.14883(16)	0.0374(9)
C1B	0.0215(4)	0.4156(3)	0.1465(2)	0.0499(13)
C2B	-0.0779(4)	0.4518(3)	0.14446(19)	0.0463(12)
C3B	0.0340(4)	0.5525(3)	0.14729(16)	0.0355(10)
C4B	0.1742(4)	0.6525(3)	0.15338(16)	0.0365(10)
C5B	0.1922(4)	0.7373(2)	0.15985(16)	0.0354(10)
C6B	0.2139(4)	0.7482(3)	0.21234(17)	0.0383(10)
C7B	0.1224(4)	0.7615(3)	0.24245(18)	0.0496(13)
C8B	0.1371(5)	0.7624(3)	0.29077(18)	0.0565(14)
C9B	0.2441(5)	0.7511(3)	0.30972(18)	0.0500(13)
C10B	0.3367(5)	0.7402(3)	0.2804(2)	0.0570(14)
C11B	0.3224(4)	0.7392(3)	0.23230(19)	0.0492(12)
C12B	0.2177(7)	0.6556(4)	0.3868(2)	0.078(2)
C13B	0.2879(4)	0.7648(3)	0.12731(18)	0.0422(11)

C14B	0.2633(4)	0.7538(3)	0.07509(16)	0.0380(10)
C15B	0.3668(4)	0.7773(4)	0.04567(18)	0.0527(13)
C16B	0.3428(5)	0.7732(4)	-0.00664(19)	0.0597(15)
C17B	0.1460(5)	0.7917(3)	0.00445(18)	0.0515(13)
C18B	0.1584(4)	0.7971(3)	0.05758(17)	0.0451(12)
O1C	0.2695(4)	0.3161(2)	0.00276(16)	0.0675(11)
O2C	0.2722(4)	0.2053(3)	0.0737(2)	0.1032(19)
C1C	0.1724(6)	0.2717(4)	0.0131(3)	0.078(2)
C2C	0.1706(7)	0.2478(5)	0.0628(3)	0.098(3)
C3C	0.3705(7)	0.2508(5)	0.0606(3)	0.105(3)
C4C	0.3660(6)	0.2746(4)	0.0122(3)	0.080(2)
O1D	0.0322(3)	0.4356(2)	-0.01907(15)	0.0621(10)
O2D	0.0383(4)	0.5799(3)	0.02484(17)	0.0796(13)
C1D	0.1352(6)	0.4790(4)	-0.0162(3)	0.081(2)
C2D	0.1115(6)	0.5619(4)	-0.0140(3)	0.0747(19)
C3D	-0.0650(6)	0.5370(4)	0.0206(3)	0.078(2)
C4D	-0.0407(6)	0.4539(4)	0.0194(3)	0.084(2)
O1E	-0.0114(5)	0.5957(3)	0.31633(18)	0.0904(15)
O2E	-0.0740(5)	0.4418(3)	0.31237(18)	0.0859(14)
C1E	-0.1024(9)	0.5645(5)	0.3442(3)	0.105(3)
C2E	-0.0907(8)	0.4862(4)	0.3530(3)	0.093(2)
C3E	0.0128(10)	0.4729(6)	0.2829(3)	0.119(3)
C4E	0.0017(11)	0.5523(6)	0.2753(3)	0.123(3)
O1F	0.3881(5)	0.2451(3)	0.2444(3)	0.128(3)
C1F	0.2907(10)	0.2098(6)	0.2313(5)	0.146(5)
C4F	0.3826(8)	0.3236(6)	0.2410(6)	0.149(5)
O2F	0.1863(12)	0.3176(8)	0.2205(6)	0.104(4)
C2F	0.1973(15)	0.2405(9)	0.2316(7)	0.082(3)
C3F	0.2772(14)	0.3588(10)	0.2385(7)	0.087(3)
O2FB	0.2361(10)	0.3220(7)	0.1901(5)	0.104(4)
C2FB	0.2336(13)	0.2405(8)	0.1941(6)	0.082(3)
C3FB	0.3444(14)	0.3487(9)	0.2014(6)	0.087(3)

Table S5. Selected bond lengths (Å).

S1A-C3A	1.717(4)	S1A-C1A	1.723(5)
S2A-C12A	1.413(5)	S2A-O2A	1.438(4)
S2A-C9A	1.778(5)	S2A-O3A	1.778(6)
O1A-C4A	1.212(6)	O4A-C16A	1.416(8)
O4A-C17A	1.420(7)	N1A-C3A	1.311(6)
N1A-C2A	1.376(6)	N2A-C4A	1.372(6)
N2A-C3A	1.381(6)	N2A-H2AA	0.76(5)
C1A-C2A	1.324(7)	C4A-C5A	1.518(7)
C5A-C6A	1.518(7)	C5A-C13A	1.533(6)
C6A-C11A	1.384(7)	C6A-C7A	1.386(7)
C7A-C8A	1.386(8)	C8A-C9A	1.369(7)
C9A-C10A	1.385(7)	C10A-C11A	1.369(7)
C13A-C14A	1.527(7)	C14A-C15A	1.518(7)
C14A-C18A	1.524(8)	C15A-C16A	1.531(9)
C17A-C18A	1.526(8)	S1B-C1B	1.723(5)
S1B-C3B	1.728(4)	S2B-O2B	1.429(5)
S2B-O3B	1.433(5)	S2B-C12B	1.748(7)
S2B-C9B	1.764(5)	O1B-C4B	1.218(5)
O4B-C16B	1.426(7)	O4B-C17B	1.427(6)
N1B-C3B	1.315(6)	N1B-C2B	1.375(6)
N2B-C4B	1.358(6)	N2B-C3B	1.379(6)
N2B-H2BA	0.69(4)	C1B-C2B	1.326(7)
C4B-C5B	1.511(6)	C5B-C6B	1.523(7)
C5B-C13B	1.529(6)	C6B-C7B	1.389(7)
C6B-C11B	1.400(7)	C7B-C8B	1.382(7)
C8B-C9B	1.377(8)	C9B-C10B	1.379(8)
C10B-C11B	1.376(8)	C13B-C14B	1.522(7)
C14B-C18B	1.526(7)	C14B-C15B	1.528(7)
C15B-C16B	1.512(8)	C17B-C18B	1.518(7)
O1C-C4C	1.369(8)	O1C-C1C	1.409(8)
O2C-C2C	1.436(9)	O2C-C3C	1.448(9)
C1C-C2C	1.472(11)	C3C-C4C	1.435(11)
O1D-C4D	1.421(8)	O1D-C1D	1.428(8)
O2D-C3D	1.428(8)	O2D-C2D	1.430(8)
C1D-C2D	1.481(9)	C3D-C4D	1.485(10)
O1E-C4E	1.398(10)	O1E-C1E	1.434(10)
O2E-C2E	1.405(9)	O2E-C3E	1.425(11)
C1E-C2E	1.401(11)	C3E-C4E	1.412(13)
O1F-C1F	1.349(10)	O1F-C4F	1.380(11)
C1F-C2F	1.218(18)	C1F-C2FB	1.362(17)
C4F-C3FB	1.285(18)	C4F-C3F	1.380(18)
O2F-C3F	1.38(2)	O2F-C2F	1.39(2)
O2FB-C3FB	1.388(19)	O2FB-C2FB	1.432(18)

Table S6. Selected bond angles (°).

C3A-S1A-C1A	88.0(2)	C12A-S2A-O2A	118.4(3)
C12A-S2A-C9A	109.3(3)	O2A-S2A-C9A	107.9(2)
C12A-S2A-O3A	108.9(3)	O2A-S2A-O3A	107.2(3)
C9A-S2A-O3A	104.2(3)	C16A-O4A-C17A	110.6(5)
C3A-N1A-C2A	108.9(4)	C4A-N2A-C3A	123.5(4)
C4A-N2A-H2AA	117(4)	C3A-N2A-H2AA	119(4)
C2A-C1A-S1A	110.8(4)	C1A-C2A-N1A	116.4(4)
N1A-C3A-N2A	120.6(4)	N1A-C3A-S1A	115.9(3)
N2A-C3A-S1A	123.5(3)	O1A-C4A-N2A	120.8(5)
O1A-C4A-C5A	123.1(4)	N2A-C4A-C5A	116.0(4)
C6A-C5A-C4A	108.9(4)	C6A-C5A-C13A	112.2(4)
C4A-C5A-C13A	109.4(4)	C11A-C6A-C7A	119.0(5)
C11A-C6A-C5A	121.9(4)	C7A-C6A-C5A	119.1(4)
C8A-C7A-C6A	119.9(5)	C9A-C8A-C7A	119.8(5)
C8A-C9A-C10A	121.1(5)	C8A-C9A-S2A	119.1(4)
C10A-C9A-S2A	119.8(4)	C11A-C10A-C9A	118.6(5)
C10A-C11A-C6A	121.6(4)	C14A-C13A-C5A	114.6(4)
C15A-C14A-C18A	109.1(5)	C15A-C14A-C13A	111.7(4)
C18A-C14A-C13A	113.6(4)	C14A-C15A-C16A	111.7(5)
O4A-C16A-C15A	111.0(5)	O4A-C17A-C18A	111.5(5)
C14A-C18A-C17A	110.4(5)	C1B-S1B-C3B	88.3(2)
O2B-S2B-O3B	118.4(4)	O2B-S2B-C12B	108.0(4)
O3B-S2B-C12B	108.0(4)	O2B-S2B-C9B	108.8(3)
O3B-S2B-C9B	108.5(3)	C12B-S2B-C9B	104.2(3)
C16B-O4B-C17B	110.7(4)	C3B-N1B-C2B	109.6(4)
C4B-N2B-C3B	123.1(4)	C4B-N2B-H2BA	121(4)
C3B-N2B-H2BA	115(4)	C2B-C1B-S1B	110.8(4)
C1B-C2B-N1B	116.3(4)	N1B-C3B-N2B	122.3(4)
N1B-C3B-S1B	115.0(3)	N2B-C3B-S1B	122.7(3)
O1B-C4B-N2B	121.0(4)	O1B-C4B-C5B	122.2(4)
N2B-C4B-C5B	116.6(4)	C4B-C5B-C6B	105.4(4)
C4B-C5B-C13B	109.8(4)	C6B-C5B-C13B	115.4(4)
C7B-C6B-C11B	118.0(5)	C7B-C6B-C5B	119.6(4)
C11B-C6B-C5B	122.2(4)	C8B-C7B-C6B	121.1(5)
C9B-C8B-C7B	119.9(5)	C8B-C9B-C10B	119.9(5)
C8B-C9B-S2B	120.0(4)	C10B-C9B-S2B	120.0(4)
C11B-C10B-C9B	120.3(5)	C10B-C11B-C6B	120.7(5)
C14B-C13B-C5B	114.2(4)	C13B-C14B-C18B	113.9(4)
C13B-C14B-C15B	110.4(4)	C18B-C14B-C15B	109.1(4)
C16B-C15B-C14B	112.1(4)	O4B-C16B-C15B	111.7(5)
O4B-C17B-C18B	111.7(4)	C17B-C18B-C14B	111.7(4)
C4C-O1C-C1C	109.4(5)	C2C-O2C-C3C	108.5(5)
O1C-C1C-C2C	111.5(6)	O2C-C2C-C1C	110.0(6)
C4C-C3C-O2C	112.1(6)	O1C-C4C-C3C	111.8(7)
C4D-O1D-C1D	110.0(5)	C3D-O2D-C2D	109.0(5)
O1D-C1D-C2D	111.5(5)	O2D-C2D-C1D	111.1(6)
O2D-C3D-C4D	110.8(6)	O1D-C4D-C3D	110.8(6)
C4E-O1E-C1E	109.4(7)	C2E-O2E-C3E	111.7(7)
C2E-C1E-O1E	113.5(7)	C1E-C2E-O2E	114.1(7)
C4E-C3E-O2E	113.6(8)	O1E-C4E-C3E	114.8(8)

C1F-O1F-C4F	113.5(7)	C2F-C1F-O1F	123.6(12)
C2F-C1F-C2FB	52.4(10)	O1F-C1F-C2FB	116.6(11)
C3FB-C4F-C3F	59.6(11)	C3FB-C4F-O1F	114.8(13)
C3F-C4F-O1F	119.3(11)	C3F-O2F-C2F	110.5(13)
C1F-C2F-O2F	120.7(15)	C4F-C3F-O2F	118.2(14)
C3FB-O2FB-C2FB	109.7(12)	C1F-C2FB-O2FB	116.4(12)
C4F-C3FB-O2FB	113.8(15)		

Table S7. Selected torsion angles (°).

C3A-S1A-C1A-C2A	-0.2(4)	S1A-C1A-C2A-N1A	0.0(7)
C3A-N1A-C2A-C1A	0.2(7)	C2A-N1A-C3A-N2A	-179.8(4)
C2A-N1A-C3A-S1A	-0.3(5)	C4A-N2A-C3A-N1A	176.9(4)
C4A-N2A-C3A-S1A	-2.6(7)	C1A-S1A-C3A-N1A	0.3(4)
C1A-S1A-C3A-N2A	179.8(4)	C3A-N2A-C4A-O1A	2.3(7)
C3A-N2A-C4A-C5A	-174.2(4)	O1A-C4A-C5A-C6A	-83.8(6)
N2A-C4A-C5A-C6A	92.6(5)	O1A-C4A-C5A-C13A	39.2(6)
N2A-C4A-C5A-C13A	-144.4(4)	C4A-C5A-C6A-C11A	-117.1(5)
C13A-C5A-C6A-C11A	121.5(5)	C4A-C5A-C6A-C7A	62.3(5)
C13A-C5A-C6A-C7A	-59.0(6)	C11A-C6A-C7A-C8A	0.7(7)
C5A-C6A-C7A-C8A	-178.7(5)	C6A-C7A-C8A-C9A	0.1(8)
C7A-C8A-C9A-C10A	-0.9(8)	C7A-C8A-C9A-S2A	177.0(4)
C12A-S2A-C9A-C8A	162.4(5)	O2A-S2A-C9A-C8A	32.4(5)
O3A-S2A-C9A-C8A	-81.3(5)	C12A-S2A-C9A-C10A	-19.7(5)
O2A-S2A-C9A-C10A	-149.7(4)	O3A-S2A-C9A-C10A	96.6(5)
C8A-C9A-C10A-C11A	0.9(8)	S2A-C9A-C10A-C11A	-177.0(4)
C9A-C10A-C11A-C6A	0.0(8)	C7A-C6A-C11A-C10A	-0.8(8)
C5A-C6A-C11A-C10A	178.7(5)	C6A-C5A-C13A-C14A	-177.1(4)
C4A-C5A-C13A-C14A	61.9(5)	C5A-C13A-C14A-C15A	-165.5(5)
C5A-C13A-C14A-C18A	70.5(6)	C18A-C14A-C15A-C16A	-50.9(7)
C13A-C14A-C15A-C16A	-177.3(5)	C17A-O4A-C16A-C15A	-61.1(7)
C14A-C15A-C16A-O4A	56.2(7)	C16A-O4A-C17A-C18A	62.6(7)
C15A-C14A-C18A-C17A	51.3(6)	C13A-C14A-C18A-C17A	176.6(5)
O4A-C17A-C18A-C14A	-57.8(7)	C3B-S1B-C1B-C2B	-0.2(4)
S1B-C1B-C2B-N1B	-0.6(7)	C3B-N1B-C2B-C1B	1.3(7)
C2B-N1B-C3B-N2B	-179.7(4)	C2B-N1B-C3B-S1B	-1.4(6)
C4B-N2B-C3B-N1B	176.2(5)	C4B-N2B-C3B-S1B	-2.0(7)
C1B-S1B-C3B-N1B	0.9(4)	C1B-S1B-C3B-N2B	179.2(5)
C3B-N2B-C4B-O1B	2.8(7)	C3B-N2B-C4B-C5B	-173.5(4)
O1B-C4B-C5B-C6B	-74.9(5)	N2B-C4B-C5B-C6B	101.4(5)
O1B-C4B-C5B-C13B	50.0(6)	N2B-C4B-C5B-C13B	-133.7(4)
C4B-C5B-C6B-C7B	-90.0(5)	C13B-C5B-C6B-C7B	148.7(5)
C4B-C5B-C6B-C11B	84.6(5)	C13B-C5B-C6B-C11B	-36.7(6)
C11B-C6B-C7B-C8B	-2.8(8)	C5B-C6B-C7B-C8B	172.1(5)
C6B-C7B-C8B-C9B	0.9(9)	C7B-C8B-C9B-C10B	1.2(9)
C7B-C8B-C9B-S2B	-176.9(4)	O2B-S2B-C9B-C8B	-36.1(6)
O3B-S2B-C9B-C8B	-166.2(5)	C12B-S2B-C9B-C8B	78.9(5)
O2B-S2B-C9B-C10B	145.8(5)	O3B-S2B-C9B-C10B	15.8(6)
C12B-S2B-C9B-C10B	-99.2(5)	C8B-C9B-C10B-C11B	-1.2(8)
S2B-C9B-C10B-C11B	176.9(4)	C9B-C10B-C11B-C6B	-0.8(8)
C7B-C6B-C11B-C10B	2.8(8)	C5B-C6B-C11B-C10B	-172.0(5)
C4B-C5B-C13B-C14B	61.6(5)	C6B-C5B-C13B-C14B	-179.5(4)
C5B-C13B-C14B-C18B	61.1(5)	C5B-C13B-C14B-C15B	-175.8(4)
C13B-C14B-C15B-C16B	-175.4(5)	C18B-C14B-C15B-C16B	-49.5(6)
C17B-O4B-C16B-C15B	-60.7(6)	C14B-C15B-C16B-O4B	55.9(6)
C16B-O4B-C17B-C18B	60.8(6)	O4B-C17B-C18B-C14B	-56.1(6)
C13B-C14B-C18B-C17B	173.2(4)	C15B-C14B-C18B-C17B	49.5(6)
C4C-O1C-C1C-C2C	59.2(8)	C3C-O2C-C2C-C1C	54.2(9)
O1C-C1C-C2C-O2C	-58.0(9)	C2C-O2C-C3C-C4C	-54.9(10)
C1C-O1C-C4C-C3C	-58.9(8)	O2C-C3C-C4C-O1C	58.2(9)

C4D-O1D-C1D-C2D	-55.7(8)	C3D-O2D-C2D-C1D	-57.2(7)
O1D-C1D-C2D-O2D	56.7(8)	C2D-O2D-C3D-C4D	58.3(8)
C1D-O1D-C4D-C3D	56.6(8)	O2D-C3D-C4D-O1D	-58.9(9)
C4E-O1E-C1E-C2E	52.4(11)	O1E-C1E-C2E-O2E	-52.7(11)
C3E-O2E-C2E-C1E	48.6(11)	C2E-O2E-C3E-C4E	-47.0(12)
C1E-O1E-C4E-C3E	-51.8(14)	O2E-C3E-C4E-O1E	50.8(15)
C4F-O1F-C1F-C2F	-23(2)	C4F-O1F-C1F-C2FB	37.5(19)
C1F-O1F-C4F-C3FB	-49.1(18)	C1F-O1F-C4F-C3F	19(2)
O1F-C1F-C2F-O2F	35(3)	C2FB-C1F-C2F-O2F	-64.5(18)
C3F-O2F-C2F-C1F	-38(3)	C3FB-C4F-C3F-O2F	76.8(18)
O1F-C4F-C3F-O2F	-26(3)	C2F-O2F-C3F-C4F	33(2)
C2F-C1F-C2FB-O2FB	77.8(16)	O1F-C1F-C2FB-O2FB	-35(2)
C3FB-O2FB-C2FB-C1F	40(2)	C3F-C4F-C3FB-O2FB	-53.2(14)
O1F-C4F-C3FB-O2FB	57.5(18)	C2FB-O2FB-C3FB-C4F	-51(2)

Table S8. Anisotropic atomic displacement parameters (Å^2).
The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2$ [h^2a^{*2} U_{11} + ... + $2hka^*$ b^* U_{12}]

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1A	0.0345(6)	0.0414(7)	0.0579(8)	0.0010(6)	-0.0051(5)	0.0079(5)
S2A	0.0669(8)	0.0419(7)	0.0516(8)	0.0028(6)	0.0121(7)	0.0031(6)
O1A	0.0322(17)	0.049(2)	0.082(3)	0.003(2)	-0.0104(17)	0.0017(15)
O2A	0.070(3)	0.075(3)	0.066(3)	-0.007(2)	0.021(2)	-0.026(2)
O3A	0.128(5)	0.114(5)	0.105(4)	-0.011(4)	0.004(4)	-0.030(4)
O4A	0.076(3)	0.085(3)	0.054(3)	-0.011(2)	-0.005(2)	-0.008(2)
N1A	0.0279(19)	0.036(2)	0.057(3)	-0.0056(18)	-0.0040(16)	0.0000(15)
N2A	0.025(2)	0.035(2)	0.052(3)	0.0019(18)	-0.0062(17)	0.0026(17)
C1A	0.047(3)	0.035(3)	0.069(4)	-0.002(3)	-0.002(3)	0.006(2)
C2A	0.035(3)	0.039(3)	0.067(3)	-0.006(2)	-0.003(2)	-0.001(2)
C3A	0.033(2)	0.034(2)	0.041(3)	0.001(2)	0.0020(18)	0.0062(19)
C4A	0.029(2)	0.045(3)	0.046(3)	0.003(2)	-0.003(2)	0.004(2)
C5A	0.028(2)	0.040(3)	0.048(3)	-0.002(2)	-0.0021(19)	-0.0030(18)
C6A	0.033(2)	0.036(2)	0.043(3)	0.000(2)	-0.0018(19)	-0.0046(19)
C7A	0.038(3)	0.058(3)	0.046(3)	0.002(2)	-0.003(2)	0.008(2)
C8A	0.034(3)	0.055(3)	0.064(4)	-0.005(3)	-0.003(2)	0.007(2)
C9A	0.053(3)	0.036(3)	0.044(3)	0.002(2)	0.004(2)	-0.003(2)
C10A	0.046(3)	0.047(3)	0.052(3)	0.009(2)	-0.001(2)	0.012(2)
C11A	0.039(3)	0.044(3)	0.054(3)	0.000(2)	0.003(2)	0.009(2)
C12A	0.109(4)	0.040(3)	0.021(2)	0.014(2)	0.021(3)	0.040(3)
C13A	0.037(2)	0.048(3)	0.048(3)	0.001(2)	0.000(2)	-0.008(2)
C14A	0.045(3)	0.044(3)	0.046(3)	0.002(2)	-0.002(2)	-0.007(2)
C15A	0.042(3)	0.087(5)	0.061(4)	-0.005(3)	-0.011(2)	-0.005(3)
C16A	0.069(4)	0.101(5)	0.053(4)	-0.007(4)	-0.015(3)	0.005(4)
C17A	0.062(4)	0.079(4)	0.054(3)	-0.004(3)	0.003(3)	0.003(3)
C18A	0.055(3)	0.071(4)	0.054(3)	-0.001(3)	-0.006(3)	0.006(3)
S1B	0.0373(6)	0.0374(6)	0.0676(8)	0.0014(6)	-0.0001(6)	0.0063(5)
S2B	0.1066(13)	0.0524(9)	0.0467(8)	-0.0042(7)	-0.0243(8)	0.0213(8)
O1B	0.0317(17)	0.0420(19)	0.080(3)	0.0001(18)	-0.0076(17)	0.0055(14)
O2B	0.184(5)	0.074(3)	0.051(3)	-0.010(2)	-0.018(3)	0.072(4)
O3B	0.113(4)	0.118(4)	0.074(3)	0.006(3)	-0.052(3)	-0.010(3)
O4B	0.059(2)	0.066(3)	0.046(2)	0.0068(18)	-0.0006(17)	-0.0181(19)
N1B	0.035(2)	0.032(2)	0.058(3)	-0.0020(19)	0.0012(18)	-0.0022(16)
N2B	0.024(2)	0.035(2)	0.053(3)	-0.001(2)	-0.0041(18)	0.0026(17)
C1B	0.049(3)	0.034(3)	0.067(3)	-0.002(2)	0.011(3)	0.001(2)
C2B	0.040(3)	0.040(3)	0.058(3)	-0.003(2)	0.009(2)	-0.006(2)
C3B	0.032(2)	0.036(2)	0.038(2)	0.004(2)	-0.0042(19)	0.0045(18)
C4B	0.029(2)	0.041(3)	0.039(3)	0.005(2)	-0.002(2)	0.0012(19)
C5B	0.027(2)	0.034(2)	0.045(3)	0.000(2)	-0.0073(18)	0.0014(17)
C6B	0.038(3)	0.031(2)	0.045(3)	0.002(2)	-0.006(2)	-0.0025(19)
C7B	0.044(3)	0.060(3)	0.046(3)	-0.001(3)	-0.005(2)	0.011(2)
C8B	0.065(3)	0.061(3)	0.043(3)	-0.004(3)	-0.006(3)	0.018(3)
C9B	0.066(4)	0.041(3)	0.044(3)	-0.001(2)	-0.014(3)	0.009(3)
C10B	0.053(3)	0.058(3)	0.060(3)	0.005(3)	-0.020(3)	-0.001(3)
C11B	0.036(3)	0.057(3)	0.055(3)	0.004(3)	-0.006(2)	-0.003(2)
C12B	0.115(5)	0.064(4)	0.056(4)	0.002(3)	-0.007(4)	0.024(4)
C13B	0.028(2)	0.045(3)	0.054(3)	0.005(2)	-0.006(2)	-0.0047(19)

C14B	0.037(2)	0.034(2)	0.043(3)	-0.002(2)	0.000(2)	-0.0023(19)
C15B	0.041(3)	0.068(4)	0.050(3)	0.000(3)	0.006(2)	-0.006(3)
C16B	0.050(3)	0.073(4)	0.056(3)	0.002(3)	0.008(3)	-0.012(3)
C17B	0.051(3)	0.056(3)	0.047(3)	0.005(3)	-0.010(2)	-0.006(3)
C18B	0.042(3)	0.050(3)	0.043(3)	-0.003(2)	-0.002(2)	0.001(2)
O1C	0.068(3)	0.059(3)	0.076(3)	0.015(2)	-0.003(2)	-0.004(2)
O2C	0.088(3)	0.103(4)	0.119(4)	0.056(4)	-0.031(3)	-0.012(3)
C1C	0.059(4)	0.081(5)	0.093(5)	0.020(4)	-0.013(4)	-0.004(3)
C2C	0.083(5)	0.090(6)	0.120(7)	0.010(5)	0.038(5)	-0.002(4)
C3C	0.075(5)	0.099(6)	0.140(8)	0.038(6)	-0.048(5)	-0.014(4)
C4C	0.063(4)	0.064(4)	0.112(6)	0.015(4)	-0.002(4)	0.000(3)
O1D	0.062(2)	0.059(2)	0.065(3)	-0.012(2)	-0.005(2)	-0.0028(19)
O2D	0.095(3)	0.066(3)	0.078(3)	-0.022(2)	-0.012(3)	0.016(3)
C1D	0.054(4)	0.075(5)	0.112(6)	-0.018(4)	0.005(4)	0.005(3)
C2D	0.058(4)	0.061(4)	0.105(5)	-0.009(4)	0.008(4)	0.001(3)
C3D	0.070(4)	0.073(5)	0.089(5)	-0.001(4)	0.024(4)	0.018(4)
C4D	0.075(5)	0.088(5)	0.087(5)	0.006(4)	0.012(4)	0.003(4)
O1E	0.134(5)	0.068(3)	0.069(3)	-0.003(2)	-0.002(3)	-0.012(3)
O2E	0.115(4)	0.064(3)	0.078(3)	-0.005(3)	-0.008(3)	0.009(3)
C1E	0.149(8)	0.079(6)	0.087(6)	-0.002(5)	0.029(5)	0.006(5)
C2E	0.120(6)	0.078(5)	0.082(5)	-0.010(4)	0.025(5)	0.000(4)
C3E	0.171(10)	0.106(7)	0.080(6)	-0.005(5)	0.040(6)	0.046(7)
C4E	0.182(10)	0.101(7)	0.085(6)	0.004(5)	0.043(7)	-0.006(7)
O1F	0.076(4)	0.073(4)	0.235(8)	-0.002(4)	-0.053(4)	0.011(3)
C1F	0.124(8)	0.084(7)	0.229(14)	0.028(8)	-0.077(9)	-0.012(6)
C4F	0.091(7)	0.087(7)	0.267(16)	-0.011(8)	-0.055(8)	0.004(5)
O2F	0.077(8)	0.077(5)	0.157(12)	-0.002(7)	-0.026(6)	0.028(5)
C2F	0.086(8)	0.075(7)	0.085(7)	-0.010(7)	-0.011(6)	-0.002(6)
C3F	0.092(8)	0.078(7)	0.091(8)	0.002(7)	-0.024(6)	0.014(6)
O2FB	0.077(8)	0.077(5)	0.157(12)	-0.002(7)	-0.026(6)	0.028(5)
C2FB	0.086(8)	0.075(7)	0.085(7)	-0.010(7)	-0.011(6)	-0.002(6)
C3FB	0.092(8)	0.078(7)	0.091(8)	0.002(7)	-0.024(6)	0.014(6)

Table S9. Hydrogen atom coordinates and isotropic atomic displacement parameters (Å^2).

	x/a	y/b	z/c	U
H2AA	0.782(4)	0.612(3)	0.1416(17)	0.032(14)
H1AA	0.7778	0.9066	0.1207	0.060
H2AC	0.9522	0.8426	0.1351	0.057
H5AA	0.6792	0.5039	0.1349	0.046
H7AA	0.4337	0.5827	0.1938	0.057
H8AA	0.3929	0.5685	0.2740	0.061
H10A	0.6781	0.4411	0.2904	0.058
H11A	0.7179	0.4553	0.2109	0.055
H12A	0.5498	0.4335	0.4038	0.085
H12B	0.6469	0.4448	0.3648	0.085
H12C	0.5413	0.3892	0.3547	0.085
H13A	0.4967	0.4480	0.1187	0.053
H13B	0.4405	0.5311	0.1180	0.053
H14A	0.5638	0.5613	0.0520	0.054
H15A	0.3722	0.5379	0.0370	0.076
H15B	0.3928	0.4476	0.0371	0.076
H16A	0.3820	0.4896	-0.0417	0.089
H16B	0.4808	0.5512	-0.0326	0.089
H17A	0.6681	0.5114	-0.0205	0.078
H17B	0.6996	0.4225	-0.0230	0.078
H18A	0.6051	0.4003	0.0494	0.072
H18B	0.7004	0.4649	0.0566	0.072
H2BA	0.020(4)	0.654(3)	0.1463(16)	0.024(13)
H1BA	0.0299	0.3616	0.1464	0.060
H2BC	-0.1483	0.4251	0.1425	0.056
H5BA	0.1201	0.7645	0.1512	0.042
H7BA	0.0486	0.7701	0.2296	0.060
H8BA	0.0735	0.7708	0.3109	0.068
H10B	0.4107	0.7334	0.2935	0.068
H11B	0.3869	0.7323	0.2124	0.059
H12D	0.2246	0.6489	0.4210	0.117
H12E	0.2658	0.6179	0.3707	0.117
H12F	0.1379	0.6483	0.3774	0.117
H13C	0.3015	0.8197	0.1333	0.051
H13D	0.3589	0.7370	0.1354	0.051
H14B	0.2496	0.6981	0.0696	0.046
H15C	0.3891	0.8301	0.0541	0.063
H15D	0.4319	0.7433	0.0533	0.063
H16C	0.4105	0.7915	-0.0242	0.072
H16D	0.3289	0.7194	-0.0157	0.072
H17C	0.1312	0.7380	-0.0045	0.062
H17D	0.0795	0.8226	-0.0057	0.062
H18C	0.0892	0.7758	0.0728	0.054
H18D	0.1649	0.8514	0.0668	0.054
H1CA	0.1719	0.2259	-0.0074	0.094
H1CB	0.1027	0.3017	0.0061	0.094
H2CA	0.1660	0.2934	0.0834	0.117
H2CB	0.1025	0.2158	0.0688	0.117

H3CA	0.3743	0.2965	0.0811	0.126
H3CB	0.4409	0.2206	0.0658	0.126
H4C1	0.4342	0.3060	0.0050	0.095
H4C2	0.3678	0.2290	-0.0084	0.095
H1DA	0.1833	0.4680	-0.0441	0.097
H1DB	0.1784	0.4635	0.0122	0.097
H2DA	0.1843	0.5902	-0.0107	0.090
H2DB	0.0747	0.5785	-0.0437	0.090
H3DA	-0.1053	0.5521	-0.0086	0.093
H3DB	-0.1155	0.5486	0.0477	0.093
H4DA	-0.0038	0.4383	0.0493	0.100
H4DB	-0.1133	0.4253	0.0163	0.100
H1EA	-0.1055	0.5920	0.3746	0.126
H1EB	-0.1757	0.5734	0.3277	0.126
H2EA	-0.1601	0.4679	0.3694	0.112
H2EB	-0.0250	0.4784	0.3745	0.112
H3EA	0.0882	0.4627	0.2974	0.143
H3EB	0.0107	0.4465	0.2520	0.143
H4EA	0.0702	0.5706	0.2583	0.147
H4EB	-0.0653	0.5612	0.2547	0.147
H1F1	0.3032	0.1913	0.1987	0.175
H1F2	0.2839	0.1638	0.2514	0.175
H1F3	0.2385	0.2081	0.2587	0.175
H1F4	0.3102	0.1564	0.2232	0.175
H4F1	0.4234	0.3452	0.2685	0.178
H4F2	0.4261	0.3387	0.2125	0.178
H4F3	0.3332	0.3434	0.2665	0.178
H4F4	0.4603	0.3444	0.2460	0.178
H2F1	0.1647	0.2333	0.2635	0.098
H2F2	0.1480	0.2118	0.2095	0.098
H3F1	0.2859	0.4055	0.2192	0.104
H3F2	0.2564	0.3753	0.2708	0.104
H2F3	0.1527	0.2242	0.1960	0.098
H2F4	0.2657	0.2186	0.1648	0.098
H3F3	0.3981	0.3336	0.1761	0.104
H3F4	0.3424	0.4051	0.2025	0.104

Table S10. Selected site occupancy factors that deviate from unity.

Atom	sof	Atom	sof	Atom	sof
O1F	1	C1F	1	C4F	1
O2F	0.476(7)	C2F	0.476(7)	C3F	0.476(7)
O2FB	0.524(7)	C2FB	0.524(7)	C3FB	0.524(7)

Table S11. Selected hydrogen bond information (Å and °).

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N2B-H2BA...N1A#1	0.69(4)	2.27(5)	2.959(6)	180(6)
N2A-H2AA...N1B#2	0.76(5)	2.22(5)	2.973(6)	170(5)

#1 x+1,y,z #2 x-1,y,z