

Syntheses of, and Structural Studies on, Benzo-fused 1,2,4-thiadiazines
Ewan R. Clark, John J. Hayward, Bryce J. Leontowicz, Dana J. Eisler and Jeremy M. Rawson
Electronic Supplementary Information

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SUP-01 Crystal Data for Compounds 1 – 9

Compound	1	2	3	4	5
Chemical formula	C ₁₃ H ₁₀ N ₂ S	C ₁₂ H ₉ N ₃ S	C ₁₂ H ₉ N ₃ S	C ₁₂ H ₉ N ₃ S	C ₁₁ H ₈ N ₂ S ₂
Formula weight	226.29	227.28	227.28	227.28	232.31
Crystal System	Monoclinic	Triclinic	Orthorhombic	Monoclinic	Orthorhombic
Space group	<i>P2₁/c</i>	<i>P-1</i>	<i>P2₁2₁2₁</i>	<i>P2₁/c</i>	<i>Pbca</i>
<i>a</i> (Å)	6.9316(2)	6.2054(2)	4.8958(2)	15.6603(3)	9.6844(6)
<i>b</i> (Å)	15.6631(5)	11.0782(4)	13.2251(6)	7.40200(10)	10.0511(6)
<i>c</i> (Å)	10.3420(3)	15.7022(4)	15.7846(8)	18.6797(3)	21.3621(14)
α (deg)	90	79.2620(18)	90	90	90
β (deg)	100.8710(18)	81.6799(18)	90	106.7799(9)	90
γ (deg)	90	81.0105(10)	90	90	90
<i>V</i> (Å ³)	1102.68(6)	1040.06(6)	1022.01(8)	2073.11(6)	2079.4(2)
<i>Z</i>	4	4	4	8	8
<i>D</i> _{calcd} (g cm ⁻³)	1.363	1.452	1.477	1.456	1.484
μ (mm ⁻¹)	0.264	0.282	0.287	0.283	0.475
θ range (deg)	1.02 – 27.88	1.02 – 27.48	4.02 – 27.44	1.02 – 27.48	2.86 – 28.40
Reflns collected	6625	9857	5661	4740	14765
Unique reflns	2619	4640	2257	4740	2587
Data/restraints/parameters	2619/0/185	4640/0/361	2257/0/181	4740/0/361	2587/0/140
<i>R</i> ₁ , <i>wR</i> ₂ (<i>I</i> > 2 σ (<i>I</i>))	0.0389, 0.0995	0.0382, 0.0991	0.0451, 0.1031	0.0376, 0.0946	0.0420, 0.1137
Residual electron density (<i>e</i> ⁻ /Å ³)	+0.31/-0.24	+0.34/-0.32	+0.33/-0.24	+0.28/-0.42	+0.39/-0.37

Compound	6	7	8	9
Chemical formula	C ₁₃ H ₉ N ₃ O ₂ S	C ₁₃ H ₈ N ₄ O ₄ S	C ₁₄ H ₁₂ N ₂ OS	C ₁₄ H ₉ F ₃ N ₂ S
Formula weight	271.29	316.29	256.32	294.29
Crystal System	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	<i>P2₁/c</i>	<i>P2₁/n</i>	<i>P2₁/c</i>	<i>Cc</i>
<i>a</i> (Å)	7.4294(3)	13.173(3)	24.399(5)	14.857(2)
<i>b</i> (Å)	12.5543(6)	7.0180(14)	5.2540(11)	13.0971(19)
<i>c</i> (Å)	12.7463(5)	14.651(3)	9.3849(19)	26.970(4)
α (deg)	90	90	90	90
β (deg)	92.878(3)	108.59(3)	95.68(3)	90.959(4)
γ (deg)	90	90	90	90
<i>V</i> (Å ³)	1187.36(9)	1283.8(4)	1197.2(4)	5247.0(13)
<i>Z</i>	4	4	4	16
<i>D</i> _{calcd} (g cm ⁻³)	1.518	1.636	1.422	1.490
μ (mm ⁻¹)	0.273	0.279	0.258	0.272
θ range (deg)	1.02 – 27.48	1.02 – 28.70	3.36– 25.00	0.76 – 25.00
Reflns collected	13481	8790	6829	17034
Unique reflns	2090	2267	2090	7611
Data/restraints/parameters	2090/0/172	2267/0/199	2090/0/164	7611/326/422
<i>R</i> ₁ , <i>wR</i> ₂ (<i>I</i> > 2 σ (<i>I</i>))	0.0611, 0.1316	0.0346, 0.1027	0.0557, 0.1344	0.1056, 0.3009
Residual electron density (<i>e</i> ⁻ /Å ³)	+0.39/-0.31	+0.40/-0.35	+0.36/-0.28	+0.80/-0.81

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SUP-02: Experimental

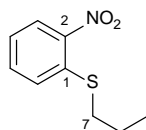
General Considerations

All chemicals were purchased from commercial suppliers and were used without further purification unless otherwise indicated. Solvents used were distilled prior to use. Glassware was dried for a minimum 1 h at 120 °C before use; air- and moisture-sensitive reagents were manipulated in a Saffron Scientific Ltd Beta Range Glove Box or MBraun Labmaster under an atmosphere of dry N₂. Microwave reactions were undertaken in sealed vessels using a Biotage Initiator 1 microwave. Analytical thin layer chromatography (TLC) was performed on glass-backed plates coated with 0.25mm thick Merck 5715 silica gel. Compounds were visualized using UV light (254 nm). NMR spectra were recorded on a Bruker AM-400 MHz, a Bruker Avance 300US or a Bruker 500 MHz Avance III with a BBFO probe with residual solvent peaks used as internal standards; coupling constants were taken directly from the spectra and are not averaged. Electron Impact mass spectrometry was performed on a Kratos MS890-EI mass spectrometer; Electrospray Mass Spectrometry was performed using a Waters LTC machine or Waters Micromass LCT Classic (ESI-TOF) Mass Spectrometer. Elemental analyses were recorded on an Exeter CE-440 Elemental Analyser or a PerkinElmer 2400 Series II CHN Analyzer. Melting points were determined using a Stanford Research Systems MPA120 EZ-Melt Automated Melting Point Apparatus. FT-IR spectra were measured as nujol mulls between NaCl plates using a Perkin Elmer Paragon 1000 spectrometer or as thin films on a Bruker Alpha FT-IR equipped with a Platinum single reflection diamond ATR module.

Preparation of Sodium Propyl-1-Thiolate

Sodium hydride (4 g, 100 mmol) was suspended in dry Et₂O (250 mL) under a nitrogen atmosphere at 0 °C and 1-propanethiol (9.06 mL, 100 mmol) was added dropwise to the suspension, which was allowed to warm to room temperature and stirred overnight. The white solid was then filtered off, washed with excess hexane, and dried under vacuum.

Preparation of (2-Nitrophenyl)(propyl)sulfane (1a)

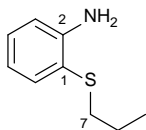


1-chloro-2-nitrobenzene (1.58 g, 10 mmol) was added to a solution of sodium propane-1-thiolate (1.08 g, 11 mmol) in dry DMF (20 mL). The reaction mixture was stirred at 130 °C for 40 min under microwave irradiation.* This process was repeated four times and the combined reaction mixtures were added to water (250 mL) and the product extracted into Et₂O (3 × 100 mL). The organic layer was then washed further with water (150 mL) and saturated Na₂CO_{3(aq)} (200 mL) and then dried over MgSO₄. The solvent was removed *in vacuo* to reveal a dark honey-brown oil (9.4 g, 95%). **Elemental Analysis** calc.(obs.) for C₉H₁₁NO₂S: C = 54.8 (54.9); H = 5.6 (5.5); N = 7.1 (7.2) %. **IR** (oil): $\nu_{\max}/\text{cm}^{-1}$ 2963w, 2930w, and 2872w (aliphatic CH), 1508s, 1331s, and 1303s (NO₂), 1104m, 852m, 780m, and 730s (*ortho*-substituted Ph). **¹H NMR** (300 MHz, CDCl₃) δ_{H} = 8.18 (1 H, dd, J = 8.3, 1.5 Hz, C³H), 7.53 (1 H, ddd, J = 7.2, 7.2, 1.5 Hz, C⁵H), 7.4 (1H, dd, J = 8.2, 1.0 Hz, C⁶H), 7.22 (1H, ddd, J = 7.2, 7.2, 1.3 Hz, C⁴H), 2.93 (2H, t, J = 7.3 Hz, SC⁷H₂), 1.76 (2H, sextet, J = 7.3 Hz, SCH₂C⁸H₂), 1.08 (3H, t, J = 7.4 Hz, C⁹H₃) ppm. **¹³C NMR** (75 MHz, CDCl₃) δ_{C} = 145.82 (C²), 138.01 (C¹), 133.32 (C⁵), 126.45 (C⁶), 125.90 (C⁴), 124.15 (C³), 34.09 (C⁷), 21.18 (C⁸), 13.56 (C⁹) ppm.

* It should also be noted that stronger (rare-earth) magnetic microwave stir bars help improve reaction time through improved mixing.

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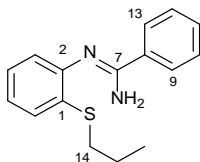
Preparation of 2-(propylthio)benzenamine (1b)



Ethanol (15 mL), 1-nitro-2-propylsulfanylbenzene (**1a**, 1.97 g, 10 mmol), H₂O (0.5 mL), and glacial acetic acid (1 mL) were combined and stirred to form a homogenous solution (< 2 min) followed by the slow addition of powdered iron (2.793 g, 50 mmol). The reaction mixture was stirred at 150 °C for 90 mins under microwave irradiation.* This was repeated three times and the combined reaction mixtures diluted with DCM (150 mL) and filtered through a silica gel plug. The silica was washed with more DCM (100 mL) and the combined filtrates were evaporated *in vacuo*. The residue was washed with 100 mL of saturated NaHCO_{3(aq)} and extracted into DCM (150 mL). The organic phase was then washed further with saturated NaHCO_{3(aq)} and brine, and then dried over MgSO₄. The DCM was removed *in vacuo* to yield a honey-coloured oil (6.35 g, 95%). **Elemental Analysis** calc.(obs.) for C₉H₁₃NS: C = 64.6 (64.4); H = 7.8 (7.7); N = 8.4 (8.5)%. **IR** (oil): $\nu_{\max}/\text{cm}^{-1}$ 3455w and 3352w (NH₂), 3063w, 3015w, 2959m, 2928w, and 2870w (aliphatic CH), 1603m (NH), 1477m, 1447m, 1300m, and 746m (*ortho*-substituted Ph). **¹H NMR** (500 MHz, CDCl₃) δ_{H} = 7.37 (1H, dd, J = 7.7, 1.5 Hz, C⁶H), 7.11 (1H, td, J = 7.5, 1.6 Hz, C⁴H), 6.73 (1H, dd, J = 8.0, 1.3 Hz, C³H), 6.70 (1H, td, J = 7.5, 1.4 Hz, C⁵H), 4.34 (2H, bs, NH₂), 2.72 (2H, t, J = 7.3 Hz, SC⁷H₂), 1.59 (2H, sextet, J = 7.3 Hz, SCH₂C⁸H₂), 0.99 (3H, t, J = 7.3 Hz, C⁹H₃) ppm. **¹³C NMR** (75 MHz, CDCl₃) δ_{C} = 148.00 (C²), 135.49 (C⁶), 129.23 (C⁴), 118.18 (C⁵), 118.00 (C¹), 114.63 (C³), 36.61 (C⁷), 22.79 (C⁸), 13.15 (C⁹) ppm. **HRMS ESI m/z [M + H]⁺ calc.** for C₉H₁₄NS: 168.0847, found 168.0849.

* It should also be noted that stronger (rare-earth) magnetic microwave stir bars help improve reaction time through improved mixing.

Preparation of N'-(2-propylthiophenyl)-benzamidine (1c)

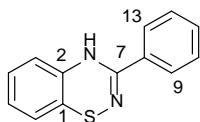


2-(Propylthio)benzenamine (**1b**, 4.0 g, 24 mmol) was dissolved in dry THF (10 mL) and added dropwise to a stirred solution of lithium bis(trimethylsilyl)amide (4.51 g, 27 mmol) in dry THF (15 mL) at 0 °C under a nitrogen atmosphere, and the dark reaction mixture was allowed to warm to room temperature and stirred for 18 h. Benzonitrile (2.46 mL, 24 mmol) was then added dropwise to the reaction mixture and stirred for a further 18 h. The volume of solvent was reduced to approximately 10 mL and the reaction mixture treated with 100 mL of NaHCO_{3(aq)} on ice, then extracted with DCM (150 mL). The organic phase was washed with NaHCO_{3(aq.)} and brine, dried over MgSO₄ and the solvent was removed *in vacuo* to yield the product as an off-white solid. The product was purified by repeated extractions with hot hexane to remove an intractable brown-red oil and recrystallized from hot hexane as a white crystalline solid (5.9 g, 91%) mp 77.9 °C (from hexane) (lit.^[2] 67-78 °C). **Elemental Analysis** calc.(obs.) for C₁₆H₁₈N₂S: C = 71.1(70.9); H = 6.7(6.7); N = 10.4(10.3)%. **IR** (solid): $\nu_{\max}/\text{cm}^{-1}$ 3443w (NH), 3291w, 3253w, 3126w, 3056w, 3044w, 2961w, 2928w, 2908w, 2869w, 1634m (CN), 1568m (NH), 1455m, 1386m, 1256m, 777m, 750m, 686m, 445m. **¹H NMR** (500 MHz, CDCl₃) δ_{H} = 7.95 (2H, d, J = 7.1 Hz, C^{9,13}H), 7.45-7.69 (3H, m, C^{10,12}H, C¹¹H), 7.31 (1H, d, J = 7.8 Hz, C³H), 7.16 (1H, t, J = 7.4 Hz, C⁵H), 7.05 (1H, t, J = 7.4 Hz, C⁴H), 6.92 (1H, d, J = 7.6 Hz, C⁶H), 4.78 (2H, bs, NH₂), 2.88 (2H, t, J = 7.3 Hz, SC¹⁴H₂), 1.69 (2H, sextet, J = 7.4 Hz, SCH₂C¹⁵H₂), 1.03 (3H, t, J = 7.4 Hz, C¹⁶H₃) ppm. **¹³C NMR** (75 MHz, CDCl₃) δ_{C} = 154.62 (C⁷), 147.74 (C²), 135.67 (C⁸), 130.74 (C¹¹), 129.64 (C¹), 128.63 (C^{10,12}), 127.72 (C³), 127.04 (C^{9,13}), 126.19 (C⁵), 123.62 (C⁴), 121.36 (C⁶), 33.88 (C¹⁴), 22.49 (C¹⁵), 13.83 (C¹⁶) ppm. **HRMS ESI m/z [M + H]⁺ calc.** for C₁₆H₁₉N₂S: 271.1269, found 271.1271.

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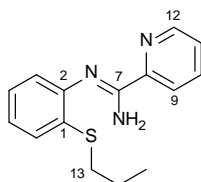
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Preparation of 3-phenyl-4H-benzo[e]-1,2,4-thiadiazine (1)



A solution of *N*-chlorosuccinimide (3.13 g, 23.5 mmol) in DCM (60 mL) was added dropwise to a solution of **1c** (5.95 g, 22 mmol) in DCM (40 mL) at -78 °C and the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was then washed with 0.1 M NaOH_(aq), water, brine and then dried over MgSO₄. The solvent was removed *in vacuo* and the oily residue re-dissolved in toluene (30 mL) and brought to reflux for 12 h. The solvent was again removed *in vacuo* to yield an off-green solid. The product was crystallized by slow diffusion of pentane into a chloroform solution to yield bright yellow crystals (2.74 g, 55%) mp 114 °C (from pentane/chloroform) (lit.^[3] 119-120 °C). **Elemental Analysis** calc.(obs.) for C₁₃H₁₀N₂S: C = 68.9(68.7); H = 4.5 (4.4); N = 12.2(12.2)%. **IR** (solid): $\nu_{\max}/\text{cm}^{-1}$ 3223w, 3180w, 3152w, 3095w, 3055w, 2995w, 1458m, 1419m, 1310m, 1240m, 756s, 735m, 693s, 667m. **¹H NMR** (500 MHz, CDCl₃) δ_{H} = 7.64 (2H, d, *J* = 7.9 Hz, C^{9,13}H), 7.46 (1H, td, *J* = 7.3, 1.2 Hz, C¹¹H), 7.40 (2H, dd, *J* = 7.8, 1.4 Hz, C^{10,12}H), 6.90-6.97 (2H, m, C⁴H, C⁵H), 6.73 (1H, d, *J* = 7.2 Hz, C⁶H), 6.68 (1H, bs, NH), 6.44 (1H, dd, *J* = 7.4, 1.4 Hz, C³H) ppm. **¹³C NMR** (75 MHz, CDCl₃) δ_{C} = 156.99 (C⁷), 136.73 (C²), 134.07 (C⁸), 131.04 (C¹¹), 128.83 (C^{10,12}), 127.58 (C⁴), 126.01 (C^{9,13}), 125.64 (C⁵), 123.10 (C⁶), 121.20 (C¹), 114.28 (C³) ppm. **MS ESI *m/z* [M + H]⁺** calc. for C₁₃H₁₁N₂S: 227.0643, found 227.06.

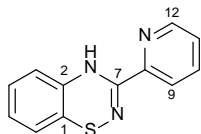
Preparation of N'-(2-propylthiophenyl)-picolinamidine (2c)



2-Propylsulphonylphenylamine (**1b**, 7 g, 42 mmol) was dissolved in dry THF (15 mL) and added dropwise to a stirred solution of lithium bis(trimethylsilyl)amide (7.69 g, 46 mmol) in dry THF (40 mL) at 0 °C under a nitrogen atmosphere, and the dark reaction mixture was allowed to warm to room temperature and stirred for 18 h. 2-Cyanopyridine (4.05 mL, 42 mmol) was dissolved in THF (15 mL) then added dropwise to the reaction mixture and stirred for a further 18 h. The volume of solvent was reduced to approximately 10 mL and the reaction mixture treated with 100 mL of NaHCO_{3(aq)} on ice, then extracted with DCM (150 mL). The organic phase was washed with NaHCO_{3(aq)} and brine, dried over MgSO₄ and the solvent was removed *in vacuo* to yield the product as a dark brown viscous oil (10.8 g, 95%). **Elemental Analysis** calc.(obs.) for C₁₅H₁₇N₃S: C = 66.4 (66.3); H = 6.3 (6.3); N = 15.5(15.2)%. **IR** (oil): $\nu_{\max}/\text{cm}^{-1}$ 3444m and 3325m (NH), 3047w, 2963w, 2961w, 2873w, 2858w, 1642s (CN), 1567s (NH), 1457m, 1376m, 802m, 743s, 686m. **¹H NMR** (500 MHz, CDCl₃) δ_{H} = 8.56 (1H, d, *J* = 4.5 Hz, C¹²H), 8.51 (1H, d, *J* = 7.8 Hz, C⁹H), 7.82 (1H, td, *J* = 7.8, 1.6 Hz, C¹⁰H), 7.39 (1H, ddd, *J* = 6.4, 4.9, 0.85 Hz, C¹¹H), 7.30 (1H, d, *J* = 7.7 Hz, C³H), 7.15 (1H, t, *J* = 7.3 Hz, C⁵H), 7.04 (1H, td, *J* = 7.7, 1.2 Hz, C⁴H), 6.95 (1H, d, *J* = 7.2 Hz, C⁶H), 6.04 (2H, bs, NH₂), 2.85 (2H, t, *J* = 7.3 Hz, SC¹³H₂), 1.68 (2H, sextet, *J* = 7.3 Hz, SCH₂C¹⁴H₂), 1.01 (3H, t, *J* = 7.4 Hz, C¹⁵H₃) ppm. **¹³C NMR** (75 MHz, CDCl₃) δ_{C} = 152.25 (C⁷), 151.37 (C⁸), 147.94 (C¹²), 147.89 (C²), 136.90 (C¹⁰), 129.92 (C¹), 127.58 (C³), 126.09 (C⁵), 125.27 (C¹¹), 123.65 (C⁴), 121.97 (C⁹), 120.94 (C⁶), 33.81 (C¹³), 22.41 (C¹⁴), 13.80 (C¹⁵) ppm. **MS ESI *m/z* [M + H]⁺** calc. for C₁₅H₁₈N₃S: 272.1221, found 272.12.

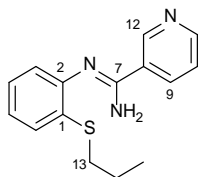
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Preparation of 3-(pyridin-2-yl)-4H-benzo[e]-1,2,4-thiadiazine (2)



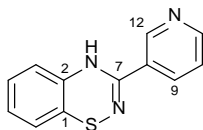
A solution of *N*-chlorosuccinimide (5.58 g, 42 mmol) in DCM (80 mL) was added dropwise to a solution of **1c** (10.86 g, 40 mmol) in DCM (80 mL) at -78 °C and the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was then washed with 0.1 M NaOH_(aq), water, brine and then dried over MgSO₄. The solvent was removed *in vacuo* and the oily residue re-dissolved in toluene (40 mL) and brought to reflux for 12 h. The solvent was again removed *in vacuo* to yield a brown solid. The product was purified by recrystallization using a heated mixture of 80% hexane and 20% DCM and allowing it to cool slowly to -17 °C to yield rich red/brown crystals (6.5 g, 72%) mp 114 °C (from hexane/DCM). **Elemental Analysis** calc.(obs.) for C₁₂H₉N₃S: C = 63.4 (63.1); H = 4.0(4.0); N = 18.5(18.2)%. **IR** (solid): $\nu_{\max}/\text{cm}^{-1}$ 3308m (NH), 3055w, 2962w, 2923w, 2849w, 1627m (NH), 1461s, 1437m, 1418m, 792m, 739s, 618m. **¹H NMR** (500 MHz, CDCl₃) δ_{H} = 8.58 (1H, bs, NH), 8.53 (1H, d, *J* = 4.8 Hz, C¹²H), 8.09 (1H, d, *J* = 8.0 Hz, C⁹H), 7.77 (1H, td, *J* = 7.8, 1.7 Hz, C¹⁰H), 7.38 (1H, ddd, *J* = 4.9, 4.9, 1.0 Hz, C¹¹H), 6.94 (1H, td, *J* = 7.6, 1.4 Hz, C⁴H), 6.88 (1H, td, *J* = 7.6, 1.2 Hz, C⁵H), 6.69 (1H, d, *J* = 7.4 Hz, C⁶H), 6.50 (1H, dd, *J* = 7.7, 1.05 Hz, C³H) ppm. **¹³C NMR** (75 MHz, CDCl₃) δ_{C} = 154.47 (C⁷), 148.20 (C⁸), 147.61 (C¹²), 137.12 (C¹⁰), 136.92 (C²), 127.83 (C⁴), 125.45 (C¹¹), 125.33 (C⁵), 122.96 (C⁶), 121.44 (C⁹), 120.27 (C¹), 114.49 (C³) ppm. **MS** ESI *m/z* [M + H]⁺ calc. for C₁₂H₁₀N₃S: 228.0595, found 228.06.

Preparation of N'-(2-propylthiophenyl)-nicotinamide (3c)



A solution of sodium bis(trimethylsilyl)amide (4.84g, 26 mmol) in THF (30 mL) was added dropwise to a solution of **1b** (4.00g, 24 mmol) in THF (10 mL) under nitrogen. The reaction mixture was left to stir for 12h at room temperature. A solution of 3-cyanopyridine (2.7g, 26 mmol) in THF (10 mL) was added dropwise and the reaction mixture stirred at room temperature for 3d. The volume of solvent was reduced to *ca.* 10 mL under vacuum and the reaction mixture quenched in 100 mL of ice-water and then extracted into DCM. The organic phase was washed with NaHCO_{3(aq)} and brine, dried over MgSO₄ and the solvent was removed *in vacuo*. The product was purified by flash column chromatography in EtOAc to yield fine yellow crystals (3.13 g, 11.5 mmol, 48%). **Elemental Analysis** calc.(obs.) for C₁₅H₁₇N₃S: C = 66.4(65.9); H = 6.3(6.3); N = 15.5(15.3)%. **¹H NMR** (400 MHz, CDCl₃) δ_{H} = 9.05 (1H, bs, C¹²H), 8.68 (1H, dd, *J* = 4.9, 1.5 Hz, C¹¹H), 8.25 (1H, bs, C⁹H), 7.40-6.95 (5H, m, C¹⁰H, C³H, C⁵H, C⁴H, C⁶H), 2.86 (2H, t, *J* = 7.3 Hz, SC¹³H₂), 1.66 (2H, sextet, *J* = 7.3 Hz, SCH₂C¹⁴H₂), 1.01 (3H, t, *J* = 7.3 Hz, C¹⁵H₃) ppm.

Preparation of 3-(pyridine-3-yl)-4H-benzo[e]-1,2,4-thiadiazine (3)



A solution of *N*-chlorosuccinimide (0.80 g, 6 mmol) in DCM (25 mL) was added dropwise to a solution of **3c** (1.55 g, 6.0 mmol) in DCM (20 mL) at -78 °C and the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was then washed with 0.1 M NaOH_(aq), water, brine and then dried over MgSO₄. The solvent was removed *in vacuo* and the oily residue re-dissolved in toluene (10 mL) and brought to

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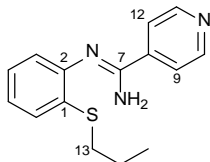
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reflux for 12 h. The solvent was again removed *in vacuo* and the crude product purified by recrystallization from DCM and hexane to yield bright red crystals (0.48 g, 33%). **Elemental Analysis** calc.(obs.) for $C_{12}H_9N_3S \cdot 0.04CH_2Cl_2$: * C = 62.7 (62.9); H = 4.0(3.8); N = 18.2 (17.7)%. 1H NMR (400 MHz, $CDCl_3$) δ_H = 9.06 (1H, d, J = 1.7 Hz, $C^{12}H$), 8.67 (1H, dd, J = 5.8, 1.2 Hz, $C^{11}H$), 8.13 (1H, unresolved dt, J = 8.0 Hz, C^9H), 7.43 (1H, dd, J = 8.0, 5.0 Hz, $C^{10}H$), 7.15-6.85 (2H, m, C^4H , C^5H), 6.66 (1H, unresolved dd, C^6H), 6.55 (1H, unresolved dd, C^3H), 2.9 (1H, bs, NH) ppm. **MS** EI m/z [M]⁺ calc. for $C_{12}H_9N_3S$: 227.0517, found 227.05.

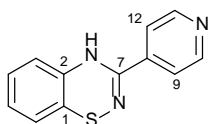
* measurements on freshly recrystallised sample from DCM.

Preparation of N'(2-propylthiophenyl)-iso-nicotinamide (4c)



A solution of sodium bis(trimethylsilylamide) (8.25g, 45mmol) in THF (40 mL) was added dropwise to a solution of **1b** (7.0g, 42 mmol) in THF (15 mL) under nitrogen and the dark reaction mixture stirred at room temperature for 12h. A solution of 4-cyanopyridine (4.68g, 48 mmol) in THF (10 mL) was added dropwise and the reaction mixture stirred at room temperature for 3d. The volume of the solvent was reduced under vacuum to approximately 10 mL and the reaction mixture quenched in 100 mL of ice and $NaHCO_{3(aq)}$. The reaction mixture was then extracted with DCM and the organic phase washed with $NaHCO_{3(aq)}$ and brine and then dried over $MgSO_4$. The solvent was removed under vacuum to yield an intractable red oil containing crystals of the product. The product was purified by repeated extractions into hot hexane and recrystallised from hexane as colourless crystals (8.28 g, 30.5 mmol, 72%). 1H NMR (400 MHz, $CDCl_3$) δ_H = 8.70 (2H, d, J = 6.0 Hz, $C^{10,11}H$), 7.75 (2H, bs, $C^{9,12}H$), 7.30 (1H, dd, J = 7.8, 1.3 Hz, C^3H), 7.10 (2H, m, C^5H , C^4H), 6.90 (1H, d, J = 7.6 Hz, C^6H), 5.10 (2H, bs, NH_2), 2.85 (2H, t, J = 7.4 Hz, $SC^{13}H_2$), 1.67 (2H, sextet, J = 7.4 Hz, $SCH_2C^{14}H_2$), 1.02 (3H, t, J = 7.4 Hz, $C^{15}H_3$) ppm.

Preparation of 3-(pyridine-4-yl)-4H-benzo[e]-1,2,4-thiadiazine (4)

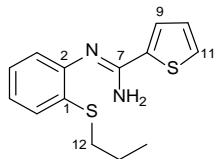


A solution of N-chlorosuccinimide (1.46g, 11 mol) in DCM (20 mL) was added dropwise to a solution of **4c** (2.43g, 10 mmol) in DCM (20 mL) at -78 °C. The reaction mixture was allowed to warm to room temperature and then stirred for a further 12h then washed with 0.1M $NaOH_{(aq)}$, H_2O and brine and finally dried over $MgSO_4$. The solvent was removed *in vacuo* and the product recrystallised from chloroform and hexane to yield orange crystals (0.79 g, 3.4 mmol, 34%). **Elemental Analysis** calc.(obs.) for $C_{12}H_9N_3S \cdot 0.05CHCl_3$: * C = 62.1(62.3); H = 3.9(3.9); N = 18.0(17.9)%. 1H NMR (400 MHz, $CDCl_3$) δ_H = 8.70 (2H, d, J = 6.0 Hz, $C^{10,11}H$), 7.50 (2H, unresolved dd, J = 4.6 Hz, $C^{9,12}H$), 6.93 (2H, m, C^4H , C^5H), 6.66 (1H, unresolved dd, C^6H), 6.39 (1H, unresolved dd, C^3H), 1.60 (1H, bs, NH) ppm. **MS** EI+ m/z [M]⁺ calc. for $C_{12}H_9N_3S$: 227.0517, found 227.06.

* freshly recrystallised from $CHCl_3$ leading to trace chloroform in analysis.

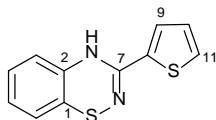
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Preparation of N'(2-propylthiophenyl)-thiophene-2-carboxamide (5c)



2-propylsulphanylphenylamine (**1b**, 7.0 g, 42 mmol) was dissolved in dry THF (15 mL) and added dropwise to a stirred solution of lithium bis(trimethylsilyl)amide (7.69 g, 46 mmol) in dry THF (40 mL) at 0 °C under a nitrogen atmosphere, and the dark reaction mixture was allowed to warm to room temperature and stirred for 18 h. 2-thiophenecarbonitrile (3.91 mL, 42 mmol) was dissolved in THF (15 mL) then added dropwise to the reaction mixture and stirred for a further 18 h which turned the mixture olive green. The volume of solvent was reduced to approximately 10 mL and the reaction mixture treated with 100 mL of NaHCO_{3(aq.)} on ice, then extracted with DCM (150 mL). The organic phase was washed with NaHCO_{3(aq.)} and brine, dried over MgSO₄ and the solvent was removed *in vacuo* to yield the product as a dark brown viscous oil. The product was purified by recrystallization using a heated mixture of hexane with a small amount of DCM to yield large dark brown/purple crystals or small sugar brown crystals (9.49 g, 82%) mp 110.9 °C (from hexane/DCM). **Elemental Analysis** calc.(obs.) for C₁₄H₁₆N₂S₂: C = 60.8 (60.7); H = 5.8 (6.1); N = 10.1(10.2)%. **IR** (oil): $\nu_{\max}/\text{cm}^{-1}$ 3457w (NH), 3287w, 3132w, 3117w, 3073w, 3049w, 2960w, 2921w, 2855w, 1621m, 1589m, 1571m, 1434m, 1218w, 1032w, 832m, 722m, 396w. **¹H NMR** (500 MHz, CDCl₃) δ_{H} = 7.45-7.42 (2H, m, C¹¹H, C⁹H), 7.30 (1H, d, *J* = 7.7 Hz, C³H), 7.15 (1H, t, *J* = 7.2, C⁵H), 7.08 (1H, t, *J* = 4.2 Hz, C¹⁰H), 7.03 (1H, td, *J* = 7.7, 1.4 Hz, C⁴H), 6.92 (1H, bd, *J* = 6.8 Hz, C⁶H), 4.76 (2H, bs, NH₂), 2.87 (2H, t, *J* = 7.4 Hz, SC¹²H₂), 1.67 (2H, sextet, *J* = 7.4 Hz, SCH₂C¹³H₂), 1.02 (3H, t, *J* = 7.4 Hz, C¹⁴H₃) ppm. **¹³C NMR** (75 MHz, CDCl₃) δ_{C} = 149.59 (C⁷), 147.08 (C²), 140.35 (C⁸), 129.86 (C¹), 129.40 (C¹¹), 128.16 (C³), 127.40 (C¹⁰), 126.29 (C⁹), 126.15 (C⁵), 123.88 (C⁴), 121.54 (C⁶), 33.95 (C¹²), 22.53 (C¹³), 13.83 (C¹⁴) ppm. **HRMS** ESI *m/z* [M + H]⁺ calc. for C₁₄H₁₇N₂S₂: 277.0833, found 277.0828.

Preparation of 3-(thiophen-2-yl)-4H-benzo[e]-1,2,4-thiadiazine (5)



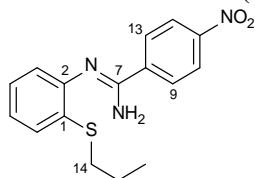
A solution of *N*-chlorosuccinimide (4.74 g, 35.5 mmol) in DCM (75 mL) was added dropwise to a solution of **5c** (9.37 g, 33.9 mmol) in DCM (100 mL) at -78 °C and the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was then washed with 0.1 M NaOH_(aq.), water, brine and then dried over MgSO₄. The solvent was removed *in vacuo* and the oily residue re-dissolved in toluene (40 mL) and brought to reflux for 12 h. The solvent was again removed *in vacuo* to yield a brown solid. The product was crystallized by slow diffusion of pentane into a DCM solution to yield red/orange crystals (1.62 g, 21%) mp 125.9-137.5 °C (from pentane/DCM). **Elemental Analysis** calc.(obs.) for C₁₁H₈N₂S₂: C = 56.9 (56.8); H = 3.5(3.7); N = 12.1(11.9)%. **IR** (solid): $\nu_{\max}/\text{cm}^{-1}$ 3234w (NH), 3175w, 3088w, 3071w, 2996w, 1586w, 1456m, 1429m, 1254w, 745m, 719m, 659w. **¹H NMR** (300 MHz, CDCl₃) δ_{H} = 7.40 (1H, dd, *J* = 5.1, 1.0 Hz, C¹¹H), 7.30 (1H, dd, *J* = 3.7, 0.9 Hz, C⁹H), 7.04 (1H, td, *J* = 5.0, 1.3 Hz, C¹⁰H), 6.99-6.89 (2H, m, C⁴H, C⁵H), 6.74 (1H, dd, *J* = 7.1, 1.7 Hz, C⁶H), 6.62 (1H, bs, NH), 6.47 (1H, dd, *J* = 7.5, 1.7 Hz, C³H) ppm. **¹³C NMR** (75 MHz, CDCl₃) δ_{C} = 152.05 (C⁷), 137.90 (C⁸), 136.50 (C²), 129.58 (C¹¹), 127.64 (C⁴), 127.31 (C¹⁰), 125.63 (C⁵), 124.90 (C⁹), 123.36 (C⁶), 121.45 (C¹), 114.43 (C³) ppm. **HRMS** ESI *m/z* [M + H]⁺ calc. for C₁₁H₉N₂S₂: 233.0207, found 233.0202.

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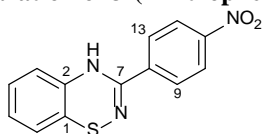
Preparation of 4-nitro- N'-(2-propylthiophenyl)-benzamide (6c)



4-nitrobenzamide (0.9 g, 6.0 mmol) was dissolved in methanol (10 mL) and sodium methoxide (54 mg, 1 mmol) added. The reaction mixture was brought to reflux for 16 h, cooled and quenched with a 10% solution of glacial acetic acid in methanol (0.5 mL, 1 mmol). 2-propylsulphanylphenylamine (**1b**) (1.0 g, 6.0 mmol) was added and the mixture returned to reflux for 72 h. The solvent was removed *in vacuo* and the residue dissolved in DCM (50 mL) and washed with aliquots of water, NaHCO_{3(aq)} and brine (20 mL each). The organic layer was then dried over MgSO₄ and the solvent removed *in vacuo*. The product was then purified by flash column chromatography, the first fractions eluted under a 50/50 mixture of DCM and hexanes and the product being the final fraction eluted under methanol which was isolated as a dark oil (1.51 g, 80%). **Elemental Analysis** calc.(obs.) for C₁₆H₁₇N₃O₂S·0.75MeOH: * C = 59.3 (59.0); H = 5.9(5.3); N = 12.4(12.9)%. ¹H NMR (400 MHz, CDCl₃) δ_H = 8.35 (2H, dt, *J* = 9.0, 2.0 Hz, C^{10,12}H), 7.88 (2H, dt, *J* = 9.0, 2.0 Hz, C^{9,13}H), 7.51 (2H, dd, *J* = 7.7, 1.4 Hz, C³H, C⁵H), 7.26 (1H, m, C⁴H), 7.13 (1H, m, C⁶H), 2.85 (2H, t, *J* = 7.2 Hz, SC¹⁴H₂), 1.61 (2H, sextet, *J* = 7.3 Hz, SCH₂C¹⁵H₂), 0.96 (3H, t, *J* = 8.0 Hz, C¹⁶H₃) ppm. **MS** ES(I) *m/z* [M + H]⁺ calc. for C₁₆H₁₈N₃O₂S: 316.1120, found 316.11.

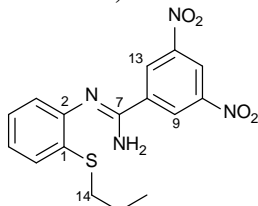
* Removal of residual MeOH from **6c** (a viscous oil) proved difficult even after exhaustive pumping, most likely due to the possibility of strong hydrogen bonding to the amidine. Trace MeOH was evident by ¹H NMR.

Preparation of 3-(4-nitrophenyl)-4Hbenzo[e]-1,2,4-thiadiazine (6)



N-chlorosuccinimide (1.0 g, 7.4 mmol) in DCM (40 mL) was added dropwise to **6c** (2.3 g, 7.0 mmol) in DCM (10 mL) maintained at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 72 hours. The reaction mixture was washed with 0.1M NaOH_(aq), water and brine (50 mL each) and dried over MgSO₄. The solvent was removed and the resultant bright yellow oil dissolved in toluene (10 mL) and brought to reflux for 72 h. The reaction mixture was allowed to cool to room temperature and then sealed and stored at 4 °C for 24 h. The mixture was filtered and the crude product isolated as a red powder. Dark red, needle-like crystals of suitable quality for single crystal XRD were grown by slow diffusion of hexanes into a dilute solution of **6** in DCM (0.38 g, 20%). **Elemental Analysis** calc.(obs.) for C₁₃H₉N₃O₂S·0.05CH₂Cl₂: C = 56.9(57.0); H = 3.3(3.4); N = 15.3(14.9)%. ¹H NMR (400 MHz, CDCl₃) δ_H = 8.25 (2H, d, *J* = 7.0 Hz, C^{10,12}H), 7.82 (2H, d, *J* = 8.0 Hz, C^{9,13}H), 6.92 (2H, m, C⁴H, C⁵H), 6.68 (1H, dd, *J* = 6.7, 1.9 Hz, C⁶H), 6.52 (1H, bs, NH), 6.41 (1H, d, *J* = 7.4 Hz, C³H) ppm. **MS** ESI *m/z* [M + H]⁺ calc. for C₁₂H₁₀N₃S: 272.0494, found 272.05.

Preparation of 3,5-dinitro-N'-(2-propylthiophenyl)-benzamide (7c)



3,5-Dinitrobenzamide (2.0 g, 10.3 mmol) was dissolved in methanol (10 mL) and sodium methoxide (54 mg, 1 mmol) added, resulting in the immediate formation of a deep red colour. The reaction mixture was brought to reflux for 16 h, cooled to room temperature and the pale precipitate of residual 3,5-dinitrobenzamide removed by filtration. The red solution was quenched with a 10% solution of glacial acetic acid in methanol (0.5 mL, 1.0 mmol)

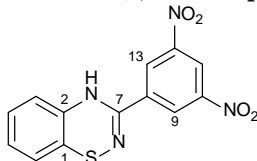
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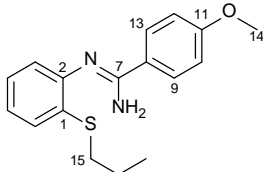
and 2-propylsulphonylphenylamine (**1b**) (1.9 g, 11 mmol) was added. The mixture was stirred at room temperature for 48 h and the volume of the reaction mixture reduced *in vacuo* by 50%. The reaction mixture was filtered and the residue washed with two aliquots of hexanes (20 mL) to yield the product as a mustard-coloured powder (1.21 g, 26%). **Elemental Analysis** calc.(obs.) for $C_{16}H_{16}N_4O_4S$: C = 53.3(53.1); H = 4.5(4.5); N = 15.6(15.4)%. **1H NMR** (400 MHz, $CDCl_3$) δ_H = 9.15 (3H, m, $C^{11}H$, $C^{9,13}H$), 7.34 (1H, d, J = 7.7 Hz, C^3H), 7.20 (1H, td, J = 7.4, 0.9 Hz, C^5H), 7.11 (1H, td, J = 7.1, 1.3 Hz, C^4H), 6.90 (1H, dd, J = 7.6, 1.2 Hz, C^6H), 4.95 (2H, bs, NH_2), 2.89 (2H, t, J = 7.4 Hz, $SC^{14}H_2$), 1.69 (2H, sextet, J = 7.3 Hz, $SCH_2C^{15}H_2$), 1.03 (3H, t, J = 7.3 Hz, $C^{16}H_3$) ppm. **MS** ESI m/z [$M + H$]⁺ calc. for $C_{16}H_{17}N_4O_4S$: 361.0971, found 361.10.

Preparation of 3-(3,5-dinitrophenyl)-4H-benzo[e]-1,2,4-thiadiazine (**7**)



Solid **7c** (0.8 g, 2.2 mmol) was suspended in chloroform (25 mL) and cooled to 0 °C. *N*-chlorosuccinimide (420 mg, 2.4 mmol) in chloroform (25 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 10 days. The reaction mixture was washed with 1M $NaOH_{(aq)}$, water and brine (50 mL each) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the oily residue dissolved in toluene (50 mL) and brought to reflux for 16 h. The solvent was removed *in vacuo* to yield a red powder which was recrystallised by slow evaporation of a methanol solution (100 mL) to yield deep red needle-like crystals (284 mg, 41%). **Elemental Analysis** calc.(obs.) for $C_{13}H_8N_4O_4S$: C = 49.4(48.6); H = 2.6(2.6); N = 17.7(17.1)%. **1H NMR** (400 MHz, $CDCl_3$) δ_H = 9.10 (1H, t, J = 2.0 Hz, $C^{11}H$), 8.83 (2H, d, J = 2.0 Hz, $C^{9,13}H$), 6.95 (2H, dq, J = 7.2, 1.7 Hz, C^4H , C^5H), 6.65 (1H, dd, J = 6.9, 1.7 Hz, C^6H), 6.48 (1H, bs, NH), 6.47 (1H, dd, J = 7.2, 1.3 Hz, C^3H) ppm. **MS** ESI m/z [$M + H$]⁺ calc. for $C_{13}H_9N_4O_4S$: 317.0345, found 317.03.

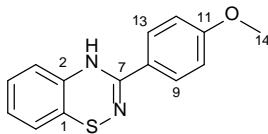
Preparation of 4-methoxy-*N'*-(2-propylthiophenyl)-benzamidinium (**8c**)



2-Propylsulphonylphenylamine (**1b**) (2.0 g, 12 mmol) was added dropwise to a stirred solution of lithium bis(trimethylsilyl)amide (2.13 g, 14 mmol) in dry THF (20 mL) under a nitrogen atmosphere, and the dark reaction mixture stirred for 16 h. 4-methoxybenzotrile (1.6g, 14 mmol) was dissolved in THF (10 mL) then added dropwise to the reaction mixture and stirred for a further 4 d. The reaction mixture was quenched in ice and water (50 mL) and the product extracted with DCM (2 x 50 mL). The organic phase was washed with successive aliquots of water and brine (50 mL each) and dried over $MgSO_4$. Residual starting materials were removed *via* flash column chromatography with the first two fractions eluted under a 50/50 mixture of DCM & hexanes. The solvent was then changed and the product eluted as the final fraction under methanol. The solvent was removed *in vacuo* to yield the product as an off-white poly-crystalline powder (3.22 g, 76%). **Elemental Analysis** calc.(obs.) for $C_{17}H_{20}N_2OS \cdot 0.75MeOH$ (supported by NMR data): C = 65.7(65.5); H = 7.1(7.1); N = 8.6(8.8)%. **1H NMR** (400 MHz, $CDCl_3$) δ_H = 7.84 (2H, bs, $C^{9,13}H$), 7.29 (1H, dd, J = 7.8, 1.1 Hz, C^3H), 7.13 (1H, t, J = 7.2 Hz, C^5H), 7.02 (1H, td, J = 7.6, 1.4 Hz, C^4H), 6.94 (3H, bd, J = 8.7 Hz, $C^{10,12}H$, C^6H), 4.76 (2H, bs, NH_2), 3.47 (3H, s, $C^{14}H$), 2.85 (2H, t, J = 6.5 Hz, $SC^{15}H_2$), 1.67 (2H, sextet, J = 6.4 Hz, $SCH_2C^{16}H_2$), 1.01 (3H, t, J = 7.3 Hz, $C^{17}H_3$) ppm. **MS** ESI m/z [$M + H$]⁺ calc. for $C_{17}H_{21}N_2OS$: 301.1375, found 301.13.

Syntheses of, and Structural Studies on, Benzo-fused 1,2,4-thiadiazines
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Electronic Supplementary Information

Preparation of 3-(4-methoxyphenyl)-4H-benzo[e]-1,2,4-thiadiazine (8)



A solution of *N*-chlorosuccinimide (1.3 g, 9.0 mmol) in DCM (40 mL) was added dropwise to a solution of **8c** (2.5 g, 8.3 mmol) in DCM (20 mL) maintained at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before warming to room temperature and stirred for 16 h producing a red-orange solution. The reaction mixture was then washed with 1 M NaOH_(aq) (20 mL), brine (50 mL) and then dried over MgSO₄. The solvent was removed *in vacuo* and the oily residue re-dissolved in toluene (25 mL) and brought to reflux for 16 h. The solvent was again removed *in vacuo* to yield a crude solid product. The product was purified by dissolving the solid in the minimum volume of hot DCM, to which hexanes (50 mL) were added and the mixture allowed to cool and settle forming a yellow-orange microcrystalline powder. The crystalline material was collected and further recrystallized from DCM and hexanes to yield fine yellow crystals (1.03 g, 48%). **Elemental Analysis** calc.(obs.) for C₁₄H₁₂N₂OS: C = 65.6(65.1); H = 4.7(4.8); N = 10.9(10.5)%. **¹H NMR** (400 MHz, CDCl₃) δ_H = 7.64 (2H, d, *J* = 6.9 Hz, C^{9,13}H), 6.95 (4H, m, C⁴H, C^{10,12}H, C⁵H), 6.77 (1H, d, *J* = 7.0, C⁶H), 6.63 (1H, bs, NH), 6.47 (1H, d, *J* = 7.6 Hz, C³H), 3.86 (3H, s, C¹⁴H) ppm. **MS ESI** *m/z* [M + H]⁺ calc. for C₁₄H₁₂N₂OS: 257.0749, found 257.08.

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