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Ewan R. Clark, John J. Hayward, Bryce J. Leontowicz, Dana J. Eisler and Jeremy M. Rawson

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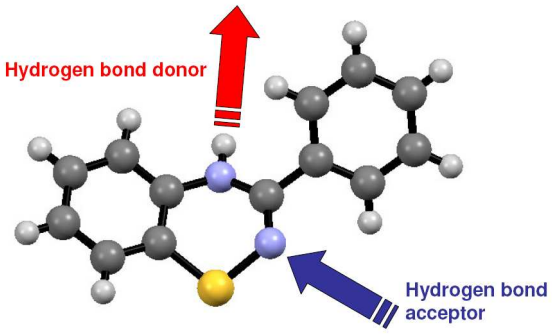
Strucutral characterisation of a series of benzothiadiazines reveal a propensity for the N-H group to act as a hydrogen bond donor. The hydrogen bond acceptor strength of the remaining heterocyclic N is probed by adjusting the hydrogen-bond acceptor strength of the R-substituent.



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PAPER

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

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The syntheses of nine benzo-fused-1,2,4-thiadizines are reported. The use of microwave synthesis has been shown to afford high yields and short reaction times in several key reaction steps. The molecular geometries of these heterocycles are discussed and their solid state packing motifs reveal a strong tendency for the N-H group to form hydrogen bonded chains.

The family of 1,2,4-benzothiadiazines in various oxidation states (Fig. 1, **A** – **C**) have attracted attention for both materials and pharmaceuticals applications. One electron oxidation of the S(II) variant **A** leads to stable free radicals,[1] some of which exhibit liquid crystalline properties.[2] Resonance-stabilized bis(thiadiazines) and related species have also attracted attention as conducting materials.[3] Whilst there are limited examples of the S(IV) derivative **B**,[4] the S(VI) system has been widely studied and the framework **C** lies at the core of a range of commercially available pharmaceuticals, classified as thiazides, which have applications in the treatment of hypertension and osteoporosis *inter alia*.[5]

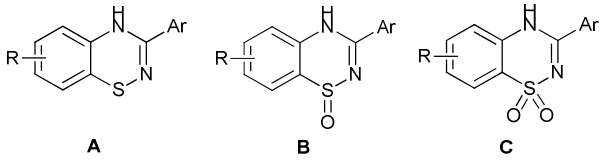

Fig. 1 Benzothiadiazines containing S^{II} (**A**), S^{IV} (**B**) and S^{VI} (**C**) centres.

Whilst there are a number of synthetic methodologies[1] to access specific derivatives of **A** depending on the fused substituent (e.g. **A1** – **A3**), a more generic method was established by Kaszynski to access a range of long-chain alkyl ether-functionalised derivatives of **A4** as liquid crystalline materials (Fig 2).[2]

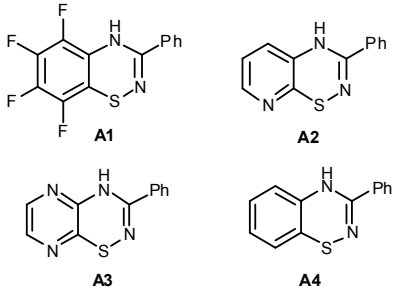

Fig. 2 Previously synthesised benzo-1,2,4-thiadiazines

In this current paper we extend this methodology to access a range of derivatives of **A** in which the group at the C(3) position is varied to include thienyl, pyridyl and functionalised phenyl rings, as well as a further derivative in which the fused benzo-ring has been functionalised (Fig. 3, **1** – **9**).

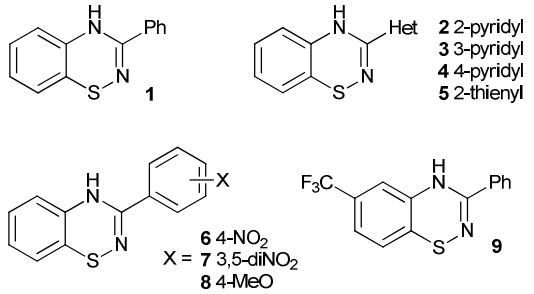

Fig. 3 Derivatives of **A** prepared in this paper.

Experimental

All chemicals were purchased from commercial suppliers and were used without further purification unless otherwise indicated. Sodium *n*-propylthiolate was prepared by treatment of ^{n}PrSH with NaH in THF. 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 N_2. 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 or a PerkinElmer 2400 Series II Elemental Analyzer. Melting points were determined using a Stanford Research Systems MPA120 EZ-Melt Automated Melting Point Apparatus. FT-IR spectra were measured as nujol

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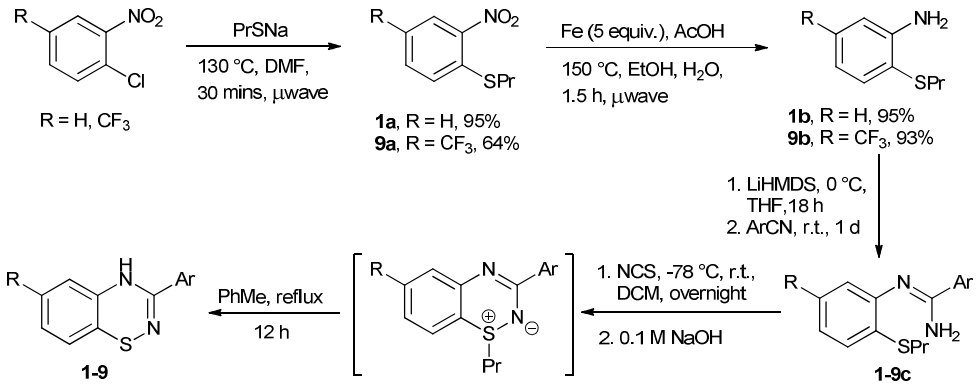

Scheme 1 Synthesis of **1** – **9**

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. Crystals for single crystal X-ray diffraction were mounted in fluoropolymer on a glass fibre or in paratone oil on a cryoloop and measured on a Nonius-Kappa CCD, Bruker APEX or Bruker APEX-II diffractometer using Mo-Kα radiation (λ = 0.71073 Å) at temperatures in the range 100-200 K using a Oxford Cryostream cooler. Data collected[6] on Nonius Kappa instruments were processed[7] using the HKL package with unit-cell parameters refined against all data. Data measured on the Bruker APEX or APEX-II were processed using the SAINTPLUS program[8] or APEX-II software[9] with an empirical absorption correction applied (SADABS).[10] Structures were solved by direct methods and refined using full-matrix least squares within SHELXTL.[11] All non-H atoms were refined anisotropically and H atoms added at calculated positions and refined using a riding model. Graphics for publication were prepared in Mercury.[12] Structural data for **1** – **9** as well as selected intermediates are available in cif format as ESI and are available from the CSD (deposit codes CCDC 969012 - 969022).

The synthesis of **9** is described in detail here and is representative of the general methodology employed. The experimental protocols and analytical data for all other compounds are reported in the ESI.

Synthesis of 9a

4-chloro-3-nitro-trifluoromethyl-benzene (1.47 mL, 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 25 min under microwave irradiation, and this process repeated a further four times for a total of 50 mmol. The combined reaction mixtures were added to water (250 mL) and the product extracted into Et_2O (3 x 100 mL); the organic layer was washed with water (150 mL), saturated $Na_2CO_{3(aq)}$ (200 mL) and then dried over $MgSO_4$. The solvent was removed *in vacuo* to reveal a waxy orange solid which was repeatedly extracted with hot hexane to remove an intractable brown-red oil and then recrystallized from hexane to yield **9a** as orange needles (8.49 g, 64%) mp 63.3 °C (lit. 69-70 °C).[13] ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.47 (1H, s, C^3*H*), 7.75 (1H, dd, *J* = 8.5, 1.5 Hz C^5*H*), 7.53 (1H, d, *J* = 8.6 Hz, C^6*H*), 2.98 (2H, t, *J* = 7.3 Hz, SC$^7H_2$), 1.80 (2H, sextet, *J* = 7.4 Hz, SCH$_2$C$^8H_2$), 1.12 (3H, t, *J* = 7.4 Hz, C$^9H_3$) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ_C = 145.23 (C^2), 143.48 (C^1), 129.41 (q, *J* = 3.2 Hz, C^5), 126.97 (C^6), 126.57 (q, *J* = 34.4 Hz, C^4), 123.24 (q, *J* = 3.9 Hz, C^3), 122.97 (q, *J* = 271.9 Hz, C^{10}), 34.27 (C^7), 21.09 (C^8), 13.63 (C^9) ppm; IR (solid/cm^{-1}): ν_{max} = 3119w, 3099w, 2975w, 2937w, 2879w (aliphatic CH), 1619w, 1521m, 1325m (NO_2), 1118s, 1089s (CF_3), 913m, 825m; Elemental Analysis calc. for $C_{10}H_{10}F_3NO_2S$: C 45.3, H 3.8, N 5.3%; found C 45.0, H 3.6, N 5.4%. Crystallography**:** Orthorhombic $P2_12_12_1$ *a* = 4.3006(12), *b* = 12.286(4), *c* = 21.406(6) Å (structure available as ESI).

Synthesis of 9b

Ethanol (15 mL), **9a** (2.65 g, 10 mmol), H_2O (0.5 mL) and glacial acetic acid (1 mL) were combined and stirred to form a homogenous mixture (< 2 min). Powdered iron (2.79 g, 50 mmol) was added slowly and the reaction mixture was stirred at 150 °C for 105 min under microwave irradiation. This process was repeated a further three times for a total of 40 mmol and the combined reaction mixture was diluted with CH_2Cl_2 (150 mL) and filtered through a silica gel plug. The silica was washed with CH_2Cl_2 (100 mL) and the solvents removed *in vacuo*. The residue was washed with 100 mL of saturated $NaHCO_{3(aq)}$ and extracted into CH_2Cl_2 (150 mL); the organic phase was washed with saturated $NaHCO_{3(aq)}$, brine, and then dried over $MgSO_4$. The CH_2Cl_2 was removed *in vacuo* to yield **9b** as an orange oil (8.76 g, 37.2 mmol, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.42 (1H, dd, *J* = 8.55, 0.65 Hz, C^6*H*), 6.93-6.92 (2H, m, C^5*H*, C^3*H*), 4.47 (2H, bs, N*H*), 2.78 (2H, t, *J* = 7.2 Hz, SC$^7H_2$), 1.60 (2H, sextet, *J* = 7.3 Hz, SCH$_2$C$^8H_2$), 1.00 (3H, t, *J* = 7.4 Hz, C$^9H_3$) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ_C = 147.73 (C^2), 134.61 (C^6), 130.94 (q, *J* = 32.2 Hz, C^4), 124.17 (q, *J* = 272.4 Hz, C^{10}), 122.84 (C^1), 114.72 (q, *J* = 3.1 Hz, C^5), 111.10 (q, *J* = 3.2 Hz, C^3), 36.40 (C^7), 22.93 (C^8), 13.33 (C^9) ppm; IR (thin film/ cm^{-1}): ν_{max} = 3464w

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and 3378w (NH_2), 2962m and 2904w (aliphatic CH), 1613w, 1258m, 1079m and 1012s (CF_3), 793s; HRMS ES(+) *m/z* $[M + H]^+$ calc. for $C_{10}H_{13}F_3NS$: 236.0721, found 236.0720.

Synthesis of 9c

9b (9.88 g, 42 mmol) in dry THF (15 mL) was 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 N_2. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. A solution of benzonitrile (4.3 mL, 42 mmol) in dry THF (15 mL) then added dropwise to the reaction mixture and stirred for a further 18 h. The volume of solvent was reduced to approx. 10 mL and the reaction mixture treated with 100 mL of $NaHCO_{3(aq.)}$ on ice and extracted into CH_2Cl_2 (150 mL). The organic phase was washed with $NaHCO_{3(aq.)}$ and brine, dried over $MgSO_4$ and the solvent was removed *in vacuo* to yield the crude product as a dark brown/red oil. Pure product was obtained by repeated extractions with a hot toluene-hexane mixture (70:30) to remove a granular brown solid and recrystallized from this solvent mixture to yield **9c** as white crystals (8.81 g, 62%) mp 108.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.94 (2H, d, J = 7.0 Hz, $C^{9,13}H$), 7.53-7.46 (3H, m, $C^{10,12}H$, $C^{11}H$), 7.32-7.27 (2H, m, C^6H, C^5H), 7.16 (1H, s, C^3H), 4.83 (2H, bs, NH_2), 2.90 (2H, t, J = 7.4 Hz, $SC^{14}H_2$), 1.73 (2H, sextet, J = 7.4 Hz, $SCH_2C^{15}H_2$), 1.06 (3H, t, J = 7.4 Hz, $C^{16}H_3$) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ_C = 155.35 (C^7), 147.00 (C^2) 135.81 (C^8), 135.17 (C^1), 131.04 (C^{11}), 128.68 ($C^{10,12}$), 127.53 (q, J = 32.0 Hz, C^4), 127.06 ($C^{9,13}$), 125.74 (C^6), 124.43 (q, J = 271.9 Hz, C^{17}), 120.20 (C^5), 117.12 (q, J = 2.77 Hz, C^3), 33.19 (C^{14}), 22.11 (C^{15}), 13.81 (C^{16}) ppm; IR (solid/cm^{-1}): ν_{max} = 3457w (NH), 3287w, 3319br, 2967w, 2868w, 1634m, 1611m, 1408m, 1238m, 1118m, 1073m, 897m, 701m, 475m; HRMS ES(+) *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}F_3N_2S$: 339.1143, found 339.1144; Elemental Analysis calc. for $C_{17}H_{17}F_3N_2S$: C 60.3, H 5.1, N 8.3%; found C 60.4, H 5.0, N 8.2%. Crystallography: Orthorhombic *Pbcn*, a = 9.359(3), b = 19.512(6), c = 18.547(6) (structure available as ESI).

Synthesis of 9

N-chlorosuccinimide (3.67 g, 27.5 mmol) in CH_2Cl_2 (70 mL) was added dropwise to a solution of **9c** (8.8 g, 26 mmol) in CH_2Cl_2 (45 mL) at -78 °C, allowed to warm to room temperature and stirred for 18 h. The reaction mixture was then washed with 0.1 M $NaOH_{(aq)}$, water and brine, and dried over $MgSO_4$. The solvent was removed *in vacuo* and the oily residue re-dissolved in toluene (30 mL) and refluxed for 12 h. The solvent was removed *in vacuo* and the solid recrystallised from hexane-toluene (70:30) at -18 °C to yield **9** as small orange crystals (6.12 g, 80%) mp 118 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.59 (2H, d, J = 7.1 Hz, $C^{9,13}H$), 7.46-7.37 (3H, m, $C^{11}H$, $C^{10,12}H$), 7.12 (1H, d, J = 7.3 Hz, C^5H), 6.83 (1H, bs, N*H*), 6.73 (1H, d, J = 7.6 Hz, C^6H), 6.61 (1H, s, C^3H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ_C = 156.53 (C^7), 137.15 (C^2), 133.49 (C^8), 131.42 (C^{11}), 129.75 (q, J = 32.9 Hz, C^4), 128.95 ($C^{10,12}$), 126.925 (q, J = 271.5 Hz, C^{14}), 126.62 (C^1), 126.00 ($C^{9,13}$), 122.92 (C^6), 122.49 (q, J = 3.69 Hz, C^5), 110.65 (C^3) ppm; IR (solid/cm^{-1}): ν_{max} = 3230w, 3195w, 3166w, 3050w, 2972w, 1456m, 1324m, 1311m, 1136m, 1122s, 878m, 690m, 662m, 457w; HRMS ES(+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{10}F_3N_2S$ 295.0512, found 295.0507; Elemental Analysis calc. for $C_{14}H_9F_3N_2S$: C 57.1, H 3.1, N 9.5%, found C 57.1, H 3.2, N 9.4%.

Results

The syntheses of the benzothiadiazines **1** – **9** were achieved using a modification of the methodology described[1b] by Kaszynski *et al.* (Scheme 1) utilising the appropriate 2-nitro-chlorobenzene and aryl nitrile as the major building blocks for construction of the benzo-fused ring and the substituent at the C(3) position respectively. The first step of the reaction sequence is the nucleophilic aromatic substitution reaction of *n*-propylthiolate on the 2-nitrochlorobenzene. Whilst the reported synthetic method[1b] afforded intermediate **1a** in 94% yield over 2 h, in our hands the reaction required extended reaction times (up to 2 days) and a Kugelruhr distillation to achieve **1a** in acceptable purity. However, the ionic nature of the nucleophile made this reaction an ideal candidate for microwave enhancement[14] and permitted us to prepare multi-gram amounts of the sulphides **1a** and **9a** in high yield without the need for distillation or column chromatography. Whilst recrystallisation of **9a** resulted in a drop in isolated yield, it is otherwise obtained in excellent purity.

The reported reduction of the nitro group to the amine using iron powder according to the literature method[2] again proved problematic in our hands (reaction times varying between 18 h and in excess of 1 week for the reaction to go to completion and was sometimes accompanied by formation of a brown intractable tar during work up) but again appeared amenable to microwave methods permitting the products to be isolated in high yield and purity after *ca.* 90 minutes. Subsequent benzamidine formation via base-promoted coupling of the amine to the aromatic nitrile proceeded under modified conditions using LiHMDS, NaHMDS or NaOMe (rather than NaH). Thus the inclusion of functionality at C(3) using this methodology requires a lack of (acidic) H atoms α to the nitrile on the substrate. Despite this restriction, this approach offers access to a potentially large range of aryl and heterocyclic derivatives and we have successfully generated aryl-, pyridyl- and thienyl-functionalised benzo-thiadiazines (**1** – **9**). This approach should also afford access to selected alkyl variants derived from ^{t}BuCN or Cl_3CCN *inter alia*. The subsequent cyclisation and pericyclic elimination reactions followed the procedures reported by Kaszynski,[1b,2] affording the target benzothiadiazines **1** – **9**. Full experimental details and characterisation data are available as ESI.

Structural Studies on Benzothiadiazines

There are few structural studies of simple benzothiadiazines (**A1** ,**A3, A4**, fig 2)[1b,c] and the main focus of this work was to elucidate the structural parameters associated with the benzothiadiazine ring and also factors which dictate their solid state structures. In particular the potential of the N-H group in the 4-position to act as a hydrogen bond donor and the N atom at the 2-position to act as a hydrogen bond acceptor offers opportunities for the construction of hydrogen-bonded networks. Here we report structural studies on the benzo-fused thiadiazines, **1** – **9** and compare them with **A1** and **A3**.

Molecular geometry:- In order to maintain consistency, the atom labelling scheme implemented for a discussion of the molecular geometry (see bond lengths and angles in Table 1) reflects the

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Table 1 Geometric parameters for Compounds **1** – **9**.

Compound	**1**	**2**	**3**	**4**	**5**
Bond length/Å					
S(1)-N(2)	1.7200(13)	1.7077(14) 1.7010(14)	1.686(2)	1.6984(13) 1.7019(13)	1.713(2)
N(2)-C(3)	1.2925(19)	1.287(2) 1.288(2)	1.291(3)	1.2898(19) 1.2844(19)	1.299(2)
C(3)-N(4)	1.3786(19)	1.3746(19) 1.3683(19)	1.367(3)	1.3782(19) 1.374(2)	1.368(2)
N(4)-C(5)	1.4157(19)	1.400(2) 1.4071(19)	1.403(4)	1.4195(19) 1.409(2)	1.417(2)
C(5)-C(6)	1.392(2)	1.399(2) 1.398(2)	1.393(3)	1.397(2) 1.396(2)	1.392(2)
C(6)-S(1)	1.7582(16)	1.7700(15) 1.7640(17)	1.764(2)	1.7642(15) 1.7665(17)	1.752(2)
Bond Angle/°					
C(6)S(1)N(2)	102.03(7)	103.94(7) 104.17(7)	105.19(11)	103.46(7) 104.31(7)	101.08(8)
S(1)N(2)C(3)	117.33(11)	118.54(11) 118.34(11)	122.52(18)	119.95(11) 119.58(12)	117.4(1)
N(2)C(3)N(4)	125.00(14)	126.54(15) 126.61(14)	126.1(2)	126.38(14) 126.71(14)	125.5(2)
C(3)N(4)C(5)	121.34(13)	122.63(13) 122.54(13)	125.0(2)	121.52(12) 123.16(13)	120.8(1)
N(4)C(5)C(6)	118.70(13)	119.57(13) 119.24(14)	121.0(2)	119.93(13) 119.72(15)	119.1(2)
C(5)C(6)S(1)	117.52(12)	118.36(12) 118.43(12)	120.1(2)	119.08(11) 119.03(12)	118.0(1)
Fold/°	35.84	27.53, 27.27	0.52	23.27, 26.54	35.97

Compound	**6**	**7**	**8**	**9**
Bond length/Å				
S(1)-N(2)	1.692(3)	1.7005(15)	1.719(3)	1.73(1), 1.71(1), 1.71(1), 1.72(1)
N(2)-C(3)	1.287(4)	1.286(2)	1.290(4)	1.30(1), 1.29(1), 1.30(1), 1.29(1)
C(3)-N(4)	1.365(4)	1.372(2)	1.385(4)	1.37(1), 1.37(1), 1.37(1), 1.37(1)
N(4)-C(5)	1.412(4)	1.408(2)	1.407(4)	1.42(2), 1.43(2), 1.41(2), 1.43(1)
C(5)-C(6)	1.389(5)	1.390(3)	1.394(5)	1.41(1), 1.39(2), 1.40(1), 1.39(2)
C(6)-S(1)	1.768(4)	1.7767(19)	1.763(3)	1.75(1), 1.75(1), 1.75(1), 1.74(1)
Bond Angle/°				
C(6)S(1)N(2)	105.50(16)	103.77(8)	101.26(14)	103.3(6), 103.6(6), 103.2(6), 101.6(6)
S(1)N(2)C(3)	121.0(3)	120.44(12)	116.3(2)	117.2(8), 117.3(9), 117.3(8), 118.4(9)
N(2)C(3)N(4)	125.8(3)	126.10(16)	123.7(3)	124(1), 125(1), 126(1), 126(1)
C(3)N(4)C(5)	125.5(3)	123.79(15)	120.0(3)	123(1), 123(1), 123(1), 121(1)
N(4)C(5)C(6)	119.9(3)	120.38(16)	118.1(3)	118(1), 118(1), 118(1), 119(1)
C(5)C(6)S(1)	119.4(3)	119.18(14)	116.2(2)	116.9(9), 117.9(9) 119.1(9), 119.3(9)
Fold, θ/°	14.18	21.42	41.18	34.46, 32.61, 31.07, 32.34

[a] The fold angle was defined as the angle between the S(1)N(2)C(3)N(4) and N(4)C(5)C(6)S(1) mean planes.

a IUPAC numbering scheme (Fig. 4) and not the atom numbering for individual structures). The geometry of the benzothiadiazine ring is consistent with the resonance form shown in Figure 4 with C(3)−N(2) distances in the range 1.286(2) – 1.299(2) Å (Table 1) consistent with predominantly double

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bond character ($d_{C=N}$ = 1.2 Å)[15] and C(3)-N(4) distances in the range 1.365(4) – 1.384(4) Å more consistent with a conjugated C-N single bond (d_{C-N} = 1.35 Å for phenylamine).[15] The S−N bond lengths (1.686(2) – 1.722(3) Å)are comparable with other S−N single bonds (1.62 – 1.74 Å for isomers of $S_{8-x}(NH)_x$).[16] The most marked feature in the geometry of the benzothiadiazine ring is the folding (θ) of the molecule about the trans-annular S(1)···N(4) vector. For the majority of benzothiadiazines, θ falls in the range 21° < θ < 42°; however in both **3** and **6** the angles are less than 20° and in **3**, in particular, the ring is essentially planar. These data are consistent with the thiadiazine framework possessing a formally 8π anti-aromatic electron count. A study of the energetics of deformation of the molecule from planarity is discussed later but reveals that there is a shallow energy minimum around 30°, consistent with the experimental observations. Moreover the shallowness of the energy landscape suggests that optimisation of other packing forces (discussed in more detail below) may modify this fold angle at minimal energetic expense.

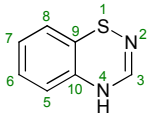

Fig. 4 IUPAC numbering scheme for the heterocyclic component of the 4*H*-benzo-1,2,4-thiadiazine ring.

Molecular Packing:- The structures of **1** – **9** all exhibit hydrogen-bonding between the N(4)-H hydrogen bond donor and a hydrogen bond acceptor. Whilst this may be the N(2) atom of a neighbouring heterocyclic ring, there is potential for other functional groups to be involved, e.g. when pyridyl and nitrophenyl derivatives are present. The parent phenyl derivative **1** has been reported previously[1b] and crystallises in the space group $P2_1/c$, with molecules linked via N(4)-H···N(2) hydrogen bonds parallel to *c* ($d_{N\cdots N}$ = 3.024(2) Å) to form chains.

In the case of **2**, the prevalence for hydrogen-bonding is reflected in an *intra*-molecular hydrogen bond to the *ortho*-pyridyl substituent rather than N(2) (Fig.5). This brings the pyridyl and benzothiadiazine rings near to coplanarity (7.07° and 12.35° for the two crystallographically independent molecules) which should be contrasted with **1** where the torsion angle is 43.60°.

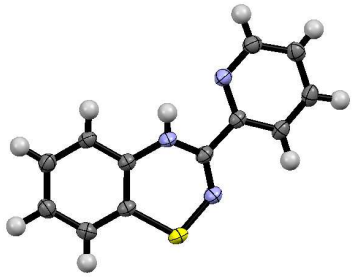

Fig. 5 Molecular structure of **2** illustrating the coplanarity of the pyridyl and benzothiadiazine rings in one of the two crystallographically independent molecules.

The propensity for the pyridyl group to be involved in hydrogen bonding is also reflected in the structure of **3** where the *meta*-pyridyl group forms a trifurcated interaction to the N-H and two C-H bonds ($d_{N\cdots N}$ = 3.094(3) Å). With each molecule offering hydrogen bond donor and acceptor character this leads to a one-dimensional chain topology (Fig. 6) in the form of helical chains parallel to the crystallographic *a* axis. The overall structure adopts the chiral space group $P2_12_12_1$. The near-planarity of the thiadiazine framework in **3** is unexpected for a formally 8π anti-aromatic system but may be due to the opportunity to optimise the slipped π-stack motif parallel to the crystallographic *a*-axis which offers a mean inter-molecular distance of 3.435Å.

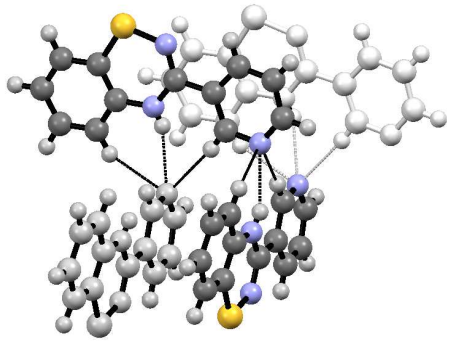

Fig. 6 Molecular packing of **3** illustrating the propagation of trifurcated hydrogen bonding interactions to form chains.

The structure of **4** also utilises the *para*-pyridyl substituent as a hydrogen bond acceptor forming a polymeric chain parallel to the crystallographic *c*-axis (Fig. 7). In **4** there are two crystallographically independent molecules which are linked *via* N-H···N contacts ($d_{N\cdots N}$ = 2.959(2) and 3.198(2) Å).

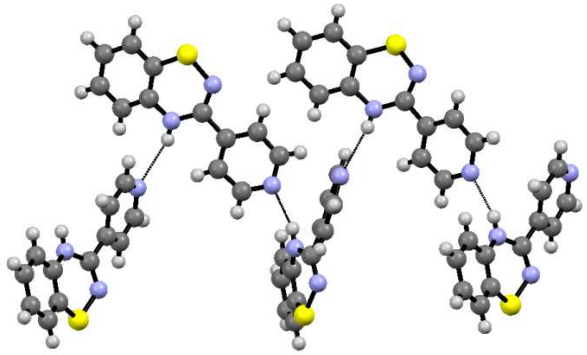

Fig. 7 Molecular packing of **4** illustrating the propagation of N-H···N hydrogen bonding interactions parallel to the crystallographic *c*-axis.

The structure of the 2-thienyl derivative **5** also exhibits N(4)-H…N(2) contacts ($d_{N\cdots N}$ = 3.125(2) Å). The structure of **5**, like **1** therefore adopts a chain-like motif (Fig. 8). In this case the N-H…N contacts propagate parallel to the crystallographic *b*-axis.

The structure of **6** utilises the *p*-nitro group to similarly direct a hydrogen bonding motif (Fig. 9). In **6**, as for **3**, the hydrogen bond acceptor forms a trifurcated contact to two C-H bonds and the N-H bond ($d_{N\cdots O}$ = 3.159(4) Å). These hydrogen bonds propagate parallel to the crystallographic *b*-axis. Notably **6**, like **3**, is also close to coplanar and this appears to optimise π-stacking in a head-to-tail fashion (parallel to the crystallographic *a* axis) with mean inter-layer separations of 3.438 Å (*cf* **3** at 3.435 Å).

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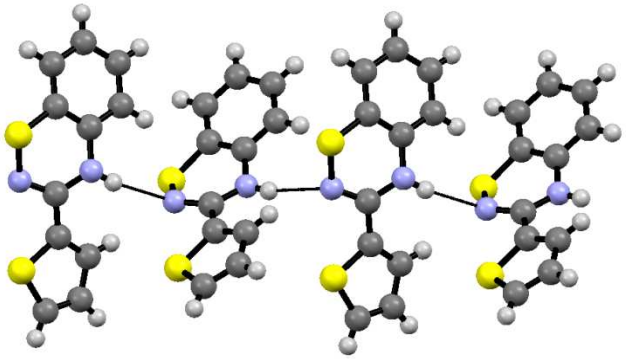

Fig. 8 Molecular packing of **5** illustrating the propagation of N-H···N hydrogen bonding interactions parallel to the crystallographic *b*-axis.

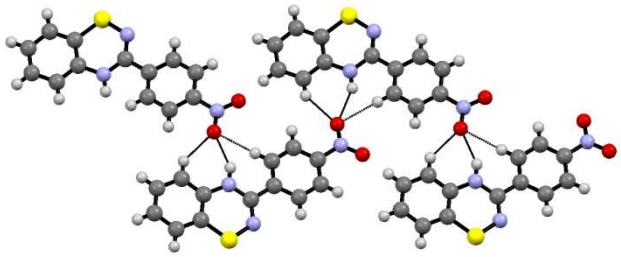

Fig. 9 Molecular packing of **6** illustrating the propagation of N-H···O hydrogen bonding interactions parallel to the crystallographic *b*-axis.

In the case of **7**, one of the two *meta*-nitro groups exhibits a similar trifurcated interaction to the N-H ($d_{N\cdots O}$ = 3.214(2) Å) group, again generating a molecular chain motif (Fig. 10), this time running parallel to the *ac* diagonal. **7** also adopts a slipped π-stack (parallel to *b*) with inter-layer separation of 3.397 Å.

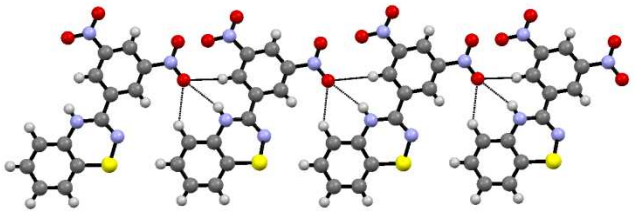

Fig. 10 Molecular packing of **7** illustrating the propagation of N-H···O hydrogen bonding interactions.

The structure of **8** offers the potential for the methoxy group to act as a hydrogen-bond acceptor but the benzothiadiazine N(2) atom appears to act as a better hydrogen bond acceptor than the methoxy group with N(4)-H···N(2) hydrogen bonds ($d_{N\cdots N}$ = 3.145(4) Å) forming a chain parallel to the crystallographic *b*-axis (Fig. 11). The methoxy groups themselves form weak pairs of centrosymmetric dimers linked via pairs of C-H···O contacts [$d_{C\cdots O}$ = 3.483(5) Å] which link the N-H···N bonded chains into a ladder motif.

Whilst C-H groups are typically considered weak H-bond donors, the ether functionality is a known hydrogen-bond acceptor (-0.53 < pK_{HB} < 1.98)[17] although the less *p*-character associated with the the O lone pair for arylalkyl ethers of sp^2-character (compared to the sp^3-O of a dialkyl ether) make such aryl-ethers less basic.[17] Nevertheless such centrosymmetric pairs of C-H···O methoxy-methoxy interactions are relatively common and are reflected in 2015 reports of this motif in the CSD.[18]

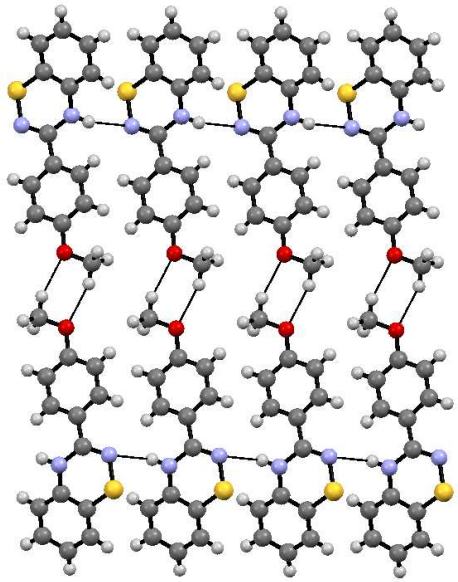

Fig. 11 Molecular packing of **8** illustrating the propagation of N-H···N hydrogen bonding interactions parallel to the crystallographic *b*-axis and C-H···O contacts which act as rungs to the H-bonded ladder structure.

The structure of **9** proved persistently problematic with clear evidence of twinning in many samples. The best crystal of many examined still proved twinned (with $F_o > F_c$ for many of the most disagreeable reflections) but provided adequate data to determine the atomic connectivity and crystal packing features. The CF_3 group is not considered a hydrogen-bond acceptor and, whilst the structure of **9** is more complex due to the presence of 4 molecules in the asymmetric unit, the structure again comprises an N(4)H···N(2) hydrogen-bonding network. In this case there are two similar but crystallographically independent chains (with two crystallographically independent molecules per chain) with each chain linked parallel to the crystallographic *a*-axis (Fig. 12).

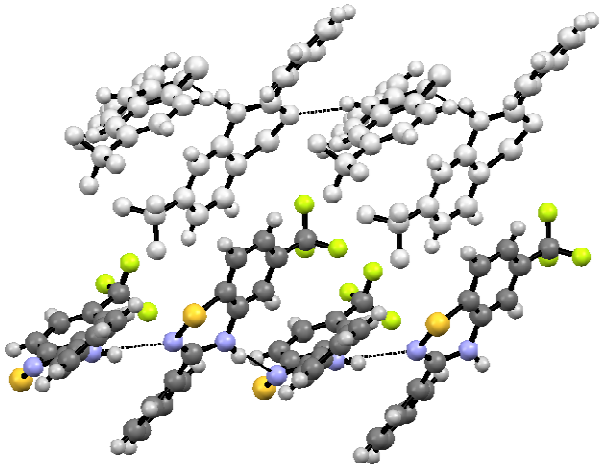

Fig. 12 Molecular packing of **9** illustrating the propagation of N-H···N hydrogen bonding interactions parallel to the crystallographic *a*-axis. One of the two crystallographically independent chains coloured grey.

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Computational Studies

At the molecular level the geometries of **1** – **9** all appear broadly similar, with the major variation between them associated with the folding of the thiadiazine ring. Geometry-optimised B3LYP/6-311G* DFT studies on **1** were undertaken to probe the energetics of the ring system, varying the fold angle of the thiadiazine ring [torsion C(3)N(4)S(1)C(6)] between planar (θ = 180°) and 90° whilst permitting the rest of the molecule to optimise. These calculations reveal an energy minimum at θ = 150° i.e. around 30° from planarity but with a range of fold angles accessible at little energetic cost, e.g. conformations with the range 130° < θ < 180° fall within 8.5 kJ/mol (Fig. 13). Thus the experimentally determined range (179.48° – 138.42°) appear in agreement with a shallow energy minimum to folding such that the small energy offset to deform the heterocyclic ring may be offset by gains in optimised intermolecular contacts such as the hydrogen-bonding motifs described previously. Notably the most planar molecular structures also favour the adoption of π-stacked motifs with **3**, **6** and **7** exhibiting small fold angles (in the range 0.52 – 21.42°) and inter-planar separations along the stacking directions in the range 3.397 – 3.438 Å.

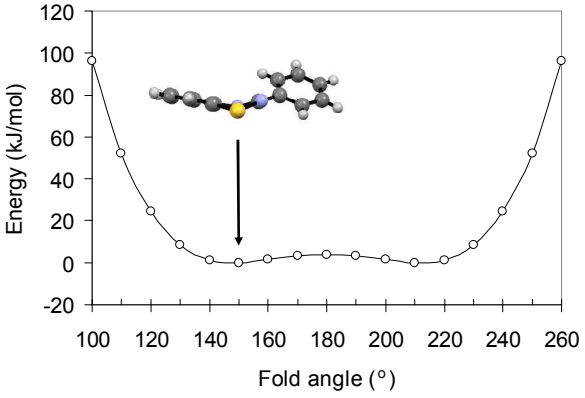

Fig. 13. B3LYP/6-311G* computed energies of **1** with the fold angle varied between 180° (planar) and 90°.

Discussion

The structures of **1** – **9** reveal that the secondary amino-nitrogen N(4)-H of the benzothiadiazine ring has a strong affinity to be involved in hydrogen bonding. In the absence of other strong H-bond acceptors, the benzothiadiazine N(2) atom is sufficiently basic to act as the H-bond acceptor, as in **1**, **5**, **8** and **9** suggesting that N(2) is a stronger acceptor than a thienyl-S atom or methoxy-O atom. However the pyridyl substituents present in **2** – **4** and the nitro groups in **6** and **7** both act as stronger H–bond acceptors [than the benzothiadiazinyl-N(2) atom]. These observations are consistent with previous studies on hydrogen-bond acceptor character of different functional groups pioneered by Taft[19] and extended by Abraham[20] and Berthelot[21] *inter alia*. The pK_{HB} scale developed by Taft focuses on equilibrium constants for H-bonded donor-acceptor complexes in solution. On this scale the H-bond acceptors relevant to this work have the following values; thiophene (-0.37),[20a] methoxybenzene (-0.08),[22] nitrobenzene (+0.48), pyrazine (+1.22) and pyridine (+1.86).[20a] This indicates that thiophene and methoxybenzene are poor H-bond acceptors in relation to the N-heterocyclic rings such as pyrazine and pyridine. Notably the benzo-thiadiazine N-H bond is involved in H-bonding to both pyridyl substituents and nitrophenyl derivatives but prefers the benzothiadiazine N(2) centre in relation to the weaker methoxy-phenyl or thiophenyl H-bond acceptors in **8** and **5**, thus placing the benzothiadiazine heterocyclic ring N intermediate between methoxybenzene and nitrobenzene as a hydrogen bond acceptor, i.e. $-0.08 < pK_{HB} < +0.48$. Whilst pK_{HB} values for S/N-containing heterocycles have not been extensively reported, benzothiadiazole[20b] has a pK_{HB} value of +0.79. Moreover it is known that hydrogen-bond acceptors in 6-membered rings have smaller pK_{HB} values than the corresponding 5-membered rings,[13b,23] potentially placing benzothiadiazines in this region.

Notably the pyrazinyl–fused thiadiazine reported[1] by Kaszynski also exhibits N-H···N donor acceptor interactions to the strong H-bond acceptor of the pyrazine ring to afford a dimer motif. Curiously the N-H group in the tetrafluorobenzo derivative[1] appears not to be involved in any N-H···E hydrogen bond, indicating a prevalence for an alternative structure-directing synthon which dictates the structure. Notably in this latter case the structure adopts a π-stacked structure with alternating fluoro-aryl/aryl rings somewhat akin to the $C_6F_6{\cdot}C_6H_6$ cocrystal.[24]

Conclusions

The syntheses of a series of benzo-1,2,4-thiadiazines have been reported. The implementation of microwave techniques substantially decreased reaction times and led to improved yields for the first two steps in the synthetic pathway. Crystallographic studies on **1** – **9** reveal a propensity for N(4)-H to exhibit hydrogen bonding motifs. In the absence of other hydrogen bond acceptors this occurs to N(2) but both pyridyl and nitro groups are sufficiently strong hydrogen bond acceptors to disrupt the N(4)-H···N(2) hydrogen bond, suggesting both pyridyl and nitro groups are superior hydrogen bond acceptors than N(2). Conversely N(2) appears a better hydrogen bond acceptor than either thiophene or methoxy groups. In addition, the shallow energy minimum for ring deformation permits some flexibility in the thiadiazine backbone with the 8π heterocycle moving closer to planarity in those structures which adopt π-stacked motifs. The coordination chemistry of **2** which offers the potential to act as an *N*,*N*′-chelate ligand will be the subject of future publications.

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Notes and references

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† Electronic Supplementary Information (ESI) available: full experimental details and analytical data for **1**–**9**; a cif file containing the crystal structures of **1**–**9** and selected intermediates. See DOI: 10.1039/b000000x/

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