Intermolecular S···π interactions in crystalline sulfanyl-triazine derivatives†

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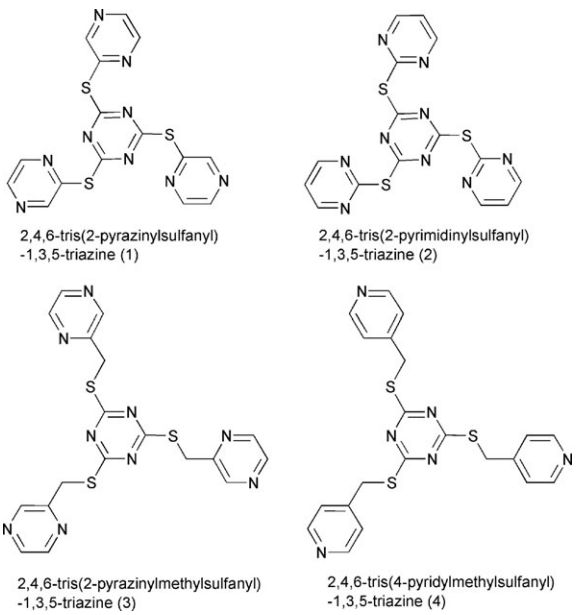
Three types of intermolecular S···π interaction geometry are identified in the crystal structures of four sulfanyl-triazine derivatives bearing pendant heterocyclic rings, in which the triazinyl, pyrazinyl, pyrimidinyl and pyridyl rings are found to exhibit different affinities for the divalent S atom.

Significant interactions between divalent S atoms and aromatic rings were first recognized in globular protein crystal structures by Morgan and co-workers in 1978.[1] They have since attracted increasing interest because of their important role in the early stages of protein folding by promoting the formation of α-helices,[2] and accordingly in the realization of drug development.[3] Many relevant studies involving experimental work,[4] theoretical calculations[5] and database searches[2b,6] have been performed with an aim of understanding their bonding strength and geometry. These studies suggest that in most protein structures, the divalent sulfur atom possesses an affinity for an edge of the aromatic ring and is located above the ring plane at a large elevation, and that the stabilization of such systems commonly involves a combination of intermolecular hydrogen bonding and S···π interactions.[5g,h,6a–d] However, an analysis of the crystal structures of small molecules in the Cambridge Structural Database (CSD) conducted by Morgan *et al.* indicated a significantly different preferred geometry for the interaction between C–S–C thioether units and six-membered aromatic rings, with the divalent sulfur atom lying within the plane of the ring and closely interacting with the ring hydrogen atoms.[6a]

The statistical analysis of Diederich *et al.*[2b] showed that in protein structures, the divalent sulfur atom stably resides above the rings of heterocycles, such as adenine[3d,7] and guanine,[3a] at a distance of less than 4 Å. Such diverse geometries and strengths indicate that steric, dispersion and hydrophobic effects (prominent in larger protein molecules), crystal packing forces (in small molecules), and electrostatic polarization interactions (significant for heterocycles) all play important roles in S···π interactions.

Although thorough CSD research[8] conducted by us indicates that S···π interactions involving heteroaromatic moieties occur widely in small molecules, to the best of our knowledge, such an interaction type has not been thoroughly discussed. In the present report, the determination of the crystal structures of two new sulfanyl-triazine compounds, namely 2,4,6-tris(2-pyrazinylsulfanyl)-1,3,5-triazine (**1**) and 2,4,6-tris(2-pyrazinylmethylsulfanyl)-1,3,5-triazine (**3**), as compared to their reported structural analogs 2,4,6-tris(2-pyrimidinylsulfanyl)-1,3,5-triazine (**2**) and 2,4,6-tris(4-pyridinylmethylsulfanyl)-1,3,5-triazine (**4**) (Scheme 1), has established that the triazinyl, pyrazinyl, pyrimidinyl and pyridyl rings in **1–4**, having inherently different π-acidities,[9] exhibit diverse affinities for divalent S atoms. Three distinct types of S···π interaction geometry involving six-membered heterocycles have been identified (Table 1).

To facilitate the subsequent discussion, the S···centroid$_{heterocycle}$ distance is defined as *r*, while *d* represents the distance from the S atom to the closest ring atom, as shown in Scheme 2 and Table 1. The angle between the S···centroid axis and the ring plane is denoted by *φ*, and the C–S···centroid angle is represented by *α*. In the present context, the values of *r* vary from 3.5 to 4.2 Å, which lie well within the 3.5∼5.0 Å range of the reported statistically preferred S···centroid$_{arene}$ separation and S···C$_{sp^2}$ van der Waals contact.[2b,6] The values of *d* range from 3.39 to 3.95 Å, which are shorter than or close to the sum of van der Waals radii (3.7 Å) of the interacting atoms based on the



Scheme 1 The structural formulas of sulfanyl-triazine derivatives **1–4**.

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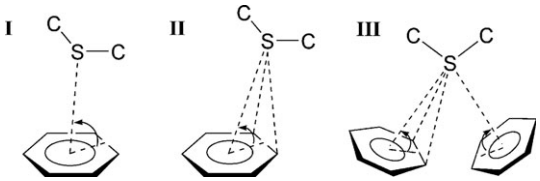
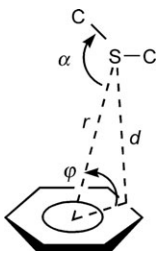
Table 1 The three types of S···π interactions (**I–III**) in compounds **1–4** and their metric parameters, as defined in Scheme 2[a]



Compound	Type	S···π (heterocycle)	Distance r/Å	Distance d/Å		Angle α (°)	Angle φ (°)
1	**I**	S3···X (triazine)	3.526	N2a C2a	3.662 3.664	91.4/107.9	84.6
	II	S3···X′ (pyrazine)	3.930	N6c C8c	3.526 3.591	106.5/132.7	60.1
	III	X···S3···X′ (triazine/pyrazine)	As above	As above		As above	As above
2	**I**	S1···X (triazine)	3.659	N1a C11a	3.524 3.684	94.7/98.3	73.1
	II	S1···X′ (pyrimidine)	3.808	C1b N4b	3.390 3.412	93.0/123.3	59.6
	III	X···S1···X′ (triazine/pyrimidine)	As above	As above		As above	As above
3	**II**	S3···X (pyrazine)	4.217	C15a N8a	3.750 3.954	58.4/107.3	60.0
4	**II**	S2···X (triazine)	3.826	C1a N1a	3.617 3.751	70.0/163.2	70.5
	II	S2···X′ (pyridine)	3.992	C8a C7a	3.666 3.888	68.3/81.6	70.5
	III	X···S2···X′ (triazine/pyridine)	As above	As above		As above	As above

[a] Symmetry codes: **1**, a = $-x+2, -y+1, -z+1$; c = $1\frac{1}{2}-x, -\frac{1}{2}+y, \frac{1}{2}-z$; **2**, a = $-x+2, -y, -z+2$; b = $-x+1, -y, -z+2$; **3**, a = $-x+1, -y-1, -z+1$; **4**, a = $-x+1, -y, -z+2$.



Scheme 2 The parameters defining the geometry of S···π interactions in this work. The six-membered ring represents a nitrogen heterocycle.

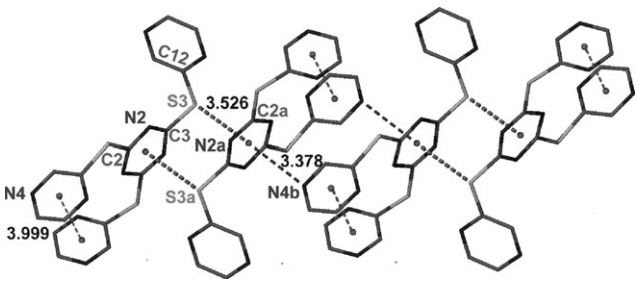


Fig. 1 Intermolecular S···π and N···π interactions form an infinite chain in **1**. Symmetry codes: a = $-x+2, -y+1, -z+1$; b = $-x+1, -y+1, -z+1$. The intramolecular π···π (dashed lines) interactions are also shown.

Pauling scale; the half thickness of a phenyl ring is taken to be 1.85 Å[10a] and the van der Waals radius of S is taken to be 1.85 Å.[10b]

In the crystal structure of **1**,† two pyrazinyl rings have a face-to-face relationship (centroid···centroid = 3.99 Å) and two inversion-related molecules associate through a pair of S···$\pi_{\text{triazinyl ring}}$ interactions to form a dimer (Fig. 1 and Fig. 2A). The S3 atom points towards the triazinyl ring center at r = 3.526 Å. The C–S–C motif is orientated almost parallel to the triazinyl ring, with a C3–S3···centroid angle (α) of 91.4° and a C12–S3···centroid angle (α′) of 107.9°; angle φ is 84.6°. The distances from S3 to the closest ring edge atoms (d) are 3.664 (S3···C2a) and 3.662 (S3···N2a) Å. We designate this interaction geometry as type **I** (Table 1); it being quite different from the preferred edge-contacted geometry found in most protein crystal structures[6b–f] and the coplanar arrangement seen in small molecules,[6a] as mentioned above. The observed distances, d, are comparable to those of S···π interactions involving adenine in protein structures (less than 4 Å).

Interestingly, the dimers interconnect pairwise through N···$\pi_{\text{triazinyl ring}}$ (N4b···centroid = 3.378 Å) interactions to form an infinite chain along the a axis. As shown in Fig. 1, the N atom of one pyrazinyl ring points towards the triazinyl ring of the adjacent dimer, with a dihedral angle of 84.6(1)°, yielding a T-shaped configuration. Such unconventional N···π interactions seldom appear in the literature, and, so far, just one example between an N atom and a metal-coordinated pyrazinyl ring (N···centroid = 3.05 Å) has been reported by Hanton *et al.*[11] The significantly shorter

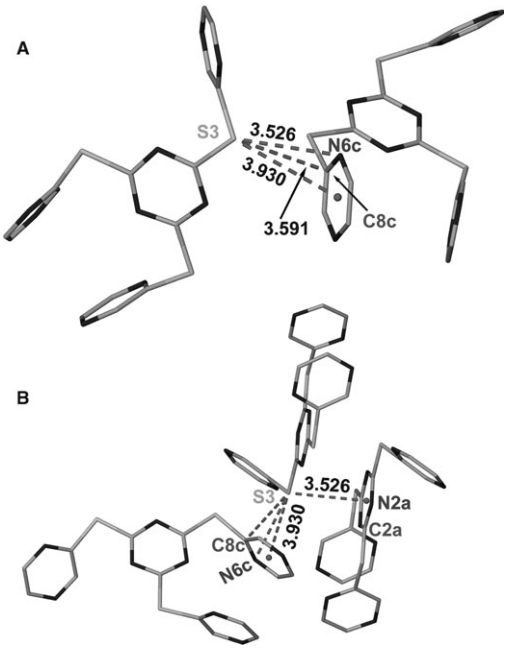


Fig. 2 Illustrations of the S···π type **II** (A) and type **III** (B) geometries in compound **1**. Symmetry codes: a = $-x + 2, -y + 1, -z + 1$; c = $1\frac{1}{2} - x, -\frac{1}{2} + y, \frac{1}{2} - z$. Note that type **III** comprises type **I** and **II**, shown in Fig. 1 and Fig. 2A, respectively.

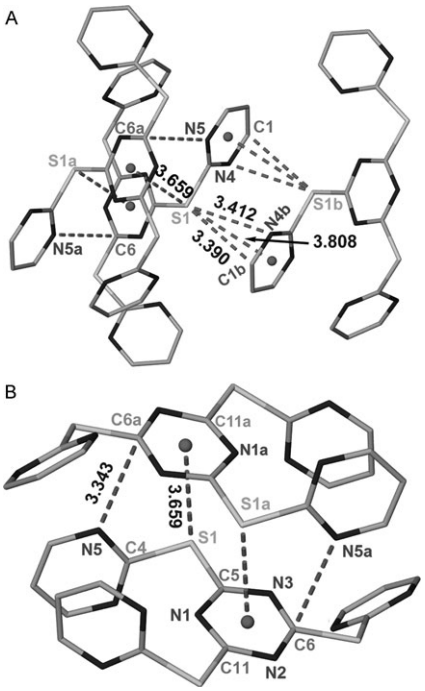


Fig. 3 A: Co-existing triazine (type **I**), S···pyrazine (type **II**) and N···triazine interactions in **2**. Symmetry codes: a = $-x + 2, -y, -z + 2$; b = $-x + 1, -y, -z + 2$. B: Detailed view of the S···$\pi_{triazinyl}$ and N···$\pi_{triazinyl}$ interactions shown in Fig. 3A. Symmetry code: a = $-x + 2, -y, -z + 2$.

distance compared with the 3.378 Å in compound **1** can be mainly ascribed to polarization of the pyrazinyl ring by metal coordination.

Notably, the N4b and S3 atoms share the same central triazinyl ring, forming an extended N···π···S interaction mode to stabilize the infinite chain structure (Fig. 1). The chains further interconnect through π···π (centroid···centroid = 3.849 Å) and S···π interactions to form a three-dimensional supramolecular framework. Herein, the S···π interaction involves one pyrazinyl ring, with the S atom shifting away from the ring center (r = 3.930 Å) to facilitate contact with one ring edge (N6c–C8c) at $d_{S3\cdots C8c}$ = 3.591 and $d'_{S3\cdots N6c}$ = 3.526 Å, as shown in Fig. 2A. With a φ value of about 60° and an r value of 3.930 Å, this S···π interaction geometry differs from type **I** (φ = 84.6°, r = 3.526 Å), but is similar to the preferred geometry of S···π_{arene} interactions in protein structures. We therefore designate it as type **II** (Table 1 and Fig. 2A). In fact, in the crystal structure of **1**, the same S3 atom is embraced by one triazinyl ring (type **I**) and one pyrazinyl ring (type **II**) through diverse S···π contacts, as shown in Fig. 2B. We designate this sandwich geometry as type **III** (Table 1). The angle between the vectors joining S3 to the triazinyl centroid and to the pyrazinyl centroid is 108.2°.

Similar S···π interactions also exist in **2**, a positional isomer of **1** reported previously by Zhao *et al.*,[12] although the authors did not explicitly suggest its presence. As shown in Fig. 3A, the S atom is in contact with one triazinyl ring (type **I**) and one pyrimidinyl ring (type **II**) through intermolecular S···π interactions, forming a type **III** interaction mode. For the type **I** contact, the S atom approaches the center of the triazinyl ring, with r = 3.659 Å, with the C–S–C motif being orientated almost parallel to the triazinyl ring ($\alpha_{C4-S1\cdots centroid}$ = 94.7 and $\alpha'_{C5-S1\cdots centroid}$ = 98.3°), similar to compound **1**. The type **II** contact is also comparable to that seen in **1**, with r = 3.808 Å, d = 3.390 Å (S1···C1b) and d' = 3.412 Å (S1···N4b). The detailed metric parameters are listed in Table 1. In addition, one 2-pyrimidinyl N atom (N5) is in contact with a triazinyl C atom of an adjacent molecule (N5···C6a = 3.343 Å; the dihedral angle between the pyrimidinyl and triazinyl rings is 105.5°), bridging them closer together in combination with the type **I** S···π interaction, as shown in Fig. 3B.

Compared to compound **1**, in **3**,† each terminal pyrazinylthio group is attached to the central triazinyl ring *via* a bridging methylene moiety. In the crystal structure of **3**, the molecule has an approximate C_3 symmetry, with the three pyrazinyl rings being nearly coplanar with the central triazinyl ring. No S···π interactions occur between the divalent S atom and the much more π-acidic triazinyl nucleus, unlike the cases observed in **1** and **2**. Instead, the S atom resides close to a pyrazinyl ring of a proximal molecule and exhibits a weak type **II** S···π interaction, with r = 4.217 Å and φ = 60.0°. As shown in Fig. 4A, the S3 atom is in contact with the N8a–C15a edge, with d = 3.750 (S3···C15a) and d' = 3.954 (S3···N8a) Å (Table 1). Such S···π interactions co-exist with intermolecular π···π interactions between the pyrazinyl and triazinyl rings to yield a molecular stack along the a axis. Further scrutiny reveals that C–H···S hydrogen bonding (C···S distance = 3.64 and 3.89 Å; C–H···S angle = 141.8 and 117.7°)[13] between molecules lying in the same plane also contributes, stabilizing the stacking of molecules. The fact that the presence of additional methylene bridges in **3** does not lead to more extensive and flexible S···π interactions, as compared

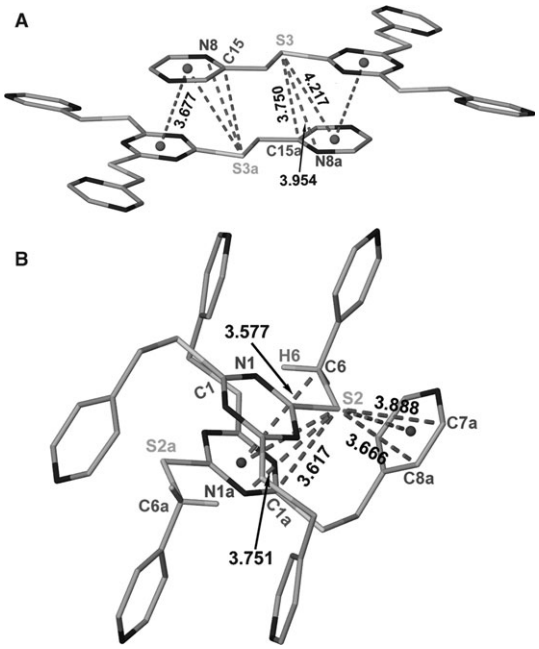


Fig. 4 A: Type **II** S···$\pi_{pyrazinyl}$ and π···π (3.677 Å) interactions between two inversion-related molecules in the crystal structure of **3**. Symmetry code: a = $-x + 1, -y - 1, -z + 1$. B: Co-existing S···triazine (type **II**), S···pyridine (type **II**) and C–H···π interactions (C6···centroid = 3.557 Å) in **4**. Symmetry code: a = $-x + 1, -y, -z + 2$.

with **1–2**, can be attributed to the collective effect of π···π, hydrogen bonding, and S···π interactions on the crystal packing.

In the reported structure of **4**,[14] a structural analog of **3**, the S atom is embraced by one pyridyl and one triazinyl ring from an adjacent molecule (Fig. 4B), both in the edge-contacting mode (type **II**), to form a bent sandwich geometry (type **III**). Further analysis reveals that the stronger C–H···π interaction[15] (C6···centroid = 3.577 Å), involving the methylene group, pushes the S atom away from the triazinyl ring center (d = 3.617 and 3.751 Å), leading to comparable edge-contacting (type **II**) S···$\pi_{triazinyl}$ and S···$\pi_{pyridyl\ ring}$ interactions (d = 3.666 and 3.888 Å) (Fig. 4B). As shown in Table 1, the r and d values of the S···π interactions in **4** are larger than those found for the triazinyl, pyrazinyl and pyrimidinyl rings in **1** and **2**, which can be ascribed to the less electropositive nature of the pyridyl ring. Notably, the lengthened methylene side chain is flexible enough to allow the less π-acidic pyridyl ring to fold back, so as to interact with the S atom. Hence the S atom in **4** is embraced by the central triazinyl and one pyridyl ring in the same neighboring molecule, rather than by heteroaromatic rings from separate molecules, as in the type **III** mode observed in **1** and **2**.

Three types of S···π interaction geometry between divalent S atoms (C–S–C motif) and six-membered heterocycles have been identified by comparing the X-ray structural parameters of new sulfanyl-triazine derivatives **1** and **3** with two of their structural analogs, **2** and **4**, in the literature. The central triazinyl ring exhibits a stronger affinity towards the S atom than peripheral pyrazinyl, pyrimidinyl and pyridyl rings, commonly interacting with the π-cloud with a type **I** geometry at a short distance (r = 3.526–3.826 Å). In contrast, the other heterocycles generally adopt the edge-contacting type **II** geometry, with a larger r value (r = 3.808–4.217 Å), owing to their less electropositive nature. Furthermore, the fact that "sandwiched" type **III** interactions are a common S···π interaction geometry (found in **1**, **2** and **4**) also implies the donor role of divalent S atoms and the acceptor role of heterocyclic rings. Our study provides insight into the effect of electrostatic polarization on S···π interactions within small molecules, which contributes towards a better understanding of its role in biological systems. Furthermore, the results provide strong support for the unconventional lone pair–aromatic interactions that are of current interest.[16]

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Experimental

All chemicals were obtained commercially from Aldrich and used without further purification. Elemental analyses of C, H and N were performed by MEDAC Ltd, Brunel Science Centre, UK. IR spectra were recorded by a Nicolet Impact 420 FT-IR spectrometer using KBr pellets. ^{1}H NMR spectra were recorded at 300 MHz by a Bruker-300 spectrometer using $CDCl_3$ as the solvent.

Synthesis of 2,4,6-tris(2-pyrazinylsulfanyl)-1,3,5-triazine (1)

Solid 2-mercaptopyrazine (1.68 g, 15 mmol) was added to a solution of KOH (0.84 g, 15 mmol) in 25 ml ethanol, pre-cooled in an ice–water bath. After stirring for 1 h, the resulting yellow solution was added dropwise to a solution of cyanuric chloride (0.92 g, 5 mmol) in 20 ml acetone over 30 min. The mixture was stirred in an ice–water bath for another 2 h, and then allowed to warm to room temperature. The precipitate of KCl was filtered off, and the filtrate was concentrated *in vacuo* to remove the solvent. Compound **1** (14.72 g) was obtained as a yellow powder, and further purification was effected by re-crystallization from acetone (yellow crystals). Yield 71%; m.p. 133–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.645 (s, 3H) and 8.516–8.548 (d, J = 9 Hz, 6H). Anal. calc. (found) for $C_{15}H_9N_9S_3$: C, 43.79 (43.45); H, 2.21 (2.33); N, 30.66 (30.54)%. IR (KBr, ν/cm^{-1}): 3061(w), 3663(w), 1694(w), 1481(vs), 1390(s), 1267(vs), 1125(s), 1060(w), 1015(m), 853(s), 788(w), 762(w), 633(w) and 535(w).

Synthesis of 2,4,6-tris(2-pyrazinylsulfanylmethyl)-1,3,5-triazine (3)

2-Methylpyrazine (7 g, 0.075 mol) and *N*-chlorosuccinimide (11 g, 0.0825 mol) were mixed in 500 ml CCl_4 and stirred for 1 h. Then, azo-bis-isobutyronitrile (0.25 g) was added to the clear solution. After refluxing for 24 h, the mixture was cooled to 0 °C and filtered to remove the undissolved solid. The solution was concentrated *in vacuo* and purified by chromatography on silica gel using ethyl hexane/diethyl ether (1 : 1) as the eluent. 2-(Chloromethyl)pyrazine was obtained as a colorless liquid (3.76 g). Yield 40%.

2,4,6-Trithiol-1,3,5-triazine (1.8 g, 0.01 mol) and KOH (1.8 g, 0.032 mol) were mixed in 30 ml ethanol and stirred at room temperature for 3 h. Then, a solution containing 2-(chloromethyl)pyrazine (0.03 mol) in ethanol was added dropwise over 1 h, yielding compound **3** as a gray-ish precipitate. After filtration, the solid was washed with 60 ml ethanol. No further purification was needed. The slow evaporation of **3** in methanol gave colorless crystals suitable for X-ray diffraction. Yield 4.1 g (90%); m.p. 174–176 C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 3H), 8.46–8.50 (d, J = 12 Hz, 6H) and 4.44 (s, 6H). Anal. calc. (found) for $C_{18}H_{15}N_9S_3$: C, 47.67 (47.39); H, 3.33 (3.32); N, 27.78 (27.94)%. IR (KBr, ν/cm^{-1}): 2925(w), 2381(m), 1474(vs), 1416(s), 1248(vs), 1209(s), 1118(m), 1066(w), 1021(w), 917(w), 846(s), 788(w) and 484(w).

X-Ray crystallography

Single-crystal X-ray diffraction measurements were carried out by a Bruker SMART 1000 CCD diffractometer operating at 50 kV and 30 mA using Mo-K$_\alpha$ radiation (λ = 0.71073 Å). Each selected crystal was mounted inside a Lindemann glass capillary. Data collection at 293 K and reduction were performed using SMART and SAINT software.[17] An empirical absorption correction was applied using the SADABS program.[18] The crystal structures of **1** and **3** were solved by direct methods and refined by full matrix least-squares on F^2 using the SHELXTL program package.[19] All non-hydrogen atoms were subjected to anisotropic refinement.

Crystal data

Compound 1. $C_{15}H_9N_9S_3$, M = 411.49, monoclinic, $P2_1/n$ (no. 14), a = 11.814(3), b = 11.411(3), c = 13.428(3) Å, β = 99.290(6)°, V = 1786.3(8) Å^3, Z = 4, T = 298 K, D_c = 1.53 g cm^{-3}; the structure, refined on F^2, converged for 3146 unique reflections (R_{int} = 0.0583) and 1609 observed reflections with $I > 2\sigma(I)$ to give $R1$ = 0.0567, w$R2$ = 0.1443 and goodness-of-fit S = 0.980. CCDC 704194.†

Compound 3. $C_{18}H_{15}N_9S_3$, M = 453.57, triclinic, $P\bar{1}$ (no. 2), a = 8.550(1), b = 11.061(2), c = 11.528(2) Å, α = 70.183(2), β = 78.748(3), γ = 81.825(3)°, V = 1001.6(2) Å^3, Z = 2, T = 298 K, D_c = 1.504 g cm^{-3}; the structure, refined on F^2, converged for 4864 unique reflections (R_{int} = 0.0214) and 3737 observed reflections with $I > 2\sigma(I)$ to give $R1$ = 0.0392, w$R2$ = 0.1096 and goodness-of-fit S = 1.057. CCDC 704195.†

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