# (E)-2-(2-Methylcyclohexylidene)-hydrazinecarbothioamide

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In the crystal of the title compound, $C_8H_{15}N_3S$, molecules are linked by N—H···S hydrogen bonds, forming chains along $[1\bar{1}0]$. An intramolecular N—H···N hydrogen bond is also present.

## Related literature

The title compound, $C_8H_{15}N_3S$, is a key intermediate for the preparation of hydrazinyl-5-arylthiazole-based monoamine oxidase B (MAO-B) inhibitors. For the synthesis of hydrazinyl-5-arylthiazoles and their MAO-B inhibitory activity, see: Chimenti *et al.* (2008, 2010). For background on our interest in radiolabelled molecules targeting MAO-B, see: Vasdev *et al.* (2011*a*,*b*). For the preparation of $^{18}$F-labelled potassium cryptand fluoride, see: Vasdev *et al.* (2009).
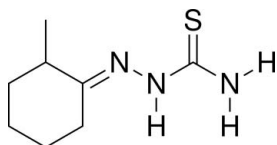


## Experimental

### Crystal data

| | |
|---|---|
| $C_8H_{15}N_3S$ | $\gamma = 68.416$ (4)° |
| $M_r = 185.29$ | $V = 490.19$ (6) Å$^3$ |
| Triclinic, $P\bar{1}$ | $Z = 2$ |
| $a = 6.0261$ (5) Å | Mo $K\alpha$ radiation |
| $b = 8.0655$ (4) Å | $\mu = 0.28$ mm$^{-1}$ |
| $c = 10.9129$ (9) Å | $T = 150$ K |
| $\alpha = 83.904$ (5)° | $0.20 \times 0.14 \times 0.04$ mm |
| $\beta = 89.386$ (4)° | |

### Data collection

| | |
|---|---|
| Nonius KappaCCD diffractometer | 5938 measured reflections |
| Absorption correction: multi-scan (*SORTAV*; Blessing, 1995) | 2184 independent reflections |
| $T_{min} = 0.710$, $T_{max} = 1.060$ | 1698 reflections with $I > 2\sigma(I)$ |
| | $R_{int} = 0.077$ |

### Refinement

| | |
|---|---|
| $R[F^2 > 2\sigma(F^2)] = 0.048$ | H atoms treated by a mixture of independent and constrained refinement |
| $wR(F^2) = 0.122$ | |
| $S = 1.05$ | |
| 2184 reflections | $\Delta\rho_{max} = 0.26$ e Å$^{-3}$ |
| 122 parameters | $\Delta\rho_{min} = -0.25$ e Å$^{-3}$ |

**Table 1**
Hydrogen-bond geometry (Å, °).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N2—H1$N$···S1$^i$ | 0.88 (3) | 2.61 (3) | 3.4645 (19) | 162 (2) |
| N3—H3$N$···S1$^{ii}$ | 0.88 (2) | 2.52 (2) | 3.3954 (19) | 170.9 (19) |
| N3—H2$N$···N1 | 0.81 (3) | 2.28 (2) | 2.601 (2) | 104.6 (19) |

Symmetry codes: (i) $-x, -y + 1, -z$; (ii) $-x + 1, -y, -z$.

Data collection: *COLLECT* (Nonius, 2002); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXTL* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXTL*.

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# supporting information

## (*E*)-2-(2-Methylcyclohexylidene)hydrazinecarbothioamide

**Justin W. Hicks, Alan J. Lough, Alan A. Wilson and Neil Vasdev**

### S1. Comment

(*E*)-2-(2-Methylcyclohexylidene)hydrazinecarbothioamide is an intermediate towards the preparation of hydrazinyl-5-arylthiazoles which are curerntly under exploration as a new class of inhibitors of the enzyme monoamine oxidase B (Chimenti *et al.* 2010). Our interest in this class of compounds is to prepare a radiotracer for imaging MAO-B in the central nervous system with positron emission tomography (PET). Chimenti *et al.* (2010) reported the synthesis of (*E*)-2-(2-(2-methylcyclohexylidene)hydrazinyl)-5-(4-nitrophenyl)thiazole, and (*E*)-2-(2-(2-methylcyclohexyl-idene)hydrazinyl)-5-(4-fluorophenyl)thiazole which demonstrated high affinity for MAO-B ($K_i > 10$ nM). We have attempted to use the 4-nitrophenyl thiazole derivative as a precursor for radiofluorination with the positron emitting isotope fluorine-18 ($t_{1/2} = 109.7$ min) to prepare [$^{18}$F]-(*E*)-2-(2-(2- methylcyclohexylidene)hydrazinyl)-5-(4-fluorophenyl)-thiazole. Although initial attempts to achieve this goal have not been successful due to degradation of the precursor under basic conditions, we continue to investigate the application of thiazoles as an activating group for aromatic radiofluorination.

The molecular structure of the title compound is shown in Fig. 1. In the crystal, molecules are linked by N—H⋯S hydrogen bonds to form chains along [1$\bar{1}$0] (see Fig. 2). An intramolecular N—H⋯N hydrogen bond is also present.

### S2. Experimental

*Synthesis*

The title compound, $C_8H_{15}N_3S$, was obtained by stirring equimolar amounts (10 mmol) of racemic 2-methylcyclo-hexanone and thiosemicarbazide with a catalytic amount of acetic acid (*ca* 350 *μL*) in 2-propanol (100 ml) for 16 h at room temperature. A white precipitate resulted and was collected by vacuum filtration and washed with cold 2-propanol (3 *x* 20 ml). This solid was then dissolved in chloroform (20 ml) and the insoluble unreacted thiosemicarbazide was removed by vacuum filtration. The solvent was removed from the filtrate by rotary evaporation and $C_8H_{15}N_3S$ was obtained as a white solid in 98% yield. X-ray quality crystals were obtained by slow evaporation of a solution of the title compound in 1:1:2 chloroform/acetonitrile/acetone. m.p. = 420 - 421 K.

*Attempted Radiosynthesis*

Dry $^{18}$F-labeled potassium cryptand fluoride ([$K_{222}$][$^{18}$F]; 760 *μ*Ci) was prepared as previously described (Vasdev *et al.*, 2009). A solution of 2-(2-cyclohexylidenehydrazinyl)-4-(4-nitrophenyl)thiazole in anhydrous $CH_3CN$ (9.5 m*M*, 1 ml) was added to the glass test tube and the solution turned a dark purple. The reaction was stirred at room temperature for 10 minutes, then an aliquot was quenched in HPLC buffer to monitor the progress of the reaction by analytical HPLC. As no reaction occurred, the mixture was then heated to 333 K and 363 K in an oil bath for 10 minutes, respectively, with still no reaction occurring. Analytical HPLC was performed using a perfluorophenyl column (Thermo Scientific Fluophase PFP, 150 *x* 10 mm, 5 *μ*m) eluted with 70:30 $CH_3OH$:$H_2O$ + 0.1 N ammonium formate using a flow of 5 ml min$^{-1}$. Authentic 2-(2-cyclohexylidenehydrazinyl)-4-(4-fluorophenyl)thiazole ($t_R$ = 12.5 min) was used as a standard.

A second reaction under microwave heating (60 W) was also attempted using dimethylsulfoxide (DMSO) as the solvent. The reaction again turned dark purple with the addition of the precursor as a DMSO solution (9.5 m$M$, 1 ml) to the dry [K$_{222}$][$^{18}$F] containing glass test tube. After heating to 393 K for 5 minutes with no reaction occurring, the temperature was increased to 453 K for 15 minutes. At this point, there was no precursor remaining intact, as determined by analytical HPLC. Proton NMR spectroscopy revealed that the hydrazinic proton is removed under basic conditions.

**S3. Refinement**

H atoms bonded to C atoms were placed in calculated positions with C—H = 0.98 - 1.00Å and were included in the refinement with $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}(C_{methyl})$. H atoms bonded to N atoms were refined independently with isotropic displacement parameters.
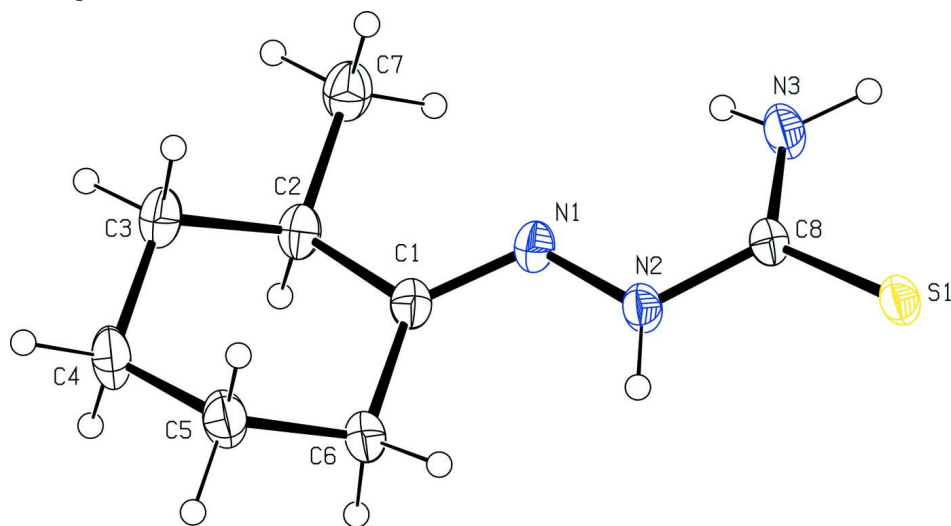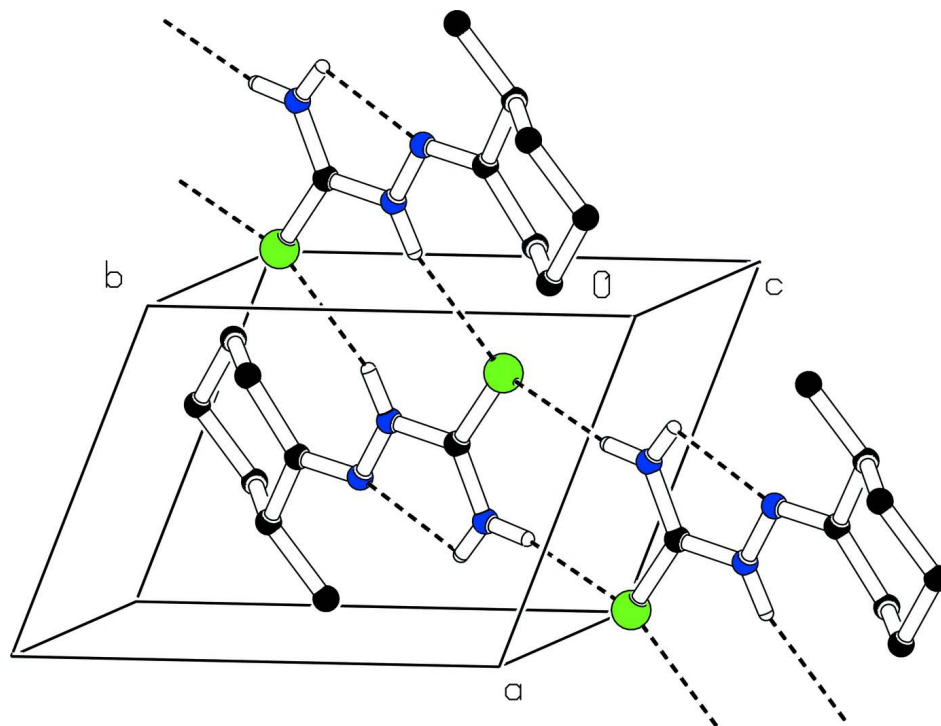


**Figure 1**

The molecular structure with ellipsoids drawn at the 30% probabilty level.

**Figure 2**

Part of the crystal structure with hydrogen bonds drawn as dashed lines. Only H atoms involved in hydrogen bonds are shown.

**(*E*)-2-(2-Methylcyclohexylidene)hydrazinecarbothioamide**

*Crystal data*

| | |
|---|---|
| $C_8H_{15}N_3S$ | $Z = 2$ |
| $M_r = 185.29$ | $F(000) = 200$ |
| Triclinic, $P\bar{1}$ | $D_x = 1.255$ Mg m$^{-3}$ |
| Hall symbol: -P 1 | Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å |
| $a = 6.0261$ (5) Å | Cell parameters from 5938 reflections |
| $b = 8.0655$ (4) Å | $\theta = 2.6$–27.5° |
| $c = 10.9129$ (9) Å | $\mu = 0.28$ mm$^{-1}$ |
| $\alpha = 83.904$ (5)° | $T = 150$ K |
| $\beta = 89.386$ (4)° | Plate, colourless |
| $\gamma = 68.416$ (4)° | $0.20 \times 0.14 \times 0.04$ mm |
| $V = 490.19$ (6) Å$^3$ | |

*Data collection*

| | |
|---|---|
| Nonius KappaCCD diffractometer | 5938 measured reflections |
| Radiation source: fine-focus sealed tube | 2184 independent reflections |
| Graphite monochromator | 1698 reflections with $I > 2\sigma(I)$ |
| Detector resolution: 9 pixels mm$^{-1}$ | $R_{int} = 0.077$ |
| $\varphi$ scans and $\omega$ scans with $\kappa$ offsets | $\theta_{max} = 27.6°$, $\theta_{min} = 2.7°$ |
| Absorption correction: multi-scan (*SORTAV*; Blessing, 1995) | $h = -7 \rightarrow 7$ |
| | $k = -10 \rightarrow 10$ |
| $T_{min} = 0.710$, $T_{max} = 1.060$ | $l = -13 \rightarrow 14$ |

*Refinement*

| | |
|---|---|
| Refinement on $F^2$ | Secondary atom site location: difference Fourier map |
| Least-squares matrix: full | |
| $R[F^2 > 2\sigma(F^2)] = 0.048$ | Hydrogen site location: inferred from neighbouring sites |
| $wR(F^2) = 0.122$ | |
| $S = 1.05$ | H atoms treated by a mixture of independent and constrained refinement |
| 2184 reflections | |
| 122 parameters | $w = 1/[\sigma^2(F_o^2) + (0.0454P)^2 + 0.1232P]$ |
| 0 restraints | where $P = (F_o^2 + 2F_c^2)/3$ |
| Primary atom site location: structure-invariant direct methods | $(\Delta/\sigma)_{max} < 0.001$ |
| | $\Delta\rho_{max} = 0.26$ e Å$^{-3}$ |
| | $\Delta\rho_{min} = -0.25$ e Å$^{-3}$ |

*Special details*

**Experimental**. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ p.p.m. 8.83 (br s, 1H), 7.25 (br s, 1H), 6.48 (br s, 1H), 2.66 (m, 1H), 2.29 - 2.40 (m, 1H), 1.84 - 2.00 (m, 3H), 1.75 - 1.83 (m, 1H), 1.41 - 1.66 (m, 2H), 1.23 - 1.36 (m, 1H), 1.10 (d, $J$= 6.6 Hz, 3H). HRMS (ESI) m/$z$ calcd for C$_8$H$_{16}$N$_3$S, 186.1059; found 186.1064 ($M^+$+H).

**Geometry**. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

**Refinement**. Refinement of $F^2$ against ALL reflections. The weighted $R$-factor $wR$ and goodness of fit $S$ are based on $F^2$, conventional $R$-factors $R$ are based on $F$, with $F$ set to zero for negative $F^2$. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating $R$-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. $R$-factors based on $F^2$ are statistically about twice as large as those based on $F$, and $R$- factors based on ALL data will be even larger.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å$^2$)*

| | $x$ | $y$ | $z$ | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| S1 | 0.17188 (9) | 0.22748 (6) | 0.01937 (5) | 0.03606 (19) |
| N1 | 0.5032 (3) | 0.4731 (2) | 0.19337 (16) | 0.0335 (4) |
| H1N | 0.185 (5) | 0.522 (3) | 0.104 (2) | 0.051 (7)* |
| N2 | 0.3306 (3) | 0.4439 (2) | 0.12560 (17) | 0.0336 (4) |
| N3 | 0.6066 (3) | 0.1654 (2) | 0.10779 (19) | 0.0428 (5) |
| H2N | 0.708 (4) | 0.195 (3) | 0.137 (2) | 0.047 (7)* |
| H3N | 0.649 (4) | 0.061 (3) | 0.078 (2) | 0.039 (6)* |
| C1 | 0.4559 (4) | 0.6253 (2) | 0.23460 (19) | 0.0334 (5) |
| C2 | 0.6541 (4) | 0.6475 (3) | 0.3062 (2) | 0.0370 (5) |
| H2A | 0.7074 | 0.7344 | 0.2537 | 0.044* |
| C3 | 0.5603 (4) | 0.7327 (3) | 0.4246 (2) | 0.0437 (5) |
| H3A | 0.5190 | 0.6458 | 0.4822 | 0.052* |
| H3B | 0.6883 | 0.7593 | 0.4646 | 0.052* |
| C4 | 0.3419 (4) | 0.9048 (3) | 0.4007 (2) | 0.0476 (6) |
| H4A | 0.2849 | 0.9524 | 0.4799 | 0.057* |
| H4B | 0.3853 | 0.9959 | 0.3487 | 0.057* |
| C5 | 0.1440 (4) | 0.8698 (3) | 0.3362 (2) | 0.0456 (6) |
| H5A | 0.0066 | 0.9842 | 0.3177 | 0.055* |
| H5B | 0.0899 | 0.7880 | 0.3919 | 0.055* |
| C6 | 0.2269 (4) | 0.7867 (3) | 0.2168 (2) | 0.0407 (5) |
| H6A | 0.1009 | 0.7509 | 0.1837 | 0.049* |

| | | | | |
|---|---|---|---|---|
| H6B | 0.2504 | 0.8778 | 0.1553 | 0.049* |
| C7 | 0.8715 (4) | 0.4756 (3) | 0.3314 (2) | 0.0450 (6) |
| H7A | 0.9305 | 0.4286 | 0.2532 | 0.067* |
| H7B | 0.8275 | 0.3866 | 0.3837 | 0.067* |
| H7C | 0.9968 | 0.5004 | 0.3735 | 0.067* |
| C8 | 0.3858 (3) | 0.2802 (2) | 0.08743 (18) | 0.0311 (4) |

*Atomic displacement parameters (Å²)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| S1 | 0.0358 (3) | 0.0288 (3) | 0.0448 (4) | −0.0112 (2) | −0.0042 (2) | −0.0115 (2) |
| N1 | 0.0343 (9) | 0.0373 (9) | 0.0338 (10) | −0.0170 (7) | 0.0000 (8) | −0.0105 (7) |
| N2 | 0.0311 (9) | 0.0303 (8) | 0.0405 (11) | −0.0104 (7) | −0.0030 (8) | −0.0120 (7) |
| N3 | 0.0352 (10) | 0.0337 (9) | 0.0588 (14) | −0.0073 (8) | −0.0075 (9) | −0.0202 (9) |
| C1 | 0.0381 (11) | 0.0348 (10) | 0.0306 (11) | −0.0162 (9) | 0.0041 (9) | −0.0089 (8) |
| C2 | 0.0385 (12) | 0.0423 (11) | 0.0371 (12) | −0.0210 (9) | 0.0026 (10) | −0.0116 (9) |
| C3 | 0.0464 (13) | 0.0503 (12) | 0.0424 (14) | −0.0240 (10) | 0.0000 (11) | −0.0173 (10) |
| C4 | 0.0531 (14) | 0.0452 (12) | 0.0505 (15) | −0.0199 (11) | 0.0035 (12) | −0.0254 (11) |
| C5 | 0.0446 (13) | 0.0413 (11) | 0.0513 (15) | −0.0126 (10) | 0.0001 (11) | −0.0190 (10) |
| C6 | 0.0478 (13) | 0.0330 (10) | 0.0422 (13) | −0.0137 (9) | −0.0056 (10) | −0.0116 (9) |
| C7 | 0.0378 (12) | 0.0528 (13) | 0.0481 (14) | −0.0185 (10) | 0.0013 (10) | −0.0155 (11) |
| C8 | 0.0344 (11) | 0.0291 (9) | 0.0309 (11) | −0.0115 (8) | 0.0031 (9) | −0.0091 (8) |

*Geometric parameters (Å, º)*

| | | | |
|---|---|---|---|
| S1—C8 | 1.698 (2) | C3—H3A | 0.9900 |
| N1—C1 | 1.284 (2) | C3—H3B | 0.9900 |
| N1—N2 | 1.385 (2) | C4—C5 | 1.518 (3) |
| N2—C8 | 1.348 (2) | C4—H4A | 0.9900 |
| N2—H1N | 0.88 (3) | C4—H4B | 0.9900 |
| N3—C8 | 1.317 (3) | C5—C6 | 1.523 (3) |
| N3—H2N | 0.81 (3) | C5—H5A | 0.9900 |
| N3—H3N | 0.88 (2) | C5—H5B | 0.9900 |
| C1—C6 | 1.506 (3) | C6—H6A | 0.9900 |
| C1—C2 | 1.508 (3) | C6—H6B | 0.9900 |
| C2—C7 | 1.518 (3) | C7—H7A | 0.9800 |
| C2—C3 | 1.532 (3) | C7—H7B | 0.9800 |
| C2—H2A | 1.0000 | C7—H7C | 0.9800 |
| C3—C4 | 1.521 (3) | | |
| | | | |
| C1—N1—N2 | 119.69 (16) | C5—C4—H4B | 109.6 |
| C8—N2—N1 | 117.61 (16) | C3—C4—H4B | 109.6 |
| C8—N2—H1N | 115.7 (16) | H4A—C4—H4B | 108.1 |
| N1—N2—H1N | 126.7 (16) | C4—C5—C6 | 111.68 (19) |
| C8—N3—H2N | 121.1 (17) | C4—C5—H5A | 109.3 |
| C8—N3—H3N | 118.9 (15) | C6—C5—H5A | 109.3 |
| H2N—N3—H3N | 119 (2) | C4—C5—H5B | 109.3 |
| N1—C1—C6 | 127.45 (18) | C6—C5—H5B | 109.3 |

| N1—C1—C2 | 116.52 (17) | H5A—C5—H5B | 107.9 |
|---|---|---|---|
| C6—C1—C2 | 116.01 (16) | C1—C6—C5 | 112.49 (18) |
| C1—C2—C7 | 113.51 (16) | C1—C6—H6A | 109.1 |
| C1—C2—C3 | 110.67 (17) | C5—C6—H6A | 109.1 |
| C7—C2—C3 | 112.02 (19) | C1—C6—H6B | 109.1 |
| C1—C2—H2A | 106.7 | C5—C6—H6B | 109.1 |
| C7—C2—H2A | 106.7 | H6A—C6—H6B | 107.8 |
| C3—C2—H2A | 106.7 | C2—C7—H7A | 109.5 |
| C4—C3—C2 | 112.57 (19) | C2—C7—H7B | 109.5 |
| C4—C3—H3A | 109.1 | H7A—C7—H7B | 109.5 |
| C2—C3—H3A | 109.1 | C2—C7—H7C | 109.5 |
| C4—C3—H3B | 109.1 | H7A—C7—H7C | 109.5 |
| C2—C3—H3B | 109.1 | H7B—C7—H7C | 109.5 |
| H3A—C3—H3B | 107.8 | N3—C8—N2 | 117.45 (18) |
| C5—C4—C3 | 110.46 (16) | N3—C8—S1 | 122.61 (15) |
| C5—C4—H4A | 109.6 | N2—C8—S1 | 119.92 (15) |
| C3—C4—H4A | 109.6 | | |

*Hydrogen-bond geometry (Å, °)*

| $D$—H⋯$A$ | $D$—H | H⋯$A$ | $D$⋯$A$ | $D$—H⋯$A$ |
|---|---|---|---|---|
| N2—H1$N$⋯S1[i] | 0.88 (3) | 2.61 (3) | 3.4645 (19) | 162 (2) |
| N3—H3$N$⋯S1[ii] | 0.88 (2) | 2.52 (2) | 3.3954 (19) | 170.9 (19) |
| N3—H2$N$⋯N1 | 0.81 (3) | 2.28 (2) | 2.601 (2) | 104.6 (19) |

Symmetry codes: (i) $-x$, $-y+1$, $-z$; (ii) $-x+1$, $-y$, $-z$.