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# Macozinone: revised synthesis and crystal structure of a promising new drug for treating drug-sensitive and drug-resistant tuberculosis

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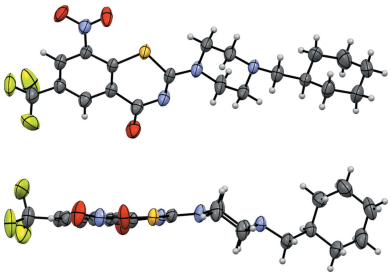
*Mycobacterium tuberculosis* (*Mtb*), the principal etiological agent of tuberculosis (TB), infects over one-quarter of humanity and is now the leading cause of infectious disease mortality by a single pathogen. Macozinone {2-[4-(cyclohexylmethyl)piperazin-1-yl]-8-nitro-6-(trifluoromethyl)-4*H*-1,3-benzothiazin-4-one, $C_{20}H_{23}F_3N_4O_3S$} is a promising new drug for treating drug-sensitive and drug-resistant TB that has successfully completed phase I clinical trials. We report the complete spectroscopic and structural characterization by $^1$H NMR, $^{13}$C NMR, HRMS, IR, and X-ray crystallography. The cyclohexyl moiety is observed to be nearly perpendicular to the core formed by the 1,3-benzothiazin-4-one and piperazine groups. The central piperazine ring adopts a slightly distorted chair conformation caused by $sp^2$-hybridization of the nitro N atom, which donates into the electron-deficient 1,3-benzothiazin-4-one group.

## 1. Introduction

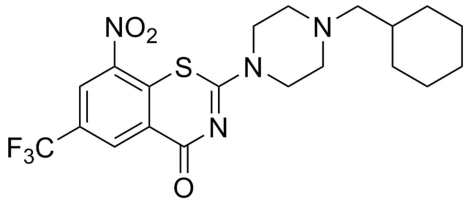
Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (*Mtb*) is the leading source of infectious disease mortality by a single pathogen (WHO, 2018). The emergence of drug-resistant (DR) TB, HIV co-infection, and comorbidity with type II diabetes mellitus further complicates treatment options and demands a new generation of TB drugs effective against DR-TB, compatible with HIV antiretrovirals, and strongly bactericidal to overcome the impaired host immune system in diabetic and HIV patients.

1,3-Benzothiazin-4-ones (BTZs) are a novel class of TB drug candidates that possess potent activity against both drug-susceptible and drug-resistant *Mtb* strains (Makarov *et al.*, 2009). Biochemical and genetic studies revealed that BTZs inhibit decaprenylphosphoryl-$\beta$-D-ribose 2′-epimerase (DprE1, Rv3790), which is a critical flavoenzyme involved in the biosynthesis of the mycobacterial cell wall (Makarov *et al.*, 2009). BTZs are bioactivated by the dihydroflavin cofactor $FADH_2$ of DprE1 through reduction of the C-8 nitro group to a nitroso intermediate, which covalently reacts with Cys387 in the enzyme active site to form a semi-mercaptal enzyme-inhibitor adduct (Trefzer *et al.*, 2010). Macozinone (PBTZ169) is the most potent BTZ derivative yet described with subnanomolar whole-cell activity and has successfully completed phase I clinical trials. The extraordinary potency of macozinone is derived from its covalent mode of inhibition, as well as the cellular location of the target DprE1 (Trefzer *et al.*, 2010, 2012; Neres *et al.*, 2012; Brecik *et al.*, 2015).

Herein we report the synthesis of macozinone using the classic Makarov route to the BTZs (Makarov *et al.*, 2007), but



with slight modification to prepare the requisite 2-chloro-3-nitro-5-(trifluoromethyl)benzamide building block that avoids generation of the reactive acid chloride. Macozinone (see Scheme) was fully characterized by single-crystal X-ray diffraction (XRD) analysis.




Macozinone

## 2. Experimental

### 2.1. Chemical synthesis

All chemicals were obtained from commercial sources and used without further preparation. 2-Chloro-3-nitro-5-(trifluoromethyl)benzoic acid was prepared as described (Makarov *et al.*, 2014). Proton and carbon NMR spectra were recorded in deuterated solvents on a Varian Mercury 400 MHz spectrometer. The chemical shifts are reported in parts per million ($\delta$) relative to an internal tetramethylsilane (TMS) standard. Coupling constants are reported in Hertz. IR spectra were recorded on a Bruker TENSOR FT–IR spectrometer. Melting points were determined using a Yanaco melting-point apparatus and are uncorrected. Mass spectra were determined on an Exactive Plus LC/MSD Orbitrap from Thermo Fisher Scientific.

**2.1.1. 2-Chloro-3-nitro-5-(trifluoromethyl)benzamide (2).** To a strirred solution of 2-chloro-3-nitro-5-(trifluoromethyl)-benzoic acid (2.7 g, 10 mmol, 1.0 equiv.), pyridine (0.50 ml, 6.2 mmol, 0.62 equiv.), and $Boc_2O$ (2.8 g, 13.0 mmol, 1.3 equiv.) in 1,4-dioxane (10 ml) at room temperature was added ammonium bicarbonate (1.00 g, 12.6 mmol, 1.26 equiv.). The reaction was stirred overnight at room temperature and then partitioned between EtOAc (50 ml) and $H_2O$ (50 ml). The organic layer was separated, washed consecutively with water (50 ml) and 0.6 *N* aqueous HCl (50 ml), dried ($Mg_2SO_4$), and filtered. The filtrate was concentrated under reduced pressure to provide **2** as a white solid [yield 2.42 g, 90%; m.p. 190–193 °C; literature (Welch *et al.*, 1969) 195–197 °C]. $^1$H NMR and MS data are consistent with previously reported spectra (Cooper *et al.*, 2013).

**2.1.2. 2-[4-(Cyclohexylmethyl)piperazin-1-yl]-8-nitro-6-(trifluoromethyl)-4*H*-1,3-benzothiazin-4-one (macozinone).** Potassium carbonate (0.62 g, 4.5 mmol, 1.2 equiv.) was added to a

**Table 1**
Experimental details.

| | |
|---|---|
| Crystal data | |
| Chemical formula | $C_{20}H_{23}F_3N_4O_3S$ |
| $M_r$ | 456.48 |
| Crystal system, space group | Monoclinic, $P2_1/c$ |
| Temperature (K) | 205 |
| $a$, $b$, $c$ (Å) | 15.051 (7), 5.295 (2), 26.548 (11) |
| $\beta$ (°) | 97.372 (7) |
| $V$ (Å$^3$) | 2098.3 (15) |
| $Z$ | 4 |
| Radiation type | Mo $K\alpha$ |
| $\mu$ (mm$^{-1}$) | 0.21 |
| Crystal size (mm) | 0.16 × 0.15 × 0.12 |
| Data collection | |
| Diffractometer | Bruker D8 Venture |
| Absorption correction | Multi-scan (*SADABS*; Bruker, 2013) |
| $T_{min}$, $T_{max}$ | 0.641, 0.746 |
| No. of measured, independent and observed [$I > 2\sigma(I)$] reflections | 11854, 4794, 3412 |
| $R_{int}$ | 0.025 |
| (sin $\theta/\lambda)_{max}$ (Å$^{-1}$) | 0.654 |
| Refinement | |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$ | 0.047, 0.122, 1.05 |
| No. of reflections | 4794 |
| No. of parameters | 326 |
| No. of restraints | 36 |
| H-atom treatment | H-atom parameters constrained |
| $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å$^{-3}$) | 0.29, −0.21 |

Computer programs: *APEX2* (Bruker, 2013), *SAINT* (Bruker, 2013), *SHELXT* (Sheldrick, 2015*a*), *SHELXL2018* (Sheldrick, 2015*b*) and *OLEX2* (Dolomanov *et al.*, 2009).

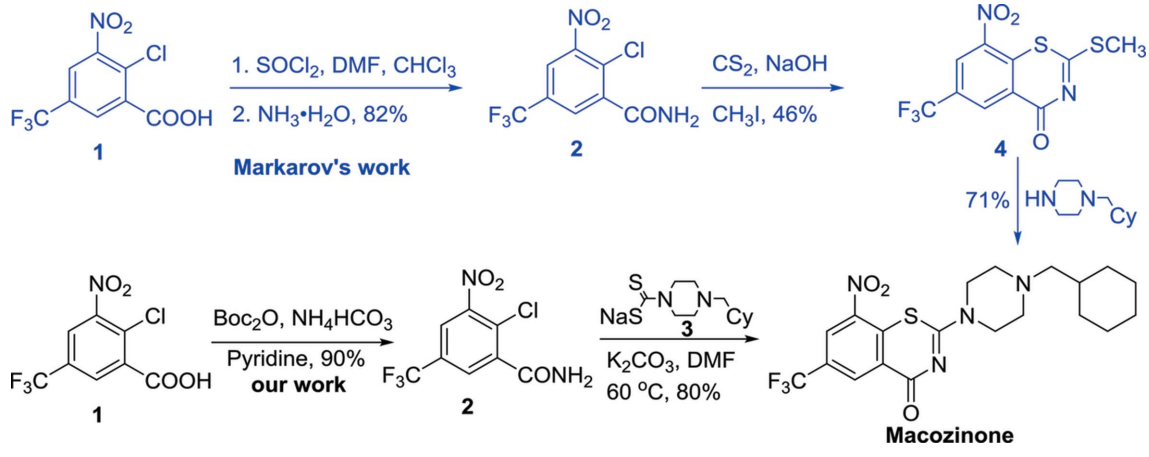



**Figure 1**
The synthesis of macozinone beginning from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (**1**), which was directly converted to the benzamide derivative (**2**). Condensation of **2** with sodium 4-(cyclohexylmethyl)piperazine-1-carbodithioate (**3**) afforded macozinone. The synthesis of macozinone reported by Makarov *et al.* (2014) is highlighted in blue.

solution of 2-chloro-3-nitro-5-(trifluoromethyl)benzamide (**2**; 1.0 g, 3.7 mmol, 1.0 equiv.), and sodium 4-(cyclohexylmethyl)piperazine-1-carbodithioate (**3**; 1.25 g, 4.5 mmol, 1.2 equiv.), in dimethylformamide (DMF, 20 ml). The mixture was heated at 60 °C for 2 h and then cooled to room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 10:1→5:1→2:1→1:1→1:2→1:10→100% ethyl acetate) on silica gel to afford the title compound (yield 1.36 g, 80%) as a yellow solid [m.p. 185–187 °C; literature (Makarov *et al.*, 2014) 184–186 °C]; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.10 (*d*, *J* = 2.1 Hz, 1H), 8.75 (*d*, *J* = 2.1 Hz, 1H), 3.87–4.15 (*m*, 4H), 2.47–2.60 (*m*, 4H), 2.17–2.20 (*m*, 2H), 1.68–1.80 (*m*, 4H), 1.50–1.58 (*m*, 1H), 1.19–1.25 (*m*, 4H), 0.84–0.93 (*m*, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 166.5, 162.0, 143.9, 134.1, 133.4 (*q*, $^4J_{C-F}$ = 4.0 Hz), 129.7 (*q*, $^2J_{C-F}$ = 35.0 Hz), 126.8, 126.0 (*q*, $^3J_{C-F}$ = 4.0 Hz), 122.4 (*q*, $^1J_{C-F}$ = 271 Hz), 65.1, 53.1, 46.6, 35.0, 31.7, 26.7, 26.0; IR (KBr) $\nu$ (cm$^{-1}$) 2923, 1649, 1298, 1141, 1000, 916, 863, 781; HRMS (ESI–TOF$^+$) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{24}F_3N_4O_3S^+$ 457.1516; found 457.1521 (error 1.1 ppm).

### 2.2. Crystal growth of macozinone

Macozinone (5.0 mg) was suspended in ethyl acetate (EtOAc, 1 ml) and stirred vigorously at room temperature for 16 h. The remaining solid was removed by gravity filtration and the filtrate was transferred to a 5 ml glass tube. Hexane (3.0 ml) was added slowly on top of the saturated EtOAc solution of macozinone. The tube was capped and placed in a cool cabinet in the dark to promote crystallization. After 7 d, crystals suitable for X-ray diffraction analysis had formed.

### 2.3. Crystal data of macozinone

A search of the Cambridge Structural Database (CSD, Version 5.37; Groom *et al.*, 2016) and *Scifinder* (Version of 2018, https://www.cas.org/products/scifinder) revealed no hits. Crystal data, data collection and structure refinement details are summarized in Table 1. H atoms were placed in calculated positions and included as riding contributions with isotropic displacement parameters. H atoms belonging to aryl groups were located in difference density maps and were refined freely. The aryl H atoms were constrained with C—H = 0.95 Å, the methylene groups with C—H = 0.99 Å [$U_{iso}$(H) = 1.2$U_{eq}$(C)] and the methyl groups with C—H = 0.98 Å [$U_{iso}$(H) = 1.5$U_{eq}$(C)].

## 3. Results and discussion

### 3.1. Chemical synthesis

The synthesis of macozinone is shown in Fig. 1, beginning from 2-chloro-3-nitro-5-(trifluoromethyl)benzoic acid (Makarov *et al.*, 2014) (**1**), which was directly converted to the benzamide derivative (**2**) in 90% yield under mild room-temperature conditions by activation with di-*tert*-butyl dicarbonate ($Boc_2O$) and subsequent *in situ* reaction with ammonia derived from ammonium bicarbonate. Condensation of **2** with sodium

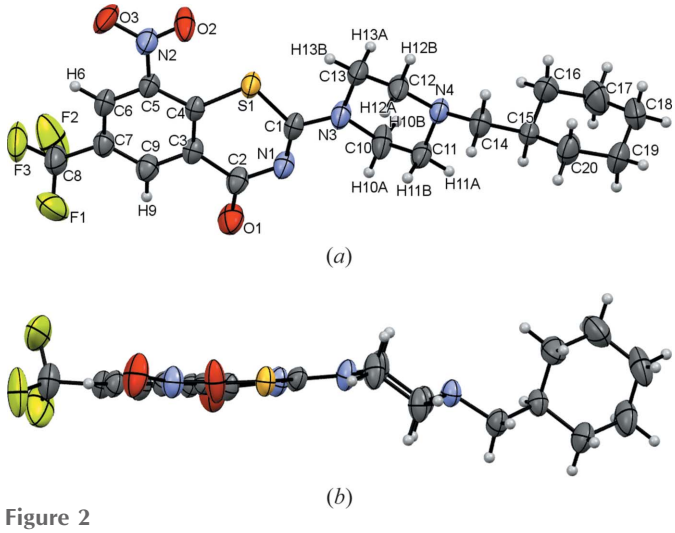



**Figure 2**
(*a*) The molecular structure of macozinone and (*b*) a structural side view of macozinone.

4-(cyclohexylmethyl)piperazine-1-carbodithioate (Makarov *et al.*, 2007) (**3**) in DMF using the conditions developed by Makarov *et al.* (2007) for the synthesis of earlier BTZ derivatives, through nucleophilic aromatic substitution followed by intramolecular cyclization and concomitant expulsion of hydrogen sulfide, afforded macozinone in 80% yield. Macozinone was fully characterized by $^1$H NMR, $^{13}$C NMR, HRMS and IR spectroscopy, and single-crystal X-ray diffraction analysis. Previously, only $^1$H NMR and HRMS data has been provided for macozinone (Makarov *et al.*, 2014). For comparison, we have illustrated the synthesis of macozinone reported by Makarov (Fig. 1, highlighted in blue), which also began from **1**, but used refluxing conditions with thionyl chloride in $CHCl_3$ to obtain the acid chloride that was reacted with ice-cold ammonium hydroxide under Schotten–Baumann conditions to yield **2** (Cooper *et al.*, 2013). Reaction of **2** with carbonyl disulfide afforded 2-(methylsulfanyl)-8-nitro-6-(trifluoromethyl)-4*H*-thiochromen-4-one, **4**, which was subsequently condensed with 5-(cyclohexylmethy)piperazine to afford macozinone in 71% yield (Makarov *et al.*, 2014).

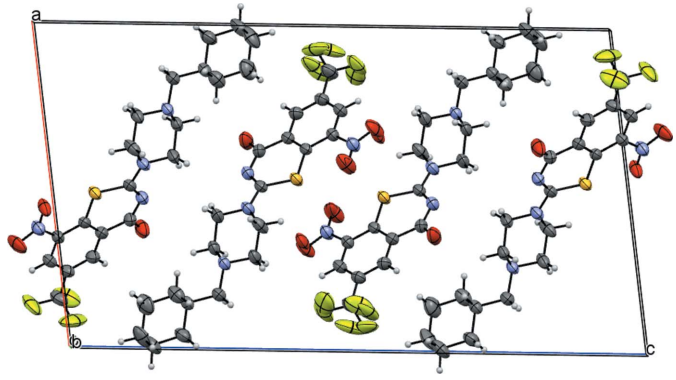



**Figure 3**
Outline of the unit cell with axes, showing all the molecular entities in the crystal. Partial crystal disorder exists at the nitro and trifluoromethyl positions of the target compound.

### 3.2. Crystal data

A search of the Cambridge Structural Database (CSD, Version 5.37; Groom *et al.*, 2016) for the thiopyran-4-one fragment resulted in 42 hits, of which 10 possessing the most similar structures were compared with those of the title compound (Table S5 in the supporting information) (Narasimhamurthy *et al.*, 2003; Duvvuru *et al.*, 2012; Gendron *et al.*, 2015; Rosiak *et al.*, 2006; Schmidt *et al.*, 2005; Ramalingam *et al.*, 1979; Xu *et al.*, 2015; Wang *et al.*, 2011; Mojtahedi *et al.*, 2011; Karisalmi *et al.*, 2003). This is the first small-molecule crystal structure reported for macozinone or any BTZ analogue.

Macozinone crystallized in the monoclinic system space group $P2_1/c$ (Fig. 2). The key feature of macozinone is the planar 1,3-benzothiazin-4-one heterocycle. The dihedral angle between 1,3-benzothiazin-4-one and the least-squares plane of the appended piperazine ring is 38.56 (5)°. The cyclohexyl ring is almost perpendicular to the 1,3-benzothiazin-4-one and piperazine core. In the 1,3-benzothiazin-4-one fragment, the C1—S1 bond length is 1.776 (2) Å, which is very close to the reported literature values (Narasimhamurthy *et al.*, 2003; Duvvuru *et al.*, 2012; Gendron *et al.*, 2015; Rosiak *et al.*, 2006; Schmidt *et al.*, 2005; Ramalingam *et al.*, 1979; Xu *et al.*, 2015; Wang *et al.*, 2011; Mojtahedi *et al.*, 2011; Karisalmi *et al.*, 2003). Similarly, the C4—S1 bond length of 1.739 (2) Å and the C1—S1—C4 bond angle of 100.61 (10)° are comparable to the control crystal structures (Table S4 in the supporting information). Interestingly, the C1—N3 bond length of 1.330 (2) Å is much shorter than the calculated C—N bond of *N*-methylpiperazine (1.455 Å). The C1—N3—C13, C1—N3—C10, and C10—N3—C13 angles are 125.62 (17), 120.85 (19), and 113.11 (17)°, respectively, which indicates that atom N3 is $sp^2$-hybridized, driven by resonance stabilization of the nitrogen lone-pair into the electron-deficient 1,3-benzothiazin-4-one moiety. The piperazine ring in the structure adopts a slightly distorted chair conformation due to the $sp^2$-hybridization of atom N3, with atoms N3 and N4 deviating by 0.689 and 0.591 Å, respectively, from the least-squares plane defined by atoms C10/C11/C12/C13.

In the crystal lattice of macozinone, there are four molecules in each cell unit (Fig. 3). Strong intermolecular hydrogen-bond interactions were observed between the O atoms of the $NO_2$ group and atoms H12*B* and H13*B* of the 1,4-piperazine moiety (N2—O2···H13*B* and N2—O3···H12*B*; Table 2 and Fig. S2 in the supporting information), as well as the N1 atoms of the 1,3-benzothiazin-4-one group and atom H10*A* of 1,4-piperazine (C10—H10*A*···N1; Fig. S1 in the supporting information). The supermolecular aggregate was formed *via* the stronger intermolecular hydrogen bond in three dimensions, which promoted crystallization along the *bc*-axis direction in the crystal lattice and crystallization of macozinone in the space group $P2_1/c$.

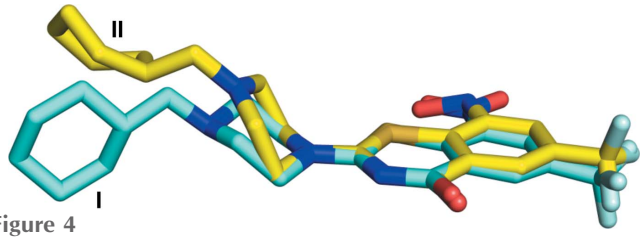



**Figure 4**
Overlay of small-molecule crystal of macozinone and its fragment from the cocrystal with DprE1 (PDB code: 4ncr). The small-molecule crystal structure of macozinone is shown as a cyan stick structure (denoted **I**) and the fragment of macozinone from the cocrystal with DprE1 is shown as a yellow stick structure (denoted **II**).

**Table 2**
Hydrogen-bond geometry (Å, °).

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N2—O2···H12*B* | 0.98 (1) | 2.68 (1) | 3.311 (3) | 123 (1) |
| N2—O3···H13*B* | 0.98 (1) | 2.94 (1) | 3.844 (15) | 153 (1) |

The crystal structure of the reduced nitroso derivative of macozinone covalently bound to DprE1 (PDB code: 4ncr) was determined by Cole and co-workers (Makarov *et al.*, 2014). Comparison of our single-molecule crystal and the reduced nitroso macozinone structure of the complex with DprE1 revealed significant differences in the conformations of the piperazine and cyclohexyl rings. The small-molecule crystal structure (Fig. 4, **I**) displays a lower energy classic chair conformation for the cyclohexyl ring, but a twist-boat conformation is observed in the adduct structure (Fig. 4, **II**), which is presumably caused by the sterically congested environment in the enzyme active site. Similarly, the piperazine adopts the lowest-energy chair conformation in the single-molecule structure, but a higher-energy distorted chair conformation in the adduct structure. The implications of this work directly impinge on future drug-discovery efforts and suggest the introduction of conformational constraints onto the piperazine ring of macozinone that enforce the higher-energy twist-boat conformation (Fig. 4, **II**) may further enhance potency. Modifications of drugs that reduce molecular symmetry and planarity have been shown to improve aqueous solubility which can in turn enhance membrane permeability, oral bioavailability, and drug distribution in the body (Ishikawa *et al.*, 2011; Degorce *et al.*, 2018; Zhang *et al.*, 2019).

## 4. Conclusion

Macozinone is a promising new drug for treating drug-sensitive and drug-resistant TB that has successfully completed phase I clinical trials. We report the complete spectroscopic and structural characterization of macozinone by $^1$H NMR, $^{13}$C NMR, HRMS, IR, and X-ray crystallography. The cyclohexyl group is nearly perpendicular to the core formed by the 1,3-benzothiazin-4-one and piperazine groups. The central piperazine ring adopts a slightly distorted chair conformation caused by the $sp^2$ hybridization of the N2 atom, which donates into the electron-deficient 1,3-benzothiazin-4-one group.

## Acknowledgements

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# supporting information

*Acta Cryst.* (2019). C**75**, 1031-1035 [https://doi.org/10.1107/S2053229619009185]

## Macozinone: revised synthesis and crystal structure of a promising new drug for treating drug-sensitive and drug-resistant tuberculosis

**Gang Zhang and Courtney C. Aldrich**

### Computing details

Data collection: *APEX2* (Bruker, 2013); cell refinement: *SAINT* (Bruker, 2013); data reduction: *SAINT* (Bruker, 2013); program(s) used to solve structure: SHELXT (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL2018* (Sheldrick, 2015b); molecular graphics: OLEX2 (Dolomanov *et al.*, 2009); software used to prepare material for publication: OLEX2 (Dolomanov *et al.*, 2009).

### {2-[4-(Cyclohexylmethyl)piperazin-1-yl]-8-nitro-6-(trifluoromethyl)-4*H*-1,3-benzothiazin-4-one

*Crystal data*

$C_{20}H_{23}F_3N_4O_3S$
$M_r$ = 456.48
Monoclinic, $P2_1/c$
$a$ = 15.051 (7) Å
$b$ = 5.295 (2) Å
$c$ = 26.548 (11) Å
$\beta$ = 97.372 (7)°
$V$ = 2098.3 (15) Å$^3$
$Z$ = 4
$F(000)$ = 952
$D_x$ = 1.445 Mg m$^{-3}$
Mo $K\alpha$ radiation, $\lambda$ = 0.71073 Å
Cell parameters from 4036 reflections
$\theta$ = 2.7–27.7°
$\mu$ = 0.21 mm$^{-1}$
$T$ = 205 K
Block, colourless
0.16 × 0.15 × 0.12 mm

*Data collection*

Bruker D8 Venture diffractometer
phi and $\omega$ scans
Absorption correction: multi-scan (SADABS; Bruker, 2014/3)
$T_{min}$ = 0.641, $T_{max}$ = 0.746
11854 measured reflections
4794 independent reflections
3412 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.025
$\theta_{max}$ = 27.7°, $\theta_{min}$ = 1.9°
$h$ = −19→18
$k$ = −6→6
$l$ = −26→34

*Refinement*

Refinement on $F^2$
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.122
$S$ = 1.05
4794 reflections
326 parameters
36 restraints
Primary atom site location: dual
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0422P)^2 + 1.0593P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.28 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.21 e Å$^{-3}$

*Special details*

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

**Refinement**. Single-crystal X-ray diffraction measurements were carried out on a Bruker SMART APEXII CCD diffractometer at 205.0 K using graphite-monochromated Mo *Kα* radiation ($\lambda$ = 0.71070 Å). Absorption correction was performed with Multi-scan BRUKER SADABS. All structures were solved by direct methods and refined by full-matrix least squares on $F^2$ using the OLEX 2-1.2 computer program package.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)*

| | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ | Occ. (<1) |
|---|---|---|---|---|---|
| S1 | 0.52703 (3) | 0.65072 (11) | 0.42522 (2) | 0.04694 (16) | |
| F1 | 0.8552 (9) | −0.1746 (17) | 0.4930 (6) | 0.108 (3) | 0.54 (2) |
| F1A | 0.8725 (9) | −0.143 (3) | 0.4794 (5) | 0.111 (4) | 0.46 (2) |
| F2 | 0.9241 (6) | 0.170 (3) | 0.4874 (6) | 0.128 (4) | 0.54 (2) |
| F2A | 0.9244 (7) | 0.184 (2) | 0.5097 (9) | 0.125 (5) | 0.46 (2) |
| F3 | 0.8780 (7) | 0.076 (3) | 0.5547 (4) | 0.102 (3) | 0.54 (2) |
| F3A | 0.8502 (11) | −0.052 (4) | 0.5517 (5) | 0.129 (5) | 0.46 (2) |
| O1 | 0.63947 (12) | 0.0187 (4) | 0.34831 (6) | 0.0694 (5) | |
| O2 | 0.5728 (11) | 0.832 (3) | 0.5164 (5) | 0.070 (4) | 0.5 |
| O3 | 0.6875 (10) | 0.755 (3) | 0.5709 (6) | 0.081 (4) | 0.5 |
| N1 | 0.54185 (11) | 0.3384 (4) | 0.34317 (6) | 0.0487 (4) | |
| N2 | 0.63712 (12) | 0.7050 (4) | 0.53079 (7) | 0.0526 (5) | |
| N3 | 0.43493 (11) | 0.6421 (4) | 0.33536 (6) | 0.0515 (5) | |
| N4 | 0.26569 (10) | 0.7797 (3) | 0.28300 (6) | 0.0434 (4) | |
| C1 | 0.50279 (12) | 0.5254 (4) | 0.36293 (7) | 0.0425 (5) | |
| C2 | 0.61018 (13) | 0.2030 (5) | 0.36797 (7) | 0.0464 (5) | |
| C3 | 0.65155 (12) | 0.2764 (4) | 0.42019 (7) | 0.0413 (5) | |
| C4 | 0.61939 (12) | 0.4688 (4) | 0.44857 (7) | 0.0372 (4) | |
| C5 | 0.66502 (12) | 0.5100 (4) | 0.49754 (7) | 0.0410 (5) | |
| C6 | 0.73970 (13) | 0.3740 (4) | 0.51622 (8) | 0.0468 (5) | |
| H6 | 0.769070 | 0.407636 | 0.548954 | 0.056* | |
| C7 | 0.77130 (13) | 0.1896 (4) | 0.48713 (8) | 0.0479 (5) | |
| C8 | 0.85604 (17) | 0.0546 (6) | 0.50615 (10) | 0.0662 (7) | |
| C9 | 0.72686 (13) | 0.1392 (5) | 0.43980 (8) | 0.0486 (5) | |
| H9 | 0.747755 | 0.009301 | 0.420233 | 0.058* | |
| C10 | 0.41082 (14) | 0.5820 (6) | 0.28127 (8) | 0.0603 (7) | |
| H10A | 0.439959 | 0.424089 | 0.273247 | 0.072* | |
| H10B | 0.431976 | 0.716647 | 0.260462 | 0.072* | |
| C11 | 0.31140 (14) | 0.5553 (5) | 0.26915 (7) | 0.0493 (5) | |
| H11A | 0.296009 | 0.523696 | 0.232706 | 0.059* | |
| H11B | 0.291271 | 0.409934 | 0.287546 | 0.059* | |
| C12 | 0.28611 (15) | 0.8181 (5) | 0.33727 (7) | 0.0543 (6) | |
| H12A | 0.266122 | 0.671138 | 0.355248 | 0.065* | |
| H12B | 0.253750 | 0.966621 | 0.347326 | 0.065* | |
| C13 | 0.38519 (16) | 0.8555 (5) | 0.35200 (9) | 0.0615 (7) | |

| | | | | | |
|---|---|---|---|---|---|
| H13A | 0.404235 | 1.010959 | 0.336436 | 0.074* | |
| H13B | 0.398081 | 0.873235 | 0.388956 | 0.074* | |
| C14 | 0.16929 (13) | 0.7631 (5) | 0.26748 (8) | 0.0508 (5) | |
| H14A | 0.139390 | 0.893787 | 0.285327 | 0.061* | |
| H14B | 0.148037 | 0.598650 | 0.277928 | 0.061* | |
| C15 | 0.14244 (13) | 0.7943 (4) | 0.21079 (7) | 0.0431 (5) | |
| H15 | 0.174017 | 0.663337 | 0.193265 | 0.052* | |
| C16 | 0.16959 (17) | 1.0481 (5) | 0.19249 (9) | 0.0625 (6) | |
| H16A | 0.235041 | 1.062146 | 0.198156 | 0.075* | |
| H16B | 0.144881 | 1.180598 | 0.212410 | 0.075* | |
| C17 | 0.1376 (2) | 1.0897 (6) | 0.13692 (10) | 0.0831 (9) | |
| H17A | 0.152016 | 1.262774 | 0.127726 | 0.100* | |
| H17B | 0.169625 | 0.974292 | 0.116704 | 0.100* | |
| C18 | 0.0386 (2) | 1.0477 (6) | 0.12409 (11) | 0.0823 (9) | |
| H18A | 0.006208 | 1.179663 | 0.140110 | 0.099* | |
| H18B | 0.022299 | 1.060636 | 0.087238 | 0.099* | |
| C19 | 0.01126 (18) | 0.7948 (6) | 0.14168 (10) | 0.0745 (8) | |
| H19A | 0.036229 | 0.662908 | 0.121730 | 0.089* | |
| H19B | −0.054178 | 0.780856 | 0.135811 | 0.089* | |
| C20 | 0.04285 (15) | 0.7530 (6) | 0.19717 (9) | 0.0645 (7) | |
| H20A | 0.028111 | 0.580029 | 0.206253 | 0.077* | |
| H20B | 0.010587 | 0.868432 | 0.217269 | 0.077* | |
| O3A | 0.6660 (9) | 0.690 (3) | 0.5751 (5) | 0.063 (2) | 0.5 |
| O2A | 0.5785 (13) | 0.850 (4) | 0.5140 (6) | 0.080 (4) | 0.5 |

*Atomic displacement parameters (Å²)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| S1 | 0.0422 (3) | 0.0577 (4) | 0.0374 (3) | 0.0079 (2) | −0.00828 (19) | −0.0052 (2) |
| F1 | 0.092 (5) | 0.053 (3) | 0.168 (8) | 0.019 (3) | −0.029 (5) | −0.001 (3) |
| F1A | 0.079 (5) | 0.132 (8) | 0.107 (5) | 0.066 (5) | −0.043 (4) | −0.058 (6) |
| F2 | 0.040 (3) | 0.164 (8) | 0.183 (8) | 0.031 (3) | 0.020 (4) | 0.080 (6) |
| F2A | 0.048 (4) | 0.091 (5) | 0.221 (12) | 0.001 (3) | −0.047 (6) | −0.023 (7) |
| F3 | 0.090 (4) | 0.129 (7) | 0.074 (3) | 0.048 (4) | −0.042 (3) | −0.010 (4) |
| F3A | 0.124 (7) | 0.174 (11) | 0.085 (5) | 0.080 (7) | −0.001 (5) | 0.042 (6) |
| O1 | 0.0746 (11) | 0.0853 (13) | 0.0458 (9) | 0.0258 (10) | −0.0022 (8) | −0.0171 (9) |
| O2 | 0.072 (6) | 0.100 (10) | 0.035 (4) | 0.050 (6) | −0.008 (4) | −0.016 (4) |
| O3 | 0.073 (7) | 0.091 (9) | 0.070 (6) | 0.017 (5) | −0.031 (5) | −0.043 (5) |
| N1 | 0.0419 (9) | 0.0666 (13) | 0.0354 (8) | 0.0050 (9) | −0.0031 (7) | −0.0064 (9) |
| N2 | 0.0508 (10) | 0.0619 (13) | 0.0419 (10) | 0.0087 (10) | −0.0067 (8) | −0.0093 (9) |
| N3 | 0.0428 (9) | 0.0688 (13) | 0.0390 (9) | 0.0082 (9) | −0.0094 (7) | −0.0053 (9) |
| N4 | 0.0404 (9) | 0.0533 (11) | 0.0337 (8) | 0.0026 (8) | −0.0065 (6) | −0.0019 (8) |
| C1 | 0.0327 (9) | 0.0573 (14) | 0.0354 (9) | −0.0037 (9) | −0.0033 (7) | 0.0010 (9) |
| C2 | 0.0411 (10) | 0.0625 (15) | 0.0353 (10) | 0.0037 (10) | 0.0037 (8) | −0.0052 (10) |
| C3 | 0.0338 (9) | 0.0532 (13) | 0.0362 (10) | −0.0008 (9) | 0.0014 (7) | 0.0007 (9) |
| C4 | 0.0305 (9) | 0.0463 (12) | 0.0337 (9) | −0.0029 (8) | −0.0002 (7) | 0.0025 (8) |
| C5 | 0.0369 (10) | 0.0489 (13) | 0.0357 (10) | −0.0004 (9) | −0.0018 (7) | −0.0031 (9) |
| C6 | 0.0384 (10) | 0.0585 (14) | 0.0405 (10) | −0.0007 (10) | −0.0066 (8) | −0.0007 (10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C7 | 0.0365 (10) | 0.0575 (14) | 0.0474 (11) | 0.0065 (10) | −0.0032 (8) | 0.0002 (11) |
| C8 | 0.0518 (14) | 0.0741 (19) | 0.0668 (16) | 0.0172 (13) | −0.0144 (12) | −0.0065 (14) |
| C9 | 0.0382 (10) | 0.0606 (15) | 0.0463 (11) | 0.0061 (10) | 0.0029 (8) | −0.0055 (11) |
| C10 | 0.0479 (12) | 0.098 (2) | 0.0328 (10) | 0.0152 (13) | −0.0042 (9) | −0.0019 (12) |
| C11 | 0.0487 (11) | 0.0646 (15) | 0.0319 (10) | 0.0043 (11) | −0.0056 (8) | −0.0067 (10) |
| C12 | 0.0557 (12) | 0.0663 (16) | 0.0369 (10) | 0.0179 (11) | −0.0095 (9) | −0.0117 (10) |
| C13 | 0.0616 (14) | 0.0593 (15) | 0.0552 (13) | 0.0123 (12) | −0.0248 (11) | −0.0148 (12) |
| C14 | 0.0394 (10) | 0.0706 (16) | 0.0403 (11) | 0.0025 (10) | −0.0025 (8) | 0.0004 (10) |
| C15 | 0.0428 (10) | 0.0447 (12) | 0.0386 (10) | 0.0037 (9) | −0.0070 (8) | −0.0023 (9) |
| C16 | 0.0654 (15) | 0.0550 (15) | 0.0618 (14) | −0.0078 (12) | −0.0122 (11) | 0.0056 (12) |
| C17 | 0.098 (2) | 0.081 (2) | 0.0654 (17) | −0.0008 (17) | −0.0073 (15) | 0.0278 (16) |
| C18 | 0.100 (2) | 0.0721 (19) | 0.0639 (16) | 0.0223 (17) | −0.0313 (15) | 0.0081 (15) |
| C19 | 0.0699 (16) | 0.078 (2) | 0.0659 (16) | 0.0025 (14) | −0.0305 (13) | −0.0043 (14) |
| C20 | 0.0483 (12) | 0.0796 (18) | 0.0602 (14) | −0.0067 (13) | −0.0136 (10) | 0.0029 (13) |
| O3A | 0.062 (5) | 0.082 (7) | 0.039 (2) | 0.011 (4) | −0.018 (3) | −0.016 (3) |
| O2A | 0.090 (8) | 0.060 (6) | 0.080 (8) | 0.026 (5) | −0.027 (6) | −0.020 (5) |

*Geometric parameters (Å, º)*

| | | | |
|---|---|---|---|
| S1—C1 | 1.776 (2) | C9—H9 | 0.9400 |
| S1—C4 | 1.739 (2) | C10—H10A | 0.9800 |
| F1—C8 | 1.262 (10) | C10—H10B | 0.9800 |
| F1A—C8 | 1.305 (11) | C10—C11 | 1.496 (3) |
| F2—C8 | 1.342 (9) | C11—H11A | 0.9800 |
| F2A—C8 | 1.229 (11) | C11—H11B | 0.9800 |
| F3—C8 | 1.293 (9) | C12—H12A | 0.9800 |
| F3A—C8 | 1.347 (10) | C12—H12B | 0.9800 |
| O1—C2 | 1.216 (3) | C12—C13 | 1.506 (3) |
| O2—N2 | 1.200 (16) | C13—H13A | 0.9800 |
| O3—N2 | 1.253 (14) | C13—H13B | 0.9800 |
| N1—C1 | 1.296 (3) | C14—H14A | 0.9800 |
| N1—C2 | 1.353 (3) | C14—H14B | 0.9800 |
| N2—C5 | 1.455 (3) | C14—C15 | 1.516 (3) |
| N2—O3A | 1.203 (14) | C15—H15 | 0.9900 |
| N2—O2A | 1.211 (18) | C15—C16 | 1.504 (3) |
| N3—C1 | 1.330 (2) | C15—C20 | 1.512 (3) |
| N3—C10 | 1.470 (3) | C16—H16A | 0.9800 |
| N3—C13 | 1.455 (3) | C16—H16B | 0.9800 |
| N4—C11 | 1.444 (3) | C16—C17 | 1.508 (3) |
| N4—C12 | 1.449 (2) | C17—H17A | 0.9800 |
| N4—C14 | 1.459 (2) | C17—H17B | 0.9800 |
| C2—C3 | 1.496 (3) | C17—C18 | 1.501 (4) |
| C3—C4 | 1.390 (3) | C18—H18A | 0.9800 |
| C3—C9 | 1.390 (3) | C18—H18B | 0.9800 |
| C4—C5 | 1.407 (3) | C18—C19 | 1.494 (4) |
| C5—C6 | 1.373 (3) | C19—H19A | 0.9800 |
| C6—H6 | 0.9400 | C19—H19B | 0.9800 |
| C6—C7 | 1.368 (3) | C19—C20 | 1.505 (3) |

| | | | |
|---|---|---|---|
| C7—C8 | 1.492 (3) | C20—H20A | 0.9800 |
| C7—C9 | 1.372 (3) | C20—H20B | 0.9800 |
| | | | |
| C4—S1—C1 | 100.61 (10) | N4—C11—H11B | 109.4 |
| C1—N1—C2 | 124.30 (17) | C10—C11—H11A | 109.4 |
| O2—N2—O3 | 121.8 (11) | C10—C11—H11B | 109.4 |
| O2—N2—C5 | 119.3 (6) | H11A—C11—H11B | 108.0 |
| O3—N2—C5 | 118.3 (9) | N4—C12—H12A | 109.5 |
| O3A—N2—C5 | 116.8 (9) | N4—C12—H12B | 109.5 |
| O3A—N2—O2A | 123.7 (11) | N4—C12—C13 | 110.69 (18) |
| O2A—N2—C5 | 118.8 (7) | H12A—C12—H12B | 108.1 |
| C1—N3—C10 | 120.85 (19) | C13—C12—H12A | 109.5 |
| C1—N3—C13 | 125.62 (17) | C13—C12—H12B | 109.5 |
| C13—N3—C10 | 113.11 (17) | N3—C13—C12 | 110.48 (19) |
| C11—N4—C12 | 108.74 (16) | N3—C13—H13A | 109.6 |
| C11—N4—C14 | 111.55 (17) | N3—C13—H13B | 109.6 |
| C12—N4—C14 | 111.45 (16) | C12—C13—H13A | 109.6 |
| N1—C1—S1 | 127.78 (15) | C12—C13—H13B | 109.6 |
| N1—C1—N3 | 119.23 (18) | H13A—C13—H13B | 108.1 |
| N3—C1—S1 | 112.98 (16) | N4—C14—H14A | 108.8 |
| O1—C2—N1 | 120.73 (19) | N4—C14—H14B | 108.8 |
| O1—C2—C3 | 118.38 (19) | N4—C14—C15 | 113.72 (17) |
| N1—C2—C3 | 120.89 (19) | H14A—C14—H14B | 107.7 |
| C4—C3—C2 | 124.04 (17) | C15—C14—H14A | 108.8 |
| C9—C3—C2 | 115.71 (19) | C15—C14—H14B | 108.8 |
| C9—C3—C4 | 120.25 (18) | C14—C15—H15 | 107.9 |
| C3—C4—S1 | 122.06 (14) | C16—C15—C14 | 111.66 (18) |
| C3—C4—C5 | 116.85 (17) | C16—C15—H15 | 107.9 |
| C5—C4—S1 | 121.09 (16) | C16—C15—C20 | 110.74 (19) |
| C4—C5—N2 | 121.74 (18) | C20—C15—C14 | 110.58 (18) |
| C6—C5—N2 | 116.08 (17) | C20—C15—H15 | 107.9 |
| C6—C5—C4 | 122.16 (19) | C15—C16—H16A | 109.1 |
| C5—C6—H6 | 120.1 | C15—C16—H16B | 109.1 |
| C7—C6—C5 | 119.89 (18) | C15—C16—C17 | 112.4 (2) |
| C7—C6—H6 | 120.1 | H16A—C16—H16B | 107.9 |
| C6—C7—C8 | 119.7 (2) | C17—C16—H16A | 109.1 |
| C6—C7—C9 | 119.47 (19) | C17—C16—H16B | 109.1 |
| C9—C7—C8 | 120.8 (2) | C16—C17—H17A | 109.1 |
| F1—C8—F2 | 108.5 (8) | C16—C17—H17B | 109.1 |
| F1—C8—F3 | 110.5 (7) | H17A—C17—H17B | 107.8 |
| F1—C8—C7 | 112.9 (6) | C18—C17—C16 | 112.6 (2) |
| F1A—C8—F3A | 101.1 (8) | C18—C17—H17A | 109.1 |
| F1A—C8—C7 | 114.4 (5) | C18—C17—H17B | 109.1 |
| F2—C8—C7 | 108.4 (5) | C17—C18—H18A | 109.3 |
| F2A—C8—F1A | 105.8 (9) | C17—C18—H18B | 109.3 |
| F2A—C8—F3A | 108.2 (7) | H18A—C18—H18B | 108.0 |
| F2A—C8—C7 | 115.5 (7) | C19—C18—C17 | 111.5 (2) |
| F3—C8—F2 | 102.6 (5) | C19—C18—H18A | 109.3 |

| | | | |
|---|---|---|---|
| F3—C8—C7 | 113.2 (4) | C19—C18—H18B | 109.3 |
| F3A—C8—C7 | 110.6 (5) | C18—C19—H19A | 109.2 |
| C3—C9—H9 | 119.3 | C18—C19—H19B | 109.2 |
| C7—C9—C3 | 121.3 (2) | C18—C19—C20 | 111.9 (2) |
| C7—C9—H9 | 119.3 | H19A—C19—H19B | 107.9 |
| N3—C10—H10A | 109.6 | C20—C19—H19A | 109.2 |
| N3—C10—H10B | 109.6 | C20—C19—H19B | 109.2 |
| N3—C10—C11 | 110.19 (17) | C15—C20—H20A | 109.0 |
| H10A—C10—H10B | 108.1 | C15—C20—H20B | 109.0 |
| C11—C10—H10A | 109.6 | C19—C20—C15 | 113.1 (2) |
| C11—C10—H10B | 109.6 | C19—C20—H20A | 109.0 |
| N4—C11—C10 | 111.31 (19) | C19—C20—H20B | 109.0 |
| N4—C11—H11A | 109.4 | H20A—C20—H20B | 107.8 |

| | | | |
|---|---|---|---|
| S1—C4—C5—N2 | 0.2 (3) | C6—C7—C8—F2A | −67.1 (12) |
| S1—C4—C5—C6 | −177.98 (16) | C6—C7—C8—F3 | 18.7 (9) |
| O1—C2—C3—C4 | −174.1 (2) | C6—C7—C8—F3A | 56.3 (13) |
| O1—C2—C3—C9 | 6.2 (3) | C6—C7—C9—C3 | 1.7 (3) |
| O2—N2—C5—C4 | 1.0 (11) | C8—C7—C9—C3 | −175.3 (2) |
| O2—N2—C5—C6 | 179.3 (11) | C9—C3—C4—S1 | 178.49 (16) |
| O3—N2—C5—C4 | −170.4 (7) | C9—C3—C4—C5 | −1.7 (3) |
| O3—N2—C5—C6 | 7.9 (8) | C9—C7—C8—F1 | −37.8 (9) |
| N1—C2—C3—C4 | 5.9 (3) | C9—C7—C8—F1A | −13.4 (11) |
| N1—C2—C3—C9 | −173.8 (2) | C9—C7—C8—F2 | 82.5 (9) |
| N2—C5—C6—C7 | −179.0 (2) | C9—C7—C8—F2A | 109.9 (12) |
| N3—C10—C11—N4 | 56.2 (3) | C9—C7—C8—F3 | −164.3 (8) |
| N4—C12—C13—N3 | −56.6 (3) | C9—C7—C8—F3A | −126.7 (13) |
| N4—C14—C15—C16 | −61.0 (3) | C10—N3—C1—S1 | 173.83 (17) |
| N4—C14—C15—C20 | 175.2 (2) | C10—N3—C1—N1 | −7.3 (3) |
| C1—S1—C4—C3 | −2.88 (19) | C10—N3—C13—C12 | 51.9 (3) |
| C1—S1—C4—C5 | 177.31 (17) | C11—N4—C12—C13 | 61.2 (2) |
| C1—N1—C2—O1 | 174.7 (2) | C11—N4—C14—C15 | −73.9 (2) |
| C1—N1—C2—C3 | −5.3 (3) | C12—N4—C11—C10 | −61.4 (2) |
| C1—N3—C10—C11 | 135.4 (2) | C12—N4—C14—C15 | 164.3 (2) |
| C1—N3—C13—C12 | −135.5 (2) | C13—N3—C1—S1 | 1.8 (3) |
| C2—N1—C1—S1 | 0.1 (3) | C13—N3—C1—N1 | −179.3 (2) |
| C2—N1—C1—N3 | −178.6 (2) | C13—N3—C10—C11 | −51.6 (3) |
| C2—C3—C4—S1 | −1.2 (3) | C14—N4—C11—C10 | 175.31 (17) |
| C2—C3—C4—C5 | 178.66 (19) | C14—N4—C12—C13 | −175.5 (2) |
| C2—C3—C9—C7 | 179.5 (2) | C14—C15—C16—C17 | −175.9 (2) |
| C3—C4—C5—N2 | −179.62 (18) | C14—C15—C20—C19 | 177.0 (2) |
| C3—C4—C5—C6 | 2.2 (3) | C15—C16—C17—C18 | 53.5 (3) |
| C4—S1—C1—N1 | 3.8 (2) | C16—C15—C20—C19 | 52.7 (3) |
| C4—S1—C1—N3 | −177.46 (16) | C16—C17—C18—C19 | −53.5 (4) |
| C4—C3—C9—C7 | −0.2 (3) | C17—C18—C19—C20 | 53.2 (3) |
| C4—C5—C6—C7 | −0.8 (3) | C18—C19—C20—C15 | −53.7 (3) |
| C5—C6—C7—C8 | 175.8 (2) | C20—C15—C16—C17 | −52.2 (3) |
| C5—C6—C7—C9 | −1.2 (3) | O3A—N2—C5—C4 | 163.6 (6) |

| | | | |
|---|---|---|---|
| C6—C7—C8—F1 | 145.3 (9) | O3A—N2—C5—C6 | −18.1 (7) |
| C6—C7—C8—F1A | 169.7 (10) | O2A—N2—C5—C4 | −7.0 (11) |
| C6—C7—C8—F2 | −94.5 (8) | O2A—N2—C5—C6 | 171.2 (11) |

*Hydrogen-bond geometry (Å, º)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N2—O2···H12*B* | 0.98 (1) | 2.68 (1) | 3.311 (3) | 123 (1) |
| N2—O3···H13*B* | 0.98 (1) | 2.94 (1) | 3.844 (15) | 153 (1) |