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Research Article

Keywords: Thiosemicarbazones, antimicrobial, antitumor, modeling, X-ray

Posted Date: June 30th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-647955/v1>

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Version of Record: A version of this preprint was published at Journal of Chemistry on July 9th, 2022. See the published version at <https://doi.org/10.1155/2022/1241470>.

Design, Characterization, X-ray Single-Crystal, Potentiometric Measurements, Molecular Modeling and Biomedical applications of thiosemicarbazones

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Abstract

series of thiosemicarbazone compounds ((E)-2-((E)-1-(2-(p-tolyl)hydrazono)propan-2-ylidene)hydrazine-1-carbothioamide (TSC1), (E)-N-ethyl-2-((E)-1-(2-(p-tolyl)hydrazono)propan-2-ylidene)hydrazine-1-carbothioamide (TSC2) and (E)-N-phenyl-2-((E)-1-(2-(p-tolyl)hydrazono)propan-2-ylidene)hydrazine-1-carbothioamide)(TSC3) were synthesized and fully characterized by assistance of diverse physicochemical and spectroscopic tools like X-ray single-crystal, IR, mass, ^1H NMR, Uv-Vis,...etc. potentiometric measurements, molecular modeling, as well as biological and antitumor activities screening. We have calculated and discussed the thermodynamics and protonation constants of TSC1 compound as a representative from the novel synthesized thiosemicarbazones. The solution speciation of different species was studied in accordance with pH. Molecular parameters of the optimized structures were calculated and discussed. The X-ray single crystal of TSC2 and TSC3 compounds have been established where TSC2 crystallizes in P21/c, $a = 11.2343(6) \text{ \AA}$, $b = 11.2575(7) \text{ \AA}$, $c = 11.8995(8) \text{ \AA}$, $\alpha = 90.00^\circ$, $\beta = 94.476(7)^\circ$, $\gamma = 90.0^\circ$, $V = 1500.34(16) \text{ \AA}^3$, $Z = 4$, however, TSC3 crystallizes in the space group P21/c, $a = 27.958(12) \text{ \AA}$, $b = 12.072(5) \text{ \AA}$, $c = 9.833(4) \text{ \AA}$, $\alpha = 90.0^\circ$, $\beta = 93.117(11)^\circ$, $\gamma = 90.0^\circ$, $V = 3486.75 \text{ \AA}^3$, $Z = 7$. Considering the antimicrobial activities and correlating structure-activity relationship for the synthesized compounds, TSC1 molecule behaves as a promising candidate as an antifungal agent versus *Candida albicans*. Consequently, that would be very helpful in the field of medicinal chemistry especially as antimicrobial agents. The results are of vital significance to the chemistry of antimicrobial agents.

Keywords: Thiosemicarbazones; antimicrobial; antitumor, modeling; X-ray.

1. Introduction

From the most global problems, infectious diseases represent a high burden in public health worldwide. Due to the high resistance of some Gram-positive and Gram-negative bacteria to many drugs, large number of infection diseases become a real dangerous that threaten the human life worldwide [1]. Globally, from more than 50 million infected people up to 110.000 of them die annually. By the middle of 21st century, it is expected that the mortality rate caused by Gram-negative bacterial infection alone could possibly be increased up to ten million deaths a year [2]. Antibiotics are the main base for microbial (bacterial and fungal) infection therapy. Antibiotic overuse, indeed, has become the main cause in the appearance and spread of multi-drug resistant strains of many microbes [3]. Emergence and increasing prevalence of antibiotic resistant bacterial strains to available antibiotics urge the discovery of new therapeutic approaches [4] additionally; the available drugs are also expensive or have a lot of unwanted side effects [5]. Therefore, the necessary to get novel antimicrobial agents is of vital significance given the evidence of fast global spread of resistant clinical isolate. Taking into consideration, the relation between bacterial infection and multi-drug resistant, the present investigation was developed to search for a new antimicrobial effective drug. Nowadays, there is a significant concern in the medicinal chemistry of Schiff-base compound like hydrazones and thiosemicarbazones due to their wide biological activities [6,7]. The groups of C=N and N-C=S are of great interest in chemotherapy and are responsible for the pharmacological activity. Perhaps the most essential step in the metal complexes implementation is the synthesis of a novel compounds that exhibit unique properties as well as reactivity, in this regards thiosemicarbazones were a topic of interest to researchers of various profiles. Thiosemicarbazone compounds and their complexes have been widely investigated as they display very interesting properties in the field of biomedicine as well as potential medicinal applications [8-12] which comprise antiparasital [13], antibacterial [14] antitumor [15], antiviral [16], fungicidal [17], antineoplastic [18] and antiamebic [19] activities. Thiosemicarbazones (TSCNs) may have thione (A) and thiol (B) forms (Scheme 1).

Scheme 1. Thione (A)-thiol (B) tautomers of thiosemicarbazones

Hydrazones were a crucial class of compounds; these compounds have impressive ligation characteristics due to the existence of several coordination sites [20]. The literature also reports hydrazine and its derivatives that have anti-inflammatory, analgesic [21], antibacterial [22] and antitumor [23] activity.

Nevertheless, cadmium is a very toxic metal ion that poses both human and animal health hazards. Its toxicity is done by its easy localization inside the liver, and then by binding of metallothionein, which eventually forms a complex and is transmitted into the blood stream to be lodged in the kidney.

The cause of Cd-toxicity is the negative effect on cell enzyme systems that are the consequence of metallic ion substitution (mainly Zn(II), Cu(II), and Ca(II)) into metalloenzymes and its large affinity to thiol group compounds [24]. Zn(II) replacement with a chemically analogous Cd(II) ion usually causes apoprotein catalytic activity to break down [25,26]. Therefore, it is of paramount importance to discover novel compounds that can form stable complexes with Cd(II), because they can be used as detoxifiers. Referable to the broad scope of pharmacological properties of thiosemicarbazone compounds and their compounds, these compounds can also very well fit for this role. Recently, the experimental studies were supplemented by computational studies [27] owing to their crucial role in recognizing the likely attitudes of the compound during reactions and recognition of valuable information on the compounds under examination, such as total energy, binding energy, electronic energy, dipole moment, bond length, HOMO and LUMO [28]. With this in mind and in the perpetuation of our studies in the subject area of bioactive compounds [29,30], it seems of great interest to synthesize and identify novel compounds involving both thiosemicarbazone and hydrazo moieties. In addition, our aim is to explore biological activities of identified compounds.

2. Experimental

2.1. Materials and reagents

All the chemicals used in this study were supplied by Aldrich Chemicals Company and used with no extra purification.

2.2. Synthesis

2.2.1. Synthesis of 1-(p-tolylhydrazono)-propan-2-one (PTHP) compound

We have synthesized 1-(p-tolylhydrazono)-propan-2-one (PTHP) compound using reported method [31,32]. Chemical equations for preparation shown below in Scheme 2.

Scheme 2. Preparation of 1-(p-tolylhydrazono)-propan-2-one compound

2.2.2. Synthesis of thiosemicarbazone compounds

Equimolar amounts of (PTHP) (0.1760 g, 1 mmol) in 30 ml ethanol with an ethanolic solution (30 ml) of thiosemicarbazide (0.091 g, 1 mmol), N-ethylthiosemicarbazide (0.119 g, 1 mmol) and N-phenylthiosemicarbazide (0.167 g, 1 mmol) were refluxed on hot plate for 3-5 h. The precipitate was separated out, filtered off, washed with $(\text{C}_2\text{H}_5)_2\text{O}$ and desiccated all night using silica gel. The target compounds are shown in Figure 1.

Fig. 1. Structural formulae of thiosemicarbazone compounds; TSC1, TSC2 and TSC3 with R = H, Et, Ph, respectively.

2.2.2.1. ((E)-2-((E)-1-(2-(p-tolyl)hydrazono)propan-2-ylidene)hydrazine-1-carbothioamide (TSC1). Yield, 77%. Colour, Brown. Anal. Calc. for $\text{C}_{11}\text{H}_{15}\text{N}_5\text{S}$: C, 52.99; H, 6.06; N, 28.09; S, 12.86. Found: C, 52.93; H, 6.01; N, 28.03; S, 12.79 %. IR (KBr, cm^{-1}): 3386, 3234 (NH_2), 1507, 1251, 1017, 805 (Thioamide bands, I-IV respectively), 3501, 3177 (N_2H), 1100 (N-N), 1603 (C=N), 1553 (C=C), 3045 (C-H). MS (m/z): 251 ($\text{M}^+ + 2$, 6.03 %), 250 ($\text{M}^+ + 1$, 18.07 %), 249 (M^+ , 100 %), 234 (2.58 %), 232 (38.20 %), 159 (2.07 %), 157 (0.59 %), 118 (3.81 %). ^1H NMR (DMSO): 11.32 (s, 1H, NH), 10.89 (s, 2H, NH), 7.8 (s, 2H, NH_2), 7.48 (s, H, CH=N), 6.94-7.01 (m, 4H, -Ar), 2.21 (s, 3H, - CH_3), 2.02 (s, 3H, - CH_3). ^{13}C -NMR (DMSO): 11.02, 20.09, 112.21, 129.51, 130.80, 136.01, 142.21, 145.62, 178.3.

2.2.2.2. ((E)-N-ethyl-2-((E)-1-(2-(p-tolyl)hydrazono)propan-2-ylidene)hydrazine-1-carbothioamide (TSC2). Yield, 69 %. Colour, Dark brown. Anal. Calc. for $\text{C}_{13}\text{H}_{19}\text{N}_5\text{S}$: C, 55.52; H, 6.17; N, 25.25; S, 11.56. Found: C, 55.48; H, 6.12; N, 25.19; S, 11.51 %. IR (KBr, cm^{-1}): 1532, 1251, 1079, 805 (Thioamide bands, I-IV respectively), 3444, 3338, 3230 (3NH),

1079 (N–N), 1615 (C=N), 1535 (C=C), 3019 (C–H). MS (m/z): 279 ($M^+ + 2$, 6.53 %), 278 ($M^+ + 1$, 21.11 %) 277 (M^+ , 100 %), 262 (0.94%), 173 (2.73 %) 118 (3.23 %). $^1\text{H-NMR}$: 11.33 (s, 1H, NH), 10.33 (s, 1H, NH), 8.91 (s, 1H, NH), 7.54 (s, H, CH=N), 6.36–7.54 (m, 4H, –Ar), 3.60 (q, 2H, –CH₂), 2.4 (t, 2H, –CH₃), 2.23 (s, 3H, –CH₃), 2.02 (s, 3H, –CH₃), $^{13}\text{C-NMR}$: 11.01, 14.32, 20.09, 39.21, 112.23, 128.07, 129.61, 136.0, 142.23, 148.24, 177.04.

2.2.2.3. (E)-N-phenyl-2-((E)-1-(2-(p-tolyl)hydrazono)propan-2-ylidene)hydrazine-1-carbothioamide (TSC3). Yield, 67 %. Colour, Brownish yellow. Anal. Calc. for C₁₇H₁₉N₅S: C, 62.74; H, 5.89; N, 21.50; S, 9.85. Found: C, 62.75; H, 5.85; N, 21.47; S, 9.81 %. IR (KBr, cm⁻¹): 1518, 1250, 1065, 748 (Thioamide bands, I-IV respectively), 3444, 3259, 3020 (3NH), 1065 (N–N), 1603 (C=N), 1551 (C=C), 3020 (C–H). MS (m/z): 326 ($M^+ + 1$, 1.78 %) 325 (M^+ , 7.41 %), 118 (5.63 %). $^1\text{H-NMR}$: 11.32 (s, 1H, NH), 10.30 (s, H, NH), 7.70 (s, H, NH), 7.61 (s, H, CH=N), 6.4–7.70 (m, 9H, –Ar), 2.21 (s, 3H, –CH₃), 2.03 (s, 3H, –CH₃). $^{13}\text{C-NMR}$: 11.33, 20.13, 39.40, 112.24, 115.63, 124.94, 128.28, 129.47, 135.87, 138.92, 142.16, 149.22, 175.9.

2.3. Instrumentation

All the chemicals used have been supplied by Aldrich. CHNS-automatic analyzer, Vario EII-Elementar was used to conduct elemental Microanalysis for C, H, N and S. A Perkin Elmer FTIR, type 1650 spectrophotometer with the potassium bromide disc was used to monitor IR spectra. On a spectrophotometer of shimadzu 3101 pc, electronic spectra are recorded. A Bruker ARX-300 device was applied to monitor the $^1\text{H-NMR}$ spectra. Chemical shifts are recorded in ppm comparative to TMS using deuterated dimethylsulphoxide (d₆-DMSO) as solvent. Mass spectrometry analyses have been carried out using Shimadzu GCMS-QP1000EX. The X-ray single-crystal of TSC2 molecule was performed by Rigaku VariMax RAPID FR-E diffractometer utilized by monochromator Mo K α radiation with radiation wavelength of $\lambda = 0.71075 \text{ \AA}$ by the ω scan mode. By applying a cold N₂ gas flow the crystal was cooled. By using the RAPID AUTO software (Rigaku), we have performed diffraction data scaling, cell refinement, indexing, collection as well as peak integration. The molecular structure was solved by Mercury 4.1.3 software. However, the X-ray crystallography data of TSC2 and TSC3 were collected by mounting a single sample crystal on glass fiber. The cell parameters and intensity data collection were done at 298 K using monochromator Mo K α radiation with radiation wavelength of $\lambda = 0.71073 \text{ \AA}$. The crystal structure was solved by SIR-92 program [33] and was refined on F² by full matrix least-

squares technique using maXus processor program for solution and refinement of Crystal Structures [34]. ORTEP program was used for molecular graphics [35].

A Metrohm 848 Titrino supplied with a Dosimat unit (Switzerland-Herisau) have been utilized for potentiometric titrations as described previously in 50 % water-DMSO mixture [29,30,32].

2.4. Potentiometric titrations

Through potentiometric technique using the method depicted above in the literature [36], the formation constant of complex was estimated. The standard buffer solutions are used for accurately calibrating the glass electrode to NBS standards [37]. Standard solution of 0.05 mol/dm³ NaOH, free from CO₂, is used to titrate all samples in the N₂ atmosphere. The sample solution developed to avoid hydrolysis during titration by mixing equal volumes of DMSO and H₂O. In addition, the ionic strength was kept constant during titration using NaNO₃ as supporting electrolyte.

As known, the calculated formation constants using a potentiometric method have been carried out using a concentration of hydrogen ion expressed in molarity. Nevertheless, the concentration in pH-meter have been expressed in activity coefficient $-\log a_{H^+}$ (pH). Thus, Van Uitert and Hass Eq. 1 was used to change pH-meter reading (B) to [H⁺] [38,39]

$$-\log_{10} [H^+] = B + \log_{10} U_H \quad (1)$$

Where $\log_{10} U_H$ = solvent composition correction factor and the ionic strength read by B. pK_w for titrated samples were estimated as previously described [40]. All precautions and procedures comply with literature requirements [41-43].

The protonation constants of TSC1 thiosemicarbazone compound were estimated potentiometrically by titrating (40 cm³) of (1.25x10⁻³ mol/dm³) TSC1 thiosemicarbazone solution with standard sodium hydroxide solution.

2.5. Processing of data

MINIQUAD-75 computer program has been applied to calculate ca. 100-150 readings for each titration [44]. Species distribution diagrams for the studied samples were given by the SPECIES program [45].

2.6. Molecular modeling studies

DFT calculations were performed using DMOL³ program [46,47] in Materials Studio package [48]. Calculations for DFT semi-core pseudopotentials (dspp) were created with dual numerical base sets and polarization properties (DNP) [49]. The RPBE model is focused on the (GGA) generalized gradient approximation as the best functional approximation [50,51].

2.7. Biological activity

2.7.1. *In vitro* antibacterial activity

Ability of the synthesized thiosemicarbazone compounds to suppress bacterial growth was checked by the disc diffusion process, [52,53]. Aerobic G^+ bacteria: *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus faecalis* and G^- aerobic bacteria: *Pseudomonas aeruginosa*, *E. coli*, *Neisseria gonorrhoeae* are among the bacterial strains that were used in the present study. Additionally, two fungal strains (*Aspergillus flavus*, *Candida albicans*) were checked. The stock novel compounds solutions were prepared in DMSO. 100 μ l of each of the synthesized thiosemicarbazone compounds was inserted into discs (0.8 cm) and then they were allowed to dry. The discs were completely saturated with the synthesized compounds. The discs were then put into the upper layer of the medium at least 25 mm from the edge. The discs were then placed gently on the same plate surface. The plate was then incubated at 37 °C for 72 h, and checked clear inhibition area. Eventually, by using the ruler millimeter we can determine the inhibition zone (an area where there is no growth around the discs).

2.7.3. *In vitro* antitumor activity

The synthesized thiosemicarbazone compounds were screened for their cytotoxicity against liver cancer (HepG2) and breast cancer (MCF-7) cells by using SRB assay protocol [54].

Potential cytotoxicity of the compounds was tested using the method of Skehan and Storeng. Cells were plated in 96-multiwell plate (104 cells/well) for 24 h before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentrations of the compounds under investigation (0, 5, 25 and 50 μ g/ml) were added to the cell monolayer and triplicate wells were prepared for each individual dose. The monolayer cells were incubated with the compounds for 48 h at 37 °C and in 5% CO₂ atmosphere. After 48 h, cells were fixed, washed and stained with SRB stain. Excess stain was washed with acetic acid and attached stain was recovered with tris-EDTA buffer. The optical density (O.D.) of each well was measured spectrophotometrically at 564 nm with an ELIZA microplate reader and the mean background absorbance was automatically subtracted and mean values of each drug concentration was calculated. The relation between drug concentration and surviving fraction is plotted to get the survival curve of breast and liver tumor cell line for each compound.

Calculation:

The percentage of cell survival was calculated as follows:

Survival fraction = O.D. (treated cells) / O.D. (control cells). The IC_{50} values (the concentrations of the Schiff base ligand (L) or complexes required to produce 50% inhibition of cell growth). The experiment was repeated 3 times.

3. Results and discussion

3.1. Characterization of the synthesized thiosemicarbazone compounds

Condensation of the 1-(p-tolylhydrazono)-Propan-2-one compound with thiosemicarbazide, N-ethylthiosemicarbazide and N-phenylthiosemicarbazide readily gives rise to the corresponding TSC1, TSC2 and TSC3 thiosemicarbazone compounds. The isolated compounds are air stable and insoluble in H_2O , but easily soluble in DMF or DMSO. Different analytical tools were employed to identify the structure of prepared compounds. The results from the basic analysis are well in line with the calculated results for the proposed formula. The novel thiosemicarbazone compounds structure is revealed in Fig. 1.

3.1.1. IR spectrum

Preliminary allocations of major IR spectrum bands of thiosemicarbazone compounds display the following features:

1- Disappearance of the $\nu(>C=O)$ and emergence of new band at $1603-1615\text{ cm}^{-1}$ that refers to $\nu(C=N)$ stretching vibration [55] supporting condensation reaction and formation of thiosemicarbazone compounds.

2-Thiosemicarbazone compounds can exhibit thione $\leftrightarrow$ thiol tautomerism [56] as a result of the existence of $-NH-C=S$ linkage but $\nu(S-H)$ absorption band at $2500-2600\text{ cm}^{-1}$ was absent with an appearance of $\nu(C=S)$ band around 750 cm^{-1} indicating existence of the prepared thiosemicarbazone compounds as thione form in the solid state.

3-For the prepared thiosemicarbazone compounds, vibrational bands with the wave numbers of 3012 cm^{-1} (ν_{C-H} , Ar-H), 1615 cm^{-1} ($\nu_{C=N}$), 1548 cm^{-1} ($\nu_{C=C}$), 1082 cm^{-1} (ν_{N-N}) were detected.

4- Vibrational bands with the wave numbers of, $3019-3045\text{ cm}^{-1}$ (ν_{C-H} , Ar-H), $1601-1615\text{ cm}^{-1}$ ($\nu_{C=N}$), $1535-1553\text{ cm}^{-1}$ ($\nu_{C=C}$), $1065-1100\text{ cm}^{-1}$ (ν_{N-N}) were observed for thiosemicarbazone compounds.

5- The ν_{sym} and ν_{asym} of TSC1 amino group were observed at 3234 and 3386 cm^{-1} .

6- In the thiosemicarbazone compounds spectra, the bands observed in the range 1494-1532, 1249-1251, 1017-1088 ,748-817 cm^{-1} are assigned to the thioamide bands, I, II, III and IV respectively [57].

3.1.2. NMR spectrum

^1H -NMR spectra of novel TSC1, TSC2 and TSC3 compounds in DMSO-d_6 display no resonance at approximately 4.0 ppm corresponding to $-\text{SH}$ proton resonance [58], whereas the presence of a peak at 10.77 ppm (signal field of existence of NH group next to $\text{C}=\text{S}$) suggests that they remain in the thione form even in polar solvent like DMSO. Signals for the methine proton of azomethine group for thiosemicarbazone compounds, $\text{CH}=\text{N}$ was detected at $\delta = 7.48\text{--}7.61$ ppm. In the region of 6.36-7.54 ppm chemical shifts were allocated for hydrogen of the aromatic ring. Methyl group was observed as a singlet signal at $\delta = 2.02\text{--}2.20$. The spectra of TSC1 compound show signals at δ 7.80 ppm assigned to the NH_2 proton.

The ^{13}C -NMR spectra of novel thiosemicarbazone compounds were carried out in DMSO-d_6 . Peaks of azomethine carbons and $\text{C}=\text{S}$ of thiosemicarbazone compounds were observed as singlet peaks. The signal for the carbon atom of $\text{C}=\text{S}$ was detected at 178.3, 177.8, 178.1 in TSC1, TSC2 and TSC3 respectively.

3.1.3. UV–Vis spectrum

The strong absorption band detected at 33003-32787 cm^{-1} were assigned to $\pi \rightarrow \pi^*$ transitions ($\text{C}=\text{N}$)_{azomethine} group while the possible assignments for the bands at 26809-27548 cm^{-1} are attributed to the $n \rightarrow \pi^*$ thiosemicarbazone compounds transitions, respectively. Forever $\pi \rightarrow \pi^*$ transitions occur at higher energy than $n \rightarrow \pi^*$ transitions [59].

3.1.4. Mass spectra

The proposed formulae can be further proven by mass spectroscopy. The electron impact mass spectrum of TSC1 confirms the suggested formula by displaying a peak at 249 equivalents to $(\text{C}_{11}\text{H}_{15}\text{N}_5\text{S})$ compound moiety in addition to a series of peaks which attributable to different fragments of TSC1 compound. These data suggest that a ketone PTHP group is condensed with the NH_2 group of thiosemicarbazide or its derivatives. The mass spectra of TSC1, TSC2 and TSC3 showed peaks at 249, 277 and 325 confirming the proposed structural formula of the synthesized TSC1, TSC2 and TSC3 compounds respectively.

3.1.5. Crystallography

The structure of the two of the representing thiosemicarbazone compounds (TSC2 and TSC3) was established through X-ray crystallography. Recrystallisation of the compounds

from hot ethanol followed by slow evaporation leads to formation of single crystals. Data of TSC2 and TSC3 are summarized in the Table 1, **CCDC 2026108 and CCDC 2033322** contain the supplementary crystallographic data for this paper.

The X-ray single-crystal structures of monomeric TSC2 and TSC3 compounds were given in Fig. 2a and 2b, respectively. It suggested that TSC2 was crystallized in monoclinic crystal system with space $P2_1/c$, $a = 27.985 (12) \text{ \AA}$, $b = 12.027 (5) \text{ \AA}$, $c = 9.833 (4) \text{ \AA}$, $\alpha = 90.0^\circ$, $\beta = 93.117 (11)^\circ$, $\gamma = 90.0^\circ$, $V = 3486.57 \text{ \AA}^3$, $Z = 7$ while TSC3 was crystallized also in monoclinic crystal system with space $P2_1/c$, $a = 11.2343 (6) \text{ \AA}$, $b = 11.2575 (7) \text{ \AA}$, $c = 11.8995 (8) \text{ \AA}$, $\alpha = 90.00^\circ$, $\beta = 94.476(6)^\circ$, $\gamma = 90.0^\circ$, $V = 1500.34 (3) \text{ \AA}^3$, $Z = 4$.

a

b

Fig. 2. X-ray structure of **a)** TSC2 **b)** TSC3 thiosemicarbazone compounds along with the atom numbering scheme.

It is worth to mention that TSC2 molecules are stacked non-covalently altogether via inter-molecular interactions i.e. van der Waals as well as H-bonding interactions. This can be clearly illustrated in Fig. 3. The packing structures of TSC2 and TSC3 compounds is shown in the Supplementary Fig. S5a and S5b, respectively. In the packing structure of TSC2 and TSC3 molecules, the unit cell includes four and seven molecules stacked to each other's per unit cell, respectively.

Fig. 3. Expansion of the intermolecular interactions (i.e. van der Waals interaction) between TSC2 molecules.

3.1.6. Molecular modeling and/or Molecular parameters

Quantum parameters like E_{HOMO} , E_{LUMO} , in addition to specific parameters like ionization potential (IP), absolute softness (σ), absolute hardness (η), electron affinity (EA), separation energy (ΔE), absolute electronegativity (χ), global softness (S), electrophilicity (ω), electron accepting power (w^+), electron donating power (w^-) and additional electronic charge (ΔN_{max}) [60-64] have been computed according to Eqs 2-11 as shown below [60-65]. The inverse of the global hardness is called softness σ [66].

$$\chi = -1/2 (E_{\text{LUMO}} + E_{\text{HOMO}}) \quad (2)$$

$$\text{IP} = -E_{\text{HOMO}} \quad (3)$$

$$\eta = 1/2 (E_{\text{LUMO}} - E_{\text{HOMO}}) \quad (4)$$

$$S = 1/2 \eta \quad (5)$$

$$\Delta N_{\text{max}} = -IE / \eta \quad (6)$$

$$\sigma = 1/\eta \quad (7)$$

$$\text{EA} = -E_{\text{LUMO}} \quad (8)$$

$$\omega = IE^2 / 2 \eta \quad (9)$$

$$\omega^- = (3 \cdot IE + EA)^2 / 16 (IE - EA) \quad (10)$$

$$\omega^+ = (IE + 3 \cdot EA)^2 / 16 (IE - EA) \quad (11)$$

Since the geometric optimization of the prepared compounds can be characterized using theoretical calculations; therefore, the optimized structure for the synthesized compounds could be obtained by calculating theoretical physical parameters like bond lengths and bond angles using DFT calculations.

Quantum parameters of the synthesized TSC1, TSC2 and TSC3 compounds have been calculated using Eqs. 2-11. From data given in Table 2 and Table 3, we can deduce each of the following:

- a) HOMO and LUMO are frontier molecular orbitals (FMOs). The energies of HOMO and LUMO are -ve, which designate the studied TSC1, TSC2 and TSC3 thiosemicarbazones are stable molecules [65].
- b) HOMO and LUMO act as an electron donor and acceptor respectively. [66,67].
- c) Hard and soft nucleophiles have low and high HOMO energies respectively while hard and soft electrophiles have high and Low LUMO energies respectively.
- d) The energies of HOMO of (TSC1), (TSC2) and (TSC3) are closely spaced (E_{HOMO} , (TSC1) -8.501 eV; E_{HOMO} , (TSC2) -8.561 eV and E_{HOMO} (TSC3) -8.556 eV).
- e) Soft molecules are characterized by small energy gap ($E_{\text{LUMO}}-E_{\text{HOMO}}$) and higher reactivity than hard ones as a result of their ease donation of electrons to an acceptor [68,69].
- f) Large values of the HOMO–LUMO energy gap (7.410-7.667) means good stability and a large chemical hardness for the synthesized thiosemicarbazone compounds.
- g) Absolute hardness (η) and softness (σ) are essential characteristics in calculation of molecular stability and reactivity. Hard molecules have a large energy gap with less reactivity ($\Delta E = E_{\text{HOMO}} - E_{\text{LUMO}}$), whereas the soft molecules have a smaller energy space and a greater reactivity. This means that ΔE is an indicator of stability and can be used to measure the chemical reactivity and kinetic stability of the compound [67,70].
- h) When HOMO energy decreases, the molecule's ability to donate electron decreases while high HOMO energy means that the molecule is an efficient donor of electrons. LUMO energy indicates a molecule's ability to receive an electron.
- i) The electrophilicity index (ω) follow the trend: TSC1 ($\omega = 3.104$) > TSC2 ($\omega = 2.936$) > TSC3 ($\omega = 2.933$). Thus, compound (TSC1) shows the maximum value of electrophilicity which confirms its largest capability to accept electrons.
- j) The HOMO level in the thiosemicarbazone compounds are commonly localized on the C=N groups demonstrating they are the favored sites for Nu attack at the central metal ion.

k) Negativity of E_{HOMO} and E_{LUMO} indicates thiosemicarbazone compounds stability [71].

3.2. Biological activity

3.2.1. Antibacterial and antifungal activities:

Antimicrobial activities of thiosemicarbazone compounds were screened. Results of antimicrobial activity of thiosemicarbazone compounds versus all tested microbes are shown in Table 4. The following observations were deduced:

- a) The investigation of the biological action of TSC3 on Gram-negative and Gram-positive bacteria indicated that TSC3 was inactive against the tested organisms.
- b) The thiosemicarbazone compound TSC1 possess effective antibacterial activity *versus* the tested bacterial strains
- c) TSC2 has a moderate antibacterial activity versus *Streptococcus faecalis* as gram-positive and *Escherichia coli* as gram-negative bacteria
- d) According to results of antifungal activity screening, the TSC1 compound possesses a very higher antifungal activity *versus Candida albicans* more than *Amphotericin* as standard antifungal agent.

3.2.2. Antitumor activities:

Cytotoxic study of thiosemicarbazones was investigated versus liver cancer cell line (HepG2) and breast cancer cell line (MCF-7). IC_{50} is the concentration which can diminish cancer cells growth by 50 % (Supplementary Fig. 7c). The results of cytotoxic study indicate that, TSC1 compound shows significant activity versus HepG2 and MCF-7 cells with IC_{50} value of 29.4 and 122 $\mu\text{g/ml}$ respectively (Table 5) while the IC_{50} towards HepG2 and MCF-7 cells for TSC2 are 46 and 172.9 $\mu\text{g/ml}$ respectively. Furthermore, the IC_{50} towards HepG2 and MCF-7 cells for TSC3 are 25 and 107 $\mu\text{g/ml}$ respectively. The antitumor results indicate that the synthesized thiosemicarbazone compounds are more effective versus HepG2 than MCF-7. The antitumor activity of the synthesized thiosemicarbazone compounds towards both HepG2 and MCF-7 cell lines obeys this order $\text{TSC3} > \text{TSC1} > \text{TSC2}$.

3.2.3. Molecular modeling and biological activity

Theoretical calculations were performed with the purpose of physicochemical properties investigation that possibly correlated to the antimicrobial action of investigated thiosemicarbazones. From the obtained data, we can deduce that:

a) TSC1 thiosemicarbazone compound, which offered the lowest value of HOMO energy among the synthesized thiosemicarbazone compounds, showed the highest biological activity among the synthesized compounds.

b) Inverse relation between dipole moment and lipophilicity indicates that as dipole moment decreases, the lipophilic nature of the compound increases, which favors its penetration more powerfully via lipid layer of microorganism [72,73], thus destroying them more violently. From the results in Table 3, the lipophilicity of the TSC1 is larger than the other thiosemicarbazone compounds, which sequentially deactivates enzymes accountable for respiration process of the investigated microbes more than other compounds and accordingly increase its cellular uptake by bacterial cells.

c) Thiosemicarbazone compounds have antibacterial activity due to existence of toxophorically essential imine groups (-C=N) where the action mode of these compounds could include formation of H-bonds via azomethine group with an active center of cells which may interfere with ordinary cell processes [74].

3.3. Equilibrium Studies

The protonation constants of TSC1 ligand are calculated (Table 6). These ligands behave as triprotic as shown by Eqs. 15-17.

We can conclude that the 1st and 2nd deprotonation constants correspond to the deprotonation of the two N-imino sites in TSC ligand as given in Scheme 3a. While the 3rd deprotonation constant correspond to the thiolate group site in TSC ligand as shown in Scheme 3b. However, a similar conclusion was obtained in literature [75].

Scheme 3. **a)** Possible deprotonation pathway of the imino groups, **b)** Possible deprotonation pathway of the thiolate group.

The $\log K_{N\text{-imino}}$ values ranges from (2.97-3.35) are similar to those found in the literature for the imino group (4.40) [76]. The $\log K_{SH}$ value ranges from (7.65–8.05) are similar to those described in the literature for the thiolate group (5.5-9.0) [77].

Protonation equilibria study for the TSC ligands under study cannot be performed in aqueous solution since it is insoluble in H_2O . DMSO solvent has been extensively used for potentiometric studies of both protonation and formation equilibria. The mixture DMSO-water 50 %:50 % was best-preferred solvent to give soluble and stable Schiff base solution [58, 79].

Fig. 4. a) Concentration distribution diagram of various species as a function pH in the TSC1 system (at concentration of TSC1 = 1.25 mM T = 25 °C), **b)** Concentration distribution diagram of various species as a function pH in the Cd-TSC1 system

Herein, three protonation constants were calculated for TSC1 ligand and the SPECIES program was utilized to give the distribution of TSC1 ligand species as a function of pH. In Fig. 4a a classic species distribution diagram is reported; it is possible to highlight, at the mentioned experimental conditions, the pH ranges at which the various species are formed

and/or where they coexist, as well as their relative formation percentages. Thus, the species distribution graph is a good tool for obtaining complete picture about the concentration of each species present as a function of pH. It enables us to obtain the best conditions for preparation a solid complex as pH, concentration and ligand: metal ratio. At low pH, (TSC1) exists initially in a fully protonated form with maximum percent of 100% as H₃L below pH < 2. On addition of base, pH value increases so the (H₃L) species loses its first proton from an imino group to form (H₂L), which is the major species at pH = 3.3. As conditions become more alkaline, the second proton released from the second imino group begins deprotonation to HL ligand accomplish highest percent of 99.1 % at pH = 5.8. More increase of pH is followed by liberation of the third H⁺ forming the fully deprotonated ligand L with maximum percent species 98.4% at pH = 10.0.

3.3.1. Species distribution curves

The calculation of equilibrium complex concentrations of Cd(II) with TSC1 (Table 7) as a function of pH gives a valuable picture of metal(II) binding in the biological system. As an illustrative example of metal complexes, Fig. 4b showed a concentration distribution diagram for the complex Cd(II)-TSC1. The Cd-TSC1 complex begins to form in acidic pH range reaching a constant concentration of 99.9 % at pH = 5.0, whereas Cd(TSC1)₂ complex species reaches a maximum concentration of 45 % at pH 9.8.

3.3.2. Thermodynamics

The data derived for ΔH° , ΔS° and ΔG° related to protonation of TSC1 and Cd(II)-complex formation were calculated from the data tabulated in tables 8 and 9. ΔH° for the ligand protonation or complexation was determined from the plot slope (Fig. 5a-b) through graphical representation of the Van't Hoff equation

$$-2.303 R T \log_{10} K = \Delta H^\circ - T \Delta S^\circ \quad (18)$$

or

$$\log K_{10} = -(\Delta H^\circ/2.303R)(1/T) + \Delta S^\circ/R \quad (19)$$

With the well-known relations (6) and (7), from the values of (ΔG) and enthalpy change (ΔH), one can calculate (ΔS):

$$\Delta G^\circ = -2.303 RT \log_{10} K \quad (20)$$

$$\Delta S^\circ = (\Delta H^\circ - \Delta G^\circ)/T \quad (21)$$

Fig. 5. a) Effect of temperature on the protonation constant of TSC1 compound, **b)** Effect of temperature on the formation constant of Cd(II)-TSC1 complexes.

The main reasons for the protonation constant determination can be explained as follows:

(1) The ratio and pH of the various substance forms can be determined using its protonation constants.

(2) Very useful in preparation of newly synthesized compounds. The suggested structure can be reliable where protonation constants are theoretically well calculated according to the experimental values.

(3) Because different types of substances have different UV spectrums, quantitative spectrophotometric analysis can be performed by choosing the appropriate pH value. To choose the pH values, the known protonation constants are required.

(4) Buffer solutions preparations at different pH values needs determination of protonation constants [43,80],

(5) Measurements of the stability constants for the complicated formation reactions of bioactive ion compounds require protonation constants to be determined.

Additionally, their protonation constants are used for calculating the stability constants of the dynamic formation of bioactive compounds with metal ions [81].

(6) The equilibrium constants of certain compounds must be understood to measure concentration of each ionized species at pH which is fundamental to understand their physiochemical behavior [81].

Tables 8, 9 describes the thermodynamic functions measured and can be interpreted as:

1. The corresponding thermodynamic processes for the protonation reactions are:

a) Exothermic processes for neutralization reactions;

ii) Endothermic for ions desolvation;

iii) Structure alteration and alignment of H-bonds around protonated and free ligands.

2. When the temperature rises the value of $\log_{10} K^H$ decreases and its acidity rises as the temperature rises.

3. Negative ΔH° for protonation of TSC1 ligand indicates that this process is exothermic followed by heat release.

4. Positive entropy of TSC1 protonation reaction indicates increased disorder due to desolvation processes and breakdown of H-bonds.

Table 7 includes the stepwise stability constants of the complexes formed at various temperatures. Such values decrease and confirm with increasing temperature that the phase of complexation is preferred at low temperature.

These results provide the following findings:

1-Negative ΔH° show that the coordinating process is exothermic suggesting that the metal-ligand bonds are fairly strong and complexity reactions are preferred at low temperatures.

2- Complexation reaction is spontaneous with negative ΔG° .

3-It is commonly found that ΔG° and ΔH° values for the 1:1 complexes are more -ve than those corresponding to the 1:2 complexes.

4-This can be due to both steric hindrances caused by addition of 2nd ligand in addition to principle of charge neutralization.

5-The electrostatic attraction in the 1:1 complex is larger than in the 1:2 complex since 1:1 complex is formed by dipositively charged M^{n+} and mononegatively charged ligand anion interaction; while 1:2 complex is generated by monopositively charged 1:1 complex and mononegatively charged ligand anion interaction.

6-The ΔS° values for all investigated complexes are +ve indicating that entropy increase resultant from release of bound solvent molecules on coordination is larger than the decrease resultant from coordination process itself due to the ordered arrangement of solvent molecules around the ligand and M^{n+} gains a random coordination pattern. This is referred to as increase in entropy for configuration.

4. Conclusions

1-(p-tolylhydrazono)-propan-2-one (PTHP) is condensed with thiosemicarbazide, N-ethylthiosemicarbazide and N-phenylthiosemicarbazide in the molar ratio (1:1) affording the novel TSC1, TSC2 and TSC3 thiosemicarbazone compounds. The novel series of thiosemicarbazones were characterized using different analysis tools. The IR spectra indicated that, thiosemicarbazone compounds present in thione form in the solid state. Antifungal activity showed equipotent antifungal activity of TSC1 or even more antifungal activity when matched to the reference standard *amphotericin* reference drug versus *Candida albicans*. Thus, TSC1 compound is considered as a hopeful compound for extra variation to get clinically valuable antifungal agent versus *Candida albicans*. SAR studies proved that there is an inverse relationship between dipole moment and antimicrobial activity which could help

in the design of more powerful antibacterial substances. Potentiometric studies have shown that thiosemicarbazone compound (TSC1) form complexes 1:1 or 1:2 with Cd(II) ion. The $\log K_1$ and $-\Delta H_1$, for Cd(II)-TSC1 thiosemicarbazone complexes are to some extent larger than $\log K_2$ and $-\Delta H_2$, indicating a change in ligand dentate character from tridentate (SNN-donors) in 1:1 chelates to bidentate (SN-donors) in 1:2; M:L chelates in addition to steric hindrance generated by entry of 2nd molecule. The coordination of Cd(II) to TSC1 has been found to be spontaneous, exothermic and entropically favorable. Molecular properties of the synthesized thiosemicarbazone compounds have been investigated by means of DFT calculations. These compounds may be considered as a good remedy for Cd²⁺ ion toxicity as it forms a highly stable complex with it. Variation of substitution in N-thiosemicarbazide moiety was considered as a vital key for functionalization of synthesized compounds owing to its significance in the inhibition process.

5. Abbreviations

PTHP: 1-(p-tolylhydrazono)-propan-2-one

TSC1: ((E)-2-((E)-1-(2-(p-tolyl)hydrazono)propan-2-ylidene)hydrazine-1-carbothioamide,

TSC2: ((E)-N-ethyl-2-((E)-1-(2-(p-tolyl)hydrazono)propan-2-ylidene)hydrazine-1-carbothioamide,

TSC3: ((E)-N-phenyl-2-((E)-1-(2-(p-tolyl)hydrazono)propan-2-ylidene)hydrazine-1-carbothioamide

6. References

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Table 1. Crystal data and structure refinement of thiosemicarbazone compounds

Crystal data	Compounds	
	TSC2	TSC3
Molecular formula	C ₁₃ H ₁₉ N ₅ S	C ₁₇ H ₁₉ N ₅ S
Formula weight	277	325
Crystal system	Monoclinic	Monoclinic
Space group	P2 ₁ /c	P2 ₁ /c
Wavelength (Å)	0.71073	0.71073
Temperature (K)	298	298
Colour	Brownish-yellow	Brownish-yellow
Radiation type	Mo K α	Mo K α
Radiation source	Fine-focus sealed tube	Fine-focus sealed tube
Unit Cell dimensions		
a (Å)	11.2343 (6)	27.958 912)
b (Å)	11.2575 (7)	12.072 (5)
c (Å)	11.8995(8)	9.833 (4)
α (°)	90.00	90.00
β (°)	94.476 (6)	93.117 (11)
γ (°)	90.00	90.00
Volume (Å ³)	1500.34 (16)	3486.75
Z	4	7
D _x	1.228 g/cm ³	1.498 g/cm ³
Data collection		
Absorption correction	Multi-scan	Multi-scan
Measured reflections	2731	12163
Independent reflections	3427	3113

Table 2. Some energetic properties of the synthesized thiosemicarbazone compounds.

Compound	Total energy (kcal/mol)	Binding energy (kcal/mol)	Electronic energy (kcal/mol)	Dipole Moment (Debyes)	HOMO	LUMO
TSC1	-58321.2	-3178.9	-368233.1	6.55	-8.501	-1.091
TSC2	-65214.1	-3735.7	-441527.7	6.82	-8.561	-0.915
TSC3	-79668.2	-4295.6	-566955.2	6.94	-8.556	-0.889

Table 3. The calculated quantum chemical parameters of the synthesized thiosemicarbazone compounds

Compound	ΔE	I	A	χ	η	S	ΔN_{max}	ω	ω^-	ω^+
TSC1	7.410	8.501	1.091	4.796	3.705	0.270	-2.294	3.104	5.965	1.169
TSC2	7.646	8.561	0.915	4.738	3.823	0.262	-2.239	2.936	5.783	1.045
TSC3	7.667	8.556	0.889	4.723	3.834	0.261	-2.232	2.909	5.749	1.027

Table 4. Antibacterial and antifungal activities of the synthesized thiosemicarbazone compounds

Concentration (µg/ml)	Gram positive				Gram negative		Fungi	
	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Streptococcus faecalis</i>	<i>E. coli</i>	<i>Neisseria gonorrhoeae</i>	<i>Pseudomonas aereuginosa</i>	<i>Aspergillus flavus</i>	<i>Candida albicans</i>
TSC1	14	13	17	17	12	21	0	30
TSC3	0	0	13	11	0	0	0	0
TSC4	0	0	0	0	0	0	0	0
<i>Ampicillin</i>	26	21	27	25	28	26	-	-
<i>Amphotericin</i>	-	-	-	-	-	-	16	19

Ampicillin: Standard antibacterial agent, *Amphotericin*: Standard antifungal agent

Table 5. Antitumor activity of the synthesized thiosemicarbazone compounds.

Concentration ($\mu\text{g/ml}$)	TSC1	TSC2	TSC3
<i>Liver cancer cell line (HepG2)</i>			
5	100	100	100
25	35.3	67	22.5
50	27.4	48.7	19
IC ₅₀	29.4	46	25
<i>Breast cancer cell line (MCF-7)</i>			
5	83.8	95	77.6
25	79.5	86.5	72
50	70.7	83	65.4
IC ₅₀	122	172.9	107

Table 6. Protonation constants for TSC1 ligand at different temperatures.

Reaction	log K ($\pm\sigma$) ^a		
	15 °C	25 °C	35 °C
L + H = HL	8.02(0.09)	7.81(0.05)	7.64(0.03)
HL + H = H ₂ L	3.31(0.08)	3.22(0.07)	3.14(0.09)
H ₂ L + H = H ₃ L	3.17(0.04)	3.08(0.06)	3.01(0.05)

^a(σ) is the standard deviation;

Table 7. Stepwise stability for the complexes of TSC1 with Cd(II) metal ion in 50% DMSO-H₂O (V/V) solution.

Temp.(°C)	logK ₁ ($\pm\sigma$) ^a	logK ₂ ($\pm\sigma$)	logK ₁ - logK ₂
	CdL	CdL ₂	Cd(II) complex
15 °C	9.82(0.07)	2.80(0.03)	7.02
25 °C	9.74(0.03)	2.75(0.06)	6.99
35 °C	9.57(0.06)	2.71(0.09)	6.86

^a(σ) is the standard deviation;

Definitions of stability constants: $K_1 = [\text{CdL}] / [\text{Cd}][\text{L}]$; $K_2 = [\text{CdL}_2] / [\text{CdL}][\text{L}]$; (L = TSC1 thiosemicarbazone ligand); (Charges are omitted for simplicity).

Table 8. Thermodynamic parameters for the protonation of ligand (TSC1) in 50% DMSO-H₂O (V/V) solution.

Parameter ^a	Reaction								
	L + H = HL ^a			L + 2H = H ₂ L			L + 3H = H ₃ L		
	15 °C	25 °C	35 °C	15 °C	25 °C	35 °C	15 °C	25 °C	35 °C
-ΔG	44.25	44.59	45.08	17.49	17.58	17.82	18.26	18.38	18.47
-ΔH	32.33			15.29			12.77		
ΔS	41.16			10.30			16.27		

ΔG: Gibbs energy/kJ.mol⁻¹; ΔH: Enthalpy/kJ.mol⁻¹; ΔS: Entropy/J.mol⁻¹.K⁻¹

Table 9. Thermodynamic parameters for Cd(II)-TSC1 complexes in 50% DMSO-H₂O (V/V) solution.

Parameter ^a	Reaction					
	Cd + L = CdL			Cd + 2L = CdL ₂		
	15 °C	25 °C	35 °C	15 °C	25 °C	35 °C
-ΔG	54.18	55.60	56.45	15.45	15.70	15.99
-ΔH	21.15			7.66		
ΔS	114.88			26.99		

^aΔG: Gibbs energy/kJ.mol⁻¹; ΔH: Enthalpy/kJ.mol⁻¹; ΔS: Entropy/J.mol⁻¹.K⁻¹.

TSC2 Compound CIF structure and checkcif report

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found.

Please wait while processing

[report](#)

[Structure factor report](#)

[CIF dictionary](#)

[Interpreting this](#)

Datablock: ahmed1_a

Bond precision:	C-C = 0.0032 A	Wavelength=0.71075
Cell:	a=11.2343 (6) b=11.2575 (7) c=11.8995 (8)	
	alpha=90 beta=94.476 (7) gamma=90	
Temperature:	293 K	
	Calculated	Reported
Volume	1500.34 (16)	1500.34 (16)
Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C13 H19 N5 S	?
Sum formula	C13 H19 N5 S	C13 H19 N5 S
Mr	277.39	277.39
Dx, g cm-3	1.228	1.228
Z	4	4
Mu (mm-1)	0.211	0.211
F000	592.0	592.0
F000'	592.64	
h, k, lmax	14, 14, 15	14, 14, 15
Nref	3435	3427
Tmin, Tmax	0.951, 0.981	0.615, 1.000
Tmin'	0.923	
Correction method=	# Reported T Limits: Tmin=0.615	
Tmax=1.000 AbsCorr =	MULTI-SCAN	
Data completeness=	0.998	Theta(max)= 27.443
R(reflections)=	0.0558 (2731)	wR2(reflections)= 0.1761 (3427)
S =	1.303	Npar= 184

The following ALERTS were generated. Each ALERT has the format

test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

● Alert level C

[ABSTY02 ALERT 1 C](#) An _exptl_absorpt_correction_type has been given without a literature citation. This should be contained in the _exptl_absorpt_process_details field.

Absorption correction given as multi-scan

[PLAT085 ALERT 2 C](#) SHELXL Default Weighting Scheme is not Optimized

Please Check

[PLAT220 ALERT 2 C](#) NonSolvent Resd 1 C Ueq(max)/Ueq(min) Range 3.1 Ratio

[PLAT241 ALERT 2 C](#) High 'MainMol' Ueq as Compared to Neighbors of C12 Check

PLAT242 ALERT 2 C Low 'MainMol' Ueq as Compared to Neighbors of
N5 Check
PLAT250 ALERT 2 C Large U3/U1 Ratio for Average U(i,j) Tensor
2.1 Note
PLAT360 ALERT 2 C Short C(sp3)-C(sp3) Bond C12 - C13 .
1.43 Ang.
PLAT906 ALERT 3 C Large K Value in the Analysis of Variance
3.847 Check

● Alert level G

PLAT002 ALERT 2 G Number of Distance or Angle Restraints on AtSite
6 Note
PLAT172 ALERT 4 G The CIF-Embedded .res File Contains DFIX Records
1 Report
PLAT199 ALERT 1 G Reported _cell_measurement_temperature (K)
293 Check
PLAT200 ALERT 1 G Reported _diffrn_ambient_temperature (K)
293 Check
PLAT860 ALERT 3 G Number of Least-Squares Restraints
3 Note
PLAT883 ALERT 1 G No Info/Value for _atom_sites_solution_primary .
Please Do !
PLAT910 ALERT 3 G Missing # of FCF Reflection(s) Below Theta(Min).
1 Note
PLAT912 ALERT 4 G Missing # of FCF Reflections Above STh/L= 0.600
8 Note
PLAT933 ALERT 2 G Number of OMIT Records in Embedded .res File ...
1 Note
PLAT941 ALERT 3 G Average HKL Measurement Multiplicity
4.1 Low
PLAT965 ALERT 2 G The SHELXL WEIGHT Optimisation has not Converged
Please Check
PLAT978 ALERT 2 G Number C-C Bonds with Positive Residual Density.
7 Info

0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
8 **ALERT level C** = Check. Ensure it is not caused by an omission or
oversight
12 **ALERT level G** = General information/check it is not something
unexpected

4 ALERT type 1 CIF construction/syntax error, inconsistent or missing
data
10 ALERT type 2 Indicator that the structure model may be wrong or
deficient
4 ALERT type 3 Indicator that the structure quality may be low
2 ALERT type 4 Improvement, methodology, query or suggestion
0 ALERT type 5 Informative message, check

PLATON version of 10/08/2020; check.def file version of 06/08/2020
Datablock ahmed1_a - ellipsoid plot

TSC3 Compound CIF structure and checkcif report

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found.

Please wait while processing

[report](#)

[Structure factor report](#)

[CIF dictionary](#)

[Interpreting this](#)

Datablock: I

Bond precision:	C-C = 0.0171 Å	Wavelength=0.71073
Cell:	a=27.958 (12) b=12.702 (5) c=9.833 (4)	
	alpha=90 beta=93.117 (11) gamma=90	
Temperature:	293 K	
	Calculated	Reported
Volume	3487 (2)	3487 (2)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C17 H19 N5 S	C2.39 H2.67 N0.70 S0.14
Sum formula	C17 H19 N5 S	C2.39 H2.67 N0.70 S0.14
Mr	325.43	45.68
Dx, g cm ⁻³	1.240	1.240
Z	8	57
Mu (mm ⁻¹)	0.192	0.192
F000	1376.0	1376.0
F000'	1377.36	
h, k, lmax	33, 15, 11	23, 10, 8
Nref	6541	2208
Tmin, Tmax	0.918, 0.946	
Tmin'	0.912	
Correction method=	Not given	
Data completeness=	0.338	Theta (max)= 25.580
R(reflections)=	0.0442 (1390)	wR2(reflections)= 0.1506 (1390)
S =	1.003	Npar= 440

The following ALERTS were generated. Each ALERT has the format

test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

🔴 Alert level A

[PLAT183](#) ALERT 1 A Missing _cell_measurement_reflms_used Value

Please Do !

[PLAT184](#) ALERT 1 A Missing _cell_measurement_theta_min Value

Please Do !

[PLAT185](#) ALERT 1 A Missing _cell_measurement_theta_max Value

Please Do !

[PLAT902](#) ALERT 1 A No (Interpretable) Reflections Found in FCF

Please Check

🟡 Alert level B

PLAT031 ALERT 4 B Refined Extinction Parameter Within Range
 2.000 Sigma
 PLAT340 ALERT 3 B Low Bond Precision on C-C Bonds
 0.01713 Ang.

● **Alert level C**

PLAT230 ALERT 2 C Hirshfeld Test Diff for N10 --N11 .
 5.2 s.u.
 PLAT230 ALERT 2 C Hirshfeld Test Diff for N33 --C25 .
 5.2 s.u.
 PLAT234 ALERT 4 C Large Hirshfeld Difference N10 --C2 .
 0.19 Ang.

And 15 other PLAT234 Alerts

PLAT234 ALERT 4 C Large Hirshfeld Difference N11 --C12 .
 0.16 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C4 --C9 .
 0.19 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C7 --C8 .
 0.20 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C8 --C9 .
 0.22 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C12 --C23 .
 0.16 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference N33 --N34 .
 0.17 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference N34 --C35 .
 0.18 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C27 --C28 .
 0.23 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C27 --C32 .
 0.20 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C28 --C29 .
 0.22 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C29 --C30 .
 0.24 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C30 --C31 .
 0.19 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C31 --C32 .
 0.20 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C35 --C37 .
0.18 Ang.

PLAT234 ALERT 4 C Large Hirshfeld Difference C43 --C44 .
0.18 Ang.

PLAT242 ALERT 2 C Low 'MainMol' Ueq as Compared to Neighbors of
C4 Check

PLAT331 ALERT 2 C Small Aver Phenyl C-C Dist C4 --C9 .
1.37 Ang.

PLAT331 ALERT 2 C Small Aver Phenyl C-C Dist C27 --C32 .
1.37 Ang.

PLAT420 ALERT 2 C D-H Without Acceptor N33 --H331 .
Please Check

● Alert level G

CELLZ01 ALERT 1 G Difference between formula and atom_site contents
detected.

CELLZ01 ALERT 1 G WARNING: H atoms missing from atom site list. Is this
intentional?

From the CIF: _cell_formula_units_Z 57

From the CIF: _chemical_formula_sum C2.39 H2.67 N0.70 S0.14

TEST: Compare cell contents of formula and atom_site data

atom	Z*formula	cif sites	diff
C	136.23	136.00	0.23
H	152.19	152.00	0.19
N	39.90	40.00	-0.10
S	7.98	8.00	-0.02

PLAT002 ALERT 2 G Number of Distance or Angle Restraints on AtSite
22 Note

PLAT042 ALERT 1 G Calc. and Reported MoietyFormula Strings Differ
Please Check

PLAT045 ALERT 1 G Calculated and Reported Z Differ by a Factor ...
0.14 Check

PLAT199 ALERT 1 G Reported _cell_measurement_temperature (K)
293 Check

PLAT200 ALERT 1 G Reported _diffrn_ambient_temperature (K)
293 Check

PLAT380 ALERT 4 G Incorrectly? Oriented X(sp2)-Methyl Moiety
C22 Check

PLAT380 ALERT 4 G Incorrectly? Oriented X(sp2)-Methyl Moiety
C44 Check

PLAT769 ALERT 4 G CIF Embedded explicitly supplied scattering data
Please Note

PLAT790 ALERT 4 G Centre of Gravity not Within Unit Cell: Resd. #
2 Note

C17 H19 N5 S

PLAT808 ALERT 5 G No Parseable SHELXL Style Weighting Scheme Found
Please Check

PLAT860 ALERT 3 G Number of Least-Squares Restraints
24 Note

PLAT882 ALERT 1 G No Datum for _diffrn_reflns_av_unetI/netI
Please Do !

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2 ALERT type 3 Indicator that the structure quality may be low

21 ALERT type 4 Improvement, methodology, query or suggestion

1 ALERT type 5 Informative message, check

PLATON version of 10/08/2020; check.def file version of 06/08/2020

TSC2 Compound CIF File (Structure without hkl data)

_audit_creation_method 'SHELXL-2018/3'
_shelx_SHELXL_version_number '2018/3'
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_chemical_formula_sum
'C13 H19 N5 S'
_chemical_formula_weight 277.39

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_atom_type_symbol
_atom_type_description
_atom_type_scatter_dispersion_real
_atom_type_scatter_dispersion_imag
_atom_type_scatter_source
'C' 'C' 0.0033 0.0016
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'H' 'H' 0.0000 0.0000
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'N' 'N' 0.0061 0.0033
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'S' 'S' 0.1246 0.1234
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

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_space_group_IT_number 14
_space_group_name_H-M_alt 'P 21/c'
_space_group_name_Hall '-P 2ybc'

_shelx_space_group_comment

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The symmetry employed for this shelxl refinement is uniquely defined by the following loop, which should always be used as a source of symmetry information in preference to the above space-group names. They are only intended as comments.

;

loop_
_space_group_symop_operation_xyz
'x, y, z'
'-x, y+1/2, -z+1/2'

'-x, -y, -z'
 'x, -y-1/2, z-1/2'

_cell_length_a 11.2343(6)
 _cell_length_b 11.2575(7)
 _cell_length_c 11.8995(8)
 _cell_angle_alpha 90
 _cell_angle_beta 94.476(7)
 _cell_angle_gamma 90
 _cell_volume 1500.34(16)
 _cell_formula_units_Z 4
 _cell_measurement_temperature 293(2)
 _cell_measurement_reflns_used 11219
 _cell_measurement_theta_min 1.81
 _cell_measurement_theta_max 27.43

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 _exptl_crystal_density_method ?
 _exptl_crystal_density_diffn 1.228
 _exptl_crystal_F_000 592
 _exptl_transmission_factor_min ?
 _exptl_transmission_factor_max ?
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 _exptl_crystal_size_mid 0.200
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 _shelx_estimated_absorpt_T_max 0.981
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 _exptl_absorpt_correction_T_min 0.6152
 _exptl_absorpt_correction_T_max 1.0000
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 _exptl_absorpt_special_details ?
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 _diffn_radiation_wavelength 0.71075
 _diffn_radiation_type MoK α
 _diffn_source 'Rotating anode X-ray tube'
 _diffn_measurement_device_type 'Rigaku VariMax RAPIDII'
 _diffn_measurement_method 'profile data from \w-scans'
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 _diffn_reflns_av_unetI/netI 0.0291
 _diffn_reflns_av_R_equivalents 0.0318
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 _diffn_reflns_limit_k_max 13
 _diffn_reflns_limit_l_min -15


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_diffn_reflms_point_group_measured_fraction_full 0.999
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_reflms_special_details
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Reflections were merged by SHELXL according to the crystal class for the calculation of statistics and refinement.

_reflms_Friedel_fraction is defined as the number of unique Friedel pairs measured divided by the number that would be possible theoretically, ignoring centric projections and systematic absences.

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;
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_computing_cell_refinement      'Rigaku RAPID AUTO'
_computing_data_reduction       'Rigaku RAPID AUTO'
_computing_structure_solution    'SHELXT 2018/2 (Sheldrick, 2018)'
_computing_structure_refinement 'SHELXL-2018/3 (Sheldrick, 2018)'
_computing_molecular_graphics    'SHELXLE rev 952'
_computing_publication_material 'CIFTAB-2014/2 (Sheldrick, 2014)'
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_refine_ls_matrix_type          full
_refine_ls_weighting_scheme      calc
_refine_ls_weighting_details
'w=1/[\sigma^2(Fo^2)+(0.1000P)^2] where P=(Fo^2+2Fc^2)/3'
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_atom_sites_solution_hydrogens   mixed
_refine_ls_hydrogen_treatment    mixed
_refine_ls_extinction_method      none
_refine_ls_extinction_coef        .
_refine_ls_number_reflms         3427
_refine_ls_number_parameters     184

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_refine_ls_wR_factor_gt       0.1679
_refine_ls_goodness_of_fit_ref  1.303
_refine_ls_restrained_S_all    1.302
_refine_ls_shift/su_max        0.001
_refine_ls_shift/su_mean       0.000

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loop_

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_atom_site_type_symbol
_atom_site_fract_x
_atom_site_fract_y
_atom_site_fract_z
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_atom_site_adp_type
_atom_site_occupancy
_atom_site_site_symmetry_order
_atom_site_calc_flag
_atom_site_refinement_flags_posn
_atom_site_refinement_flags_adp
_atom_site_refinement_flags_occupancy
_atom_site_disorder_assembly
_atom_site_disorder_group
S1 S 0.32591(4) 0.56067(4) 1.03601(4) 0.0481(2) Uani 1 1 d . . . . .
N1 N 0.68511(15) 0.75290(15) 0.46644(13) 0.0471(4) Uani 1 1 d D . . . .
H14 H 0.6795(19) 0.8271(9) 0.4803(17) 0.057 Uiso 1 1 d D U . . .
N2 N 0.63686(13) 0.67170(14) 0.53219(12) 0.0401(4) Uani 1 1 d . . . . .
N3 N 0.46564(14) 0.67628(13) 0.76474(12) 0.0413(4) Uani 1 1 d . . . . .
N4 N 0.43152(14) 0.60082(14) 0.84903(13) 0.0426(4) Uani 1 1 d D . . . .
H15 H 0.4828(15) 0.5491(15) 0.8750(16) 0.051 Uiso 1 1 d D U . . .
N5 N 0.29717(17) 0.74135(15) 0.89309(17) 0.0589(5) Uani 1 1 d D . . . .
H16 H 0.301(2) 0.767(2) 0.8257(11) 0.071 Uiso 1 1 d D U . . .
C1 C 0.9615(2) 0.6150(3) 0.10378(19) 0.0756(8) Uani 1 1 d . . . . .
H1A H 0.950609 0.671986 0.043853 0.113 Uiso 1 1 calc R U . . .
H1B H 0.936122 0.538126 0.076446 0.113 Uiso 1 1 calc R U . . .
H1C H 1.044405 0.611848 0.130297 0.113 Uiso 1 1 calc R U . . .
C2 C 0.88835(17) 0.6512(2) 0.19936(16) 0.0536(5) Uani 1 1 d . . . . .
C3 C 0.82973(19) 0.5679(2) 0.25959(18) 0.0568(6) Uani 1 1 d . . . . .
H3 H 0.835196 0.488297 0.239820 0.068 Uiso 1 1 calc R U . . .
C4 C 0.76262(18) 0.59836(19) 0.34890(17) 0.0496(5) Uani 1 1 d . . . . .
H4 H 0.724557 0.539822 0.388030 0.060 Uiso 1 1 calc R U . . .
C5 C 0.75313(16) 0.71686(17) 0.37889(14) 0.0417(4) Uani 1 1 d . . . . .
C6 C 0.81120(18) 0.80226(19) 0.31888(16) 0.0492(5) Uani 1 1 d . . . . .
H6 H 0.805702 0.882002 0.338245 0.059 Uiso 1 1 calc R U . . .
C7 C 0.87712(18) 0.7693(2) 0.23052(17) 0.0536(5) Uani 1 1 d . . . . .
H7 H 0.914878 0.827681 0.190970 0.064 Uiso 1 1 calc R U . . .

```

C8 C 0.57274(16) 0.71098(16) 0.60970(15) 0.0417(4) Uani 1 1 d
 H8 H 0.556359 0.791705 0.614667 0.050 Uiso 1 1 calc R U . . .
 C9 C 0.52647(16) 0.62817(16) 0.68895(14) 0.0384(4) Uani 1 1 d
 C10 C 0.55503(18) 0.49883(17) 0.68002(16) 0.0470(5) Uani 1 1 d
 H10A H 0.565262 0.479277 0.602837 0.071 Uiso 1 1 calc R U . . .
 H10B H 0.490808 0.452641 0.706026 0.071 Uiso 1 1 calc R U . . .
 H10C H 0.627357 0.481594 0.725461 0.071 Uiso 1 1 calc R U . . .
 C11 C 0.35214(16) 0.64045(15) 0.92035(15) 0.0402(4) Uani 1 1 d
 C12 C 0.2111(3) 0.7985(3) 0.9615(3) 0.1174(15) Uani 1 1 d
 H12A H 0.157908 0.738322 0.987452 0.141 Uiso 1 1 calc R U . . .
 H12B H 0.253907 0.833270 1.027433 0.141 Uiso 1 1 calc R U . . .
 C13 C 0.1409(3) 0.8892(3) 0.9035(3) 0.0956(10) Uani 1 1 d
 H13A H 0.191889 0.953572 0.884850 0.143 Uiso 1 1 calc R U . . .
 H13B H 0.082090 0.917877 0.951162 0.143 Uiso 1 1 calc R U . . .
 H13C H 0.101857 0.856907 0.835644 0.143 Uiso 1 1 calc R U . . .

loop_

_atom_site_aniso_label
 _atom_site_aniso_U_11
 _atom_site_aniso_U_22
 _atom_site_aniso_U_33
 _atom_site_aniso_U_23
 _atom_site_aniso_U_13
 _atom_site_aniso_U_12
 S1 0.0537(3) 0.0439(3) 0.0500(3) 0.0048(2) 0.0254(2) 0.0002(2)
 N1 0.0628(10) 0.0416(9) 0.0399(9) 0.0029(7) 0.0229(8) 0.0080(7)
 N2 0.0446(8) 0.0447(8) 0.0321(8) 0.0021(6) 0.0096(6) 0.0033(6)
 N3 0.0451(8) 0.0403(8) 0.0405(8) 0.0044(6) 0.0152(7) 0.0044(6)
 N4 0.0483(9) 0.0382(8) 0.0439(9) 0.0049(7) 0.0195(7) 0.0057(6)
 N5 0.0670(11) 0.0428(9) 0.0724(13) 0.0150(8) 0.0401(10) 0.0131(8)
 C1 0.0592(14) 0.119(2) 0.0519(14) -0.0193(14) 0.0224(11) 0.0065(14)
 C2 0.0397(10) 0.0844(16) 0.0376(10) -0.0083(10) 0.0089(8) 0.0075(10)
 C3 0.0526(12) 0.0671(14) 0.0518(13) -0.0196(10) 0.0114(10) 0.0053(10)
 C4 0.0510(11) 0.0544(11) 0.0451(11) -0.0046(9) 0.0143(9) 0.0033(8)
 C5 0.0426(10) 0.0530(11) 0.0302(9) 0.0006(7) 0.0072(7) 0.0081(8)
 C6 0.0539(11) 0.0528(11) 0.0425(11) 0.0055(8) 0.0141(9) 0.0068(9)
 C7 0.0501(11) 0.0711(14) 0.0412(11) 0.0078(10) 0.0146(9) 0.0062(10)
 C8 0.0491(10) 0.0393(9) 0.0381(9) 0.0021(7) 0.0113(8) 0.0091(7)
 C9 0.0393(9) 0.0411(10) 0.0357(9) 0.0001(7) 0.0088(7) 0.0034(7)
 C10 0.0598(12) 0.0398(10) 0.0435(10) -0.0023(8) 0.0171(9) 0.0033(8)
 C11 0.0399(9) 0.0339(9) 0.0487(10) -0.0021(7) 0.0164(8) -0.0025(7)
 C12 0.146(3) 0.0753(19) 0.147(3) 0.0477(19) 0.109(2) 0.058(2)
 C13 0.0587(15) 0.113(2) 0.115(3) -0.026(2) 0.0057(16) 0.0306(16)

_geom_special_details

;

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.

;

```

loop_
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  _geom_bond_atom_site_label_2
  _geom_bond_distance
  _geom_bond_site_symmetry_2
  _geom_bond_publ_flag
S1 C11 1.6885(18) . ?
N1 N2 1.345(2) . ?
N1 C5 1.399(2) . ?
N1 H14 0.854(9) . ?
N2 C8 1.292(2) . ?
N3 C9 1.292(2) . ?
N3 N4 1.391(2) . ?
N4 C11 1.354(2) . ?
N4 H15 0.859(9) . ?
N5 C11 1.321(2) . ?
N5 C12 1.460(3) . ?
N5 H16 0.856(9) . ?
C1 C2 1.511(3) . ?
C1 H1A 0.9600 . ?
C1 H1B 0.9600 . ?
C1 H1C 0.9600 . ?
C2 C3 1.378(3) . ?
C2 C7 1.388(3) . ?
C3 C4 1.393(3) . ?
C3 H3 0.9300 . ?
C4 C5 1.387(3) . ?
C4 H4 0.9300 . ?
C5 C6 1.390(3) . ?
C6 C7 1.383(3) . ?
C6 H6 0.9300 . ?
C7 H7 0.9300 . ?
C8 C9 1.451(2) . ?
C8 H8 0.9300 . ?
C9 C10 1.497(3) . ?
C10 H10A 0.9600 . ?
C10 H10B 0.9600 . ?
C10 H10C 0.9600 . ?
C12 C13 1.434(4) . ?
C12 H12A 0.9700 . ?
C12 H12B 0.9700 . ?
C13 H13A 0.9600 . ?
C13 H13B 0.9600 . ?
C13 H13C 0.9600 . ?

```

loop_
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 _geom_angle_atom_site_label_2
 _geom_angle_atom_site_label_3
 _geom_angle
 _geom_angle_site_symmetry_1
 _geom_angle_site_symmetry_3
 _geom_angle_publ_flag
 N2 N1 C5 120.30(16) .. ?
 N2 N1 H14 120.9(14) .. ?
 C5 N1 H14 118.7(14) .. ?
 C8 N2 N1 117.09(15) .. ?
 C9 N3 N4 115.96(15) .. ?
 C11 N4 N3 118.87(15) .. ?
 C11 N4 H15 117.0(14) .. ?
 N3 N4 H15 117.3(14) .. ?
 C11 N5 C12 123.98(18) .. ?
 C11 N5 H16 117.8(17) .. ?
 C12 N5 H16 116.9(17) .. ?
 C2 C1 H1A 109.5 .. ?
 C2 C1 H1B 109.5 .. ?
 H1A C1 H1B 109.5 .. ?
 C2 C1 H1C 109.5 .. ?
 H1A C1 H1C 109.5 .. ?
 H1B C1 H1C 109.5 .. ?
 C3 C2 C7 117.08(17) .. ?
 C3 C2 C1 121.2(2) .. ?
 C7 C2 C1 121.7(2) .. ?
 C2 C3 C4 122.6(2) .. ?
 C2 C3 H3 118.7 .. ?
 C4 C3 H3 118.7 .. ?
 C5 C4 C3 119.3(2) .. ?
 C5 C4 H4 120.3 .. ?
 C3 C4 H4 120.3 .. ?
 C4 C5 C6 118.97(17) .. ?
 C4 C5 N1 121.85(18) .. ?
 C6 C5 N1 119.16(18) .. ?
 C7 C6 C5 120.35(19) .. ?
 C7 C6 H6 119.8 .. ?
 C5 C6 H6 119.8 .. ?
 C6 C7 C2 121.68(19) .. ?
 C6 C7 H7 119.2 .. ?
 C2 C7 H7 119.2 .. ?
 N2 C8 C9 119.48(16) .. ?
 N2 C8 H8 120.3 .. ?
 C9 C8 H8 120.3 .. ?
 N3 C9 C8 114.84(16) .. ?
 N3 C9 C10 125.83(16) .. ?

C8 C9 C10 119.29(15) .. ?
 C9 C10 H10A 109.5 .. ?
 C9 C10 H10B 109.5 .. ?
 H10A C10 H10B 109.5 .. ?
 C9 C10 H10C 109.5 .. ?
 H10A C10 H10C 109.5 .. ?
 H10B C10 H10C 109.5 .. ?
 N5 C11 N4 116.59(16) .. ?
 N5 C11 S1 123.33(13) .. ?
 N4 C11 S1 120.08(13) .. ?
 C13 C12 N5 114.1(2) .. ?
 C13 C12 H12A 108.7 .. ?
 N5 C12 H12A 108.7 .. ?
 C13 C12 H12B 108.7 .. ?
 N5 C12 H12B 108.7 .. ?
 H12A C12 H12B 107.6 .. ?
 C12 C13 H13A 109.5 .. ?
 C12 C13 H13B 109.5 .. ?
 H13A C13 H13B 109.5 .. ?
 C12 C13 H13C 109.5 .. ?
 H13A C13 H13C 109.5 .. ?
 H13B C13 H13C 109.5 .. ?

_refine_diff_density_max 0.427
 _refine_diff_density_min -0.366
 _refine_diff_density_rms 0.061

_shelx_res_file

;

TITL ahmed1_a.res in P2(1)/c

ahmed1_a.res

created by SHELXL-2018/3 at 18:41:38 on 04-Apr-2019

REM Old TITL

REM SHELXT solution in P2(1)/c: R1 0.188, Rweak 0.054, Alpha 0.024

REM <I/s> 0.739 for 165 systematic absences, Orientation as input

REM Formula found by SHELXT: C14 N4 S

CELL 0.71075 11.2343 11.2575 11.8995 90.000 94.476 90.000

ZERR 4.000 0.0006 0.0007 0.0008 0.000 0.007 0.000

LATT 1

SYMM -X, 1/2+Y, 1/2-Z

SFAC C H N S

UNIT 52 76 20 4

L.S. 20

SIZE 0.38 0.20 0.09

BOND \$h

LIST 6

FMAP 2

PLAN 20

OMIT 1 2 2

ACTA
 DFIX 0.86 0.01 N1 H14 N4 H15 N5 H16
 WGHT 0.100000
 FVAR 0.35726
 S1 4 0.325908 0.560673 1.036013 11.00000 0.05375 0.04387 =
 0.05004 0.00477 0.02544 0.00024
 N1 3 0.685111 0.752904 0.466437 11.00000 0.06285 0.04165 =
 0.03987 0.00286 0.02293 0.00804
 H14 2 0.679529 0.827073 0.480316 11.00000 -1.20000
 N2 3 0.636861 0.671699 0.532192 11.00000 0.04461 0.04467 =
 0.03209 0.00205 0.00965 0.00332
 N3 3 0.465640 0.676284 0.764739 11.00000 0.04507 0.04025 =
 0.04046 0.00442 0.01522 0.00436
 N4 3 0.431521 0.600822 0.849029 11.00000 0.04827 0.03818 =
 0.04392 0.00494 0.01952 0.00572
 H15 2 0.482774 0.549149 0.874972 11.00000 -1.20000
 N5 3 0.297166 0.741352 0.893094 11.00000 0.06697 0.04282 =
 0.07240 0.01498 0.04011 0.01308
 H16 2 0.300615 0.767125 0.825724 11.00000 -1.20000
 C1 1 0.961540 0.614991 0.103780 11.00000 0.05922 0.11859 =
 0.05185 -0.01933 0.02237 0.00646
 AFIX 137
 H1A 2 0.950609 0.671986 0.043853 11.00000 -1.50000
 H1B 2 0.936122 0.538126 0.076446 11.00000 -1.50000
 H1C 2 1.044405 0.611848 0.130297 11.00000 -1.50000
 AFIX 0
 C2 1 0.888346 0.651201 0.199363 11.00000 0.03966 0.08440 =
 0.03763 -0.00828 0.00888 0.00753
 C3 1 0.829727 0.567924 0.259588 11.00000 0.05260 0.06705 =
 0.05177 -0.01959 0.01138 0.00525
 AFIX 43
 H3 2 0.835196 0.488297 0.239820 11.00000 -1.20000
 AFIX 0
 C4 1 0.762616 0.598356 0.348901 11.00000 0.05104 0.05436 =
 0.04512 -0.00459 0.01433 0.00330
 AFIX 43
 H4 2 0.724557 0.539822 0.388030 11.00000 -1.20000
 AFIX 0
 C5 1 0.753129 0.716863 0.378888 11.00000 0.04264 0.05297 =
 0.03021 0.00056 0.00722 0.00810
 C6 1 0.811200 0.802265 0.318880 11.00000 0.05393 0.05281 =
 0.04252 0.00545 0.01409 0.00680
 AFIX 43
 H6 2 0.805702 0.882002 0.338245 11.00000 -1.20000
 AFIX 0
 C7 1 0.877117 0.769274 0.230518 11.00000 0.05014 0.07112 =
 0.04123 0.00785 0.01463 0.00620
 AFIX 43
 H7 2 0.914878 0.827681 0.190970 11.00000 -1.20000

```

AFIX 0
C8 1 0.572736 0.710979 0.609705 11.00000 0.04906 0.03928 =
    0.03814 0.00207 0.01130 0.00908
AFIX 43
H8 2 0.556359 0.791705 0.614667 11.00000 -1.20000
AFIX 0
C9 1 0.526472 0.628173 0.688951 11.00000 0.03934 0.04109 =
    0.03574 0.00008 0.00878 0.00343
C10 1 0.555035 0.498827 0.680018 11.00000 0.05982 0.03977 =
    0.04353 -0.00228 0.01712 0.00328
AFIX 137
H10A 2 0.565262 0.479277 0.602837 11.00000 -1.50000
H10B 2 0.490808 0.452641 0.706026 11.00000 -1.50000
H10C 2 0.627357 0.481594 0.725461 11.00000 -1.50000
AFIX 0
C11 1 0.352143 0.640453 0.920351 11.00000 0.03991 0.03389 =
    0.04875 -0.00209 0.01640 -0.00249
C12 1 0.211143 0.798501 0.961491 11.00000 0.14584 0.07529 =
    0.14661 0.04767 0.10944 0.05818
AFIX 23
H12A 2 0.157908 0.738322 0.987452 11.00000 -1.20000
H12B 2 0.253907 0.833270 1.027433 11.00000 -1.20000
AFIX 0
C13 1 0.140945 0.889209 0.903495 11.00000 0.05874 0.11290 =
    0.11513 -0.02626 0.00572 0.03063
AFIX 137
H13A 2 0.191889 0.953572 0.884850 11.00000 -1.50000
H13B 2 0.082090 0.917877 0.951162 11.00000 -1.50000
H13C 2 0.101857 0.856907 0.835644 11.00000 -1.50000
REM #####
REM #####
AFIX 0
HKLF 4

```

```

REM ahmed1_a.res in P2(1)/c
REM wR2 = 0.1761, GooF = S = 1.303, Restrained GooF = 1.302 for all data
REM R1 = 0.0558 for 2731 Fo > 4sig(Fo) and 0.0688 for all 3427 data
REM 184 parameters refined using 3 restraints

```

END

```

WGHT 0.0921 0.4882

```

```

REM Highest difference peak 0.427, deepest hole -0.366, 1-sigma level 0.061
Q1 1 0.3173 0.5831 0.9659 11.00000 0.05 0.43
Q2 1 0.1603 0.7608 0.8904 11.00000 0.05 0.42
Q3 1 0.1775 0.8614 0.9865 11.00000 0.05 0.35
Q4 1 0.4511 0.6515 0.7971 11.00000 0.05 0.31
Q5 1 0.7135 0.7364 0.4214 11.00000 0.05 0.31

```


Q6	1	0.2601	0.7192	0.8333	11.00000	0.05	0.30
Q7	1	0.7598	0.7543	0.3288	11.00000	0.05	0.29
Q8	1	0.6132	0.6902	0.5843	11.00000	0.05	0.29
Q9	1	0.5410	0.6627	0.6437	11.00000	0.05	0.29
Q10	1	0.3854	0.6092	0.8787	11.00000	0.05	0.29
Q11	1	0.2039	0.7775	1.0295	11.00000	0.05	0.28
Q12	1	0.6529	0.7071	0.4955	11.00000	0.05	0.28
Q13	1	0.8224	0.5872	0.3142	11.00000	0.05	0.27
Q14	1	0.3553	0.5707	1.1036	11.00000	0.05	0.27
Q15	1	0.4866	0.6431	0.7229	11.00000	0.05	0.27
Q16	1	0.7463	0.6697	0.3567	11.00000	0.05	0.26
Q17	1	0.3280	0.5649	1.0656	11.00000	0.05	0.25
Q18	1	0.2874	0.5784	1.0821	11.00000	0.05	0.25
Q19	1	0.3413	0.7874	0.8632	11.00000	0.05	0.25
Q20	1	0.5320	0.5693	0.6844	11.00000	0.05	0.23

;

TSC3 Compound CIF File (Structure without hkl data)

```
#####  
#  
# This file contains crystal structure data downloaded from the  
# Cambridge Structural Database (CSD) hosted by the Cambridge  
# Crystallographic Data Centre (CCDC).  
#  
# Full information about CCDC data access policies and citation  
# guidelines are available at http://www.ccdc.cam.ac.uk/access/V1  
#  
# Audit and citation data items may have been added by the CCDC.  
# Please retain this information to preserve the provenance of  
# this file and to allow appropriate attribution of the data.  
#  
#####  
  
_database_code_depnum_ccdc_archive 'CCDC 2033322'  
loop_  
The crystal was  
placed in the cold stream of an Oxford  
Cryosystems open-flow nitrogen cryostat (Cosier &  
Glazer, 1986) with a nominal stability of 0.1K.  
Cosier, J. & Glazer, A.M., 1986. J. Appl. Cryst. 105-107.  
_refine_special_details  
#-----  
# _oxford_ data items, April 2010:  
# There is some uncertainty about the correct way of forming local data  
# names, e.g.  
# _atom_site_special_shape_oxford  
# or  
# _oxford_atom_site_special_shape  
# see:  
# http://www.iucr.org/resources/cif/spec/version1.1/semantics#namespace
```

```
# A reserved prefix, e.g. foo, must be used in the following way
# " If the data file contains items defined in a DDL1 dictionary, the
# local data names assigned under the reserved prefix must contain it as
# their first component, e.g. _foo_atom_site_my_item. "
```

```
# However, this seems to say the opposite:
```

```
# http://www.iucr.org/\_\_data/iucr/cif/standard/cifstd8.html
```

```
# According to advice from the IUCr, CRYSTALS is correct
```

```
#-----
```

```
# End of 'script/refcif.dat'
```

```
#end of refcif
```

```
_cell_length_a      27.958(12)
```

```
_cell_length_b      12.702(5)
```

```
_cell_length_c      9.833(4)
```

```
_cell_angle_alpha    90
```

```
_cell_angle_beta     93.117(11)
```

```
_cell_angle_gamma    90
```

```
_cell_volume         3487(2)
```

```
_symmetry_cell_setting      monoclinic
```

```
_symmetry_space_group_name_H-M  'P 1 21/c 1 '
```

```
_symmetry_space_group_name_Hall  '-P 2ybc '
```

```
loop_
```

```
_symmetry_equiv_pos_as_xyz
```

```
x,y,z
```

```
-x,-y,-z
```

```
-x,y+1/2,-z+1/2
```

```
x,-y+1/2,z+1/2
```

```
loop_
```

```
_atom_type_symbol
```

```

_atom_type_scatter_dispersion_real
_atom_type_scatter_dispersion_imag
_atom_type_scatter_Cromer_Mann_a1
_atom_type_scatter_Cromer_Mann_b1
_atom_type_scatter_Cromer_Mann_a2
_atom_type_scatter_Cromer_Mann_b2
_atom_type_scatter_Cromer_Mann_a3
_atom_type_scatter_Cromer_Mann_b3
_atom_type_scatter_Cromer_Mann_a4
_atom_type_scatter_Cromer_Mann_b4
_atom_type_scatter_Cromer_Mann_c
_atom_type_scatter_source
C 0.0033 0.0016 2.3100 20.8439 1.0200 10.2075 1.5886 0.5687 0.8650 51.6512
0.2156 'International Tables Vol C 4.2.6.8 and 6.1.1.4'
H 0.0000 0.0000 0.4930 10.5109 0.3229 26.1257 0.1402 3.1424 0.0408 57.7998
0.0030 'International Tables Vol C 4.2.6.8 and 6.1.1.4'
N 0.0061 0.0033 12.2126 0.0057 3.1322 9.8933 2.0125 28.9975 1.1663 0.5826
-11.5290 'International Tables Vol C 4.2.6.8 and 6.1.1.4'
S 0.1246 0.1234 6.9053 1.4679 5.2034 22.2151 1.4379 0.2536 1.5863 56.1720
0.8669 'International Tables Vol C 4.2.6.8 and 6.1.1.4'
_cell_formula_units_Z      57

```

Given Formula = C1 H1 N1 S1

Dc = 1.60 Fooo = 1710.00 Mu = 9.22 M = 59.09

Found Formula = C2.39 H2.67 N0.70 S0.14

Dc = 1.24 FOOO = 1376.00 Mu = 1.92 M = 45.68

```

_chemical_formula_sum      'C2.39 H2.67 N0.70 S0.14'
_chemical_formula_moiety   'C2.39 H2.67 N0.70 S0.14'
_chemical_compound_source   'local laboratory'
_chemical_formula_weight    45.68

```

```

_cell_measurement_reflns_used  0
_cell_measurement_theta_min    0
_cell_measurement_theta_max    0
_cell_measurement_temperature  293
_exptl_crystal_description     cube
_exptl_crystal_colour          colourless
_exptl_crystal_size_min        0.290
_exptl_crystal_size_mid        0.370
_exptl_crystal_size_max        0.480
_exptl_crystal_density_diffn   1.240
_exptl_crystal_density_meas    ?
_exptl_crystal_density_method  'not measured'
# Non-dispersive F(000):
_exptl_crystal_F_000           1376
_exptl_absorpt_coefficient_mu   0.192

# Sheldrick geometric approximat 0.93 0.95
_exptl_absorpt_correction_type  none
_diffn_measurement_device_type  KappaCCD
_diffn_measurement_device       Serial
_diffn_radiation_monochromator  graphite
_diffn_radiation_type           'Mo K\alpha'
_diffn_radiation_wavelength     0.71073
_diffn_measurement_method       \w

# If a reference occurs more than once, delete the author
# and date from subsequent references.
_computing_data_collection      'USER DEFINED DATA COLLECTION'
_computing_cell_refinement      'USER DEFINED CELL REFINEMENT'
_computing_data_reduction       'DENZO/SCALEPACK (Otwinowski & Minor, 1997)'
_computing_structure_solution   'SIR92 (Altomare et al., 1994)'
_computing_structure_refinement 'CRYSTALS (Betteridge et al., 2003)'
_computing_publication_material 'CRYSTALS (Betteridge et al., 2003)'

```

_computing_molecular_graphics 'CAMERON (Watkin et al., 1996)'

_diffn_standards_interval_time .

_diffn_standards_interval_count .

_diffn_standards_number 0

_diffn_standards_decay_% ?

_diffn_ambient_temperature 293

_diffn_reflns_number 14423

_reflns_number_total 2208

_diffn_reflns_av_R_equivalents 0.070

Number of reflections without Friedels Law is 0

Number of reflections with Friedels Law is 2208

Theoretical number of reflections is about 4483

_diffn_reflns_theta_min 0.729

_diffn_reflns_theta_max 25.580

_diffn_measured_fraction_theta_max 0.983

_diffn_reflns_theta_full 25.052

_diffn_measured_fraction_theta_full 0.995

_diffn_reflns_limit_h_min -23

_diffn_reflns_limit_h_max 23

_diffn_reflns_limit_k_min -10

_diffn_reflns_limit_k_max 10

_diffn_reflns_limit_l_min -8

_diffn_reflns_limit_l_max 8

_reflns_limit_h_min -23

_reflns_limit_h_max 23

_reflns_limit_k_min 0

```

_reflns_limit_k_max      10
_reflns_limit_l_min      0
_reflns_limit_l_max      8

_atom_sites_solution_primary  direct #heavy,direct,difmap,geom,iterative
#_atom_sites_solution_secondary difmap
_atom_sites_solution_hydrogens difmap

_refine_diff_density_min  -0.14
_refine_diff_density_max  0.14

# The current dictionary definitions do not cover the
# situation where the reflections used for refinement were
# selected by a user-defined sigma threshold

# The values actually used during refinement

_refine_ls_number_reflns    1390
_refine_ls_number_restraints  24
_refine_ls_number_parameters  440

_refine_ls_wR_factor_ref     0.0980
_refine_ls_goodness_of_fit_ref 1.0035
_refine_ls_shift/su_max      0.0018275
_refine_ls_shift/su_mean     0.0000630

# The values computed with all filters except I/sigma

```

```
_refine_ls_R_factor_all      0.0935
_refine_ls_wR_factor_all     0.1506
```

The values computed with a 2 sigma cutoff - a la SHELX

```
_reflns_threshold_expression  I>2.0\sigma(I)
_reflns_number_gt            1390
_refine_ls_R_factor_gt       0.0442
_refine_ls_wR_factor_gt      0.0980
```

choose from: rm (reference molecule of known chirality),
 # ad (anomalous dispersion - Flack), rmad (rm and ad),
 # syn (from synthesis), unk (unknown) or . (not applicable).
 _chemical_absolute_configuration .

```
_refine_ls_structure_factor_coef Fsqd
_refine_ls_matrix_type      full
_refine_ls_hydrogen_treatment mixed #undef, noref, refall,
# refxyz, refU, constr or mixed
_refine_ls_weighting_scheme  calc
_refine_ls_weighting_details
```

```
;
```

Method, part 1, Chebychev polynomial, (Watkin, 1994, Prince, 1982)

$[weight] = 1.0/[A_0 \cdot T_0(x) + A_1 \cdot T_1(x) \dots + A_{n-1} \cdot T_{n-1}(x)]$

where A_i are the Chebychev coefficients listed below and $x = F_{calc}/F_{max}$

Method = Robust Weighting (Prince, 1982)

$W = [weight] \cdot [1 - (\Delta F / 6 \cdot \sigma F)^2]^2$

A_i are:

4.04 5.84 2.49 0.530

```
;
```

Uequiv = arithmetic mean of U_i i.e. $U_{equiv} = (U_1 + U_2 + U_3)/3$

Replace last . with number of unfound hydrogen atoms attached to an atom.

..._refinement_flags_...

. no refinement constraints S special position constraint on site

G rigid group refinement of site R riding atom

D distance or angle restraint on site T thermal displacement constraints

U Uiso or Uij restraint (rigid bond) P partial occupancy constraint

loop_

_atom_site_label

_atom_site_type_symbol

_atom_site_fract_x

_atom_site_fract_y

_atom_site_fract_z

_atom_site_U_iso_or_equiv

_atom_site_occupancy

_atom_site_adp_type

_atom_site_refinement_flags_posn

_atom_site_refinement_flags_adp

_atom_site_refinement_flags_occupancy

_atom_site_disorder_assembly

_atom_site_disorder_group

_atom_site_attached_hydrogens

S1 S 0.55448(8) 0.58862(18) 1.0980(2) 0.0847 1.0000 Uani

C2 C 0.5318(4) 0.6895(8) 1.0025(9) 0.0610 1.0000 Uani D

N3 N 0.5471(3) 0.7891(7) 1.0109(7) 0.0659 1.0000 Uani D

C4 C 0.5865(4) 0.8352(10) 1.0822(12) 0.0621 1.0000 Uani D

C5 C 0.6102(5) 0.9168(10) 1.0233(10) 0.0948 1.0000 Uani

C6 C 0.6480(5) 0.9680(8) 1.0919(17) 0.1052 1.0000 Uani

C7 C 0.6621(4) 0.9343(13) 1.2206(16) 0.1016 1.0000 Uani

C8 C 0.6388(6) 0.8536(12) 1.2780(11) 0.1038 1.0000 Uani

C9 C 0.6008(4) 0.8050(8) 1.2095(14) 0.0874 1.0000 Uani

N10 N 0.4952(3) 0.6727(6) 0.9084(9) 0.0648 1.0000 Uani D
 N11 N 0.4743(3) 0.7551(6) 0.8382(10) 0.0675 1.0000 Uani D
 C12 C 0.4450(4) 0.7363(9) 0.7353(12) 0.0587 1.0000 Uani
 C13 C 0.4228(4) 0.8254(7) 0.6721(12) 0.0618 1.0000 Uani
 N14 N 0.3912(3) 0.8149(6) 0.5761(10) 0.0650 1.0000 Uani D
 N15 N 0.3717(3) 0.9018(7) 0.5210(9) 0.0752 1.0000 Uani D
 C16 C 0.3391(3) 0.8959(10) 0.4098(11) 0.0607 1.0000 Uani D
 C17 C 0.3227(3) 0.8018(8) 0.3567(11) 0.0660 1.0000 Uani
 C18 C 0.2907(4) 0.8003(8) 0.2438(12) 0.0789 1.0000 Uani
 C19 C 0.2739(3) 0.8909(12) 0.1827(9) 0.0720 1.0000 Uani
 C20 C 0.2908(4) 0.9855(9) 0.2368(12) 0.0730 1.0000 Uani
 C21 C 0.3226(4) 0.9874(8) 0.3494(12) 0.0671 1.0000 Uani
 C22 C 0.2378(3) 0.8923(7) 0.0615(9) 0.1048 1.0000 Uani
 C23 C 0.4345(3) 0.6281(7) 0.6808(8) 0.0799 1.0000 Uani
 S24 S 0.92736(9) 1.09072(19) 0.9319(2) 0.0849 1.0000 Uani
 C25 C 0.9481(4) 1.1701(9) 1.0574(9) 0.0671 1.0000 Uani D
 N26 N 0.9295(3) 1.2657(8) 1.0827(7) 0.0770 1.0000 Uani D
 C27 C 0.8895(5) 1.3151(7) 1.0099(14) 0.0690 1.0000 Uani D
 C28 C 0.8483(6) 1.3280(8) 1.0788(10) 0.0853 1.0000 Uani
 C29 C 0.8090(5) 1.3761(9) 1.0161(17) 0.0967 1.0000 Uani
 C30 C 0.8110(4) 1.4112(8) 0.8852(18) 0.0923 1.0000 Uani
 C31 C 0.8513(6) 1.3992(8) 0.8165(10) 0.0938 1.0000 Uani
 C32 C 0.8911(4) 1.3523(9) 0.8805(13) 0.0858 1.0000 Uani
 N33 N 0.9851(3) 1.1425(6) 1.1463(10) 0.0665 1.0000 Uani D
 N34 N 1.0052(3) 1.2149(6) 1.2341(11) 0.0673 1.0000 Uani D
 C35 C 1.0341(4) 1.1826(9) 1.3327(12) 0.0651 1.0000 Uani
 C36 C 1.0437(3) 1.0684(8) 1.3636(8) 0.0860 1.0000 Uani
 C37 C 1.0572(4) 1.2623(7) 1.4134(14) 0.0651 1.0000 Uani
 N38 N 1.0868(4) 1.2406(7) 1.5111(11) 0.0673 1.0000 Uani D
 N39 N 1.1084(3) 1.3199(6) 1.5786(10) 0.0699 1.0000 Uani D
 C40 C 1.1429(4) 1.2974(10) 1.6816(11) 0.0576 1.0000 Uani D
 C41 C 1.1646(4) 1.3799(8) 1.7513(13) 0.0727 1.0000 Uani
 C42 C 1.1991(4) 1.3590(10) 1.8513(12) 0.0775 1.0000 Uani

C43 C 1.2135(3) 1.2588(12) 1.8843(9) 0.0706 1.0000 Uani
 C44 C 1.2528(3) 1.2381(7) 1.9934(8) 0.0961 1.0000 Uani
 C45 C 1.1911(4) 1.1774(8) 1.8143(11) 0.0752 1.0000 Uani
 C46 C 1.1562(4) 1.1945(9) 1.7125(10) 0.0738 1.0000 Uani
 H51 H 0.6007 0.9372 0.9329 0.1178 1.0000 Uiso R
 H61 H 0.6638 1.0259 1.0531 0.1344 1.0000 Uiso R
 H71 H 0.6882 0.9673 1.2696 0.1145 1.0000 Uiso R
 H81 H 0.6491 0.8300 1.3666 0.1290 1.0000 Uiso R
 H91 H 0.5839 0.7499 1.2509 0.1186 1.0000 Uiso R
 H131 H 0.4327 0.8932 0.7031 0.0884 1.0000 Uiso R
 H171 H 0.3329 0.7380 0.3997 0.0888 1.0000 Uiso R
 H181 H 0.2809 0.7337 0.2085 0.1013 1.0000 Uiso R
 H201 H 0.2792 1.0484 0.1946 0.0999 1.0000 Uiso R
 H211 H 0.3333 1.0537 0.3837 0.0872 1.0000 Uiso R
 H221 H 0.2324 0.9642 0.0389 0.1229 1.0000 Uiso R
 H222 H 0.2498 0.8566 -0.0144 0.1229 1.0000 Uiso R
 H223 H 0.2085 0.8609 0.0848 0.1229 1.0000 Uiso R
 H231 H 0.4117 0.6320 0.6057 0.1145 1.0000 Uiso R
 H232 H 0.4633 0.5979 0.6519 0.1145 1.0000 Uiso R
 H233 H 0.4222 0.5858 0.7504 0.1145 1.0000 Uiso R
 H281 H 0.8480 1.3019 1.1693 0.1092 1.0000 Uiso R
 H291 H 0.7808 1.3834 1.0649 0.1274 1.0000 Uiso R
 H301 H 0.7837 1.4457 0.8444 0.1166 1.0000 Uiso R
 H311 H 0.8517 1.4232 0.7251 0.1169 1.0000 Uiso R
 H321 H 0.9199 1.3442 0.8343 0.1157 1.0000 Uiso R
 H361 H 1.0654 1.0588 1.4402 0.1169 1.0000 Uiso R
 H362 H 1.0566 1.0377 1.2854 0.1169 1.0000 Uiso R
 H363 H 1.0140 1.0356 1.3803 0.1169 1.0000 Uiso R
 H371 H 1.0500 1.3338 1.3923 0.0859 1.0000 Uiso R
 H411 H 1.1562 1.4508 1.7310 0.0903 1.0000 Uiso R
 H421 H 1.2139 1.4155 1.9011 0.0992 1.0000 Uiso R
 H441 H 1.2586 1.1648 2.0038 0.1259 1.0000 Uiso R
 H442 H 1.2812 1.2723 1.9685 0.1259 1.0000 Uiso R

H443 H 1.2430 1.2664 2.0770 0.1259 1.0000 Uiso R
 H451 H 1.1998 1.1069 1.8365 0.1008 1.0000 Uiso R
 H461 H 1.1406 1.1380 1.6650 0.1002 1.0000 Uiso R
 H151 H 0.3889(13) 0.958(2) 0.527(5) 0.090(2) 1.0000 Uiso D
 H101 H 0.4840(18) 0.6104(19) 0.896(6) 0.078(2) 1.0000 Uiso D
 H31 H 0.5319(17) 0.831(2) 0.954(5) 0.079(2) 1.0000 Uiso D
 H391 H 1.103(2) 1.3842(17) 1.554(5) 0.084(2) 1.0000 Uiso D
 H331 H 0.994(2) 1.078(2) 1.150(6) 0.080(2) 1.0000 Uiso D
 H261 H 0.9470(15) 1.305(2) 1.134(6) 0.092(2) 1.0000 Uiso D

loop_

_atom_site_aniso_label

_atom_site_aniso_U_11

_atom_site_aniso_U_22

_atom_site_aniso_U_33

_atom_site_aniso_U_23

_atom_site_aniso_U_13

_atom_site_aniso_U_12

S1 0.0867(17) 0.0643(17) 0.1003(18) 0.0090(16) -0.0198(14) 0.0055(15)

C2 0.063(7) 0.048(8) 0.072(7) 0.006(6) 0.006(6) 0.012(6)

N3 0.072(6) 0.056(7) 0.067(6) 0.002(4) -0.025(5) -0.003(5)

C4 0.067(8) 0.072(9) 0.044(8) -0.014(7) -0.020(7) 0.006(7)

C5 0.120(9) 0.064(7) 0.098(8) 0.014(8) -0.017(9) -0.019(7)

C6 0.113(10) 0.091(8) 0.111(11) -0.002(9) -0.006(8) -0.051(8)

C7 0.072(8) 0.142(13) 0.088(10) -0.031(8) -0.022(8) 0.003(9)

C8 0.110(10) 0.122(10) 0.078(8) 0.013(9) -0.011(10) 0.002(8)

C9 0.080(8) 0.107(8) 0.073(10) -0.017(8) -0.012(6) -0.022(7)

N10 0.052(5) 0.070(7) 0.071(5) -0.007(6) -0.017(4) -0.012(5)

N11 0.068(5) 0.064(6) 0.069(6) 0.031(5) -0.010(5) 0.012(5)

C12 0.042(6) 0.089(10) 0.044(7) 0.017(8) -0.006(5) 0.004(7)

C13 0.056(6) 0.057(8) 0.071(7) 0.017(7) -0.014(6) 0.008(6)

N14 0.055(5) 0.070(7) 0.068(6) 0.020(5) -0.015(5) 0.001(5)

N15 0.074(6) 0.071(7) 0.078(6) 0.015(6) -0.021(5) -0.001(5)

C16 0.057(6) 0.050(8) 0.073(7) 0.005(8) -0.010(6) 0.005(7)

C17 0.064(7) 0.059(9) 0.074(8) 0.009(6) -0.005(6) -0.002(6)
 C18 0.097(8) 0.068(9) 0.070(7) -0.004(7) -0.012(7) -0.001(7)
 C19 0.064(6) 0.085(9) 0.066(7) 0.004(8) -0.009(6) -0.005(8)
 C20 0.069(7) 0.079(10) 0.070(8) 0.016(7) -0.008(6) 0.008(6)
 C21 0.074(7) 0.051(8) 0.076(8) 0.002(6) -0.002(7) 0.008(6)
 C22 0.095(7) 0.117(8) 0.099(7) -0.010(7) -0.026(7) 0.002(7)
 C23 0.088(7) 0.070(7) 0.081(6) -0.004(6) -0.005(5) -0.008(6)
 S24 0.1056(19) 0.0761(18) 0.0708(16) -0.0077(16) -0.0165(14) -0.0066(15)
 C25 0.087(8) 0.064(8) 0.051(7) -0.016(6) 0.014(7) -0.017(7)
 N26 0.070(6) 0.082(7) 0.076(6) -0.020(5) -0.022(5) -0.007(5)
 C27 0.061(9) 0.073(7) 0.074(10) -0.031(7) 0.009(8) -0.005(6)
 C28 0.112(10) 0.071(7) 0.072(7) 0.008(6) -0.008(10) 0.015(7)
 C29 0.114(12) 0.080(8) 0.099(10) 0.007(7) 0.030(8) -0.008(8)
 C30 0.071(9) 0.066(7) 0.139(13) -0.018(8) -0.005(8) 0.018(6)
 C31 0.126(10) 0.087(8) 0.066(7) -0.002(6) -0.025(10) 0.030(8)
 C32 0.110(11) 0.109(8) 0.040(8) -0.009(6) 0.018(7) -0.003(8)
 N33 0.064(5) 0.074(6) 0.059(5) 0.002(6) -0.019(4) -0.007(5)
 N34 0.064(5) 0.083(6) 0.054(5) -0.037(6) -0.004(4) -0.017(5)
 C35 0.048(7) 0.103(12) 0.043(7) -0.005(8) -0.007(6) 0.004(7)
 C36 0.088(7) 0.094(9) 0.075(7) 0.002(6) -0.002(5) 0.006(6)
 C37 0.068(7) 0.063(7) 0.063(7) -0.021(7) -0.004(6) -0.011(7)
 N38 0.059(6) 0.090(8) 0.052(6) -0.009(6) -0.010(5) 0.002(5)
 N39 0.071(5) 0.067(6) 0.070(6) -0.014(6) -0.020(5) -0.005(6)
 C40 0.064(7) 0.062(9) 0.046(7) -0.006(7) 0.000(6) 0.004(8)
 C41 0.077(7) 0.066(9) 0.073(7) -0.004(8) -0.009(6) 0.006(7)
 C42 0.077(8) 0.078(10) 0.076(8) -0.006(6) -0.009(7) -0.011(7)
 C43 0.062(7) 0.094(10) 0.054(7) 0.004(7) -0.017(6) 0.000(8)
 C44 0.094(7) 0.109(8) 0.083(7) 0.005(6) -0.012(7) -0.001(6)
 C45 0.079(7) 0.065(8) 0.079(7) -0.012(7) -0.014(6) 0.001(7)
 C46 0.066(7) 0.077(10) 0.075(7) -0.016(6) -0.019(6) -0.005(6)

_refine_ls_extinction_coef 26(13)

_refine_ls_extinction_method 'Larson (1970), Equation 22'

loop_

_geom_bond_atom_site_label_1

_geom_bond_site_symmetry_1

_geom_bond_atom_site_label_2

_geom_bond_site_symmetry_2

_geom_bond_distance

_geom_bond_publ_flag

S1 . C2 . 1.692(8) yes

C2 . N3 . 1.337(9) yes

C2 . N10 . 1.358(9) yes

N3 . C4 . 1.401(10) yes

N3 . H31 . 0.863(19) no

C4 . C5 . 1.375(11) yes

C4 . C9 . 1.350(11) yes

C5 . C6 . 1.383(12) yes

C5 . H51 . 0.950 no

C6 . C7 . 1.373(12) yes

C6 . H61 . 0.950 no

C7 . C8 . 1.355(12) yes

C7 . H71 . 0.950 no

C8 . C9 . 1.372(12) yes

C8 . H81 . 0.950 no

C9 . H91 . 0.950 no

N10 . N11 . 1.368(8) yes

N10 . H101 . 0.857(19) no

N11 . C12 . 1.288(9) yes

C12 . C13 . 1.419(11) yes

C12 . C23 . 1.498(10) yes

C13 . N14 . 1.263(9) yes

C13 . H131 . 0.950 no

N14 . N15 . 1.334(9) yes

N15 . C16 . 1.387(10) yes

N15 . H151 . 0.857(19) no
 C16 . C17 . 1.373(10) yes
 C16 . C21 . 1.374(10) yes
 C17 . C18 . 1.388(10) yes
 C17 . H171 . 0.950 no
 C18 . C19 . 1.369(10) yes
 C18 . H181 . 0.950 no
 C19 . C20 . 1.386(10) yes
 C19 . C22 . 1.520(10) yes
 C20 . C21 . 1.381(10) yes
 C20 . H201 . 0.950 no
 C21 . H211 . 0.950 no
 C22 . H221 . 0.950 no
 C22 . H222 . 0.950 no
 C22 . H223 . 0.950 no
 C23 . H231 . 0.950 no
 C23 . H232 . 0.950 no
 C23 . H233 . 0.950 no
 S24 . C25 . 1.673(9) yes
 C25 . N26 . 1.350(9) yes
 C25 . N33 . 1.362(10) yes
 N26 . C27 . 1.438(11) yes
 N26 . H261 . 0.851(19) no
 C27 . C28 . 1.377(11) yes
 C27 . C32 . 1.361(11) yes
 C28 . C29 . 1.375(12) yes
 C28 . H281 . 0.950 no
 C29 . C30 . 1.366(12) yes
 C29 . H291 . 0.950 no
 C30 . C31 . 1.352(12) yes
 C30 . H301 . 0.950 no
 C31 . C32 . 1.385(11) yes
 C31 . H311 . 0.950 no

C32 . H321 . 0.950 no
N33 . N34 . 1.361(8) yes
N33 . H331 . 0.856(19) no
N34 . C35 . 1.295(9) yes
C35 . C36 . 1.503(11) yes
C35 . C37 . 1.420(12) yes
C36 . H361 . 0.950 no
C36 . H362 . 0.950 no
C36 . H363 . 0.950 no
C37 . N38 . 1.265(10) yes
C37 . H371 . 0.950 no
N38 . N39 . 1.333(9) yes
N39 . C40 . 1.388(10) yes
N39 . H391 . 0.864(19) no
C40 . C41 . 1.376(10) yes
C40 . C46 . 1.388(11) yes
C41 . C42 . 1.364(10) yes
C41 . H411 . 0.950 no
C42 . C43 . 1.369(11) yes
C42 . H421 . 0.950 no
C43 . C44 . 1.516(10) yes
C43 . C45 . 1.374(10) yes
C44 . H441 . 0.950 no
C44 . H442 . 0.950 no
C44 . H443 . 0.950 no
C45 . C46 . 1.376(10) yes
C45 . H451 . 0.950 no
C46 . H461 . 0.950 no

loop_

_geom_angle_atom_site_label_1

_geom_angle_site_symmetry_1

_geom_angle_atom_site_label_2

_geom_angle_site_symmetry_2

_geom_angle_atom_site_label_3

_geom_angle_site_symmetry_3

_geom_angle

_geom_angle_publ_flag

S1 . C2 . N3 . 124.9(8) yes

S1 . C2 . N10 . 120.3(9) yes

N3 . C2 . N10 . 114.7(7) yes

C2 . N3 . C4 . 131.9(8) yes

C2 . N3 . H31 . 113.3(14) no

C4 . N3 . H31 . 114.4(14) no

N3 . C4 . C5 . 119.2(11) yes

N3 . C4 . C9 . 122.0(12) yes

C5 . C4 . C9 . 118.6(9) yes

C4 . C5 . C6 . 121.4(9) yes

C4 . C5 . H51 . 118.9 no

C6 . C5 . H51 . 119.7 no

C5 . C6 . C7 . 118.5(9) yes

C5 . C6 . H61 . 121.9 no

C7 . C6 . H61 . 119.6 no

C6 . C7 . C8 . 119.9(10) yes

C6 . C7 . H71 . 120.3 no

C8 . C7 . H71 . 119.8 no

C7 . C8 . C9 . 120.8(10) yes

C7 . C8 . H81 . 119.5 no

C9 . C8 . H81 . 119.7 no

C8 . C9 . C4 . 120.7(10) yes

C8 . C9 . H91 . 120.8 no

C4 . C9 . H91 . 118.5 no

C2 . N10 . N11 . 120.6(7) yes

C2 . N10 . H101 . 119.8(14) no

N11 . N10 . H101 . 119.5(14) no

N10 . N11 . C12 . 119.3(8) yes

N11 . C12 . C13 . 116.2(9) yes

N11 . C12 . C23 . 123.7(9) yes
 C13 . C12 . C23 . 120.1(8) yes
 C12 . C13 . N14 . 121.0(9) yes
 C12 . C13 . H131 . 118.0 no
 N14 . C13 . H131 . 121.0 no
 C13 . N14 . N15 . 118.0(8) yes
 N14 . N15 . C16 . 120.8(8) yes
 N14 . N15 . H151 . 116.2(17) no
 C16 . N15 . H151 . 116.2(17) no
 N15 . C16 . C17 . 122.6(10) yes
 N15 . C16 . C21 . 119.1(11) yes
 C17 . C16 . C21 . 118.3(9) yes
 C16 . C17 . C18 . 120.2(8) yes
 C16 . C17 . H171 . 119.2 no
 C18 . C17 . H171 . 120.5 no
 C17 . C18 . C19 . 122.0(8) yes
 C17 . C18 . H181 . 117.7 no
 C19 . C18 . H181 . 120.2 no
 C18 . C19 . C20 . 117.3(8) yes
 C18 . C19 . C22 . 123.4(12) yes
 C20 . C19 . C22 . 119.2(12) yes
 C19 . C20 . C21 . 120.9(8) yes
 C19 . C20 . H201 . 117.4 no
 C21 . C20 . H201 . 121.7 no
 C20 . C21 . C16 . 121.2(8) yes
 C20 . C21 . H211 . 118.5 no
 C16 . C21 . H211 . 120.3 no
 C19 . C22 . H221 . 106.5 no
 C19 . C22 . H222 . 111.3 no
 H221 . C22 . H222 . 109.5 no
 C19 . C22 . H223 . 110.5 no
 H221 . C22 . H223 . 109.5 no
 H222 . C22 . H223 . 109.5 no

C12 . C23 . H231 . 109.9 no
 C12 . C23 . H232 . 109.0 no
 H231 . C23 . H232 . 109.5 no
 C12 . C23 . H233 . 109.5 no
 H231 . C23 . H233 . 109.5 no
 H232 . C23 . H233 . 109.5 no
 S24 . C25 . N26 . 123.8(9) yes
 S24 . C25 . N33 . 122.6(10) yes
 N26 . C25 . N33 . 113.6(7) yes
 C25 . N26 . C27 . 126.7(8) yes
 C25 . N26 . H261 . 115.4(15) no
 C27 . N26 . H261 . 116.3(15) no
 N26 . C27 . C28 . 117.1(12) yes
 N26 . C27 . C32 . 123.5(12) yes
 C28 . C27 . C32 . 119.4(10) yes
 C27 . C28 . C29 . 120.1(10) yes
 C27 . C28 . H281 . 118.0 no
 C29 . C28 . H281 . 121.8 no
 C28 . C29 . C30 . 119.7(10) yes
 C28 . C29 . H291 . 118.8 no
 C30 . C29 . H291 . 121.5 no
 C29 . C30 . C31 . 120.8(10) yes
 C29 . C30 . H301 . 118.3 no
 C31 . C30 . H301 . 120.9 no
 C30 . C31 . C32 . 119.5(9) yes
 C30 . C31 . H311 . 119.3 no
 C32 . C31 . H311 . 121.1 no
 C31 . C32 . C27 . 120.5(9) yes
 C31 . C32 . H321 . 120.7 no
 C27 . C32 . H321 . 118.8 no
 C25 . N33 . N34 . 120.4(8) yes
 C25 . N33 . H331 . 119.1(14) no
 N34 . N33 . H331 . 120.4(14) no

N33 . N34 . C35 . 118.7(8) yes
 N34 . C35 . C36 . 123.6(10) yes
 N34 . C35 . C37 . 116.0(10) yes
 C36 . C35 . C37 . 120.3(9) yes
 C35 . C36 . H361 . 112.6 no
 C35 . C36 . H362 . 107.7 no
 H361 . C36 . H362 . 109.5 no
 C35 . C36 . H363 . 108.1 no
 H361 . C36 . H363 . 109.5 no
 H362 . C36 . H363 . 109.5 no
 C35 . C37 . N38 . 121.9(10) yes
 C35 . C37 . H371 . 118.4 no
 N38 . C37 . H371 . 119.7 no
 C37 . N38 . N39 . 118.3(8) yes
 N38 . N39 . C40 . 119.1(8) yes
 N38 . N39 . H391 . 120.3(14) no
 C40 . N39 . H391 . 120.5(14) no
 N39 . C40 . C41 . 118.5(11) yes
 N39 . C40 . C46 . 121.4(11) yes
 C41 . C40 . C46 . 120.1(9) yes
 C40 . C41 . C42 . 119.1(9) yes
 C40 . C41 . H411 . 121.3 no
 C42 . C41 . H411 . 119.6 no
 C41 . C42 . C43 . 122.6(8) yes
 C41 . C42 . H421 . 119.7 no
 C43 . C42 . H421 . 117.7 no
 C42 . C43 . C44 . 121.4(12) yes
 C42 . C43 . C45 . 117.4(8) yes
 C44 . C43 . C45 . 121.1(12) yes
 C43 . C44 . H441 . 111.1 no
 C43 . C44 . H442 . 108.8 no
 H441 . C44 . H442 . 109.5 no
 C43 . C44 . H443 . 108.5 no

H441 . C44 . H443 . 109.5 no
 H442 . C44 . H443 . 109.5 no
 C43 . C45 . C46 . 122.1(8) yes
 C43 . C45 . H451 . 119.4 no
 C46 . C45 . H451 . 118.6 no
 C40 . C46 . C45 . 118.7(9) yes
 C40 . C46 . H461 . 119.6 no
 C45 . C46 . H461 . 121.7 no

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#LIST 12

BLOCK

CONT SCALE

CONT S (1,X'S,U'S) UNTIL C (46)

CONT H (151,X'S,U[ISO]) UNTIL H (261)

CONT EXTPARAM

RIDE C (5,X'S) H (51,X'S)

RIDE C (6,X'S) H (61,X'S)

RIDE C (7,X'S) H (71,X'S)

RIDE C (8,X'S) H (81,X'S)

RIDE C (9,X'S) H (91,X'S)

RIDE C (13,X'S) H (131,X'S)

RIDE C (17,X'S) H (171,X'S)

RIDE C (18,X'S) H (181,X'S)

RIDE C (20,X'S) H (201,X'S)

RIDE C (21,X'S) H (211,X'S)

RIDE C (22,X'S) H (221,X'S) H (222,X'S) H (223,X'S)

RIDE C (23,X'S) H (231,X'S) H (232,X'S) H (233,X'S)

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RIDE C ( 28,X'S) H ( 281,X'S)
RIDE C ( 29,X'S) H ( 291,X'S)
RIDE C ( 30,X'S) H ( 301,X'S)
RIDE C ( 31,X'S) H ( 311,X'S)
RIDE C ( 32,X'S) H ( 321,X'S)
RIDE C ( 36,X'S) H ( 361,X'S) H ( 362,X'S) H ( 363,X'S)
RIDE C ( 37,X'S) H ( 371,X'S)
RIDE C ( 41,X'S) H ( 411,X'S)
RIDE C ( 42,X'S) H ( 421,X'S)
RIDE C ( 44,X'S) H ( 441,X'S) H ( 442,X'S) H ( 443,X'S)
RIDE C ( 45,X'S) H ( 451,X'S)
RIDE C ( 46,X'S) H ( 461,X'S)

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END

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#LIST 16

NO

REM HREST START (DO NOT REMOVE THIS LINE)

REM NO H NO #H U MULT DIST

REM C-H

REM >4 1.5 .96 DISORDER

REM 1 1 1.2 .93 C C-H (ACETYLENE)

REM 1 2 1.2 .93 C-C(H)-C

REM 1 3 1.2 .98 (C)3-C-H

REM 2 1 1.2 .93 C=C-H(2)

REM 2 2 1.2 .97 (C)2-C-(H)2

REM 3 1 1.5 .96 C-C-(H)3

REM N-H

REM >4 1.5 .89 DISORDER

REM 1 1 1.2 .86 N-N/H

REM 1 2 1.2 .86 (C)2-N-H

REM 1 3 1.2 .89 (C)3-N-H

```

REM 2    1    1.2    .86 C-N-(H)2
REM 2    2    1.2    .89 (C)2-N-(H)2
REM 3    1    1.2    .89 C-H-(H)3
REM O-H
REM 1    1    1.5    .82 O-H
REM
REM DIST    ESD = 0.02
REM VIB     ESD = 0.002
REM ANGLE   ESD = 2.0
REM
REM TO ACTIVATE THE VIB RESTRAINTS, REMOVE LEADING REM
REM        H1-N-R2
DIST 0.86, 0.02 =
CONT N ( 3) TO H(31)
REST 0.079, 0.002 = H(31,U[ISO])
ANGLE 0.0, 2.0 = MEAN
CONT H(31) TO N ( 3) TO C(2)
CONT H(31) TO N ( 3) TO C(4)
REM        H1-N-R2
DIST 0.86, 0.02 =
CONT N ( 10) TO H(101)
REST 0.078, 0.002 = H(101,U[ISO])
ANGLE 0.0, 2.0 = MEAN
CONT H(101) TO N ( 10) TO C(2)
CONT H(101) TO N ( 10) TO N(11)
REM        H1-N-R2
DIST 0.86, 0.02 =
CONT N ( 15) TO H(151)
REST 0.090, 0.002 = H(151,U[ISO])
ANGLE 0.0, 2.0 = MEAN
CONT H(151) TO N ( 15) TO N(14)
CONT H(151) TO N ( 15) TO C(16)
REM        H1-N-R2

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DIST 0.86, 0.02 =
CONT N ( 26) TO H(261)
REST 0.092, 0.002 = H(261,U[ISO])
ANGLE 0.0, 2.0 = MEAN
CONT H(261) TO N ( 26) TO C(25)
CONT H(261) TO N ( 26) TO C(27)
REM      H1-N-R2
DIST 0.86, 0.02 =
CONT N ( 33) TO H(331)
REST 0.080, 0.002 = H(331,U[ISO])
ANGLE 0.0, 2.0 = MEAN
CONT H(331) TO N ( 33) TO C(25)
CONT H(331) TO N ( 33) TO N(34)
REM      H1-N-R2
DIST 0.86, 0.02 =
CONT N ( 39) TO H(391)
REST 0.084, 0.002 = H(391,U[ISO])
ANGLE 0.0, 2.0 = MEAN
CONT H(391) TO N ( 39) TO N(38)
CONT H(391) TO N ( 39) TO C(40)
REM  HREST  END (DO NOT REMOVE THIS LINE)
END

```