Design, Characterization, X-ray Single-crystal, Potentiometric Measurements, Molecular Modeling and Biomedical Applications of Thiosemicarbazones

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

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Abstract

A 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, $^1$HNMR, 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) Å, b = 11.2575 (7) Å, c =11.8995 (8) Å, α = 90.00°, β = 94.476(7) °, γ = 90.0°, V = 1500.34 (16) Å³, Z = 4, however, TSC3 crystallizes in the space group P21/c, a = 27.958 (12) Å, b = 12.072 (5) Å, c = 9.833 (4) Å, α = 90.0°, β = 93.117(11) °, γ = 90.0°, V = 3486.75 Å³, 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 21\textsuperscript{st} 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](attachment:scheme.png)
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.
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 (C$_2$H$_5$)$_2$O and desiccated all night using silica gel. The target compounds are shown in Figure 1.

![Structural formulae of thiosemicarbazone compounds; TSC1, TSC2 and TSC3 with R = H, Et, Ph, respectively.](image)

**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-1carbothioamide (TSC1).** Yield, 77%. Colour, Brown. Anal. Calc. for C$_{11}$H$_{15}$N$_5$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$_2$H), 1100 (N=N), 1603 (C=N), 1553 (C=C), 3045 (C-H). MS (m/z): 251 (M$^+$+2, 6.03 %), 250 (M$^+$+1, 18.07 %) 249 (M$, 100 %), 234 (2.58 %), 232 (38.20 %), 159 (2.07 %) 157 (0.59 %) 118 (3.81 %). $^1$H NMR (DMSO): 11.32 (s, 1H, NH), 10.89 (s, 2H, NH), 10.89 (s, 2H, NH), 7.8 (s, 2H, NH), 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-1carbothioamide (TSC2). Yield, 69 %. Colour, Dark brown. Anal. Calc. for C$_{13}$H$_{19}$N$_5$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 %). \textsuperscript{1}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, –CH\textsubscript{2}), 2.4 (t, 2H, –CH\textsubscript{3}), 2.23 (s, 3H, –CH\textsubscript{3}), 2.02 (s, 3H, –CH\textsubscript{3}). \textsuperscript{13}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 C\textsubscript{17}H\textsubscript{19}N\textsubscript{5}S: 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\textsuperscript{-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\textsuperscript{+}+1, 1.78 %) 325 (M\textsuperscript{+}, 7.41 %), 118 (5.63 %). \textsuperscript{1}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, –CH\textsubscript{3}), 2.03 (s, 3H, –CH\textsubscript{3}). \textsuperscript{13}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 ELII-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 schimadzu 3101 pc, electronic spectra are recorded. A Bruker ARX-300 device was applied to monitor the \textsuperscript{1}H-NMR spectra. Chemical shifts are recorded in ppm comparative to TMS using deuterated dimethylsulphoxide (d\textsubscript{6}-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 Ka radiation with radiation wavelength of \(\lambda = 0.71075 \text{ Å}\) by the \(\omega\) scan mode. By applying a cold N\textsubscript{2} 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 Ka radiation with radiation wavelength of \(\lambda = 0.71073 \text{ Å}\). The crystal structure was solved by SIR-92 program [33] and was refined on F\textsuperscript{2} 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/dm$^3$ NaOH, free from CO$_2$, is used to titrate all samples in the N$_2$ atmosphere. The sample solution developed to avoid hydrolysis during titration by mixing equal volumes of DMSO and H$_2$O. In addition, the ionic strength was kept constant during titration using NaNO$_3$ 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]

$$-\log_{10} [H^+] = B + \log_{10} U_H$$

(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 cm$^3$) of (1.25x10$^{-3}$ mol/dm$^3$) 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 DMOL$^3$ program [46,47] in Materials Studio package [48]. Calculations for DFT semi-core pseudopods (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 μl 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 μg/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% CO$_2$ 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\textsubscript{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\textsubscript{2}O, 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 ν(>C=O) and emergence of new band at 1603-1615 cm\textsuperscript{-1} that refers to ν(C=N) stretching vibration [55] supporting condensation reaction and formation of thiosemicarbazone compounds.

2- Thiosemicarbazone compounds can exhibit thione ↔ thiol tautomerism [56] as a result of the existence of -NH-C=S linkage but ν(S-H) absorption band at 2500-2600 cm\textsuperscript{-1} was absent with an appearance of ν(C=S) band around 750 cm\textsuperscript{-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\textsuperscript{-1} (v\textsubscript{C-H}, Ar-H), 1615 cm\textsuperscript{-1} (v\textsubscript{C=N}), 1548 cm\textsuperscript{-1} (v\textsubscript{C=C}), 1082 cm\textsuperscript{-1} (v\textsubscript{N-N}) were detected.

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

5- The v\textsubscript{sym} and v\textsubscript{asym} of TSC1 amino group were observed at 3234 and 3386 cm\textsuperscript{-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

\( ^1\)H-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 C=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, CH=N was detected at \(\delta = 7.48\) 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 \(\delta = 2.02\) ppm. The spectra of TSC1 compound show signals at \(\delta 7.80\) ppm assigned to the NH\(_2\) proton.

The \(^{13}\)C-NMR spectra of novel thiosemicarbazone compounds were carried out in DMSO-d6. Peaks of azomethine carbons and C=S of thiosemicarbazone compounds were observed as singlet peaks. The signal for the carbon atom of C=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 (C=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 P2₁/c, \( a = 27.985 \) (12) Å, \( b = 12.027 \) (5) Å, \( c = 9.833 \) (4) Å, \( \alpha = 90.0^\circ \), \( \beta = 93.117 \) (11)°, \( \gamma = 90.0^\circ \), \( V = 3486.57 \) Å³, \( Z = 7 \) while TSC3 was crystallized also in monoclinic crystal system with space P2₁/c, \( a = 11.2343 \) (6) Å, \( b = 11.2575 \) (7) Å, \( c = 11.8995 \) (8) Å, \( \alpha = 90.00^\circ \), \( \beta = 94.476 \) (6)°, \( \gamma = 90.0^\circ \), \( V = 1500.34 \) (3) Å³, \( Z = 4 \).

![Fig. 2. X-ray structure of a) TSC2 b) TSC3 thiosemicarbazone compounds along with the atom numbering scheme.](image)

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 is 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 $E_{\text{HOMO}}$, $E_{\text{LUMO}}$, in addition to specific parameters like ionization potential (IP), absolute softness ($\sigma$), absolute hardness ($\eta$), electron affinity (EA), separation energy ($\Delta E$), absolute electronegativity ($\chi$), global softness ($S$), electrophilicity ($\omega$), electron accepting power ($\omega^+$), electron donating power ($\omega^-$) and additional electronic charge ($\Delta N_{\text{max}}$) [60-64] have been computed according to Eqs 2-11 as shown below [60-65]. The inverse of the global hardness is called softness $\sigma$ [66].

\[
\chi = -\frac{1}{2} (E_{\text{LUMO}} + E_{\text{HOMO}}) \quad (2)
\]

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

\[
\eta = \frac{1}{2} (E_{\text{LUMO}} - E_{\text{HOMO}}) \quad (4)
\]

\[
S = \frac{1}{2} \eta \quad (5)
\]

\[
\Delta N_{\text{max}} = -\frac{\text{IE}}{\eta} \quad (6)
\]

\[
\sigma = \frac{1}{\eta} \quad (7)
\]

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

\[
\omega = \frac{\text{IE}^2}{2} \eta \quad (9)
\]

\[
\omega' = \frac{(3*\text{IE}+\text{EA})^2}{16} \text{ (IE-EA)} \quad (10)
\]

\[
\omega'' = \frac{(\text{IE}+3*\text{EA})^2}{16} \text{ (IE-EA)} \quad (11)
\]
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_{LUMO}-E_{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 hardnes (η) and softness (σ) are essential characteristics in calculation of molecular stability and reactivity. Hard molecules have a large energy gap with less reactivity (ΔE = E_{HOMO} –E_{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 (ω = 3.104) > TSC2 (ω = 2.936) > TSC3 (ω = 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 Steptococcus 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 $\mu$g/ml respectively (Table 5) while the IC$_{50}$ towards HepG2 and MCF-7 cells for TSC2 are 46 and 172.9 $\mu$g/ml respectively. Furthermore, the IC$_{50}$ towards HepG2 and MCF-7 cells for TSC3 are 25 and 107 $\mu$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 TSC3 > TSC1 > 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.

\[
\begin{align*}
L^- + H^+ & \rightleftharpoons HL; & K_1 = \frac{[HL]}{[L^-][H^+]} \quad (15) \\
HL + H^+ & \rightleftharpoons H_2L^+; & K_2 = \frac{[H_2L^+]}{[HL][H^+]} \quad (16) \\
H_2L^+ + H^+ & \rightleftharpoons H_3L^{2+}; & K_3 = \frac{[H_3L^{2+}]}{[H^+][H_2L^+]} \quad (17)
\end{align*}
\]

We can conclude that the 1\textsuperscript{st} and 2\textsuperscript{nd} deprotonation constants correspond to the deprotonation of the two N-imino sites in TSC ligand as given in Scheme 3a. While the 3\textsuperscript{rd} 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 range from (2.97-3.35) are similar to those found in the literature for the imino group (4.40) [76]. The log $K_{\text{SH}}$ 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$_2$O. 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].
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 H$_3$L below pH $< 2$. On addition of base, pH value increases so the (H$_3$L) species loses its first proton from an imino group to form (H$_2$L), 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 $\Delta H^\circ$, $\Delta S^\circ$ and $\Delta G^\circ$ related to protonation of TSC1 and Cd(II)-complex formation were calculated from the data tabulated in tables 8 and 9. $\Delta H^\circ$ for the ligand protonation or complexation was determined from the plot slope (Fig. 5a-b) through graphical representation of the Van’t Hoff equation

\[-2.303 \text{R } T \log_{10} K = \Delta H^\circ - T \Delta S^\circ\] 

or

\[\log_{10} K_{10} = -(\Delta H^\circ/2.303\text{R})(1/T) + \Delta S^\circ/R\] 

With the well-known relations (6) and (7), from the values of ($\Delta G$) and enthalpy change ($\Delta H$), one can calculate ($\Delta S$):

$\Delta G^\circ = -2.303 \text{ RT log}_{10} K$ 

$\Delta S^\circ = (\Delta H^\circ-\Delta G^\circ)/T$
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 \( \Delta H^o \) 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 \( \Delta H^o \) 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 $\Delta G^\circ$.
3- It is commonly found that $\Delta G^\circ$ and $\Delta H^\circ$ 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 $\Delta S^\circ$ 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 Cd$^{2+}$ 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

[1] World health statistics, WHO Library Cataloguing-in-Publication Data (2014).

[2] A. Anandan, G.L. Evans, K. Condic-Jurkic, M.L. O’Mara, C.M. John, N.J., G.A. Jarvis, S.S. Wills, K.A. Stubbs, I. Moraes, C.M. Kahler, A. Vrielink, Proc Natl Acad Sci. 114(9) (2017) 2218-2223.

[3] Harbottle, H.; Thakur, S.; Zhao, White, D. G. Anim. Biotechnol. 2006, 17, 111-124.

[4] B. Li, T.J. Webster, J Orthop Res. 36(1) (2018) 22-32.

[5] Berger, S. Horm. Metab. Res. 1985, 17, 111-115.

[6] Lakshmi, B.; Avaji, P. G.; Shivananda, K. N.; Nagella, P.; Manohar, S. H.; Mahendra, K. N. Polyhedron 2011, 30, 1507-1515.

[7] Chan, J.; Huang, Y.; Liu, G.; Afrasiabi, Z.; Sinn, E.; Padhye, S.; Ma, Y. Toxicol. Appl. Pharm. 2004, 197, 40-48.

[8] K.J. Duffy, A.N. Shaw, E. Delorme, S.B. Dillon, C. Erickson-Miller, L. Giampa, Y. Huang, R.M. Keenan, P. Lamb, N. Liu, S.G. Miller, A.T. Price, J. Rosen, H. Smith, K.J. Wiggall, L. Zhang, J.I. Luengo, J. Med. Chem. 45 (2002) 3573.

[9] J.R. Dilworth, R. Hueting, Inorg. Chim. Acta 389 (2012) 3.

[10] Sarah A. Andres, Kritika Baja, Nicholas S. Vishnosky, Peterson, Mark S. Mashuta, Robert M. Buchanan, Paula j. Bates and Craig A. Grapperhaus, inorg. chem. 59, 7, (2020), 4924-4935.

[11] Peter Heffeter et al., antioxidants and redox signaling 30, 8, (2017), 7487.

[12] R.J. Glisoni, M.L. Cuestas, V.L. Mathet, J.R. Oubina, A.G. Moglioni, A. Sosnik, Eur. J. Pharm. Sci. 47 (2012) 596.

[13] X. Du, C. Guo, E. Hansel, P.S. Doyle, C.R. Caffrey, T.P. Holler, J.H. McKerrow, F.E. Cohen, J. Med. Chem. 45 (2002) 2695.

[14] D. Kovala-Demertzi, M.A. Demertzis, E. Filiou, A.A. Pantazaki, P.N. Yadav, J.R. Miller, Y. Zheng, D.A. Kyriakidis, Biometals 16 (2003) 411.

[15] J.P. Scovill, D.L. Klayman, D.G. Franchino, J. Med. Chem. 25 (1982) 1261.

[16] L. Klayman, J.P. Scovill, J.F. Bartosevich, J. Bruce, J. Med. Chem. 26 (1983) 35.

[17] D.K. Demertzis, M.A. Demertzis, J.R. Miller, C. Papadopoulou, C. Dodorou, G. Filousis, J. Inorg. Biochem. 86 (2001) 555.

[18] P.K. Singh, D.N. Kumar, Spectrochim. Acta A 64 (2006) 853.

[19] N. Bharti, S.S. Sharma, A. Azam, J. Bioorganic and Medicinal Chemistry 11 (2003) 2923-2929.
[20] A. Walcourt, M. Loyevsky, D.B. Lovejoy, V. R. Gordeuk, D.R. Richardson, J. Biochemistry and Cell biology, 36 (2004) 401-407.
[20] A.A. El-Sherif, A. Fetoh, Y. Kh. Abdulhamed, G. M. Abu El-Reash, Inorganica Chimica Acta 480 (2018) 1–15
[21] O.M.I. Adly, A.A.A. Emara, Spectrochim. Acta Mol. Biomol. Spectrosc. 132 (2014) 91-101.
[22] O.A. El-Gammal, T.H. Rakha, H.M. Metwally, G.M. Abu, El-Reash, Spectrochim. Acta Mol. Biomol. Spectrosc. 127 (2014) 144.
[23] R. Kaplanek, M. Havlík, B. Dolensky, J. Rak, P. Dzub_a, P. Konecny, M. Hajdúch, J. Kr_alova, V. Kral, Bioorg. Med. Chem. 23 (2015) 1651–1659.
[24] M. M. Brzoska and J. Moniusko-Jakoniuk, Toxicol. 39, 967-980 (2001).
[25] I. M. Armitage, A. J. M. Schoot Viterkamp, J. R. Chlebowksi, J. E. Coleman, $^{113}$Cd NMR As A Probe of The Active Sites of Metalloenzymes J. of Magnetic Resonance (1969), 29, 375-392 (1978).
[26] H. Beinert, Structure and Function of Copper Proteins: Report, On the Fourth La Cura Conference Held at Villa Giulia, Manziana, Rome, Italy, 4-8 September 1979, Coord. Chem. Rev., 33, 55-85 (1980).
[27] F. Jensen, Introduction to Computational Chemistry, Wiley, Chichester, UK, 1999.
[28] Y.D. Scherson, S.J. Aboud, J. Wilcox, B.J. Cantwell, J. Phys. Chem. 115 (2011) 11036.
[29] A.A. El-Sherif, J. Coord. Chem. 64 (7) (2011) 1240–1253.
[30] A.A. El-Sherif, J. Solution Chem. 41 (2012) 392–409
[31] N. Rabjohn, Organic Synthesis, Collective Volume 4, John Wiley and Sons Inc., 1963.
[32] A.A. El-Sherif, Inorg. Chim. Acta 362 (2009) 4991–5000
[33] A. Altomare, G.Cascarano, C. Giacovazzo, A., Guagliardi, M.C. Burla, G. Polidori, M. Camalli, J. Appl. Cryst. 27 (1994) 435.
[34] S. Mackay, C.J. Gilmore, C. Edwards, N. Stewart, K. Shankland, maXus Computer Program for the Solution and Refinement of Crystal Structures. Bruker Nonius, The Netherlands, MacScience, Japan & The University of Glasgow (1999).
[35] C. K. Johnson, ORTEP-II. A Fortran Thermal-Ellipsoid Plot Program. Report ORNL-5138. Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA (1976).
[36] A.A. El-Sherif, J. Solution Chem. 39, 131–151 (2010).
[37] Bates, R.G., Determination of pH, Theory and Practice, 2nd edn. John Wiley and Sons, New York (1975).
[38] E.M. Woolley, D.G. Hurkot, L.G. Hepler, J. Phys. Chem. 74, 3908–3913 (1970).
[39] G.L. Van Uitert, C.G. Hass, J. Am. Chem. Soc. 75, 451 (1971).
[40] E.P. Serjeant, Potentiometry and potentiometric titrations. Wiley, New York (1984).
[41] A. Golcu, M. Tumer, H. Demirelli, R.A. Wheatley, Inorg. Chim. Acta 358, 1785–1797 (2005).
[42] A.E. Martell, R.J. Motekaitis, The Determination and Use of Stability Constants. VCH, Weinheim (1988).
[43] M. Meloun, J. Havel, E. Högfelt, Computation of Solution Equilibria: A Guide to Methods in Potentiometry, Extraction and Spectrophotometry; Ellis Horwood Limited: Chichester, Wiley, New York (1988).
[44] P. Gans, A. Sabatini, A. Vacca, Inorg. Chim. Acta 18, 237-239 (1976).
[45] L. Pettit, University of Leeds, Personal Communication.
[46] B.A. Delley, Int. J. Quantum Chem. 69, 423–433 (1998).
[47] B. Delley, From molecules to solids with the DMOl3 approach. J. Chem. Phys. 113, 7756–7764 (2000).
[48] Materials Studio (Version 5.0), Copyright 2009. Accelrys software Inc., San Diego, USA.
[49] W.J. Hehre, L. Radom, P.V.R. Schlyer, J.A. Pople, Ab Initio Molecular Orbital Theory, Wiley, New York, (1986).
[50] B. Hammer, L.B. Hansen, J.K. Nørskov, Phys. Rev. B 59, 7413–7421 (1999).
[51] A. Matveev, M. Stauffer, M. Mayer, N. Rösch, Int. J. Quantum Chem. 75, 863–873 (1999).
[52] A. W. Bauer, M.D., W. M. M. Kirby, M.D., J. C. Sherris, M.D., M. Turck, M.D., American Journal of Clinical Pathology, 45(4) (1966) 493–496.
[53] A. A. El-Sherif, J Solution Chem. 39 (2010) 1562–1581
[54] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J.T. Warren, H. Bokesch, S. Kenney, M.R. Boyd, J. Natl. Cancer Inst, 82 (1990) 1107-1112.
[55] M. P. Swami, D. Gupta, M. Mohan, A.K. Srivastava, Prog. Natl. Acad. Sci. India A 1980, 50(3), 176-181.
[56] Kurup, M. R. P.; Joseph, M. Synth. React. Inorg. Met. Org. Chem. 2003, 33, 275-281.
[57] D.M. Wileasn, D.T. Suprunchuk, Candian J. of Chem.,47, (1969) 1087-1089.
[58] M. Aljahdali, A.A. EL-Sherif, Inorganica Chimica Acta 407 (2013) 58–68
[59]. Philip, V.; Suni, V.; Kurup, M. R. P. Polyhedron 2006, 25, 1931-1938.
[60] R.G. Pearson, J. Org. Chem. 54 (1989) 1423.
[61] P. Geerlings, F. De Proft, W. Langenaeker, Chem. Rev. 103 (2003) 1793.
[62] R.G. Parr, J. Am. Chem. Soc. 121 (1999) 1922.
[63] P.K. Chattaraj, S.Giri, J. Phys. Chem. A 111 (2007) 11116.
[64] G. Speie, J. Csihony, A.M. Whalen, C.G. Pie-Pont, Inorg. Chem. 35 (1996) 3519
[65] S.W. Xia, X. Xu, Y.L. Sun, Y.L. Fan, Y.H. Fan, C.F. Bi, D.M. Zhang, L.R. Yang, Chin. J. Struct. Chem. 25 (2006) 197-203.
[66] S. Sagdinc, B. Koksoy, F. Kandemirli, S.H. Bayari, J. Mol. Struct. 917 (2009) 63–70.
[67] R.G. Pearson, Hard and Soft acids and bases, Dowden, Hutchinson and Ross, Stroudsburg, PA, 1973.
[68] K.H. Kim, Y.K. Han, J. Jung, Theor. Chem. Acc. 113 (2005) 233.
[69] A. Ghosh, A. Sarkar, P. Mitra, A. Banerji, J. Banerjee, S. Mandal, Manosi Das, J. Mol. Struct. 980 (2010) 7.
[70] J.I. Aihara; J. Phys. Chem. A 103 (1999) 7487.
[71] J.A. Wellman, F.B. Hulsbergen, J. Verbiest, J. Reedijk, J. Inorg. Nucl. Chem. 40 (1978) 143–147
[72] A.A. El-Sherif, A. Fetoh, Y. Kh. Abdulhamed, G.M. Abu El-Reash, Inorg. Chim. Acta 480 (2018) 1–15.
[73] C. Jayabalakrishnan and K. Natarjan, Synth. React. Inorg. Met. -Org. Chem. 31 (2001) 983-991.
[74] A.A. El-Sherif, J. Inorg. Chim. Acta 360 (2007) 473-487.
[75] M. A. Hassan, A. El-Roudi, M. T. J. Quenawy, Pharm. Sci. 34 (1993) 253
[76] T. Gunduz, E. Kilic, F. Koseoglu and E. Canel. Anal. Chim. Acta, 282 (1993) 489
[77] F.G. Bordwell, D.L. Hughes, J. Organic Chemistry 47(17) (1982) 3224-3232
[78] K.M. Honório, A.B.F. Da Silva, Inter. J. Quant. Chem. 95 (2003) 126-132.
[79] A.A. El-Sherif, M.M. Shoukry, M.M.A. Abd-Elgawad, J. Solution Chem. 42 (2013) 412-427
[80] H. Rossotti, The Study of Ionic Equilibria, Longman, London, 1987.
[81] H. Sigel, R.B. Martin, Chem. Rev. 82 (1982) 385.
Table 1. Crystal data and structure refinement of thiosemicarbazone compounds

| Crystal data                          | Compounds     |
|---------------------------------------|---------------|
| **Table 1. Crystal data and structure refinement of thiosemicarbazone 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 Kα         | Mo Kα        |
| 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 (Å³)                           | 1500.34 (16)  | 3486.75     |
| Z                                      | 4             | 7           |
| D_\text{x}                             | 1.228 g/cm³   | 1.498 g/cm³ |

| 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     | ΔNmax  | 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) | Bacillus subtilis | Staphylococcus aureus | Streptococcus faecalis | E. coli | Neisseria gonorrhoeae | Pseudomonas aeruginosa | Aspergillus flavus | Candida albicans |
|-----------------------|------------------|----------------------|------------------------|--------|-----------------------|------------------------|------------------|-----------------|
| 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               |
| Ampicillin            | 26               | 21                   | 27                     | 25     | 28                    | 26                     | -                | -               |
| Amphotericin          | -                | -                    | -                      | -      | -                     | -                      | 16               | 19              |

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

Table 5. Antitumor activity of the synthesized thiosemicarbazone compounds.

| Concentration (μg/ml) | Liver cancer cell line (HepG2) | Breast cancer cell line (MCF-7) |
|-----------------------|-------------------------------|-------------------------------|
|                       | TSC1                          | TSC2                          | TSC3                          |
| 5                     | 100                           | 100                           | 100                           |
| 25                    | 35.3                          | 67                            | 22.5                          |
| 50                    | 27.4                          | 48.7                          | 19                            |
| IC<sub>50</sub>       | 29.4                          | 46                            | 25                            |
| 5                     | 83.8                          | 95                            | 77.6                          |
| 25                    | 79.5                          | 86.5                          | 72                            |
| 50                    | 70.7                          | 83                            | 65.4                          |
| IC<sub>50</sub>       | 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) |
| \( HL + H = H_2L \)| 3.31(0.08) | 3.22(0.07) | 3.14(0.09) |
| \( H_2L + H = H_3L \)| 3.17(0.04) | 3.08(0.06) | 3.01(0.05) |

\(^a(\sigma \) is the standard deviation;

### Table 7. Stepwise stability for the complexes of TSC1 with Cd(II) metal ion in 50% DMSO-H\(_2\)O (V/V) solution.

| Temp.(°C) | \( \log K_1(\pm\sigma)^a \) | \( \log K_2(\pm\sigma) \) | \( \log K_1-K_2 \) |
|-----------|-----------------------------|---------------------------|---------------------|
|           | 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                |

\(^a(\sigma \) is the standard deviation;

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

### Table 8. Thermodynamic parameters for the protonation of ligand (TSC1) in 50% DMSO-H\(_2\)O (V/V) solution.

| Parameter\(^a\) | Reaction |
|-----------------|----------|
|                 | L + H = HL\(^a\) | L + 2H = H\(_2\)L | L + 3H = H\(_3\)L |
| \(-\Delta G\)   | 44.25 | 45.08 | 17.49 | 17.58 | 17.82 | 18.26 | 18.38 | 18.47 |
| \(-\Delta H\)   | 32.33 | 17.49 | 15.29 | 12.77 |
| \(\Delta S\)    | 41.16 | 10.30 | 16.27 |

\(\Delta G\): Gibbs energy/kJ.mol\(^{-1}\); \(\Delta H\): Enthalpy/kJ.mol\(^{-1}\); \(\Delta S\): Entropy/J.mol\(^{-1}\).K\(^{-1}\)
Table 9. Thermodynamic parameters for Cd(II)-TSC1 complexes in 50% DMSO-H$_2$O (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 |
| -$\Delta G$  | 54.18 | 55.60 | 56.45 | 15.45 | 15.70 | 15.99 |
| -$\Delta H$  | 21.15 |       |       |       | 7.66   |       |
| $\Delta S$   | 114.88 |       |       |       | 26.99  |       |

$^a$$\Delta G$: Gibbs energy/kJ.mol$^{-1}$; $\Delta H$: Enthalpy/kJ.mol$^{-1}$; $\Delta S$: 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.

Structure factor report

Datablock: ahmed1_a

Bond precision: C-C = 0.0032 Å

Cell:

\[
\begin{align*}
a &= 11.2343(6) \\
b &= 11.2575(7) \\
c &= 11.8995(8) \\
\alpha &= 90 \\
\beta &= 94.476(7) \\
\gamma &= 90
\end{align*}
\]

Temperature: 293 K

| Calculated     | Reported     |
|----------------|--------------|
| Volume         | 1500.34(16)  | 1500.34(16)  |
| Space group    | P 21/c       | P 21/c       |
| Hall group     | -P 2ycb      | -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

\[
\begin{align*}
R(\text{reflections}) &= 0.0558( 2731) \\
wR2(\text{reflections}) &= 0.1761( 3427) \\
S &= 1.303 \\
Npar &= 184
\end{align*}
\]

The following ALERTS were generated. Each ALERT has the format test-name_ALERT_alert-type_alert-level.

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 SHEXL 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 _differnt_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 ....

Structure factor report

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          |                    |
| 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_reflns_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

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

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!

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

11 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
7 ALERT type 2 Indicator that the structure model may be wrong or deficient
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)

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_atom_type_description
_atom_type_scat_dispersion_real
_atom_type_scat_dispersion_imag
_atom_type_scat_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_name_Hall  '-P 2ybc'

_shelx_space_group_comment
;
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.
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'-x, y+1/2, -z+1/2'
'x, -y, -z'
'x, -y-1/2, z-1/2'

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_cell_length_c  11.8995(8)
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_cell_volume  1500.34(16)
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_cell_measurement_reflns_used  11219
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_cell_measurement_theta_max  27.43

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_diffrn_reflns_limit_k_max  13
_diffrn_reflns_limit_l_min  -15
Reflections were merged by SHELXL according to the crystal class for the calculation of statistics and refinement.

\_reflns\_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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\_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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loop_
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_atom_site_fract_z
_atom_site_U_iso_or_equiv
_atom_site_adp_type
_atom_site_occupancy
_atom_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 . . . . .
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 . . . . .
N5 N 0.29717(17) 0.74135(15) 0.89309(17) 0.0589(5) Uani 1 1 d D U . . . . .
N6 N 0.301(2) 0.767(2) 0.8257(11) 0.071 Uiso 1 1 d D U U . . . . .
C1 C 0.9615(2) 0.6150(3) 0.10378(19) 0.0756(8) Uani 1 1 d . . . . .
H1 A H 0.950609 0.671986 0.043853 0.113 Uiso 1 1 calc R U . . . . .
H1 B H 0.936122 0.538126 0.076446 0.113 Uiso 1 1 calc R U . . . . .
C1 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 . . . . .
H12A H 0.157908 0.738322 0.987452 0.141 Uiso 1 1 calc R U . . .
H12B H 0.253907 0.832701 1.027433 0.141 Uiso 1 1 calc R U . . .
H12C H 0.1409(3) 0.8892(3) 0.9035(3) 0.0956(10) Uani 1 1 d . . . . .
H13A H 0.191889 0.953572 0.884580 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) 0.0067(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 0.1463(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_
  _geom_angle_atom_site_label_1 
  _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 | 0.649919 | 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  0.725461  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 ahmedl_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
| Q  |   |   |   |   |   |   |
|----|---|---|---|---|---|---|
| Q6 | 1 | 0.2601 | 0.7192 | 0.8333 | 11.00000 | 0.05 |
| Q7 | 1 | 0.7598 | 0.7543 | 0.3288 | 11.00000 | 0.05 |
| Q8 | 1 | 0.6132 | 0.6902 | 0.5843 | 11.00000 | 0.05 |
| Q9 | 1 | 0.5410 | 0.6627 | 0.6437 | 11.00000 | 0.05 |
| Q10| 1 | 0.3854 | 0.6092 | 0.8787 | 11.00000 | 0.05 |
| Q11| 1 | 0.2039 | 0.7775 | 1.0295 | 11.00000 | 0.05 |
| Q12| 1 | 0.6529 | 0.7071 | 0.4955 | 11.00000 | 0.05 |
| Q13| 1 | 0.8224 | 0.5872 | 0.3142 | 11.00000 | 0.05 |
| Q14| 1 | 0.3553 | 0.5707 | 1.1036 | 11.00000 | 0.05 |
| Q15| 1 | 0.4866 | 0.6431 | 0.7229 | 11.00000 | 0.05 |
| Q16| 1 | 0.7463 | 0.6697 | 0.3567 | 11.00000 | 0.05 |
| Q17| 1 | 0.3280 | 0.5649 | 1.0656 | 11.00000 | 0.05 |
| Q18| 1 | 0.2874 | 0.5784 | 1.0821 | 11.00000 | 0.05 |
| Q19| 1 | 0.3413 | 0.7874 | 0.8632 | 11.00000 | 0.05 |
| Q20| 1 | 0.5320 | 0.5693 | 0.6844 | 11.00000 | 0.05 |
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_scat_dispersion_real
_atom_type_scat_dispersion_imag
_atom_type_scat_Cromer_Mann_a1
_atom_type_scat_Cromer_Mann_b1
_atom_type_scat_Cromer_Mann_a2
_atom_type_scat_Cromer_Mann_b2
_atom_type_scat_Cromer_Mann_a3
_atom_type_scat_Cromer_Mann_b3
_atom_type_scat_Cromer_Mann_a4
_atom_type_scat_Cromer_Mann_b4
_atom_type_scat_Cromer_Mann_c
_atom_type_scat_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'

# 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_absorp_coefficient_mu   0.192

# Sheldrick geometric approximatio 0.93 0.95
_exptl_absorp_correction_type  none
_diffrn_measurement_device_type KappaCCD
_diffrn_measurement_device     Serial
_diffrn_radiation_monochromator graphite
_diffrn_radiation_type         'Mo K\alpha'
_diffrn_radiation_wavelength   0.71073
_diffrn_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)'

_diffrn_standards_interval_time .
_diffrn_standards_interval_count .
_diffrn_standards_number 0
_diffrn_standards_decay_% ?

_diffrn_ambient_temperature 293
_diffrn_reflns_number 14423
_reflns_number_total 2208
_diffrn_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

_diffrn_reflns_theta_min 0.729
_diffrn_reflns_theta_max 25.580
_diffrn_measured_fraction_theta_max 0.983

_diffrn_reflns_theta_full 25.052
_diffrn_measured_fraction_theta_full 0.995

_diffrn_reflns_limit_h_min -23
_diffrn_reflns_limit_h_max 23
_diffrn_reflns_limit_k_min -10
_diffrn_reflns_limit_k_max 10
_diffrn_reflns_limit_l_min -8
_diffrn_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
# The values computed with a 2 sigma cutoff - a la SHELX

- \_reflns\_threshold\_expression
  \text{I}>2.0\text{s(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/\[A~0~*T~0~(x)+A~1~*T~1~(x) ... +A~n-1~*T~n-1~(x)\]

where A~i~ are the Chebychev coefficients listed below and x= Fcalc/Fmax

Method = Robust Weighting (Prince, 1982)

W = [weight] * \[1-(\text{deltaF}/6*\text{sigmaF})^2]\]^2^\^

A~i~ are:

4.04 5.84 2.49 0.530

;

# Uequiv = arithmetic mean of Ui i.e. Uequiv = (U1+U2+U3)/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 . . . . .
| Atom | Type | X        | Y        | Z        | Temperature | Occupancy | Uani |
|------|------|----------|----------|----------|-------------|-----------|------|
| N10  | N    | 0.4952(3)| 0.6727(6)| 0.9084(9)| 0.0648      | 1.0000    |      |
| N11  | N    | 0.4743(3)| 0.7551(6)| 0.5761(10)| 0.0650      | 1.0000    |      |
| C12  | C    | 0.4450(4)| 0.7363(9)| 0.7353(12)| 0.0587      | 1.0000    |      |
| C13  | C    | 0.4228(4)| 0.8254(7)| 0.6721(12)| 0.0618      | 1.0000    |      |
| N14  | N    | 0.3912(3)| 0.8149(6)| 0.5761(10)| 0.0650      | 1.0000    |      |
| N15  | N    | 0.3717(3)| 0.9018(7)| 0.5210(9) | 0.0752      | 1.0000    |      |
| C16  | C    | 0.3391(3)| 0.8959(10)| 0.4098(11)| 0.0607     | 1.0000    |      |
| C17  | C    | 0.3227(3)| 0.8018(8)| 0.3567(11)| 0.0660      | 1.0000    |      |
| C18  | C    | 0.2907(4)| 0.8003(8)| 0.2438(12)| 0.0789      | 1.0000    |      |
| C19  | C    | 0.2739(3)| 0.8909(12)| 0.1827(9)| 0.0720      | 1.0000    |      |
| C20  | C    | 0.2908(4)| 0.9855(9)| 0.2368(12)| 0.0730      | 1.0000    |      |
| C21  | C    | 0.3226(4)| 0.9874(8)| 0.3494(12)| 0.0671      | 1.0000    |      |
| C22  | C    | 0.2378(3)| 0.8923(7)| 0.0615(9) | 0.1048      | 1.0000    |      |
| C23  | C    | 0.4345(3)| 0.6281(7)| 0.6808(8) | 0.0799      | 1.0000    |      |
| S24  | S    | 0.92736(9)| 1.09072(19)| 0.9319(2)| 0.0849    | 1.0000    |      |
| C25  | C    | 0.9481(4)| 1.1701(9)| 1.0574(9) | 0.0671      | 1.0000    |      |
| N26  | N    | 0.9295(3)| 1.2657(8)| 1.0827(7)| 0.0770      | 1.0000    |      |
| C27  | C    | 0.8895(5)| 1.3151(7)| 1.0099(14)| 0.0690     | 1.0000    |      |
| C28  | C    | 0.8483(6)| 1.3280(8)| 1.0788(10)| 0.0853      | 1.0000    |      |
| C29  | C    | 0.8090(5)| 1.3761(9)| 1.0161(17)| 0.0967      | 1.0000    |      |
| C30  | C    | 0.8110(4)| 1.4112(8)| 0.8852(18)| 0.0923      | 1.0000    |      |
| C31  | C    | 0.8513(6)| 1.3992(8)| 0.8165(10)| 0.0938      | 1.0000    |      |
| C32  | C    | 0.8911(4)| 1.3523(9)| 0.8805(13)| 0.0858      | 1.0000    |      |
| N33  | N    | 0.9851(3)| 1.1425(6)| 1.1463(10)| 0.0665      | 1.0000    |      |
| N34  | N    | 1.0052(3)| 1.2149(6)| 1.2341(11)| 0.0673      | 1.0000    |      |
| C35  | C    | 1.0341(4)| 1.1826(9)| 1.3327(12)| 0.0651      | 1.0000    |      |
| C36  | C    | 1.0437(3)| 1.0684(8)| 1.3636(8) | 0.0860      | 1.0000    |      |
| C37  | C    | 1.0572(4)| 1.2623(7)| 1.4134(14)| 0.0651      | 1.0000    |      |
| N38  | N    | 1.0868(4)| 1.2406(7)| 1.5111(11)| 0.0673      | 1.0000    |      |
| N39  | N    | 1.1084(3)| 1.3199(6)| 1.5786(10)| 0.0699      | 1.0000    |      |
| C40  | C    | 1.1429(4)| 1.2974(10)| 1.6816(11)| 0.0576    | 1.0000    |      |
| C41  | C    | 1.1646(4)| 1.3799(8)| 1.7513(13)| 0.0727      | 1.0000    |      |
| C42  | C    | 1.1991(4)| 1.3590(10)| 1.8513(12)| 0.0775    | 1.0000    |      |
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
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
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

_iucr_refine_instructions_details
;
#
# Punched on 22/09/20 at 12:02:33
#
#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)
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)
END
#
# Punched on 22/09/20 at 12:02:33
#
# 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-(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-(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
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