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ORIGINAL PAPER

Crystal Structure and Conformation Study of 3-Methyl-2, 6-bis (4-chlorophenyl) Piperidin-4-one Thiosemicarbazone Derivative

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Abstract Thiosemicarbazones (TSCs) are very versatile tridentate ligands having the ability to bind transition metal ions by bonding through sulfur and hydrazinic terminal nitrogen atoms. TSC also inhibits the enzyme ribonucliotide diphosphate reductase (RDR) which is involved in the synthesis of DNA precursors in the mammalian cells. One of the important heterocyclic thiosemicarbazones, the title compound (MBCPT) has been synthesized based on the Mannich reaction and it was characterized by X-ray diffraction methods. The crystallographic data of MBCPT are: $C_{19}H_{20}Cl_2N_4S$; M.W = 407.35, Monoclinic, space group, $P2_1/n$, with cell parameters a = 12.053(8) Å, b = 11.431(10) Å, c = 14.695(7) Å, $\beta = 95.82(4)^\circ$; V = 2014(2) $Å^3$, Z = 4, D_{cal} = 1.343 Mg/m^3, λ (Cu K_α) = 1.54184 Å. The ring piperine adopts chair conformation. The phenyl rings are oriented equatorially at 2 and 6th positions of the piperidine ring. Molecular packing can be viewed as a dimer held together by two N–H···S intermolecular hydrogen bonds. Molecules are tightly bound in the unit cell by C–H···N, N–H···S and N–H···N types inter and intra molecular hydrogen bonds.

Keywords Thiosemicarbazone · Heterocyclic · Conformation, hydrogen bond · Space group

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Introduction

The hydrazine group combines with aldehydes or ketones to generate the thiosemicarbazone derivatives, which have a wide range of biological activities such as antitumour [1], antimalarial [2], antileukemic properties [3], antiviral activity [4], antibacterial [5] and antifertility property [6] because of its reduction capability. The thiosemicarbazone moiety is planar and adopts an extended (E) conformation. This planar conformation is due to the extensive electron delocalization throughout the moiety. In general, the N, S-donor ligands of thiosemicarbazones and thiosemicarbazides are attributed to their ability to form metal chelates [7], non-linear optical properties [8] and their reductive capacities [9].

The total electron charges are smearing on the sulfur atom due to electron delocalization which helps in complexation with positively charged metal ions. Here, another electron rich hydrazinic N atom is also involved in the complex formation with metal ions. Both these S and N atoms chelate to metal ion of the biological molecule and believed to possess the pharmaceutical activity of this molecule. In addition to the biological properties, the TSCs possess second-order nonlinear optical (NLO) properties which have broad applications in opto-electronics, such as optical frequency conversion [10, 11] and optical parameter oscillator (OPO).

The relationship between the metal ions and cancer are intriguing and controversial. French and Freedlander [12] suggested that some antitumour agents also possess the ability to function as chelating agents. French and Blanz [1] prepared many TSC derivatives and found that all the tumor inhibitors potentially act as N–N–S type ligands. The biological activities of heterocyclic thiosemicarbazones (TSCs) depend on the parent aldehydes or ketones [13]. Pyridine-2-carbaldehyde thiosemicarbazone was the first heterocyclic compound (HFoTsc), reported to have carcinostatic

properties [14]. The mechanism of action of HFoTsc, is due to its ability to inhibit the biosynthesis of DNA, possibly by blocking the enzyme ribonucleotide reductase (RNR) or blocking base replication; creation of lesions in DNA strands by oxidative rupture [14, 15].

The skeletal ring of piperidine present in the molecules has many synthetic and natural medicaments [16]. Piperidine derivatives, namely, 4-piperidones are the synthetic intermediates in various alkaloids and pharmaceutical products [17]. This functionalized derivatives exhibit antidepressant [18], antiarrhythmic, tranquilizing and blood cholesterol lowering activities [19].

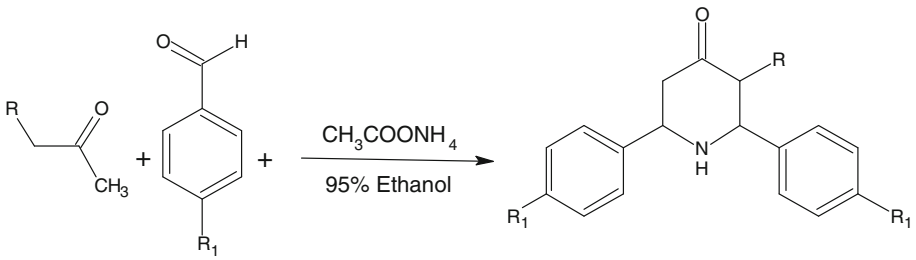
As part of the ongoing study on thiosemicarbazone derivatives, the title compound 3-Methyl-2, 6-bis (4-chlorophenyl) piperidin-4-one thiosemicarbazone (MBCPT) was prepared and characterized by X-ray crystallography methods to establish the molecular geometry and stereochemistry. The chemical diagram of the title compound (MBCPT) is shown in Scheme 1.

Experimental

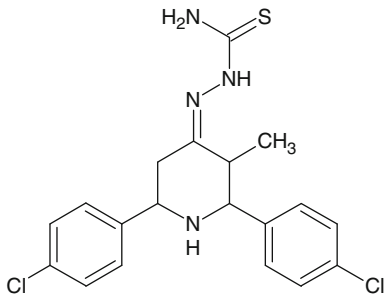
Preparation of MBCPT

Step-1: Synthesis of Piperidin-4-one

Piperidin-4-one was prepared by Mannich condensation reaction using respective aldehydes and ketones with ammonium acetate in the ratio of [2:1:1], respectively, in the medium of 95% ethanol, heated on a hot plate up to the boiling range and kept overnight [20]. The product piperidin-4-one was separated after 3 days and it was recrystallized by slow evaporation method in ethanol.



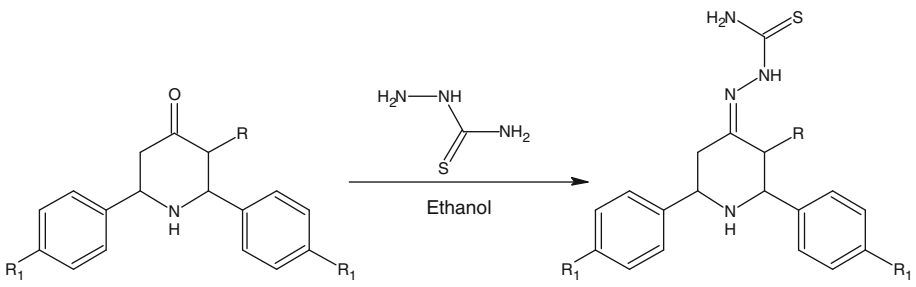
R= CH_3; R_1= Cl



Scheme 1 Chemical diagram of molecule MBCPT

Step-2: Synthesis of Piperidin-4-one Thiosemicarbazones

The resulting product was treated with equimolar (1:1) quantity of thiosemicarbazide in the presence of a small amount of conc. HCl in pure ethanol in a water bath and refluxed for 2 h. The product was separated out and dried. Colorless crystals were grown by slow evaporation using acetonitrile as solvent. Good quality crystal was chosen for structural studies.



R= CH_3; R_1= Cl

X-ray Data Collection and Reduction

A prismatic crystal of MBCPT was mounted on a glass fiber and used for data collection. Cell parameters and an orientation matrix for data collection were obtained by least-squares refinement of the diffraction data from 25 reflections in an ENRAF–NONIUS CAD4 automatic diffractometer [21]. Data were collected at 293(2) K using Cu K_α radiation ($\lambda = 1.54184$ Å) and the data reduction was carried out by XCAD4 [22] program. Out of 4045 reflections collected, 3856 reflections with $I \geq 2\sigma(I)$ were used for structure solution and refinement. The intensity data were corrected for Lorentz and polarization absorption effects.

Structure Solution and Refinement

The structure was solved by direct-methods using the program *SHELXS97* [23], which revealed the position of all non-hydrogen atoms, and refined on F^2 by a full-matrix least squares procedure using *SHELXL97* [23]. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were allowed to ride over their parent atoms. The final cycle of refinement converged to R = 0.0824 and $wR_2 = 0.2249$ for the observed reflections. The maximum and minimum heights in the final difference Fourier map were found to be 0.632 and −0.655 e Å^{-3}, respectively. Least-squares planes and asymmetry calculations were done using the program *PARST97* [24]. The thermal ellipsoid plot and packing were done using *ORTEP* [25] and *PLATON* [26]. Non-bonded interaction graphics were created using the program *PLATON* [26]. The crystallographic data and methods of data collection, solution and refinement are shown in Table 1. All other information about MBCPT structure is included in the deposited material (CCDC 740952), as a complete list of bond distances and angles.

Table 1 Crystal data and other relevant details for **MBCPT**

Parameters	MBCPT
CCDC	CCDC 740952
Empirical formula	$C_{19}H_{20}Cl_2N_4S$
Formula weight	407.35
Temperature	293(2) K
Wavelength	1.54184 Å (Cu K_α)
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a = 12.053(8) Å
	b = 11.431(10) Å
	c = 14.695(7) Å
	$\beta = 95.82(4)^\circ$
Volume	2014(2) Å^3
Z, Calculated density	4, 1.343 Mg/m^3
F(000)	848
Theta range for data collection	4.53 to 72.38°
Limiting indices	
0 <= h <= 14	
0 <= k <= 14	
−18 <= l <= 18	
Reflections collected/unique	4045/3856 [$R_{int} = 0.0467$]
Completeness to theta = 26.29	97.00%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3856/0/236
Goodness-of-fit on F^2	1.075
Final R-indices [$I > 2\sigma(I)$]	R1 = 0.0824, $wR_2 = 0.2249$
R-indices (all data)	R1 = 0.0922, $wR_2 = 0.2386$
Largest diff. peak and hole	0.632 and −0.655 e Å^{-3}

Results and Discussion

The perspective view of the molecule MBCPT is shown in Fig. 1. The bond lengths and bond angles for the non-hydrogen atoms of MBCPT is shown in Fig. 2a, b, respectively. The thiosemicarbazone (TSC) moiety is planar and oriented to the best plane of piperidine ring at an angle of 38.7(1)°. The S1 atom of MBCPT is *trans* to N7 and shows an extended (E) configuration. These zig-zag E configurations are supported extensively by N–H···N intra molecular of hydrogen bonds [27]. The bond lengths of TSC moiety show variations from their normal values and this may be due to the partial double bond

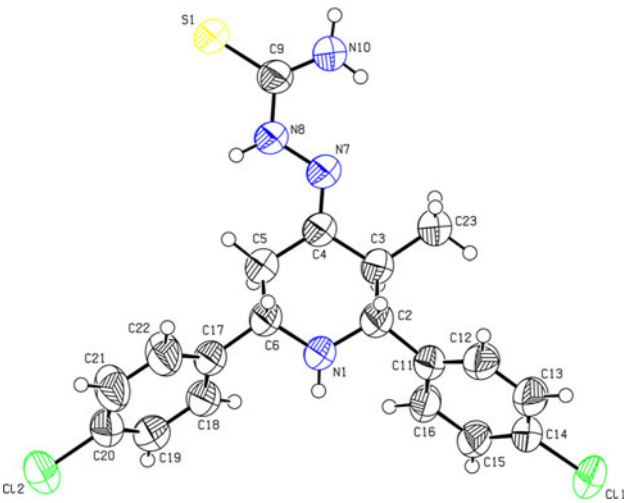


Fig. 1 ORTEP diagram of the molecule MBCPT showing the thermal ellipsoids at 30% probability level. Hydrogen atoms were removed for clarity

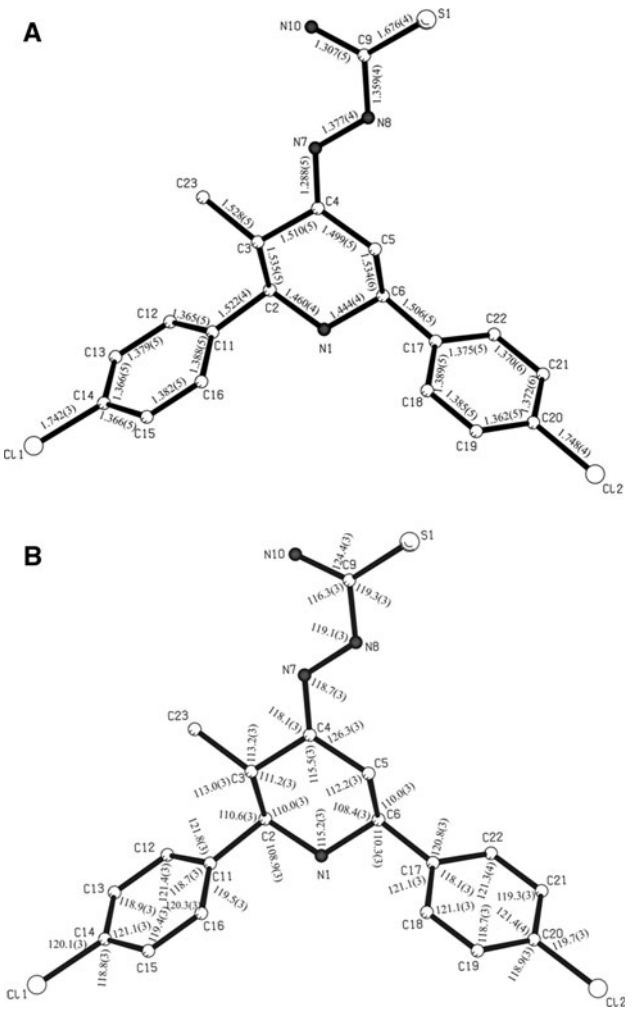


Fig. 2 **a** Bond lengths (Å) diagram of molecule MBCPT. **b** Bond angles (°) diagram of molecule **MBCPT**. Hydrogen atoms are removed for clarity

character (Scheme 2), a common feature observed in TSC moieties [N7–N8 = 1.377(4) Å; N8–C9 = 1.359(4) Å; C9–N10 = 1.307(5) Å; C9–S1 = 1.676(4) Å] for MBCPT [28]. The moiety adopts an extended conformation which is evidenced by the torsion angles given below.

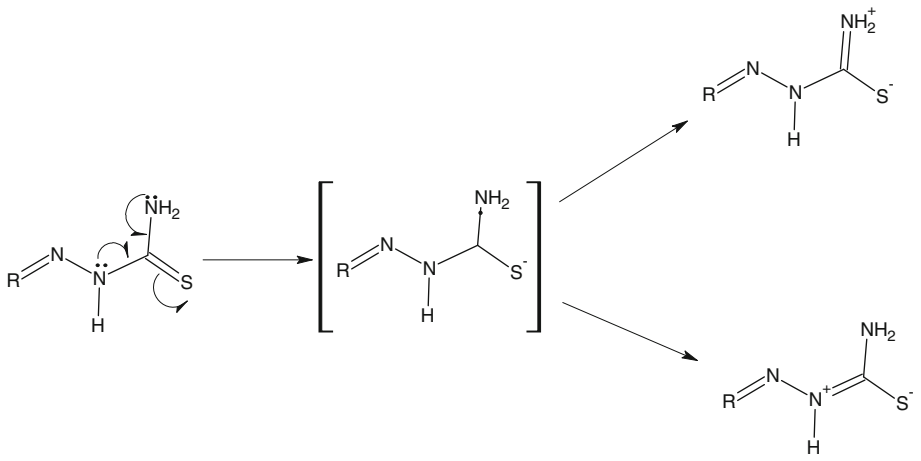
Conformation bonds	MBCPT Torsion angles (°)
C4–N7–N8–C9	−174.5(4)
N7–N8–C9–N10	−7.0(5)
N7–N8–C9–S1	174.1(3)

The extensive hetero π-electron delocalization is responsible for stable extended conformation (Scheme 2). In thiosemicarbazone, the negative charges on the terminal free amino group N10 atom increases while that on N7 decreases, as it is commonly observed for thiosemicarbazone moieties [29, 30]. It is well known that N10 does not take part either in metal complexation or in the reduction process [30] in the biological systems. Either one or both these processes are thought to be responsible for the biological activity of these groups [9]. Localization of electron density on N10 atom cannot be expected to have any effect on the biological activity of these compounds. It is believed that the atoms N7 and S play key roles in metal chelation and biological activities [30].

All the geometrical parameters and a least-squares plane calculation [24] strongly confirm that the piperidine ring adopts *chair* conformation. This conformation is supported by the torsion angles (Fig. 3) and asymmetry parameters also support the above fact. Based on the least-squares plane computed for the piperidine ring of MBCPT, the atoms N1 and C4 deviate by 0.641(3) and −0.536(4) Å on either side of the ring.

The phenyl rings A (atoms C11 through C16) and B (atoms C17 through C22) are substituted equatorially at 2nd and 6th positions of the piperidine ring in MBCPT and it is confirmed with corresponding orientation angles of

Scheme 2 Resonance structure of thiosemicarbazone moiety



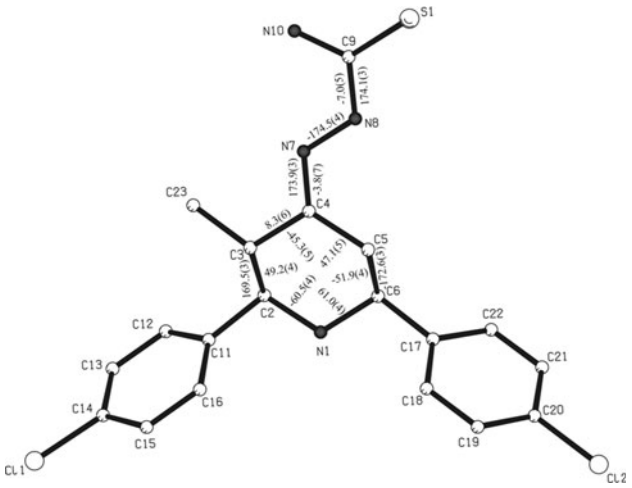


Fig. 3 Selected torsion angle diagram of molecule MBCPT. Hydrogen atoms are removed for clarity

phenyl rings with respect to the piperidine ring by 67.7(1) & 68.9(2)°, respectively. Both these phenyl rings are oriented at an angle of 47.0(1)° to each other. The methyl group at 3rd position of the piperidine ring is in equatorial orientation and the orientation angle of this group to the piperidine ring is 70.0(3)°. This equatorial substitution is also supported by the torsion angles [N1–C2–C3–C23=] 177.8(3) and [C23–C3–C4–C5=] 173.8(4)°.

Packing Features

The packing of the molecule MBCPT viewed down b-axis is shown in Fig. 4. C–H···N, N–H···N and N–H···S types of intra and intermolecular hydrogen bonds play vital roles

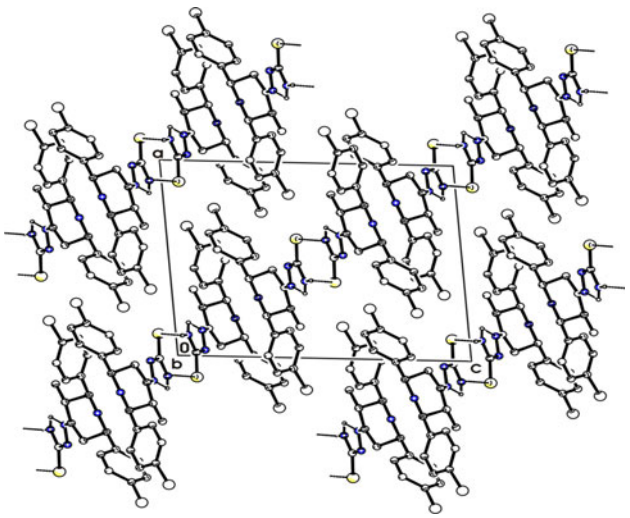


Fig. 4 Packing of the molecules MBCPT viewed down the b- axis. *Dashed lines* represent hydrogen bonds

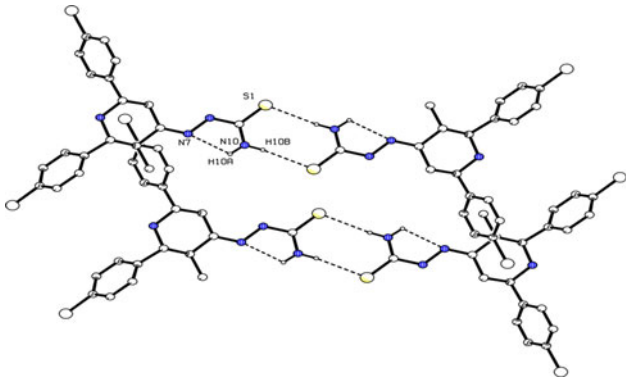


Fig. 5 Dimerized structure between the symmetry related molecules of **MBCPT**

Table 2 Hydrogen bondings and possible non-bonded interactions for MBCPT (°, Å)

D–H···A	d(D–H)	d(D···A)	d(H···A)	<D–H···A
C5–H5B···N8	0.970(4)	2.838(5)	2.458(3)	103.0(3)
N10–H10A···N7	0.860(3)	2.613(5)	2.247(3)	105.6(3)
C5–H5B···Cl2^{i}	0.970(4)	3.753(5)	2.889(2)	148.9(2)
N10–H10B···S1^{ii}	0.860(4)	3.427(4)	2.575(2)	171.0(2)
C19–H19···S1^{iii}	0.930(4)	3.825(4)	2.927(2)	162.6(2)

Equivalent positions: (i) $-x + 1/2 + 1$, $y + 1/2$, $-z + ½$, (ii) $-x + 2$, $-y + 1$, $-z$, (iii) x, y − 1, z

in crystal packing. Here N–H···N intramolecular hydrogen bond stabilizes the molecular conformation of the thiosemicarbazone moiety. Similar intramolecular hydrogen bonds have been observed in some of the thiosemicarbazones [27, 28]. The pair of intermolecular N–H···S hydrogen bonds across the center of inversion results in the formation of dimer (Fig. 5). Relevant details of all hydrogen bonds are given in Table 2.

Supplementary Material

Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Database Centre as supplementary publication no. CCDC740952. Copies of available material can be obtained, free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223336033; e-mail: deposit@ccdc.cam.ac.uk).

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