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تحضير وتوصيف وبنية الأشعة السينية ونشاط مضادات الأكسدة ودراسات الالتحام الجزيئي لـ 1-BENZOYL-3-[2-(3-BENZOYLTHIOUREIDO)-PHENYL]THIOUREA

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SYNTHESIS, CHARACTERIZATION, X-RAY STRUCTURE, ANTIOXIDANT ACTIVITY AND MOLECULAR DOCKING STUDIES OF 1-BENZOYL-3-[2-(3-BENZOYLTHIOUREIDO)-PHENYL]THIOUREA

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الملخص:

تم تحضير مشتق جديد ثنائي بنزويل ثايوريا وهو 1-Benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea من تفاعل بنزويل إيزوثيوسيانات مع أورثو- فينيلين ثنائي الأمين في الأسيتون كمذيب. تم تأكيد البنية الجزيئية لبنزويل ثنائي الثايوريا المحضرة بواسطة طيف الأشعة تحت الحمراء FT-IR والرنين النووي المغناطيسي (H^1 و C^{13}- NMR) تقنيات التحليل الطيفي كما تم إجراء حيود الأشعة السينية أحادية البلورة لتحديد البنية الجزيئية التي تشير إلى أن بنزويل ثنائي الثايوريا الجديدة المتبلورة في نظام البلورات ثلاثية الميل مع المجموعة الفراغية (P-1) مع أطوال المحاور البلورية a = 9.356(2) Å, b= 13.484(3) Å, c = 17.346(4) Å and α = 81.122(3) °, β = 77.234(3) °, γ = 82.009(3) and v = 2096.1(8)Å^3. أظهرت دراسات الخواص المضادة للأكسدة باستخدام طريقة DPPH أن المركب يظهر نشاطًا مضادًا للأكسدة قويًا بنسبة 85٪ تقريبًا. تم إجراء تحقيق الالتحام الجزيئي لتحديد التأثير المثبط ضد فيروس كورونا وكانت طاقة الارتباط المحسوبة بين البروتين الرئيسي 6LU7 وثنائي البنزويل ثايوريل هي -6.92 kcal/mol .

الكلمات الدالة: مشتقات البنزويل ثايوريا؛ الأشعة السينية؛ التحليل الطيفي؛ الالتحام الجزيئي.

Abstract:

A new bisbenzoyl thiourea derivative namely, 1-Benzoyl-3-[2-(3-benzoylthioureido)-phenyl] thiourea was prepared from the reaction of benzoylisothiocyanate with ortho-phenylenediamine in acetone as solvent. The molecular structural of the synthesized bisbenzoyl thiourea was confirmed by FT-IR and nuclear magnetic resonance (^{1}H and ^{13}C-NMR) spectroscopy techniques. Single Crystal X-ray diffraction (SCXRD) was also carried out to determine molecular structure which indicating that the new bisbenzoyl thiourea crystallized in the triclinic crystal system with space group of P-1 and the dimension of the unit cell are a = 9.356(2) Å, b= 13.484(3) Å, c = 17.346(4) Å and α = 81.122(3)° , β = 77.234(3)° , γ = 82.009(3) and v=

2096.1(8)Å^3. The antioxidant properties studies by using DPPH method showed that the compound exhibits a strong antioxidant activity of about 85%. The molecular docking investigation was carried out to determine the inhibitory effect of the synthesized bisbenzoyl thiourea against the COVID-19 coronavirus and the estimated binding energy between the 6LU7-main protease of the coronavirus and the bisbenzoyl thiourea ligand is -6.92 kcal/mol.

Keywords: Benzoyl thiourea derivatives; X-ray; Spectroscopy; Molecular docking.

1. Introduction:

The crystal structural of bisbenzoyl thiourea derivatives with two rims of carbonoyl thiourea moieties are relatively less reported comparable to the other structures of mono substituted benzoylthiourea derivatives depending of substitution on the nitrogen atoms of the thiourea moiety (Abosadiya, Yamin et al. 2007, Khawar Rauf, Badshah et al. 2007, Yamin, Yusof et al. 2013, Okuniewski, Rosiak et al. 2017, Abosadiya and Yamin 2019, Abosadiya 2020, Rosiak, Okuniewski et al. 2021). It is may due to the instability of the conformations of the two adjacent central thiourea moieties although the presence of two or more thiourea moieties was envisaged to be a better antibacterial activities(Arshad, Parveen et al. 2023). Most of biscabonoyl thiourea derivatives synthesized so far having aromatic benzene linkages (Ugur, Flörke et al. 2003, Dong, Yan et al. 2008, Woei Hung and Kassim 2010). Compounds containing thiourea moieties have been studied extensively not only because their unique structures and synthetic simplicity but also for their potential applications in biological activities such as antiviral(Ravichandran, Shalini et al. 2019), antibacterial(Abbas, El-Sharief et al. 2013), anticancer(Kirishnamaline, Magdaline et al. 2021) and antioxidant as well (Huong, Van Bay et al. 2021). The ability of central carbonyl thiourea moieties with more one donor atoms played an important role in the design of new potential drugs against diseases in recent years, by investigation of the molecular docking to examine the interactions between the thiourea derivatives as ligands with main protease protein such as coronavirus, For example, the target molecule of *N*-((2-acetylphenyl)carbamothioyl)benzamide with the main protease 6LU7 protein of coronavirus and it was shown that the target thiourea molecule might interact with the three active site Cys128, Lys137 and Gly138 amino acids by hydrogen bonds interactions with binding energy value -4.93 kcal/mol (Oztaslar and Arslan 2023). In the present study, 1-Benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea (**Figure 1**) has been successfully synthesized and fully characterized by FT-IR, nuclear magnetic resonance (^{1}H and ^{13}C-NMR) spectroscopy techniques and X-ray chemical crystallographic studies. To study the inhibitory effect of the new synthesized bisthiourea

compound against COVID-19 coronnavirus's primary protease, molecular docking investigations was carried out. Finally, the antioxidant activity was also investigated using the DPPH method.

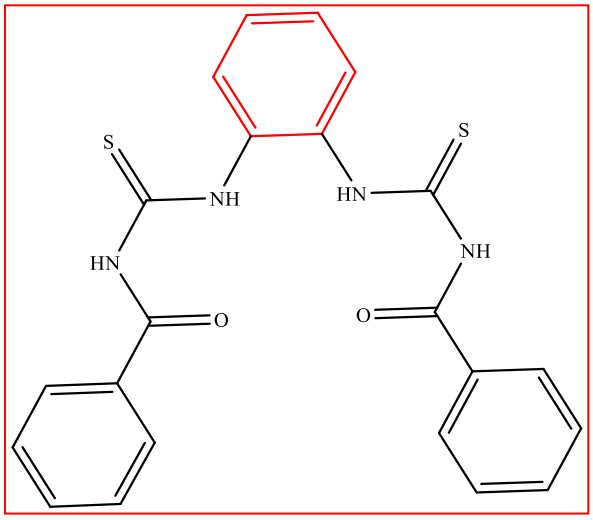


Figure. 1. The proposed structure of 1-Benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea

MATERIAL AND METHODS

Chemicals and Instruments

The compounds utilized in this work were used without further purification and are commercially available from Sigma-Aldrich and Acros Organics. The solvents were distilled before use. The microelemental analysis for CHNS-O was carried out by using Carlo Erba 1108. The melting points were determined by Electrothermal Digital Melting point apparatus model IA 9100 (0-400 ºC). FT-IR spectra were recorded using Perkin Elmer Spectrum GX spectrophotometer using KBr method in 400–4000cm^{-1} range, and 4cm^{-1} resolution. Electronic UV/vis spectra were recorded using the 1800-PC Shimadzu spectrophotometer in the range of 200-800 nm with the highest resolution. Nuclear Magnetic Resonances (NMR) for ^{1}H and ^{13}C experiments were performed with Joel ECP 400MHz in d_6-DMSO. The X-ray single crystal data were generated at room temperature from the Bruker D-QUEST diffractometer using graphite-monochromated Mo-Kα radiation (λ =0.71073Å). The SHELXL-2014 program was used to refine the crystal structures by direct methods (Sheldrick 2008).

Preparation of 1-Benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea

All preparation of thiourea derivatives were started with the addition of carbonoyl chloride and ammonium thiocyanate. In the most experiments the white precipitate of ammonium chloride was filtered and the filtrate was further reacted with selected amino compounds. The addition of ortho-phenylenediamine (0.015mol, 2.44gm) into the solution of benzoylisothiocyanate (0.03mol) in 25ml acetone causes the temperature to increase indicting an exothermic reaction. The yellow precipitate was formed after the solution was stirred for about 15 minutes. The yellow precipitate was washed with cold distilled water and dried under the vacuum. The product was recrystallized from DMSO. The title compound was obtained as colorless crystalline 82% yield after recrystallization. Mp 421-422 K. IR (KBr pellets) υ/cm^{-1}: 3416.43 (N-H), 1674.90 (C=O), 1341.98 (C-N), 751.05 (C=S); ^{1}H NMR (400MHz; DMSO) δ_H, 7.43 (3H, m, Ar-H), 7.58 (1H, m, Ar-H), 7.88 (3H, d, j=6.96, Ar-H) 11.67 (1H, s, N*H*), 12.49 (1H, s, N*H*); ^{13}C NMR (150 MHz; DMSO) δ_C, 126.9 (2 x *C*H$_{Ar}$), 127.4 (2 x *C*H$_{Ar}$), 128.6 (4 x *C*H$_{Ar}$), 128.8 (4 x *C*H$_{Ar}$), 132.1 (2 x *C*H$_{Ar}$), 133.4 (2 x *C*$_{Ar}$), 133.6 (2 x NH*C*$_{Ar}$), 168.6 (2 x *C*=O), 180.6 (2 x *C*=S). Analysis calculated for $C_{22}H_{18}N_4O_2S_2$: Experiment values; C = 59.81, H = 4.12, N=12.02, S = 15.41 % and calculated values, C = 60.81, H = 4.18, N=12.89, S = 14.76%.

Antioxidant Activity Studies

The concentration of 15mg/5mL from 1-Benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea was prepared in dimethyl sulfoxide solvent. The free radical stock solution of diphenylpicrylhydrazyl (DPPH, 97% purity) was also prepared daily at a concentration of 0.4gm in 1000mL in methanol solvent and protected from light (A_{DPPH} = 1.012). 1mL DPPH solution was mixed with 100µL from the stock solution of the new synthesized bisbenzoylthiourea compound. The mixture was shaken well and kept in the dark at room temperature for 2 hours. The absorbance of the mixture was recorded at 517nm using a spectrophotometer (A_{Sample} = 0.152). The percentage reduction of the DPPH was calculated using **Equation 1**:

DPPH Scavenging activity (%) = $[(A_{DPPH} - A_{Sample})/(A_{DPPH})] \times 100$ (**1**)

Where: A_{DPPH} is the absorbance of 2,2-diphenyl-1-picrylhydrazyl (DPPH) and A_{Sample} is the absorbance of the mixture (DPPH and the synthesized compound).

1. Molecular Docking Studies

The molecular docking studies have been investigated by using AutoDockTools (ADT) and it was also used for the preparation of protein molecule(Morris, Huey et al. 2009). The protein structure of PDB ID = 6LU7 of the COVID-19 with an inhibitor N3 was downloaded from the protein data bank with resolution of 2.16 Å(Jin, Du et al. 2020). The X-ray geometrical coordinates of the main protease (M^{pro}) and its N3 ligand were extracted from the 6LU7 pdb file. The water molecules were also removed and the polar hydrogen atoms and Kollman charges were edited to the protein structure. The coordination geometry from the X-ray diffraction (Cif file) of the bisthiourea ligand 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea was used after converted to the pdb input file for molecular docking. The interactions and binding between protein and inhibitor ligand was visualized and analyzed by using the Biovia Discovery Studio 2020 software.

RESULTS AND DISCUSSION

Spectroscopic Studies

The CHNS-O microelemental analysis data of the precipitate is in agreement with the expected formula of 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea, the experiment values; C = 59.81, H = 4.12, N=12.02, S = 15.41% and calculated values, C = 60.81, H = 4.18, N=12.89, S = 14.76%. The infrared FTIR spectrum shows N–H stretching vibration at 3416.43cm^{-1}. The stretching frequencies at 1674.90 and 842.58cm^{-1} are due to C=O and C=S, respectively. The ^{1}H NMR spectrum of the new synthesized compound indicting the molecule has plan of asymmetry and showing signals for the chemical shifts of the amide and thiomide protons and appeared as a singlet at 11 and 12 ppm, respectively. The assigned chemical shifts of the aromatic protons are between 7.43 and 7.88ppm. The ^{13}C NMR spectrum shows the chemical shifts at 180.68 and 168.60ppm are due to C=S and C=O, respectively. The other aromatic carbon chemicals shifts appeared at the normal range between 126.9 to 133.6ppm.

The X-ray single crystal diffraction of title compound showed that the crystal system of the bisthiourea compound is a triclinic with space group of Pī and the unit cell dimension are, a = 9.356(2)Å, b= 13.484(3)Å, c = 17.346(4) Å and α = 81.122(3)° , β = 77.234(3)° , γ = 82.009(3)° and v= 2096.1(8)Å^3. The crystal and the refinement data are shown in **Table 1**

Table 1 Crystal data and structure refinement 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea

Crystal parameters	Data/values	
CCDC. deposition number	2403293	
Empirical formula	$C_{22}H_{18}N_4O_2S_2$	
Formula weight	434.52	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	Pī	
Unit cell dimensions	a = 9.356(2) Å	α = 81.122(3)°.
	b = 13.484(3) Å	β = 77.234(3)°.
	c = 17.346(4) Å	γ = 82.009(3)°.
Volume	2096.1(8) Å^3	
Z	4	
Density (calculated)	1.377 Mg/m^3	
Absorption coefficient	0.281 mm^{-1}	
F(000)	904	
Crystal size	0.50 x 0.32 x 0.30 mm^3	
Theta range for data collection	1.54 to 26.00°.	
Index ranges	-11<=h<=11, -16<=k<=15, -18<=l<=21	
Reflections collected	11768	
Independent reflections	8040 [R(int) = 0.0180]	
Completeness to theta	26.00° to 97.3 %	
Max. and min. transmission	0.9205 and 0.8723	
Refinement method	Full-matrix least-squaresm on F^2	
Data / restraints / parameters	8040 / 8 / 573	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.1015	
R indices (all data)	R1 = 0.0729, wR2 = 0.1126	
Largest diff. peak and hole	0.264 and -0.188 e.Å^{-3}	

The molecular structure of 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea is shown in the **Figure 2** with the numbering scheme and the asymmetric unit contains two crystallographically

independent molecules. There are two carbonoyl thiourea groups attached to the adjacent amino nitrogen atoms of the 1,2-diamino benzene. The structure molecule are analogous to the previously reported 1,2-bis(*N′*-benzoylthioureido)benzene except that the unit cell dimensions are different with one molecule only in the asymmetric unit (Thiam, Diop et al. 2008).

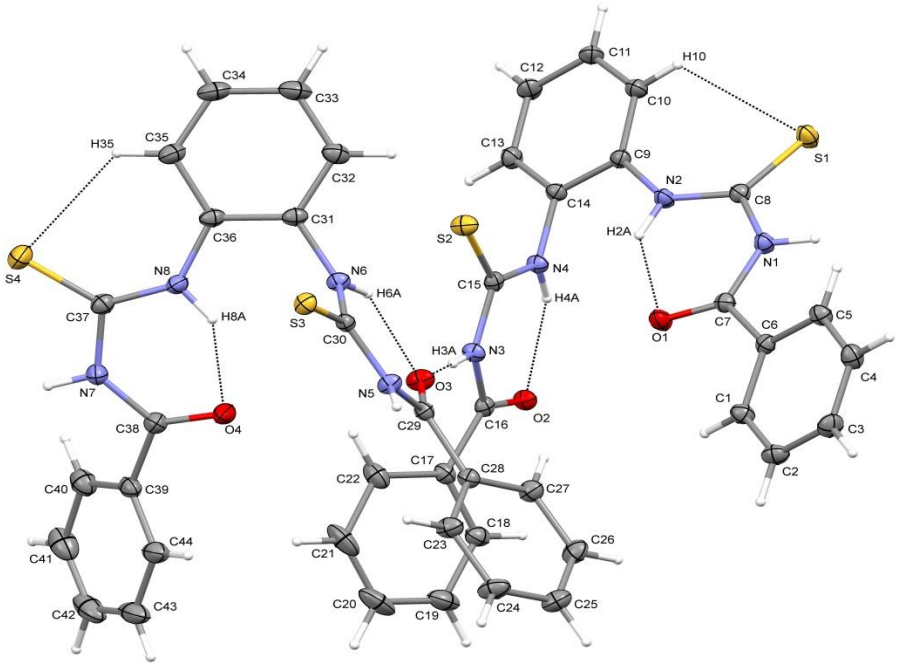


Figure.2. ORTEP diagram of 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea drawn at 50% probability displacement ellipsoids. The dashed line indicates the intramolecular hydrogen bonds.

The both molecules adopts *trans-cis* configuration with respect to the positions of the benzoyl and *N*-benzoyl-*N′*-Phenylthiourea groups, respectively, relative to the thiono S atoms across their C–N bonds. The central thiourea moieties (S1\N1\N2\C8), (S2\N3\N4\C15) and (S4\N7\N8\C37) are essentially planar with a maximum deviations of 0.014(2) Å for N2 atom from the plane (S1\N1\N2\C8). The carbonoyl thiourea moiety (S3\N5\N6\C30\O3\C29) is also essentially planar with a maximum deviation of 0.041(2) Å for O3 atom. In the first molecule, the central thiourea moieties (S1\N1\N2\C8) and (S2\N3\N4\C15) formed a dihedral angles of 27.42(10) and 78.28(11)° with the aromatic linkage ring (C9–C14), respectively. In the second molecule, the carbonoyl thiourea moiety (S3\N5\N6\C30\O3\C29) formed a dihedral angle of 79.63(10)° with benzene ring (C31–C36), whereas the other central thiourea moiety (S4\N7\N8\C37) makes a dihedral angles of 47.61(14) and 14.93(12)° with corresponding phenyl ring (C39–C44) and its aromatic linkage ring (C31–C36), respectively. The bond lengths and angles **Table 2** are in

normal ranges and comparable to those in 1,2-bis(*N′*-benzoylthioureido)benzene and 1-benzoyl-3-[4-(3-benzoylthioureido)-phenyl]thiourea (Thiam, Diop et al. 2008, Woei Hung and Kassim 2010).

Table 2. Selected bond lengths and angles (Å, °) of 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea

Bond	Length, Å	Bond	Angles,°
C8-S1	1.652(2)	N1-C8-S1	117.01(17)
C15-S2	1.657(2)	N2-C8-S1	128.54(18)
C30-S3	1.659(2)	N3-C15-S2	119.52(16)
C37-S4	1.648(3)	N4-C15-S2	124.68(17)
C7-O1	1.218(3)	N5-C30-S3	119.37(16)
C16-O2	1.233(2)	N6-C30-S3	124.10(17)
C29-O3	1.219(2)	N7-C37-S4	117.62(19)
C38-O4	1.219(3)	N8-C37-S4	129.32(19)
C7-N1	1.375(3)	O1-C7-N1	122.2(2)
C8-N2	1.325(3)	N2-C8-N1	114.44(19)
C14-N4	1.431(3)	O2-C16-N3	122.72(19)
C15-N3	1.388(3)	N4-C15-N3	115.80(19)
C30-N5	1.386(3)	O3-C29-N5	121.2(2)
C30-N6	1.340(3)	N6-C30-N5	116.52(19)
C37-N8	1.342(3)	O4-C38-N7	122.5(2)

As in most of the benzoyl thiourea derivatives, there are intramolecular hydrogen bonds N2—H2A····O1, N4—H4A····O2, N6—H6A····O3 and N8—H8A····O4 lead to the formation a pseudo-six membered rings *S*(6). However, the molecules in the structure are stabilized by C10—H10····S1 and C35—H35····S4 hydrogen bonds. An additional, the two molecules are connected by N3—H3A····O3 hydrogen bond with a contact distance of 1.98Å. In the crystal structure, the molecules are linked by N1—H1A····O2, N5—H5A····O2 and N7—H7A····S3 intermolecular hydrogen bonding, (**Table 3**), forming infinite two dimensional network along the **c** axis (**Figure 3**).

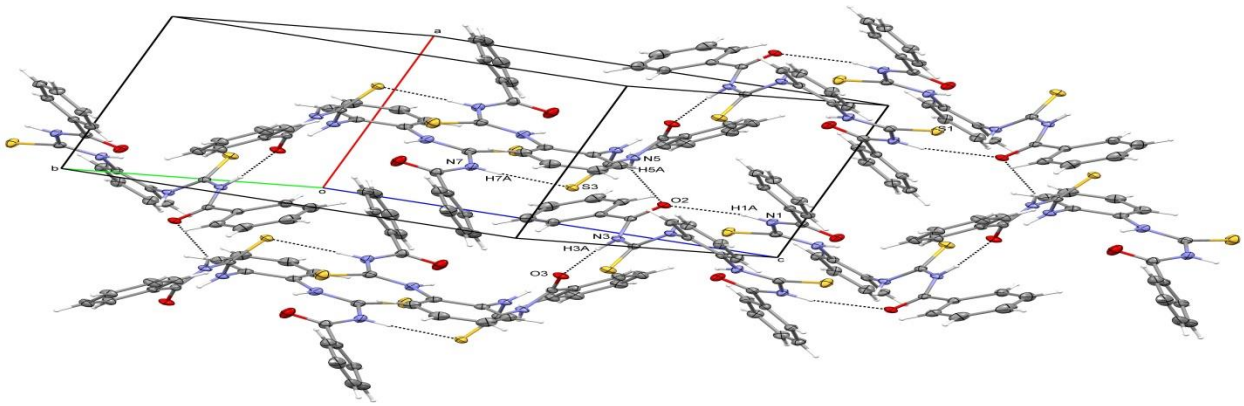


Figure. 3. Molecular packing of 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea viewed down the b axis. Dashed lined indicate intermolecular, N—H···O and N—H···S hydrogen bonds.

Table 3. Hydrogen geometric parameters (Å, °) of 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea

D-H···A	**D-H**	**H···A**	**D···A**	**D-H···A**
N2—H2A···O1	0.871(17)	1.92(2)	2.645(3)	139.2(19)
N4—H4A···O2	0.87(2)	1.97(2)	2.684(2)	138.5(18)
N6—H6A···O3	0.87(2)	1.94(2)	2.630(3)	135(2)
N8—H8A···O4	0.884(12)	1.886(18)	2.642(3)	142(2)
C10—H10···S1	0.93	2.66	3.212(3)	119
C35—H35···S4	0.93	2.59	3.253(3)	128
N3—H3A···O3	0.864(16)	1.981(15)	2.836(3)	170.6(18)
N1—H1A···O2^{i}	0.881(18)	2.323(18)	3.181(3)	165(2)
N5—H5A···O2^{ii}	0.866(19)	2.35(2)	3.027(3)	135.8(19)
N7—H7A···S3^{iii}	0.864(17)	2.763(16)	3.499(2)	144(2)

Symmetry codes: ^{i} 2-x,-y,2-z; ^{ii} *-1+x,y,z*; ^{iii} 1-x,1-y,1-z

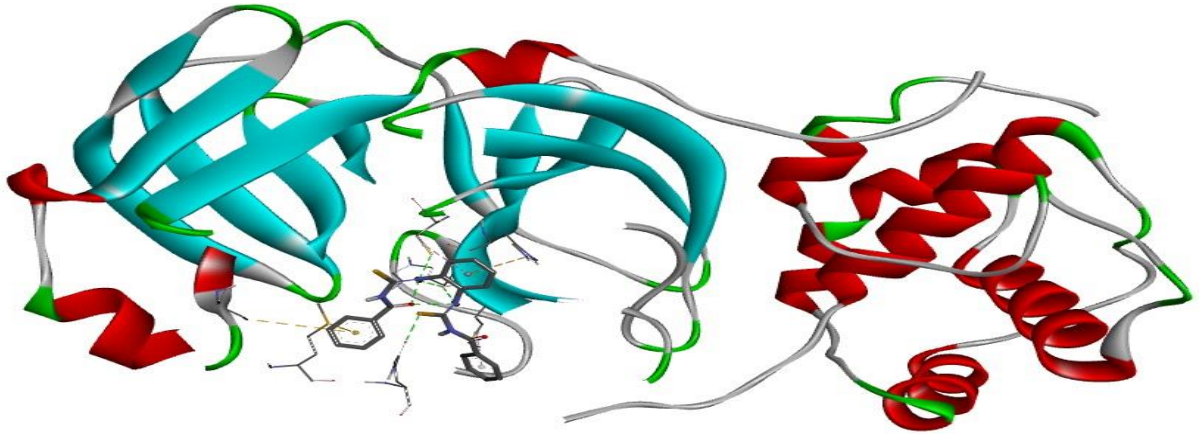
2. Molecular Docking Study

Molecular docking investigation of 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea against coronavirus disease was estimated by determining their binding affinities towards the target protein structure of ID, 6LU7 of the COVID-19. The estimated free binding energies value of the stable protein–ligand complex is -6.92 kcal/mol, relatively higher score comparable to the estimated free binding energies value of -4.93 kcal/mol for *N*-((2-Acetylphenyl)carbamo thioyl)benzamid (Oztaslar and Arslan 2023). The hydrogen bonds interactions between the title

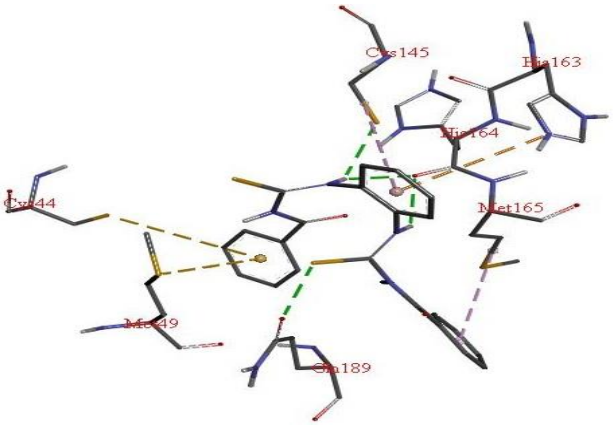
compound and the 6LU7 protein are a predictor of the stability and strength of the interaction. **Table 4** shows the number of amino acid residues interacting with inhibitor ligand into the binding site of M^{pro}. **Figure 4** displays receptor-ligand interaction on a 2D and 3D diagrams, respectively, with active site consists 7 amino acid residues interacted with bisthiourea ligand via hydrogen bonds as well Pi-cation and Pi-sulfur interactions.

Table 4. Estimated free binding energy, inhibition constant K_i, number of hydrogen bonds and interacted amino acid of 6LU7 Protein with new synthesized bisthiourea ligand.

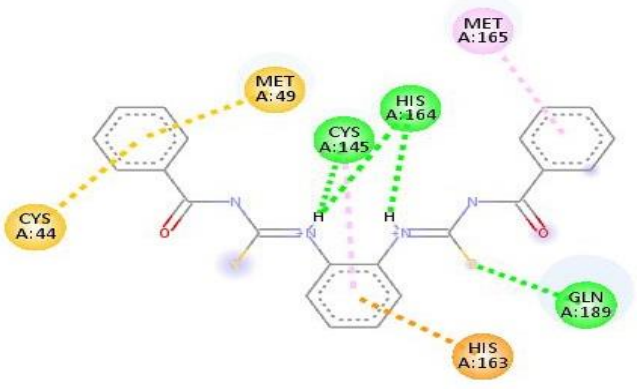
Protein (ID)	Bonding energy (kcal/mol)	Inhibition constant (k_i) (micromolar)	No of hydrogen bonds	Amino acid involved in interaction
6LU7	-6.92	8.42	4	Cys145, His164, Gln189 His163,Met165,Cys44 Met49,



(a)



(b)



(c)

Figure 4. The docking conformations of protein-ligand interaction **(a)** with **(b)** and **(c),** the three and two dimensional molecular structures showing the interactions between the ligand and the main protease (6LU7) of the coronavirus.

Antioxidant Evaluation

The antioxidant activity of 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea was 84.98% by using DPPH scavenging method, this percentage of antioxidant test indicates that the new synthesized bisthiourea has a good antioxidant properties compared to the other scavenging activity of the mono substituted and biscarbonoyl thiourea derivatives such as 1,3-diphenyl-2-thiourea compound of about 60% at the higher concentration of C_m = 0.80 mM (Huong, Van Bay et al. 2021). The presence of two thioamide H-N-C=S and amide groups on the molecular structure of the compound causes its higher antioxidant properties by donation of a hydrogen atom from the thioamide or amide groups to the free radical diphenylpicrylhydrazyl (DPPH) to form non-radical DPPH-H, and the color of the reaction mixture changes from purple to yellow when the DPPH radical is scavenged.

CONCLUSION

In this work, as a continuation of interest in the synthesis, chemical characterization and biological activities of the new bisthiourea derivatives, 1-benzoyl-3-[2-(3-benzoylthioureido)-phenyl]thiourea was synthesized and investigated experimentally by FTIR, ^{1}H and ^{13}C-NMR spectroscopies. Single crystal X-ray diffraction study reveals that the molecule crystallizes in the triclinic crystal system. The antioxidant activity was investigated by DPPH method indicting the synthesized bisthiourea compound has a good antioxidant activity of about 85%. The molecular docking study was also investigated and the estimated free binding energies value of the stable protein–ligand complex is -6.92 kcal/mol with 6LU7 protein of the COVID-19.

SUPPLEMENTARY MATERIAL

The structure of Crystallographic data for this paper has been deposited with the Cambridge Crystallographic Data Center, CCDC No **2403293**. These data can be obtained free of charge at the Cambridge Crystallographic Centre, www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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