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Research paper

Molecular docking, Hirshfeld surface analysis and spectroscopic investigations of 1-(adamantan-1-yl)-3-(4-fluorophenyl)thiourea: A potential bioactive agent

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HIGHLIGHTS

- The vibrational assignments of the title compound were obtained using VEDA 4.
- 3D structure is elucidate using XRD and confirmed by DFT calculations.
- DFT calculations at B3LYP allow a better reproduction of the experimental data.
- The molecular docking studies of the title compound may exhibit antibacterial activity.

ARTICLE INFO

Keywords: Adamantane Thiourea Vibrational spectroscopy Density functional theory Molecular docking

ABSTRACT

In this study, the optimized molecular structure, Hirshfeld surface analysis, vibrational frequencies and corresponding vibrational modes of a potential bioactive agent namely; 1-(adamantan-1-yl)-3-(4-fluorophenyl) thiourea were studied experimentally and theoretically. The theoretical calculations of the title compound were carried out using the density functional theory (DFT/B3LYP and DFT/M06-2X) quantum mechanical method with 6-311 + + G(d,p) basis set and Gaussian 09W program. The vibrational assignments of the title compound were obtained using VEDA 4 program by %10 precision with the help of potential energy distributions (PED). The experimental (FT-IR and Laser-Raman) spectra were recorded in solid phase at 4000–400 cm⁻¹ (FT-IR) and 4000–100 cm⁻¹ (Laser-Raman). Additionally, the experimental and theoretical¹H and ¹³C NMR chemical shifts in DMSO- d_6 and UV–Vis. Spectral analysis in DMF were studied theoretically and experimentally. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) analyses were performed. The molecular docking studies of the title compound revealed that it may exhibit antibacterial activity *via* inhibition of bacterial DNA gyrase PDB: 3U2D enzyme.

1. Introduction

The highly lipophilic adamantane cage constitutes the core pharmacophore of several drugs possessing chemotherapeutic activities [1–3]. Following the discovery of amantadine as efficient antiviral drug against influenza Viruses [4,5] and as antiparkinsonian [6] drug, adamantane derivatives attracted the attention of several drug manufacturers for the discovery of more potent and safer adamantane analogues as potential bioactive agents. As a result of this intensive search, several adamantane derivatives were developed and currently used as effective therapeutic agents. Among the major biological activities displayed by adamantane based derivatives, the antiviral [7–11], anticancer [12–14] antibacterial and antifungal [15–19], antimalarial [20,21] and central nervous activities [22,23] are the most

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important ones. On the other hand, thiourea derivatives were reported to exhibit marked chemotherapeutic activities as anticancer [24–26] and antimicrobial [27,28] activities. In addition, thiourea derivatives are frequently utilized are essential building blocks for the synthesis of biologically active compounds [29–31]. In contrary to the adamantanebased derivatives, the insertion of the polar thiourea moieties into biologically-active compounds greatly diminish the lipophilicity and consequently alter the biological activities. Thus, the title compound was synthesized as an adamantane-thiourea hybrid derivatives [32] with reasonable lipophilicity to be evaluated as potential bioactive agent and as a precursor for the synthesis of its related derivatives.

To the best of our knowledge, the experimental (FT-IR and Laser-Raman, NMR) spectral studies, structural and electronic properties, Hirshfeld surface and HOMO-LUMO analysis studies of the title molecule were not previously reported. All theoretical computations were defined based on the previous single crystal X-ray crystallography work [32] and DFT/B3LYP and DFT/M06-2X-two different methods were used. In addition, the interaction of the title molecule with DNA gyrase PDB: 3U2D receptor was investigated by docking process.

2. Experimental and computational methods details

2.1. Sample and instrumentation

The title compound was prepared in 88% yield *via* heating 1-adamantylamine and 4-fluorophenyl isothiocyanate in ethanol for four hours. The pure single crystals were obtained by slow evaporation of the compound solution in $EtOH/CHCl_3$ (1:1) at room temperature.

Fourier transform infrared (FT-IR) spectrum was recorded by Perkin-Elmer Spectrum Two FT-IR Spectrometer at room temperature between and 4000 cm⁻¹ and 400 cm⁻¹ and its resolution is 4 cm^{-1} . The Laser-Raman spectrum was recorded between 4000 cm^{-1} and 100 cm^{-1} by Renishaw Invia Raman microscope spectrophotometer. The excitation line at 785 nm has been taken from a diode laser. Both FT-IR and Laser-Raman measurement were done in solid phase.

2.2. Computational details

The primary atomic coordinates for geometry optimization were recorded using the Gauss View molecular visualization program [33] and Gaussian 09 W package program package [34]. The molecular structure of the title compound in the ground state (in gas phase) were optimized by DFT/B3LYP and M06-2X methods with 6-311 + + G(d,p) basis set level, and the optimized structure was used in the vibrational frequency calculations. For the vibrational frequency computations, the optimized structure was used and harmonic modes were multiplied by

0.9614 for DFT/B3LYP and 0.9489 for DFT/M06-2X in level in 6-311 + G(d,p) basis set. The calculated vibrational frequencies and their corresponding assignments were dissolved and clarified using the potential energy distribution (PED) analysis using VEDA 4 program [35,36].

The theoretical ¹H and ¹³C NMR chemical shift were computed at both the B3LYP/6-311 + +G(d,p) level and the M06-2X/6-311 + +G(d,p) one using IEFPCM model and GIAO method in DMSO solvent.

The HOMO-LUMO energy computations, their clouds in DMF solvent, the contributions to HOMOs and LUMOs were obtained with Chemissian software [37]. Additionally, in the next step to underpin HOMO-LUMO results, the theoretical UV–Vis. analyses were made using IEFPCM model and DMF solvent based on optimized molecular structures in DMF. The GaussSum 3.0 program was used to evaluate the results [38].

Lastly in this study, the molecular docking interactions of the title molecule and PDB: 3U2D receptor were investigated by AutoDock Vina program [39].

3. Results and discussion

3.1. Molecular geometric properties

In the title molecule ($C_{17}H_{21}FN_2S$), the mean planes of the benzene ring and thiourea component form a dihedral angle of 61.93° (9). The crystal structure of our compound is triclinic and its space group is PI. The crystal structure parameters are a = 6.4274 Å, b = 11.4727 Å, c = 11.5870 Å and $\alpha = 113.510^\circ$, $\beta = 94.721^\circ$, $\gamma = 94.837^\circ$ and its volume is 774.39 Å³. For the title compound, the molecular density was determined as 1.306 mg/m³ [32]. The optimized molecular structure with atom numbering of the title compound and experimental ORTEP structure at 50% probability level are shown in Fig. 1(a) and (b), respectively.

The optimized bond lengths, bond angles and dihedral angles of the title compound were calculated using the B3LYP and M06-2X methods with 6-311 + + G(d,p) basis set in gas phase. The theoretical and experimental structure parameters (bond lengths and bond angles) are shown in Table 1. The differences between experimental and calculated values are attributed to the phase situation, and this is normal and expected. The R^2 linear regression values indicated that the scaled B3LYP is more skillful than the scaled M06-2X.

The title molecule is composed of three groups, these are adamantane, thiourea and fluorophenyl groups. The important bond lengths and bond angles that need to be emphasized and interpreted. In the adamantane group, the C–C bond lengths were reported between 1.514 Å and 1.537 Å in the experimental study [32]. These bond lengths



Fig. 1. The optimized molecular structure (a) and an ORTEP plot (b) of the title molecule.

Experimental and calculated geometric parameters of the title compound.

Geometric parameters	Experimental values [29]	Calculated values		
Bond lengths (Å)		B3LYP/6-311 + + G(d,p)	M06-2X/6-311++G(d,p)	
C1-H2	0.930	1.084	1.084	
C1-C3	1.370	1.392	1.389	
C1-C7	1.381	1.400	1.395	
C3-H4	0.930	1.083	1.083	
C3–C5	1.350	1.386	1.383	
C5-F6	1.360	1.354	1.342	
C5–C8	1.364	1.386	1.384	
C7-C10	1.380	1.401	1.397	
C7-N33	1.420	1.420	1.419	
C8-H9	0.930	1.083	1.083	
C8-C10	1.380	1.393	1.389	
C10-H11	0.930	1.083	1.084	
C12-N33	1.350	1 382	1.377	
C12-N35	1 345	1 351	1 345	
C12 = 842	1.687	1.687	1.678	
C12 - 542	1.534	1.546	1.578	
C12 C22	1 522	1.540	1.539	
C12 N25	1.555	1.340	1.339	
C13 C17	1.4/3	1.400	1.4/4	
	1.535	1.545	1.538	
C14-C15	1.514	1.542	1.536	
C14-C27	1.533	1.541	1.535	
C14–C37	1.537	1.542	1.536	
C14-H40	0.980	1.095	1.094	
C15-H16	0.970	1.096	1.096	
C15-C17	1.526	1.542	1.536	
C15-H41	0.970	1.095	1.095	
C17-H18	0.980	1.095	1.094	
C17-C19	1.530	1.542	1.536	
C17-C30	1.524	1.540	1.535	
C19–H20	0.980	1.090	1.091	
C19-H21	0.970	1.096	1 096	
C22_H23	0.970	1.097	1.097	
C22_H24	0.970	1.099	1.009	
$C_{22} = 1124$	1 526	1.090	1.098	
C22-C25	0.020	1.005	1.002	
C25-H26	0.980	1.095	1.093	
C25-C27	1.52/	1.541	1.535	
C25-C30	1.514	1.541	1.535	
C27-H28	0.970	1.096	1.095	
C27-H29	0.970	1.096	1.096	
C30-H31	0.970	1.096	1.096	
C30-H32	0.970	1.096	1.095	
N33-H34	0.860	1.009	1.009	
N35-H36	0.860	1.011	1.011	
C37-H38	0.970	1.096	1.096	
C37-H39	0.970	1.090	1.09	
R^2		0.9944	0.9940	
Bond Angles (°)				
H2-C1-C3	120.7	119.9	120.3	
H2-C1-C7	119.7	119.4	119.2	
C3-C1-C7	120.5	120.7	120.5	
C1-C3-H4	120.7	121.5	121.8	
C1-C3-C5	115.5	118.6	118.5	
H4-C3-C5	120.7	119.9	119.6	
C3-C5-F6	119.4	118.9	118.9	
C3-C5-C8	100.7	122.1	122.2	
C3-C3-C8	122.7	122.1	122.3	
	11/.0	110.9	110./	
$C_1 = C_7 = C_1 O_2$	119.4	119.2	119.0	
CI-C/-N33	120.3	119.4	119.5	
C10-C7-N33	120.3	121.3	120.8	
С5-С8-Н9	120.7	119.8	119.6	
C5-C8-C10	120.2	118.8	118.6	
H9-C8-C10	119.9	121.4	121.7	
C7-C10-C8	120.2	120.5	120.3	
C7-C10-H11	119.9	119.6	119.3	
C8-C10-H11	119.9	119.9	120.4	
N33-C12-N35	115.4	115.5	115.2	
N33-C12-S42	119.6	117.7	118.1	
N35-C12-S42	125.0	126.9	126.8	
	123.0	140.7	120.0	
$C_{19} - C_{10} - C_{22}$	109.2	100.4	108.3	
C19-C13-N35	111.5	111.9	111.0	
C19-C13-C37	109.9	110.1	110.3	
C22-C13-N35	109.2	105.9	105.5	

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Table 1 (continued)

Geometric parameters	Experimental values [29]	Calculated values		
Bond lengths (Å)		B3LYP/6-311 + + G(d,p)	M06-2X/6-311 + + G(d,p)	
C22-C13-C37	108.3	108.4	108.4	
N35-C13-C37	112.5	111.9	112.0	
C15-C14-C27	109.9	109.5	109.6	
C15-C14-C37	109.7	109.5	109.5	
C15-C14-H40	109.4	109.7	109.6	
C27-C14-C37	109.1	109.6	109.7	
C27-C14-H40	109.9	109.7	109.7	
$C_{14} - C_{15} - H_{16}$	109.8	108.8	108.8	
C14-C15-C17	109.4	109.5	109.9	
C14-C15-H41	109.9	110.1	109.9	
H16-C15-C17	109.7	110.1	109.9	
H16-C15-H41	108.2	107.1	107.5	
C17-C15-H41	109.7	110.1	109.9	
C15-C17-H18	109.7	109.7	109.7	
C15-C17-H19	109.5	109.4	109.2	
C15-C17-C30	109.3	109.6	109.7	
H18-C17-C19	108.2	108.8	108.9	
H18-C17-C30	109.7	109.7	109.7	
C19-C17-C30	109.9	109.6	109.6	
C13-C19-C17	109.6	109.8	109.5	
$C_{13} = C_{19} = H_{20}$	100.8	109.5	109.5	
C13 - C19 - H21	109.8	109.1	108.8	
C17 - C19 - H20 C17 - C19 - H21	109.8	110.7	110.8	
$H_{20}-C_{19}-H_{21}$	109.8	107.5	107.9	
C13-C22-H23	109.2	109.5	109.2	
C13-C22-H24	109.7	109.5	109.3	
C13-C22-C25	110.0	110.4	110.4	
H23-C22-H24	108.2	107.5	107.9	
H23-C22-C25	109.3	109.9	110.1	
H24-C22-C25	109.3	109.9	109.9	
C22-C25-H26	109.3	108.8	108.9	
C22-C25-C27	109.4	109.4	109.4	
C22-C25-C30	109.6	109.5	109.3	
C22-C25-H26	109.3	109.8	109.9	
C22-C25-C30	109.6	109.8	109.9	
C27-C25-C30	109.8	109.5	109.5	
C14-C27-C25	108.8	109.3	109.3	
C14-C27-H28	109.9	110.4	110.2	
C14 - C27 - H29 C25 - C27 - H28	109.9	100.0	100.7	
C25-C27-H29	109.9	109.9	110.1	
H28-C27-H29	108.3	106.9	107.4	
C17-C30-C25	109.7	109.3	109.3	
C17-C30-H31	109.7	110.2	110.0	
C17-C30-H32	109.7	110.4	110.2	
C25-C30-H31	109.7	110.2	110.0	
C25-C30-H32	109.7	109.9	109.8	
H31-C30-H32	108.2	106.9	107.3	
C7-N33-C12	125.7	129.1	127.5	
C7–N33–H34	117.2	117.9	118.1	
C12-N33-H34	117.2	112.3	112.8	
G12-N35-G13	131.4	130.2	129.4	
C12-N35-H30	114.3	113.0	110.0	
C13 - C37 - C14	109.3	110.7	114.1	
C13-C37-H38	109.8	109.1	108.8	
C13-C37-H39	109.8	109.6	109.7	
C14-C37-H38	109.8	110.3	110.5	
C14-C37-H39	109.8	110.7	110.4	
H38-C37-H39	108.3	107.4	107.9	
R^2		0.9651	0.9618	
Dihedral Angles (°)				
H2-C1-C3-H4		0.5	0.6	
H2-C1-C3-C5		-178.6	- 178.5	
C7-C1-C3-H4		-179.6	- 179.6	
C7-C1-C3-C5	-1.4	1.2	1.2	
H2-C1-C7-C10		179.8	179.5	
H2-C1-C7-N33	2.1	-2.9	-2.3	
$C_{3} - C_{1} - C_{7} - C_{10}$	-2.1	-0.0	-0.3	
$C_3 - C_1 - C_7 - N_{33}$	- 178 2	1//.1	1//.9	
01-03-03 - F0	-1/0.3	1/7.4	1/3.3	
			(continued on next page)	

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Table 1 (continued)

Geometric parameters	Experimental values [29]	Calculated values	Calculated values	
Bond lengths (Å)		B3LYP/6-311 + + G(d,p)	M06-2X/6-311++G(d,p)	
C1-C3-C5-C8	3.3	-1.0	-0.8	
H4-C3-C5-F6		0.1	0.1	
H4-C3-C5-C8		179.8	179.9	
C3-C5-C8-H9		-178.7	- 178.9	
C3-C5-C8-C10	1.0	-0.4	-0.5	
F6-C5-C8-H9	-1.9	0.9	0.8	
F0 - C3 - C8 - C10	2.7	-14	-11	
C1 - C7 - C10 - H11	5.7	177 1	177 9	
N33-C7-C10-C8	-176.2	-178.5	-179.3	
N33-C7-C10-H11		-0.0	-0.1	
C1-C7-N33-C12	-117.2	123.2	116.0	
C1-C7-N33-H34		-46.5	- 48.6	
C10-C7-N33-C12	62.7	-59.6	-65.8	
C10-C7-N33-H34		130.6	129.5	
C5-C8-C10-C7	-1.9	1.6	1.5	
C5-C8-C10-H11		-176.9	-177.5	
H9 - C8 - C10 - C7		179.9	179.9	
N35-C12-N33-C7	-0.8	0.7	5.8	
N35-C12-N33-H34	0.0	170.9	171.1	
S42-C12-N33-C7	178.6	-178.8	-174.1	
S42-C12-N33-H34		-8.6	-8.8	
N33-C12-N35-C13	176.0	-178.8	-178.7	
N33-C12-N35-H36		-5.7	-6.3	
S42-C12-N35-C13	-3.4	0.7	1.2	
S42-C12-N35-H36		173.8	173.6	
C22-C13-C19-C17	-59.0	59.8	59.8	
C22-C13-C19-H20		-178.4	- 178.7	
C22-C13-C19-H21	174.0	-61.1	-61.0	
N35-C13-C19-C17	-1/4.9	61.0	1/5.8	
N35-C13-C19-H20		- 01.9	- 02.0	
C37 - C13 - C19 - C17	59.6	-58.5	-58.8	
C37-C13-C19-H20		63.2	62.6	
C37-C13-C19-H21		-179.4	-179.6	
C19-C13-C22-H23		179.1	178.9	
C19-C13-C22-H24		61.6	61.1	
C19-C13-C22-C25	59.3	-59.6	- 59.8	
N35-C13-C22-H23		58.8	58.9	
N35-C13-C22-H24	150.1	-58.8	-58.8	
N35-C13-C22-C25	179.1	- 179.9	- 179.9	
$C_{37} - C_{13} - C_{22} - H_{23}$		- 61.4	- 01.2	
C37 - C13 - C22 - 1124 C37 - C13 - C22 - C25	-60.4	- 179.0 59 7	60.0	
C19-C13-N35-C12	-64.7	62.4	63.4	
C19-C13-N35-H36		-110.7	-109.0	
C22-C13-N35-C12	177.0	-179.6	-178.8	
C22-C13-N35-H36		7.1	8.8	
C37-C13-N35-C12	59.3	-61.6	-61.0	
C37-C13-N35-H36		125.1	126.5	
C19-C13-C37-C14	-58.7	58.4	58.6	
C19 - C13 - C37 - H38		179.4	179.4	
$C_{19} - C_{13} - C_{37} - C_{139}$	60.5	- 63.2	-62.7	
$C_{22} - C_{13} - C_{37} - C_{14}$	00.5	61.0	60.8	
C22 - C13 - C37 - H39		178.4	178.6	
N35-C13-C37-C14	176.4	-176.4	-176.0	
N35-C13-C37-H38		-55.4	-55.2	
N35-C13-C37-H39		61.9	62.6	
C27-C14-C15-H16		61.3	61.3	
C27-C14-C15-H17		- 59.7	- 59.6	
C27-C14-C15-H41		179.1	179.5	
C37-C14-C15-H16	(0.0	-178.4	-178.3	
C37-C14-C15-C17	- 60.3	60.5	60.7	
U3/-U14-U15-H41 H40-C14-C15-H16		- 60.6 - 59.0	- 50.1	
H40-C14-C15-C17		- 39.0 179.9	- 39.0	
H40-C14-C15-H41		58.7	59 1	
C15-C14-C27-C25	- 59.5	60.0	60.0	
C15-C14-C27-H28		-60.9	-60.7	
C15-C14-C27-H29		-178.7	-178.9	
C37-C14-C27-C25	60.9	-60.2	-60.1	

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Geometric parameters	Experimental values [29]	Calculated values	
Bond lengths (Å)		B3LYP/6-311++G(d,p)	M06-2X/6-311++G(d,p)
C37-C14-C27-H28		178.9	179.2
C37-C14-C27-H29		61.0	60.9
H40-C14-C27-C25		-179.5	-179.6
H40-C14-C27-H28		59.5	59.7
H40-C14-C27-H29		-58.3	-58.6
C15-C14-C37-C13	59.0	-59.4	- 59.3
C15-C14-C37-H38		-179.6	-179.1
C15-C14-C37-H39		61.7	61.6
C27-C14-C37-C13	-61.4	60.8	60.9
C27-C14-C37-H38		-59.3	-58.9
C27-C14-C37-H39		-178.1	-178.2
H40-C14-C37-C13		-179.3	- 179.1
H40-C14-C37-H38		60.5	61.0
H40-C14-C37-H39		-58.2	-58.2
C14-C15-C17-H18		- 179.8	- 179.9
C14-C15-C17-H19	50.4	-60.5	-60.6
C14 - C15 - C17 - C30	- 59.4	59.7	59.5
HI6-CI5-CI7-HI8		59.1	59.0
HIG-CI5-CI7-HI9		1/8.4	1/8.3
H41 - C15 - C17 - C30		- 59.7	- 01.4
H41-C15-C17-H18		- 58.7	- 59.1
H41 - C15 - C17 - H19		170.1	170 6
H41 - C13 - C17 - C30	60.2	- 1/9.1	- 179.6
C15 - C17 - C19 - C13	-80.2	59.3 61 E	59.5
C15 - C17 - C19 - H20		-01.5	-01.3
$H_{18} - C_{17} - C_{19} - C_{12}$		179.0	179.9
H18-C17-C19-C13		59.2	59.4
H18-C17-C19-H21		-60.6	- 60.9
$C_{30} - C_{17} - C_{19} - C_{13}$	59.6	-60.8	-60.7
$C_{30} - C_{17} - C_{19} - C_{13}$	39.0	178.2	178 5
$C_{30} - C_{17} - C_{19} - H_{21}$		50 4	50 1
C15-C17-C30-C25	59.8	-60.0	-59.8
C15-C17-C30-H31	0,10	178.8	179 1
C15-C17-C30-H32		60.9	61.0
H18-C17-C30-C25		179.5	179.7
H18-C17-C30-H31		58.3	58.7
H18-C17-C30-H32		-59.5	- 59.4
C19-C17-C30-C25	- 59.8	60.1	60.1
C19-C17-C30-H31		-61.1	-60.9
C19-C17-C30-H32		-178.9	-179.0
C13-C22-C25-H26		179.9	179.9
C13-C22-C25-C27	60.8	-60.0	- 59.9
C13-C22-C25-C30	- 59.6	59.9	59.9
H23-C22-C25-H26		-59.1	- 59.3
H23-C22-C25-C27		60.9	60.8
H23-C22-C25-C30		-179.1	-179.4
H24-C22-C25-H26		59.0	59.3
H24-C22-C25-C27		179.0	179.5
H24-C22-C25-C30		-61.0	-60.7
C22-C25-C27-C14	-60.4	59.5	59.2
C22-C25-C27-H28		-179.3	-179.7
C22-C25-C27-H29		-61.7	-61.7
H26-C25-C27-C14		178.9	178.8
H26-C25-C27-H28		- 59.9	-60.2
H26-C25-C27-H29		57.7	57.8
C30-C25-C27-C14	59.9	-60.5	-60.5
C30-C25-C27-H28		60.8	60.5
C30-C25-C27-H29		178.3	178.5
C22-C25-C30-C17	59.6	- 59.4	- 59.4
C22-C25-C30-H31		61.7	61.5
C22-C25-C30-H32		179.3	179.5
H26-C25-C30-C17		-178.9	-178.9
H26-C25-C30-H31		- 57.7	-58.0
H26-C25-C30-H32		59.8	60.0
C27-C25-C30-C17	-60.6	60.4	60.4
C27-C25-C30-H31		-178.3	- 178.7
C27-C25-C30-H32		-60.8	-60.6
R^2		0.9995	0.9993



Fig. 2. The interaction forms in the structure.

were computed between 1.540 Å and 1.546 Å in B3LYP and 1.534 Å and 1.539 Å in M06-2X methods. Almutairi et al. reported the adamantane C–C bond lengths for a related adamantane derivative at 1.544 Å [40]. The adamantane C–H bond were reported at between 0.97 Å and 0.98 Å in experimental study [32], these bond lengths were computed at between 1.090 Å and 1.098 Å in B3LYP, and 1.090 Å and 1.098 Å in M06-2X methods which agrees with the previously reported values in the range 1.092–1.097 Å [40]. The adamantane bond angles were calculated at about 109° with both methods in accordance with the reported values [40].

In the thiourea moiety, the C12-S42, N33-H34 and N35-H36 bond lengths were computed as 1.687 Å /1.678 Å, 1.009 Å/1.009 Å and 1.011 Å/1.011 Å with B3LYP/M062X methods and 6-311 + + G(d,p)basis level, respectively. These bond lengths were reported at 1.68 Å, 1.37 Å and 1.37 Å, respectively for related thiourea molecule [41]. In another study, the C-S bond lengths of 1,3-diphenylthiourea were found to be 1.6636 Å with DFT/B3LYP method and 6-311 + + G(d,p)basis set [42]. Mary et al. [43] reported the C–S bond length of 1-(3chloro-4-fluorophenyl)-3-[3-(trifluoromethyl)phenyl]thiourea at 1.6770 Å/1.6853 Å (DFT/XRD). The N33-C12 and N35-C12 bond lengths were calculated at 1.382 Å/1.377 Å and 1.351 Å/1.345 Å in B3LYP/M06-2X methods and these bonds were reported at 1.350 Å and 1.345 Å in experimental study [32], respectively. The H34-N33-C12, S42-C12-N33, S42-C12-N35, N33-C12-N35 and H36-N35-C12 bond angles were computed at 112.3°/112.8°, 117.7°/118.1°, 126.9°/126.8°, 115.5°/115.2° and 115.6°/116.0° in B3LYP/M06-2X methods respectively, and these angles experimentally were found to be 117.2°, 119.6°, 125.04°, 115.4° and 114.3°, respectively. These results were consistent with previously reported values [42,43].

In the fluorophenyl group, the aromatic C–C bond lengths were calculated in the ranges 1.386 Å-1.401 Å/1.383 Å-1.397 Å in B3LYP/ M06-2X methods, and experimentally in the ranges 1.350 Å-1.381 Å. The aromatic DFT/XRD C–C bond lengths of 1-(3-chloro-4-

fluorophenyl)-3-[3-(trifluoromethyl)phenyl]thiourea molecule [43] were reported in the ranges 1.4035 Å-1.3887 Å/1.3895 Å-1.3765 Å. Additionally, the C5-F6 bond length was calculated at 1.354 Å/1.342 Å in B3LYP/M06-2X methods, and experimentally was determined as 1.360 Å. Meanwhile, the C–F bond was reported at 1.3392 Å/1.3474 Å in DFT/XRD [43]. Finally, the aromatic C–C–C bond angle values were calculated in the ranges 118.6°-122.1°/118.5°-122.3° in B3LYP/M06-2X methods, and experimentally in the ranges 115.5°-122.7°. The C3-C5-F6 and C8-C5-F6 angles were calculated at 118.9°/118.9° and 118.9°/118.7° in B3LYP/M06-2X methods, respectively. These calculated values were also consistent with the previously reported values [43].

3.2. Hirshfeld surface analysis

The Hirshfeld surface analysis of the title molecule was carried out using the Crystal Explorer 3.1 program [44] to explore the interactions of the crystal molecules. To visualize the Hirshfeld surface, dnorm: the normalized contact distance is used and formulized in Eq. (1).

$$d_{norm} = \frac{d_i - r_i^{\nu dw}}{r_i^{\nu dw}} + \frac{d_e - r_e^{\nu dw}}{r_e^{\nu dw}}$$
(1)

In here, d_e , d_i and r^{vwd} are described as follows: d_e is the distance from the Hirshfeld surface to the nearest nucleus outside the surface; secondly d_i is the corresponding distance to the nearest nucleus inside the surface; and as a thirdly r^{vwd} is a vdw (van der Waals) radius of the atom. Finally in Eq. (1), d_{norm} is a surface and visualized using a red, white, blue colour.

The results are shown as 3D Hirshfeld surfaces (d_{norm}) and 2D fingerprint histogram in Fig. 2 and Fig. 3, respectively. Fig. 2 shows the intermolecular contacts over the surface and the red colors indicate the intercontacts in the hydrogen bonds (and bond distances in hydrogen bond). The blue regions are contact sites longer than sum of van der



Waals radii with positive d_{norm} ; and white regions correspond to the inter-molecular distances close to van der Waals radii with d_{norm} equal to zero [45,46]. The d_{norm} values were found to be in the range of -0.2337 (red color) to 1.3609 (blue color) Å. In Fig. 3, the H-H interactions (with 61% the contribution of intercontacts-), F-H/H-F interactions (with 12.5% contribution), S-H/H-S interactions (with 12% contribution) and C-H/H-C interactions (with 11.6% contribution) were obtained as shown in Fig. 3(a)-(d), respectively, with included reciprocal interactions. Both Fig. 2 and Fig. 3 were obtained by using B3LYP/6-311 + +G(d,p).

3.3. Vibrational frequencies

The title molecule with 42 atoms has 120 vibrational modes. As can be seen from the optimized structure (Fig. 1) and output results, the title compound is in C₁ point group symmetry. Because of C₁ symmetry, all the vibrational modes are active in both IR and Raman spectra. In this section, the harmonic vibrational frequencies were computed by using both B3LYP and M06-2X method and 6-311 + + G(d,p) basis set in gas phase. The assignments of the calculated wavenumbers were determined as in terms of potential energy distribution (PED) using VEDA 4 program [35] and tabulated in Table 2. The calculated IR and Raman spectrum were compared with the experimental FT-IR and Laser-Raman spectra and for comparison were given Fig. 4(a and b) and Fig. 5 (a and b), respectively.

3.3.1. Adamantane cage vibrations

The adamantane moiety of the title molecule contains six CH₂ and three CH groups attached on cage skeleton of ten carbon atoms in sp³ hybridized state. Accordingly, the adamantyl group is expected to show the molecular vibrations corresponding mainly to scissoring, rocking, wagging, and twisting vibrations of the CH₂ groups, C-H stretching, C-H bending, in addition to the C-C stretching, C-C-C deformation and C-C-C-C torsion vibrations. The wavenumber of asymmetric stretching vibration is generally found to be higher than that of the symmetric one. In the present study, the six CH₂ asymmetric were computed at 2980/2974, 2977/2966, 2935/2931, 2928/2928, 2925/ 2923 and 2917/2912 cm⁻¹ in B3LYP/M06-2X methods and 6-311+ +G(d,p) basis level. These asymmetric modes were experimentally observed at 2974/2974, 2934/2926, 2907/2902 cm⁻¹ in FT-IR/Laser-Raman spectra. The symmetric CH₂ modes were calculated at 2901/ 2887 cm⁻¹, 2895/2886 cm⁻¹, 2891/2883 cm⁻¹, 2890/2880 cm⁻¹ and 2880/2864 cm⁻¹ in B3LYP/M06-2X methods and 6-311 + + G(d,p) basis level. These modes were observed at 2907/2902 $\rm cm^{-1}$ and 2859/ 2870 cm⁻¹ in FT-IR/Laser-Raman spectra. The symmetric CH₂ modes in adamantane group were reported at 2999, 2983, 2966, 2956 and 2955 cm^{-1} with DFT/B3LYP/6-311 + + G(d,p) method for a related adamantane derivative [40].

The CH₂ scissoring modes were calculated in the range 1443/ 1424 cm⁻¹-1427/1405 cm⁻¹ in B3LYP/M06-2X methods (five scissoring band: ν 28- ν 32). The wagging modes were calculated in the range 1338/1327–1292/1281 cm⁻¹ in B3LYP/M06-2X methods (six wagging

Observed and calculated vibrational frequencies of title compound with 6-311 + + G(d,p) basis set.

Vibration no.	Assignments		ed frequencies	Calculated frequencies in cm^{-1} (IR intensities/Raman activity)	
		FT-IR	Laser-Raman	B3LYP	M06-2X
V1	vNH (1 0 0) in the N33-H34	3390		3466	3456
V2	vNH (100) in the N35-H36	3370		3426	3415
2 Va	wCH (99) in the ring 1	3092		3081	3061
×3	wCH (98) in the ring1	3092		3080	3053
×4	wCH (92) in the ring1	3053	3069	3066	3039
5	wCH (82) in the ring1	3033	3069	3060	3039
6	vCH(81) asymmetric mode	2074	2074	2080	2074
7	oCH(8 E) asymmetric mode	2974	2974	2900	2974
8	CH(0.0) asymmetric mode	2974	2974	2977	2966
9	OCH(8.8) asymmetric mode	2934	2926	2935	2931
10	vCH(76) asymmetric mode	2934	2926	2928	2928
'11	vCH(69) asymmetric mode	2934	2926	2925	2923
12	vCH(73)	2934	2926	2922	2916
'13	υCH(7 4) asymmetric mode	2907	2902	2917	2912
14	vCH(83)	2907	2902	2915	2909
15	vCH(89)	2907	2902	2913	2909
16	vCH(93)	2907	2902	2904	2889
17	υCH(78) symmetric mode	2907	2902	2901	2887
18	υCH(97) symmetric mode			2895	2886
19	vCH(84) symmetric mode			2891	2883
 /20	vCH(90) symmetric mode			2890	2880
20	pCH(9.6) symmetric mode	2859	2870	2880	2864
21	$0C(55)$ in the ring 1 + $\delta HCC(18)$ in the ring 1	1610	1602	1580	1602
22	$\nabla C(6 A)$ in the ring $1 \pm S \square C(11)$ in the ring 1	1540	1540	1567	1502
23	SUNC (74) in the HIGE NOT (12) in the NOT (12) in the NOT (12)	1548	1540	1507	1509
/24	σ mNG (74) in the H30- N35-G12 + 0NG(15) in the N35-G12	1509	1502	1504	1503
25	$\delta HCC(45)$ in the ring1 + $vCC(12)$ in the ring1	1451	1444	1477	1483
26	δHCH(79)	1451	1444	1466	1452
27	δ HNC(53) in the H34-N33-C7 + vNC(11) in the N35-C12	1451	1444	1460	1446
28	δ HCH(76) scissoring mode	1425	1444	1443	1424
29	δ HCH(75) scissoring mode	1425	1444	1443	1420
30	δ HCH(82) scissoring mode	1425	1444	1439	1419
31	δ HCH(85) scissoring mode	1425	1416	1430	1407
32	δ HCH(85) scissoring mode	1425	1416	1427	1405
52 /00	$vCC(38)$ in the ring1 + $\delta HCC(28)$		1368	1387	1385
33	$\sigma HCCC (10) in H16-C15-C17-C19$	1350	1358	1345	1337
34	SHCC(4E)	1250	1250	1343	1337
35		1050	1336	1343	1333
36	NG(1.2) is the N25 G12 + NGGG (1.0) second as the	1359	1358	1338	1327
'37	vNC(13) in the N35-C12 + tHCCC (10) wagging mode	1359	1358	1325	1325
'38	τ HCCC (23) wagging mode + δ HCC(17) in H16-C15-C17	1301	1306	1323	1312
'39	$vNC(29)$ in the N35-C12 + δ HNC(15) in the H34-N33-C7	1301	1306	1319	1311
40	τHCCC (59) wagging mode	1301	1306	1300	1286
41	τ HCCC (28) wagging mode + δ HCC(11) inH16-C15-C17	1301	1306	1295	1284
42	τHCCC (28) wagging mode	1301	1287	1292	1281
43	δ HCC(27)		1284	1281	1280
44	vCC(51) in the ring1			1271	1267
45	δHCC(61) in H2-C1-C3	1248	1253	1267	1264
.5	δ HCC(24) H16-C15-C17 + pCC(11) C14-C37 + pCC(10) C22-C25	1248	1253	1262	1262
47	δHCC(31)	1248	1253	1260	1258
4/	$8 \text{HCC}(15) \pm \pi \text{HCCC}(12) \pm \pi \text{CC}(10) = \frac{14}{2} \text{CC}(12)$	1940	1252	1259	1200
48	$U_{1}U_{2}U_{1}U_{3} + U_{1}U_{2}U_{2}U_{3} + U_{2}U_{2}U_{1}U_{3} + U_{2}U_{2}U_{1}U_{3} + U_{2}U_{2}U_{1}U_{3} + U_{2}U_{2}U_{3}U_{3} + U_{2}U_{2}U_{3}U_{3} + U_{2}U_{2}U_{3}U_{3} + U_{2}U_{2}U_{3}U_{3} + U_{2}U_{2}U_{3} + U_{2}U_{3}U_{3} + U_{2}U_{3} + U_{$	1240	1255	1230	1244
49	$O_{11}(15) + T_{11}(15) + 0.00(10)$	1248	1200	1249	1243
50	THULU (24) + 0CC(15) C37-C13	1248	1253	1238	1231
'51	vCC(29) in the ring1 + $vNC(21)$ in the N33-C7 + $vFC(11)$ in the F6-C5	1213	1220	1213	1226
52	$vFC(35)$ in the F6-C5 + δ HCC(19) in the ring1 + δ CCC(10) + $vCC(10)$ in the	1213	1191	1188	1195
	ring				
/53	δHCC(24)	1169	1153	1169	1159
54	δHCC(39)	1156	1153	1165	1154
55	δ HCC(42) in the ring1 + vCC(16) in the ring1 + vNC(11) in the N33-C12	1138	1134	1131	1139
56	δ HCC(27) in the ring1 + vNC(23) in the N33-C12	1138	1134	1126	1114
55	pNC(27) in the N35-C13	1103	1100	1104	1110
37 50	$\delta HCC(23) + \tau HCCC(16)$	1008	1100	1092	1081
58	SHCC(20) + HCCC(20)	1000	1100	1092	1077
59	0HUU(39) + THUUU (20) -HUUU (15)	1098	1100	1009	1077
60		1098	1100	1080	10/0
61	τHCCC (17)	1098	1100	1079	1068
62	δ HCC(55) in the ring1 + vCC(24) in the ring	1050	1038	1075	1064
63	δCCC(11)	1050	1038	1069	1054
64	δ CCC(10)	1015	1000	1010	1022
65	υCC(35) C37-C13	1015	1000	1008	1021
66	vCC(16) C37-C13 + vCC(11) C22-C25	1015	1000	1007	1016
	$\delta CCC(61)$ in the ring 1 + $\delta HCC(22)$ in the ring 1	979	986	989	981
37	vCCCC (29) C19-C15-C30-C17	970	986	973	969
30	$\frac{1}{10000}$ (27) (17-010-017) $\frac{1}{10000}$ (15) (10 (15 (20 (17 + $\frac{2}{1000}$) (14 (27 (12)	057	957	052	051
69	γ_{0000} (10) (19-010-000-017 \pm 0000(10) 14-037-013	957	937 057	90Z	931
70	$\gamma CCCC(12) + \delta CCC(10)$	957	957	951	950

(continued on next page)

Table 2 (continued)

Vibration no.	ion no. Assignments Observed frequencies		d frequencies	Calculated frequencies in cm ⁻¹ (IR intensities/Raman activity)		
		FT-IR	Laser-Raman	B3LYP	M06-2X	
ν_{71}	τHCCN (90)	931	928	938	949	
V72	vCC(11) C14-C37	931	928	933	939	
ν_{73}	τ HCCN (57) in the ring1 + τ CCCC (12) in the ring1		928	919	927	
ν_{74}	vCC(2 4)		928	908	918	
ν_{75}	υCC(45)		928	905	913	
ν_{76}	τHCCC (51)	873	871	868	858	
ν_{77}	τ HCCC (41) + δ HCC(12)	873	871	864	855	
ν_{78}	τHCCC (25)	873	871	862	852	
V79	vCC(2 3) in the ring1	847	837	843	850	
ν_{80}	$vCC(1 8)$ in C1-C3 + τ HCCN (10)	816	823	826	835	
ν_{81}	τHCCN (45)	816	780	798	808	
ν_{82}	τHCCN (46)	816	780	794	803	
ν_{83}	vCC(39)	816	780	786	795	
ν_{84}	ν CC(16) + ν CC(14)	816		784	792	
ν ₈₅	$vFC(21)$ in the F6-C5 + δ CCC(16) in the ring1	772		757	759	
V86	vCC(72) C–C breathing mode in adamantane ring			741	751	
ν_{87}	τ CCCC (34) + γ NCCC (13)	697	694	696	699	
V88	τ HCCC (13) + ν SC(10) in the S42-C12			679	682	
V89	vSC(14) in the S42-C12	657	656	640	637	
V ₉₀	γ CCCC (14) + δ CCC(11)	631	637	630	625	
V ₉₁	$\delta CCC(10)$	631	637	628	621	
V92	δCCC(51)	631		622	615	
V93	γSNNC (79) S42-N35-N33-C12	609	598	603	603	
V94	$\delta CCC(10)$ in the ring1	547	541	544	544	
1/05	γ FCCC (14) + γ NCCC (10) + δ CCC(12) + δ SCN(12)	520	527	503	501	
V96	τHNCC (68)	481	484	484	486	
Voz	τ HNCC (12)	481	484	473	472	
Voe	τHNCC (57)	446	460	448	448	
1/00	τ HNCC (16) + τ HCCC (13)	446	460	441	443	
V100	δCCC(24) C19-C17-C30	428	412	429	423	
V101	δ FCC(29) F6-C5-C8 + δ CNC(11)	428	412	425	421	
V102	τ CCCC (73) in the ring1		412	412	408	
V102	\sqrt{FCCC} (12) + $\tau CCCC$ (10) + $\delta FCC(10)$			398	340	
V104	$\tau CCCN (17) + \delta CCC(13) + \tau CCCC (11)$		370	395	391	
V105	$\delta CCC(24) + \tau CCCN (14)$		370	392	386	
V106	$\delta \text{CCN}(19) + \tau \text{CCCC}(18) + \tau \text{HCCC}(10) + \tau \text{CCCN}(10)$		370	384	383	
V107	$\tau \text{NCCC} (12) + \delta \text{FCC}(10)$			350	349	
V108	δ FCC(26) in the F6-C5-C8 + τ NCCC (10)			348	348	
- 108 V100	$\delta CCC(25) + \tau HCCC (15)$		297	302	296	
V110	δ SCN(11) in S42-C12-N33 + ν NC(11) in N33-C7		278	276	283	
V111	$\tau CCCN (23) + \delta CCN(14)$		278	267	266	
- 111 V112	$\tau CCCN (12) + \delta CNC(10)$		230	260	260	
- 112 V113	δ SCN(41) in the S42-C12-N33 + δ CNC(12)		230	211	214	
V114	τ CCCC (31) in the ring1		173	149	151	
V115	$\delta CNC (28) + \tau CCCC (14)$ in the ring1			109	111	
V116	$\tau CNCC (15) + \tau CNCN (11)$			88	100	
V117	τ CNCC (13) + τ CNCN (10)			61	56	
- 11/ V110	$\tau CNCC (26) + \tau CNCN (16)$			45	46	
- 118	$\tau CNCN (12) + \tau CNCC (10)$			30	28	
- 119	$\tau CNCN (10) + \tau CNCC (10)$			22	12	
R ²				0.9997		
-						

v, stretching; δ, in-plane bending; γ, out-of-plane bending; τ, torsion. ^aPotential energy distribution (PED), less than 10% are not shown.

band: ν 36- ν 42). The CH₂ scissoring and wagging modes were reported in the range 1456–1416 cm⁻¹ and 1341–1287 cm⁻¹, respectively [40].

The adamantane C–C symmetric breathing mode was calculated at 741/751 cm⁻¹ in B3LYP/M06-2X methods. This mode was not detected in both FT-IR and Laser-Raman spectra. In the literature [40,47,48], this mode was calculated at 736, 743 and 729 cm⁻¹, respectively.

3.3.2. Thiourea group vibrations

The N-H stretching modes are generally observed in the range of $3500-3200 \text{ cm}^{-1}$ [49]. In the present study, we determined two important N-H mode in ν_1 and ν_2 . These modes were calculated at 3466/ 3456 cm⁻¹ and 3426/3415 cm⁻¹ in B3LYP/M06-2X methods with 100% PED contribution, and experimentally at 3390 cm⁻¹ and 3370 cm⁻¹ in the FT-IR spectrum. The N-H stretching modes of 1-(4-methoxyphenyl)-3-(pyridine-3-ylmethyl)thiourea were reported at

3570 cm⁻¹ and 3583 cm⁻¹ by B3LYP/6-311 + + G(d,p) level of theory [41]. Additionally, these assignments were also supported by the other related structures [42,43]. The out-of-plane τ HNCC modes were computed in the range 484/486–441/443 cm⁻¹ as four modes in the B3LYP/M06-2X methods (ν_{96} , ν_{97} , ν_{98} and ν_{99}). These modes were observed at 481/484 and 446/460 cm⁻¹ in FT-IR/Laser-Raman spectra.

The thiourea C12-N35 stretching vibrations were computed at $1504/1503 \text{ cm}^{-1}$, $1460/1446 \text{ cm}^{-1}$, $1325/1325 \text{ cm}^{-1}$ and $1319/1311 \text{ cm}^{-1}$ in the B3LYP/M06-2X methods (ν_{24} , ν_{27} , ν_{37} and ν_{39}). These modes were experimentally observed at $1509/1502 \text{ cm}^{-1}$, $1451/1444 \text{ cm}^{-1}$, $1359/1358 \text{ cm}^{-1}$ and $1301/1306 \text{ cm}^{-1}$ in FT-IR/Laser-Raman spectra. The N33-C7(ν_{51}), N33-C12 (ν_{55} and ν_{56}) and N35-C13 (ν_{57}) stretching modes were calculated at $1213/1226 \text{ cm}^{-1}$, $1131/139 \text{ cm}^{-1}$, $1126/1114 \text{ cm}^{-1}$ and $1104/1110 \text{ cm}^{-1}$ with B3LYP/M06-2X method and 6-311 + + G(d,p) basis set. These assignments were also



Fig. 4. The experimental (a) and theoretical (b) FT-IR spectra of the title compound.

supported by the literature [41–43].

The C-S stretching modes were reported in the region $930-670 \text{ cm}^{-1}$ [44]. In this study, the C–S stretching modes were calculated at 679/682 and $640/637 \text{ cm}^{-1}$ in the B3LYP/M06-2X methods. These modes were observed at 657/656 cm⁻¹ in FT-IR/Laser-Raman spectra. Mushtaque et al. [41] reported the thiourea C–S modes 1-(4-methoxyphenyl)-3-(pyridine-3-ylmethyl)thiourea of at 728.23 cm⁻¹ experimentally and theoretically calculated at 698 and 743 cm^{-1} . Meanwhile, Mary et al. [43] observed these modes at 887/ 892 cm^{-1} in the IR/Raman spectra, and theoretically at 889 cm^{-1} . The in-plane and out-of-plane or torsion modes of thiourea group could be controlled easily in Table 2. These C-S deformation modes are found at lower frequencies.

3.3.3. Fluorophenyl group vibrations

The aromatic C-F stretching mode generally observed at 1270–1100 cm⁻¹. In this study, we observed two C–F stretching modes calculated at 1213/1226 cm⁻¹ and 1188/1195 cm⁻¹ in B3LYP/M06-2X methods and 6-311 + + G(d,p) basis set with 11% and 35% PED contribution, respectively. These stretching modes were observed at $1213/1220 \text{ cm}^{-1}$ and $1213/1191 \text{ cm}^{-1}$ in FT-IR/Laser-Raman spectra. This C-F mode of 1-(3-chloro-4-fluorophenyl)-3-[3-(trifluoromethyl) phenyl]thiourea were reported at 1231 cm⁻¹ with 35% PED [43]. Furthermore, these C–F modes were reported at 1227, 1225 cm^{-1} in the IR spectrum and at 1239 and 1223 cm^{-1} theoretically [50,51].



Fig. 5. The experimental (a) and theoretical (b) Laser-Ra spectra of the title compound.

The phenyl C-H stretching usually appears in the region $3150-2900 \text{ cm}^{-1}$ regardless the nature of the aromatic substituents [52]. In this study, the phenyl C–H stretching was calculated at 3081/ 3061 cm⁻¹, 3080/3053 cm⁻¹, 3066/3039 cm⁻¹ and 3060/3036 cm⁻¹ in B3LYP/M06-2X methods and 6-311 + + G(d,p) basis set. These modes were observed at 3092 cm^{-1} (FT-IR), $3053/3069 \text{ cm}^{-1}$ (FT-IR/Laser-Raman) and $3044/3069 \text{ cm}^{-1}$ (FT-IR/Laser-Raman). The δ HCC in-plane bending modes were calculated at 1580/1602 cm⁻¹, 1567/ $1589 \text{ cm}^{-1}, 1477/1483 \text{ cm}^{-1}, 1387/1385 \text{ cm}^{-1}, 1267/1264 \text{ cm}^{-1}, 1131/1139 \text{ cm}^{-1}, 1126/1114 \text{ cm}^{-1}, 1075/1064 \text{ cm}^{-1} \text{ and } 989/1000 \text{ cm}^{-1}$ 981 cm^{-1} in B3LYP/M06-2X methods and 6-311 + + G(d,p) basis set. The C-H out-of-plane bending vibrations were observed in the region $650-900 \text{ cm}^{-1}$ in literature [53]. In this study, the out-of-plane modes were calculated at 938/949 cm⁻¹, 919/927 cm⁻¹, 843/850 cm⁻¹, $826/835 \text{ cm}^{-1}$, 798/808 cm⁻¹ and 794/803 cm⁻¹ in B3LYP/M06-2X methods and 6-311 + + G(d,p) basis set.

The fundamental vibrational assignments of the experimental and calculated frequencies (with B3LYP and M06-2X functionals) of the other modes excluding of the aforementioned modes (the remaining modes) were given in detailed in Table 2. These modes could be determined from Fig. 4 (a and b) and Fig. 5 (a and b), respectively.

3.4. ¹H and ¹³C NMR chemical shifts

The ¹H and ¹³C NMR chemical shift spectra of the title compound





The experimental and computed ¹H and ¹³C NMR isotropic chemical shifts (with respect to TMS, all values in ppm) of 1-(adamantan-1-yl)-3-(4-fluorophenyl) thiourea.

$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Atoms	$\delta_{ ext{exp.}}$	$\delta_{\mathrm{cal.}}$ (B3LYP)	$\delta_{\rm cal.}$ (M06-2X)	Atoms	$\delta_{ ext{exp.}}$	$\delta_{\rm cal.}$ (B3LYP)	$\delta_{\rm cal.}$ (M06-2X)
C3125.97-126.05123.95138.69H47.448.15C5160.33172.97184.07H97.418.18C7157.93140.33153.89H117.588.16C8151.9115.41120.09136.26H161.641.681.63C10136.28135.76152.29H411.791.82C12179.60189.79209.30H281.751.67C1353.7562.7159.71H291.661.84C1425.0537.2032.50H311.611.84C1536.4641.3341.16H321.711.62C1729.5037.3332.14H182.051.951.61C1841.3243.6443.7842.051.951.69C2241.3243.6443.78H202.233.533.55C2736.4642.3842.93H211.351.29C3036.4642.1542.74H231.671.35C3741.4243.0443.53H241.671.36C3741.4243.0443.53H241.641.30C3741.4243.0443.53H241.581.60C3741.425.542.74H241.681.60H3443.94H241.581.601.64C375.66.857.225.86	C1	136.28	135.80	152.77	H2	7.09–7.13 and 7.43	7.41	8.07
C5160.33172.97184.07H97.418.18C7157.93140.33153.89H117.588.18C8115.19-115.41123.09137.62H161.641.681.63C10136.28135.76152.29H411.791.82C12179.60189.79209.30H281.751.67C1353.7562.7159.71H291.761.94C1429.5037.2032.50H311.661.84C1536.4641.3341.16H321.711.62C1729.5037.3332.14H182.051.881.63C1941.3243.6443.78H261.881.63C2241.3249.3150.04H402.051.69C3036.4642.3842.93H211.351.29C3741.4243.0443.53H241.441.30C3741.4243.0443.53H241.441.30H391.881.661.591.58C3741.4243.0443.53H241.441.30H349.246.857.287.28H367.225.585.791.35	C3	125.97-126.05	123.95	138.69	H4		7.44	8.15
C7157.93140.33153.89H117.588.18 $C8$ 115.19-115-41123.09137.62H61.641.681.63 $C10$ 136.28135.76152.29H411.791.82 $C12$ 179.60189.79209.30H281.751.67 $C13$ 53.7562.7159.71H291.761.94 $C14$ 29.5037.2032.50H311.661.84 $C15$ 36.4641.3341.16H321.711.62 $C17$ 29.5037.3332.14H182.051.951.61 $C19$ 41.3249.3150.04H402.051.691.63 $C22$ 41.3249.3150.04H402.051.691.63 $C22$ 41.3249.3150.04H402.051.691.69 $C30$ 36.4642.3842.93H211.351.29 $C30$ 36.4642.1542.74H231.671.59 $C37$ 41.4243.0443.53H241.441.30 $H39$ $L84$ $L924$ $L84$ 1.681.60 $H39$ $L84$ $L924$ $L84$ 1.681.60 $L95$ $L95$ $L95$ $L924$ $L84$ 1.581.60 $L95$ $L95$ $L95$ $L924$ $L84$ 1.581.60 $L95$ $L95$ $L924$ $L924$ $L924$ $L924$ $L924$ $L924$ <	C5	160.33	172.97	184.07	H9		7.41	8.18
C8115.19-115-41123.09137.62H161.641.681.63 $C10$ 136.28135.76152.29H411.791.82 $C12$ 179.60189.7929.30H281.751.67 $C13$ 53.7562.7159.71H291.761.94 $C14$ 29.5037.2032.50H311.661.84 $C15$ 36.4641.3341.16H321.711.62 $C17$ 29.5037.3332.14H182.051.951.61 $C19$ 41.3243.6443.78H261.881.63 $C22$ 41.3249.3150.04H402.051.69 $C25$ 29.5037.4132.38H202.233.533.55 $C27$ 36.4642.3842.93H211.671.59 $C37$ 41.4243.0443.53H241.441.30 $H38$ $L53$ H241.581.60 $H39$ $H39$ $H34$ 9.246.857.28 $H36$ 7.225.585.791.66	C7	157.93	140.33	153.89	H11		7.58	8.18
C10136.28135.76152.29H411.791.82C12179.60189.79209.30H281.751.67C1353.7562.7159.71H291.761.94C1429.5037.2032.50H311.661.84C1536.4641.3341.66H321.711.62C1729.5037.3332.14H182.051.951.61C1941.3243.6443.78H261.881.63C2241.3249.3150.04H402.051.69C2529.5037.4132.38H202.233.533.55C2736.4642.3842.93H211.351.29C3036.4642.1542.74H231.671.59C3741.4243.0443.53H241.441.30FH381.581.601.581.60FH395.995.865.79	C8	115.19-115-41	123.09	137.62	H16	1.64	1.68	1.63
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	C10	136.28	135.76	152.29	H41		1.79	1.82
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	C12	179.60	189.79	209.30	H28		1.75	1.67
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	C13	53.75	62.71	59.71	H29		1.76	1.94
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	C14	29.50	37.20	32.50	H31		1.66	1.84
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	C15	36.46	41.33	41.16	H32		1.71	1.62
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	C17	29.50	37.33	32.14	H18	2.05	1.95	1.61
C22 41.32 49.31 50.04 H40 2.05 1.69 C25 29.50 37.41 32.38 H20 2.23 3.53 3.55 C27 36.46 42.38 42.93 H21 1.35 1.29 C30 36.46 42.15 42.74 H23 1.67 1.59 C37 41.42 43.04 43.53 H24 1.44 1.30 C37 41.42 43.04 43.53 H24 1.88 1.60 L4 1.30 H38 1.58 1.60 1.58 1.60 L58 L44 H34 9.24 6.85 7.28 H36 7.22 5.58 5.79	C19	41.32	43.64	43.78	H26		1.88	1.63
C25 29.50 37.41 32.38 H20 2.23 3.53 3.55 C27 36.46 42.38 42.93 H21 1.35 1.29 C30 36.46 42.15 42.74 H23 1.67 1.59 C37 41.42 43.04 43.53 H24 1.44 1.30 H38 1.58 1.60 1.59 1.58 1.60 H39 5.80 5.80 7.28 5.58 5.79	C22	41.32	49.31	50.04	H40		2.05	1.69
C27 36.46 42.38 42.93 H21 1.35 1.29 C30 36.46 42.15 42.74 H23 1.67 1.59 C37 41.42 43.04 43.53 H24 1.44 1.30 H38 1.58 1.60 1.60 1.60 1.60 H39 1.89 1.80 1.60 1.60 H39 1.80 1.60 1.60 1.60 H34 9.24 6.85 7.28 H36 7.22 5.58 5.79	C25	29.50	37.41	32.38	H20	2.23	3.53	3.55
C30 36.46 42.15 42.74 H23 1.67 1.59 C37 41.42 43.04 43.53 H24 1.44 1.30 H38 1.58 1.60 1.60 1.69 H39 3.80 4.04 1.60 1.60 H34 9.24 6.85 7.28 H36 7.22 5.58 5.79	C27	36.46	42.38	42.93	H21		1.35	1.29
C37 41.42 43.04 43.53 H24 1.44 1.30 H38 1.58 1.60 H39 3.80 4.04 H34 9.24 6.85 7.28 H36 7.22 5.58 5.79	C30	36.46	42.15	42.74	H23		1.67	1.59
H381.581.60H393.804.04H349.246.857.28H367.225.585.79	C37	41.42	43.04	43.53	H24		1.44	1.30
H393.804.04H349.246.857.28H367.225.585.79					H38		1.58	1.60
H349.246.857.28H367.225.585.79					H39		3.80	4.04
H36 7.22 5.58 5.79					H34	9.24	6.85	7.28
					H36	7.22	5.58	5.79

Table 4

The UV-Vis. spectral parameters and electronic transitions measured and computed in DMF of 1-(adamantan-1-yl)-3-(4-fluorophenyl)thiourea.

The UV–Vis. spectral parameters computed with the B3LYP/6-311 $+$ $+$ G(d,p) level				
Exp. λ (nm)	Transition	Calc. λ (nm)	Oscillator strength	Major contributions
272	$n \rightarrow \pi^{*}$	306.05	0.0009	$H \rightarrow L + 1$ (77%), $H \rightarrow L + 3$ (15%)
		281.24	0.0004	$H \rightarrow L (92\%)$
		275.74	0.0773	H-1 → L (88%)
		274.30	0.2054	$H-1 \rightarrow L + 1$ (88%)
		254.67	0.0061	$H \rightarrow L + 3$ (83%), $H \rightarrow L + 1$ (14%)
		247.69	0.0102	$H-2 \rightarrow L$ (74%), $H-2 \rightarrow L + 1$ (11%)
		242.89	0.0695	$H-2 \rightarrow L + 1$ (49%), $H \rightarrow L + 2$ (32%)
		241.56	0.1543	$H \rightarrow L + 2$ (53%), $H-2 \rightarrow L + 1$ (31%)
The UV-Vis. spects	ral parameters compu	ted with the M06-2X/6-3	$G_{11} + G(d,p)$ level	
Exp. λ (nm)	Transition	Calc. λ (nm)	Oscillator strength	Major contributions
272	$n \rightarrow \pi^{\star}$	280.74	0.0013	$H \rightarrow L + 1$ (37%), $H \rightarrow L + 8$ (14%), $H \rightarrow L + 13$ (10%)
		247.50	0.4070	$H-1 \to L + 1$ (50%)
		238.44	0.0253	H-2 \rightarrow L (21%), H-1 \rightarrow L (16%), H-2 \rightarrow L + 2 (13%)
		224.94	0.0170	$\mathrm{H} \rightarrow \mathrm{L} + 5$ (28%), $\mathrm{H} \rightarrow \mathrm{L} + 2$ (20%), $\mathrm{H} \rightarrow \mathrm{L}$ (19%)
		223.15	0.1343	$H-2 \rightarrow L + 1$ (23%), $H-1 \rightarrow L + 5$ (14%)
		220.10	0.0681	H-1 → L (20%), H-1 → L + 5 (17%), H-1 → L + 2 (16%), H-2 → L + 1 (15%)
		215.34	0.0089	$H \rightarrow L + 1$ (23%), $H \rightarrow L + 7$ (13%), $H \rightarrow L + 8$ (13%)
		212.86	0.0074	$H \rightarrow L$ (41%), $H \rightarrow L + 2$ (28%)

were recorded in DMSO- d_6 (Fig. 6 a and b). The ¹H and ¹³C NMR chemical shift were calculated at both the B3LYP/6-311 + +G(d,p) level and the M06-2X/6-311 + +G(d,p) using IEFPCM model and GIAO method in DMSO. The computed and experimental NMR chemical shifts are shown in Table 3.

The electronegativity, conjugation, inductive effect and nature of the substituents influence the electron distribution in the molecules and consequently its NMR chemical shifts [54]. In the ¹³C NMR spectrum, the thiourea carbon atom (C12) was experimentally assigned at δ 179.60 ppm, and computed at δ 189.79 ppm with B3LYP level and δ 209.30 ppm with M06-2X. The C5 and C7 carbon atoms attached to the electronegative fluorine and nitrogen atoms were normally observed at

slightly higher values. The recorded and calculated NMR chemical shifts for these carbons were found at δ 160.33 (exp.)/172.97 (B3LYP)/ 184.07 (M06-2X) and 157.93 (exp.)/140.33 (B3LYP)/153.89 (M06-2X) ppm, respectively. The chemical shifts of aromatic carbons usually observed in the range of δ 100–175 ppm, depending on the nature of the substituent groups attached to these carbons [55–57]. The aromatic carbons (C1, C3, C5, C7, C8 and C10) of the title molecule were shown as characteristic signals in the expected region. The C1, C3, C8 and C10 carbons were shown at δ 136.28, 125.95–126.05, 115.19–115.41 and 136.28 ppm, while they were computed at 135.80, 123.95, 123.09 and 135.76 ppm with B3LYP level and 152.77, 138.69, 137.62 and 152.29 ppm with M06-2X, respectively. The aliphatic carbons give



Fig. 7. The experimental (a) and theoretical (b) UV–Vis. spectra of the title compound.

NMR signals within the region up to about 60 ppm [54]. The adamantane group which is a cycloalkane compound showed the ¹³C NMR chemical shift signals at the interval of δ 28.24–49.09 ppm. The NMR chemical shifts for C13, C14, C15, C17, C19, C22, C25, C27, C30 and C37 carbons in this group were recorded in the range of δ 29.50–53.75 ppm, while they were computed at the intervals of δ 37.20–62.71 ppm with B3LYP level and 32.14–59.71 ppm with M06-2X. The adamantane ¹³C NMR chemical shifts are consistent with the previously reported data [58].

The aromatic ring protons give chemical shift signals in the region of δ 6.5–8.0 ppm [54–56]. The ¹H NMR spectrum showed the aromatic protons (H2, H4, H9 and H11) at δ 7.09–7.13 and 7.43 ppm. These protons were computed at the intervals of δ 7.41–7.58 ppm with B3LYP level and 8.07–8.18 ppm with M06-2X. The adamantane protons (15H) were experimentally detected at three different locations in the ¹H NMR spectrum. The H16, H28, H29, H31, H32 and H41 (6 protons) and H18, H26 and H40 (3 protons) were assigned at δ 1.64/1.66–1.79 (B3LYP)/1.62–1.94 (M06-2X) ppm and 2.05/1.88–2.05 (B3LYP)/1.61–1.69 (M06-2X) ppm, respectively. The H20, H21, H23, H24, H38 and H39 (6 protons), which are adjacent to the electronegative nitrogen atom were assigned at δ 2.23 ppm, and calculated at the intervals of δ

1.35–3.80 ppm with B3LYP level and δ 1.29–4.04 ppm with M06-2X. The thiourea NH protons (H34 and H36) were assigned at δ 9.24 and δ 7.22 ppm and they were calculated at δ 6.85 and 7.28 ppm with B3LYP level and δ 5.58 and 5.79 ppm with M06-2X. This discrepancy between NMR signals of these two NH protons could be attributed to the relative electron withdrawing effect of the aromatic ring compared to the aliphatic adamantane cage.

3.5. UV-Vis. spectroscopic analysis

The TD-DFT method for B3LYP and M06-2X functionals at the 6-311 + +G(d,p) basis set was used to obtain UV–Vis. spectroscopic parameter of the title compound. The theoretical UV–Vis. parameters such as wavelengths, oscillator strengths and excitation energies computed with IEFPCM solvent model (solvent = DMF) based on optimized molecular structures in DMF are listed in Table 4. The major contributions to the electronic transitions corresponded to the computed wavelengths were found by GaussSum 3.0 program [38]. The measured and simulated UV–Vis. spectra at the interval of 200–500 nm in DMF are depicted in Fig. 7 (a and b). An experimental electronic wavelength was arisen at 272 nm and it was ascribed to $n \rightarrow \pi^*$ electronic transition, and the obtained all theoretical values were given in detailed in Table 4. These values computed with B3LYP and M06-2X computational levels are the most intensity values obtained of oscillator strengths in both levels.

3.6. HOMO and LUMO analyses

The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are known as the frontier molecule orbitals (FMOs). They have an important role in chemical reactivity [59]. They provide great convenience to determine intramolecular charge transfers and molecular electronic transitions. Additionally, they can be used to compute many molecular electronic properties [60]. The HOMOs can be taken as donor groups filled by electrons, whereas the LUMOs are defined as acceptor groups unfilled by electrons [61].

The HOMOs (H and H-1) and LUMOs (L and L + 1) surfaces were simulated by .chk file of the optimized molecular structures in DMF with the B3LYP and M06-2X/6-311 + +G(d,p) levels. Fig. 8 (a and b) shows the HOMO-1, HOMO, LUMO and LUMO + 1 simulations and their calculated energies.

The HOMO-1, HOMO, LUMO, LUMO + 1, HOMO-LUMO and HOMO-1-LUMO + 1 energy values were calculated as -6.2428, -6.0734, -1.1249, -1.0966 4.9485 and 5.1462 eV for the B3LYP/6-311 + +G(d,p) level and -7.5966, -7.5038, -0.2316, -0.1695, 7.2722 and 7.4271 eV for the M06-2X/6-311 + +G(d,p) level, respectively. The HOMO and LUMO analyses were performed to verify the presence of the $n \rightarrow \pi^*$ electronic transition corresponding to the observed wavelength at 272 nm in the experimental UV–Vis. spectrum of the compound. In this connection, we can conclude from Fig. 8 (a and b) that the HOMO and HOMO-1 localizations obtained with both computational levels are mostly placed on lone pairs of sulfur atom of the thiourea group of the title molecule, whereas the LUMO and LUMO + 1 are mainly formed from π -type anti-bonding molecular orbitals of phenyl ring. These localizations on HOMOs and LUMOs confirm electronic transition mentioned in the compound.

3.7. Molecular docking studies

Protein (receptor) and ligand interactions play an important role in



Fig. 8. Calculated HOMO-LUMO plots of the title compound with B3LYP/6-311 + G(d,p) (a) and M06-2X (b)/6-311 + G(d,p).

the distribution mechanism, metabolism and transport of small molecules in biological systems and processes [62]. Therefore, the aim of this section is to research molecular docking between the potential bioactive agent 1-(adamantan-1-yl)-3-(4-fluorophenyl)-thiourea (ligand) and the protein DNA gyrase (PDB: 3U2D) receptor interaction mechanism. The researched mechanism was prepared in two step: firstly, we optimized the structure with B3LYP/6-311+ + method/ basis set for most stable situation, so ligand structure was converted into PDB format (Protein Data Bank). Later, the 3U2D-target or receptor structure was determined and obtained from SwissTargetPrediction [63] and Protein Data Bank (PDB) [64]. The X-ray crystal structure of protein DNA gyrase (3U2D) was studied by Eakin et al. [65]. Both ligand and receptor were arranged with Discover Studio Visualizer 4.0 (DSV 4.0) software [66] for docking study using AutoDock Vina program [39]. For docking process, the docking positions or grid box sizes were taken as $60 \times 74 \times 74 \text{ Å}^3$ and x, y, z centers were determined as

AutoDock Vina results of the binding affinity and RMSD values of different poses in 3U2D receptor of the title compound.

Mode	Affinity (kcal/mol)	Distance from best mode (Å)		
		RMSD 1.b.	RMSD u.b.	
1	-7.5	0.000	0.000	
2	-7.0	31.497	32.406	
3	-6.5	17.226	19.617	
4	-6.3	16.893	19.349	
5	-6.3	18.881	19.838	
6	-6.2	29.332	30.679	
7	-6.2	2.916	4.036	
8	-6.1	5.093	7.669	
9	-6.1	13.986	16.427	
10	-6.1	29.612	30.570	

18.276, -0.553 and 11.015, respectively. The general assumption is that for a good docking should be 2 Å according to the RMSD analysis [67]. In this section, 10 different modes were determined for ligand which is within the 3U2D receptor, and the obtained docking results are given in Table 5. The results shown in Table 5 revealed that the best docking pose was obtained with the binding energy of -7.5 kcal/mol. The amino acids ASP-81 which interacts with NH hydrogen atom (the distance is 2.24 Å), ASP-81 which interacts with CS sulfur atom (the distance is 3.70 Å), THR-173 which interacts with CS sulfur atom (the distance is 3.52 Å) and ASN-54 which interacts with NH hydrogen atom (the distance is 2.41 Å) as shown in Fig. 9.

In this figure, the surfaces around ligand (a) and 2D forms of molecular positions (b) could be seen. Additionally, between fluorophenyl ring and ILE-175/ILE-86 amino acids were observed as alkyl and π -alkyl interactions. These interactions also were observed between

adamantan-1-yl and ILE-102/ILE-86. Also, between NH and GLU-58/ASP-81 attractive charge interactions could be observed from the Fig. 9 (a) and (b). In this section finally we computed the inhibition constant (K_i) as 3.18024 μ M from K_i = exp(Δ G/RT) equation, where Δ G, R and T are the docking energy (binding free energy), gas constant (1.9872036 $\times 10^{-3}$ kcal/mol) and room temperature (298.15 K), respectively.

4. Conclusions

The vibrational analysis (FT-IR/Laser-Raman) of potential bioactive agent namely, 1-(adamantan-1-vl)-3-(4-fluorophenvl)thiourea was studied experimentally and theoretically using the DFT-B3LYP/M06-2X methods with 6-311 + + G(d,p) basis set. The wavenumbers were calculated theoretically using Gaussian 09 W software and the results were analyzed with VEDA 4 program. The comparison of the observed (experimental) and the calculated outcomes indicated that the scaled B3LYP method is more accurate than the M06-2X method for both the vibrational frequencies and the geometric parameters. Their sum of electronic and zero-point energies was calculated as -1267.924782 a.u and -1267.540659 a.u, respectively, these energy values also supported the above mentioned results. Later, the ¹H and ¹³C NMR chemical shift spectra recorded in DMSO- d_6 of the title compound and these NMR chemical shift were calculated at the B3LYP/M06-2X methods 6-311 + + G(d,p) basis level IEFPCM model and GIAO method in DMSO- d_6 . In addition, the molecular orbital energies and their distributions (HOMO-LUMO clouds) were obtained and experimental/ theoretical UV-Vis. analysis was performed to support the HOMO-LUMO analysis. Finally, the molecular docking outcomes showed that the title compound may exhibit antibacterial activity via inhibition of bacterial DNA gyrase-3U2D enzyme.



Fig. 9. The molecular docking results of the title compound with 3U2D protein, surfaces around ligand (a) and 2D forms (b).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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