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Research Article

SYNTHESIS AND DFT BASED QUANTUM CHEMICAL STUDIES OF 2-(3-BROMOPHENYL)-4-(4-BROMOPHENYL)-2,3-DIHYDRO-1H-1,5-BENZODIAZEPINE

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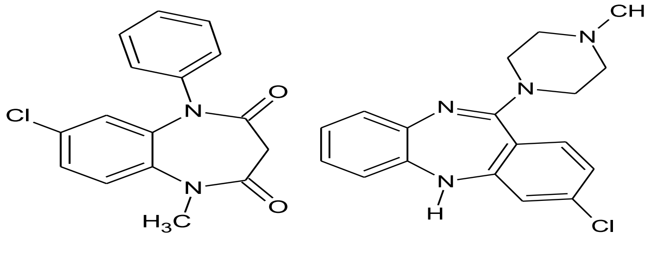
ABSTRACT

The 2-(3-bromophenyl)-4-(4-bromophenyl)-2,3-dihydro-1H-1,5-benzodiazepine has been synthesized by condensation of o-phenylenediamine with 3-(3-bromophenyl)-1-(4-bromophenyl)-prop-2-en-1-one (chalcone) in ethanol as a solvent. The structure of synthesized compound was characterized by using spectroscopic techniques. The optimized molecular geometry, vibrational spectra and geometrical parameters such as bond lengths, bond angles, mulliken atomic charges, dipole moment of synthesized compound are computed by Density Functional Theory (DFT) with employing B3LYP method at 6-311++G(d,p) basis set by using Gaussian-03 (W) package. The various thermochemical properties, global chemical reactivity descriptors, FMO analysis and molecular electrostatic potential (MEP) were also investigated at same level of theory. Theoretically computed vibrational frequencies of titled compound were compared with experimental FT-IR frequencies which show good agreement with experimental data.

Keywords: Benzodiazepine, vibrational spectra,DFT, B3LYP, Gaussian

1. INTRODUCTION

Chalcones are important starting materials for the synthesis of various heterocyclic compounds such as pyrazolines, pyrimidines, isoxazoles, thiazines, flavones, benzodiazepines etc. [1]. 1,5-benzodiazepines are bicyclic organic compounds having two nitrogen atoms at 1 and 5 position in seven member rings fused with benzene ring. Benzodiazepines are interesting heterocycles possessing high pharmacological, industrial and synthetic applications [2]. The 1,5-benzodiazepine nucleus is a privileged scaffold and core structure of various drugs which received great attention of medicinal research searching for new derivatives with enhanced pharmacological activities. 1,5 benzodiazepines show anticancer [3], anticonvulsant [4], anti-inflammatory[5], antimicrobial, antioxidant and antibacterial activities [6-7]. Some important drugs which contain benzodiazepine moieties are shown in Figure 1. Benzodiazepine derivatives are also commercially used as dyes for cyclic fibers. Moreover 1,5-benzodiazepines derivatives are valuable synthons for preparation of other fused ring compounds such as triazolo, oxazino or furanobenzodiazepines. Density functional theory (DFT) is the one of the popular method for computational study of compounds. The B3LYP method at 6-311++G(d,p) basis set exhibit good performance on geometry, vibrational frequencies and other theoretical properties of molecule [8-18]. This manuscript describes the synthesis and characterization of title compound along with computational investigation of the structural parameters, thermodynamic functions, vibrational frequencies and global chemical reactivity descriptors.



Clobazam Clozapine

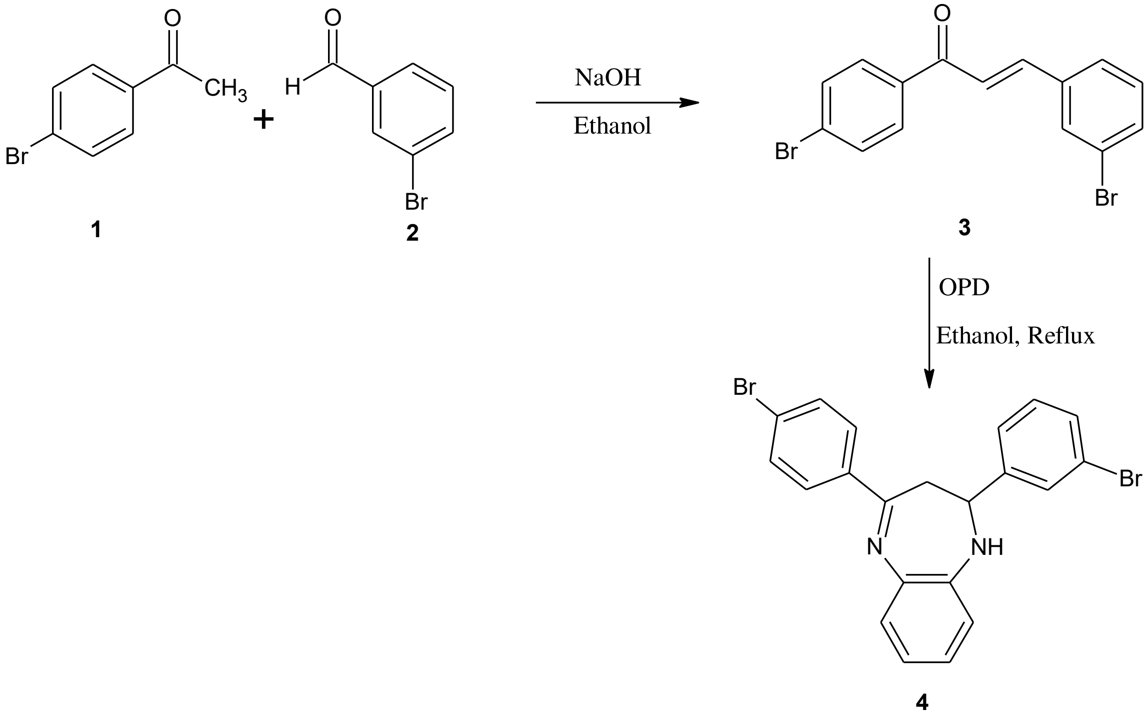
Fig. 1: Medicinally active compounds

2. MATERIAL AND METHODS

All the chemicals needed for synthesis were obtained from commercial source (AR grade with purity > 99%) and used without further purification. Melting point of the compound was determined in open capillary tube and is uncorrected, IR spectra was recorded on Shimadzu FT-IR spectrometer using potassium bromide pellets. 1H NMR was determined on BrukerAvance II 500 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard.

2.1. General procedure for the synthesis of chalcone (3)

A mixture of 4-bromo acetophenone(1.99 g, 0.01 mol) and 3-bromo benzaldehyde(1.85 g, 0.01 mol) in ethanol (15 ml) was stirred together at room temperature for 24 hrs in presence of 10% NaOH (10 ml). The reaction mixture was then poured into crushed ice and acidified with dil HCl. The solid obtained (chalcone) was filtered, washed with water, dried and recrystallized from ethanol.



Scheme: Synthesis of 2-(3-bromophenyl)-4-(4-bromophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine.

2.2. General procedure for synthesis of 1,5-benzodi-azepine (4)

A reaction mixture of chalcone (0.73 g, 0.002 mol) and orthophenylenediamine (0.22 g, 0.002 mol) in ethanol (10 ml) and few drops of piperidine were refluxed for 6 hrs. The progress of reaction was monitored by TLC. After completion of reaction the reaction mixture was poured into crushed ice. The solid obtained was filtered, washed, dried and recrystalized from ethanol to get pure compound.

Yield: 85%, Pale yellow solid, M.P. 98-100ºC. ***FT-IR (KBr, in cm^{-1}):*** 3337 (N-H str), 2920 (Ar-H str), 1680 (C=N str), 685 (Ar-Br str).***^{1}H NMR (500 MHz, $CDCl_3$):*** δ 7.60-7.56 (m, 2H), 7.53-7.47 (m, 3H), 7.40 (dt, 1H), 7.25-7.17 (m, 4H), 7.07-7.00 (m, 2H), 6.82 (m, 1H), 5.24 (dd, 1H), 3.82 (dd, 1H), 3.09 (dd, 1H).

2.3. Computational details

All the computational calculations are determined in gas phase by using Gaussian-03(W) package. In order to analyzed the theoretical parameters of title compound geometry optimized by DFT/B3LYP method with 6-311 ++G(d,p) basis set. Optimized structure of title compound was used for the frequency calculations by using same level of theory. For a good agreement between a theoretical and experimental data the calculated frequencies were scaled using the Pulay scaled quantum mechanical force field methodology.

3. RESULTS AND DISCUSSION

3.1. Molecular geometry

The molecular structure of title compound have C1 point group symmetry. Geometry optimized in ground state by DFT/B3LYP method with 6-311++G(d,p) basis set. Optimized structure with numbering scheme is shown in Figure 2. Computed optimized structure shows non-planarity of molecule. The title compound consists of three six member and one seven member rings. Geometry optimization predicts that two six member and seven-member ring are planar while 3-bromophenyl ring is perpendicular to the average plane of molecule (Figure 2). The optimized geometrical parameters i.e. bond lengths and bond angles are given in Table 1. C32-Br41 bond has highest bond length (1.9178 Å) due to electronegative bromine which having larger atomic size and N10-H11 bond has lowest bond length (1.0813 Å). The various thermochemical parameters computed by same level of theory are listed in Table 2.

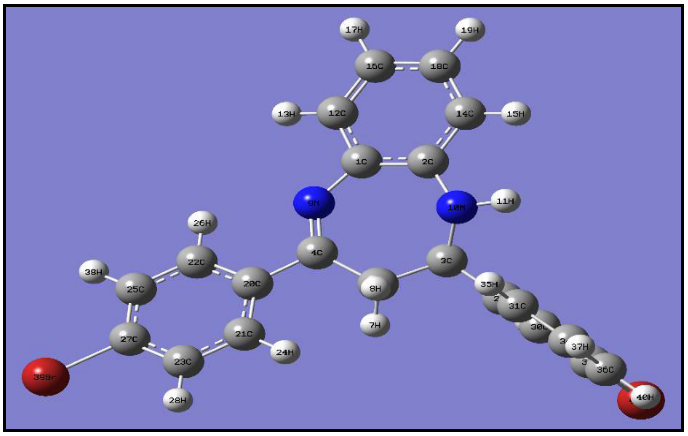


Fig. 2: Optimized structure of title molecule with atomic labeling.

Table 1: Optimized geometrical parameters of title molecule by DFT/B3LYP with 6-311++G(d,p) basis set.

Bond	Bond length	Bond	Bond length
C1-C2	1.4206	C20-C21	1.4030
C1-N9	1.3950	C20-C22	1.4048
C1-C12	1.4112	C21-C23	1.3941
C2-N10	1.3945	C21-H24	1.0824
C2-C14	1.4056	C22-C25	1.3878
C3-C5	1.5339	C22-H26	1.0818
C3-H6	1.0983	C23-C27	1.3888
C3-N10	1.4679	C23-H28	1.0824
C3-C29	1.5196	C25-C27	1.3940
C4-C5	1.5177	C25-H38	1.0826
C4-N9	1.2823	C27-Br39	1.9168
C4-C20	1.4977	C29-C30	1.3973
C5-H7	1.0942	C29-C31	1.4001
C5-H8	1.0955	C30-C32	1.3921
N10-H11	1.0813	C30-H33	1.0832
C12-H13	1.0832	C31-C34	1.3922
C12-C16	1.3844	C31-H35	1.0841
C14-H15	1.0862	C32-C36	1.3903
C14-C18	1.3861	C32-Br41	1.9178
C16-H17	1.0833	C34-C36	1.3944
C16-C18	1.3968	C34-H37	1.0841
C18-H19	1.0842	C36-H40	1.0822

Bond	Bond angle	Bond	Bond angle
C2-C1-N9	128.680	C4-C20-C21	122.303
C2-C1-C12	117.642	C4-C20-C22	119.974
N9-C1-C12	113.561	C21-C20-C22	117.714
C1-C2-N10	122.555	C20-C21-C23	121.475
C1-C2-C14	118.945	C20-C21-H24	120.755
N10-C2-C14	118.475	C23-C21-H24	117.763
C5-C3-H6	108.155	C20-C22-C25	121.513
C5-C3-N10	111.084	C20-C22-H26	118.286
C5-C3-C29	110.448	C25-C22-H26	120.201
H6-C3-N10	109.794	C21-C23-C27	119.175
H6-C3-C29	107.927	C21-C23-H28	120.319
N10-C3-C29	109.370	C27-C23-H28	120.506
C5-C4-N9	128.448	C22-C25-C27	119.269
C5-C4-C20	115.793	C22-C25-H38	120.421
N9-C4-C20	115.752	C27-C25-H38	120.310
C3-C5-C4	115.899	C23-27-C25	120.851
C3-C5-H7	107.835	C23-C27-Br39	119.595
C3-C5-H8	108.593	C25-C27-Br39	119.555
C4-C5-H7	108.322	C3-C29-C30	119.951
C4-C5-H8	109.397	C3-C29-C31	120.921
C7-C5-H8	106.378	C30-C29-C31	119.124
C1-N9-C4	132.252	C29-C30-C32	119.763
C2-N10-C3	119.536	C29-C30-H33	120.223
C2-N10-H11	111.742	C32-C30-H33	120.014
C3-N10-H11	111.798	C29-C31-34	120.376
C1-C12-H13	116.370	C29-C31-H35	119.811
C1-C12-C16	122.812	C34-C31-H35	119.812
H13-C12-C16	120.806	C30-C32-C36	121.480
C2-C14-H15	118.451	C30-C32-Br41	119.102
C2-C14-C18	121.835	C36-C32-Br41	119.417
H15-C14-C18	119.712	C31-C34-C36	120.689
C12-C16-H17	120.360	C31-C34-H37	119.959
C12-C16-C18	118.928	C36-C34-H37	119.352
H17-C16-C18	120.707	C32-C36-C34	118.565
C14-C18-C16	119.815	C32-C36-H40	120.566
C14-C18-H19	119.624	C34-C36-H40	120.870
C16-C18-H19	120.557		

3.2. Mulliken atomic charges

The electronic charge on atoms within molecule is crucial factor to decide the bonding capability of molecule. The net atomic charge in molecule provides the picture of electron density distribution over the molecule. The mulliken population analysis of title compound has been calculated using B3LYP/6-311++G(d,p) basis set. The Mulliken atomic charge plot of title molecule is shown in Fig. 3 and net atomic charges are listed in Table 3.

Table 2: Thermochemical Parameters computed by DFT/B3LYP with 6-311++G (d,p) basis set

Theoretically computed energy (a.u.), zero-point vibrational energy (kcal/mol), rotational constant (GHz), entropy (Cal/mol)	
Parameters	**Values**
Total E Thermal kcal/mol	210.928
Translational	0.889
Rotational	0.889
Vibrational	209.151
Total Molar capacity at constant volume (CV) Cal mol^{-1}Kelvin^{-1}	81.641
Translational	2.981
Rotational	2.981
Vibrational	75.680
Total entropy (S) Cal mol^{-1}Kelvin^{-1}	161.012
Translational	44.228
Rotational	37.806
Vibrational	78.978
Zero-point vibrational energy (kcal/mol)	197.77975
Rotational Constant (GHz)	0.1571209
	0.0611867
	0.0470123
E (RB3LYP) (a.u.)	-6067.88845416
Dipole moment (Debye)	3.4788

Table 3: Mulliken atomic charges

Atom	Charge	Atom	Charge
C1	0.34189	C22	0.06476
C2	-0.18952	C23	-0.72371
C3	-0.50397	H24	0.16254
C4	0.13577	C25	-0.46469
C5	-1.58017	H26	0.17998
H6	0.21149	C27	0.11130
H7	0.13310	H28	0.23223
H8	0.20840	C29	0.87717
N9	0.23610	C30	-0.32092
N10	0.13900	C31	-0.13253
H11	0.22043	C32	0.26025
C12	-0.10891	H33	0.22423
H13	0.15959	C34	-0.24210
C14	-0.10382	H35	0.20479
H15	0.12852	C36	-0.32379
C16	-0.56805	H37	0.18821
H17	0.16587	H38	0.24051
C18	-0.33467	Br39	-0.19214
H19	0.16595	H40	0.21281
C20	0.93837	Br41	-0.16055
C21	-0.19375		

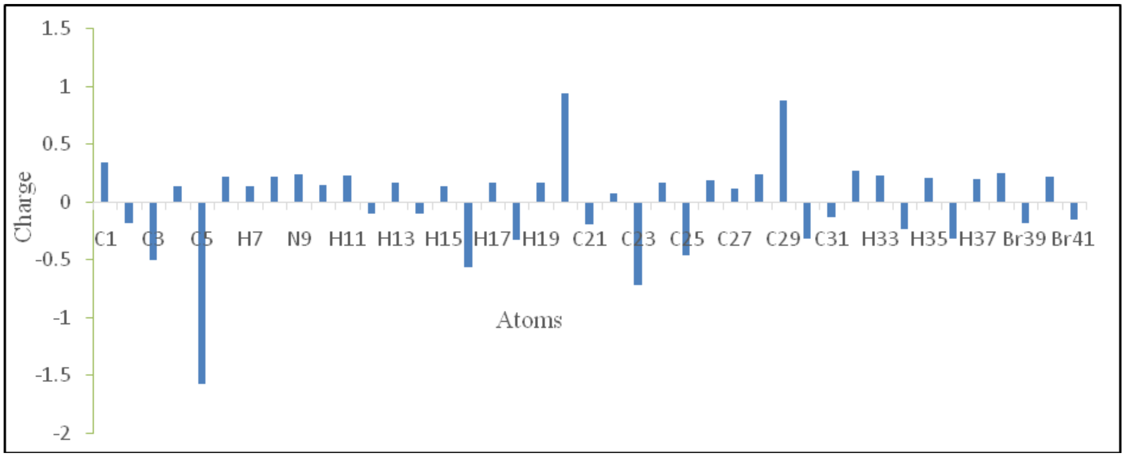
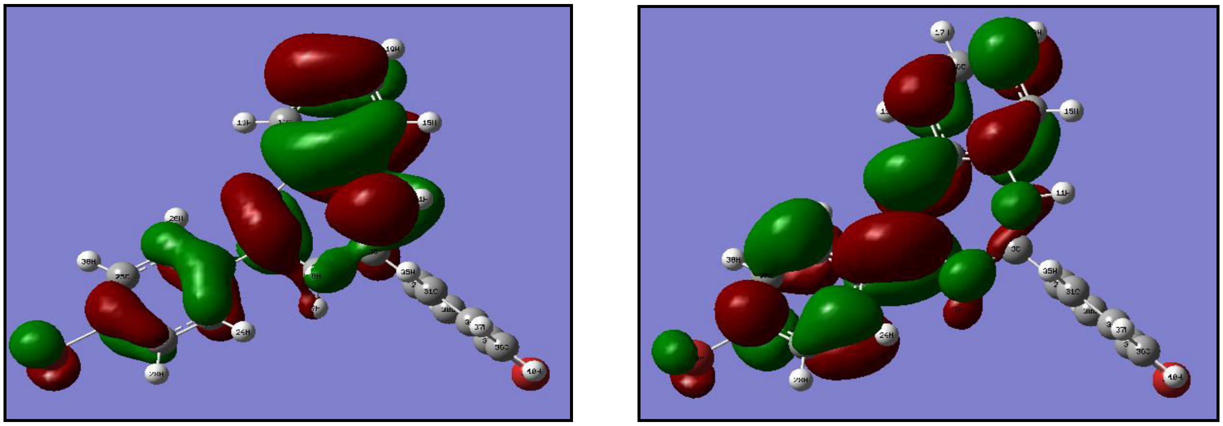


Fig. 3: The atomic charge plot of title molecule

3.3. *HOMO-LUMO*

The Frontier Molecular Orbital (FMO) analysis considers interactions of filled molecular orbitals of one reactant with empty molecular orbitals of the other. HOMO stands for highest occupied molecular orbital and LUMO for lowest unoccupied molecular orbital both are important parameters used in quantum chemistry. The HOMO is the outermost orbital having ability to donate electrons while LUMO is the innermost orbital acts as electron acceptor. The difference between the energies of HOMO and LUMO is referred as energy gap which determines the reactivity and kinetic stability of molecules [19]. Hard molecules have a high energy gap and soft molecules have a small energy gap. The HOMO-LUMO energy gap value for title compound was found to be 3.8472 eV. The pictorial illustration of the frontier molecular orbitals with their energies is shown in Fig. 4.



HOMO (E_{HOMO}= -5.8412 eV) **LUMO (E_{LUMO}= -1.9940 eV)**

Fig. 4: HOMO-LUMO

3.4. *Molecular Electrostatic Potential*

Molecular Electrostatic Potential (MEP) illustrates the charge distribution of molecules three dimensionally. MEP maps allow visualizing variable charge regions within molecule which used to determine how molecules interact with one another. The electrostatic potential at the surface of molecule is represented by distinct colors. The red region corresponds to the region of greatest electron density while blue region indicates the poor electron density and green represents the region of zero potential. MEP for title compound was plotted by employing 6-311++G(d,p) basis set is presented in Figure 5. In titled compound phenyl and 4-bromo phenyl rings having the region of most negative potential while the electron deficient region located over the diazepine ring and 3-bromo phenyl ring.

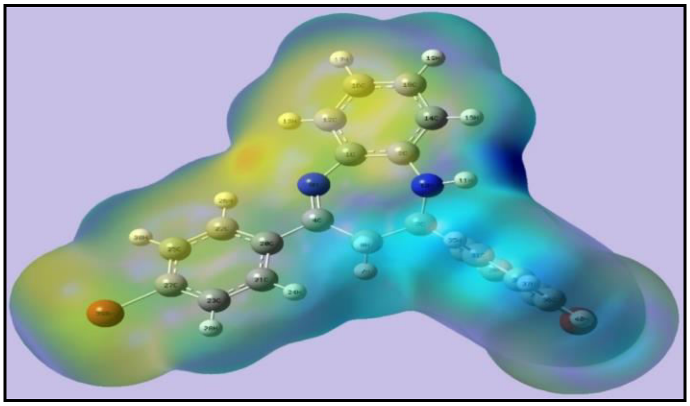


Fig. 5: MEP diagram of title molecule.

3.5. Global reactivity descriptors

Density functional theory based global chemical reactivity descriptors like Chemical hardness, chemical softness, electronegativity, chemical potential, electrophilicity index etc. are calculated from HOMO and LUMO energies using Koopmans theorem [20, 21] are given in Table 4. Global chemical reactivity descriptors used to understand the relationship between structure, stability and global chemical reactivity of compounds. Title molecule has the lower softness value (0.5198 eV) which indicates that it is less polarizable molecule.

Table 4: The global chemical reactivity descriptors of title molecule obtained using B3LYP method with 6-311G++(d,p) basis set.

Molecular Properties	Value (eV)
E_{HOMO}	-5.8412
E_{LUMO}	-1.9940
ΔE (E_{LUMO}-E_{HOMO})	3.8472
Ionisation energy (I)	5.8412
Electron affinity (EA)	1.9940
Electronegativity (χ)	3.9176
Chemical hardness (η)	1.9236
Chemical softness (S)	0.5198
Chemical potential (μ)	-3.9176
Global electrophilicity index (ω)	3.9893
Maximum number of electron transferred (ΔNmax)	2.0366

3.6. Vibrational assignments

There are total 41 atoms in title molecule with 117 fundamental modes of vibration. The experimental FT-IR spectrum has been recorded in solid state shown in Figure 6. Theoretically frequencies are predicted by DFT/B3LYP method using 6-311++G(d,p) basis set presented in Fig. 7. The theoretically predicted vibrational frequencies are scaled by an empirical factor 0.9613 [22]. The selected experimental and theoretical vibrational frequencies of title compound with their assignments are listed in the Table 5. The normal N-H stretching vibration appears at 3300-3500 cm^{-1} [23, 24]. The experimental N-H stretching frequency appeared at 3337 cm^{-1} and theoretically it is observed at 3433 cm^{-1}. Computed frequencies at 3061-3087 cm^{-1} indicate the aromatic C-H stretching. The experimental peak at 1680 cm^{-1} is due to C=N stretching vibration and theoretically it is assigned at 1614 cm^{-1}. The aromatic C=C stretching frequency theoretically appeared at 1528-1590 cm^{-1} which is close with experimental values, also calculated frequencies of C-C, C-H, C-Br stretching are well matches with experimental frequencies.

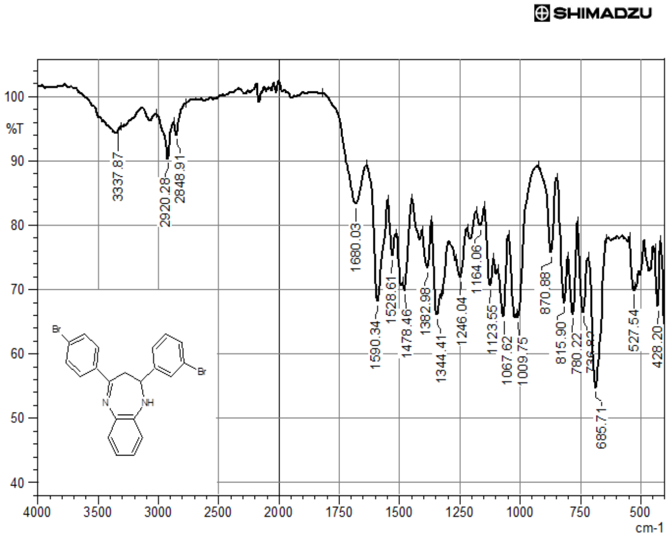


Fig. 6: Experimental IR spectrum of title compound

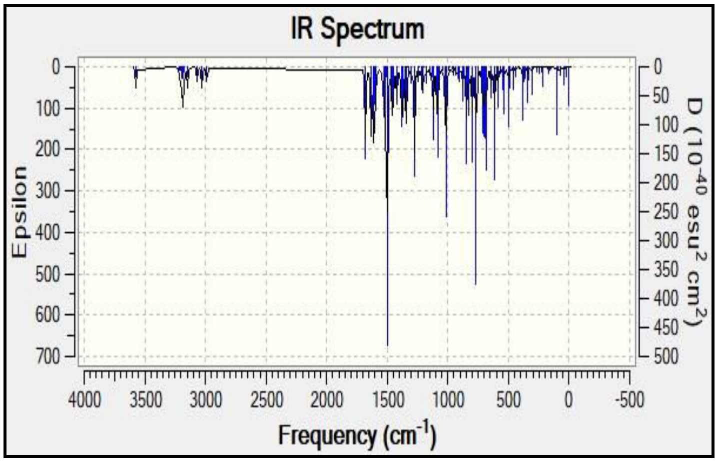


Fig. 7: Theoretical IR spectrum of title compound

Table 5: Selected experimental and theoretical vibrational assignments of title compound calculated at B3LYP/6-311++G(d,p) level

Mode	Calculated scaled frequencies (cm^{-1})	IR Intensity (km) mol^{-1}	Experimental frequencies (cm^{-1})	Assignment
117	3433	15.17	3337	N-H str
116	3087	3.76	-	C22-H, C25-H str (sym)
115	3081	2.07	2920	C34-H, C36-H str (sym)
114	3080	4.73	-	C21-H, C23-H str (sym)
113	3075	14.81	-	C12-H,C16-H,C18-H str(asym)
112	3069	0.39	-	C22-H, C-25-H str (asym)
110	3064	5.54	-	C2-H, C23-H str (asym)
109	3061	5.40	-	C31-H, C34-H str (sym)
103	2910	18.54	2849	C5-H str
101	1614	66.66	1680	C=N str
100	1570	22.64	1590	C=C str aro(Ph ring)
99	1567	34.14	1528	C=C str aro(3-Br Ph ring)
94	1470	32.23	1478	N10-H bend
90	1409	10.87	1382	C5-H bend
85	1319	29.35	1344	C3-H bend
72	1156	13.23	1123	C-H ip bend (4-Br Ph ring)
69	1103	3.53	-	C3-C5 str
68	1087	4.49	1067	C-H ip bend (3-Br Ph ring)
67	1078	34.85	1009	C-H ip bend (Ph ring)
38	677	21.16	685	C27-Br str

str-stretching, sym-symmetric, asym- asymmetric, aro- aromatic, bend-bending,ip- in plane

4. CONCLUSION

The title compound was synthesized and characterized by FTIR and ^{1}H NMR spectroscopy. Quantum chemical calculations on the structure and vibrational spectrum of title molecule were carried out by DFT using B3LYPmethod at 6-311++G(d,p) basis set. Comparison between calculated and experimental vibrational frequencies indicates that B3LYP/6-311++G(d,p) method results are in good agreement with experimental values. Mulliken charge analysis explains the charge distribution over the molecule. The low value of HOMO and LUMO energy gap explains the eventual charge transfer interactions takes place within the molecule. Molecular electrostatic potential surface illustrates the distribution of electron density over the molecule.

5. ACKNOWLEDGEMENTS

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