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Synthesis, Characterization and Theoretical Study of 3-(4-bromophenyl)-5-(2,4-dichlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole

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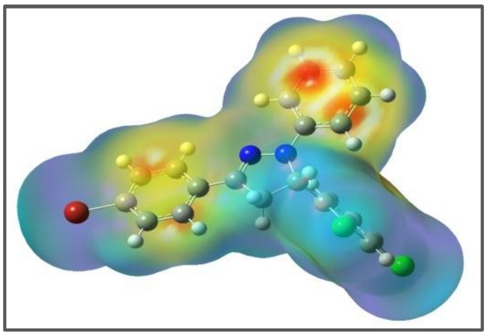
ABSTRACT

The 3-(4-bromophenyl)-5-(2,4-dichlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (BCPP) was synthesized from chalcone. The optimized geometrical parameters and vibrational spectra of BCPP have been investigated by Density Functional Theory (DFT) using B3LYP method at 6-311++G(d,p) basis set with Gaussian-03(W) package. Structural parameters such as atomic charges, bond lengths, bond angels, dipole moment, molecular electrostatic potential, HOMO-LUMO energies and various thermochemical parameters of titled compound also investigated with same level of theory. Experimental FT-IR vibrational frequencies have been analyzed and compared with theoretically predicted vibrational frequencies.

Graphical Abstract



MEP diagram for BCPP

Keywords: Chalcone, DFT, HOMO-LUMO, FT-IR.

INTRODUCTION

Pyrazolines are important nitrogen containing 5-membered heterocyclic compounds. Numerous pyrazoline derivatives have been found to possess a broad spectrum of biological activities [1-3]. Pyrazolines have been reported to show biological activities including anti- bacterial [4], antifungal

[5], anti-inflammatory [6], and antidepressant activities [7]. Pyrazolines have played a very important role in development of heterocyclic chemistry and are extensively useful synthons in organic chemistry. The chalcones are important intermediates for the synthesis of various heterocyclic compounds including pyrazolines. Synthesis of chalcones involves the base catalysed Claisen Schmidt condensation of substituted acetophenone and aryl aldehydes which undergoes subsequent cyclisation with phenyl hydrazine yields pyrazoline.

DFT is the computational quantum mechanical modelling method has become a powerful tool for the theoretical investigation of various physical and thermochemical parameters of molecules. Rodrigo *et al* [8] reported the synthesis and DFT study of some pyrazoles, Asmaa *et al* reported the synthesis and DFT study of thiophene, 1,3 thiazole and 1,3,4-thiadiazole derivatives [9]. Structure activity relationship and HOMO-LUMO study of pyrazole carboxamide derivatives were reported by Jim-Xia *et al* [10]. Sawant *et al* study the synthesis and theoretical investigation of 4-chloro chromones by DFT/B3LYP method using 6-311++G(d,p) basis set [11]. Synthesis, characterization and DFT study of dibenzylidine cyclohexanone derivative were investigated by A. Sumathi *et al* [12].

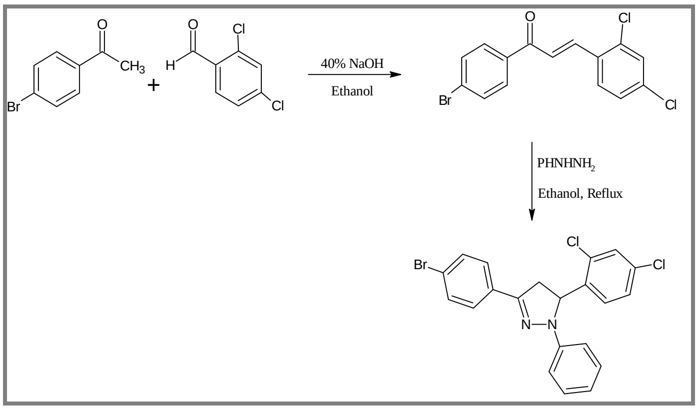
Present work deals with the synthesis and characterization of the BCPP from chalcone. Theoretical investigation of parameters like vibrational frequency, atomic charges, bond angle, bond length, molecular electrostatic potential and HOMO-LUMO energies of BCPP are also report here by using DFT/B3LYP method at 6-311++G(d,p) basis set.

MATERIALS AND METHODS

All the chemicals needed for synthesis were obtained from commercial source (AR grade with purity > 99%) and used without further purification.

Synthesis of chalcone: A mixture of 4-bromo acetophenone (1.99 g, 0.01 mol) and 2,4-dichloro benzaldehyde (1.75 g, 0.01 mol) in ethanol (15 ml) was stirred together for 24 hrs in the presence of 40% NaOH (10 ml). The reaction mixture was then poured into crushed ice and acidified with dil HCl. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol.

Synthesis of Pyrazoline (BCPP): The solution of chalcone (0.71 g, 0.002 mol) and phenyl hydrazine (0.39 mL, 0.002 mol) in ethanolic sodium hydroxide (15 mL) was refluxed for 6 h. Completion of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction the reaction mixture was poured into crushed ice and product obtained (BCPP) was filtered, washed, dried and recrystallized from ethanol.



Scheme 1. Synthesis 3-(4-bromophenyl)-5-(2,4-dichlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole.

IR spectra were recorded in KBr on a Shimadzu spectrometer (Japan). ^{1}H NMR spectra was recorded on advanced Nuclear Magnetic Resonance Spectrometer 400-MHz frequency using $CDCl_3$ as a solvent and TMS as an internal standard. Yield: 88% and m.p. 112-114°C. Figure 1 shows experimental IR of BCPP. Experimental ^{1}H NMR: δ 6.80-6.99 (dd, 3H, chlorophenyl ring), δ 7.10-7.35 (m, 4H, bromophenyl ring), δ 7.48-7.65 (m, 5H, phenyl ring).

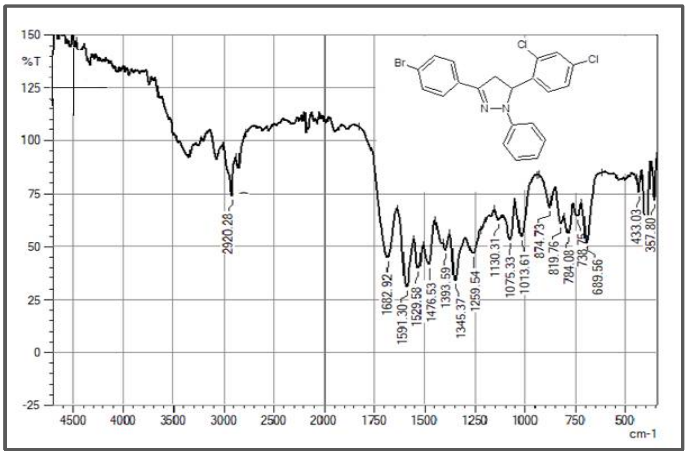


Figure 1. Experimental IR spectrum of BCPP.

Computational details: The quantum mechanical calculations by DFT were performed on an Intel (R), Pentium (R) dual core personal computer using Gaussian-03(W) program package using Gauss View 4.1.2 molecular visualization program without any constraint on the geometry. Geometry of the BCPP in the ground state was optimized by DFT/B3LYP method with 6-311 ++G (d,p) basis set. Optimized structural parameters were used in the vibrational frequency calculations by DFT at same level of theory. All the calculations were done for the optimized structure in the gas phase.

RESULTS AND DISCUSSION

Molecular geometry: Titled molecule possesses the C1 point group symmetry. The optimized molecular structure along with numbering scheme is shown in figure 2. The optimized geometrical parameters calculated by DFT/B3LYP method with 6-311++G(d,p) basis set i.e. bond lengths, bond angles are listed in table 1. The bond length of aromatic carbon belonging from phenyl, chlorophenyl and bromophenyl rings show the double bond character while C1-C26, C1-C2, C2-C3, C3-C18, C7-N36, N35-N36 possess single bond character. Bond C33-Br38 shows higher bond length due to electronegative bromine. The various theoretically computed thermochemical parameters i.e. energy, zero-point vibrational energy, rotational constant, entropy of BCPP is listed in table 2.

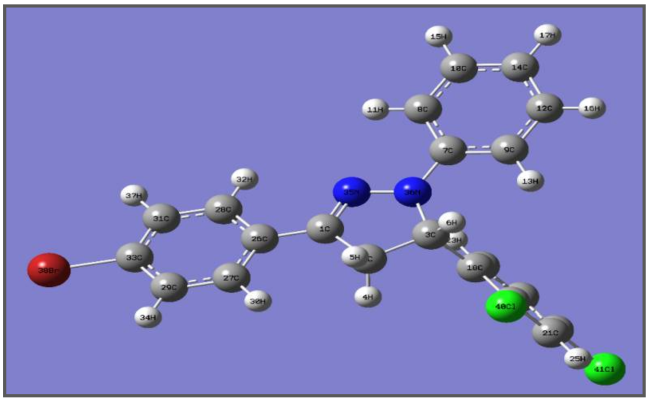


Figure 2. Optimized structure and atomic labeling of titled compound.

Table 1. Optimized geometrical parameters of BCPP by DFT/ B3LYP with6-311++G(d,p) basis set

Bond	**Bond Length(Å)**	**Bond**	**Bond Length(Å)**	**Bond**	**Bond Length(Å)**
C1-C2	1.5169	C9-H13	1.0821	C22-H39	1.0821
C1-C26	1.4613	C10-C14	1.3958	C24-Cl41	1.7549
C1-N35	1.2904	C10-H15	1.0846	C26-C27	1.4029
C2-C3	1.5535	C12-C14	1.3921	C26-C28	1.4072
C2-H4	1.0916	C12-H16	1.0844	C27-C29	1.3933
C2-H5	1.0939	C14-H17	1.0834	C27-H30	1.0837
C3-H6	1.0918	C18-C19	1.3987	C28-C31	1.3868
C3-C18	1.5235	C18-C20	1.3977	C28-H32	1.0827
C3-N36	1.4760	C19-C21	1.3915	C29-C33	1.3893
C7-C8	1.4062	C19-Cl40	1.7645	C29-H34	1.0823
C7-C9	1.4048	C20-C22	1.3907	C31-C33	1.3956
C7-N36	1.3982	C20-H23	1.0833	C31-H37	1.0825
C8-C10	1.3891	C21-C24	1.3898	C33-Br38	1.9165
C8-H11	1.0806	C21-H25	1.0812	N35-N36	1.3645
C9-C12	1.3929	C22-C24	1.3904	--	--
Bond	**Bond angle(°)**	**Bond**	**Bond angle(°)**	**Bond**	**Bond angle(°)**
C2-C1-C26	124.951	C8-C10-H15	118.938	C21-C24-C22	121.082
C2-C1-N35	112.707	C14-C10-H15	119.936	C21-C24-Cl41	119.106
C26-C1-N35	122.326	C9-C12-C14	120.922	C22-C24-Cl41	119.811
C1-C2-C3	101.992	C9-C12-H16	118.952	C1-C26-C27	120.662
C1-C2-H4	111.719	C14-C12-H16	120.126	C1-C26-C28	121.135
C1-C2-H5	111.056	C10-C14-C12	118.844	C27-C26-C28	118.202
C2-C2-H4	111.719	C10-C14-H17	120.587	C26-C27-C29	121.225
C3-C2-H5	112.011	C12-C14-H17	120.568	C26-C27-H30	120.251
H4-C2-H5	107.483	C3-C18-C-19	121.540	C29-C27-H30	118.524
C2-C3-H6	110.779	C3-C18-C20	121.322	C26-C28-C31	121.056
C2-C3-C18	112.748	C3-N36-N35	112.730	C26-C28-H32	119.103
C2-C3-N36	101.807	C7-N36-N35	120.520	C31-C28-H32	119.841
H6-C3-C18	109.073	C19-C18-C20	117.106	C27-C29-C33	119.182
H6-C3-N36	109.456	C-18-C19-C21	122.379	C27-C29-H34	120.348
C18-C3-N36	112.805	C18-C19-Cl40	120.254	C33-C29-H34	120.469
C8-C7-C9	118.979	C21-C19-Cl40	117.366	C28-C31-C33	119.411
C8-C7-N36	120.664	C18-C20-C22	121.956	C28-C31-H37	120.340
C9-C7-N36	120.354	C18-C20-H23	118.542	C33-C31-H37	120.248
C7-C8-C10	119.992	C22-C20-H23	119.496	C29-C33-C31	120.922
C7-C8-H11	119.225	C19-C21-C24	118.505	C29-C33-Br38	119.622
C10-C8-H11	120.782	C19-C21-H25	120.544	C31-C33-Br38	119.455
C7-C9-C12	120.138	C24-C21-H25	120.950	C1-N35-N36	110.225
C7-C9-H13	120.663	C20-C22-C24	118.967	C3-N36-C7	125.167
C12-C9-H13	119.195	C20-C22-H39	120.715	--	--
C8-C10-C14	121.123	C24-C22-H39	120.316	--	--

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

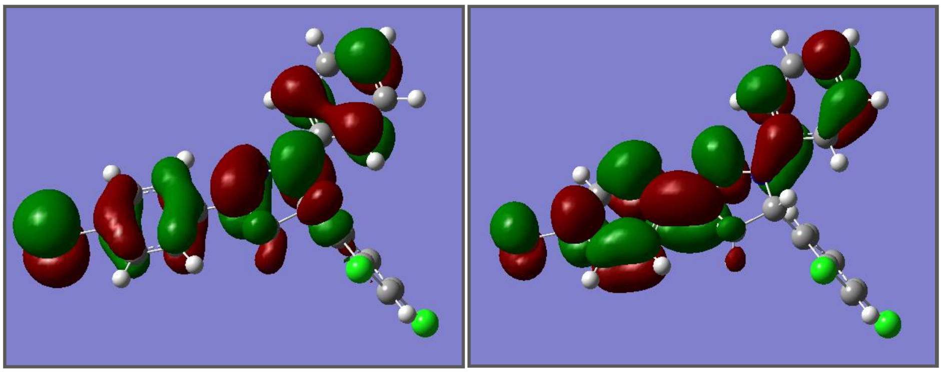
Theoretically computed energy (a.u.), zero-point vibrational energy (Kcal mol^{-1}), rotational constant (GHz), entropy (Cal mol^{-1}) of BCPP			
Parameters	**Values**	**Parameters**	**Values**
Total E Thermal kcal/mol	205.347	**Total entropy (S) Cal mol^{-1}Kelvin^{-1}**	168.187
Translational	0.889	Translational	44.161
Rotational	0.889	Rotational	37.515
Vibrational	203.570	Vibrational	86.511
Total Molar capacity at constant volume (CV) Cal mol^{-1} Kelvin^{-1}	85.090	**Zero-point vibrational energy (Kcal mol^{-1})**	191.37668
Translational	2.981	**Rotational Constant (GHz)**	0.05204 0.18938 0.06148
Rotational	2.981	**E (RB3LYP) (a.u.)**	-4413.57365000
Vibrational	79.128	**Dipole moment (Debye)**	1.2101

Mullikan atomic charges: Mullikan atomic charges are based on the electron density. Charge distribution is found to be affected by the presence of halogen in BCPP. C2 possesses more negative charge (-0.96004) and C26 has more positive charge (0.83955). All hydrogens have positive charge. Both nitrogen N35 and N36 possesses same positive charge (0.53077) while Cl41 has more positive charge (0.48648) than Cl40 (0.43142). Mullikan atomic charges calculated at B3LYP level with 6-311++G(d,p) basis set are listed in table 3.

Table 3. Mullikan atomic charges

Atom	Charge	Atom	Charge	Atom	Charge
C1	-0.40776	H15	-0.33277	C29	-0.67309
C2	-0.96004	H16	0.18477	H30	0.15819
C3	-0.44336	H17	0.14340	C31	-0.37734
H4	0.16633	C18	0.68529	H32	0.15023
H5	0.20777	C19	-0.19553	C33	0.10446
H6	0.23084	C20	-0.60142	H34	0.23503
C7	-0.00879	C21	-0.14665	N35	0.53077
C8	-0.09232	C22	-0.85118	N36	0.53077
C9	-0.25839	H23	0.19800	H37	0.24024
C10	-0.18034	C24	0.24389	Br38	-0.18886
H11	0.19645	H25	0.23503	H39	0.20867
C12	-0.25979	C26	0.83955	Cl40	0.43142
H13	0.08878	C27	-0.20406	Cl41	0.48648
C14	0.17857	C28	-0.07702	--	--

HOMO-LUMO Energy: Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are the main orbitals that take part in chemical stability of molecules. HOMO acts as electron donor and LUMO as electron acceptor. The HOMO-LUMO energy gap is the energy difference between HOMO and LUMO and this energy gap of organic molecules are significant because they are relating to specific movements of electrons. This energy gap has been used to predict the reactivity of molecule, more reactive molecule having the small energy gap. The HOMO-LUMO energy gap value for BCPP was found to be 0.08416 eV. The pictorial illustration of the frontier molecular orbitals has been given in figure 3.



HOMO= -0.30111 eV LUMO = -0.21695 eV

Figure 3. HOMO-LUMO of BCPP.

Molecular Electrostatic Potential: Molecular Electrostatic Potential (MEP) illustrates the charge distributions of molecules three dimensionally. MEP is used to find the reactive sites of molecules which enable to predict how molecule can interact with other molecules. The different values of electrostatic potential at the surface of molecule are represented by distinct colors. The red and yellow regions correspond to the region of high electron density and are associated with electrophilic reactivity. The blue regions represent low electron density and tend to nucleophilic reactivity. MEP for BCPP was plotted by employing 6-311++G(d,p) basis set is presented in fig. 4. In BCPP phenyl ring joint to nitrogen tend to electrophilic reactivity and chlorophenyl ring tend to nucleophilic reactivity.

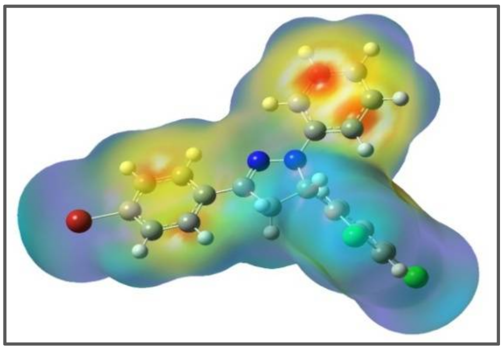


Figure 4. MEP diagram for BCPP.

Vibrational assignments: The experimental FT-IR spectrum of BCPP has been recorded (solid phase) which is as shown in Figure 1. Theoretically frequencies are predicted by DFT/B3LYP method using 6-311 ++ G(d,p) basis set. There are total 41 atoms in BCPP with 117 fundamental modes of vibration. The theoretically predicted vibrational frequencies are scaled by an empirical factor 0.9613. The selected experimental and theoretical vibrational frequencies of BCPP along with their assignments are listed in the table 4.

It is known that the C=N stretching vibration is normally appears in the spectral range 1500-1600 cm^{-1}. The C=N stretching frequency appeared at 1529 cm^{-1} experimentally and theoretically it is assigned at 1573 cm^{-1}. In BCPP experimental bands at 1476 and 1494 cm^{-1} are due to aromatic C-H in plane bending vibrations and theoretically this vibration appeared at 1460 and 1471 cm^{-1} respectively. The theoretical bands in the range 2946 -3095 cm^{-1} are due to aromatic C-H stretching vibrations. The normal stretching frequency of C-Cl vibration is 600-800 cm^{-1}. Theoretically C-Cl stretching vibrations for BCPP appeared at 786 cm^{-1} and experimentally it is observed at 784 cm^{-1}.

Table 4. Selected experimental and theoretical vibrational assignments of BCPP 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	3095	1.25	--	C8-H str
116	3092	0.57	--	C21-H str
114	3082	1.11	--	C28-H, C-31-H str
112	3076	6.84	--	C9-H, C12-H, C14-H, C10-H str
105	2970	6.92	--	C2-H str
104	2946	6.10	2920	C3-H str
102	1576	164.15	1591	Ring C def
101	1573	112.42	1529	C=N str
100	1562	25.34		Ring A def
95	1471	143.93	1494	Ring C C-H ip bend
94	1460	176.25	1476	Ring A C-H ip bend
93	1437	86.47		Ring D C-H ip bend
90	1376	63.57	1393	Ring A C-H ip bend
89	1362	109.27	1345	C3-H ip bend
86	1308	20.02		Ring C C-H ip bend
81	1248	23.33	1259	C7-N35 str
63	993	18.57	1036	C1-C2 str
61	973	29.82		C2-C3 str
45	786	38.80	784	C-Cl str

Abbreviations: str-stretching; def-deformation; ip bend-in plane bending; Ring A-chlorophenyl ring; Ring B- five membered ring; Ring C- Phenyl ring; Ring D-bromophenyl ring.

APPLICATION

The Pyrazolines are of great interest due to their pharmacological properties. This is the simple and convenient synthetic method which gives good yield of target molecule BCPP. DFT study explains the electronic structure, thermal behavior and chemical reactivity of titled compound.

CONCLUSION

The titled molecule was synthesized and characterized by FTIR and ^{1}H NMR spectroscopy. The optimized structure of the BCPP have been obtained and various structural parameters for the optimized structure were studied by DFT/B3LYP method at 6-311++G(d,p) basis set with Gaussian-03(W) package. This method predicts relatively accurate molecular structure and vibrational spectra of titled molecule. Vibrational frequencies of the fundamental modes of BCPP have been obtained from DFT calculations. The theoretical data obtained by DFT/B3LYP method with 6-311++G(d.p) basis set shows good agreement with the experimental values. The small energy gap of HOMO-LUMO indicates that BCPP has a good chemical stability. Molecular electrostatic potential explains the intermolecular interactions of the titled molecule.

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