Molecular Docking and Spectroscopic Analysis of (Z)-3-(3-chloro-2,6-difluorophenyl)-1-(1H-imidazol-1-yl)prop-2-en-1-one

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Abstract

Theoretical and experimental FT-IR and FT-Raman spectra characterization of 2(Z)-3-(3-chloro-2,6-difluorophenyl)-1-(1H-imidazol-1-yl)prop-2-en-1-one were recorded and calculated. The vibrational wavenumbers were computed using DFT quantum chemical calculations. The molecular geometry (bond length, bond angle) and vibrational frequencies of the title compounds have been calculated by using DFT/B3LYP method with 6-311++G(d,p) basis set. The title compounds were screened in vitro for antimicrobial activity against three bacterial and three fungal strains. Molecular docking studies reveal that title compound play a vital role in bonding and results draw us to the concluded that title compound inhibit different antimicrobial proteins and that have good biological activities.

Keywords: DFT; FTIR; FT-Raman; Antimicrobial; Molecular docking.
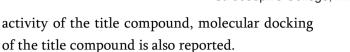
1. Introduction

The imidazole nucleus is well known to play an important role in living organisms since it is incorporated into the histidine molecule and many other important biological systems. Imidazole derivatives are the most used class of antifungal drugs [1], being active against pathogenic and nonpathogenic fungi [2]. Particularly, imidazole and its derivative of (Z)-3-(3-chloro-2,6-difluorophenyl)-1-(1H-imidazol-1-yl)prop-2-en-1-one have broadened scope in clinical medicines. Its molecular formula is $C_{12}H_7ClF_2N_2O$. Medicinal properties of imidazoles include anti-inflammatory, anticancer, anticoagulants, antifungal, antibacterial, antitubercular, antiviral, antimalarial and antidiabetic [3,4]. In the present work has been undertaken to give a complete description of the molecular geometry and molecular vibration of the 3CDIPO.

In the present work has been undertaken to give a complete description of the molecular geometry and molecular vibration of the 3CDIPO. FTIR and Raman spectra of (Z)-3-(3-chloro-2,6-difluorophenyl)-1-(1H-imidazol-1-yl)prop-2-en-1-one (3CDIPO) have been reported together with the assignments of the vibrational modes supported by PED. The agar diffusion methods were used to study the antimicrobial activity of the title compound against three bacteria (Moraxella, Enterobacter and Pseudomonas aeruginosa), and three fungi organisms (Candida albicans, A.niger and Trichophyton) and the title showed a broad spectrum of activities against the microbes. Due to the different potential biological

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activity of the title compound, molecular docking of the title compound is also reported.

2. Material and Methods
2.1. Synthesis

For the synthesis of ((Z)-3-(3-chloro-2,6-difluorophenyl)-1-(1H-imidazol-1-yl)prop-2-en-1-one (3CDIPO) compound, Equimolar quantity of 1-acetyl imidazole (0.01 mol) and 3-chloro-2,6-diflurobenzaldehyde (0.01 mol) were dissolved in 20 ml of ethanol in a 150 mL round bottomed flask. The reaction mixture was magnetically stirred for 3h in ice-cold condition, during stirring 10 ml of 10% sodium hydroxide solution was added drop wise. A flocculants precipitate was formed. The precipitate was filtered and washed with cold water. The solid obtained was purified by column chromatography using silica gel 60-120 mesh and n-hexane: acetone (7:3 v/v) as elevate. The reaction scheme is shown in Figure 1.

Figure 1. The scheme of the synthesis of 3CDIPO

2.2. Experimental details

The FT-IR spectrum of the synthesis compound (Z)-3-(3-chloro-2,6-difluorophenyl)-1-(1H-imidazol-1-yl)prop-2-en-1-one (3CDIPO) was recorded in the region 4000-450 cm^{-1} in evacuation mode using a KBr pellet technique with 1.0 cm^{-1} resolution on a PERKIN ELMER FT-IR spectrophotometer. The FT-Raman spectrum of the 3CDIPO compound was recorded in the region 4000-100 cm^{-1} in a pure mode using Nd: YAG Laser excitation wavelength of Raman 100 mW with 2 cm^{-1} resolution on a BRUCKER RFS 27 at SAIF, IIT, Chennai, India.

2.3. Computational details

In this work, all the calculations were performed by using Gauss-View molecular visualization program [5] and Gaussian 09 W program package [6]. Molecular docking (ligand-protein) simulations have been performed by using autoDock 4.2.6 software package.

3. Results and discussion
3.1. Geometrical structure analysis

The optimized geometry is performed at B3LYP/6-311++G(d,p) basis set of 3CDIPO molecule with atom numbering scheme is shown in Figure 2. The theoretical results are compared with related molecule such as (Z)-3-(9-Anthryl)-1-(4-chlorophenyl)-2-(4-nitro-1H-imidazol-1-yl)prop-2-en-1-one [7]. The comparative optimized structural parameters such as bond length, bond angle along with its experimental data's are presented in Table 1. This title molecule has ten C – C bond lengths, seven C – H bond lengths, five C – N bond lengths, two C – F bond lengths, one (C – O) bond length presented in title molecule and these values are listed in Table 1. From table 1 shows the calculated and experimental results are very good agreement. So the title molecule optimized successfully.

Figure 2. The theoretical optimized geometric structure with atoms numbering of 3CDIPO

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International Journal of
Scientific Research in Science and Technology (IJSRST)
Print ISSN : 2395-6011, Online ISSN : 2395-602X
International Conference on Advanced Materials
Held on 14, 15 December 2017, Organized by Department of Physics,
St. Joseph's College, Trichy, Tamilnadu, India

3.2. FT-IR and FT-Raman spectra

The maximum number of potentially active observable fundamentals of a nonlinear molecule which contains N atoms is equal to (3N-6), apart from three translational and three rotational degrees of freedom. Hence, 3CDIPO molecule, that was planar, has 25 atoms with 69 normal modes of vibrations. The observed and simulated infrared and Raman spectra of 3CDIPO are shown in Figs. 3 and 4, respectively. The observed and scaled theoretical frequencies using DFT (B3LYP) method with PEDs are listed in Table 2.

The C-C stretching vibrations are expected in the range from 1650 to 1100 cm^{-1} which are not significantly influenced by the nature of the substituents [8]. The C-C stretching vibrations of the 3CDIPO compound were observed from1670 to 890 cm^{-1}. In this present study, the C-C stretching vibrations are found at 1568(vs), 1597(vs), 1444(vs), 1235(vs), 1162(vs), 1067(s), 938(m) cm^{-1} in FT-IR and 1647(s), 1595(vs), 1415(s), 1177(w), 1104(m), 973(w), 947(m), 905(m) cm^{-1} in FT-Raman respectively. The theoretical wavenumbers at 1697, 1583, 1443, 1411, 1239, 1190, 1146, 1100, 1080, 989, 944 and 891 cm^{-1} are assigned as C-C stretching vibrations with PED contribution of 68, 46, 24, 63, 34, 24, 30, 25, 22, 21, 25 and 36% respectively.

Table 1. Optimized geometrical parameters of 3CDIPO obtain by B3LYP/6-311++G(d,p) basis set

Parameters	Exp[a]	B3LYP/	Parameters	Exp[a]	B3LYP
Bond length(Å)			Bond angle(°)		
C1-N4	1.364	1.391	N4-C1-H5	123.9	122.6
C1-H5	0.930	1.078	N4-C1-N8	112.2	111.9
C1-N8	1.305	1.301	C1-N4-C3	106.9	106.0
C2-C3	1.357	1.361	C1-N4-C9	128.0	129.7
C2-H6	0.930	1.078	H5-C1-N8	127.9	125.5
C2-N8	1.369	1.389	C1-N8-C2	106.9	105.6
C3-N4	1.369	1.393	C3-C2-H6	127.9	128.0
C3-H7	0.930	1.075	C3-C2-N8	112.8	110.9
N4-C9	1.431	1.418	C2-C3-N4	104.2	105.6
C9-C10	1.488	1.483	C2-C3-H7	127.9	133.4
C9-O14	1.216	1.210	H6-C2-N8	123.9	121.1
C10-C11	1.341	1.342	N4-C3-H7	123.9	120.9
C10-H12	0.930	1.083	C3-N4-C9	125.0	124.3
C11-H13	0.930	1.086	N4-C9-C10	116.1	115.6
C11-C15	1.477	1.470	N4-C9-O14	118.1	119.9
C15-C16	1.402	1.399	O14-C9-O14		124.4
C15-C17	1.402	1.400	C9-O14-C11		125.4
C16-C18	1.384	1.382	C9-C10-H12	115.3	116.9
C16-F24		1.352	C11-C10-H12	119.7	117.5
C17-C19	1.402	1.391	C10-C11-H13	115.3	116.6
C17-F23		1.339	C10-C11-C15	129.4	129.4
C18-C20	1.402	1.391	H13-C11-C15	115.3	114.1
C18-H21	0.930	1.082	C11-C15-C16	119.6	119.6
C19-C20	1.402	1.392	C11-C15-C17	123.4	124.4
C19-Cl25		1.744	C16-C15-C17	117.3	115.9
C20-H22	0.930	1.082	C15-C16-C18	123.5	123.6
			C15-C16-F24		117.7
			C15-C17-C19	122.4	122.1
			C15-C17-F23		118.9
			C18-C16-C24	118.8	118.7
			C16-C18-C20	118.6	118.6
			C16-C18-H21	119.8	119.8
			C19-C17-F23		118.9
			C17-C19-C20	119.6	119.6
			C17-C19-CL25		119.8
			C20-C18-H21	120.7	121.6
			C18-C20-C19	120.4	120.2
			C18-C20-H22	120.5	120.5
			C20-C19-CL25		120.6
			C19-C20-H22	119.3	119.3

[a] Taken from Ref [13]

In the heterocyclic compounds, the C-H stretching wavenumbers appear in the range 3000-3100 cm^{-1} [9]. In this present study, the C-H stretching vibrations are observed at 3166, 3122, 3090 and 3031 cm^{-1} by B3LYP/6-311++G(d,P) method show good agreements with experimental vibrations. The bands observed in the recorded

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FT-Raman spectrum 3163(w), 3106(m), 3082(m) and 3034(w) cm^{-1}. The PED corresponding to this pure mode of title molecule contributed 95, 94, 97 and 92% is shown in Table 2.
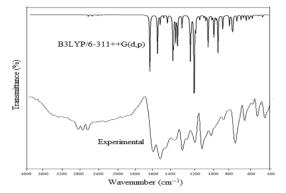

Figure 3. Experimental and theoretical FT-IR spectra of 3CDIPO

Table 2. Calculated vibrational frequencies (cm^{-1}) assignments of 3CDIPO based on B3LYP/6-311++G(d,p) basis set

Mode no	Experimental wave number (cm^{-1})		Theoretical wave number (cm^{-1})		I_{IR} [c]	I_{RAMAN} [d]	Assignments (PED)[a,b]
	FTIR	FT-Raman	**Unscaled**	Scaled			
69			3295	3166	1	7	γCH(95)
68			3259	3132	0	5	γ CH (96)
67		3106(m)	3248	3122	1	13	γ CH (94)
66		3082(m)	3215	3090	0	22	γ CH (97)
65			3203	3078	0	6	γ CH (97)
64			3186	3062	1	11	γ CH (91)
63			3154	3031	0	7	γ CH (92)
62	1668(vs)	1647(s)	1765	1697	49	9	γ CC (68)
61			1678	1612	34	100	γ CC(40)+ β HCN (14)
60	1597(vs)	1595(vs)	1647	1583	8	19	γ CC (46)
59		1513(m)	1607	1544	2	3	β HCC (31)
58			1564	1503	7	3	γ CC (60)
57	1444(vs)		1502	1443	35	4	β HCN(14) +γ NC(31) + γ CC (24)
56			1493	1435	23	1	β HCC(26)
55		1415(s)	1468	1411	23	8	γ CC (63)
54	1365(vs)	1376(w)	1447	1390	26	3	β HCC(19)+ β HCN(10)
53	1317(s)		1396	1342	11	1	β HCN(42) + γ NC (12)
52			1324	1272	1	3	γ CC (61)
51			1309	1258	5	6	γ NC (45) + β CNC(20)
50			1300	1249	38	4	γ CC (36)
49	1235(vs)		1289	1239	8	8	β HCN (12) + γ CC (34)
48		1218(w)	1267	1217	1	3	
47			1256	1207	100	1	β HCN (15) + γ (13)
46		1177(w)	1238	1190	11	0	γ CC(24) + β HCC (24)
45	1162(vs)		1193	1146	4	2	β HCC (11) + γ CC (14)
44		1104(m)	1145	1100	2	1	β HCC (20) + γ CC (10)

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Mode no	Experimental wave number (cm⁻¹)		Theoretical wave number (cm⁻¹)		I_{IR} [c]	I_{RAMAN} [d]	Assignments (PED)[a,b]
	FTIR	FT-Raman	**Unscaled**	Scaled			
43	1067(s)		1124	1080	4	1	γ NC (37) + γ CC (12) + βHCN (12)
42			1096	1054	28	6	β HCN (36)+ γ CC (27)
41		1021(w)	1052	1011	4	0	γ NC (30)
40			1030	989	19	1	γ CC (21)
39			1005	966	3	7	τ HCCN (38)
38	938(m)	947(w)	983	944	33	1	γ CC (25)+ β HCN (12)
37			948	911	0	0	τ HCCCI (68) +τ HCCF (15)
36			927	891	12	1	γ CC (36)
35			908	872	1	1	β HCN (63)
34		855(w)	893	858	0	0	τ HCCH (90)
33	816(vs)		851	817	9	1	γ CC (10) +β HCC (10)
32			820	788	10	0	τ HCCC (70)
31			813	782	10	0	τ HCNC (76)
30			809	777	6	4	
29		745(w)	766	736	5	0	τ HCNC (53)
28	718(m)		760	730	1	1	τ HCNC (21)
27			718	690	4	1	γ CC (14)
26		669(w)	690	663	2	0	τ HCCO (24)
25	633(w)	633(w)	658	632	5	0	τ HCNC (49)
24			624	600	4	1	
23			618	594	1	0	τ HCCC (28)
22	586(w)		611	588	1	3	τ HCNC (11)
21			588	565	3	0	γ CC (10) + τ HCCC (11)+ β HCC (10)
20	508(w)		547	525	0	0	β HCC (25)
19			518	498	1	1	
18			502	483	0	0	τ HCCC (10) +τ HCCO (18)
17		437(w)	470	451	2	0	β HCC (39)
16			400	384	0	3	τ HCCC (18)
15		377(w)	381	366	1	1	β HCC (35) +τ HCCC (12) +γ CC (13)
14		346(w)	349	335	0	0	β CNC (10)
13			331	318	0	0	τ HCCF (51)
12			304	292	4	0	β HCC (12)
11			271	260	0	1	τ HCCC (19)
10		205(w)	245	235	0	0	β CCC (35)
9			201	193	0	0	τ HCNC (11)
8			157	151	0	0	β HCC (10)+ τ HCNC (14)
7			149	143	1	0	τ HCNC (54)
6			124	119	0	0	τ HCCCI (64)
5		107(w)	115	110	1	1	τ HCCN (11)+ τ HCCC (24)
4		72(w)	82	79	0	0	τ HCCC (14)
3			49	47	0	0	τ HCCN (11) +τ HCCC (22)
2			38	37	0	1	β HCC (11) +τ HCCC (11)
1			17	16	0	0	τ HCCN (30)

[a]γ-stretching, β- bending , τ-torsion, vs-very strong, s- strong,   m-medium, w-weak, vw-very weak.

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International Journal of
Scientific Research in Science and Technology (IJSRST)
Print ISSN : 2395-6011, Online ISSN : 2395-602X
International Conference on Advanced Materials
Held on 14, 15 December 2017, Organized by Department of Physics,
St. Joseph's College, Trichy, Tamilnadu, India

[b]scaling factor : 0.961 for B3LYP/6-311+G(d,p)
[c]Relative absorption intensities normalized with highest peak absorption equal to 100.
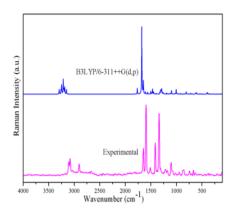[d]Relative Raman intensities normalized to 100.

Figure 4. Experimental and theoretical FT-Raman spectra of 3CDIPO

3.3. Antimicrobial studies

The title compound have been examined for in-vitro antibacterial activity against three bacterial strains such as, Moraxella, Enterobacter, Pseudomonas aeruginosa and three fungal strains such as, Candida albicans, A.niger and Trichophyton, which were selected for the present investigation by agar-disk diffusion method. Antimicrobial (antibacterial and antifungal) activity of DMSO extracts with different concentration (25, 50, 75 and 100 µl) inhibition Zone (mm) in agar well diffusion method is tabulated in Table 3.
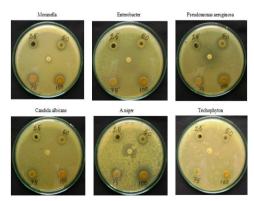

Figure 5. Antibacterial activity and antifungal activity of title molecule

Title compound is more active Moraxella, Enterobacter, Pseudomonas aeruginosa, Candida albicans, A.niger and Trichophyton compared than standard drug. Together, these results indicate that 3CDIPO shows broad-spectrum antimicrobial activity against. The activities of 3CDIPO against bacterial and fungal pathogens are shown in Figure5.

Table 3. Antimicrobial activity of 3CDIPO

Organism	DMSO Extract added and Zone of inhibition (mm/ml)				
	Control	25 µl	50 µl	75 µl	100 µl
Moraxella	11	12	15	17	19
Enterobacter	25	15	19	22	26
Pseudomonas aeruginosa	25	12	15	16	20
Candida albicans	13	13	15	18	20
A.niger	20	12	15	18	25
Trichophyton	10	12	15	20	24

3.4. Molecular docking

The molecular docking is used to predict the preferred binding orientation, binding energy and activity of molecules and their protein targets. The aim to investigate the binding mode, a molecular modeling study was performed and 3CDIPO was selected to be docked into the active site of three receptors 3F03, 4UM7 and 4HOE of antimicrobial proteins.

The AutoDockTools graphical user interface [10] was used to remove the ligand and water molecules present in the target proteins. The first rank docking parameters such as binding energy, inhibition constant and intermolecular energy of the molecule with respect to the targeted proteins are listed in Table 4. The preferred binding orientation of the 3CDIPO ligand with respect to the target proteins are represented in Figs. 6-8. In Figure 6-8, the yellow line indicates the formation of intermolecular hydrogen bond between 3CDIPO

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ligand and the proteins. These results indicate that the 3CDIPO ligand exhibits the lower binding energy and inhibition constant for the targeted protein associated with the 3F03 compared with the other targeted proteins associated with the 4UM7, 4HOE. Among them, 3F03 exhibited the lowest free energy at -6.50 kcal/mol and most docked inhibitors interacted with the ligand within the 3F03 binding site. They exhibited up to two hydrogen bonds involving ARG 324 and ARG 324 with RMSD being 8.79 Å. The docking simulation shows the best binding mode of the 3CDIPO into 3F03. These findings confirm that the 3CDIPO molecule can act as a good inhibitor against 3F03.
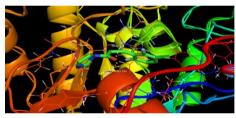

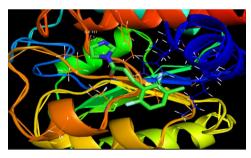**Figure 6**. Docking and Hydrogen bond interactions 3CDIPO with 3F03 protein structure

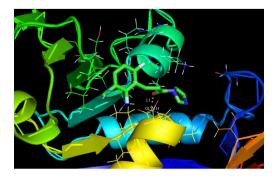**Figure 7.** Docking and Hydrogen bond interactions 3CDIPO with 4UM7 protein structure

Figure 8. Docking and Hydrogen bond interactions 3CDIPO with 4HOE protein structure

Table 4. Hydrogen bonding and molecular docking with antimicrobial protein targets

Protein (PDB ID)	Bonded residues	No. of hydrogen bond	Bond distance (Å)	Estimated Inhibition Constant (μm)	Binding energy (kcal/mol)	Reference RMSD (Å)
3F03	ARG 324	2	2.0	17.15	-6.50	8.79
	ARG 324		1.8			
4UM7	ILE 141	1	2.0	245.72	-4.92	21.75
4HOE	GLY 114	1	2.1	17.20	-6.48	33.45

4. Conclusion

The investigation of the present work is illuminate the spectroscopic properties such as molecular parameters, frequency assignments and electronic transition and of title compound by using FTIR, FT-Raman and tools derived from the density functional theory. Due to the lack of experimental information on the structural parameters available in the literature, the optimized geometric parameters (bond lengths and bond angles) was theoretically determined at B3LYP/6-311++G(d,p) level of theory and compared with the structurally similar compound. The vibrational FT-IR and FT-Raman spectra of the 3CDIPO were recorded and computed vibrational wavenumbers and their PED were calculated.

References

[1] Bell, A.S., Triazole antifungals: Itraconazole (Sporanox), fluconazole (Diflucan), Voriconazole (Vfend) and fosfluconazole (Prodif), In The Art of Drug Synthesis, 5 (2007)72–73.2

[2] Narasimhan, B., Sharma, D., Kumar, P., Biological importance of the imidazole nucleus in the new millennium. Med. Chem. Res. 20 (2011) 1119-1140.

Papers presented in ICAM-2017 Conference can be accessed from www.ijsrst.com- Volume 3, Issue 11, November-December-2017

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[3] Congiu, C., Cocco, M.T., Onnis, V., Design, synthesis and in vitro antitumor activity of new 1, 4-diarylimidazole-2-ones and their 2-thione analogues. Bioorg Med Chem Lett 18 (2008) 989–993.

[4] Siddiqui, I.R., Singh, P.K., Srivastava, V., Singh, J., Facile synthesis of acyclic analogues of carbocyclic nucleoside as potential anti-HIV pro-drug. Indian Journal of Chemistry 49B (2010) 512-520.

[5] GaussView, Version 5, Roy Dennington, Todd Keith, and John Millam, Semichem Inc., Shawnee Mission, KS, 2009.

[6] Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A. Gaussian 09, Revision E.01, Gaussian, Inc., Wallingford CT, 2009

[7] Wang, G.Z., Lu, Y.H., Zhou, C.H., Zhang, Y.Y., (Z)-3-(9-Anthryl)-1-(4-chlorophenyl)-2-(4-nitro-1H-imidazol-1-yl)prop-2-en-1-one, Acta Cryst. E65 (2009) o1113.

[8] Sundaraganesan, N., Illakiamani, S. Meganathan, C., Joshua, B.D., Vibrational spectroscopy investigation using ab initio and density functional theory analysis on the structure of 3-aminobenzotrifluoride, Spectrochim. Acta A 67 (2007) 214-224.

[9] Swarnalatha, N., Gunasekaran, S., Muthu, S., Nagarajan, M. Molecular structure analysis and spectroscopic characterization of 9-methoxy-2H-furo[3,2-g]chromen-2-one with experimental (FT-IR and FT-Raman) techniques and quantum chemical calculations, spectrochim. Acta part A 137 (2015) 721-729.

[10] Morris, G.M., Goodsell, D.S., Halliday, R.S., Huey, R., Hart, W.E., Belew, R.K., Olson, A.J., J. Comput. Chem. 19 (1998) 1639–1662.

Papers presented in ICAM-2017 Conference can be accessed from www.ijsrst.com- Volume 3, Issue 11, November-December-2017

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