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Synthesis, Molecular structure, spectroscopic (FT-IR and NMR), NLO, HOMO-LUMO and NLO properties of 2-Azetidinone derivatives: A comprehensive experimental and DFT study

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Abstract

Five 2-Azetidinone derivatives (**5a-e**) have been synthesized and characterized by using FT-IR, ¹H spectra. A comparison of calculated geometrical parameters shows that the 2-Azetidinone derivative possesses C₁ symmetry. The electrical dipole moment (μ) and first hyperpolarizability (β) values have been computed using DFT/B3LYP method. The calculated result (β) shows that the title molecule might have nonlinear optical (NLO) behavior. Atomic charges and molecular electrostatic potential (MEP) were calculated using B3LYP/6-31G (d,p). Thus, it is predicted that the 2-Azetidinones will be preferred for electrophilic and nucleophilic attack. The calculated HOMO and LUMO energies were used to analyze the charge transfer within the molecule.

Keywords: 2-Azetidinones, NMR, MEP, hyperpolarizability, HOMO –LUMO.

Introduction

2-Azetidinone, commonly known as β -lactam, is considered as one of the most frequently encountered structural motifs in alkaloids and attracting increasing attention in the contemporary biomedical research and drug discovery programmes.¹ As evident, a large number of synthetic protocols have been reported for the preparation of these heterocycles viz. penicillin, cephalosporin, carbapenem and carbacephem.²⁻⁹ Besides their importance as key structural component of β -lactam antibiotics, this four-membered ring system has been attracting considerable interest in organic synthesis as a versatile synthetic intermediate.¹⁰⁻¹² This usefulness is based on the impressive variety of transformations that can be derived from this ring system in a stereocontrolled manner.¹³⁻¹⁴ Recent revelation from our lab has shown the utilization of β -lactam synthon protocol for the synthesis of 2-Azetidinone derivatives.

The methodology was further utilized towards quantum chemical calculation and spectral analysis is powerful approaches for study of different aspects of compounds. Since, now a day's spectrographic analysis combined with quantum chemical computations are employed as an effective tool in the vibrational analysis of biological compounds.^{15,16} However, literature surveys revealed that till date neither completes spectroscopic nor quantum chemical calculations for 2-Azetidinone has been reported. Therefore the present investigation was undertaken to taking into account the molecular structural properties, electronic and polarizability data of 2-Azetidinone, in gas phase, due to its pharmaceutical importance. The ground state properties of the title molecules are calculated using DFT/B3LYP level of theory using 6-31G(d,p) basis set. As molecular structural optimized parameters provides very useful information about the structure and conformation of the

-lactam ring. In this present study, we report synthesis, FT-IR, NMR, molecular structure, dipole moment, polarizability, first order hyperpolarizability, HOMO–LUMO, Mulliken population analysis along with the molecular electrostatic potential surface would possibly give a clear understanding of the structural and spectral characteristics of the compound chosen for study.

Experimental

Materials and Methods

All the solvents were of spectral grade and used without further purification. The melting points of all the compounds were measured in open capillaries and are uncorrected. IR spectra were recorded on an AVATAR-330 FT-IR spectrometer (Thermo Nicolet) using KBr (pellet form). ¹H and ¹³C NMR spectra were recorded at 400 MHz, Bruker, using DMSO-*d*₆ as solvent for all the compounds. Tetramethylsilane (TMS) was used as an internal reference for all NMR spectra, with chemical shifts reported in units (parts per million) relative to the standard.

¹H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q) and multiplet (m). Coupling constants are expressed in Hertz (Hz).

General procedure for the synthesis of compounds (5a–e)

Hydrazone¹⁷ (4a-e) (0.04 mol) and triethylamine (0.02 mol) in dioxan (20 mL) at 0–5°C mixture was stirred for 5 h. During stirring, chloroacetyl chloride (0.01 mol) in dioxin (10 mL) was added dropwise. The mixture was refluxed for 2 h and kept for two days on room temperature. The resulting mixture was poured in the water and the solid was separated out. Recrystallization was done with ethanol–water to give the 2-Azetidinone (5a-e) compounds.

All the synthesized compounds were obtained in good yield. The chemical reactions are shown in Scheme. 1. For the compounds 5a–e, IR and ¹H spectra have been recorded and IR stretching and the chemical shifts values are given in Tables 1 -2, respectively.

Analytical data

N-(3-chloro-2-(4-difluoromethoxy)-3-hydroxyphenyl)-4-oxoazetidin-1-yl)benzamide (5a)

Colourless solid; Yield 64%., M.P: 208-210°C, MF: C₁₇H₁₃ClF₂N₂O₄ ; elemental analysis: Calcd (%): C, 53.35; H, 3.42; Cl, 9.26; F, 9.93; N, 7.32; O, 16.72; found (%):C, 53.25; H, 3.35; N, 7.30. IR (KBr, cm⁻¹): 3425 (O-H), 3051 (Ar-C-H), 2926 (AlC-H), 1681 (C=O); ¹H-NMR (DMSO-*d*₆) 4.53 (d, 1H, -CH-Cl), 4.83

(d, 1H, -N-CH-), 7.09-8.04 (m, 8H, Ar-H), 9.73 (s, 1H, O-H).

4-chloro-N-(3-chloro-2-(4-difluoromethoxy)-3-hydroxyphenyl)-4-oxoazetidin-1-yl)benzamide (5b)

Colourless solid; Yield 60%., M.P: 235-237°C, MF: C₁₇H₁₂Cl₂F₂N₂O₄ ; elemental analysis: Calcd (%): C, 48.94; H, 2.90; Cl, 17.00; F, 9.11; N, 6.71; O, 15.34; found (%):C, 48.35; H, 2.85; N, 6.69. IR (KBr, cm⁻¹): 3435 (O-H), 3047 (Ar-C-H), 2920 (AlC-H), 1664 (C=O); ¹H-NMR (DMSO-*d*₆) 4.48(d, 1H, -CH-Cl), 4.62 (d, 1H, -N-CH-), 6.86-7.82 (m, 7H, Ar-H), 9.89 (s, 1H, O-H).

N-(3-chloro-2-(4-difluoromethoxy)-3-hydroxyphenyl)-4-oxoazetidin-1-yl)-4-nitrobenzamide (5c)

Yellow solid; Yield 56%., M.P: 240-242°C, MF: C₁₇H₁₂ClF₂N₃O₆ ; elemental analysis: Calcd (%): C, 47.73; H, 2.83; Cl, 8.29; F, 8.88; N, 9.82; O, 22.44; found (%):C, 47.69; H, 2.79; N, 9.79; IR (KBr, cm⁻¹): 3431 (O-H), 3051 (Ar-C-H), 2926 (AlC-H), 1664 (C=O); ¹H-NMR (DMSO-*d*₆) 4.14(d, 1H, -CH-Cl), 4.37 (d, 1H, -N-CH-), 7.16-8.35 (m, 7H, Ar-H). 11.89 (s, 1H, O-H).

N-(3-chloro-2-(4-difluoromethoxy)-3-hydroxyphenyl)-4-oxoazetidin-1-yl)isonicotinamide (5d)

Colourless solid; Yield 65%., M.P: 210-212°C, MF: C₁₆H₁₂ClF₂N₃O₄ ; elemental analysis: Calcd (%): C, 50.08; H, 3.15; Cl, 9.24; F, 9.98; N, 10.95; O, 16.68; found (%):C, 50.18; H, 3.10; N, 10.65; IR (KBr, cm⁻¹): 3425 (O-H), 3045 (Ar-C-H), 2924 (AlC-H), 1674 (C=O); ¹H-NMR (DMSO-*d*₆) 4.72(d, 1H, -CH-Cl), 4.77 (d, 1H, -N-CH-), 7.16-8.35 (m, 7H, Ar-H) 11.69 (s, 1H, O-H).

N-(3-chloro-2-(4-difluoromethoxy)-3-hydroxyphenyl)-4-oxoazetidin-1-yl)-4-methoxy benzamide (5e)

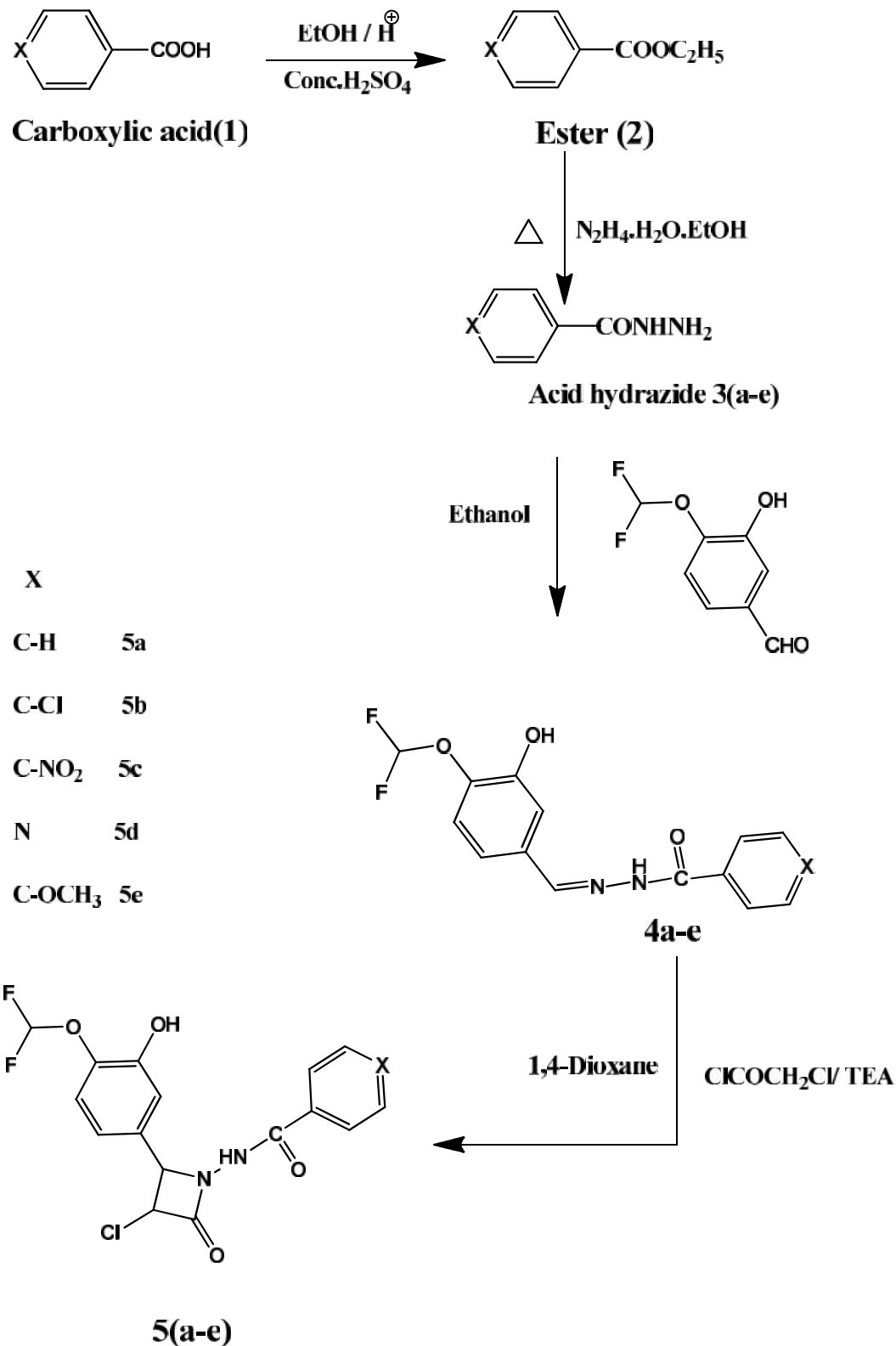
Yellow solid; Yield 60%., M.P: 182-184°C, MF: C₁₈H₁₅ClF₂N₂O₅ ; elemental analysis: Calcd (%): C, 52.38; H, 3.66; Cl, 8.59; F, 9.21; N, 6.79; O, 19.38; found (%):C, 52.80; H, 3.53; N, 6.80; IR (KBr, cm⁻¹): 3425 (O-H), 3043 (Ar-C-H), 2927 (AlC-H), 1672 (C=O); ¹H-NMR (DMSO-*d*₆) 4.69(d, 1H, -CH-Cl), 4.78 (d, 1H, -N-CH-), 6.91-7.91 (m, 7H, Ar-H). 11.69 (s, 1H, O-H).

Theoretical background

All calculations were carried out by density functional theory (DFT) on a personal computer using Gaussian 03W program package¹⁸. The calculations were done with the B3LYP level and the basis set 6-31G(d,p) was used in the present study to investigate the molecular

and vibrational frequency of molecules in the ground observations. Furthermore, HOMO and LUMO energy values and energy gap for 2-Azetidinones were calculated by using B3LYP method with 6-31G(d,p) basis set. Molecular Electrostatic Potential (MEP) of 2-

state in order to support and explain the experimental Azetidinones were plotted in 3D by using optimized structures at B3LYP/6-31G(d,p) level. Mulliken and Non-linear optics (NLO) were calculated from optimized geometry of the molecule.



Scheme 1 Synthesis of the 2-Azetidinone derivatives 5(a-e)

Results and Discussion

FT-IR spectral analysis

The important IR stretching frequencies of compounds **5a-e** are given Table 1. The presence of carbonyl stretching frequencies around 1681-1664 cm^{-1}

confirms the cyclic ketone formation of the β -lactam moiety. A collection of bands observed in the region of 3435-3425 cm^{-1} is due to O-H stretching frequency of aromatic ring. The absorption band found in the region of 3051-2920 cm^{-1} are due to aromatic and aliphatic C-H stretching frequencies.

Table 1 Physical data and IR stretching frequency (cm^{-1}) of 2-Azetidinones (**5a-e**)

Compound	Stretching frequency (cm^{-1})				Physical data	
	O-H	ArC-H	AliphC-H	C=O	Mp($^{\circ}\text{C}$)	Yield (%)
5a	3425	3051	2926	1681	208-210	64
5b	3435	3047	2920	1664	235-237	60
5c	3431	3051	2926	1664	240-242	56
5d	3425	3045	2924	1674	210-212	65
5e	3425	3043	2927	1672	182-184	60

NMR

The ^1H NMR spectra of compounds **5a-e** showed an N-CH- group proton doublet (~4.83 ppm), a CH-Cl proton doublet ~4.72 ppm, an aromatic proton multiplet (~6.56-8.35 ppm).

Geometry optimization

The optimized bond lengths, bond and dihedral angles of 2-Azetidinone were calculated by B3LYP method with 6-31G (d,p) basis set level theory and the results are listed in Table 2, in accordance with atom numbering scheme as shown in Fig.1. The optimized structure of compounds is shown in Fig.2.

Table 2 Proton chemical shift of (, ppm) of 2-Azetidinones (**5a-e**)

Proton	5a	5b	5c	5d	5e
O-H	9.73s	9.89	11.89	11.84	11.69
CH-N	4.83d	4.62	4.37	4.77	4.78
CH-Cl	4.53d	4.48	4.14	4.72	4.69
Ar-H	7.09-8.04	6.86-7.82	7.16-8.35	6.56-8.35	6.91-7.91

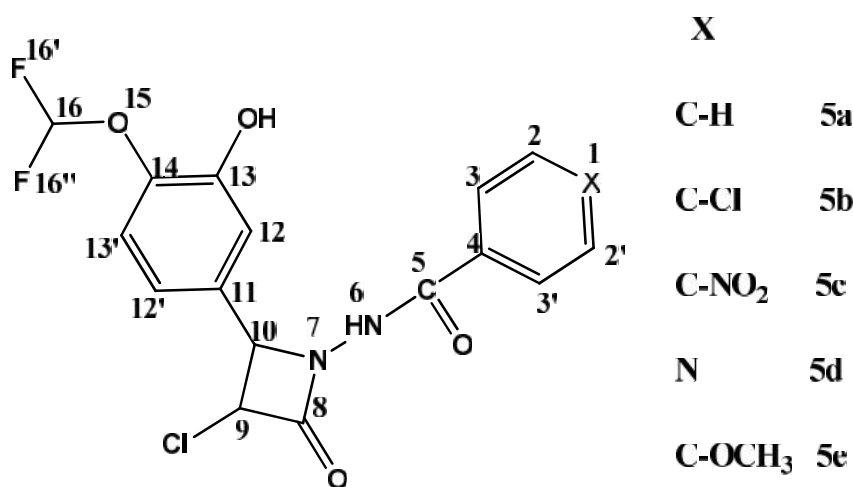


Fig. 1. Numbering Pattern of 2-Azetidinones.

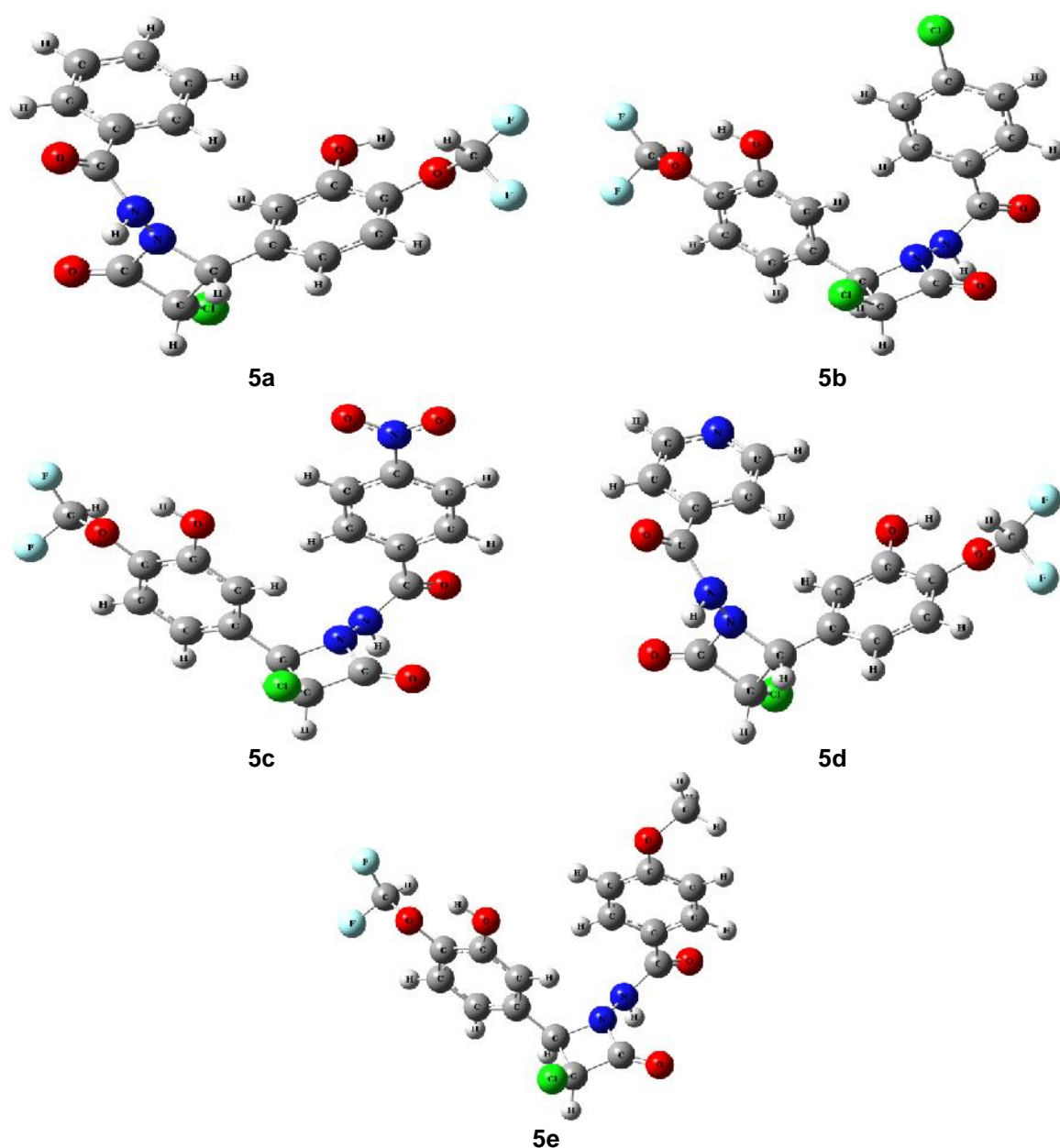


Fig.2. Optimized structures of 2-Azetidinones.

The molecules possess C1 symmetry. Introduction of substitution in phenyl group does not alter much deviation in optimized parameter. The optimized C9-C19 bond length is calculated as $\sim 1.78 \text{ \AA}$ by B3LYP method with 6-31G(d, p) basis set. The asymmetry of the N7-C10 ($\sim 1.49 \text{ \AA}$) and C5-N6 ($\sim 1.41 \text{ \AA}$) bonds can be explained due to the presence of the two different electron density atom attached with carbon. It leads to the asymmetry of N7-C10 and C5-N6 bonds. The conformation of the N7-N6-C5-O5 linkage is *anti* with torsion angle of $\sim 144.77^\circ$, which giving a folded

appearance to the molecule. These effects also reflect in crystal structure¹⁹.

As we seen from Table 3, phenylhydrazone ring are twisted away from another phenyl group and also it is evident from the torsional angles C5-N6-N7-C10 ($\sim 151^\circ$) and C12-C11-C10-C7 [$\sim -46^\circ$]. The crystal structure of synthesized compound has not been reported but geometrical parameters are taken from optimization from the crystal structure^{19,20}.

Table 3 Selected bond lengths, bond angles and dihedral angles of 2-Azetidinones.

Bond length (Å)	5a	5b	5c	5d	5e
C5-O5	1.2196	1.2197	1.2186	1.2184	1.2196
C5-N6	1.4114	1.4094	1.4039	1.4041	1.4114
N6-N7	1.3899	1.3901	1.3889	1.3885	1.3899
N7-C8	1.3959	1.3970	1.3974	1.3973	1.3959
N7-C10	1.4927	1.4935	1.4939	1.4935	1.4927
C8-C9	1.5449	1.5448	1.5446	1.5446	1.5449
C9-C19	1.7851	1.7846	1.7836	1.7840	1.7851
C14-O15	1.3947	1.3935	1.3925	1.3937	1.3947
C16-O15	1.3795	1.3799	1.3802	1.3800	1.3795
C16-F16'	1.3610	1.3610	1.3610	1.3610	1.3610
C16-F16''	1.3435	1.3428	1.3422	1.3429	1.3435
Bond angle (°)					
C4-C5-O5	122.91	122.59	122.09	122.23	122.91
C3-C4-C5	122.53	117.53	122.33	123.17	122.53
C3'-C4-C5	117.63	122.89	117.49	118.34	117.63
N6-N7-C8	126.41	126.25	126.23	126.18	126.41
N6-N7-C10	126.05	125.93	126.25	126.10	126.05
N7-C10-C11	118.50	118.32	118.19	118.33	118.50
C9-C10-C11	121.94	122.11	122.19	122.06	121.94
Dihedral(°)					
C5-N6-N7-C10	151.38	151.58	150.87	150.15	151.38
C5-N6-N7-C8	-74.75	-75.19	-75.23	-76.34	-74.75
N7-C10-C11-C12	-45.63	-46.30	-46.05	-45.74	-45.63
N7-C10-C11-C12'	135.00	134.05	134.24	134.81	135.00
C12-C11-C10-C9	58.68	58.01	58.10	58.47	58.68
C12'-C11-C10-C9	-120.70	-121.64	-121.61	-120.98	-120.70
C13-C14-O15-C16	139.99	142.34	143.28	140.85	139.99
C13'-C14-O15-C16	-41.59	-39.25	-38.37	-40.77	-41.59
C12-C11-C10-C7	-45.42	-46.30	46.35	-45.54	-45.62
C12-C11-C10-C9	58.58	56.58	57.87	58.15	58.68
C11-C10-C9-C19	-663	-6.30	-6.05	-6.64	-6.65
C11-C10-C9-H9	120.70	121.34	121.71	121.98	121.02
N7-N6-C5-O5	144.77	144.76	144.57	144.77	144.71

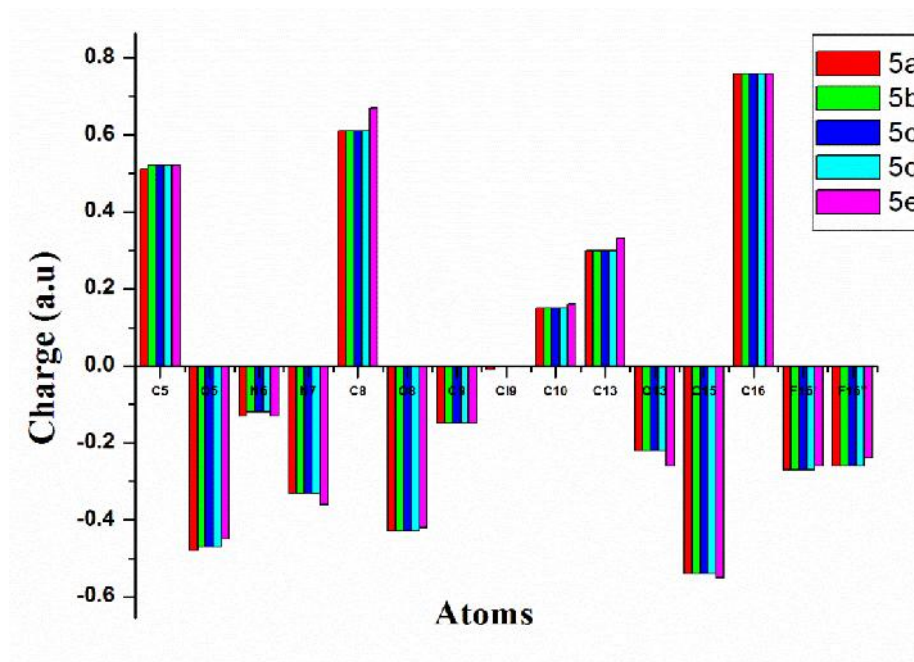
Mulliken charge analysis

Mulliken charge distributions were calculated by determining the electron population in title molecules. The calculated Mulliken charge values are listed in Table 4. The better represented graphical forms of the results were depicted in Fig. 3. Considering the method used in the atomic charge calculation, O5, N7,

O8, C9, O13, O15, F16' and F16'' atoms exhibit a substantial negative charge, which are donor atom. C5, C8, C13 and C16 atoms exhibit a positive charge, which is an acceptor atom (see Table 4). On oxygen are in the order of O15 > O5 > O8 > O13. Electron densities of C5, C8, C13 and C16 are relatively bigger because they are affected by the electron densities of Oxygen atom.

Table 4 Mulliken atomic charges of 2-Azetidinones.

Atom	5a	5b	5c	5d	5e
C5	0.51	0.52	0.52	0.52	0.52
O5	-0.48	-0.47	-0.47	-0.47	-0.45
N6	-0.13	-0.12	-0.12	-0.12	-0.13
N7	-0.33	-0.33	-0.33	-0.33	-0.36
C8	0.61	0.61	0.61	0.61	0.67
O8	-0.43	-0.43	-0.43	-0.43	-0.42
C9	-0.15	-0.15	-0.15	-0.15	-0.15
C19	-0.01	0.00	0.00	0.00	0.00
C10	0.15	0.15	0.15	0.15	0.16
C13	0.30	0.30	0.30	0.30	0.33
O13	-0.22	-0.22	-0.22	-0.22	-0.26
O15	-0.54	-0.54	-0.54	-0.54	-0.55
C16	0.76	0.76	0.76	0.76	0.76
F16'	-0.27	-0.27	-0.27	-0.27	-0.26
F16''	-0.26	-0.26	-0.26	-0.26	-0.24

**Fig. 3.** Mulliken atomic charges of 2-Azetidinones.

MEP analysis

The molecular electrostatic potential (MEP) are related to the electron density and may be a helpful descriptor in understanding sites for electrophilic and nucleophilic attacks and also hydrogenbonding interactions²¹⁻²³. MEP surfaces of the studied compounds are illustrated in Fig. 4. The colour scheme for the MEP surface is

red-electron rich or partially negative charge; blue-electron deficient region; and yellow-slightly electron rich, respectively. As seen in Fig. 4, negative regions, where come into existence nucleophilic attack, are oxygen atoms in C=O moiety. Conversely, the regions having positive potential where electrophilic attacks to molecule happens, are C13 and C16 atoms in benzene ring.

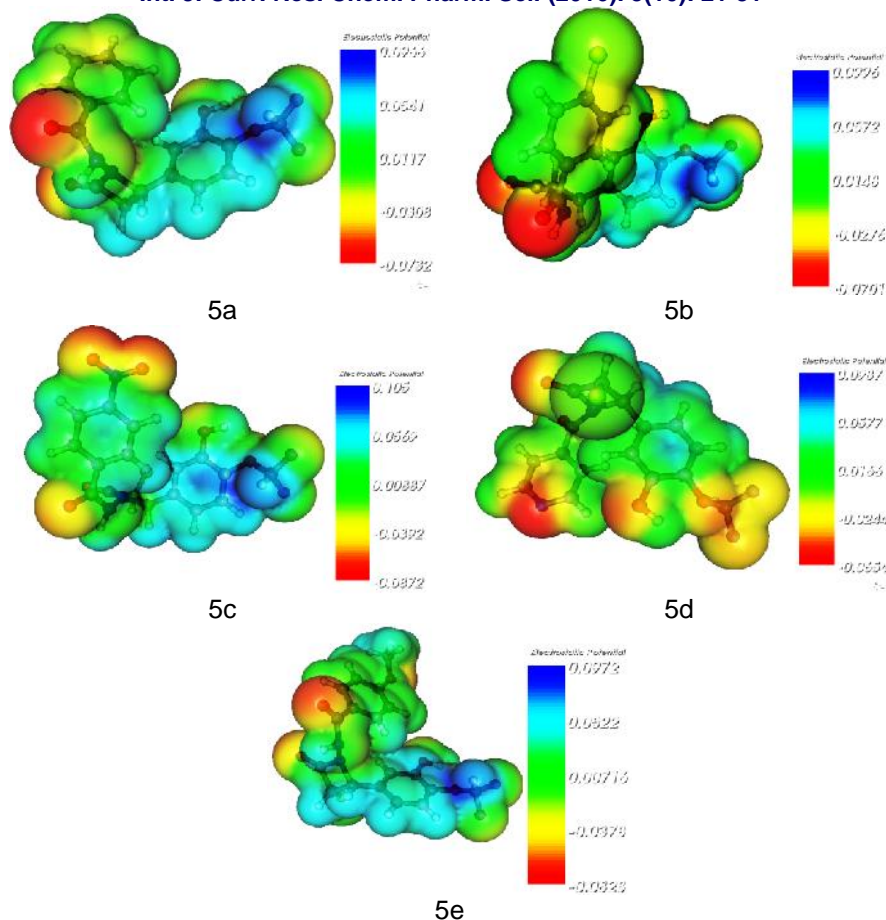


Fig. 4. MEP diagrams of 2-Azetidinones.

HOMO-LUMO analysis

Electron transport characteristics of a molecule are mainly controlled by the nature of the molecular orbitals. The spatial distribution and the energy level of molecular orbital give information about the conductivity²⁴⁻²⁶.

HOMO, LUMO plots, energy levels which are depicted in Figs. 5, are calculated at B3LYP/6-31G(d,p) level of

theory. As can be seen from Fig. 5, the HOMO is localized on phenyl group at C10 position for **5a-5d**, HOMO resides over the whole molecule for **5e**, whereas the electron-cloud distribution of LUMO is spread over the phenyl group at C5 position for **5a-5e**. The HOMO-LUMO gaps lie over a range of 3.98 to 5.36 eV (Fig. 5). The increasing order of HOMO-LUMO energy gap is as follows **5c < 5d < 5b < 5eb < 5a**.

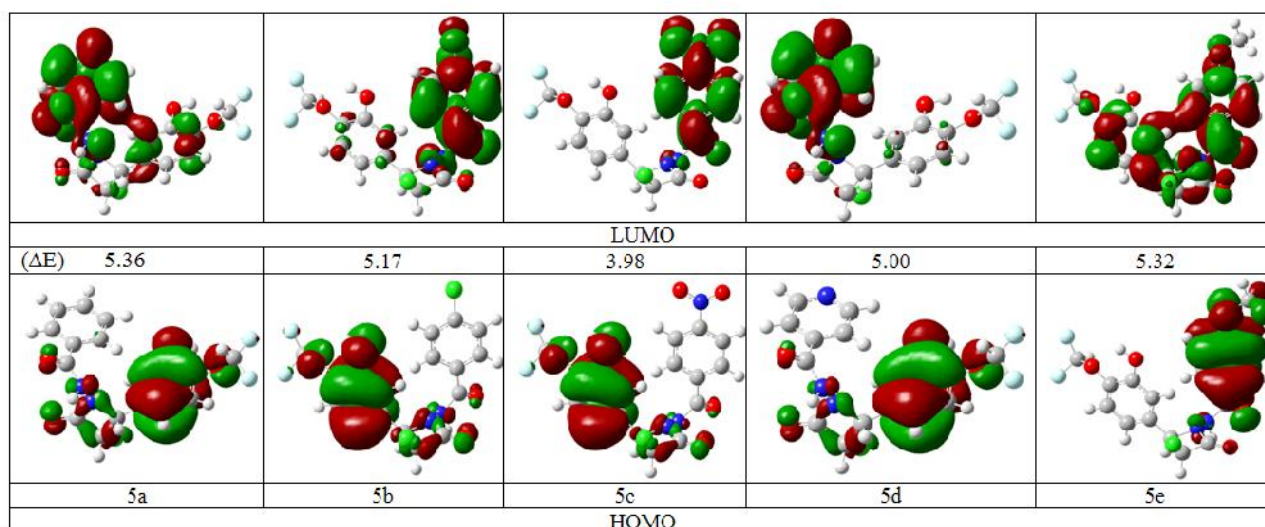


Fig. 5. Molecular orbitals and energies for the HOMO and LUMO in gas phase.

By using the HOMO and LUMO energy values, the quantum chemical reactivity descriptors like hardness, chemical potential, electronegativity and electrophilicity index as well as local reactivity have been defined²⁷. Pauling introduced the idea of electronegativity as the power of an atom in a molecule to attract electrons to it. Hardness (χ), chemical potential (μ) and electronegativity (χ) are defined using Koopman's theorem as $\chi = (I - A)/2$, $\mu = -(I + A)/2$ and $\chi = (I + A)/2$, where $I = -E_{\text{HOMO}}$ and $A = -E_{\text{LUMO}}$ are the ionization potential and electron affinity of the molecule. Global electronegativity values of investigated molecules are given in Table 5. According to Table 5, the **5e** molecule has the bigger electronegativity. Thus, electronegativity of **5e**

molecule carrying methoxy group in *para*-position has affected on the entire of molecular structure. Large electronegativity increases the interaction level of molecule with medium²⁸. If a molecule has higher electron affinity and ionization potential values, it has unstable molecular structure. Thus, molecule must come in different interactions, which is hydrogen bonding or other different interactions (van der Waals interactions). Molecular softness is a measure of molecular reactivity, while molecular hardness is a measure of molecular stability²⁸. We can say from Table 5 that the lowest active molecules are **5e**, **5b** and **5d**, whereas the bigger stable one is **5c** molecule. Resultantly, **5e** molecule is the most active molecule.

Table 5 Calculated energy values (eV) of 2-Azetidinones in gas phase.

DFT/B3LYP/6-31G(d,p)	5a	5b	5c	5d	5e
E_{HOMO}	-6.56	-6.63	-6.71	-6.64	-6.41
E_{LUOMO}	-1.2	-1.46	-2.73	-1.64	-1.10
$E_{\text{LUMO-HOMO}}$ (E)	5.36	5.17	3.98	5.00	5.32
Electrnegativity()	-3.88	-4.04	-4.72	-4.14	-3.75
Hardness()	2.68	2.59	1.99	2.50	2.66
Electrophilicity index()	2.81	3.16	5.59	3.43	2.65
Softness(s)	138.17	143.11	185.85	148.19	139.25

Non-linear optical studies

NLO is important property providing key for areas such as telecommunications, signal processing and optical interactions^{29,30}. Therefore, NLO is an important for current research. Some quantum chemical descriptors which are total static dipole moment (μ), the mean polarizability (α), the anisotropy of the polarizability (α_{an}) and first order hyperpolarizability (β) have been used for explaining the NLO properties in many computational studies²³.

Dipole moment reflects the molecular charge distribution and is given as a vector in three dimensions. Therefore, it can be used as descriptor to depict the charge movement across the molecule. The

direction of the dipole moment vector in a molecule depends on the centers of positive and negative charges. The **5c** molecule has the highest dipole moment, in that, it has the highest charge distribution among the other molecules. This is attributed to inductive and steric effects on **5c** molecule. Afterwards, the order of dipole moments for the other compounds is **5b** > **5a** > **5e** > **5d** (Table 6). **5b** molecule includes Cl atom in *para*-position while **5a** molecule has hydrogen atom in *para*-position. Electronegativity of Cl atom is bigger than H atom. So, dipole moment of **5b** molecule is bigger than **5a** molecules. The dipole moment in a molecule is an important property that is mainly used to study the intermolecular interactions involving the non-bonded type dipole-dipole interactions.

Table 6 Non-linear optical properties of 2-Azetidinones calculated using B3LYP method using 6-31G(d,p) basis set.

NLO behavior	5a	5b	5c	5d	5e
Dipole moment(μ) D	4.07	4.86	6.99	3.21	3.58
Mean polarizability () $\times 10^{-23}$ esu	2.32	2.50	2.6	2.4	2.4
Anisotropy of the					
Polarisability () $\times 10^{-24}$ esu	5.75	3.68	1.79	3.43	6.37
First order polarizability () $\times 10^{-30}$ esu	1.62	1.57	2.19	1.61	1.43

Polarizability is proportional with molecular volume. The bigger molecular polarizability means the more interaction with the electric field of light. Thus, molecular electronic charge distributions have been rearranged by interaction with electric field of light.

According to Table 6, all values of 2-Azetidinone derivatives are greater than the urea³¹. Therefore, our compounds have NLO properties. Results from Table 6, the general ranking of NLO properties should be as follows: **5c** > **5a** > **5d** > **5b** > **5e**. According to this ranking, molecule **5c** is the best candidate for NLO material.

Conclusion


All the synthesized 2-Azetidinone derivatives were characterized by FT- IR, NMR spectra. The spectral data supported the formation of 2-Azetidinone derivatives. A comparison of calculated geometrical parameters shows that the 2-Azetidinone derivative possesses C1 symmetry. In addition, Mulliken charge analysis predicts the most reactive parts in the molecule. The electronic transitions and states were investigated computationally and show good agreement with the experimental data. The calculated HOMO and LUMO energies were used to analyze the charge transfer within the molecule. The calculated dipole moment and first order hyperpolarizability results indicate that the molecule has a reasonably good nonlinear optical behavior.

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