MOLECULAR STRUCTURE, HOMO-LUMO AND VIBRATIONAL ANALYSIS OF ERGOLINE BY DENSITY FUNCTIONAL THEORY

Bhawani Datt Joshi*, Ghanshyam Thakur** and Manoj Kumar Chaudhary***

*Department of Physics, Siddhanath Science Campus, Tribhuvan University, Mahendranagar, Nepal.
**Department of Physics, Amrit Science Campus, Tribhuvan University, Kathmandu, Nepal.
***Central Department of Physics, Tribhuvan University, Kirtipur, Kathmandu, Nepal.

Abstract: In this work, quantum chemical study on a natural product ergoline has been presented using density functional theory (DFT) employing 6-311++G (d,p) basis set. A complete vibrational assignment has been performed for the theoretical FT-IR and Raman wavenumbers along with the potential energy distribution (PED) with the result of quantum chemical calculations. The structure–activity relationship has been interpreted by mapping electrostatic potential surface (MEP). Graphical representation of frontier molecular orbitals with their energy gap have been analyzed theoretically for both the gaseous and solvent environment employing time dependent density functional theory (TD-DFT) employing 6-31G basis set.

Keywords: Ergoline; ab initio; Vibrational spectroscopy; Density functional theory.

INTRODUCTION

The plant derived natural products cover a large field of medicine, which play very important role in the life threatening conditions due to their biological activity. Ergoline alkaloids (also called ergot alkaloids), the natural products occurring in the flowering plants *Rivea corymbosa* and *Ipomoea violacea* (Convolvulaceae; called morning glory) and taxonomically unrelated fungal, are known to inhibit the release of prolactin\(^1\)\(^-\)\(^2\). Ergot alkaloids, the derivatives of the tetracyclic ergoline scaffold, divided into three main groups; display a diverse spectrum of pharmacological properties; including central, peripheral, and neurohormonal activities that arise from their activities at various monaminergic receptors\(^3\). Naturally occurring alkaloids like; the D-lysergic acid amides, produced by the “ergot fungus” *Claviceps purpurea*, have been used as medicinal agents for a long time. They are active ingredients in medications designed to treat migraine disease or are used in childbirth and weaning\(^4\)\(^-\)\(^6\).

Ergoline alkaloids are also used as hallucinogens by native Central American people in religious ceremonial practices\(^7\). Historically, some ergots (e.g., ergoline and ergopeptine) have been used as probes to study various 5-HT receptor subtypes\(^8\)\(^-\)\(^12\). However, during the middle Ages, they were known for poisoning and sever toxicosis in cattle feeding with ergoline alkaloid producing clavicipitaceous fungi\(^13\)\(^-\)\(^16\).

Alkaloids occupy unique place in the natural product. Their complex structures and dynamical behaviors attract the chemists towards the challenging problems in structural elucidation and synthesis. Vibrational spectroscopy is a valuable method for determining dynamical behavior and the electronic structure of the alkaloids microscopically\(^17\). Raman and infrared (IR) are the traditional methods of vibrational analysis for the structural characterization of the substances\(^18\). They have been widely used to study energetic, thermal, electronic and dynamical behavior from vibrational dynamics of the...
large number of biomolecules. In the recent years, the application of ab initio methods has also become a part of keen interest as they provide additional vibrational spectroscopic data. In this study, the theoretical vibrational spectra of ergoline (6aR)-4,6,6a,7,8,9,10a-Octahydroindolo[4,3-fg] quinoline) with the identification of various normal modes have been investigated. The aim of this study was to study the molecular structure, vibrational wavenumbers and the electronic absorption band theoretically. The molecular structure, harmonic vibrational wavenumbers, electrostatic potential surfaces, absolute Raman scattering activities and IR absorption intensities have been calculated by density functional theory (DFT) using Gaussian 09 program package employing B3LYP/6-311++G(d,p) basis set. The highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), energy band gap (∆E) and the dipole moment were determined for the optimized structure. A theoretical time dependent density functional theory (TD-DFT) method has been used to calculate absorption parameters in gas phase employing 6-31G basis set. The graphical representation of HOMO and LUMO can provide valuable information that elucidates the nature of reactivity and some of the structural and physical properties of the molecule.

RESULTS AND DISCUSSION

Geometry optimization

Using the standard geometric parameters, geometry optimization was performed as the first task in ab initio calculation without using any constraints. The optimized geometric parameters were used in the vibrational frequency calculations to characterize all the stationary points as minima. The related energies of the molecule are calculated employing ab initio HF functions and DFT functional. The energy calculated by DFT (- 652.8040 Hartree) is lower showing more stable than that by HF (- 648.5243 Hartree) due to some electron correlations in the former. The enthalpy difference between these two theories is 12.0725 kcal/mol. The optimized ground state structure (in the gas phase) is as shown in figure 1.
Molecular electrostatic potential

The molecular electrostatic potential (MEP) in a molecule at a point \( r(x,y,z) \) is the force on unitary positive test charge at that point due to its whole electrical charge and is given by:

\[
V(r) = \sum_{A=1}^{N} \frac{Z_A}{|\mathbf{R_A} - \mathbf{r}|} - \int \frac{\rho(\mathbf{r'})d\mathbf{r'}}{|\mathbf{r'} - \mathbf{r}|}
\]

where \( Z_A \) is the charge on nucleus A located at \( R_A \) and \( \rho(r') \) is the electron density. The first term is due to the nucleus and the second due to electron cloud.

The MEP provides a visual method to understand the relative polarization of molecule\(^\text{17}\). Such surfaces depict the size, shape, charge density, and site of chemical reactivity of the molecules. In the surface generated, negative electrostatic potential (shades of red color) corresponds to an attraction of the proton by the concentrated electron density in the molecules (from lone pairs, pi-bonds, etc.) and positive electrostatic potential (shades of blue color) corresponds to repulsion of the proton by the atomic nuclei in the regions where low electron density exists and the nuclear charge is incompletely shielded. The largely white or lighter color shades on the surface indicate that the molecule is mostly non-polar. The potential increases in the order red < orange < yellow < green < blue.

The calculated electronic transitions with high oscillator strength are listed in Table 1.

UV-visible spectroscopy

UV-vis spectroscopy provides some valuable information about the nature of electronic transitions between the two prominent frontier molecular orbitals named as; HOMO (characterized by highest occupied molecular orbital) and LUMO (characterized by lowest unoccupied molecular orbital). The nature of electronic transition has been studied by using TD-DFT employing 6-31G basis set\(^\text{25,26}\) for both the gas and solvent (MeOH) phases. The theoretical absorption spectra are shown in the figure 3.
Table 1. Electronic transitions with absorption wavelength (λ\text{max} in nm), excitation energy (eV), oscillator strength, frontier orbital energies (eV) and the dipole moment (μ in D).

| Excited states | Gas Phase | | | MeOH Phase | | |
|---|---|---|---|---|---|---|
| | Transitions | eV | λ\text{max} | Oscillator strength | Transitions | eV | λ\text{max} | Oscillator strength |
| 1 | H → L | 4.7240 | 262.45 | 0.1017 | H → L | 4.6077 | 269.08 | 0.1338 | π → π* |
| 2 | H-3 → L | 6.1719 | 200.89 | 0.2617 | H → L+1 | 5.8791 | 210.89 | 0.3184 | .. |
| 3 | H → L+2 | 6.3689 | 194.67 | 0.1881 | H-1 → L+1 | 6.0278 | 205.69 | 0.1682 | .. |
| 4 | H-1 → L+2 | 6.5217 | 190.11 | 0.0798 | H-3 → L | 0.1682 | 198.09 | 0.1968 | .. |
| 5 | H-2 → L+1 | 6.7531 | 183.60 | 0.2367 | H-2 → L+1 | 6.5887 | 188.18 | 0.3575 | .. |
| 6 | H-2 → L+2 | 7.0700 | 175.37 | 0.1412 | H-2 → L+2 | 6.9796 | 177.64 | 0.1235 | .. |
| 7 | H-3 → L+1 | 7.5295 | 164.66 | 0.1117 | H-3 → L+1 | 7.4289 | 166.89 | 0.1739 | .. |
| 8 | H-3 → L+2 | 8.4539 | 146.66 | 0.1868 | H-3 → L+2 | 8.3861 | 147.85 | 0.1552 | .. |

| | E\text{HOMO} | E\text{LUMO} | ΔE | μ (D) |
|---|---|---|---|---|
| Gas | - 5.147798 | 0.035511 | 5.183310 | 1.3941 |
| MetOH | - 5.277569 | -0.162751 | 5.114818 | 1.8221 |

Figure 3: Plot of theoretical UV-vis spectra taken in gas (black) and the solvent (red).

HOMO and LUMO, the frontier molecular orbitals (FMOs), are very important quantum chemical parameters. These two vicinal orbitals play the same role of electron donor and acceptor, respectively. Their energy gap is an important stability index. A higher value of the energy difference more is the stability of the molecular system\textsuperscript{36}. The HOMO-LUMO plots are given in figure 4. TD-DFT calculations predict the intense electronic transitions at 262.45 nm (H → L), 200.89 nm (H-3 → L), 183.60 nm (H-2 → L+1) and 146.66 nm (H-3 → L+2) with oscillator strengths 0.1017, 0.2617, 0.2367 and 0.1868, respectively in the gaseous phase. Similarly, in the solvent phase, the transitions are centered at 269.08 nm (H → L), 205.69 nm (H-1 → L+1), 210.89 nm (H → L+1), 188.18 nm (H-2 → L+1) and 147.85 nm (H-3 → L+2) with the oscillator strengths 0.1338, 0.1682, 0.3184, 0.3575 and 0.1552, respectively. On the basis of calculated molecular orbital coefficient analysis, the main electronic excitations are due to → π* transitions.
Vibrational analysis

This molecule has 32 atoms and hence gives 90 (3N-6; N number of atoms) modes of vibration. All the modes are both Raman and IR active. Some selected fundamental vibrational wavenumbers, intensities and the PED distribution obtained by HF and DFT methods with 6-311++G (d,p) basis set are given in Table 2. Details of vibrational wavenumbers and their PED is listed in Table S (supplementary Material). The wavenumbers obtained by DFT have smaller values than that by HF methods due to inclusion of electron correlations in it. The assignments are given as per the internal coordinate system recommended by Pulay et al. 1979 using DFT. The theoretical wavenumbers, generally higher than the observed values, were corrected by a scaling factor given by Yoshida et al.32 using the expression: $\nu_{\text{obs}} = (1.0087 - 0.0000163 \nu_{\text{cal}}) \nu_{\text{cal}}$. The Raman scattering cross-sections, $\partial \sigma / \partial \nu$, which are proportional to the Raman intensities may be calculated from the Raman scattering amplitude and predicted wavenumbers for each normal modes using the relationship38,39:

$$\frac{\partial \sigma_j}{\partial \nu} = \frac{2\pi A^4}{45} \left( \frac{(\nu - \nu_j)^8}{1 - \exp \left( -\frac{\nu - \nu_j}{h} \right)} \right) \left( \frac{h}{8\pi^2 c^4} \right) S_j$$

where $S_j$ and $\nu_j$ are the scattering activities and the predicted wavenumbers (in cm$^{-1}$), respectively of the j$^{th}$ normal mode, $\nu_j$ is the Raman exciting wavenumber (in cm$^{-1}$), and h, c and k are universal constants. The FT-IR and Raman spectra are given in figures 5 and 6, respectively. The assignments of some prominent modes are discussed below:

### Ring R1 vibrations

The N–H stretching absorption generally occurred in the region 3500–3220 cm$^{-1}$. In this study, pure N-H stretching vibration was calculated at 3320 cm$^{-1}$ with IR intensity 0.4759 and Raman activity 73.268 units, respectively. The mixed in-plane-bending was calculated at 1473 cm$^{-1}$.

The CH$_2$ asymmetric stretching vibration was calculated at 2937, 2930 and 2919 cm$^{-1}$. The symmetric stretching of the mode was predicted at 2889, 2886 and 2878 cm$^{-1}$. The wagging vibration was predicted at 1371, 1366 and 1351 cm$^{-1}$ in the scaled DFT. The twisting vibrations were calculated at 1308, 1274 and 1194 cm$^{-1}$. The C4-H /C3-H stretching vibrations calculated at 2877/2833 cm$^{-1}$ have intensities 42.173/11.63 units in the IR spectra and 115.142/106.889 units in the Raman spectra. The highly mixed rocking vibrations related to these modes were calculated at 1345 and 1338 cm$^{-1}$.

Table 2. Selected calculated IR and Raman wave numbers (cm$^{-1}$) of ergoline.

|   | DFT   | HF   | Raman activity (Å$^4$/a.m.u.) | IR intens. (km-mol$^{-1}$) | Potential energy distribution (PED%) |
|---|-------|------|-------------------------------|---------------------------|--------------------------------------|
| Unscaled | 3676  | 3488 | 3703                          | 176.582                   | R3[υ(NH)](100)                       |
|       | 3488  | 3320 | 3540                          | 73.268                    | R1[υ(NH)](100)                       |
|       | 3241  | 3098 | 3233                          | 134.288                   | R3[υ(CH)](98)                        |
|       | 3185  | 3047 | 3194                          | 269.652                   | R4[υ(CH)](100)                       |
|       | 3174  | 3037 | 3183                          | 83.815                    | R4[υ(CH)](97)                        |
| 3161 | 3026 | 3165 | 63.869 | 1.458 | R4[ω(CH)](86) |
| 3069 | 2942 | 3082 | 112.236 | 23.105 | R2[υ(CH2)](96) |
| 3063 | 2937 | 3069 | 156.889 | 56.344 | R1[υ(CH2)](97) |
| 3056 | 2930 | 3064 | 50.957 | 37.593 | R1[υ(CH2)](96) |
| 3044 | 2919 | 3050 | 231.545 | 81.004 | R1[υ(CH2)](96) |
| 3010 | 2889 | 3025 | 71.513 | 51.843 | R1[υ(CH2)](86)+υ(C4H)(8) |
| 3007 | 2886 | 3020 | 33.024 | 27.533 | R1[υ(CH2)](93) |
| 2999 | 2878 | 3015 | 127.905 | 14.386 | R1[υ(CH2)](60)+υ(C4H)(27) |
| 2997 | 2877 | 3005 | 115.142 | 42.173 | R1[υ(CH2)](45)+υ(CH2)(43) |
| 2978 | 2859 | 3002 | 144.925 | 18.564 | R2[υ(CH2)](71)+R1[υ(CH2)](15) |
| 2949 | 2833 | 2976 | 106.889 | 11.763 | R1[υ(CH2)](90) |
| 1651 | 1621 | 1764 | 27.684 | 6.155 | R4[(CC)(45)+δtrig(26)]+R2[δtrig](15)+R3[υ(C=C)](12) |
| 1633 | 1604 | 2976 | 27.304 | 12.490 | R3[δ′ring(33)+υ(CC)(12)]+R2[υ(CC)](33)+R4[δa](14) |
| 1590 | 1563 | 1701 | 72.071 | 8.583 | R3[υ(CC)(48)+δ′ring(18)]+R4[δ′a](14)+R2[δtrig](6) |
| 1535 | 1510 | 1632 | 3.843 | 3.897 | R3[δ′ring(33)+υ(CC)(12)]+R2[δtrig](11) |
| 1499 | 1475 | 1608 | 1.483 | 3.198 | R1[δ(CH2)(68)+p(CH2)(19)] |
| 1496 | 1473 | 1597 | 0.777 | 13.512 | R1[δ(CH2)(46)+p(C4H)(23)+δ(CH2)(19)] |
| 1487 | 1464 | 1585 | 14.838 | 3.032 | R1[δ(CH2)(27)+δ′ring(14)]+R2[δ(CH2)(22)]+δ′ring(15) |
| 1485 | 1462 | 1581 | 6.954 | 5.071 | R2[δ(CH2)(46)+R1[δ(CH2)](34)] |
| 1479 | 1456 | 1577 | 12.824 | 17.448 | R1[δ(CH2)(37)+δa(NH)(30)+p(CH2)(11)] |
| 1458 | 1436 | 1551 | 11.749 | 21.852 | R4[δ′a(30)+δa(CH)(21)]+R3[υ(CC)](26)+R2[δring(11)] |
| 1444 | 1423 | 1538 | 60.106 | 10.565 | R3[δa(NH)(25)+υ(NC)(17)]+R2[υ(CC)](30)+R4[δ′a](15) |
| 1395 | 1375 | 1499 | 39.051 | 2.082 | R3[δ′ring(21)+υ(CC)(14)]+R2[υ(CC)](27)+R4[δring(15)] |
| 1390 | 1371 | 1494 | 16.434 | 1.897 | R1[ω(CH)](18) \(γ(8)(CH2)+p(CH)(15)+R2[ω(CH2)](18)+υ(CC)(11)\) |
| 1385 | 1366 | 1479 | 0.763 | 1.014 | R1[ω(CH2)](42)+δring(23)+R2[p(CH3)(12)]+δ′a(9) |
| 1373 | 1354 | 1475 | 4.532 | 6.295 | R1[ω(CH2)](35)+δring(14)+R4[υ(CC)](21) |
| 1372 | 1353 | 1472 | 1.715 | 18.654 | R2[ω(CH2)(24)+υ(CC)(8)]+R1[ω(CH2)](31)+R3[υ(C=C)](18) |
| 1356 | 1338 | 1426 | 7.158 | 9.850 | R1[γ(CH2)(39)+γ(CH2)(15)]+R2[γ(CH2)(17)]+δ′a(15) |
| 1309 | 1292 | 1377 | 18.185 | 15.722 | R2[υ(CC)(35)+δ′a(5)]+R4[δa(CH)](14)+δring(12)]+R3[υ(NC)](23) |
| 1290 | 1274 | 1369 | 5.039 | 1.007 | R1[γ(CH2)](46)+R2[δ′a(20)+R2[γ(CH2)](20) |
| 1285 | 1269 | 1367 | 4.722 | 1.603 | R4[δring(44)+υ(CC)(5)]+R3[δ′ring(20)+υ(CC)(9)] |
| 1253 | 1238 | 1332 | 2.294 | 17.712 | R2[δ′a(40)+δring(7)]+R4[δring(28)]+R3[δ′ring(10)] |
| 1240 | 1226 | 1324 | 9.112 | 7.109 | R1[δring(44)+R2[δring(22)]+R3[υ(NC)(9)+υ(CC)(5)] |
| 1234 | 1220 | 1313 | 14.237 | 3.165 | R4[δring(44)+R3[υ(CC)(13)+δ′ring(12)+υ(NC)(12)]+R2[δ′a](8)] |
Proposed assignments and potential energy distribution (PED) for vibrational normal modes.

Types of vibration: ν, stretching; δ, deformation (bending), scissoring; oop, out-of-plane bending; ω, wagging; γ, twisting; ρ, rocking; τ, torsion.

Potential energy distribution (contribution ≥ 5).

Figure 5: Calculated FT-IR spectrum between the ranges 200-3500 cm⁻¹.
Ring R2 vibrations
The asymmetric stretching of CH₂ predicted at 2942 cm⁻¹ has intensity 23.105/112.236 units in the IR/Raman spectra. The symmetric stretching was calculated at 2859 cm⁻¹. The deformation, wagging and twisting mode vibrations were calculated at 1462, 1353 and 1194 cm⁻¹, respectively.

Highly mixed C-C ring stretching was predicted at 1292 cm⁻¹. The ring deformation and puckering vibrations are below 1200 cm⁻¹ in the mixed modes.

Ring R3 vibrations
The N-H stretching vibration was calculated at 348 cm⁻¹. This pure mode (100% contribution in PED) has intensity 176.582 units in the Raman spectra and 80.067 units in the IR spectrum. The in-plane vibration of this mode was predicted at 1423 cm⁻¹, while out-of-plane vibration was at 381 cm⁻¹ as listed in the Table 2.

The frequency of ring deformation vibration was calculated at 1604 cm⁻¹. The C=C stretching predicted at 1563 cm⁻¹ is a mixed mode. The mixed NC stretching is below 1430 cm⁻¹.

Ring R4 vibrations
One can easily expect three modes of stretching vibration related to each CH moiety. In this study, the C-H stretching vibration was predicted at 3047, 3037 and 3026 cm⁻¹. The in-plane deformation was calculated at 1510 cm⁻¹. The out-of-plane vibration of this mode is 951 cm⁻¹. In the ring, C-C stretching and deformation vibrations were predicted at 1621 and 1436 cm⁻¹, respectively. The trigonal ring deformations were calculated below 1269 cm⁻¹.

CONCLUSION
The investigated molecule has 90 modes of vibrations. All the modes are both IR and Raman active. In this study, the vibrational wavenumbers along with their potential energy distribution has been analyzed by ab initio and DFT methods. Information about the shape, size, charge density and the structure-activity relation have been analyzed by mapping MEP. The large value of the band gap obtained from the HOMO and LUMO analysis supports that the title molecule is stable; however, there occur intramolecular charge transfer (ICT) within the molecule. This study could be a better starting for further investigations on structure-activity relation of the compound.

ACKNOWLEDGEMENTS
B.D. Joshi would like to acknowledge Professor Poonam Tandon, HoD, Physics Department, Lucknow University, India for providing software facilities.
REFERENCES

1. Rusterholz, D.B., Barfknecht C. F. & Clemens, J. A. 1977. Ergoline congeners as potential inhibitors of prolactin release. 3. Derivatives of 3-phenylpiperidine. Journal of Medicinal Chemistry. 20 (1): 85–88. http://dx.doi.org/10.1021/jm00211a017

2. Ahimsa-Müller, M.A., Markert, A., Hellwig, S., Knoop, V., Steiner, U., Drewke C. & Leistner, E. 2007. Clavicipitaceae fungi associated with ergoline alkaloid-containing Convolvulaceae. Journal of Natural Products. 70(12): 1955-1960. http://dx.doi.org/10.1021/jn np070315t

3. Krogsgaard-Larsen, N., Jensen, A.A., Schroder, T.J., Christoffersen, C.T. & Kehler, J. 2014. Novel Aza-analogues Ergoline Derived Scaffolds as Potent Serotonin 5-HT6 and Dopamine D3 Receptor Ligands. Journal of Medicinal Chemistry. 57(13): 5823-5828. http://dx.doi.org/10.1021/jm5003759

4. Gröger D. & Floss, H.G. 1998. G.A. Cordell (Editors). The alkaloids: Chemistry and Biology. Biochemistry of ergot alkaloids-achievements and challenges. Academic Press, San Diego, 50: 171.

5. Schardl, C.F., Pannacione, D.G. & Tuzdynski, P. 2006. G. A. Cordell (Ed). The Alkaloids: Chemistry and Biology. Ergot alkaloids-biology and molecular biology. Academic Press, New York, 63: p 45.

6. Markert, A. et al., 2008. Biosynthesis and Accumulation of Ergoline Alkaloids in a Mutualistic Association between Ipomoea asarifolia (Convolvulaceae) and a Clavicipitalean Fungus. Plant Physiology. 147(1): 296-305. http://dx.doi.org/10.1104/pp.108.116699 Hofmann, A. 1961. Die Wirkstoffe der Mexikanischen Zauberdroge “Ololiuqui” in eine Alkaloid-Verbindung. Planta Medica. 9(4): 354-367. http://dx.doi.org/10.1055/s-0028-1100366

7. Clay, K. 1991. In P. Barbosa, V. A. Krischik, C.G. Jones (Eds). Microbial Mediation of Plant-Herbivore Interactions. John Wiley & Sons, New York, p. 199.

8. Gröger, M. 1997. In S. Ajl (Ed.), Microbial Toxin. Academic Press, New York, 8: 321.

9. Rosse, G. & Schaffhauser, H. 2010. 5-HT6 receptor antagonists as potential therapeutics for cognitive impairment. Current Topics in Medicinal Chemistry. 10(2): 207-221. http://dx.doi.org/10.2174/156802610790411036

10. Medeiros, R.M.T., Barbosa, R.C., Riet-Corea, F., Lima, E.F., Tabosa, I.M., de Barros, S.S., Gardner D.R. & Molyneux, R.J. 2003. Tremorgenic syndrome in goats caused by Ipomoea asarifolia in Northeastern Brazil. Toxicon. 41(7): 933-335. http://dx.doi.org/10.1016/S0041-0101(03)00448-8

11. Choudhary, M.S., Sachs, N., Uluer, A., Glennon, R. A., Westkaemper, R. B. & Roth, B. L. 1995. Differential ergoline and ergopeptide binding to 5-hydroxytryptamine2A receptors: ergolines require an aromatic residue at position 340 for high affinity binding. Molecular Pharmacology. 47: 450-457. http://dx.doi.org/10.1124/molpharm.47.2.450

12. Ramírez, M. J. 2013. 5-HT6 receptors and Alzheimer's disease. Alzheimer's research & therapy. 5(2): 1-8. http://dx.doi.org/10.1186/alzrt169

13. Geldenhuys, W.J. & Van der Schyf, C.J. 2008. Serotonin 5-HT6 Receptor Antagonists for the Treatment of Alzheimer's Disease. Current Topics in Medicinal Chemistry. 8(12): 1035-1048. http://dx.doi.org/10.2174/156802608785161420

14. Novi, F., Millan, M.J., Corsini, G.U. & Maggio, R. 2007. Partial agonist actions of aripiprazole and the candidate antipsychotics S33592, bifeprunox, N-desmethylclozapine and preclanol at dopamine D3 receptors are modified by co-transfection of D3 receptors: potential role of heterodimer formation. Journal of Neurochemistry. 102(4): 1410-1424. http://dx.doi.org/10.1111/j.1471-4142.2007.04606.x

15. Wang, C., et al., 2013. Structural Basis for Molecular Recognition at Serotonin Receptors. Science. 340(6132): 610-614. http://dx.doi.org/10.1126/science.1232807

16. Mishra, R., Joshi, B.D., Srivastava, A., Tandon P. & Jain, S. 2014. Quantum chemical and experimental studies on the structure and vibrational spectra of an alkaloid–Corlumine. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 118: 470 - 480. http://dx.doi.org/10.1016/j.saa.2013.09.015

17. Chomers, J.M. & Griffiths, P.R. (Eds.), 2002. Handbook of Vibrational Spectroscopy, John Wiley and Sons. ISBN-13: 978-0471988472

18. Joshi, B.D., Mishra, R., Tandon, P., Oliveira, A.C. & Ayala, A.P. 2014. Quantum chemical studies of structural, vibrational, NBO and hyperpolarizability of ondansetron hydrochloride. Journal of Molecular Structure. 1058: 31-40. http://dx.doi.org/10.1016/j.molstruc.2013.10.062

19. Joshi, B.D. Tandon P. & Jain, S. 2013. Structure, MESF and HOMOLUMO study of 10-Acetyl10H-phenothiazine 5-oxide using vibrational spectroscopy and quantum chemical methods. BIBECHANA. 9; 38-49. BMHSS, p.38-49.

20. Hohenberg, P. Kohn, W. 1964. Inhomogeneous Electron Gas. Physical Review B-136(3): 864-871. http://dx.doi.org/10.1103/PhysRev.136.B864

21. Frisch, M.J. et al., 2009. GAUSSIAN 09, Revision, Gaussian Inc, Wallingford, CT.

22. Becke, A.D. 1993. Density-functional thermochemistry. III. The role of exact exchange. Journal of Chemical Physics. 98: 5648-5652. http://dx.doi.org/10.1063/1.464913

23. Parr, R.G. & Yang, W. Density Functional Theory of Atoms and Molecules, Oxford University Press, Oxford, New York, p 333.

24. Petersson, G.A. & Allaham, M.A. 1991. A complete basis set model for first-row atoms. Journal of Chemical Physics. 94(9): 6081-6090. http://dx.doi.org/10.1063/1.460447

25. Glendering, E.D., Reed, A.E., Carpenter, J. E. & Weinhold, F. 1998. NBO Version 3.1, TCI, University of Wisconsin, Madison.

26. Casida, M.E. 1995. D. P Chong (Eds.). Developments in Density Functional Theory. World Scientific, Singapore. 1: 155.
27. Casida, M. E. Casida K. C. and Salahub, D. R. 1998. Excited-state potential energy curves from time-dependent density-functional theory: A cross section of formaldehyde's $^1A_1$ manifold. *International journal of Quantum Chemistry. 70*: 933-941. [https://dx.doi.org/10.1002/(SICI)1097-461X](https://dx.doi.org/10.1002/(SICI)1097-461X)

28. Lee, C. Yang W. & Parr, R.G. 1998. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Physical Review. B-37*: 785-789. [http://dx.doi.org/10.1103/PhysRevB.37.785](http://dx.doi.org/10.1103/PhysRevB.37.785)

29. Martin, J.M.L. & Van Aslenoy, C. 1995. Gar2ped, University of Antwerp.

30. Pulay, P., Fogarasi, G., Pang, F. & Boggs, J.E. 1979. Systematic *ab initio* gradient calculation of molecular geometries, force constants, and dipole moment derivatives. *Journal of American Chemical Society. 101*: 2550-2560. [http://dx.doi.org/10.1021/ja00504a009](http://dx.doi.org/10.1021/ja00504a009)

31. Pulay, P., Fogarasi, G., Pongor, G., Boggs, J.E. & Vargha, A. 1983. Combination of theoretical *ab initio* and experimental information to obtain reliable harmonic force constants. Scaled quantum mechanical (QM) force fields for glyoxal, acrolein, butadiene, formaldehyde, and ethylene. *Journal of American Chemical Society. 105(24)*: 7037-7047. [http://dx.doi.org/10.1021/ja00362a005](http://dx.doi.org/10.1021/ja00362a005)

32. Frisch, A., Nielson, A.B. & Holder, A.J. 2000. GaussView User Manual, Gaussian Inc, Pittsburgh, P.A.

33. Zhurko, G.A. & Zhurko, D.A. 2005. Chemcraft. [http://www.chemcraftprog.com](http://www.chemcraftprog.com).

34. https://pubchem.ncbi.nlm.nih.gov/search/search.

35. Singh, R.N., Kumar, A., Tiwari, R.K., Rawat, P., Baboo, V. & Verma, D. 2012. Molecular structure, heteronuclear resonance assisted hydrogen bond analysis, chemical reactivity and first hyperpolarizability of a novel ethyl-4-[(2,4-dinitrophenyl)-hydrazono]-ethyl]-3,5-dimethyl-1H-pyrole-2-carboxylate: A combined DFT and AIM approach. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 92*: 295-304. [http://dx.doi.org/10.1016/j.saa.2012.02.086](http://dx.doi.org/10.1016/j.saa.2012.02.086)

36. Yoshida, H., Takeda, K., Okamura, J., Ehara, A. & Matsurra, H. 2002. A New Approach to Vibrational Analysis of Large Molecules by Density Functional Theory: Wavenumber-Linear Scaling Method. *Journal of Physical Chemistry. A-106(14)*: 3580-3586. [http://dx.doi.org/10.1021/jp013084m](http://dx.doi.org/10.1021/jp013084m)

37. Guirgis, G.A., Klaboe, P., Shen, S., Powell, D.L., Gruodis, A., Aleksa, V., Nielsen, C.J. Tao, J., Zheng, C. & Durig, J.R. 2003. Spectra and structure of silicon-containing compounds. XXXVI† — Raman and infrared spectra, conformational stability, *ab initio* calculations and vibrational assignment of ethylidibromosilane. *Journal of Raman Spectroscopy. 34(4)*: 322-336. [http://dx.doi.org/10.1002/jrs.989](http://dx.doi.org/10.1002/jrs.989)

38. Polavarapu, P. L. 1990. *Ab initio* vibrational Raman and Raman optical activity spectra. *Journal of Physical Chemistry. 94(21)*: 8106-8112. [http://dx.doi.org/10.1021/j100384a024](http://dx.doi.org/10.1021/j100384a024)

39. Silverstein, R.M. Bassler G.C. & Morrill, T.C. 1991. *Spectrometric Identification of Organic Compounds (Fifth Edition).* Wiley, New York. p 430. ISBN 0471 63404 2.