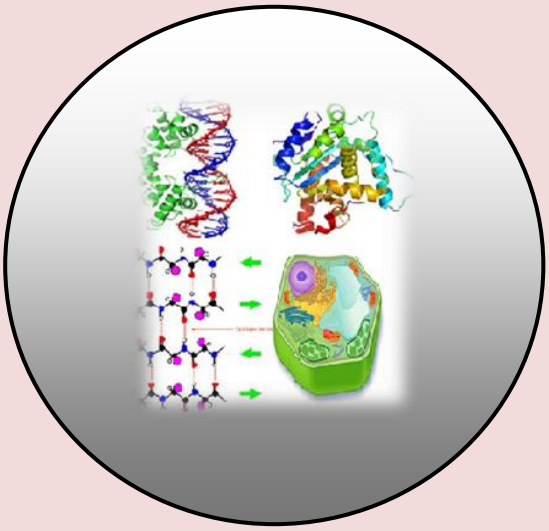
Facile Synthesis of Diosgenin Thiosalicylate its Spectroscopic Analysis Chemical Reactivity and Intramolecular Interaction by Quantum Chemical Calculations

By
Sangeeta Srivastava

ISSN 2319-3077 Online/Electronic
ISSN 0970-4973 Print

UGC Approved Journal No. 62923
MCI Validated Journal
Index Copernicus International Value
IC Value of Journal 82.43 Poland, Europe (2016)
Journal Impact Factor: 4.275
Global Impact factor of Journal: 0.876
Scientific Journals Impact Factor: 3.285
InfoBase Impact Factor: 3.66



J. Biol. Chem. Research
Volume 36 (1) 2019, Pages No. 215-224

Journal of Biological and Chemical Research

An International Peer Reviewed / Referred Journal of Life Sciences and Chemistry

Indexed, Abstracted and Cited: Index Copernicus International (Europe), Validated Medical Council of India, World Science Index, Polish Ministry of Science and Higher Education (Poland, Europe) Research Bible (Japan), Scientific Journals Impact Factor Master List, Directory of Research Journals Indexing (DRJI), Indian Science. In, Database Electronic Journals Library (Germany), Open J-Gate, J Gate e-Journal Portal, Info Base Index, International Impact Factor Services (IIFS) (Singapore), Scientific Indexing Services (USA), International Institute of Organized Research (I2OR), Cosmos Science Foundation (Germany), Science Library Index (UAE), Eye Source, Swedish Scientific Publication, World Cat, International Innovative Journal Impact Factor, Einstein Institute for Scientific Information {EISI} and Impact Factor.pl - Kompendiumwiedzy o czasopismachnaukowych, Philadelphia citefactor.org journalsindexing Directory Indexing of International Research Journals

Published by Society for Advancement of Sciences®

J. Biol. Chem. Research. Vol. 36, No. 1: 215-224, 2019
(An International Peer Reviewed / Refereed Journal of Life Sciences and Chemistry)
Ms 36/01/7909/2019

ISSN 2319-3077 (Online/Electronic)
ISSN 0970-4973 (Print)

Dr. Sangeeta Srivastava
http:// www.sasjournals.com
http:// www.jbcr.co.in
jbiolchemres@gmail.com

RESEARCH PAPER
Received: 27/02/2019 Revised: 29/04/2019 Accepted: 30/04/2019

Facile Synthesis of Diosgenin Thiosalicylate its Spectroscopic Analysis Chemical Reactivity and Intramolecular Interaction by Quantum Chemical Calculations

Sangeeta Srivastava
Department of Chemistry, Lucknow University, Lucknow-226007, U.P., India

ABSTRACT

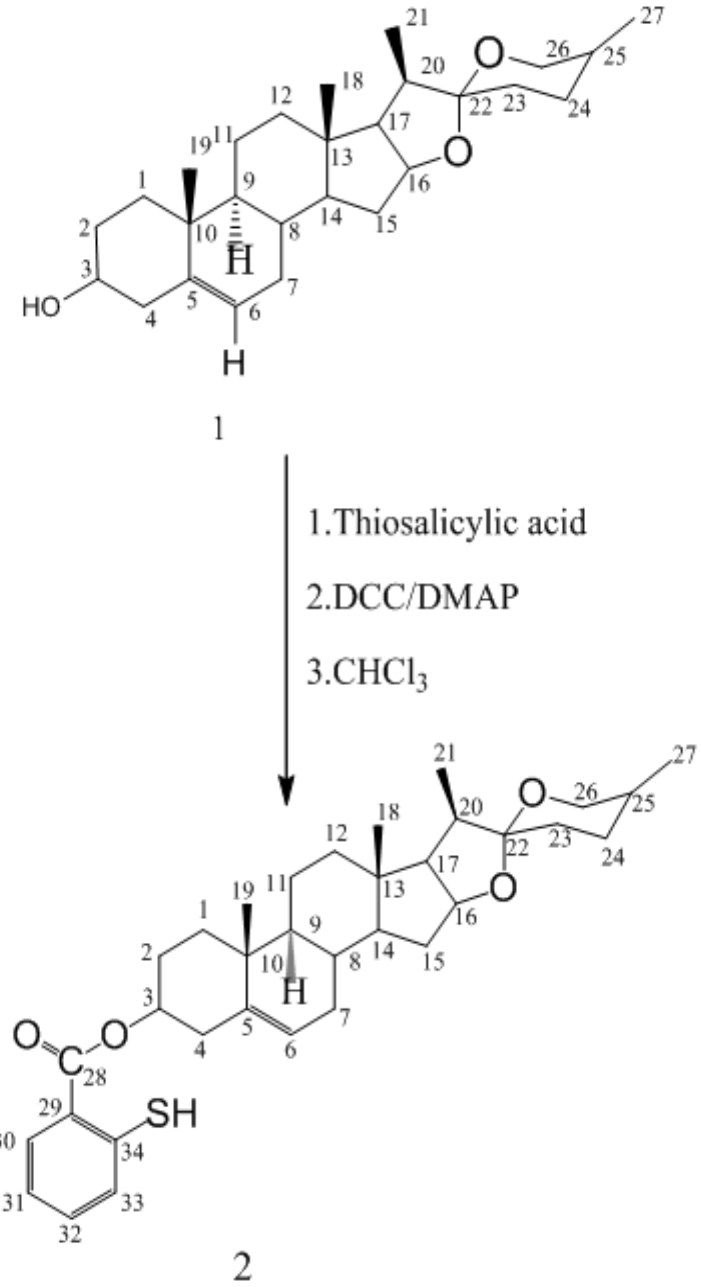
In the present work the molecular structure and detailed spectroscopic analysis of newly synthesized conjugate of diosgenin have been performed using experimental techniques like 1H, 13C NMR, FT-IR, UV-visible spectroscopy, mass spectrometry, as well as theoretical calculations. Quantum chemical calculations have been performed by density functional theory (DFT) using B3LYP functional and 6-31G (d, p) basis set. The electronic properties such as frontier orbitals and band gap energies have been calculated using time dependent density functional theory (TD-DFT). The strength and nature of weak intramolecular interactions have been studied by AIM approach. The vibrational wave numbers have been calculated using DFT method. Molecular electrostatic potential (MEP) analysis has also been carried out.

Keywords: Diosgenin, Thiosalicylic acid, Steglich Esterification, MEP, AIM, HOMO and LUMO.

INTRODUCTION

Steroids are perhaps one of the most widely used groups of drugs in present day. Beside the established utilization as immunosuppressive, anti-inflammatory, anti-rheumatic, progestational, diuretic, sedative, anabolic and contraceptive agents, recent applications of steroid compounds include the treatment of some forms of cancer, osteoporosis, HIV infections and treatment of declared AIDS. Pregnanes are one of the most versatile steroidal derivatives, which have been dynamically studied. They are the important class of steroid known for possessing remarkable biological activities like anti-inflammatory Nobile et al., 1955 anti-asthmatic Shen and Burgoyne., 2002 anti-viral Comin et al., 1999 and anti-feedant Purushothaman et al., 1987 b-oxyketones derivatives of pregnanes, synthesized by Michael addition reaction on a, b-unsaturated pregnanes Wabnitz and Spencer., 2003 have been reported to exhibit anti-hyperlipidemic and anti-oxidant activity Sethi et al., 2011 Ester derivatives of steroids have also been reported to exhibitpotential anti-hyperlipidemic, anti-oxidant Wabnitz and Spencer., 2003 anti-diabetic Xing et al., 2013 and anti-adipogenic activities Sethi et al., 2012. Diosgenin, chemically named as 25R-spirost-5-en-3_-ol, is prominent among the sapogenins used in steroid industry. Diosgenin has been reported to inhibit proliferation and induces apoptosis in a wide variety of tumor cells of human colon Raju et al., 2004 osteosarcoma Corbiere et al., 2003, leukemia.

Liu et al., 2005, erythroleukemia Leger et al.,2004 breast Srinivasan et al.,2009 and liver Li et al 2010., The anti-cancer effect of diosgenin has been well demonstrated through cell cycle arrest Moalic et al.,2001 activation of p53 and caspase-3 Corbiere et al.,2004. Diosgenin also abolishes cyclooxygenase-2 and lipoxygenase Nappez et al., 1995 which are implicated in carcinogenesis and as important targets for cancer chemoprevention and therapy. Therefore, diosgenin may possess the cancer chemotherapeutic potential and its activity involves multiple cellular and molecular targets.



Scheme 1

Series of optical amino acid diosgenyl esters and diosgenyl salicylate conjugates have been reported to possess anticancer and anti-inflammatory activity. Preliminary structure activity relationship studies have shown that diosgenyl salicylate conjugates exhibit stronger anti-inflammatory activities in comparison to amino acid diosgenyl esters Huang et al., 2012.
Series of novel 17-oxo-17a-aza-D-homo-5-androsten-3_-yl esters were synthesized from commercially available diosgenin and they were evaluated for their in vitro antiproliferative activity, acute toxicity and effect on serum androgen level Dhingra et al., 2011
The synthesis and evaluation of two new 26-hydroxy-22-oxocholestanic steroids from diosgenin and hecogenin on cervical cancer CaSki cells was carried out and the synthesized compounds showed anti-proliferative and anti-tumor activity Ferández-Herrera et al., 2010.
Taking into account the biological importance of these diosgenin, we herein report the synthesis, characterization of newly synthesized pregnane derivative supported by theoretical studies. A detailed study regarding the structural and spectroscopic properties of these newly synthesized pregnane helped in better understanding the chemical reactivity of these compounds. Density Functional Theory (DFT) with the help of B3LYP functional and 6-31G (d, p) basis set was used for optimizing the geometry of the newly synthesized compound **2.** Further, nuclear magnetic chemical shifts were calculated by same functional basis set using Gauge Including Atomic Orbital (GIAO) method and result were then compared with the experimental data. The DFT calculations incorporating MESP, AIM and electronic absorption transition, were probe by same DFT basis atomic set. The atom in molecule (AIM) theory has been comprehensively used to classify and figure out hydrogen bonding and π-electron delocalization in the synthesized moiety. Energy gap between HOMO and LUMO depicts the molecular chemical stability and charge transfer interactions.

MATERIAL AND METHODS

Materials and physical measurements

All reagents for synthesis were purchased from Sigma Aldrich (St. Louis, MO) and used without further purification. Thin layer chromatography (TLC) was performed on silica gel G coated plates to detect completion of reaction. Compounds were purified by column chromatography using silica gel (60-120 mesh). ^{1}H NMR spectrum was recorded on Bruker DRX-300 MHz spectrometer using $CDCl_3$ and DMSO as the solvent and TMS as an internal standard, chemical shift was reported as δ (ppm) and ^{13}C NMR spectra were recorded on JOEL AL 300 FTNMR (75Mz) using TMS as an internal reference. FT-IR spectra were recorded on Perkin Elmer FT-IR spectrometer from 4000–450 cm^{-1} range. The spectra were analyzed using Spectrum™ Software suite. Ultraviolet absorption spectra were obtained (in the range of 200-500 nm) using ELICO BL-200 UV-Vis spectrophotometer equipped with a 10 mm quartz cell in chloroform.

Synthesis of 3β, 25R-spirost-5-en-3yl 2 mercaptobenzoate

100mg (0.241 mmol) of **1** and 37.18 mg (0.241mmol) of thiosalicylic acid was dissolved in 15 mL of dioxane and then DCC (51.58 mg, 0.25 mmol) and DMAP (30.54 mg, 0.25 mmol) were added. The reaction mixture was stirred at room temperature. The completion of reaction was monitored with the help of thin layer chromatography (TLC). Reaction mixture was washed with 5% HCl, water and dried over anhydrous sodium sulphate and filtered. The organic layer was concentrated under reduced pressure and purified by column chromatography using ethyl acetate: hexane (15:85) yielding compound **2** 80mg (58.83%) as viscous. Molecular formula:$C_{34}H_{46}O_4S$, ^{1}H NMR(300MHz, $CDCl_3$) δ(ppm):0.85 (6H, s,OCH_3-18 & OCH_3-27), 1.19 (3H, s OCH_3-19), 1.43 (3H, s, OCH_3-21), 3.39 (1H, s, SH), 3.53-3.43 (2H, m, H-26), 4.68 (1H, m, H-3), 5.36 (1H, br. s, H-6), 7.22-7.20 (3H, m, H-31, H-32, H-33), 8.14-8.12 (1H, d, J=7.5Hz, H-30), ^{13}C NMR(75 MHz, $CDCl_3$) δ (ppm): 14.53 (C-21Me), 16.31 (C-18Me), 17.16 (C-27Me), 19.44(C-19Me), 20.87 (C-1), 28.77 (C-2 & C-24), 29.72 (C-11), 30.29 (C-7), 31.42 (C-15), 31.82(C-23), 32.05(C-25),36.61(C-4), 37.19(C-12), 39.78 (C-13),40.21 (C-9), 41.61 (C-10), 42.15 (C-20), 50.42 (C-8), 50.88 (C-14), 62.01 (C-17), 66.87 (C-26), 71.86 (C-3), 80.47 (C-16), 109.01 (C-22), 121.52 (C-6), 124.83 (C-31), 124.89(C-32), 131.04(C-34, C-29), 132.66 (C-30), 133.25 (C-33), 139.24 (C-5), 170.06(C-28).], IR νmax (in cm^{-1}): 3040, 2980, 2654, 2519, 1678, 1587-1411, 1317, 1265, 1165, 1060, 977, 740.

RESULT AND DISCUSSION

^{1}H and ^{13}C NMR Spectroscopy

In the experiment ^{1}H and ^{13}C NMR chemical shift of compound **2** are listed Table 1. In the ^{1}H NMR spectrum of compound **2** four proton multiplet observed at δ 3.28-3.75 due to H-3 methine proton, proton of SH group, one equatorial and one axial proton at C-26 position in the spiroketal ring. One proton quartet signal observed at δ 4.68 for H-16 methene. Observed peak at δ 0.77 and 0.79 corresponds to CH_3-18 and CH_3-27 methyl protons respectively. Three proton doublet at δ 0.98 (J=5.4Hz) corresponds to CH_3-21 methyl whereas, another three proton singlet observed at δ 1.03 was due to CH_3-19 angular methyl.

Table 1. *Experimental ^{1}H and ^{13}C NMR of compound 1.*

Atom no.	Experimental value of ^{1}H NMR	Atom no.	Experimental value (in ppm) of ^{13}C NMR
CH3-18 & CH3-27 (s)	0.85	C-21	14.53
CH3-19 (br, s)	1.19	C-18	16.31
CH3-21 (s)	1.43	C-27	17.16
SH (s)	3.39	C-19	19.44
H-26 (m)	3.53-3.43	C-1	20.87
H-3 (m)	4.68	C-2 & C-24 C-11	28.77 29.72
H-6 (br, s)	5.36	C-11	30.29
H-31, H-32 & H-33 (d)	7.22-7.20 (J=6.0 Hz)	C-15	31.42
H-30 (d)	8.14-8.12 (J=7.5 Hz)	C-23	31.82
		C-25	32.05
		C-4	36.64
		C-12	37.19
		C-13	39.78
		C-9	40.27
		C-10	41.61
		C-20	42.15
		C-8 C-14 C-17 C-26 C-3 C-16 C-22 C-6 C-31 C-32 C-34 &29 C-30 C-33 C-5 C-28	50.42 50.88 62.01 66.87 71.86 80.47 109.01 121.52 124.83 124.89 131.04 132.66 133.25 139.24 170.01

In the ^{13}C NMR spectrum peak at δ 16.31 and 19.44 were observed due to the presence of two angular methyl group CH_3-18 and CH_3-19 respectively. Two peaks at δ 14.53 and 17.16 were observed for two methyl group C-21 and C-27 respectively. Signal at δ 139.24 was observed due to C-5 vinylic carbon.

Signal for C-28 ester moiety was also observed at δ 170.06 along with the signals of aromatic carbons C-31 at δ 124.83, C-32 at 124.89, C-34 at 131.04, C-30 at 132.66 and C-33 at 133.25 of thiosalicylate group thus confirms the esterification of thiosalicylic acid with C-3 hydroxyl group of diosgenin in compound **2.**

Vibrational spectral analysis

An experimental FT-IR spectrum of synthesized compound has been recorded in the range of 4000–450 cm^{-1}. The calculated and experimental FT-IR wave numbers for 3 with their assignments are given in Table 2. The calculated wave numbers are scaled down by a single scaling factor 0.9608 **Sundaraganesan et al.,2009.** The position of carbonyl group C=O stretching vibration is determined by factors like conjugation, ring strain, hydrogen bonding and physical state. These factors give particulars about the environment of C=O group. Generally C=O stretching vibrations appear in the region of 1870–1540 cm^{-1} **Srivastava et al.,2017; Silverstein and Webster.,1963.**

In the experimental IR spectrum of synthesized compound **2**, the aromatic C-H stretching was observed at 3040 cm-1. The symmetric and asymmetric C-H stretching vibration of -CH3 and –CH2 groups was observed between 2900-2800 cm^{-1}. The CH_3 stretching vibration was observed at 2980 and 2654 cm^{-1}. The thiol group –S-H stretching was observed at 2519 cm-1. In general the stretching vibration for carbon-carbon bond for alkene appeared around 1600 cm-1 as in original compound but the stretching vibration for carbonyl C=O of ester and aliphatic C=C were merged and observed at 1678 cm^{-1}. In aromatic hydrocarbon, C=C stretching vibrations within the ring are observed in the region between 1566-1510 cm^{-1} **Krishnakumar et al.,2008.** Aromatic C=C stretching vibration of compound 2 were observed at 1587, 1558 cm^{-1} and 1465, 1411 cm^{-1}. C-O stretching vibration of ester group was observed at 1317 cm^{-1}. C-O stretching vibrations of five and six membered ring were observed at 1265 and 1165 cm^{-1} respectively. Aromatic C-H bending was observed at 1060 cm^{-1}. The experimental wave numbers for compound **2** with their assignment of vibrational modes are given in **Table 2.**

Table 2 Experimental vibrational wave numbers (in cm^{-1}) of compound 2 and their assignments.

Experimental		Calculated Vibrational assignment
3040	3040	Aromatic C-H stretching
2980	2983	Aliphatic C-H stretching
2654	2871	Aliphatic C-H stretching
2519	2392	S-H Stretching of thiol group
1678	1687	Ester C=O Stretching and aliphatic
		C=C overlap
1587-1411	1587-1408	Aromatic C=C stretching
1317	1316	C-O stretching
1265	1236	C-O stretching of 5 membered ring
1165	1156	C-O stretching of 6 membered ring
1060	1035	C-H in plane bending of aromatic
977	967	C-H out of plane bending
740	726	O-disubstitued aromatic

Molecular Electrostatic Potential

Molecular electrostatic potential surface (MEP) for the compounds 2 was calculated by DFT/B3LYP at 6-31G (d, p) basis set and MEP surface are plotted in Fig. 1. The MEP is a plot of the electrostatic potential mapped onto the constant electron density surface. It simultaneously displays the molecular shape, size, and charge distribution, as well as reactive sites of a molecule Srivastava et al.,2016; Alkorta and Perez 1996 ; Scrocco and Tomasi 1978; Luque et al.,1993. The red and yellow regions of the MEP are related to electrophilic reactivity and the blue regions to nucleophilic reactivity Powell et al.,2004. In compound 2 the carboxyl group of thiosalicylate is characterized by red region indicating relative surplus of electrons and may be a site for electrophilic interactions. There by confirming that carboxyl group at thiosalicylic acid in 2 was esterified with the OH at C-3 of diosgenin leading to the synthesis of an ester.

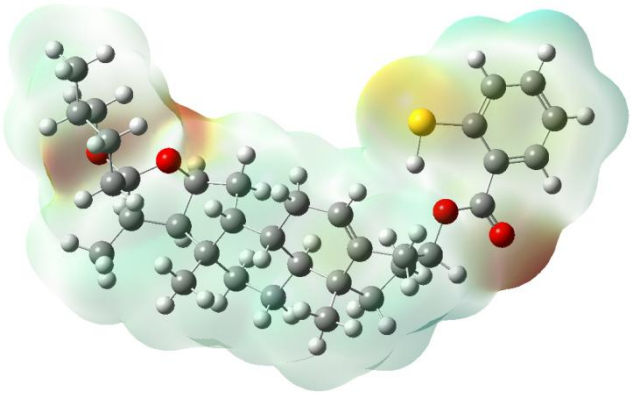


Figure 1. Molecular electrostatic potential of compound 2.

Table 3. Electronic transitions (calculated and experimental).

Major contributing Molecular orbitals	ΔE (eV)		Assignment	Observed (λ_{max})
H→L	4.6010		n →π*	335
H-4→L	5.7400		π →π*	265

UV–Vis absorption spectra

An experimental UV–Visible spectrum analysis of 2 indicates that an intense electronic transition at λmax=335nm was attributed to n→π* transition through highest occupied molecular orbital (H, 149) to the excited unoccupied molecular orbital (L, 150). Experimental UV for compound 2 showed two electronic transitions at 335 nm and 265 nm. The electronic transition at 335 nm may be attributed mainly due to H→Ltransition which was assigned due to n → π* transition while electronic transition at 265 nm were attributed mainly to H-4→L which was assigned due to π → π* transition. Fig 2 shows that orbitals HOMO and HOMO-4 are localized over S- carbons of benzene ring of thiosalicylic moiety, however orbitals LUMO is localized over C28-O2 of carbonyl group in between benzene ring and steroidal ring. The value of the energy gap between HOMO and LUMO is 4.6010 eV. Frontier orbital energy gap assists in characterising the chemical reactivity and kinetic stability Aihara., 1993 of the molecule. The energies of the HOMO are directly related to the ionization potential and therefore preferable site for electrophilic attack. The energy of LUMO is directly proportional to the electron affinity and therefore preferable site for nucleophililic attack. A small Frontier orbital energy gap describes low kinetic stability, since it is energetically favourable to add electrons to a LUMO and to extract electrons from a HOMO. Thus, compound 2 with low frontier orbital gap is more polarizable and associated with high chemical reactivity which may affect the molecular activity and also illustrating eventual charge transfer interaction occurring within the molecule Bhavani et al., 2015.

AIM approach

Topological parameters are useful tool to characterize the strength of hydrogen bond. The geometrical criteria for the existence of hydrogen bond are as follows: (i) the distance between proton (H) and acceptor (A) should be less than the sum of the Van der Waal's radii of these atoms. (ii) The angle between 'donor (D), proton (H) and acceptor (A)' should be greater than 90°. (iii) There should be elongation of 'donor (D) proton (H)' bond length. As the above criteria were often considered insufficient, hence the existence of hydrogen bond was supported further by Koch and Popelier criteria Kleinman.,1962 based on 'Atoms in Molecules' theory (i) the existence of bond critical point for the 'proton (H)……acceptor (A)' contact as a confirmation of the existence of hydrogen bonding interaction. (ii) The value of electron density (ρH. . .A) should be within the range 0.002–0.040 a.u. (iii) The corresponding Laplacian $^2\rho(r_{BCP})$ should be within the range 0.024–0.139 a.u. Murray and Sen.,1996.

According to Rozas et al., 2000 the interactions may be classified as follows: (i) strong H-bonds are characterized by $\nabla^2\rho_{(BCP)} < 0$ and $H_{BCP} < 0$ and their covalent character is established. (ii) Medium H-bonds are characterized by $\nabla^2\rho_{(BCP)} > 0$ and $H_{BCP} < 0$ and their partially covalent character is established. (iii) Weak H-bonds are characterized by $\nabla^2\rho_{(BCP)} > 0$ and $H_{BCP} > 0$ and they are mainly electrostatic. The weak interactions are characterized by $\nabla^2\rho_{(BCP)} > 0$ and $H_{BCP} > 0$ and the distance between interacting atoms is greater than the sum of Van der Waal's radii of these atoms. Molecular graph of the compound 2 using AIM program at B3LYP/6- 31G (d,p) level is presented in Fig.3. The topological parameters for bonds of interacting atoms are given in Table 4. on the basis of above criteria, as $\nabla^2\rho$(BCP) and H_{BCP} parameters were greater than zero hence C-6…H(S), H11..H18, H18..H23, H1..H11, H19…H8, H21…H18 are weak interactions. In this article, the Bader's theory application was used to estimate hydrogen bond energy (E). Espinosa proposed proportionality between hydrogen bond energy (E) and potential energy density (V_{BCP}): $E = 1/2(V_{BCP})$ Espinosa et al., 1998. According to AIM calculation, the total energy of intramolecular interactions was calculated as -6.586 kcal/mol.

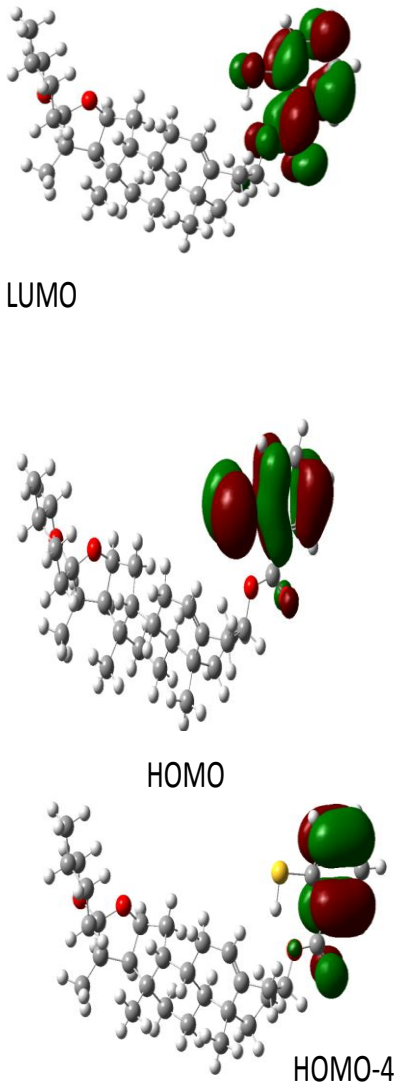


Figure 2. HOMO – LUMO diagram of compound 2.

Table 4. Topological parameters for intramolecular interaction in compund; electron density (ρ_{BCP}), Laplacian of electron density ($\nabla^2\rho_{BCP}$), electron kinetic energy density (G_{BCP}), electron potential energy density (V_{BCP}), total electron energy density (H_{BCP}), Hydrogen bond energy (E_{HB}) at bond critical point (BCP).

Interaction	$\rho_{(BCP)}$	$\nabla^2\rho(\mathbf{r}_{BCP})$	G_{BCP}	V_{BCP}	H_{BCP}	E_{int}
Compound **2**						
C-6…H(S)	+0.003	+0.010	+0.002	-0.001	0.001	-0.313
H11....H18	+0.009	+0.037	+0.007	-0.005	0.002	-1.568
H18..H23	+0.006	+0.022	+0.004	-0.002	0.002	-0.627
H1...H11	0.010	+0.042	+0.008	-0.006	0.002	-1.255
H19…H8	+0.008	+0.035	+0.006	-0.004	0.002	-1.255
H21…H18	+0.009	+0.040	+0.007	-0.005	0.002	-1.568

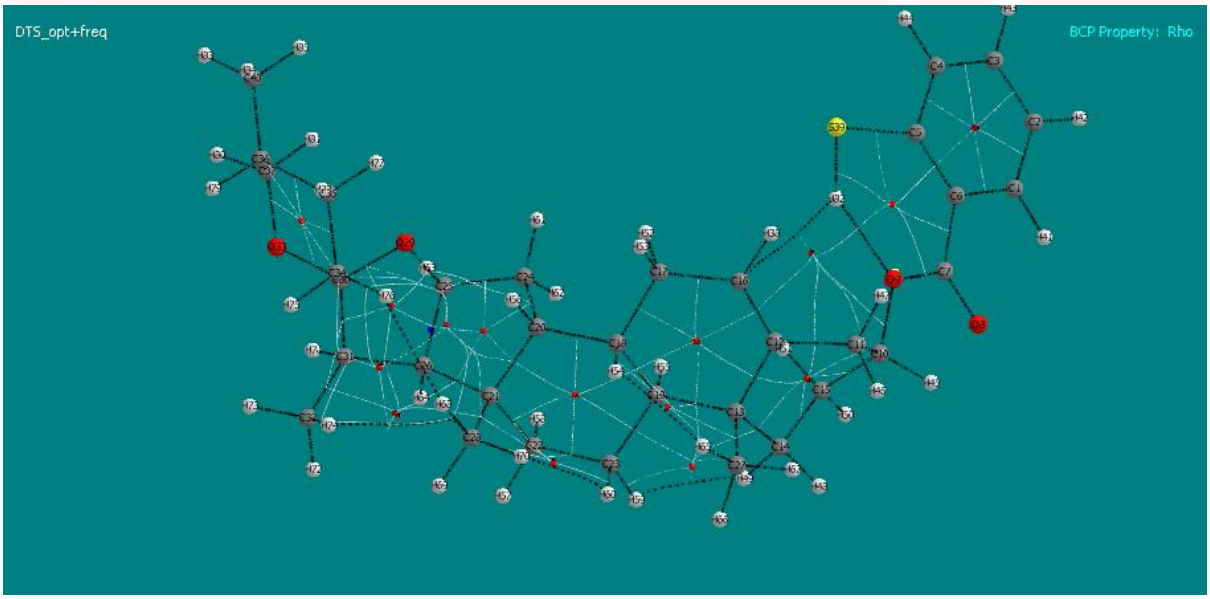


Figure 3. Molecular graph of compound 2.

CONCLUSION

Synthesis of compound **2**, a derivative of diosgenin was carried out by using Steglich method and was obtained in high yield. The synthesized compound was characterised with the help of ^{1}H, ^{13}C NMR, FT-IR and UV-visible spectroscopy. Theoretical analysis performed with the help of density functional theory using B3LYP functional and 6-31-G (d, p) basis set has supported experimental results. Molecular electrostatic potential surface analysis helps in identifying electrophilic and nucleophilic sites in the molecule as well as probable reaction path that leads to the formation of **2**. The optimized structure of **2** is stabilized by weak intramolecular interactions, as ascertained by AIM approach. Frontier orbital energy gap assists in characterising the chemical reactivity and kinetic stability of the molecule. Thus, compound **2** with low frontier orbital gap is more polarizable and associated with high chemical reactivity which may affect the molecular activity and also illustrating eventual charge transfer interaction occurring within the molecule.

ACKNOWLEDGEMENTS

The authors are grateful to Central Facility for Computational Research, Department of Chemistry, University of Lucknow for computational work and also thankful to Department of Chemistry, University of Lucknow for spectral data.

REFERENCES

Nobile, A., Charney, A. W., Perlman, P. L., Herzog, H. L., Paynee, C. C., Tully, M. E., Jevnik M. A. and Hershberg, E. B., (1955). Advances in applied microbiology. *J. Am. Chem. Soc.* 77 4184.

Shen, Y. and Burgoyne, D. L. (2002). Efficient synthesis of IPL576, 092: a novel anti-asthma agent, *J. Org. Chem.* 67, 3908.

Comin, M. J., Maria, M. S., Roccatagliate, A. J., Pujal, C. A. and Damonate, E. B. (1999). Evaluation of the antiviral activity of natural sulfated polyhydroxysteroids and their synthetic derivatives and analogs. *Steroids.* 64 335.

Purushothaman, K.K., Sarada, A. and Saraswathi A. (1987). Chemical constituents of *Lansium anamallayanum* Bedd. *Can. J. Chem.* 65 150.

Wabnitz, T. C. and Spencer, J. B., (2003). A General, Brønsted Acid-Catalyzed Hetero-Michael Addition of Nitrogen, Oxygen, and Sulfur Nucleophiles Org. *Lett.*, Vol. 5 2141-2144.

Sethi, A., Bhatia, G., Khanna, A. K., Khan, M. M., Bishnoi, A., Pandey, A. K. and Maurya, A. (2011). Expedient synthesis of some novel pregnane derivatives and their evaluation as anti-oxidant and anti-dyslipidemic agents *Med Chem Res.* 20 36–46.

Xin, G., Wang, Y., Guo, X., Huang, B., Du, D., He, S., Zhang, R., Xing, Z., Zhao, H., Chen, Q., Huang, W. and He, Y., (2013). Synthesis of Diosgenin-Ibuprofen Derivatives and Their Activities against Insulin-Dependent Diabetes Mellitus, *Chem. Pharm. Bull.* 61 532–538.

Sethi, A., Bhatia, A., Shukla, D., Kumar, A., Sonker, R., Prakash, R. and Bhatia, G. (2012). Synthesis of diosgenin *p*-nitrobenzoate by Steglich method, its crystal structure and quantum chemical studies**.** *J. Mol. Struct.* 1028 88–96.

Raju, J., Patlolla, J.M., Swamy, M.V. and Rao, C.V. (2004). Diosgenin, a Steroid Saponin of *Trigonella foenum graecum* (Fenugreek), Inhibits Azoxymethane-Induced Aberrant Crypt Foci Formation in F344 Rats and Induces Apoptosis in HT-29 Human Colon Cancer Cells. *Cancer Epidemiol Biomarkers Prev***.** 13, 1392- 1398.

Corbiere, C., Liagre, B., Bianchi, A., Bordji, K., Dauca, M., et al (2003). Different contribution of apoptosis to the antiproliferative effects of diosgenin and other plant steroids, hecogenin and tigogenin, on human 1547 osteosarcoma cells, *Int J Oncol*. 22 899-905.

Liu, M.J., Wang, Z., Ju, Y., Wong, R.N. and Wu, Q.Y. (2005). Diosgenin induces cell cycle arrest and apoptosis in human leukemia K562 cells with the disruption of Ca^{2+} homeostasis, *Cancer Chemother Pharmacol*. 55 79-90**.**

Leger, D.Y., B. Liagre, P.J. Cardot, J.L. Beneytout and Battu, S. (2004). Diosgenin dose-dependent apoptosis and differentiation induction in human erythroleukemia cell line and sedimentation field-flow fractionation monitoring**,** *Anal Biochem*. 335 267-278.

Srinivasan, S., Koduru, S., Kumar, R., G. Venguswamy, R. Kyprianou, N., et al, (2009). Diosgenin targets Akt-mediated prosurvival signaling in human breast cancer cells, *Int J Cancer* 125 961-967.

Li, F., Fernandez, P.P., P. Rajendran, K.M. Hui and G. Sethi (2010). Diosgenin, a steroidal saponin, inhibits STAT3 signaling pathway leading to suppression of proliferation and chemosensitization of human hepatocellular carcinoma, *Cancer Lett.* 292 197- 207.

Moalic, S., Liagre, B., Corbiere, C., Bianch, A., Dauca, M., et al., (2001). A plant steroid, diosgenin, induces apoptosis, cell cycle arrest and COX activity in osteosarcoma cells, *FEBS Lett.* 506 225-230.

Corbiere, C., Liagre, B., Terro, F. and Beneytout, J.L. (2004). Induction of antiproliferative effect by diosgenin through activation of p53, release of apoptosis-inducing factor (AIF) and modulation of caspase-3 activity in different human cancer cells, *Cell Res*. 14 188–196.

Nappez, C., Liagre, B. and Beneytout, J.L. (1995). Changes in lipoxygenase activities in human erythroleukemia (HEL) cells during diosgenin-induced differentiation, *Cancer Lett.* 96 133–140.

Huang, B., Du, D., Zhang, R., Wu, X., Xing, Z., He, Y. and Huang, W. (2012). Synthesis, characterization and biological studies of diosgenyl analogues. *Bioorg Med Chem Lett* 22(24) 7330-4.

Dhingra, N., Bhardwaj, T.R., Mehta, N., Mukhopadhyay, T., Kumar, A. and Kumar, M. (2011). 17-Oximino-5-androsten-3β-yl esters: synthesis, antiproliferative activity, acute toxicity, and effect on serum androgen level, *Medicinal chemistry research* 20 817-825.

Ferández-Herrera M.A., López- Munoz H., Herández- Vázquez J.M., López- Dávila M., Sánchez M.L., Sánchez-Sánchez L., Pinto B.M. and Sandoval- Ramírez, J. (2010). Steroidal saponins and cell death in cancer, *Bioorg Med Chem*. 18(7) 2474-84.

Sundaraganesan, N., Kavitha, E., Sebastian, S., Cornard, J. P. and Martel, M. (2009). Experimental FT-IR, FT-IR (gas phase), FT-Raman and NMR Hyperpolarizability studies and DFT calculations of 3,5-dimethylpyrazole *Spectra. Acta* Part A., 74 : 788-797.

Srivastava, S., Gupta, P., Singh, R. P., Jafri, A., Arshad, M. and Banerjee, M. (2017). Synthesis, spectroscopic characterization, theoretical study and anti-hepatic cancer activity study of 4 (1E,3Z,6E)-3-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-5-oxohepta-1,3,6-trien-1-yl)-2 methoxyphenyl 4-nitrobenzoate, a novel curcumin congener. *J. Mol. Struct*. 1109 58-66

Silverstein, R.M. and Webster, F.X. (1963). Spectrometric Identification of Organic Compounds, sixth Edi., Jon Willey Sons Inc., New York.

Krishnakumar, V., Manohar, S. and Nagalakshmi R (2008). Crystal growth and characterization of *N*-hydroxyphthalimide ($C_8H_5NO_3$) crystal *Molecular and biomoleculr spectroscopy*. 71 110-115.

Srivastava, S., Gupta, P., Amandeep Singh and R. P. Singh (2016). Synthesis of 4-((1E, 6E)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl)-2-methoxyphenyl 4-fluorobenzoate,a novel monoester derivative of curcumin, its experimental and theoretical (DFT) studies. *J. Mol. Struct.* 1109: 58-66.

Alkorta, I. and Perez, J. J. (1996). Molecular polarization potential maps of the nucleic. *J. Quant. Chem.* 57:123-135.

Scrocco, E. and Tomasi, J. (1978). Electronic molecular structure, intermolecular forces: An Euristic interpretation by means of electrostatic molecular potential Advances in Quantum Chemistry. Lowdin P (Ed.) Academic Press, New York

Luque, F. J., Orozco, M., Bhadane, P. K. and Gadre, S. R. (1993). SCRF calculation of the effect of water on topology of molecular electrostatic potential. *J. Phys. Chem*. 97: 9380-9384.

Powell, C.E., Morrall, J.P., Ward, S.A., Cifuentes, M.P., Motaras, E.G.A., Samoc, M. and Humphrey, M.G. (2004). Molecular organometallic materials for optics. *J. Am. Chem. Soc*. 126, 12234-12235.

Aihara, J., J. Phy-Chem A. 103. (1993). Reduced HOMO−LUMO Gap as an Index of Kinetic Stability for Polycyclic Aromatic Hydrocarbons 7487-7495**.**

Bhavani, K., S. Renuga, S. Muthu and K. Sankaranarayanan (2015). Quantum mechanical study and spectroscopic (FT-IR, FT-Raman, ^{13}C, ^{1}H) study, first order hyperpolarizability, NBO analysis, HOMO and LUMO analysis of 2-acetoxybenzoic acid by density functional methods Spectrochimica Acta Part A: *Molecularspectroscopy* 136 1260-1268.

Kleinman, D.A. (1962). Nonlinear Dielectric Polarization in Optical Media. Eikonal method in magnetohydrodynamics. *Phys.* Rev.126:1977.

Murray, J. S. and Sen, K. (1996). Molecular Electrostatic Potentials, Concepts and Applications. Elsevier, Amsterdam;. Molecular electrostatic potentials.

Rozas, I., Alkorta, I. and Elguero, J. (2000). Behavior of Ylides Containing N, O, and C Atoms as hydrogen bond acceptors. *J. Am. Chem. Soc*. 122: 11154-11161.

Espinosa, E., Molins, E. and Lecomte, C. (1998). Hydrogen bond strengths revealed by topological analyses of experimentally observed electron densities. *Chem. Phys. Lett.* 285: 170-173.

Corresponding author: Dr. Sangeeta Srivastava, Department of Chemistry, University of Lucknow, Lucknow-226007, U.P., India
Email: sangeetas.lu@gmail.com Phone: 91-9415410949