Indian Journal of Chemistry
Vol. 63, November 2024, pp. 1096-1101
DOI: 10.56042/ijc.v63i11.10911

Synthesis, characterization, *in silico* anti-ovarian cancer activity and quantum chemical calculations of 3-β-(2-(6-methoxynaphthalene-2yl)propionoxy)-stigmast-5-en

Rohit Prakash[a], Arun Sethi[b], Sanjay Srivastava[a] & Ranvijay Pratap Singh*[c]

[a] Department of Applied Science & Humanities, Institute of Engineering and Technology, Lucknow 226 021, India
[b] Department of Chemistry, University of Lucknow, Lucknow 226 007, India
[c] Department of Applied Science and Humanities, Faculty of Engineering and Technology,
University of Lucknow, Lucknow 226 031, India
E-mail: rsingh0777@gmail.com

Received 5 May 2024; accepted (revised) 22 October 2024

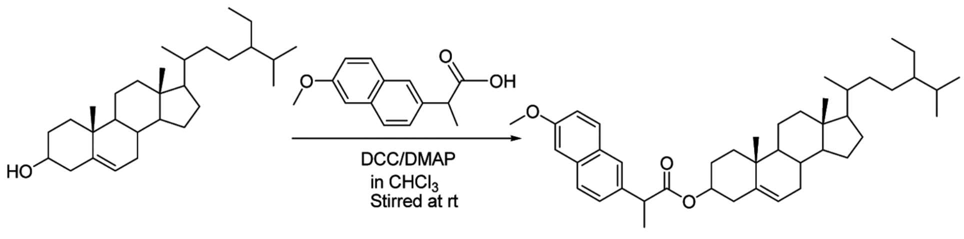
The current research work incorporates the synthesis, spectroscopic analysis, and *in silico* studies to evaluate anti-ovarian cancer potential and theoretical studies of 3-β-(2-(6 methoxynaphthalene-2yl)propionoxy)-stigmast-5-en (**2**). Synthesis of compound **2** was carried out by conjugating β-sitosterol (**1**) with Naproxen through highly efficient Steglich esterification. The structure elucidation of the synthesised compound has been done using ^{1}H NMR, IR and UV as well as mass spectrometry. Anti-ovarian cancer potential of the compound **2** has been evaluated using its interaction with the ovarian cancer protein 2UZR (binding energy (ΔG) of –6.0 Kcal/mole) with the help of molecular docking studies. Topological parameters have been analyzed by "Atom in molecule" AIM theory. High value of first hyper polarizability ($\beta_o = 6.071 \times 10^{-30}$ esu) of compound **2** indicates that it can be utilized as an ideal material for NLO applications.

Keywords: β-Sitosterol, Anti-ovarian cancer activity, Molecular docking, NLO, AIM

Steroids and specifically phytosterols are one of the most important classes of steroidal derivatives that play a significant role in pharmaceuticals and nutrition as they are known to lower cholesterol and are associated with wide range of biological activities[1-5]. However poor solubility of phytosterol limits their applications in pharmaceutical and nutraceutical industries. Chemical or enzymatic modifications have been proven to be effective in improving physiochemical properties, bioavailability and cholesterol lowering ability of phytosterols[6]. Their ester prodrugs are comparatively greater lipophilic, and can thus easily be incorporated into variety of lipid matrices[7,8]. The physiologically active form of drug is released after the hydrolysis of the prodrug by the intestinal enzymes. Varieties of phytosterol derivatives have been found to be associated with cytotoxic activities against different cell lines[9-11].

Among the different forms of cancers in women, ovarian cancer is the seventh most commonly diagnosed cancer across the globe and is typically diagnosed at later stage with overall 5 year survival rate ranging between 30%-40% in the world[12]. The AKT1 gene, responsible for generation of the AKT1 kinase protein, is one of the genes causing ovarian cancer. It appears in the body in a variety of forms. AKT1 helps in controlling cell growth. The protein 2UZR could be the possible protein aiding mutation in AKTI gene. As phytosterols have been reported to alleviate different forms of cancers including ovarian cancer[13], there is increasing interest in synthesizing this class of compounds and evaluating their anti-cancerous properties. In this research work a new phytosterol derivative, 3-β-(2-(6 methoxynaphthalene-2yl)propionoxy) -stigmast-5-en (Compound 2) has been synthesized through high yielding Steglich esterification reaction by conjugating β-sitosterol with a non-steroidal anti-inflammatory drug naproxen using DCC and DMAP (Scheme 1) and identified with the help of ^{1}H NMR, IR and UV spectroscopy as well as mass spectrometry.

During the past few decades, molecular docking is growing as indispensible tool for chemists and biologists to evaluate the potential of natural as well as synthetic compounds against variety of target proteins in order to search better leads in drug discovery. Docking study involves the analysis of the conformation and orientation



Scheme 1 — Synthesis of compound **2** by conjugating β-sitosterol with NSAID, naproxen.

of molecules into the binding site of a macromolecular target. Searching algorithms generate possible conformations and orientations, which are ranked by scoring functions[14-16]. Docking study on ovarian cancer protein (2UZR) suggested the significance of the synthesized compound (**2b**) as interesting lead in the treatment of ovarian cancer. Quantum chemical calculations were performed by density functional theory (DFT) using B3LYP functional and 6-31G (d, p) basis set. Weak interactions in molecules play significant role in explaining and understanding the conformational stability of the ligands as well as their interactions with the biological receptors and hence in eliciting biological response[16]. Here atoms in molecules (AIM) theory, was utilized in order to understand the nature and strength of these interactions in compound **2**. Nonlinear optical behavior of materials has wide range of applications in material science and technology and this has created interest to investigate the non-linear optical response of this newly synthesized sterol ester.

Experimental Section

Material and Measurements

All the solvents and reagents used were of analytical grade purchased from Merck (India) and dried, distilled according to known procedure before use[17]. Dried solvents were stored over activated 4 Å molecular sieves before use. Column chromatography was performed on silica gel (60–120 and 100– 200 mesh E). Thin layer chromatography (TLC) was performed on silica gel G coated plates to detect position of compounds and completion of reaction by visualization of spots by 10% H_2SO_4.

^{1}H NMR spectra was recorded on Bruker DRX-300 MHz spectrometer using $CDCl_3$ as the solvent and TMS as internal standard, chemical shifts were reported as δ (ppm). IR spectra were recorded on Perkin Elmer FTIR spectrometer with the range of IR spectrum from 4000-400 cm^{-1}. ESI-MS was recorded on Agilent 6520 Q-TOF mass spectrometer. Ultraviolet absorption spectra were obtained (in the range of 200-400 nm) using ELICO BL-200 UV-Vis spectrophotometer equipped with a 10 mm quartz cell in chloroform. Melting point was determined using open capillary tube method and uncorrected.

Synthesis of compound 2

Compound **2** was synthesised from previously isolated β-sitosterol (**1**) from the plant *Allamanda violacea*[16]. 6 mg of compound **1** (β-sitosterol) was dissolved in 3.5 mL of chloroform and 3.3 mg of 2-(6-methoxynaphthalene) propanoic acid was added followed by the addition of 1.8 mg of DMAP (N,N'-dimethyl-4-aminopyridine) and 2 mg of DCC (N,N′-dicyclohexyldicarbodiimide). The reaction mixture was stirred at room temperature until reaction was complete (Scheme 1). Progress of reaction was monitored by thin layer chromatography. N,N′-dicyclohexyl urea (DCU) formed as by product was filtered off and the filtrate was treated with 5% HCl, dried over anhydrous sodium sulphate. Chloroform was distilled off under reduced pressure. The crude product obtained was subjected to column chromatography for purification of synthesized compound using silica gel (60-120 mesh) as absorbent and n-hexane/ ethyl acetate (98.5:1.5) as eluent yielding compound **2** (7.6 mg , 81.72 % yield) as white crystalline solid. Molecular formula: $C_{43}H_{62}O_3$. m.p = 388 K,λ_{max} : 256 nm, 278 nm, ^{1}H NMR spectrum, δ, ppm: 0.65 s (3H, CH_3-18),0.81 d (6H, CH_3-26, CH_3-27, J = 6.6 Hz),0.86 d (3H, CH_3-24, J = 7.2 Hz),0.92 d (3H, CH_3-21, J = 6.3 Hz),0.98 s (3H, CH_3-19) 1.56 d (3H, CH_3-14', J = 6 Hz),1.96-1.97 m (2H, H-7), 3.79 q (1H, H-2', J =6.9 Hz),3.91 s (3H, CH_3-13'), 4.58-4.65 m (1H, H-3),5.30-5.29 d (1H, H-6, J = 4.8 Hz),7.11 s (1H, H-9'),7.15 d (1H, H-7', J = 2.4 Hz),7.42-7.39 dd (1H, H-12', J = 2.1 Hz, 1.8 Hz),7.66 s (1H, H-4'),7.69 d (1H, H-11', J = 2.4 Hz), 7.72 d (1H, H-6', J = 2.7Hz). IR spectrum, ν, cm^{-1}: 3055, 2954, 2939, 2867, 1917, 1728, 1605, 1504, 1457, 1376, 1327, 1265, 1232, 1180, 1157, 1121, 1089, 1030, 1004, 926, 893, 854, 815, 750. Mass spectrum:*m/z* =672, 644, 413, 397, 396, 360, 274, 188.

Computational studies

Preparation of protein, docking method and cell culture

The X-ray crystallographic structures of ovarian cancer protein (PDB ID: 2UZR) has been obtained from the Protein Data Bank (PDB) (http://www.pdb.org.) database. Graphical User Interface program "Auto Dock Tools (ADT) 1.5.6 from Molecular Graphics Laboratory (MGL) developed by Scripps Research Institute has been used for the preparation of protein for docking study[18]. Input file of receptor protein for the docking study has been created by removal of water molecules and heteroatoms along with the co-crystallised ligands in PDB crystal structures and then the receptor .pdbqt file created by adding polar hydrogen atoms and Kollman united atom charges[19].

Docking Study by AutoDock Vina

All molecular docking simulations were carried out in the AutoDockVina program 1.1.2 developed by Scripps Research institute[20]. The conformations having the lowest root mean square deviation (RMSD) values, along with the highest Vina score were selected and the results of the docking study and the intermolecular interactions between receptors and the ligand molecules were analyzed using BIOVIA Discovery Studio 2021 (DS), version 21.1.0.0 (https://discover.3ds.com, Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Release 2017, San Diego: Dassault Systèmes, 2016) and pyMOL version 2.4.1.0[21]. The three dimensional (3D) affinity (grid) maps and electrostatic a grid boxes of 40×40×40 Å grid points and grid center (X, Y, Z) of 12.845, –0.666,3.360 with a spacing of 0.375 Å.

NLO and QTAIM

Geometry optimization and evaluation of NLO properties for compound **2** was carried out with the help of Gaussian 09 Program package using B3LYP functional and 6-31G (d,p) basis set using density functional theory (DFT)[22] and Gaussview[23]. A QTAIM study was carried out using AIMAll program[24].

Results and Discussion

Chemistry

Compound **2** was synthesized by reacting compound **1** with well-known NSAID naproxen using DCC as coupling agent and DMAP as catalyst. Identity of compound was confirmed by modern spectroscopic techniques like 1H-NMR, IR, UV and ESI-MS. In the ^{1}H-NMR spectrum of compound **2**, formation of ester at C-3 position was confirmed by the downfield shifting of the proton at C-3 position. This proton was observed as a multiplet at δ 4.58– δ 4.65. Two singlets each corresponding to three protons was observed at δ 0.81 and δ 0.98 for methyl protons at CH_3-18 and CH_3-19 respectively. A six proton doublet was observed at δ 0.81 (*J* = 6.6 Hz) corresponding to CH_3-26, CH_3-27 methyl protons of isopropyl group. A three proton doublet was observed at δ 0.92 (*J* = 6.3 Hz) due to methyl protons corresponding to CH_3-21. Olefinic proton at C-6 position was observed as doublet at δ 5.30 with *J* value equal to 4.8 Hz. Methylene protons at C-7 position were observed as multiplet from δ 1.96-1.97. Protons of naproxen are well observed in ^{1}H NMR spectrum and assignment of all protons is done.Methine proton at H-2' position was well observed as quartet δ 3.79. Aromatic protons are observed in between δ 7.11- δ 7.72.H-4' and H-9' protons of naphthalene ring was observed as singlets at δ 7.66 and δ 7.11 respectively. While H-6', H-7' and H-11' protons were observed as doublets at δ 7.72 (*J* = 2.7 Hz), δ 7.15 (*J* = 2.4 Hz) and δ 7.692 (*J* = 2.4 Hz) respectively. H-12' was observed as one proton double doublet at δ 7.42-7.39. Methoxy protons of naphthalene ring was observed as sharp singlet of three protons at δ 3.91 and threeprotons doublet at δ 1.56 (*J* = 6.0 Hz) was assigned to methyl protons at H-14'position.

In the IR spectrum of compound **2**, aromatic C-H stretch (weak) was observed at 3055 cm^{-1} while asymmetric and symmetric -C-H stretching of methyl groups were observed at 2954 cm^{-1} and 2867 cm^{-1}. Asymmetric C-H stretching vibrations of methylenes were observed at 2939 cm^{-1}. An overtone at 1917 cm^{-1} was observed indicating the presence of aromatic ring in compound **2**. Aromatic skeleton was further confirmed by the characteristic aromatic C=C stretching vibrations at 1605 cm^{-1} and 1504 cm^{-1}. Introduction of ester group in compound **2** was well indicated by strong ester C=O stretching frequency at 1728 cm^{-1}. Asymmetric and symmetric deformations of methyls were observed at 1457 cm^{-1} and 1376 cm^{-1} respectively. A band was observed at 1327 cm^{-1} and assigned to C-C stretching of isopropyl group. CH_2 out of plane bending vibrations (wagging and twisting) were observed at 1265 cm^{-1} and 1180 cm^{-1} respectively. Presence of ester group was further confirmed by C-O stretching frequencies of ester group at 1232 cm^{-1} and C3-O1 stretching vibration at 1121 cm^{-1}. C-H in plane bending vibration of phenyl

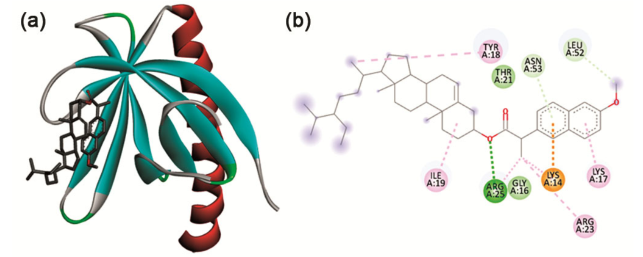


Fig. 1 — A) Representation of docking results of **2** embedded into ovarian cancer protein (PDB ID: 2UZR), B) Representation of 2D interaction of **2**.

Table 1 — Target protein (2UZR) and β-sitosterol derivatives **2** (ligand) molecular docking results

S. No.	Ligands	Binding energy (Kcal/mol)	H-bonding
1	1	–6.0	Arg-A25

ring was observed at 1157 cm^{-1} and 1089 cm^{-1}. Rocking vibrations of methylene groups of the ring were observed at 893 cm^{-1}, 854 cm^{-1}, 815 cm^{-1} and 750 cm^{-1}.

In the ESI-MS spectrum of compound **2,** molecular ion peak was not recorded but other important peaks were observed like loss of ester group from the parent moiety leads to the generation fragment at m/z = 397. Mac-Lafferty rearrangement on parent moiety leads to the loss of $C_{14}H_{14}O_3$ fragment and generated a fragment at m/z = 396. Fragment at m/z = 360 was generated by retro Diels-Alder rearrangement followed by loss of CH_3^+ and hydrogen free radical. Another important fragment at m/z = 300 was generated by formation of β-sitosterol followed by loss of C_8H_8 fragment of the side chain.

Theoretical Studies

Molecular docking

To implement the molecular docking study on synthesized β-sitosterol derivative, 3D molecular structure of target receptor in Ovarian cancer (PDBID: 2UZR) was obtained from the Protein Data Bank. According to a closed analysis of compound **2** interaction with the protein 2UZR (as depicted in Fig. 1), **2** binds to the protein with a binding energy (ΔG) of –6.0 Kcal/mole. With protein 2UZR, ligand **2** forms one hydrogen bond. The amino acid residue Agr25 forms a hydrogen bond at a distance of 2.43 Å with the H atom of the C-3 hydroxyl group of ligand **2**. Other interactions are also observed, one pi-cation interaction was observed between aromatic ring of ligand **2** and H atom of –NH_2 of residue Lys14 at a distance 3.01 Å (Table 1).

According to the aforementioned docking analysis, the synthetic β-sitosterol derivative is effective against ovarian cancer protein (PDB ID: 2UZR). It may have an inhibitor effect on protein inhibitors.

QTAIM analysis: Geometrical and topological parameters at bond critical points (BCP)

The theory of Atoms in molecule (AIM) consider separate atoms and their electron densities for obtaining the interactions and other desired parameters. It is one of the best methods for studying intermolecular interactions. Geometrical as well as topological parameters are useful tools to characterize the strength of hydrogen bond. According to Koch and Popelier criteria[25], the existence of hydrogen bond based on 'Atoms in molecule' theory states that: (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 ($\rho_{H......A}$) should be within the range 0.002–0.040 a.u. (iii) The corresponding Laplacian $\nabla^2\rho(_{BCP})$, should be within the range 0.024–0.139 a.u. According to Rozas *et al.*[26] 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.

Molecular graphs of the compound **2** obtained using AIM program at B3LYP/6-31G (d,p) level is shown in Fig. 2. Topological parameters for bonds of interacting atoms are given in Table 2. From the table it was concluded that, all the intramolecular interactions follow Koch and Popelier criteria. For all the intramolecular interactions $\nabla^2\rho(_{BCP}) >0$ and $H_{BCP}> 0$, hence all intramolecular interactions at BCP are weak in nature.

Espinosa proposed proportionality between hydrogen bond energy (*E*) and potential energy density (V_{BCP}): $E = 1/2(V_{BCP})^{27}$. The total energy of intramolecular interactions was calculated as –14.07 kcal/mol for **2**. The ellipticity (ε) at BCP is used to monitor the π-character of bond. The ε is related to λ_1 and λ_2, which correspond to the eigen values of Hessian and defined by a relationship: $\varepsilon = (\lambda_1/\ \lambda_2) - 1$. The ellipticity values of compound **2** for bonds C100-C96, C96-C89, C89-C90, C89-C88, C88-C87, C87-C-92, C92-C91, C91-C90, C90-C97, C97-C99, and C99-C100 were 0.305, 0.173,

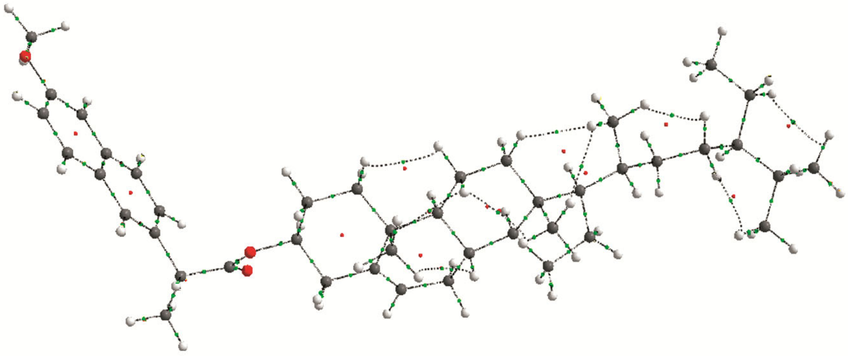


Fig. 2 — Molecular graph of compound **2** representing H···H interactions

Table 2 — Topological parameters for bonds of interacting atoms: electron density (ρ_{BCP}), Laplacian of electron density ($\nabla^2\rho(r_{BCP})$), electron kinetic energy density (G_{BCP}), electron potential energy density (V_{BCP}), total electron energy density (H_{BCP}) at bond critical point (BCP) and estimated interaction energy (E_{int}) for compound **2**.

Atom	$\rho_{(BCP)}$	$\nabla^2\rho(r_{BCP})$	G_{BCP}	V_{BCP}	H_{BCP}	E_{int}
H31-H42	+0.0093	+0.0378	+0.0072	–0.0050	0.002	–1.56
H43-H52	+0.0096	+0.0408	+0.0077	–0.0053	0.002	–1.56
H43-H55	+0.0107	+0.0469	+0.0089	–0.0062	0.002	–1.88
H53-H59	+0.0066	+0.0250	+0.0048	–0.0033	0.001	–0.94
H44-H59	+0.0103	+0.0378	+0.0076	–0.0057	0.002	–1.56
H61-H64	+0.0103	+0.0402	+0.0079	–0.0057	0.002	–1.56
H63-H68	+0.0110	+0.0464	+0.0089	–0.0063	0.002	–1.88
H56-H40	+0.0079	+0.0325	+0.0062	–0.0043	0.002	–1.25
H70-H73	+0.0116	+0.0510	+0.0098	–0.0068	0.003	–1.88

Note: $\rho_{(BCP)}$, $\nabla^2\rho(r_{BCP})$, G_{BCP}, V_{BCP}, H_{BCP} (in a.u.); E_{int} (kcal/mol)

0.155, 0.163, 0.257, 0.170, 0.261, 0.170, 0.157, 0.273 and 0.196 respectively. The lower values of ellipticity indicate towards the delocalization of electrons in aromatic ring[28].

Non-linear optical (NLO) properties

NLO is important to our research because it provides the fundamental functionalities of frequency shifting, optical modulation, optical switching, optical logic, and optical memory for the emerging technologies in industries including telecommunications, signal processing, and optical interconnections[29]. Here we calculated NLO properties like first hyperpolarizability (β_0) of molecular system and related properties ($|\alpha_0|$) for compound **2** using Gaussian 09 with B3LYP/6-31G (d, p) basis set. The total static dipole moment (μ_0), mean polarizability ($|\alpha_0|$) and first hyperpolarizability (β_0) are defined as[30]:

$$\mu_0 = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2}$$

$$|\alpha_0| = 1/3\ (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$$

$$\beta_0 = [(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{xxy} + \beta_{yzz})^2 + (\beta_{zzz} + \beta_{xxz} + \beta_{yyz})^2]^{1/2}$$

Table 3 — Calculated NLO properties of compound 2

Dipole moment		Polarizability		Hyperpolarizability	
μ_x	0.259	α_{xx}	577.3	β_{xxx}	192.4
μ_y	2.514	α_{yy}	–65.00	β_{xxy}	–298.5
μ_z	1.641	α_{zz}	450.1	β_{xyy}	350.7
μ_0	3.014	$\lvert\alpha_0\rvert$	47.54	β_{yyy}	–258.8
				β_{xxz}	14.85
				β_{xyz}	–1.189
				β_{yyz}	–21.88
				β_{xzz}	–76.84
				β_{yzz}	32.20
				β_{zzz}	–22.60
				β_0	6.071

Note: μ_o in Debye; $|\alpha_o|$ in 10^{-24} esu; β_o in 10^{-30} esu.

The calculated values of first hyperpolarizability (β_0) were correlated with the prototypical molecule urea. The first hyperpolarizability (β_0) of **2** was calculated as 6.071 × 10^{-30}esu as shown in the Table 3. The above given value of compound **2** is of 16 times greater than urea (β_0 of urea 0.3728 × 10^{-30}esu). According to the findings, this compound may be further explored to utilize as excellent NLO material.

Conclusions

A new ester derivative of β-sitosterol has been synthesized by high yielding Steglich esterification method and identified with the help of modern spectroscopic techniques. Molecular docking studies revealed that synthesized compound interact effectively with ovarian cancer protein 2UZR with binding energy – 6.0 Kcal/mole, thus the molecule may play crucial role at some stages in the management of ovarian cancer. Analysis of non-covalent interactions by AIM approach helped in understanding the stability of the compound. Significant NLO response of the compound **2** as compared to urea suggests that the synthesized compound can be utilized as future NLO material.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Acknowledgement

Authors are grateful to SAIF CDRI, Lucknow for spectral analysis and Central Facility for Computational Research (CFCR), University of Lucknow for theoretical analysis.

References

1 Moreau R A, Whitaker B D & Hicks K B, *Prog Lipid Res*, 41 (2002) 457.

2 Bohm T, Tian Q, Chitchumroonchokchai C, Failla M L, Schwartz S J, Cotter R & Waksman J A, *J Agric Food Chem*, 55 (2007) 267.

3 Yoshida Y & Niki E, *J Nutr Sci Vit*, 249 (2003) 277.

4 Katan M B, Grundy S M, Jones P, Law M, Miettinen T & Paoletti R, *Mayo Clin Proc*, 78 (2003) 965.

5 Li X, Xin Y, Mo Y, Marozik P, He T & Guo H, *Molecules*, 27 (2022) 523.

6 Hu Y, Ma C, Chen X, Bai G & Guo S, *Grain Oil Sci Tech*, 5 (2022) 146.

7 Delaney B, Stevens L A, Schmelzer W, Haworth J, McCurry S, Hilfinger J M, Kim J S, Tsume Y, Amidon G L & Kritchevsky D, *J Nutr Biochem*, 15 (2004) 289.

8 Sethi A, Prakash R, Srivastava S, Deep A, Bishnoi A & Singh R P, *J Mol Struct,* 1070 (2014) 28.

9 Gao J, Chen S, Zhang L, Cheng B, Xu A, Wu L & Zhang X, *J Agric Food Chem*, 63 (2015) 1035.

10 Carvalho J F S, Silva M M C, Moreira J N, Simões S & Sáe Melo M L, *J Med Chem*, 53 (2010) 7632.

11 Xu R L, Wang R, Ding L & Shi Y P, *Steroids*, 78 (2013) 711.

12 Reid B M, Permuth J B & Sellers T A, *Cancer Biol Med*, 14 (2017) 9.

13 Ramprasath V R & Awad A B, *J AOAC Int*, 98 (2015) 735.

14 Torres P H M, Sodero A C R & Silva Jofily P P, *Int J Mol Sci*, 20 (2019) 4574.

15 Liu Z, Liu Y, Zeng G, Shao B, Chen M, Li Z, Jiang Y, Liu Y, Zhang Y & Zhong H, *Chemosphere*, 203 (2018) 139.

16 Singh R P, Prakash R, Yadav A, Singh A, Yadav P, Srivastava S & Sethi A, *Asian J Chem*, 34 (2022) 2947.

17 Brain S, Hannaford F, Smith A J P WG & Tatchell A R, *Vogel's, Textbook of Practical Organic Chemistry*, Pearson Ed:. 5, 2012.

18 Huey R & Morris G M, *Using Auto Dock 4 with Auto Dock tools: a tutorial*, (La Jolla, CA, USA: The Scripps Research Institute, Molecular Graphics Laboratory, USA) 2008, p. 54.

19 Trott O & Olson A J, *J Comp Chem*, 31 (2009) 455.

20 DeLano W L, *Crystallography*, 40 (2002) 82.

21 Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman, J R, Scalmani G, Barone V, Mennucci B, Petersson G A, Nakatsuji H, Caricato M, Li X, Hratchian H P, Izmaylov A F, Bloino J, Zheng G, Sonnenberg J L, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery J A,Peralta J E, Ogliaro F, Bearpark M, Heyd J J, Brothers E, Kudin K N, Staroverov, V N, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant J. C, Iyengar S. S, Tomasi J, Cossi M, Rega, N, Millam, J M, Klene M, Knox J E, Cross J B, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann R. E, Yazyev O, Austin A J, Cammi, R, Pomelli C, Ochterski J W, Martin R L, Morokuma K, Zakrzewski V. G, Voth G. A, Salvador P, Dannenberg J J, Dapprich S, Daniels A D, Farkas Ö, Foresman J B, Ortiz J V, Cioslowski J & Fox D J, *Gaussian 09, Revision A I,* (Gaussian, Inc, Wallingford C T), 2009.

22 Lee C, Yang W & Parr R G, *Phys Rev,* 37 (1988) 785.

23 Computer Program Gauss View 3.09, Ver. 2, Gaussian, Inc, Pittsburgh: PA (2003).

24 Keith, T A, *AIMAll (Version 10.05.04, Professional),* (TK Gristmill Software, Overland Park K S, USA) 2019.

25 Bader R F W, *Atoms Molecules, A Quantum Theory,* (Oxford University Press, Oxford) 1990.

26 Rozas I & Alkorta I, *J Am Chem Soc,* 122 (2000) 11154.

27 Shainyan B A, Chipanina N N, Aksamentova T N, Oznobikhina L P, Rosentsveig G N & Rosentsveig I B, *Tetrahedron,* 66 (2010) 8551.

28 Sethi A, Singh R P, Prakash R & Amandeep, *J Mol Struc,* 1130 (2017) 860.

29 Singh R P, Sharma S, Kant R, Singh A P & Sethi A, *J Mol Struct,* 1105 (2016) 423.

30 Kleinmann D A, *Phys Rev,* 126 (1962) 1977.