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Efficient Synthesis of Fluorinated Derivatives from Isolated 24-Ethyl cholest-5-en-3β-ol: Characterization, Quantum Chemical Calculations by DFT and Molecular Docking

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The current work focuses on the synthesis, characterization and docking study of two new fluorine containing steroidal esters, *viz.* **1a** (3-β-(4-fluoro benzoyloxy)stigmast-5-en) and **1b** (3-β-(2-fluoro benzoyloxy)stigmast-5-en). Synthesis of compounds **1a** and **1b** was done by conjugating β-sitosterol (**1**) with 4-fluorobenzoic acid and 2-fluorobenzoic acid, respectively using high yielding Steglich esterification method and their structures were identified using ^{1}H NMR, FT-IR and UV spectroscopy as well as mass spectrometry. Docking studies of compounds **1**, **1a** and **1b** assisted in evaluating the inhibitory effect of these steroids against the 2ITO a lung cancer protein. The ΔG values (binding energy) of all the compounds revealed that synthetic derivatives **1a** (with binding energy –9.6 Kcal/mol) and **1b** (with binding energy –9.5 Kcal/mol) are more potent than the parent molecule, compound **1** (with binding energy –7.5 Kcal/mol). A comparative atoms in molecules (AIM) studies predicted greater stability of compound **1b** over **1a**. High value of β_0 of **1a** (4.1×10^{-30} esu) suggested that they may be used as NLO materials.

Keywords: β-Sitosterol, Steglich esterification, Molecular Docking, NLO, AIM.

INTRODUCTION

Phytosterols, an important sub-class of plant steroids, are either found in free state or conjugated with fatty acid or in the form of steryl glycoside or acyl steryl glycoside. They are structurally and functionally identical to cholesterol as in plants they stabilize phospholipid bilayer with increasing sterol/ phospholipid ratio causing membrane rigidification [1]. Phytosterols and their derivatives are also associated with several biological activities such as anti-inflammatory, immunomodulatory, antidiabetic [2-4], antioxidant [5], antileishmanial [6], *etc*. Variety of phytosterol derivatives have also been found to exhibit cytotoxic activities against different cell lines [7-10]. However, poor absorption of phytosterols restricts their uses in drug delivery system, hence in order to obtain promising biological response from phytosterols, their prodrug is prepared by esterification. These esters are more lipophilic and hence can easily be incorporated into variety of lipid matrices [11,12]. Thus, there is increasing interest in synthesizing and exploring the properties of esters of phytosterols. In current research work, highly efficient Steglich esterification method is used for carrying out the synthesis of new esters (compound **1a** and **1b**) of β-sitosterols (compound **1**).

Molecular docking has been growing as indispensible tool for drug discovery during the last few decades. The investigation of the conformation and orientation of molecules within the binding site of a macromolecular target is the main focus of the study. Possible conformations and orientations are generated by search algorithms and scoring systems ranking [13,14].

The molecular docking study on the lung cancer protein (2ITO) reveals the significance of the synthesized compounds (**1a** and **1b**) as interesting leads in the discovery of drugs for the treatment of lung cancer and possibly other malignancies. Both the synthetic derivatives (**1a** and **1b**) were found to exhibit more inhibitory action than the parent compound **1** as indicated by their higher binding energy values (ΔG) against the lung cancer protein (2ITO).

The theoretical studies have been carried out using density functional theory (DFT), weak interactions in molecules explaining the conformational stability of the ligands as well as their interactions with the biological receptors and hence in eliciting biological response. Atoms in molecules (AIM) theory is used to identify the strength of several intramolecular interactions of these synthesized compounds. The NLO behaviour of materials has applications in various fields like in material sciences and information technology [15] and this led interest to investigate the NLO response of these newly synthesized fluorinated steroids. The present article reports synthesis of two new fluorine containing steroidal esters, *viz.* **1a** (3-β-(4-fluoro benzoyloxy)stigmast-5-en) and **1b** (3-β-(2-fluoro benzoyloxy)stigmast-5-en) isolated from 24-ethyl cholest-5-en-3β-ol and its characterization, intramolecular interactions, QTAIM, NLO and molecular docking studies.

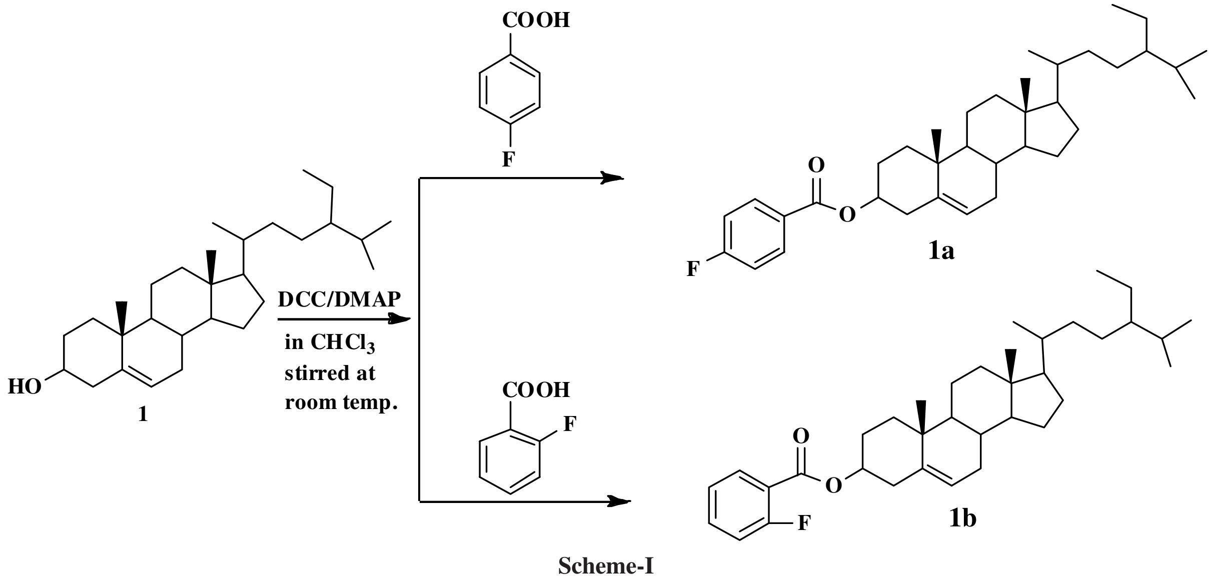
EXPERIMENTAL

All the reagents and solvents were purchased from Merck (India) and dried by standard methods [16]. Position of isolated and synthesized compounds were detected by TLC on glass plates coated with silica gel G. Column chromatography (CC) was used in isolation of β-sitosterol (**1**) and purification of (3-β-(4-fluoro benzoyloxy)stigmast-5-en) (**1a**) and (3-β-(2-fluoro benzoyloxy)stigmast-5-en) (**1b**). For ^{1}H NMR and ^{13}C NMR spectra, Bruker DRX-300 MHz and JOEL AL 300 FTNMR (75 MHz) spectrometer were used respectively. The Perkin-Elmer spectrometer was used for the analysis of FT-IR spectrum in the range of 4000-400 cm^{-1}. Agilent 6520 Q-TOF mass spectrometer and ELICO BL-200 UV-Vis spectrophotometer were used to record ESI-MS and ultraviolet absorption spectra, respectively.

Isolation of 24-ethyl cholest-5- en-3β-ol or β-sitosterol (1): Column chromatography of 430 mg of petroleum ether extract of flowers of *Allamanda violacea* was done by silica gel based glass column and hexane/ethyl acetate (of varying polarity) as mobile phase. This resulted in the isolation of 24-ethyl cholest-5-en-3β-ol or stigmast-5-en-3β-ol commonly called as β-sitosterol (38 mg) in pure form. Physical state: Crystalline solid; m.f.: $C_{29}H_{50}O$, m.p: 138 ºC; λ_{max}: 202 nm; ^{1}H NMR (300 MHz, δ ppm): 0.681 (3H, s, H-18), 0.825 (6H, d, H-26, H-27, J = 6.6 Hz), 0.847 (3H, unresolved triplet, H-24^2), 0.912 (3H, d, H-21, J = 6.3 Hz), 1.01 (3H, s, H-19), 1.861 (2H, m, H-1), 2.022 (2H, m, H-12), 1.829 (2H, m, H-16), 1.844 (2H, m, H-2), 3.509-3.561 (1H, m, H-3), 2.234-2.309 (2H, m, H-4), 5.343-5.360 (1H, m, H-6), 1.992-2.002 (2H, m, H-7), 1.429-1.442 (1H, m, H-8), 1.510 (1H, m, H-11) 1.34 (2H, m, H-22, H-23). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.47, 29.39, 72.00, 39.05, 140.97, 121.91, 31.86, 32.12, 50.36, 36.36, 21.47, 40.25, 42.52, 56.98, 26.25, 28.45, 56.29, 18.99, 24.51, 37.47, 19.25, 34.16, 23.29, 46.02, 32.30, 19.60, 20.02, 26.33, 12.19. FT-IR (CH_2Cl_2, ν_{max}, cm^{-1}): 3070.10-3605.15, 3428.66, 2959.79, 2940.20, 2868.04, 1661.85, 1459.79, 1375.25, 1330.92, 1245.36, 1140.20, 1043.29, 957.73, 802.06, 734.02. ESI-MS (positive mode) in methanol m/z = 414, 412, 397, 313.

Synthesis of fluorinated derivatives: Two new fluorinated esters (**1a and 1b**) were synthesized from the isolated β-sitosterol (**1**) by incorporating 4-fluorobenzoic acid and 2-fluorobenzoic acid, respectively at C-3 position of the β-sitosterol using well known Steglich esterification reaction [17] **(Scheme-I)**.

3-β-(4-Fluoro benzoyloxy)stigmast-5-en (1a): For the synthesis of compound **1a**, 5 mg of compound **1** dissolved in chloroform (3 mL) after that 1.7 mg of 4-fluorobenzoic acid, 1.5 mg of DMAP (as catalyst) and 1.7 mg of DCC (as coupling agent) were added. The whole mixture stirred at room temperature and progress of reaction was observed by TLC. Byproduct *N*,*N*′-dicyclohexyl urea formed was removed and 5% HCl was added to treat the remaining filtrate, the later was dried over anhydrous Na_2SO_4. The excess chloroform was removed by distillation under reduced pressure. The compound was purified by column chromatography using 60-120 mesh silica gel as absorbent and 98.5:1.5 ratio of *n*-hexane/ethyl acetate as solvent,



Scheme-I

yielding 86.56% compound **1a** (5.8 mg) as white needle shaped crystals which were recrystallized by hexane/ethyl acetate. m.f.: $C_{36}H_{53}O_2F$. m.p.: 121 ºC; λ_{max}: 262 nm, 273 nm; ^{1}H NMR at 300 MHz (δ): 0.691 (3H, s, CH_3-18), 0.827 (3+3H, d, CH_3-26 & 27, *J* = 6.6 Hz), 0.868 (3H, unresolved triplet, H-24^2), 0.940 (3H, d, CH_3-21, *J* = 6.3 Hz), 1.067 (3H,s, CH_3-19), 1.965-2.045 (2H, m, H-7), 2.468 (2H, d, H-4, *J* = 7.8 Hz), 4.792-4.964 (1H, m, H-3), 5.429-5.414 (1H, broad doublet, H-6, *J* = 4.5 Hz), 7.064-7.139 (2H, ddd, H-4′, H-6′, *J* = 2.4 Hz, *J* = 2.1 Hz, *J* = 2.7 Hz), 8.022-8.090 (2H, m, H-3′, H-7′). FT-IR (CH_2Cl_2, n_{max}, cm^{-1}): 2957.73, 2928.86, 2870.10, 2847.42, 1921.64, 1716.49, 1608.24, 1510.30, 1461.85, 1321.64, 1377.31, 1285.56, 1223.71, 1158.76, 1112.37, 1083.50, 998.96, 851.54, 763.91, 685.56. ESI-MS (positive mode) in methanol *m/z* = 504, 434, 431, 362, 234.

3-β-(2-Fluoro-benzoyloxy)-stigmast-5-en (1b): For synthesis of **1b**, 6 mg of **1** dissolved in chloroform (3.5 mL) after that 2 mg of 2-fluorobenzoic acid, 1.8 mg of DMAP (as catalyst) and 2.0 mg of DCC (as coupling agent) were added. Rest of the process was repeated as in case of **1a**. m.f.: $C_{36}H_{53}O_2F$. m.p.: 101 ºC; λ_{max}: 274 nm; ^{1}H NMR at 300 MHz (δ): 0.689 (3H, s, CH_3-18), 0.821 (6H, d, CH_3-26 & 27), 0.864 (3H, unresolved triplet, H-24^2), 0.925 (3H, d, CH_3-21), 1.053 (3H, s, H-19), 2.474 (d, H-4) 4.7-4.9(1H, m, H-3), 5.427 (1H, d, H-6), 7.125 (1H, m, H-4′), 7.186 (1H, m, H-6′), 7.497 (1H, m, H-5′), 7.916 (1H, m, H-7′). FT-IR (CH_2Cl_2, ν_{max}, cm^{-1}): 3081.44, 2954.63, 2938.14, 2870.10, 1941.23, 1730.92, 1610.30, 1492.78, 1460.82, 1375.25, 1297.93, 1245.36, 1196.90, 1154.63, 1124.74, 1081.44, 1029.89, 863.91, 818.55, 802.06, 762.88, 690.72. ESI-MS (positive mode) in methanol *m/z* = 412, 396, 394, 391, 311, 266, 264.

Computational studies

Preparation of protein, docking method and cell culture

Preparation of protein & AutoDock Vina: The structures of lung cancer protein (2ITO) obtained from the protein data bank (PDB) database. Auto Dock Tools 1.5.7 used for the devising of protein for docking [18]. The reported method was used to develop input file of receptor protein [19]. AutoDock Vina programe-1.1.2 used for molecular docking simulations [20] study. The results of the docking and the interactions were identify by BIOVIA Discovery Studio 2021 (DS), version 21.1.0.0 and pyMOL version 2.4.1.0 [21].

NLO and QTAIM: Optimized geometries of the compounds using were obtained by Gaussian 09 Program package, [22] and Gaussview [23]. The NLO property was evaluated by B3LYP and 6-31G (d,p) basis set using density functional theory (DFT). QTAIM was performed by program AIMAll [24].

RESULTS AND DISCUSSION

Compound 1a: In ^{1}H NMR spectrum, a downfield signal in range of δ 4.792-4.964 ppm was observed for one methine proton present at H-3 position, confirmed the introduction of ester group at C-3 position. Signals observed at δ 0.691 and δ 0.827 ppm confirmed the presence of methyl groups at CH_3-18 and 19 positions, respectively. Apart from these singlets, a doublet of six protons was also observed at δ 0.827 (*J* = 6.6 Hz) due to CH_3-26 & 27 methyl groups of isopropyl moiety. CH_3-24^2 methyl proton was observed as unresolved triplet due to overlapping with other strong signals at Δ 0.868.

The protons of CH_3-21 was observed at δ 0.940 (*J* = 6.3 Hz). Olefinic proton at H-6 observed at δ 5.429 (*J* = 4.5 Hz) as a doublet. Signals of aromatic protons observed in the range of δ 7.064-8.090. Protons, *ortho* to ester group (H-3′, H-7′), were observed downfield at δ 8.022-8.090 ppm while protons, meta to ester group (H-4′, H-6′) were found upfield at δ 7.064-7.139 ppm as double-double doublet (ddd) with their *J* value being 2.4 Hz, 2.1 Hz and 2.7 Hz.

In the FT-IR spectrum of **1a**, a asymmetric and symmetric -C-H stretching at 2957.73 cm^{-1} and 2870.10 cm^{-1} observed for methyl groups, respectively. The presence of aromatic ring in compound **1a** is supported by the overtone seen at 1921.64 cm^{-1}. The C=O and C-O stretching frequency at 1716.49 cm^{-1} and 1223.71 cm^{-1} observed for ester group, respectively. The C=C stretching vibrations of aromatic ring were observed at 1608.24 cm^{-1}, 1510.30 cm^{-1} and 1461.85 cm^{-1}. In the ESI-MS spectrum of **1a**, important fragments were observed like loss of both angular methyl groups and corresponding hydrogen from parent molecule leading to the generation of fragment at *m/z* = 504. This fragment on losing side chain ($C_{10}H_{22}$) gives peak at *m/z* = 362. A fragment with the highest abundance was observed due to breakdown of fluorine atom at *m/z* = 431 and a fragment (C_6H_{14} from the side chain) from the arent moiety. Another important fragment was observed at *m/z* = 274 by retro Diels-Alder rearrangement on parent molecule.

Compound 1b: In ^{1}H NMR of compound **1b**, a downfield signal in range of δ 4.7-4.9 ppm observed for one methine proton present at H-3 position, confirmed the introduction of ester group at C-3 position. Two singlets, were observed at δ 0.689 and δ 1.053 ppm due to methyl groups CH_3-18 and 19, respectively. Signal at δ 0.821 ppm was observed as a doublet for two methyl protons CH_3-26 and CH_3-27. Methyl protons at C-24^2 position were observed as unresolved triplet due to strong overlapping with other signals at δ 0.864 ppm. A three proton doublet at δ 0.925 ppm was assigned to methyl protons of CH_3-21. Signals of aromatic protons observed in the range δ 7.125- 7.916 ppm.

In the FT-IR spectrum of **1b**, asymmetric and symmetric -C-H stretching at 2954.63 cm^{-1} and 2870.10 cm^{-1} observed for methyl groups, respectively. The C=O and C-O stretching frequency at 1730.92 cm^{-1} and 1245.36 cm^{-1} observed for ester group, respectively. The C=C stretching vibrations of aromatic ring were observed at 1610.30 cm^{-1} and 1492.78 cm^{-1}.

In ESI-MS of **1b**, several important fragments have been observed as loss of acetate moiety and generation of keto group at C-3 shows peak at *m/z* = 412. Another important fragment was generated at *m/z* = 394 by the breakdown of side chain from parent moiety leading to the generation of double bond in D-ring. McLafferty rearrangement on compound **1** generates a fragment at *m/z* = 396, from this fragments various fragment like *m/z* = 311, 296, 266, 264.

Molecular docking: The docking analysis was performed to determine whether synthetic steroidal substances might be pharmaceutical in nature. The protein data bank was used to obtain the 3D molecular structure of the target receptor in lung cancer (PDBID: 2ITO) in order to carry out the molecular docking study on synthetic steroidal drugs. Target protein (2ITO) Ramachandran plot is shown in Fig. 1 [25]. All of the amino acid residues in the protein structure were plotted on the Ramachandran graph between the phi-psi torsion angles. The red area of this plot is where the majority of the amino acids (79.8%) were located. With a ratio of 17.6%, the colour yellow indicates the permitted zones and the colour light yellow with a percentage of 2.2%, the generously permitted regions. The fact that so few (0.4%) do demonstrates the stability of the protein selected for the binding relationship.

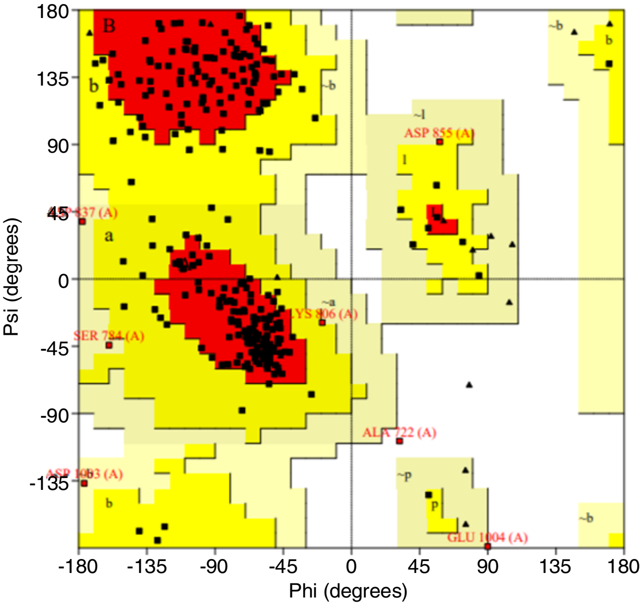


Fig. 1. Ramachandran plot for 2ITO protein

The bonding energy values of docking compounds **1a** and **1b** are given in Table-1. By removing the co-crystallized inhibitor from the target receptor, the docking process was put to the test (PDBID: 2ITO). The docked **1**, **1a** and **1b** molecules significantly inhibited the lung cancer receptor and their relative binding energies (ΔG) against the protein 2ITO were reported to be -7.5 Kcal/mol, -9.6 Kcal/mol and -9.5 Kcal/mol (Table-1). The rigid molecule docking of **1**, **1a** and **1b** with 2ITO produced the energetically most advantageous docked structures, which are displayed in Figs. 2-4.

TABLE-1
TARGET PROTEIN (2ITO) AND STEROID DERIVATIVES **1**, **1a** AND **1b** (LIGANDS) MOLECULAR DOCKING RESULTS

Ligands	Binding energy (Kcal/mol)	H-bonding
1	-7.5	Met-A793
1a	-9.6	Met-A793
1b	-9.5	–

According to a closed analysis of compound **1** interaction with the protein 2ITO (as depicted in Fig. 2), **1** binds to the protein with a binding energy (ΔG) of -7.5 Kcal/mol. With protein 2ITO, ligand **1** forms one hydrogen bond. The amino acid residue Met793 forms a hydrogen bond at a distance of 2.54 Å with the H atom of the C-3 hydroxyl group of ligand **1**.

When the ligand **1a** (Fig. 3) docked with the protein 2ITO, it was revealed that the binding energy (ΔG) of the interaction was -9.6 Kcal/mol. With protein 2ITO, ligand **1a** forms one hydrogen bond. Amino acid residue Met793 ($-NH_2$ group) formed a bond with F atom of phenyl moiety present at C-3

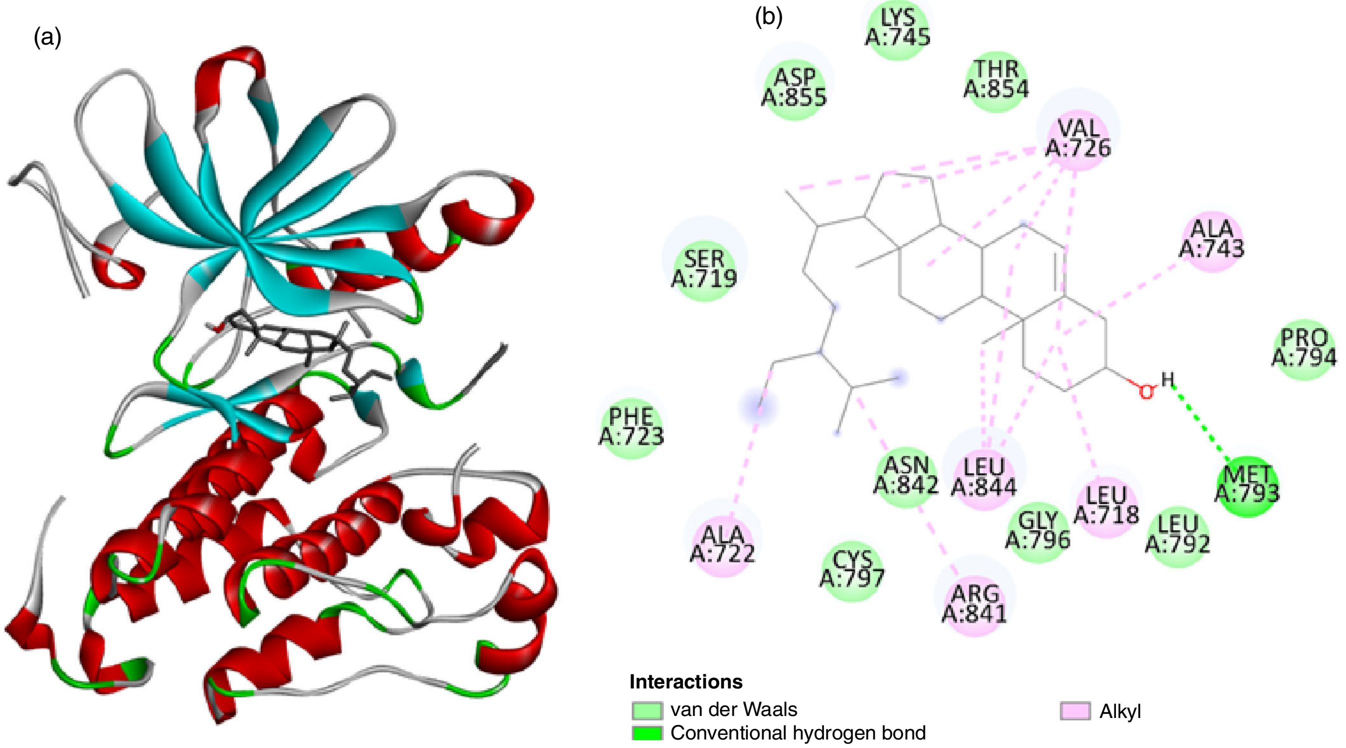


Fig. 2. (a) Representation of docking results of **1** embedded into lung cancer protein (PDB ID: 2ITO), (b) representation of 2D interaction of **1**

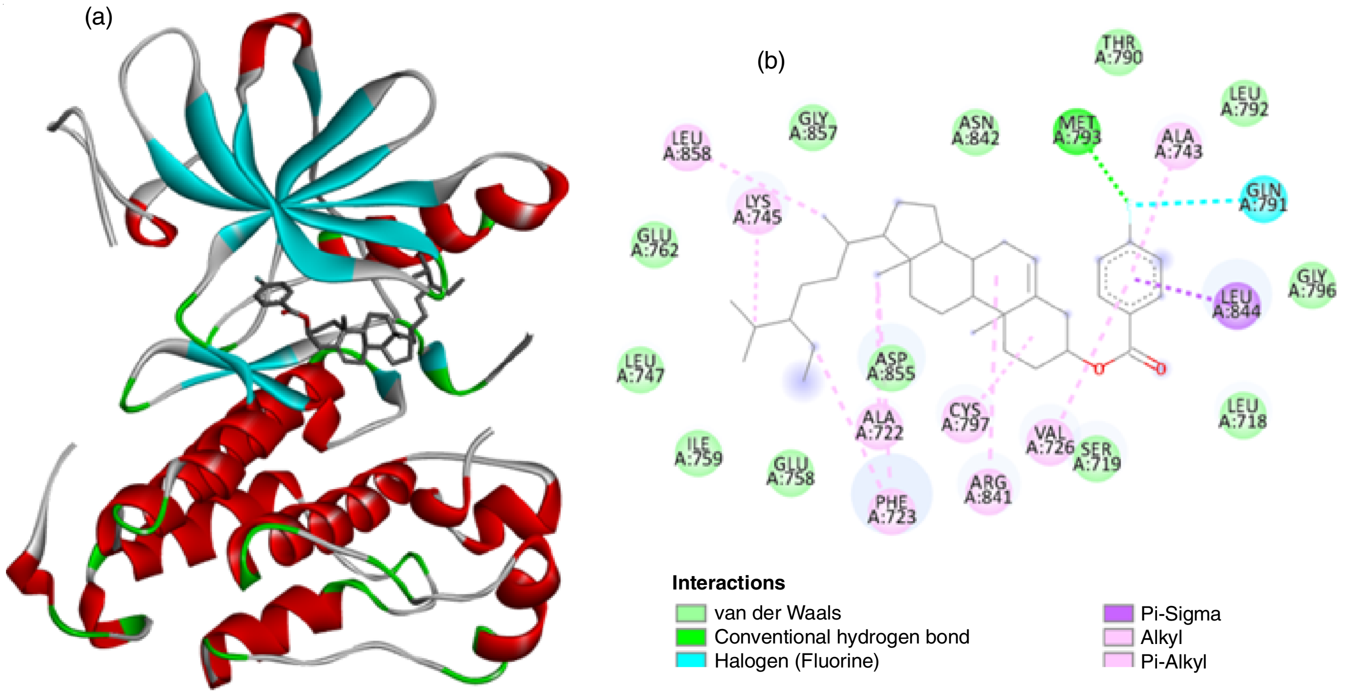


Fig. 3. (a) Representation of docking results of **1a** embedded into lung cancer protein (PDB ID: 2ITO), (b) representation of 2D interaction of **1a**

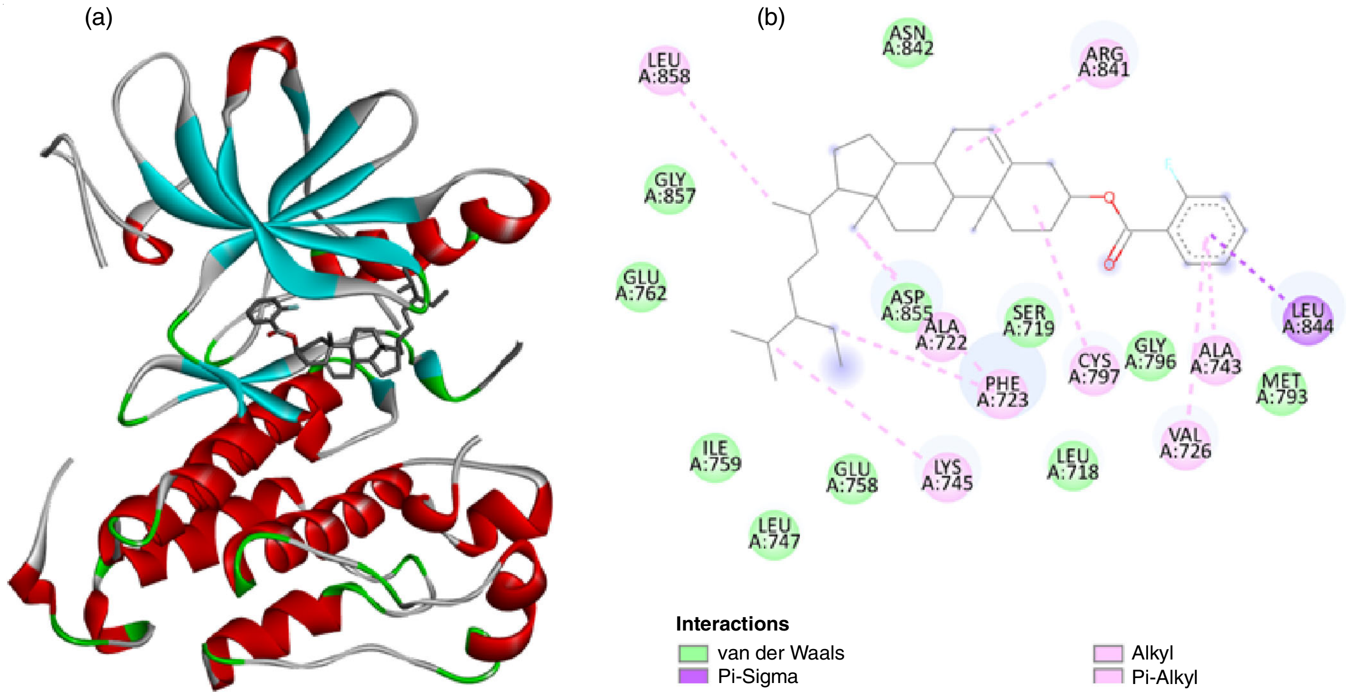
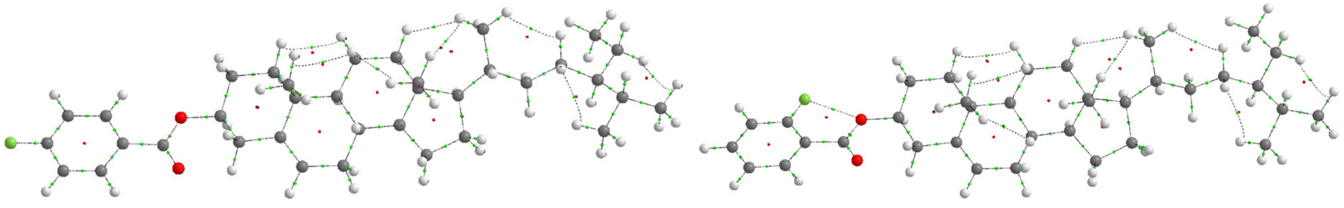


Fig. 4. (a) Representation of docking results of **1b** embedded into lung cancer protein (PDB ID: 2ITO), (b) representation of 2D interaction of **1b**

position of ligand **1a** at a distance 2.56 Å. O atoms of the amino acid residue Gln791 (-COOH group) were shown interacting with F atoms phenyl moiety at a distance of 3.40 Å.

When ligand **1b** (Fig. 4) docked with the protein 2ITO, **1b** binding energy (ΔG) of the interaction was –9.5 Kcal/mol. **1b** does not form hydrogen bond with protein 2ITO. But other interaction also observed. According to the aforementioned docking analysis, the synthetic steroidal derivatives are effective against lung cancer protein (2ITO). They may have an inhibiting effect on protein inhibitors.

QTAIM: Using the calculated QTAIM topological parameters like electron density (ρ), its Laplacian ($\nabla^2\rho$), local potential energy density (V) and index of delocalization (DI) at the BCP, the types, nature and strength of the NCIs (H-bonding and other weak interactions) between two interatomic interacting atoms are described. Fig. 5 displays the QTAIM topolo-



1a **1b**

Fig. 5. Molecular graphs of two steroids **1a** and **1b** showing F···O and H···H interactions

gically linked structures of all species. As it reveals the charge concentration in terms of shared interaction, the sign of the Laplacian of the electron density at a BCP [$\nabla^2\rho < 0$ and $\rho >$ 0.1 in au] is crucial.

In the case of a depleted (closed shell) contact, such as an H-bonding, ionic or vdW interaction, the Laplacian of electron density is more than zero ($\nabla^2\rho > 0$), but the values are often small. It is noteworthy to observe that both show numerous bonding characteristics of intramolecular H-bonded NCIs (Table-2).

In **1a**, various weak H···H bonding intramolecular interactions were observed with positive value of $\nabla^2\rho$. In **1b**, the value electron density ρ and $\nabla^2\rho$ for the interactions C34-F···O4 (E = -4.6 kcal/mol) are found at 0.015 and 0.063 a.u. respectively with G/V ratios for C34-F···O4 is 1.07. The aforementioned ratios also imply that interactions that fall under the category of non-covalent interactions (NCIs). Again, the closed shell interaction is demonstrated by the positive sign of the $\nabla^2\rho$ for all eight weak H–H bonding interactions.

According to Espinosa *et al.* [26] interactions energy (IE) for interactions can be calculated with the help of expression E_{IE}= 1/2V (*r*BCP). The total interactions energy (IE) for **1a** and **1b** were calculated as -12.00 and -16.6 kcal/mol respectively. From the energy value, it is found that compound **1b** is more stable than compound **1a**.

Non-linear optical (NLO) properties: For the rising technologies in fields like telecommunications, signal processing and optical interconnections, NLO is crucial for research because it offers the essential functions of frequency shifting, optical modulation, optical switching, optical logic and optical memory [27-29]. Thus, the NLO properties like first hyperpolarizability (β_0) of molecular system and related properties ($|\alpha_0|$) for compounds **1a** and **1b** using Gaussian 09 with B3LYP/6-31G (d,p) basis set were calculated. The total static dipole moment (μ_0), mean polarizability ($|\alpha_0|$) and first hyperpolarizability (β_0) are defined as [30]:

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

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

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

The calculated values of first hyperpolarizability (β_0) were correlated with the prototypical molecule urea. The first hyperpolarizability (β_0) of compounds **1a** and **1b** were calculated as 4.1×10^{-30} and 1.31×10^{-30} esu, respectively (Table-3). The above mentioned values of **1a** and **1b** were of 11 and 3.5 times greater than urea (β_0 of urea 0.3728×10^{-30} esu). Thus, these compounds may be used as NLO materials.

Conclusion

Synthesis of two novel fluorinated compounds *viz.* (3-β-(4-fluoro benzoyloxy)stigmast-5-en) (**1a**) and (3-β-(2-fluoro benzoyl-oxy)stigmast-5-en) (**1b**), a sterol derivatives of β-sitosterol, has been reported. Their structures were confirmed using spectroscopic techniques. Docking studies of synthetic

TABLE-2
TOPOLOGICAL PARAMETERS FOR THE COMPOUNDS **1a** AND **1b**

Interaction	$\rho_{(BCP)}$	$\nabla^2\rho_{(r_{BCP})}$	G_{BCP}	V_{BCP}	H_{BCP}	E_{int}
Compound **1a**						
H31···H42	+0.009210	+0.037337	+0.007154	-0.004974	0.003	-1.2
H55···H43	+0.010787	+0.047406	+0.009070	-0.006288	0.003	-1.8
H44···H59	+0.010590	+0.038496	+0.007792	-0.005959	0.002	-1.5
H53···H59	+0.006557	+0.024788	+0.004759	-0.003322	0.001	-0.9
H73···H70	+0.011641	+0.050405	+0.009708	-0.006816	0.003	-1.8
H63···H68	+0.010802	+0.046749	+0.008975	-0.006263	0.002	-1.8
H61···H64	+0.010273	+0.040271	+0.007879	-0.005691	0.002	-1.5
H43···H52	+0.009545	+0.040910	+0.007763	-0.005299	0.002	-1.5
Compound **1b**						
F···O4	+0.015856	+0.063070	+0.015251	-0.014734	0.001	-4.6
H31···H42	+0.009271	+0.037644	+0.007212	-0.005014	0.002	-1.5
H55···H43	+0.010755	+0.046875	+0.008969	-0.006219	0.002	-1.8
H44···H59	+0.010459	+0.038225	+0.007703	-0.005850	0.002	-1.5
H53···H59	+0.006664	+0.025145	+0.004832	-0.003377	0.001	-0.9
H73···H70	+0.011648	+0.050344	+0.009700	-0.006813	0.003	-1.8
H63···H68	+0.010780	+0.046766	+0.008973	-0.006254	0.002	-1.8
H61···H64	+0.010337	+0.040131	+0.007892	-0.005752	0.002	-1.5
H56···H40	+0.008034	+0.032395	+0.006212	-0.004326	0.002	-1.2

TABLE-3
CALCULATED NLO PROPERTIES OF COMPOUND **1a** AND **1b**

Compound **1a**						Compound **1b**					
Dipole moment		Polarizability		Hyperpolarizability		Dipole moment		Polarizability		Hyperpolarizability	
μ_x	1.631	α_{xx}	536.138	β_{xxx}	426.099	μ_x	-0.405	α_{xx}	533.942	β_{xxx}	29.977
μ_y	-0.329	α_{yy}	332.581	β_{xxy}	68.294	μ_y	0.193	α_{yy}	541.085	β_{xxy}	60.131
μ_z	-0.337	α_{zz}	7.845	β_{xyy}	14.289	μ_z	0.014	α_{zz}	336.599	β_{xyy}	-2.225
μ_0	1.698	$\lvert\alpha_0\rvert$	43.30	β_{yyy}	-20.380	μ_0	0.449	$\lvert\alpha_0\rvert$	69.73	β_{yyy}	27.422
				β_{xxz}	107.564					β_{xxz}	73.423
				β_{xyz}	-65.442					β_{xyz}	-77.767
				β_{yyz}	7.905					β_{yyz}	30.708
				β_{xzz}	17.094					β_{xzz}	8.148
				β_{yzz}	2.164					β_{yzz}	14.661
				β_{zzz}	7.510					β_{zzz}	23.459
				β_0	4.11					β_0	1.31

steroids have proven that the binding energy values (ΔG) of **1a** (with binding energy –9.6 Kcal/mol) and **1b** (with binding energy –9.5 Kcal/mol) are higher than **1** (with binding energy –7.5 Kcal/mol). Therefore we can say that molecules may play a significant role in cancer chemotherapy. Good NLO responses of these synthesized derivatives indicated that they can be further explored for future NLO materials. Atoms in molecules approach explained the stability of the compounds by analyzing the non-covalent interactions and also helped in giving the better insight into the drug receptor interactions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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