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# Expedient synthesis of novel pregnane-NSAIDs prodrugs, XRD, stereochemistry of their C-20 derivatives by circular dichroism, conformational analysis, their DFT and TD-DFT studies

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ABSTRACT

Four novel pregnane-NSAIDs prodrugs 3β-(2-(6-methoxynaphthalene-2yl) propionoxy)-16α-methoxy-pregn-5-ene-20-one (**3**), 16α-methoxy-pregn-5-ene-20-one-3yl-2(4-iso butyl phenyl) propanoate (**4**), 3β-(2-(6-methoxynaphthalene-2yl) propionoxy) 20-hydroxy-16α-methoxy-pregn-5-ene (**5**) and 20-hydroxy-16α-methoxy-pregn-5-ene-20-one-3yl-2(4-iso butyl phenyl) propanoate (**6**) have been synthesized. They were analyzed experimentally by spectroscopic techniques like $^{1}H$, $^{13}C$ NMR, FT-IR, UV−visible spectroscopy, mass spectrometry and correlated by theoretical calculations. The structure and conformations of **3** was established by single crystal X-ray diffraction, which crystallized in orthorhombic form having $P2_12_12_1$ space group. Absolute configuration of C-20 hydroxy derivatives **5** and **6** was established by circular dichroism (CD) analysis. Conformational analysis of **5** was carried out to determine the most stable conformation. The electronic properties, such as frontier orbitals, band gap energies, oscillator strength and wavelength have been calculated using time dependent density functional theory (TD-DFT). The vibrational wavenumbers have been calculated using DFT method and assigned with the help of potential energy distribution (PED). Global and local reactivity descriptors have been computed to predict reactivity and reactive sites in the molecule. First hyperpolarizability ($\beta_0$) of synthesized compounds has been computed to evaluate non-linear optical (NLO) response. Molecular electrostatic potential (MEP) for synthesized compounds have also been determined to check their electrophilic or nucleophilic reactivity as well as reaction path.



## 1. Introduction

Non steroidal anti-inflammatory drugs (NSAIDs) like naproxen and Ibuprofen possess one or more anti-inflammatory properties such as analgesic, anti-pyretic and edema-reducing effect [1,2] whereas pregnane and its derivatives, both synthetic and isolated, have also been reported to possess anti-inflammatory activity, anti-asthmatic, anti-feedant, anti-dyslipidimic, anti-oxidant [3–9] anti-microbial [10] anti-cancer [11–13] and anti-diabetic activity [14]. However, frequent use of NSAIDs, often lead to serious side effects such as gastric lesions and renal toxicity [15]. As most NSAID posses a carboxyl group, hence one of the strategy adopted to avoid gastrointestinal (GI) damage involves carrying out the esterification of the NSAID. It has been reported that esterification of the carboxylic acid moiety of NSAIDs suppress gastro-toxicity without adversely affecting their anti-inflammatory activity [16,17]. Thus, if pregnane and NSAIDs are present in one moiety, then this single moiety may possess both biological properties of pregnane and NSAIDs. Thus keeping both the above factors in mind, we synthesized pregnane-NSAIDs prodrug.

The esterification of NSAIDs was achieved in high yield by Steglich method using N, N′-Dicylcohexylcarbodiimide (DCC) as a coupling reagent and 4-Dimethylaminopyridine (DMAP) as a catalyst [18]. The synthesized pregnane-NSAIDs prodrugs are shown in Scheme 1.

The structures of pregnane-NSAIDs derivatives have been investigated by spectroscopic techniques like $^{1}H$, $^{13}C$ NMR, FT-IR, UV−visible spectroscopy and mass spectrometry. Single crystal X-

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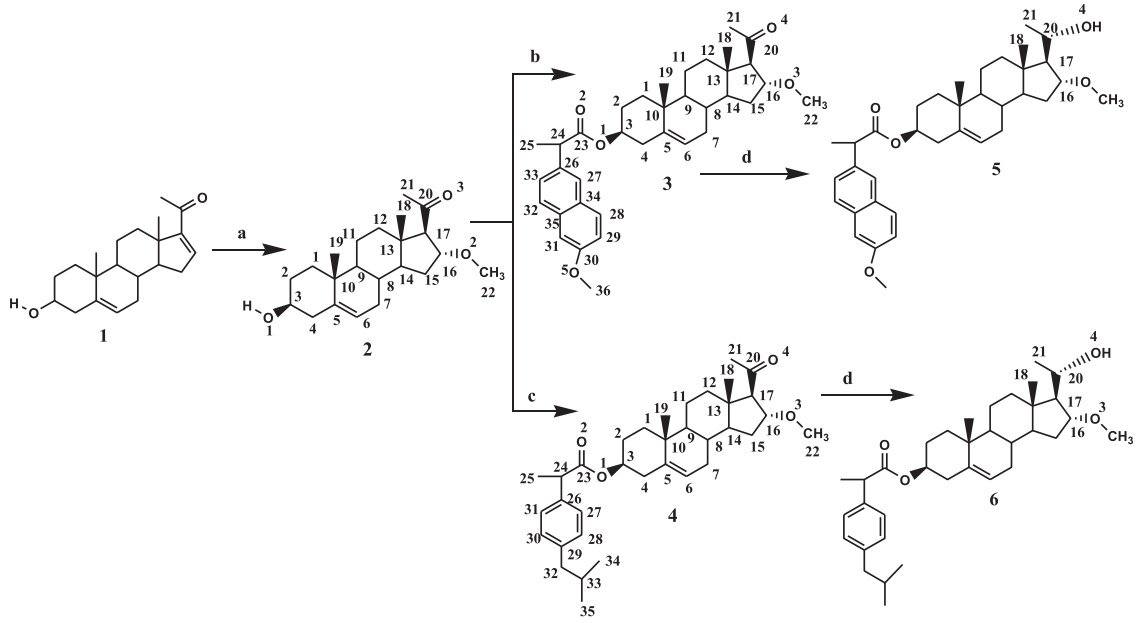

**Scheme 1.** a) MeOH/KOH/reflux, yield 87.5%, b) $CH_3OC_{12}H_{10}COOH/CHCl_3/DCC/DMAP$, yield 82.60%, c) $C_{12}H_{16}COOH/CHCl_3/DCC/DMAP$, yield 84.0%, d) $NaBH_4/CH_3COOC_2H_5$.

ray studies of **3** not only helped in establishing the geometry but also in predicting the orientation of groups present at C-3, C-16 and C-17 positions. The crystal structure is stabilized by weak intermolecular hydrogen bonding.

Energy gap between HOMO and LUMO characterized the molecular chemical stability and molecular electrical transport properties. Development of materials with large nonlinear optical (NLO) property has been of great interest because of their application in ultrafast image-processing, optical data processing, transmission, and storage.

In the present paper we report synthesis, XRD, conformation, configuration, vibrational assignments, electronic transitions, global and local reactivity descriptors, molecular electrostatic potential surface analysis and non-linear optical property using experimental and theoretical approaches, of the newly synthesized pregnane-NSAIDs prodrugs.

## 2. Experimental details

### 2.1. Materials and methods

All solvents used were of analytical grade, purified and dried according to standard procedures (A.I. Vogel, Practical Organic Chemistry) prior to their use. Thin layer chromatography (TLC) on Silica Gel 'G' (Merck, India) coated plates were used for monitoring the progress of reaction and purity of the compounds. Column chromatography was performed using silica gel (60–120 mesh) (Merck, India) as stationary phase. $^1$H NMR spectra were recorded on Bruker DRX-300 MHz and Bruker AVANCE-800 MHz spectrometer using $CDCl_3$ as the solvent and TMS as internal standard, chemical shifts were reported as $\delta$ (ppm) and $^{13}$C NMR were recorded on JOEL AL 300 FTNMR (75Mz) using TMS as an internal reference. IR spectra were recorded on Perkin Elmer FTIR spectrometer from 4000 to 450 $cm^{-1}$ range. The spectra were analyzed using Spectrum™ Software suite. ESI–MS spectra were recorded on Agilent 6520 Q–TOF mass spectrometer. CD spectra were recorded by a JASCO J-815 spectrometer in solid form. Ultraviolet absorption spectra were obtained (in the range of 200–450 nm) using ELICO BL-200 UV–Vis spectrophotometer equipped with a 10 mm quartz cell in chloroform. Optical rotations were measured with on automatic polarimeter, optical activity (Model: AA-5 series). Melting point was determined using open capillary tube method and uncorrected.

### 2.2. Synthesis of 3β-hydroxy-16α-methoxy-pregn-5-ene-20-one (**2**)

3β-hydroxy-16α-methoxy-pregn-5-ene-20-one was synthesized by reported method [19] and identified by melting point and $^1$H NMR. $[\alpha]_D^{25} = +170^\circ$ (c = 0.1, $CHCl_3$).

### 2.3. Synthesis of 3β- (2-(6-methoxynaphthalene-2yl) propionoxy) 16α-methoxy pregn-5-ene-20-one (**3**)

200 mg (0.577 mmol) of 3β-hydroxy-16α-methoxy-pregn-5-ene-20-one (**2**) was dissolved in 10 mL of chloroform and then naproxen (132.9 mg, 0.577 mmol), DCC (118.9 mg, 0.576 mmol) and DMAP (70.4 mg, 0.576 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 and water, dried over anhydrous sodium sulphate and filtered. The organic layer was concentrated under reduced pressure and the crude concentrated product was purified by column chromatography using ethyl acetate: hexane (2:98) yielding 275 mg (82.60%) of **3** as solid. m.p = 443 K, Molecular formula: $C_{36}H_{46}O_5$, $[\alpha]_D^{25} = +70^\circ$ (c = 0.1, $CHCl_3$), $^1$H NMR (800 MHz, $CDCl_3$) $\delta$ (ppm): 7.70 (2H, t, H-28 & H-32, J = 8.0 Hz), 7.69 (1H, s, H-27), 7.41 (1H, d, H-33, J = 8.8 Hz), 7.14 (1H, d, H-29, J = 8.8 Hz), 7.11 (1H, s, H-31), 5.30 (1H, br d, H-6, J = 4.8 Hz), 4.63–4.59 (1H, m, H-3), 4.38 (1H, m, H-16), 3.91 (3H, s, $OCH_3$-36), 3.82 (1H, q, H-24, J = 7.2 Hz), 3.21 (3H, s, $OCH_3$-22), 2.54 (1H, d, H-17, J = 6.4 Hz), 2.17 (3H, s, $CH_3$-21), 1.55 (3H, d, $CH_3$-25, J = 7.2 Hz), 0.96 (3H, s, $CH_3$-19), 0.61 (3H, s, $CH_3$-18). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 208.31 (C=O, C-21), 174.27 (C-23, C=O), 157.81 (C-30), 139.80 (C-5), 136.19 (C-26), 133.84 (C-35), 129.49 (C34), 129.16 (C32), 127.25 (C-27), 126.46 (C-33), 126.06 (C-28), 122.34 (C-6), 119.09 (C-29), 105.82 (C-31), 81.67 (C-16), 74.22(C-3), 71.77 (C-17), 57.36 (C-22), 55.51 (C-36), 54.58 (C-9), 49.92 (C-14), 45.86 (C-24), 44.60 (C-4), 38.97 (C-10), 37.95 (C-12), 37.06 (C-13), 36.78 (C-8),