Journal of Molecular Structure 1125 (2016) 616–623

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Synthesis of novel pregnane-diosgenin prodrugs via Ring A and Ring A connection: A combined experimental and theoretical studies

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ARTICLE INFO

Article history:
Received 2 May 2016
Received in revised form
2 July 2016
Accepted 8 July 2016
Available online 9 July 2016

Keywords:
Pregnane
Diosgenin
Prodrugs
AIM approach
NLO
Reactivity descriptors

ABSTRACT

Novel pregnane-diosgenin prodrugs have been synthesized. The route involved preparation of 3β-25R-spirost-5ene 3yl-benzoate-2-carboxylic acid (**2**) by the esterification of diosgenin (**1**) with phthalic anhydride. The pregnane-diosgenin prodrugs **5** & **6** were synthesized by treating 3β-25R-spirost-5ene 3yl-benzoate-2-carboxylic acid (**2**) with 3β-hydroxy16α-methoxy pregn-5-ene-20-one (**3**) and 3β-hydroxypregn-5, 16-diene-20-one (**4**) respectively. The synthesized compounds have been characterized with the help of spectroscopic techniques like ^{1}H, ^{13}C NMR, FT-IR, UV–visible spectroscopy and mass spectrometry. Density functional theory (DFT) with B3LYP functional and 6-31G (d, p) basis set has been used for the Quantum chemical calculations. UV–Vis spectra of the synthesized compounds were also recorded and electronic properties such as frontier orbitals and band gap energies were calculated by TD-DFT approach. Intramolecular interactions have been identified by AIM approach and vibrational wavenumbers have been calculated using DFT method. The reactivity and reactive site within the synthesized prodrugs were examined with reactivity descriptors (global and local). Dipole moment, polarizability and first static hyperpolarizability were calculated to get a better insight of the properties of synthesized prodrugs. The probable reaction paths of prodrugs were calculated with molecular electrostatic potential (MEP) surface analysis.

1. Introduction

Diosgenin, a steroidal sapogenin exhibited biological activity like anti-oxidant, anti-diabetes, anti-inflammatory, anti-cancer and anti-adipogenic [1–6]. On the other hand pregnane derivatives have been reported to exhibit anti-inflammatory, anti-asthmatic, anti-dyslipidemic, anti-oxidant and anti-feedant activity [7–10]. It was thus conceptualized that diosgenin and pregnane the two active pharmacophores, if linked together then the resultant novel prodrugs may exhibit pharmacological activity. Taking this into account, we planned to synthesize novel pregnane-diosgenin prodrugs with the help of Steglich esterification method using N, *N′*-Dicylcohexylcarbodiimide (DCC) as a coupling reagent and 4-Dimethylaminopyridine (DMAP) as a catalyst. The synthesized pregnane-diosgenin prodrugs are shown in Scheme 1.

Quantum chemical calculations have been performed by density functional theory (DFT) using B3LYP functional and 6-31G (d, p) basis set. Atoms in molecules (AIM) theory have been extensively applied to classify and understand hydrogen bonding interactions and π– electron delocalization in a molecule [11]. Energy gap between HOMO and LUMO characterized the chemical stability and charge transfer interaction in the molecules. Development of materials with large nonlinear optical (NLO) property has been of great interest because of their application as an ultrafast image-processing, optical data processing, transmission, and storage [12].

Therefore, the present paper aims to give a complete description of the molecular geometry, chemical shifts, vibrational assignments, intramolecular interactions, electronic transitions, global reactivity descriptors and non-linear optical (NLO) features of the synthesized prodrugs.

2. Experimental

2.1. 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

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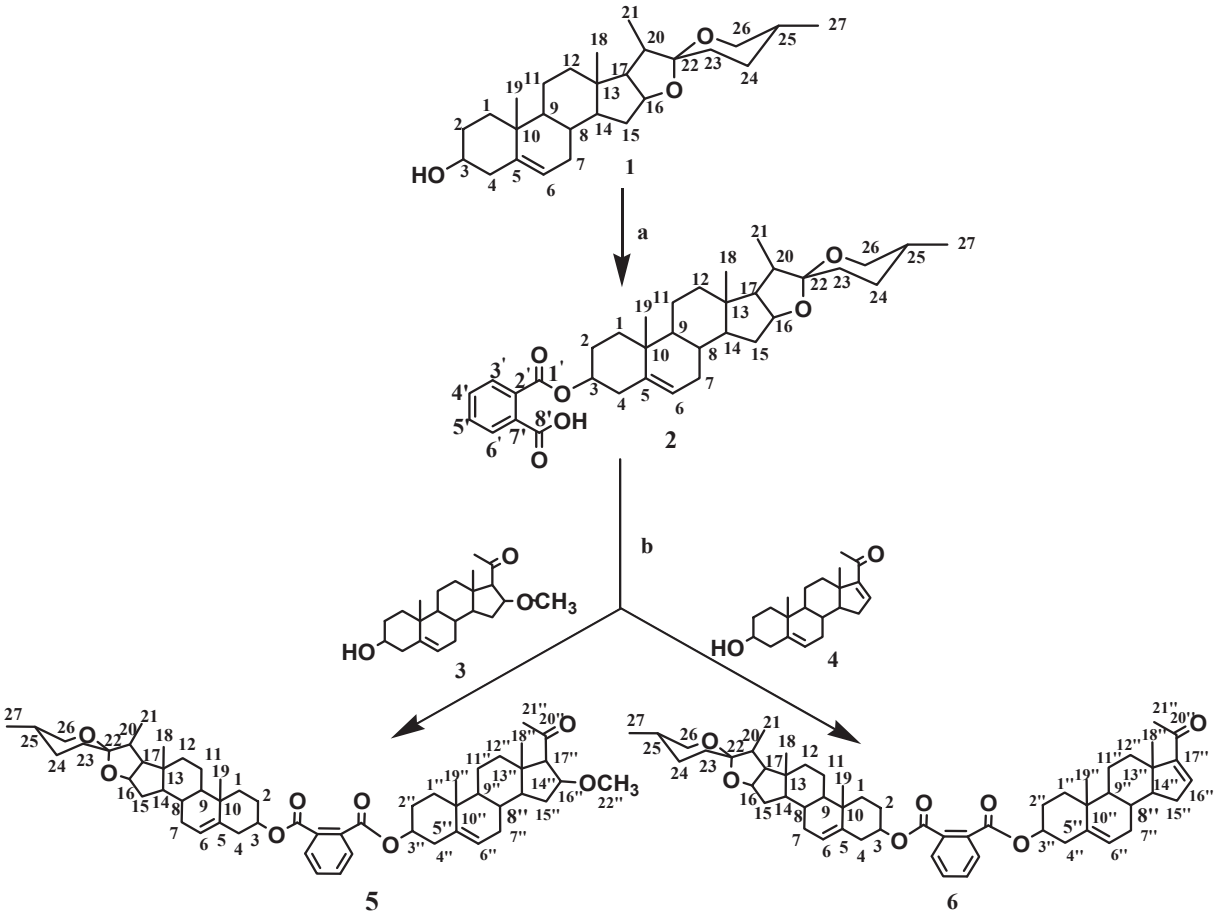
http://dx.doi.org/10.1016/j.molstruc.2016.07.020
0022-2860/



Scheme 1. a) Phthalic anhydride/Py, yield 85.4% (**2**), b) DCC/DMAP/$CHCl_3$, yield 80.4% (**5**), 86.0% (**6**).

column chromatography using silica gel (60–120 mesh). ^{1}H NMR spectra were recorded on Bruker DRX-300 MHz spectrometer using $CDCl_3$ as the solvent and TMS as an internal standard, chemical shifts were reported as δ (ppm) and ^{13}C NMR spectrum was 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 to 450 cm^{-1} range. The spectra were analyzed using Spectrum™ Software suite. ESI–MS spectrum was recorded on Agilent 6520 Q–TOF mass spectrometer. 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 dichloromethane. Melting point was determined using open capillary tube method and uncorrected.

2.2. 3β-25R-spirost-5ene 3yl-benzoate-2-carboxylic acid (*2*)

A solution of phthalic anhydride (118.8 mg, 0.724 mmol), DCC (149.2 mg, 0.724 mmol), DMAP (88.4 mg, 0.724 mmol) and **1** (300 mg, 0.724 mmol) in 20 mL of chloroform were stirred mechanically at room temperature until the reaction was complete. Progress of the reaction was monitored by thin layer chromatography (TLC). N, *N*′- dicyclohexylurea formed during the reaction was filtered off and the filtrate washed successively with 5% HCl and water, dried over anhydrous sodium sulphate and filter. The organic layer was concentrated under reduced pressure and the crude concentrated product was purified by column-chromatography using ethyl acetate: hexane (15: 85) as eluent, yielding 357 mg (85.4%) of pure compound. m. p. 498 K. Molecular formula: $C_{35}H_{47}O_6$. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.91 (1H, d, H-5′, $J = 7.5$ Hz), 7.72 (1H, d, H-7′, $J = 6.6$ Hz), 7.61–7.53 (2H, m, H-3′ & H-6′), 5.42 (1H, d, H-6, $J = 3.3$ Hz), 4.91–4.84 (1H, m, H-3), 4.43 (1H, q, H-16, $J = 7.2$ Hz), 3.49 (1H, m, Heq-26), 3.38 (1H, m, Hax-26), 1.03 (3H, s, H-19), 0.98 (3H, d, H-21, $J = 6.6$ Hz), 0.78 (6H, s, H-18, H-27). ^{13}C NMR ($CDCl_3$, 75 MHz, δ(ppm): 171.65 (C-1′), 167.47 (C-8′), 139.48 (C-5), 133.56 (C-6′), 132.01 (C-5′), 130 (C-2′), 130.10 (C-3′), 129.83(C-4′), 128.85(C-7′), 122.62 (C-6), 109.34 (C-22), 80.83 (C-16), 75.65 (C-3), 66.82(C-26), 62.03(C-17), 56.43(C-9), 49.95(C-14), 41.61(C-20), 40.25(C-4), 39.72(C-13), 37.74(C-10), 36.97(C-12), 36.74(C-15) 32.05(C-8), 31.82(C-23), 31.37(C-7), 30.26(C- 1), 29.67(C-25), 28.77(C-2), 27.41(C-24), 20.81 (C-19), 19.30 (C-11), 17.12 (C-18), 16.27(C- 27), 14.50(C-21). FT-IR ν_{max} in (cm^{-1}): 2950.69, 2871.86, 1724.93, 1600.05, 1579.93, 1453.42, 1376.90, 1289.91, 1131.66, 1067.44, 740.43 and 704.54. HRMS: *m/z* 563 [M^++1], Molecular formula: $C_{35}H_{46}O_6$ (calculated) and $C_{35}H_{47}O_6$ (experimental).

2.3. 3β-25R-spirost-5ene 3yl 3β-16-methoxy pregn-5-ene-20-one 3yl phthalate (*5*)

A solution of **2** (50 mg, 0.088 mmol), DCC (18.3 mg, 0.088 mmol), DMAP (10.8 mg, 0.088 mmol) and **3** (30.78 mg, 0.088 mmol) [36] in 5 mL of chloroform were stirred mechanically at room temperature until the reaction was complete. Progress of the reaction was monitored by thin layer chromatography (TLC). *N,N*′-dicyclohexylurea formed during the reaction was filtered off and the filtrate washed successively, with water, 5% HCl and water, dried over