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Facile synthesis of corticosteroids prodrugs from isolated hydrocortisone acetate and their quantum chemical calculations

Arun Sethi [a, *], Ranvijay Pratap Singh [a], Rohit Prakash [b], Amandeep [a]

[a] Department of Chemistry, University of Lucknow, Lucknow, 226007, India
[b] Faculty of Chemical Sciences, Shri Ramswaroop Memorial University, Barabanki, 225003, India

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ABSTRACT

In the present research paper corticosteroids prodrugs of hydrocortisone acetate (**1**) have been synthesized, which was isolated from the flowers of *Allamanda Violacea*. The hydrocortisone acetate (**1**) was hydrolyzed to hydrocortisone (**2**) which was subsequently converted to prednisolone (**3**). Both the hydrocortisone (**1**) and prednisolone (**2**) underwent Steglich esterification with naproxen and Ibuprofen yielding compounds 11, 17 dihydroxy-21-(2-(6-methoxynaphthalene-2yl) propionoxy)-pregn-4-ene-3, 20-dione (**4**), 11, 17-dihydroxy-21-(2-(4-isobutylphenyl) propionoxy)-pregn-4-ene-3, 20-dione (**5**), 21-(2-(6-methoxynaphthalene-2-yl) propionoxy) 11,17-di-hydroxy-3,20-diketo-pregn-1,4-diene (**6**) and 11,17-di-hydroxy-3,20-diketo-pregn-1,4-diene-21-yl-2-(4-isobutylphenyl) propanoate (**7**). The synthesized compounds have been characterized with the help of spectroscopic techniques like ^{1}H, ^{13}C NMR, FT-IR 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. The electronic properties such as frontier orbitals and band gap energies were calculated by TD-DFT approach. Intramolecular interactions have been identified by AIM (Atoms in Molecule) approach and vibrational wavenumbers have been calculated using DFT method. The reactivity and reactive site within the synthesized prodrugs have been examined with the help of reactivity descriptors. Dipole moment, polarizability and first static hyperpolarizability have been calculated to get a better insight of the properties of synthesized prodrugs. The molecular electrostatic potential (MEP) surface analysis has also been carried out.

1. Introduction

Corticosteroids (CS) or corticoids also belong to C-21 class of carbon compounds having a cyclopentanoperhydro-phenanthrene (steroid) nucleus. The synthetic as well natural analogs of these hormones have virtually affected every aspect of human physiology and are most widely used for various inflammatory and autoimmune disorders. Modifications of 21-hydroxy group of corticosteroids by esterification with carboxylic acids have been found to increase its clinical utility. The C-21 esters of corticosteroids like 9α-fluoro-prednisolone 21-acetate [1], and flu-perolone acetate [2] were found to be active anti-inflammatory agents. The dexamethasone-21-isonicotinate aerosol was highly effective in treating in bronchial asthma [3]. The C-21 derivative of hydrocortisone exhibited potent anti-inflammatory activity [4]. The recently synthesized hydrocortisone C-21 mercaptobenzothiazole and C-21 mercapto derivatives of prednisolone showed significant anti-inflammatory activity [5,6].

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 [7,8]. As most NSAID posses free carboxyl group, which damage gastrointestinal (GI) track. It has been reported that esterification of the carboxylic acid moiety of NSAIDs suppress gastro-toxicity without adversely affecting their anti-inflammatory activity [9,10] Thus, if corticosteroids and NSAIDs are present in one moiety, then this single moiety may possess both biological properties of corticosteroid and NSAIDs. Thus keeping the above factors in mind, we synthesized corticosteroids-NSAIDs prodrug by adopting Steglich esterification method using N, N′-Dicylcohexylcarbodiimide (DCC) as a coupling reagent and 4-Dimethylaminopyridine (DMAP) as a catalyst. Hydrocortisone (**2**) needed for the present synthetic process was derived from hydrocortisone acetate (**1**), isolated from the chloroform extract of the flowers of *Allamanda Violacea* [11]. The

* Corresponding author.
E-mail address: alkaarunsethi@rediffmail.com (A. Sethi).

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synthesized corticosteroid-NSAIDs 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. Development of materials with large nonlinear optical (NLO) property has been of great interest because of their vast varieties of application. Energy gap between HOMO and LUMO characterized the chemical stability and charge transfer interaction in the molecules. Atoms in molecules (AIM) theory have been extensively applied to classify and understand hydrogen bonding interactions in the molecules.

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

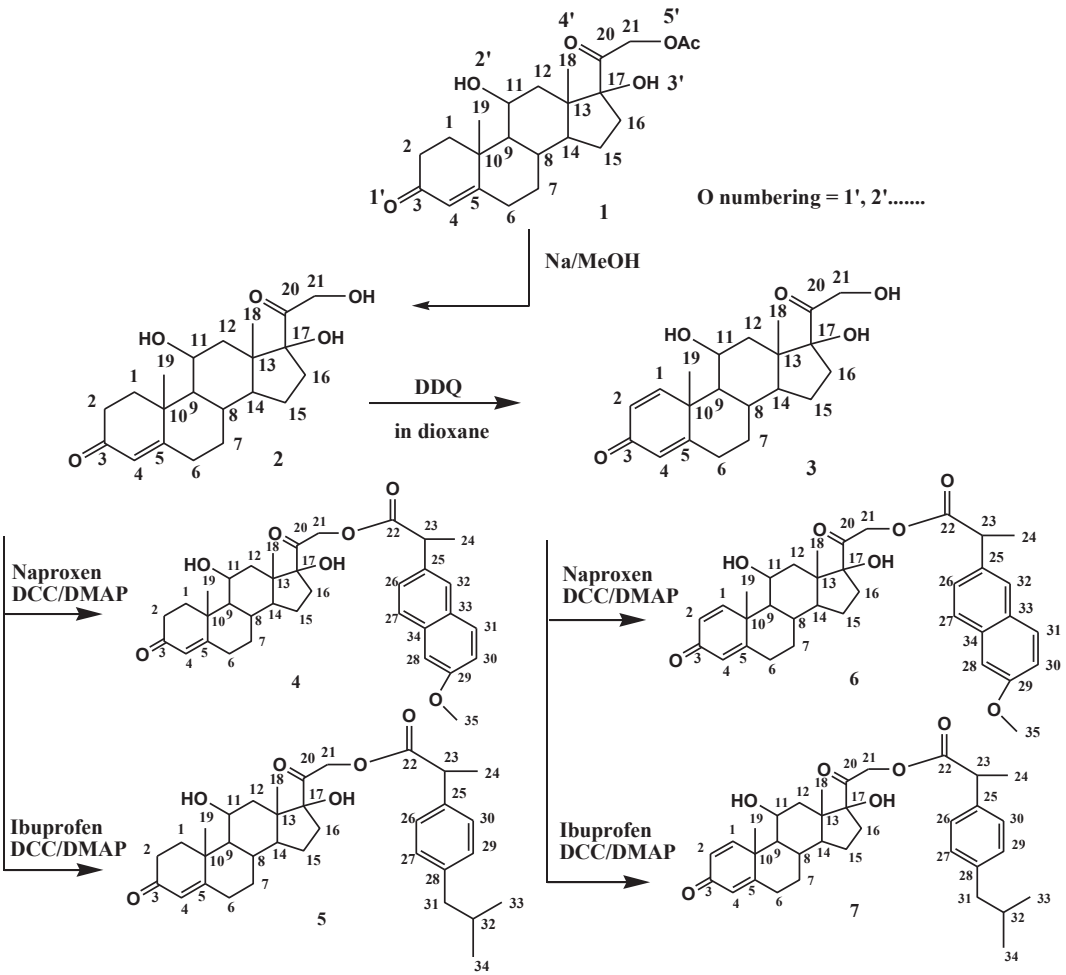
2. Experimental

2.1. Materials and physical measurements

The whole plant of the A. violacea was collected in the month of October 2010 from Lucknow, India. The identity of the plant was confirmed by Dr. Tariq Hussain, Scientist and Head, Department of Taxonomy and Herbarium, National Botanical Research Institute, Lucknow, India where Voucher specimen, no-97108 was deposited. 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 spectra were recorded on Bruker DRX-300 MHz spectrometer using $CDCl_3$ and DMSO-d_6 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 (75 Mz) using TMS as an internal reference. FT-IR spectra were recorded on Perkin Elmer FT-IR spectrometer from 4500 to 400 cm^{-1} range. The spectra were analyzed using Spectrum™ Software suite. ESI–MS spectrum was recorded on Agilent 6520 Q–TOF mass spectrometer. Melting point was determined using open capillary tube method and uncorrected.

2.2. Extraction and isolation of hydrocortisone acetate (*1*)

Extracts were prepared as reported earlier by Sethi et al. [12]. Dry chloroform extract (690 mg) of the flowers of *A. violacea* was subjected to column chromatography using silica gel (60–120 mesh) and Chloroform/methanol of increasing polarity. Chloroform/methanol (97:3–96:4) afforded 20 fractions which contained **1** in impure form. Compound **1** (32 mg) was obtained in pure form with repeated column chromatography using chloroform/methanol of increasing polarity. m.p: 497 K, Molecular formula: $C_{23}H_{32}O_6$, ^{1}H NMR in $CDCl_3$ at 300 MHz (ppm): δ 7.262(D, s, $CDCl_3$),



Scheme 1. The synthesis of corticosteroids-NSAIDs prodrugs **4**, **5**, **6** and **7**.

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