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

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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

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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.

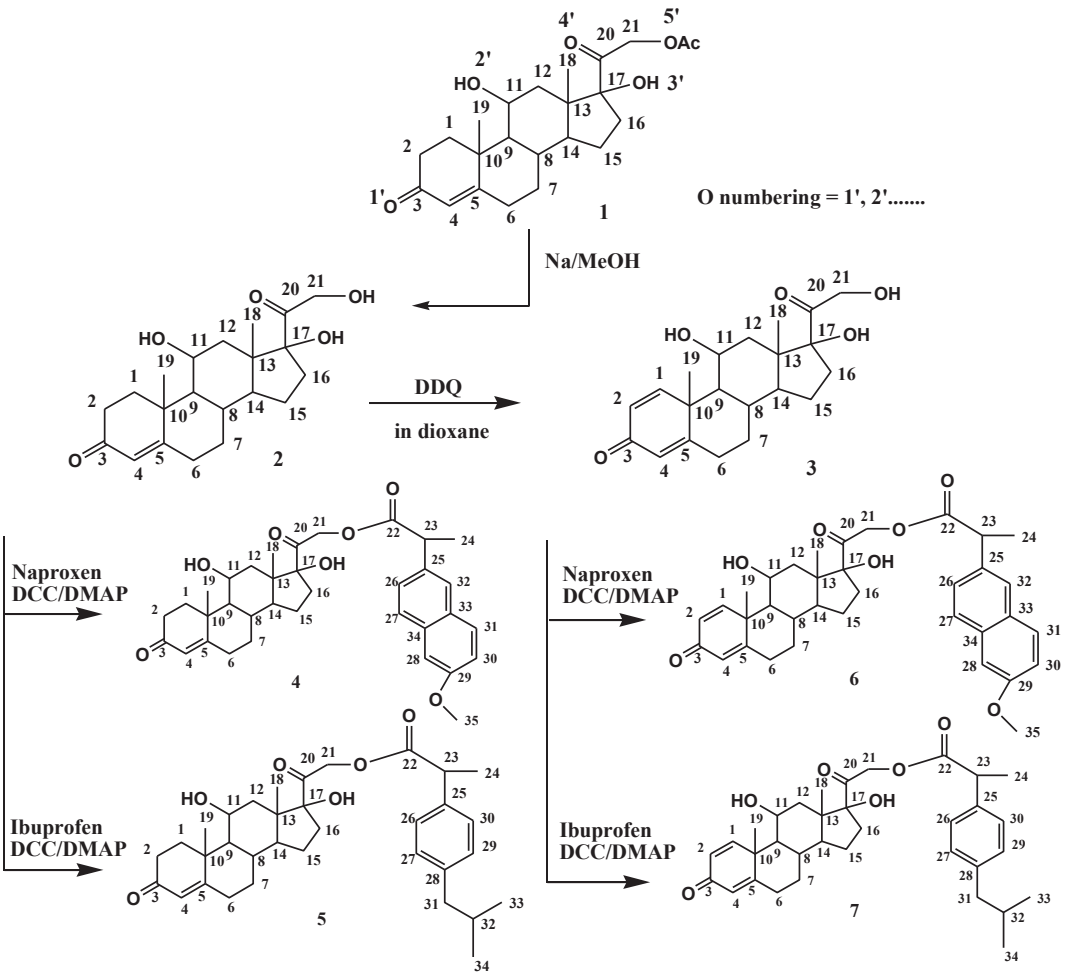
2. Experimental

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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δ 1.862 (1H, m, H-1α), δ 2.222 (1H,m, H-1β), δ 2.317 (1H, m, H-2α), δ 2.534 (1H, d, H-2β), δ 5.690 (1H, s, H-4), δ 2.271 (1H, d, H-6α), δ 2.504 (1H, m, H-6β), δ 1.143 (1H, m, H-7α), δ 2.001 (1H, m, H-7β), δ 2.091 (1H, m, H-8), δ 0.999, 1.036 (1H, dd, H-9), δ 4.478 (1H, q, J = 2.7 Hz, H-11), δ 2.02 (1H, m, H-12α), δ 1.707 (1H, m, H-12β), δ 1.75 (1H, m, H-14), δ 1.797 (1H, m, H-15α), δ 1.479 (1H, m, H-15β), δ 1.479 (1H, m, H-16α), δ 2.832 (1H, m, H-16β), δ 0.972 (1H, s, H-18), δ 1.253 (1H, s, H-19), δ 5.007 (1H, d, J = 17.4 Hz, H-21A), δ 4.879(1H, d, J = 17.4 Hz, H-21B), δ 2.186 (1H, s, H-23). ESI-MS: m/z = 427, 404, 386, 362, 302.

2.3. Synthesis of 11, 17, 21-trihydroxy-pregn-4-ene-3, 20-dione (**2**)

Compound **2** was synthesized by dissolving 29 mg (0.071 mmol) of compound (**1**) in 1.5 mL of methanol followed by addition of 0.3 mL of sodium methoxide as a catalyst. The mixture was kept at room temperature for 30 min. The reaction mixture was neutralized with IR 120H + resin and filtered. Filtrate was concentrated and compound **2** was purified with column chromatography using Chloroform/methanol as eluent yielding 27.5 mg (94.82%) of compound **2** in pure state. m.p: 490–491 K, Molecular formula: $C_{21}H_{30}O_5$, ^{1}H NMR in $CDCl_3$ at 300 MHz: δ 7.260(D, s, $CDCl_3$), δ 0.962 (1H, s, H-18), δ 1.054, 1.017 (1H, dd, H-9, J = 3.3 Hz), δ 1.442 (1H, s, H-19), δ 3.061 (1H, broad signal, OH-21), δ 4.337(1H, d, J = 19.8 Hz, H-21A), δ 4.686 (1H, d, J = 19.8 Hz, H-21B) δ 4.468–4.499 (1H,q, J = 3 Hz, H-11), δ 5.689 (1H, d, H-4, J = 1.2 Hz). FT-IR ν_{max} (in cm^{-1}): 3381.44, 2950.5, 2924.74, 2859.79, 1711.34, 1658.76, 1462.88, 1378.35, 1271.13, 1235.05, 1090.72, 1025.77, 869.07, 763.91, 743.29. ESI-MS: 385, 362, 346, 302.

2.4. Synthesis of 11, 17, 21-tri-hydroxy-3, 20-diketo-pregn-1, 4-diene (**3**)

Mixture of 11,17,21-tri-hydroxy-3,20-diketo-pregn-4-ene (**2**) 15 mg (0.041 mmol) in 1, 4- dioxane (3 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (21.0 mg, 0.092 mmol) at room temperature and the mixture was refluxed for 4 h (progress of reaction was monitored by TLC). The reaction mixture was cooled down and filtered, washed with 1, 4-dioxane and concentrated to give crude product, which was purified by column chromatography using ethyl acetate: hexane (7:93) to yielding 12.5 mg (83.33%) of the pure compound. The compound was identified by comparing its data as reported in literature [13]. Melting Point: 506 K, Molecular formula: $C_{21}H_{28}O_5$, ^{1}H NMR at 300 MHz (in DMSO-d_6) δppm: 7.29 (1H, d, H-1, J = 9.9 Hz), 6.17–6.13 (1H, dd, H-2, J = 1.2, 10.2 Hz), 5.91 (1H, s, H-4), 5.19 (1H, br s, H-17(OH)), 4.70–4.64 (2H, 11-OH, 22-OH), 4.52–4.44 (1H, dd, H-21A, J = 6.0, 19.2 Hz), 4.26 (1H, s, H-11), 4.10–4.02 (1H, dd, H-21B, J = 6.0,19.2 Hz), 1.38 (3H, s, CH_3-19), 0.76 (3H, s, CH_3-18).

2.5. Synthesis of 11, 17 dihydroxy-21-(2-(6-methoxynaphthalene-2yl) propionoxy)-pregn-4-ene-3, 20-dione (**4**)

4.0 mg (0.011 mmol) of compound **2** (11,17,21-tri-hydroxy-3,20-diketo-pregn-4-ene), dissolved in 2.5 mL of chloroform and 2.5 mg (0.011 mmol) of naproxen was added followed by the addition of 1.34 mg (0.011 mmol) of DMAP and 2.2 mg (0.011 mmol) of DCC. The reaction mixture was stirred at room temperature until reaction was complete. 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 and water, 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 chloroform/methanol (98:2) as eluent yielding 5.6 mg (86.15%) of compound **4** as white crystalline solid. m.p: 482 K, Molecular formula: $C_{35}H_{42}O_7$, ^{1}H NMR in $CDCl_3$ at 300 MHz (ppm): δ 7.260 (D, s, $CDCl_3$), δ 0.961 (1H, s, H-18), δ 1.013–0.976 (1H, dd, H-9, J = 3.3 Hz), δ 1.446 (1H, s, H-19), δ 1.624 (3H, d, H-24, J = 7.2), δ 3.911 (3H, s, CH_3-35), δ3.959 (1H, q, H-23, J = 6.9 Hz, 7.2 Hz), δ 4.428–4.408 (1H, q, J = 3 Hz, H-11), δ 4.800 (1H, d, J = 17.4, H-21A), δ 5.046 (1H, d, J = 17.1, H-21B), δ 5.676 (1H, d, H-4, J = 1.2), δ 7.120 (1H, s, H-28), δ 7.149 (1H, d, H-30, J = 2.7), δ 7.451–7.417 (1H, dd, H-26, J = 1.8 Hz), δ 7.698 (2H, d, H-31, H-32, J = 1.8 Hz), δ 7.726 (1H,d. H-27, J = 2.4 Hz). FT-IR ν_{max} (in cm^{-1}): 3486, 2948, 2922, 2870, 2850, 1729, 1654, 1608, 1507, 1484, 1458, 1389, 1367, 1324, 1265[1], 1229, 1181, 1030, 893, 858, 812, 753, 669. ESI-MS: 575, 574, 557, 539, 362, 345, 302.

2.6. Synthesis of 11, 17-dihydroxy-21-(2-(4-isobutylphenyl) propionoxy)-pregn-4-ene-3, 20-dione (**5**)

A solution of ibuprofen 2.2 mg (0.011 mmol), DCC 2.2 mg (0.011 mmol), DMAP 1.34 mg (0.011 mmol) and compound **2**, 4.0 mg (0.011 mmol) in $CHCl_3$ (2 mL) was stirred mechanically at room temperature for 3–4 h and the progress of reaction was monitored by TLC. DCU formed during the reaction was filtered off and the filtrate washed successively with 5% HCl and water, dried over anhydrous sodium sulphate and filtered. Filtrate obtained was evaporated under reduced pressure and the crude product was purified by column chromatography using ethyl acetate–hexane (2:98) as eluent yielding 4.1 mg (66.12%) of compound **5** as solid. M. P. = 489 K, Molecular formula: $C_{34}H_{46}O_6$, ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.24 (2H, dd, H-27 &H-29, J = 8.1, 2.2 Hz), 7.12 (2H, dd, H-26 & H-30, J = 7.8, 1.5 Hz), 5.67 (1H, br s, H-4), 5.11 (1H, d, H-21A, J = 17.4 Hz) 4.91 (1H, br s, H-17), 4.78 (1H, d, H-21B, J = 17.4 Hz), 4.45 (1H, br d, H-11, J = 3.0 Hz), 3.88–3.80 (1H, m, H-23), 1.56 (3H, d, CH_3-24, J = 7.2 Hz), 1.43 (3H, s, CH_3-19), 0.96 (3H, s, CH_3-18), 0.90 (6H, d, CH_3-33 & CH_3-34, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 204.77 (C-20), 199.8 (C-3), 174.62 (C-22 & C-5), 140.89 (C-28), 137.52 (C-25), 129.5 (C-30 & C-26), 127.50 (C-29 & C-27), 122.2 (C-4), 89.84 (C-17), 68.48 (C-11), 68.11 (C-21), 56.50 (C-9) 52.11 (C-14), 47.75 (C-31), 45.27 (C-13), 45.10 (C-23), 39.42 (C-12), 35.20 (C-1), 34.84 (C-2), 34.03 (C-6), 32.93 (C-7), 32.22 (C-10), 31.58 (C-16), 30.38 (C-8), 29.92 (C-32), 23.83 (C-19), 22.62 (C-33 & 34), 21.21 (C-15), 18.92 (C-24), 17.39 (C-18). FT-IR ν_{max} (in cm^{-1}): 3480, 2952, 2930, 2864, 1717, 1657, 1515, 1459, 1411, 1377, 1367, 1229, 1185, 1163, 1127, 1111, 1081, 1055, 1033, 1017, 1003, 973, 943, 897, 861, 785, 743, 697, 645, 545, 523, 499, 457. ESI-MS: m/z = 551, 550, 513, 225.

2.7. Synthesis of 21-(2-(6-methoxynaphthalene-2-yl) propionoxy) 11, 17-di-hydroxy-3, 20-diketo-pregn-1, 4-diene (**6**)

4.0 mg (0.011 mmol) of 11, 17, 21-tri-hydroxy-3, 20-diketo-pregn-1, 4-diene (**3**) was dissolved in 2 mL of chloroform and then naproxen 2.5 mg (0.011 mmol), DCC 2.2 mg (0.011 mmol) and DMAP 1.34 mg (0.011 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 4.8 mg (73.84%) of **6** as amorphous. m.p = 462 K, Molecular formula: $C_{35}H_{40}O_7$, ^{1}H NMR at 300 MHz (in DMSO-d_6) δppm: 7.80 (3H, d, H-27, H-31 & H-32, J = 9.6 Hz), 7.45 (1H, d, H-26, J = 8.4 Hz), 7.32 (2H, d, H-30 & H-28, J = 9.0 Hz), 7.17 (1H, d, H-1, J = 9.0 Hz), 6.13 (1H, d, H-2, J = 10.2 Hz), 5.91 (1H, s, H-4), 5.38 4.90 (1H, br s, H-17(OH)), 5.07 (1H, d, H-21A, J = 17.7 Hz),

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4.72 (1H, d, H-21B, $J = 17.7$ Hz), 4.26 (1H, br s, H-11), 4.01 (1H, q, H-23), 3.86 (3H, s, CH_3-35), 1.52 (3H, d, H-24, $J = 6.9$ Hz), 1.38 (3H, s, CH_3-19), 0.85 (3H, s, CH_3-18), 0.88 (6H, d, CH_3-33 & CH_3-34, $J = 6.6$ Hz). IR (KBr) νmax (cm^{-1}): 3415, 2930, 2853, 1724, 1656, 1607, 1452, 1391, 1265, 1232, 1174, 1033, 888, 818. ESI-MS: *m/z* 572 [M^+], *m/z* 574 [M^++2], *m/z* 537, *m/z* 324.

2.8. Synthesis of 11, 17-di-hydroxy-3, 20-diketo-pregn-1, 4-diene-21-yl-2-(4-isobutylphenyl) propanoate (**7**)

4.0 mg (0.011 mmol) of prednisolone (**3**) was dissolved in 2 mL of chloroform and then Ibuprofen 2.2 mg (0.011 mmol), DCC 2.2 mg (0.011 mmol) and DMAP 1.35 mg (0.011 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 4.7 mg (75.80%) of **7** as crystalline powder. m.p = 504 K, Molecular formula: $C_{34}H_{44}O_6$, ^{1}H NMR at 300 MHz (in $CDCl_3$) δppm: 7.22 (2H, d, H-27 & H-29, $J = 7.8$ Hz), 7.27 (1H, d, H-1, $J = 9.3$ Hz), 7.10 (2H, d, H-26 & H-30, $J = 7.8$ Hz), 6.24 (1H, dd, H-2, $J = 1.5, 10.2$ Hz), 6.01 (1H, s, H-4), 5.01 (1H, d, H-21A, $J = 17.4$ Hz), 4.90 (1H, br s, H-17(OH)), 4.75 (1H, d, H-21B, $J = 17.4$ Hz), 4.46 (1H, s, H-11), 3.82 (1H, q, H-23), 1.56 (3H, d, CH_3-24, $J = 7.2$ Hz), 1.44 (3H, s, CH_3-19), 0.97 (3H, s, CH_3-18), 0.88 (6H, d, CH_3-33 & CH_3-34, $J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ(ppm) 204.81 (C-20), 186.84 (C-3), 174.85 (C-22), 170.35 (C5), 156.53 (C-1), 140.28 (C-28), 137.47 (C-25), 129.58 (C-27 & C-29), 128.02 (C-2), 127.49 (C-26 & C-30), 122.60 (C-4), 89.83 (C-17), 70.34 (C-21), 68.32 (C-11), 55.50 (C-9), 51.51 (C-14), 47.95 (C-31), 45.26 (C-13), 45.13 (C-23), 44.29 (C-12), 39.78 (C-40), 34.74 (C-4), 34.22 (C-7), 32.19 (C-16), 31.42 (C-8), 30.37 (C-32), 24.05 (C-19), 22.61 (C-33 & C-34), 21.27 (C-15), 18.89 (C-24), 17.21 (C-18). IR (KBr) νmax (cm^{-1}): 3461, 2933, 2870, 1722, 1657, 1615, 1513, 1453, 1409, 1366, 1263, 1239, 1114, 1058, 1040, 938, 859, 819, 737, 701, 534. ESI-MS: *m/z* 548 [M^+], *m/z* 531.

3. Computational methods

All the calculations of synthesized compounds were carried out with help of Gaussian 09 program package [14] using B3LYP functional and 6-31G (d, p) basis set. The electronic transitions and electronic properties such as HOMO-LUMO were computed with the help of time-dependant DFT (TD-DFT) method. The molecular structures were visualized with the help of Gauss View [15]. AIM calculations were performed by AIMALL program [16].

4. Result and discussion

4.1. ^{1}H, ^{13}C NMR, FT-IR spectroscopy and ESI-MS

In the ^{1}H NMR spectrum of compound **1** two singlets of three protons each were observed at δ 0.972 and δ 1.445 which are characteristic signals of angular methyl groups corresponding to CH_3-18, and CH_3-19 respectively, of pregnanes. This signifies that the isolated compound may be a pregnane derivative. Another three proton singlet was observed at δ 2.186 which is also a characteristic signal of methyl protons of acetate moiety this confirms that molecule has one acetate group in the structure. Two doublets were observed at and δ 4.879 ($J = 17.4$ Hz) and δ 5.007($J = 17.4$ Hz) which is probably due to mutually coupled protons of methylene group which is directly attached with ester group. These protons are most often due to methylene protons at C-21 position with directly attached ester group. In the ESI-MS of compound **1**, molecular ion and M^++ Na peaks were recorded at *m/z* 404 and *m/z* 427 respectively.

In ^{1}H NMR spectrum of compound **2** showed two, 3 proton singlets, for angular methyl groups at δ 0.962 and δ 1.442 corresponding to CH_3-18, CH_3-19 groups respectively, which are characteristic of pregnane nucleus. Formation of compound **2** was confirmed by absence of signal due to methyl protons of acetate moiety which was present in compound **1**; deacetylation of compound **1** was further confirmed by the appearance of a broad signal of proton at δ 3.061 due to primary hydroxyl group at C-21 position. An upfield shifting of methylene protons of C-21 further confirmed the structure of compound **2**. These methylene protons were observed as doublets at δ 4.686 ($J = 19.8$ Hz) δ 4.337 ($J = 19.8$ Hz). A well defined quartet was observed at δ 4.468 ($J = 3$ Hz) this quartet is due to methine proton at C-11 position. The splitting pattern of H-11 proton was further support the structure of compound **1** where hydroxyl group was found to be β-oriented. In the IR spectrum of compound **2**, hydrogen bonded O-H stretching was observed from 3551.54 cm^{-1}–3145.36 cm^{-1}, centered at 3381.41 cm^{-1}. The C=O stretching frequency of carbonyl group at C-21 position was observed at 1711.34 cm^{-1} while α, β unsaturated carbonyl stretching frequency corresponding to C_5=C_4-C_3=O was observed at 1658.76 [17], which further support the presence of unsaturated carbonyl group. In the ESI-MS spectrum of compound **2** molecular ion was recorded as $M^+ = 362$ with 100% abundance, while M^++Na was also present at 385.

The double bond is well recognized in the ^{1}H NMR spectrum of compound **3**, which besides other signals of the hydrocortisone shows two new doublet of one proton each at δ 7.29 ($J = 9.9$ Hz) and δ 6.17–6.13 ($J = 1.2, 10.2$ Hz) for H-1 and H-2 respectively.

In the ^{1}H NMR spectrum of **4**, the downfield shifting of methylene protons as compared to compound **2** confirms that ester group has been introduced, these methylene protons were observed as one proton doublets at δ 5.046 ($J = 17.1$ Hz) and δ 4.800 ($J = 17.4$ Hz). A quartet of one proton was appeared at δ3.959 ($J = 6.9$ Hz, 7.2 Hz) which is due to methine proton of naproxen designated as H-23. Six aromatic protons of naproxen moiety were well observed from δ 7.12–7.72. H-31 and H-32 protons of aromatic ring were observed at same position as two proton doublet at δ 7.698 ($J = 1.8$ Hz) while H-27 was observed as doublet at δ 7.726 ($J = 2.4$ Hz). A proton doublet at δ 7.149 ($J = 2.7$ Hz) was assigned to H-30, while H-28 proton was observed as singlet at δ 7.120. The H-26 proton of the aromatic ring was observed as double doublet at δ 7.451 ($J = 1.8$ Hz). Protons of the methoxy group of naphthalene ring were observed as sharp singlet at δ 3.911. A three proton doublet was observed at δ 1.624 ($J = 7.2$ Hz) this doublet is due to methyl protons corresponds to CH_3-24. In the IR-spectrum of compound, introduction of ester group is well indicated by strong ester C=O stretching frequency at 1729.89 cm^{-1} [18]. Aromatic C=C stretching vibrations were well observed at 1608.24 cm^{-1} and 1510.30 cm^{-1}. Asymmetric deformation of methyl was observed at 1461.85 cm^{-1} and symmetric deformation of methyls was observed at 1377.31 cm^{-1}. C-C stretching of isopropyl group was assigned to the band observed at 1321.64 cm-1 CH_2 out of plane bending vibrations (wagging and twisting) were observed at 1285.56 cm^{-1} and 1158.76 cm^{-1} respectively. C-O stretching of ester group is observed at 1223.71 cm^{-1} while C3-O1 stretching vibration of ester group was observed at 1112.37 cm^{-1}. In the ESI-MS spectrum of compound **4,** molecular ion was as well as M^++1 was recorded at 574 (with 100% abundance) and 575 respectively.

In the ^{1}H NMR spectrum of the compound **5**, absence of one proton singlet for OH-21 at δ 3.06 and appearance of downfield shifting of H-21A and H-21B protons as doublets at δ 5.11 ($J = 17.4$ Hz) and δ 4.78 ($J = 17.4$ Hz) (initially observed at δ 4.337 ($J = 19.8$

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Hz) and δ 4.686 (J = 19.8 Hz) for H-21A and H-21B in compound **2**) along with the appearance of four aromatic protons at δ 7.24 (2H, dd, H-27 & H-29, J = 8.1, 2.2 Hz), δ 7.21 (2H, dd, H-26 & H-30, J = 7.8, 1.5 Hz), methine proton (H-23) at δ 3.88–3.80, and six proton doublet observed at δ 0.90 (J = 6.6 Hz) due to methyl protons of isopropyl group corresponding to CH_3-33 & CH_3-34 confirmed the esterification of compound **2** at C-21 with ibuprofen. In the ^{13}C NMR of the compound **5**, the peak observed at δ 68.11 and δ 174.62 for C-21 and (C-22) (carbonyl carbon of ester group) respectively along with the aromatic carbons at δ140.89 (C-28), δ137.52 (C-25), δ 129.5 (C-30 & C-26) and δ 127.50 (C-29 & C-27) confirmed the esterification at C-21 of the compound **2**. In the IR spectrum of the compound **5**, the band at 1717 cm^{-1} and 1229 cm^{-1} [17,18] due to C═O (C22═O) and C–C(═O)–O [C–C22(═O)–O] stretching of ester along with the C═C stretching of aromatic ring at 1515 and 1459 cm^{-1} and C-C stretching vibration (of isopropyl side chain of Ibuprofen) at 1367 cm^{-1} confirmed the esterification of compound **2** with ibuprofen. In the ESI-MS of the compound **5**, both the molecular ion peak and protonated molecular ion peak were observed at m/z = 550 and 551 respectively.

In the ^1H NMR spectrum of **6**, the downfield shifting of methylene protons (CH_2-21) to δ 5.07 (d, J = 17.7 Hz) and δ 4.72 (d, J = 17.7 Hz) in comparison to methylene protons of **3** [δ 4.52–4.44 (d, J = 6.0, 19.2 Hz) and δ 4.10–4.02 (d, J = 6.0, 19.2 Hz)], confirms that the 21-OH group has been esterified. The signals for aromatic protons of naproxen were observed at 7.80 (3H, d, H-27, H-31 & H-32, J = 9.6 Hz), 7.45 (1H, d, H-26, J = 8.4 Hz), 7.32 (2H, d, H-30 & H-28, J = 9.0 Hz). In the FT-IR spectrum of **6**, sharp band at 1724 cm^{-1} [18] appears to be due to carbonyl groups at C-20 and C-22, however band at 1265 cm^{-1} appears to be due to C-O stretching of ester group. In the ESI-MS spectrum of **6**, the molecular ion peak was observed at m/z 572 [M^+].

In the ^1H NMR spectrum of **7**, the downfield shifting of methylene protons (CH_2-21) to δ 5.01 (d, J = 17.4 Hz) and δ 4.75 (d, J = 17.4 Hz) in comparison to methylene protons of **3** [(δ 4.52–4.44 (d, J = 6.0, 19.2 Hz) and δ 4.10–4.02 (d, J = 6.0, 19.2 Hz)], confirms that the 21-OH group has been esterified. The signal for aromatic protons of ibuprofen were observed at δ 7.22 (2H, d, H-27 & H-29, J = 7.8 Hz), δ 7.10 (2H, d, H-26 & H-30, J = 7.8 Hz). In the ^{13}C NMR spectrum of **7**, the observed carbon signal at δ 174.85 for C22 along with aromatics carbon at δ 129.58 (C-27 & C-29), and δ 127.49 (C-26 & C-30) confirm the formation of ester at C-21 position. In the FT-IR spectrum of **7**, sharp band at 1722 cm^{-1} [18] appears to be due to carbonyl groups at C-20 and C-22, however band at 1263 cm^{-1} appears to be due to C-O stretching of ester group. In the ESI-MS spectrum of **7,** the molecular ion peak was observed at m/z 548 [M^+].

4.2. Frontier molecular orbital

The frontier orbitals, HOMO and LUMO determine the way how the molecule interacts with other species and helps to characterize the chemical reactivity and kinetic stability of the molecule. They play an important role in the electric and optical properties, as well as in the UV–Vis spectra and chemical reactions. HOMO energy determines the ability to donate an electron and LUMO energy determines the ability to accept an electron. The energy gap between the HOMO and LUMO is very important in determining the chemical reactivity of the molecule. A small HOMO-LUMO energy gap implies low kinetic stability, because it is energetically favorable to add electrons to a low-lying LUMO and to receive electrons from a high-lying HOMO. Thus, molecules with low frontier orbital gap are more polarizable and associated with high chemical reactivity. Fig. 1 shows the HOMO-LUMO molecular orbital diagrams for prodrugs **4, 5, 6** and **7**. For compound **4**, HOMO lying at −5.38 eV (computed by TD-DFT) whereas the LUMO lying at −1.10 eV. The energy difference between the HOMO and LUMO was obtained as 4.27 eV in the gas phase calculations. For compound **5**, the HOMO lying at −6.09 eV whereas the LUMO lying at −1.09 eV. The energy difference between the HOMO and LUMO was obtained as 4.99 eV in the gas phase calculations. For compound **6**, the HOMO lying at −5.45 eV whereas the LUMO lying at −1.27 eV. The energy difference between the HOMO and LUMO was obtained as 4.17 eV in the gas phase calculations. For compound **7**, HOMO whereas LUMO lying at −6.09 and −1.27 eV respectively. The energy difference between the HOMO and LUMO was obtained as 4.82 eV in the gas phase calculations. Low charge separation in **6** explains eventual charge transfer interactions within the molecule and high chemical reactivity, which may influence the biological activity of the molecule.

4.3. AIM approach

In the topological theory of AIM (Atoms In Molecule), when two atoms are chemically bonded, a bond critical point appears between them and the nature of chemical bonds and molecular reactivity are described by total electronic density $\rho(r)$, and its corresponding Laplacian $\nabla^2\rho(r)$. Laplacian of total electronic density is related to energetic topological parameters by a local expression of the virial theorem at critical points [19]:

$$\frac{1}{4}\nabla^2\rho(r) = 2G(r) + V(r)$$

Where, $G(r)$ and $V(r)$ are the kinetic and potential electron energy densities at critical points respectively. In the characterization of IHB (Intramolecular Hydrogen Bonding), bond critical point (BCP) in the hydrogen bond and ring critical point (RCP) in the ring are useful. Positive values of $\nabla^2\rho(r)$at BCP indicate that $G(r)$ is greater than that of $V(r)$ and shows depletion of electronic charge along the bond path, which is specific for closed-shell interactions such as hydrogen bonds. However negative value of $\nabla^2\rho(r)$ indicates excess potential energy at BCP and which is specific of shared interactions, such as covalent bonds. In the later case, electronic charge is focused on the internuclear region and shared by two nuclei [20]. As Rozas et al. [21] explained that hydrogen bonds can be classified as (1) Weak hydrogen bonds, when $\nabla^2\rho(r\text{BCP}) > 0$ and $G(r\text{BCP}) + V(r\text{BCP}) > 0$; (2) Medium hydrogen bonds, when $\nabla^2\rho(r\text{BCP}) > 0$ and $G(r\text{BCP}) + V(r\text{BCP}) < 0$; (3) Strong hydrogen bonds, when $\nabla^2\rho(r\text{BCP}) < 0$ and $G(r\text{BCP}) + V(r\text{BCP}) < 0$; Where $G(r\text{BCP}) + V(r\text{BCP})$ is also known as total electron energy density $H(r\text{BCP})$. The ranges of $\rho(r)$ and $\nabla^2\rho(r)$ for hydrogen bond in BCP are 0.002–0.035e/Å^3 and 0.02–0.139e/Å^5 respectively [22]. The nature of IHB can be determined using ratio of $-G(r\text{BCP})/V(r\text{BCP})$. When this ratio is >1, then IHB has non-covalent nature, while when this ratio is <1, then it is partly covalent [23]. Several theoretical methods [24,25] have been proposed to estimate hydrogen bond energy. One of the most useful of these methods has been explained by Espinosa et al. [26] who found that IHB energy may be correlated with the potential electron energy density at critical point by the expression $E_{IHB} = 1/2V(r\text{BCP})$. Molecular graphs of the synthesized compounds using AIM program at B3LYP/6- 31G (d, p) level are shown in Fig. 2. For compounds topological parameters for bonds of interacting atoms are given in Table 1 and on the basis of above criteria $\nabla^2\rho(r\text{BCP})$ and H_{BCP} parameters are greater than zero, which suggested that all the interactions are weak. The ratio $-G(r\text{BCP})/V(r\text{BCP})$ of the synthesized prodrugs **4, 5, 6** and **7** were greater than unity, which suggested that hydrogen bond interactions are non-covalent in nature. According to AIM calculation, the total energy of intramolecular interaction for prodrugs **4, 5, 6**

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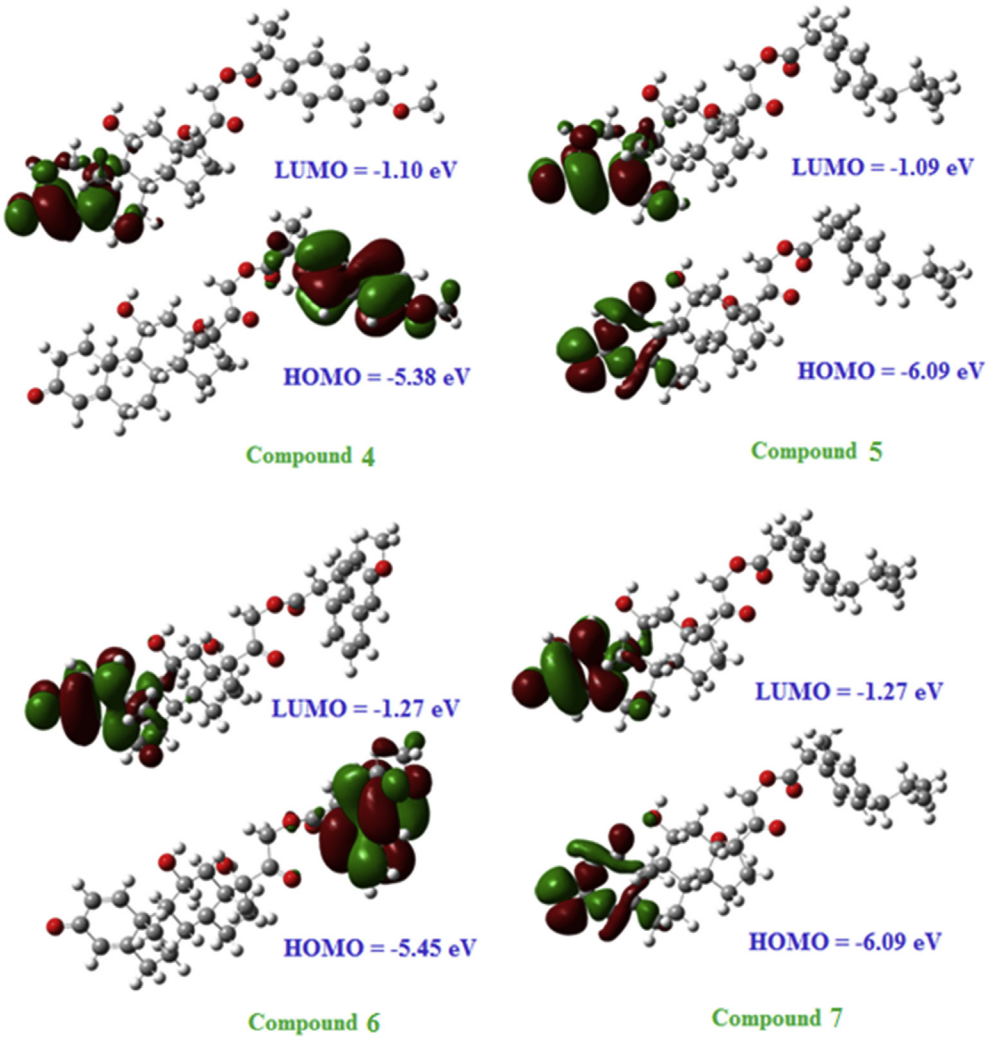

Fig. 1. HOMO-LUMO molecular orbital diagrams for prodrugs **4, 5, 6** and **7**.

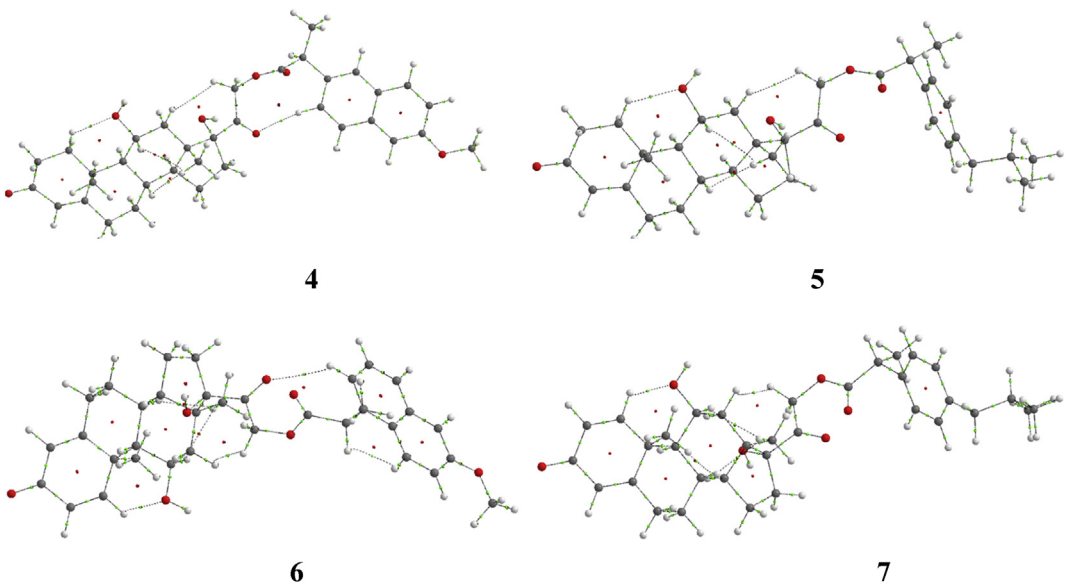

Fig. 2. Molecular graphs of the synthesized compounds using AIM program at B3LYP/6- 31G (d, p) level.

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Table 1
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 **4**, **5**, **6** and **7**.

Interaction	$\rho_{(BCP)}$	$\nabla^2\rho_{(rBCP)}$	G_{BCP}	V_{BCP}	H_{BCP}	$-G/V$	E_{int}
Compound 4							
O2···H1B	0.019	0.066	0.0158	−0.0151	0.0007	1.0	−4.73
H12B···H21A	0.048	0.017	0.003	−0.002	0.001	1.5	−0.62
O4···H26	0.006	0.023	0.0049	−0.0041	0.0008	1.1	−1.28
H8···H18B	0.009	0.039	0.007	−0.005	0.002	1.4	−1.56
H11···H18B	0.009	0.037	0.007	−0.005	0.002	1.4	−1.56
Compound 5							
O2···H1B	0.019	0.066	0.016	−0.015	0.001	1.0	−4.70
H12B···H21A	0.045	0.016	0.003	−0.001	0.002	3.0	−0.31
H11···H18B	0.009	0.037	0.007	−0.005	0.002	1.4	−1.56
H8···H18B	0.010	0.039	0.007	−0.005	0.002	1.4	−1.56
Compound 6							
O2···H1	0.021	0.073	0.017	−0.016	0.001	1.0	−5.02
O4···H26	0.066	0.025	0.005	−0.004	0.001	1.2	−1.25
H12B···H21A	0.004	0.017	0.003	−0.002	0.001	1.5	−0.62
H11···H18B	0.008	0.037	0.007	−0.004	0.003	1.7	−1.25
H8···H18B	0.009	0.039	0.007	−0.005	0.002	1.4	−1.56
Compound 7							
O2···H1	0.020	0.072	0.017	−0.016	0.001	1.0	−5.02
H12B···H21A	0.004	0.017	0.003	−0.002	0.001	1.5	−0.62
H18B···H11	0.008	0.037	0.007	−0.004	0.003	1.7	−1.25
H18B···H8	0.010	0.040	0.007	−0.005	0.0004	1.4	−1.56
H19C···H8	0.008	0.033	0.006	−0.004	0.002	1.5	−1.25

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

and **7** are calculated as -9.97, -8.11, -9.70 and -9.70 kcal/mol respectively. The ellipticity (ε) at BCP is a sensitive index to monitor the π-character of a 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 for bond C5═C6 (alkene) is 0.397 for all synthesized compounds suggesting the accumulation of electron density at this position. The ellipticity values for bonds C25–C32, C32–C33, C33–C31, C31–C30, C30–C29, C29–C28, C28–C34, C34–C27, C34–C33, C27–C26 and C26–C25 in compound **4** are 0.267, 0.162, 0.170, 0.261, 0.211, 0.291, 0.184, 0.150, 0.153, 0.263 and 0.163 respectively whereas it was very similar to ellipticity value of compound **6**. The lower values of ellipticity confirm that there is delocalization of electron in the aromatic ring [27,28].

5. Conclusion

Corticosteroids prodrugs (**4, 5, 6** and **7**) have been synthesized by adopting Steglich reaction. The structures of these compounds were well characterized with the help of ^{1}H, ^{13}C NMR, FT-IR spectroscopy and mass spectrometry. Lower charge separation in **6** explains eventual charge transfer interactions within the molecule and high chemical reactivity. According to AIM approach, the total energy (−9.97 kcal/mol) of intramolecular interactions for compound **4** was higher than other compounds. Out of all synthesized compounds, compound **7** was found to be a good electrophile (global electrophilicity index (ω) = 2.81). On the basis of first hyperpolarizability, we conclude that compound **4** ($\beta_0 = 5.66 \times 10^{-30}$ esu) showed good attractive materials for non linear optical (NLO) application.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.molstruc.2016.10.087.

Appendix A

All the spectra, optimized geometries, NLO properties, global reactivity descriptors and MEP analysis of all compounds were given in supplementary data.

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