

Theoretical and experimental investigations into the structural, electronic, and molecular properties of 1,5-dihydropyrano[2,3-c]chromene derivatives

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ABSTRACT

In this study, a simple and efficient method for the synthesis of 1,5-dihydropyrano[2,3-c]chromene derivatives is reported by three component reaction of aromatic aldehydes, malononitrile, and 3-hydroxycoumarin in the presence of piperidine as base in ethanol, under reflux conditions. Also, the experimental results involving new and already synthesized compounds are compared with the theoretical calculations. The energy, molecular electrostatic potential (MEP), HOMO–LUMO energy gap, chemical properties and NMR analyses of 1,5-dihydropyrano[2,3-c]chromene derivatives in DMSO solution were estimated using density functional theory and 6-311++G (d,p) basis set. The solvent effect was explored using the polarizable continuum model (PCM) method. Increasing polarity and having no much difference in energies show the more effects of newly synthesized compounds (R₂-DHPC) towards already synthesized compounds (R₄-DHPC) in human body. Also, the results display that there is a good agreement between experimental and theoretical data.

Keywords: Dihydropyrano[2,3-c]chromene; three component reactions; 3-hydroxycoumarin; DFT; solvent effect.

1. INTRODUCTION

1,5-Dihydropyrano[3,2-c]chromene and its derivatives are of considerable interest as they have possessed a wide range of biological properties such as antihyperglycemic and antidyslipidemic [1], cytotoxic [2], anti-inflammatory [3], antifungal [4], anticancer [5] and antimalarial activities [6]. These compounds also widely employed as cosmetics, pigments [7] and potential biodegradable agrochemicals [8].

In order to get deeper insights in to the molecular, structural, and biological properties of the synthesized compounds, the DFT analysis was applied. In this aim, several calculations were performed. The structures were optimized in DMSO media by the polarized continuum model (PCM), for the calculation of molecular energies [1][9-11]. Reactivity sites towards positively negatively charged reactants were studied. NMR calculations were

also performed as the same level. Molecular electrostatic potential surface (MEPS) study was achieved to predict reactivity sites towards positively and negatively charged reactants. Finally, Frontier molecular orbitals (FMOs) and chemical properties such as ionization potential [12], electron affinity, chemical potential, hardness and softness considerations according to Koopmans theorem were carried out [13].

Based on the results, not the only polarity of all structures is more in the solvent environment than gas phase but also the polarity of R₂-DHPC molecules is higher than R₄ positions. Therefore, solubility of R₂-DHPC compounds is more than R₄-DHPC ones. Also, comparing total energies imply that spatial steric does not have a special effect in the stability of investigated structures.

2. MATERIALS AND METHODS

2.1. Experimental section.

Solvents and reagents were purchased from commercial sources and were used without further purification. Melting points were measured on an Electrothermal-9100 apparatus and are uncorrected. TLC was performed on the Aluminium-backed silica gel sheets (silica GF₂₅₄) and visualized in UV light. IR spectra were recorded on a Bruker FTIR (Alpha model). ¹H NMR spectra were recorded on a Bruker Avance III 300 MHz model Spectrometer. ¹³C NMR spectra were recorded on the same instruments at 75 MHz, using TMS as an internal standard. Elemental analyses were performed using a Costech Elemental Combustion System CHNS-O (ECS 4010).

2.2. General procedure for the preparation of 1,5-dihydropyrano[2,3-c]chromene derivatives (4b-e).

To a 50 mL two-necked round bottomed flask, equipped with a magnetic stirring bar and a reflux condenser, were added a mixture of aromatic aldehydes (**1**) (2 mmol), 3-hydroxycoumarin (**2**) (2 mmol) and malononitrile (**3**) (2 mmol), and two drops of piperidine in EtOH (10 mL) was refluxed for 30 min (the progress of the reaction being has been monitored by TLC and hexane/ethyl acetate was used as an eluent). The reaction mixture was cooled after completion of the reaction, and the crude product was filtered, washed with n-hexane and dried. The collected IR, ¹H NMR and ¹³C NMR spectra for **4a**, **4f**, **4g**, **4h**, **4i** [14-17], are consistent with the previously reported NMR data for these components.

3-Amino-5-oxo-1-(*o*-tolyl)-1,5-dihydropyrano[2,3-c]chromene-2-carbonitrile (4b)

Pale yellow powder; yield: 89%; mp 297-298 °C (dec.); IR (KBr, $\nu_{\max}/\text{cm}^{-1}$) 3435, 3303, 2202, 1726, 1665, 1633, 1595; ^1H NMR (300 MHz, DMSO- d_6) δ_{ppm} : 7.51-7.42 (m, 1H, Ar), 7.41-7.39 (m, 1H, Ar), 7.38-7.21 (m, 4H, Ar), 7.16-7.09 (m, 4H, Ar, NH₂), 5.29 (s, 1H), 2.64 (s, 3H, CH₃); ^{13}C NMR (75 MHz, DMSO- d_6) δ_{ppm} : 159.21, 154.41, 150.57, 141.76, 135.10, 134.80, 131.36, 130.68, 128.71, 127.72, 127.65, 127.09, 125.32, 125.05, 120.15, 117.43, 116.92, 56.69, 34.56, 19.62. Anal. calcd. For C₂₀H₁₄N₂O₃: C, 72.72; H, 4.27; N, 8.48. Found: C, 72.54; H, 4.10; N, 8.32%.

3-Amino-1-(2-chlorophenyl)-5-oxo-1,5-dihydro-pyrano[2,3-c]chromene-2-carbonitrile (4c)

White powder; yield: 92%; mp 307-308 °C (dec.); IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3455, 3319, 2192, 1750, 1660, 1629, 1583. ^1H NMR (300 MHz, DMSO- d_6) δ_{ppm} : 7.53-7.47 (m, 2H, Ar), 7.46-7.40 (m, 2H, Ar), 7.32-7.23 (m, 6H, Ar, NH₂), 5.46 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ_{ppm} : 159.51, 154.33, 150.52, 140.37, 135.28, 131.86, 131.14, 130.82, 130.27, 129.87, 126.96, 125.58, 125.40, 124.45, 119.44, 117.35, 117.08, 55.82, 35.47. Anal. calcd. For C₁₉H₁₁ClN₂O₃: C, 65.06; H, 3.16; N, 7.99. Found: C, 64.85; H, 3.01; N, 7.83%.

3-Amino-1-(2-methoxyphenyl)-5-oxo-1,5-dihydro-pyrano[2,3-c]chromene-2-carbonitrile (4d)

White powder; yield: 88%; mp 288-289 °C (dec.); IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3436, 3276, 2199, 1737, 1659, 1629, 1603. ^1H NMR (300 MHz, DMSO- d_6) δ_{ppm} : 7.51-7.38 (m, 3H, Ar), 7.28-7.21 (m, 3H, Ar), 7.16 (brd, 2H, NH₂), 7.07-7.05 (d, 1H, $J = 8$ Hz, Ar), 6.93-6.87 (td, 1H, $J_1 = 5$ Hz, $J_2 = 2.2$ Hz, Ar), 5.31 (s, 1H), 3.87 (s, 3H, OCH₃). ^{13}C NMR (75 MHz, DMSO- d_6) δ_{ppm} : 159.95, 156.60, 154.49, 150.52, 134.82, 131.06, 130.67, 129.74, 129.42, 127.01, 125.31, 124.79, 121.71, 120.04, 117.67, 116.91, 112.38, 56.43, 56.22, 32.54. Anal. calcd. For C₂₀H₁₄N₂O₄: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.15; H, 3.92; N, 7.89%.

3-Amino-1-(2-bromophenyl)-5-oxo-1,5-dihydro-pyrano[2,3-c]chromene-2-carbonitrile (4e)

Pale yellow powder; yield: 91%; mp 294-295 °C (dec.); IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3445, 3321, 2191, 1749, 1662, 1629, 1588. ^1H NMR (300 MHz, DMSO- d_6) δ_{ppm} : 7.69-7.67 (d, 1H, $J = 8$ Hz, Ar), 7.53-

7.47 (m, 1H, Ar), 7.44-7.37 (m, 2H, Ar), 7.34-7.18 (m, 6H, Ar, NH₂), 5.44 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ_{ppm} : 159.40, 154.38, 150.54, 142.16, 135.29, 133.49, 131.19, 130.82, 130.11, 129.60, 125.74, 125.39, 124.58, 122.54, 119.30, 117.43, 117.13, 55.98, 40.82. Anal. calcd. For C₁₉H₁₁BrN₂O₃: C, 57.74; H, 2.81; N, 7.09. Found: C, 57.57; H, 2.69; N, 6.98%.

2.3. Computational details.

Computational calculations were carried out in order to enable structural explanations of NMR and to the investigation of molecular energies and chemical properties using DFT. All structures were optimized at B3LYP level and 6-311++G (d,p) basis set using Gaussian 09 series of programs [18]. To study the effect of DMSO solvent, the polarized continuum model (PCM), which defines the cavities as envelopes of spheres centered on atoms or atomic groups was applied [19]. NMR calculations were also performed at the same level. Molecular electrostatic potential surface (MEPS) study was achieved to predict reactivity sites towards positively and negatively charged reactants. Frontier molecular orbitals (FMOs) were studied to describe chemical behavior of investigated compounds. Chemical reactivity and stability of the compounds according to Koopmans theorem were calculated as defined in equations (1-4):

$$\mu = \left(\frac{\partial E}{\partial N} \right)_{V(r),T} \quad (1)$$

$$\eta = \left(\frac{\partial^2 E}{\partial N^2} \right)_{V(r),T} \quad (2)$$

$$S = \frac{1}{2\eta} \quad (3)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (4)$$

where E is the total electron energy, N is the number of electrons; V(r) is the external potential, μ is chemical potential, η is chemical hardness, S is global softness and ω is electrophilicity index [20].

3. RESULTS

3.1. The results of experimental sections.

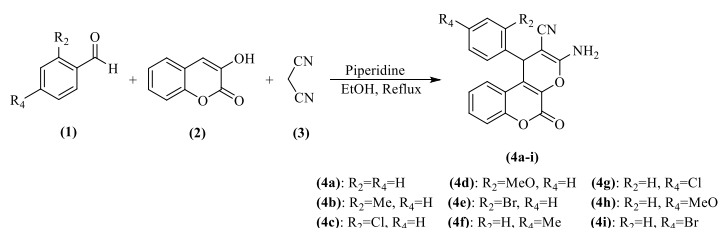
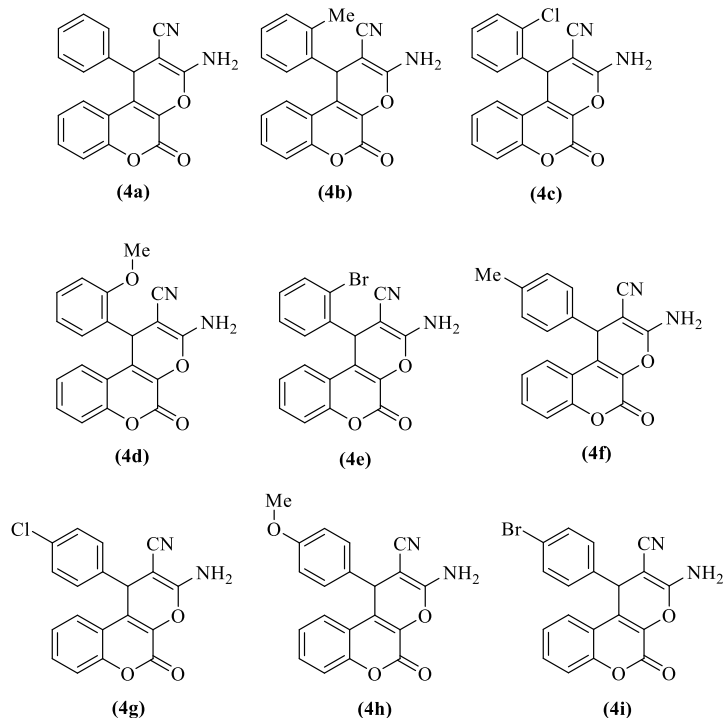
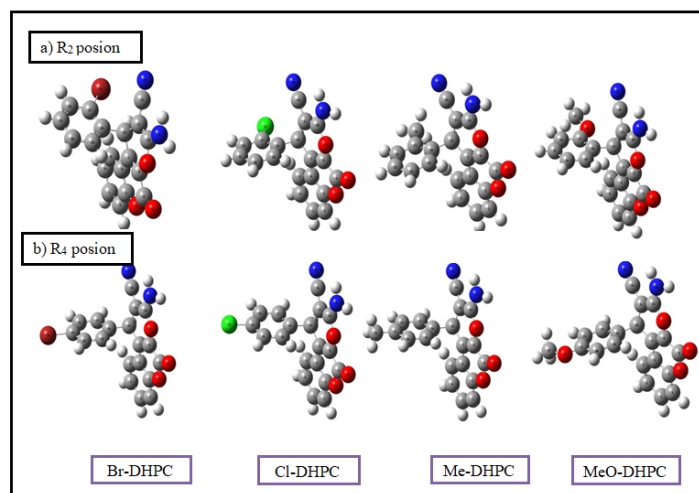
Following our previous works on environmentally friendly multi-component reaction[21-23], we synthesized a series of 1,5-dihydropyrano[2,3-c]chromene derivatives (4a-i) by three-component reaction of aromatic aldehydes (1), 3-hydroxycoumarin (2) and malononitrile (3) in the presence of piperidine as base in EtOH, under reflux conditions (Scheme 1).

3.2. Optimized structures.

In this study, we investigated nine compounds containing 4a-4i structures (Scheme 2). The 4a structure is without substitute, 4b-4e structures have a substitute on C₂₇ or C₃₀ and 4f-4i structures have a substitute on C₃₂ which we name them R₂-DHPC, R'₂-DHPC and R₄-DHPC respectively.

All structures were full optimized at B3LYP level and 6-311++G (d,p) basis set using Gaussian 09. The results show that R₂-DHPC structures are more stable than R'₂-DHPC ones. Fig. 1 shows optimized structures. Also, according to the total energies,

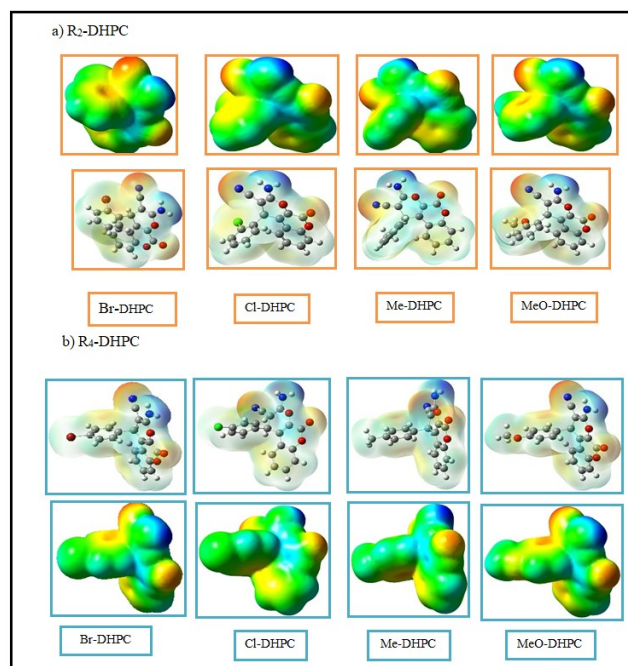
as expected, locating substitutes on R₄-DHPC towards R₂-DHPC structures are more stable, but there is not a very big difference between them (Table 1). Therefore, spatial steric does not have special effect in stability of structures. Meanwhile, the dipole moments of molecule systems increase in solvent media. In the following, we study R₂-DHPC structures and compare them with R₄-DHPC structures. The dipole moment shows a special property of a molecule that considers data in the case electronic and geometrical properties. Table 1 displays dipole moment of all molecules in solvent media is more than gas phase showing increasing polarity of the structures and solubility in solution environment. Also, dipole moment of R₂-DHPC structures in comparison to R₄-DHPC structures is more; so, their effects in human body are higher.


Scheme 1. Synthesis of 1,5-dihydropyrano[2,3-c]chromene derivatives.

Scheme 2. Nine derivatives (4a-i) used in this study.

Figure 1. The optimized structures: a) R_2 -DHPC and b) R_4 -DHPC compounds calculated at the DFT/B3LYP/6-311++G (d,p) level of theory.

3.3. Molecular electrostatic potential surface analysis.

Mapping molecular electrostatic potential surface (MEPS) is useful in exploring reactivity sites (the nucleophilic and electrophilic), electronegativity, and partial charges of the titled compounds. MEPS counter maps were forecasted by DFT and at the B3LYP/6-311++G (d,p) level shown in Fig. 2. As seen increasing in charge density and electrostatic potential is the following: orange < yellow < blue < green. So, the areas with red color and blue color characterize the most negative and most positive electrostatic potential and charge density. The areas with green color have no electrostatic potential. From Fig. 2, it is obvious that for R_2 and R_4 positions except MeO, R_2 -DHPC

structures are covered by the negative charge and R_4 -DHPC structures are shielded by the positive charge. In methoxy substitute, there is no difference in both positions; the negative charge is over on oxygen atom and the positive charge is over on methyl group.


Figure 2. The electron density isosurfaces for a) R_2 -DHPC and b) R_4 -DHPC compounds computed at the DFT/B3LYP/6-311++G (d,p) level of theory.

3.4. Frontier molecular orbitals analysis.

According to the frontier molecular orbital (FMO) theory, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) play a key role in stability, reactivity and electric properties of molecules. Also, the gap energy (E_g) defined as the difference between HOMO and LUMO, has an important role in chemical reactivity, the structural stability, polarizability, the electron conductivity, electrophilicity index (ω) [20], chemical hardness (η), and softness (S) of a molecule [24]. The chemical hardness and softness are one way to consider the structural stability of the compound. Gap energy indicates whether the molecule is soft or not. The large E_g expresses the molecule is hard and stable while the small gap energy is the sign of soft and more polarizable molecule. Fig. 3 and 4 show the distributions and energy levels of the HOMO and LUMO orbitals for the titled molecules. The green and red colors represent the negative and positive phases respectively. Table 2 shows the value of HOMO, LUMO, E_g , hardness, softness, chemical potential, electrophilicity and Fermi level energy (E_f). As seen from Table 2, difference E_g between R_2 and R_4 positions in Br and Cl substitutes is zero and for Me and MeO substitutes are -0.03 and 0.08 eV respectively. It shows that in Br-DHPC and Cl-DHPC compounds, there is no preferential between R_2 and R_4 positions and this difference is so slight in Me-DHPC and MeO-DHPC compounds. According to chemical hardness and softness values both positions (R_2 and R_4) are the same in Br-DHPC and Cl-DHPC compounds and in Me-DHPC and MeO-DHPC compounds, R_2 and R_4 positions are a little harder than that ones. Meanwhile, although, Me-DHPC and MeO-DHPC compounds are larger than Br-DHPC and Cl-DHPC ones, but they are very similar

from the point of view hardness and softness. Electrophilicity index represented as $\omega = \mu^2/2\eta$ shows that the titled compounds have rich electrophilic nature.

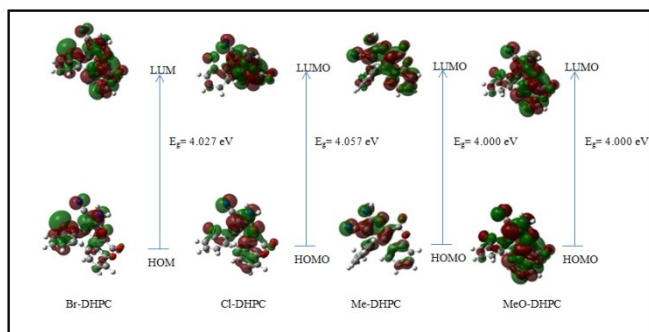


Figure 3. The distribution of HOMO and LUMO orbitals of R₂-DHPC molecules in DMSO solvent.

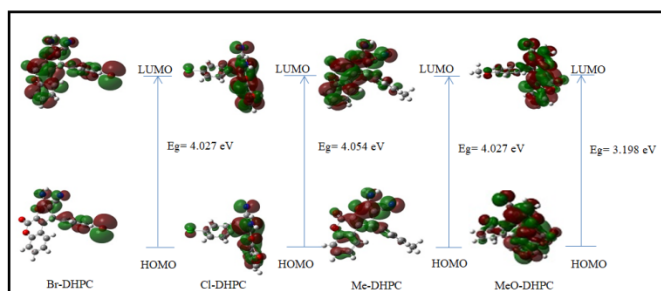


Figure 4. The distribution of HOMO and LUMO orbitals of R₄-DHPC molecules in DMSO solvent.

Also, gap energy of DHPC molecule is more than other compounds and therefore has more hardness and less softness towards them; so, R₂ and R₄- DHPC structures have higher chemical activity. Meanwhile, the results show the value of

hardness and less softness for R₂ and R₄- DHPC structures are very similar. So, in human body there is no much difference between their activity values.

3.5. NMR analysis

¹H and ¹³C NMR of the investigated compounds were estimated experimentally in DMSO solvent and TMS as an internal standard. We calculated ¹H and ¹³C NMR in similar media (DMSO) using GIAO method at the same level of optimization [25-30]. Table 3 displays experimental and theoretical results of ¹H and ¹³C NMR data of R₂ and R₄(Cl)-DHPC compounds. NMR data of other compounds are presented in supplementary data section. The experimental results of R₄ position are in references [14-17]. Experimental and theoretical ¹³C NMR revealed the presence of 20 assignable resonances to compounds with MeO and Me substitutes and 19 specific resonances to Br and Cl substitutes because of existence of carbon atom in MeO and Me substitutes. As seen in Table 3 and supplementary data, shielding of carbon joined to substitute in R₄ position is higher than R₂ position in all compounds. Also, as expected, MeO substitute because of large electron density has the highest shielding (168 ppm) among other substitutes. Meanwhile, there is good agreement between experimental and theoretical results. Similarly, ¹H NMR revealed the presence of 11 or 14 protons, that which 10 protons correspond to aromatic ring and NH₂ group in the range of 6.80-7.69 ppm which were calculated in the range of 6.96-7.88 ppm, one proton as CH group in the range of 5.29-5.46 ppm calculated using DFT in the range of 5.03-5.53 ppm, three protons as Me group in 2.64 ppm calculated in 2.79 ppm and three protons as MeO group in 3.87 ppm calculated in 3.89 ppm which again revealed a reasonable agreement.

Table 1. Energies and Dipole Moments (Debye) of investigated compounds in gas phase and DMSO solvent.

Compound	subordinate position	Gas phase		DMSO	
		E(eV)	Dipole Moment	E(eV)	Dipole Moment
Br-DHPC	R ₄	-99056.513	3.0258	-99057.091	4.2382
	R ₂	-99056.436	3.2882	-99056.989	4.4018
	R ₂	-99056.343	3.9756	—	—
Cl-DHPC	R ₄	-41533.377	3.0273	-41533.954	4.2467
	R ₂	-41533.322	3.3100	-41533.875	4.4175
	R ₂	-41533.247	3.8694	—	—
Me-DHPC	R ₄	-30096.495	3.5111	-30097.055	4.6424
	R ₂	-30096.403	3.3557	-30096.944	4.6722
	R ₂	-30096.335	3.1940	—	—
MeO-DHPC	R ₄	-32143.591	4.1847	-32144.205	5.6884
	R ₂	-32143.602	4.4624	-32144.190	6.0619
DHPC	R ₂	-32143.573	3.5145	—	—
	—	-29026.320	3.2791	-29026.882	4.4034

Table 2. Orbital energies (HOMO and LUMO), energy gap (E_g), difference between gap energies (ΔE_g), Fermi level energy (E_f), hardness (η), softness (S), chemical potential (μ), and electrophilicity index (ω) of the titled compounds in the DMSO solvent. Energies are in eV.

Compound	substitute position	HOMO	LUMO	E _g	ΔE _g	E _f	η	S	μ	ω
Br-DHPC	R ₄	-6.59	-2.56	4.03	0.00	-4.57	2.01	0.25	-4.57	5.19
	R ₂	-6.50	-2.48	4.03		-4.49	2.01	0.25	-4.49	5.01
Cl-DHPC	R ₄	-6.59	-2.53	4.05	0.00	-4.56	2.03	0.25	-4.56	5.12
	R ₂	-6.53	-2.48	4.05		-4.50	2.03	0.25	-4.50	5.00
Me-DHPC	R ₄	-6.42	-2.40	4.03	-0.03	-4.41	2.01	0.25	-4.41	4.83
	R ₂	-6.42	-2.42	4.00		-4.42	2.00	0.25	-4.42	4.89
MeO-DHPC	R ₄	-6.29	-2.37	3.92	0.08	-4.33	1.96	0.26	-4.33	4.78
	R ₂	-6.31	-2.31	4.00		-4.31	2.00	0.25	-4.31	4.65
DHPC	—	-6.84	-2.45	4.39	—	-4.64	2.20	0.23	-4.64	4.91

Table 3. Comparison of theoretical (Theo.) and experimental (Exp.) NMR data of R₂(Cl)-DHPC and R₄(Cl)-DHPC.

¹ H NMR						¹³ C NMR					
R ₂ (Cl)-DHPC			R ₄ (Cl)-DHPC			R ₂ (Cl)-DHPC			R ₄ (Cl)-DHPC		
Exp. (δ ppm)	No. of H atom	Theo.	Exp. (δ ppm)	No. of H atom	Theo.	Exp. (δ ppm)	No. of C atom	Theo.	Exp. (δ ppm)	No. of C atom	Theo.
5.46 (s, 1H)	12,14	7.62 (s, 2H)	5.34 (s, 1H)	34	7.62(s,1H)	159.51	10	166.5	158.75	10	166.26
7.23-7.32(m, 6H)	32	7.52 (s, 1H)	7.18-7.79 (m,7H)	30	7.59(s,1H)	154.33	3	160.99	153.83	3	161.57
7.40-7.46(m, 2H)	13	7.50 (s, 1H)	8.04 (s,1H)	12	7.58(s,1H)	150.52	9	157.92	150.08	9	150.6
7.47-7.53(m, 2H)	36	7.42 (s, 1H)	8.07 (s,1H)	13	7.54(s,1H)	140.37	26	152.54	140.59	33	150.42
	33	7.33 (s, 1H)	8.29 (s,1H)	14	7.37(s,1H)	135.28	27	148.48	133.95	26	149.11
	15	7.29 (s, 1H)		35	7.36(s,1H)	131.86	8	141.36	132.75	8	142.39
	34	7.25 (s, 1H)		15	7.28(s,1H)	131.14	29	140.18	130.02	31	136.74
	20	5.32 (s, 1H)		32	7.19(s,1H)	130.82	28	137.4	128.82	1	139.66
	22	4.58 (s, 1H)		20	4.73(s,1H)	130.27	7	137.14	128.47	29	135.82
	23	3.98 (s, 1H)		22	4.51(s,1H)	129.87	1	136.79	—	27	135.3
				23	4.05(s,1H)	128.96	32	135.08	—	7	135.09
						125.58	30	134.11	125.97	28	134.37
						125.4	5	131.91	124.54	5	131.24
						124.45	6	130.12	124.41	6	130.04
						119.44	4	124.15	118.88	4	124.06
						117.35	2	123.1	116.42	2	123.25
						117.08	24	121.57	116.24	24	123.01
						55.82	11	64.84	57.15	11	65.56
						35.47	19	42.96	37.63	19	45.74

4. CONCLUSIONS

In conclusion, the 1,5-dihydropyrano[3,2-*c*]chromene derivatives have been synthesized *via* three-component reaction of 3-hydroxycoumarin, aromatic aldehydes, and malononitrile in EtOH, at reflux and in the presence of piperidine as base. The density functional theory was employed to investigate structural, electrical and molecular properties of DHPC, R₂-DHPC and R₄-DHPC structures and the results were compared with performed experimental in this study and done study on R₄ position. Molecular electrostatic potential surface analysis, frontier molecular orbitals analysis and gap energy, hardness, softness,

chemical potential, electrophilicity, Fermi level energy, and NMR calculations were carried out. The results revealed E_g difference between R₂ and R₄ positions in Br and Cl substitutes is zero and for Me and MeO substitutes are so small. Therefore, there is no difference between R₂ and R₄ positions for Br and Cl substitutes in point of view chemical hardness, but for MeO and Me substitutes R₄ position is a little harder and softness respectively. Therefore, spatial steric does not have special effect on electronic properties and stability of R₂-DHPC and R₄-DHPC structures.

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