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 antidiyslipidemic [1], cytoxic [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 into 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, 1HNMR and 13CNMR spectra for 4a, 4f, 4g, 4h, 4i [14-17], are consistent with the previously reported NMR data for these components.

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3-Amino-5-oxo-1-(o-toly)-1,5-dihydropyrano[2,3-c]chromene-2-carbonitrile (4b)
Pale yellow powder; yield: 89%; mp 297-298 °C (dec.); IR (KBr, ν/cm\(^{-1}\)) 3435, 3303, 2202, 1726, 1665, 1633, 1595; \(^1\)H 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, NH\(_2\)), 5.29 (s, 1H), 2.64 (s, 3H, CH\(_3\)); \(^1^C\) 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. calcld. For C\(_{23}\)H\(_{14}\)N\(_2\)O\(_5\): C, 67.22; 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-pyra-no[2,3-c]chromene-2-carbonitrile (4e)
White powder; yield: 92%; mp 307-308 °C (dec.); IR (KBr, ν/cm\(^{-1}\)) 3455, 3319, 2192, 1750, 1660, 1629, 1583. \(^1\)H 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, NH\(_2\)), 5.46 (s, 1H). \(^1^C\) 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. calcld. For C\(_{21}\)H\(_{14}\)ClN\(_2\)O\(_5\): 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-pyra-no[2,3-c]chromene-2-carbonitrile (4d)
White powder; yield: 88%; mp 288-289 °C (dec.); IR (KBr, ν/cm\(^{-1}\)) 3436, 3276, 2199, 1737, 1659, 1629, 1603. \(^1\)H 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, NH\(_2\)), 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, OCH\(_3\)). \(^1^C\) 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. calcld. For C\(_{21}\)H\(_{15}\)O\(_4\)N\(_2\): 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-pyra-no[2,3-c]chromene-2-carbonitrile (4e)
Pale yellow powder; yield: 91%; mp 294-295 °C (dec.); IR (KBr, ν/cm\(^{-1}\)) 3445, 3321, 2191, 1749, 1662, 1629, 1588. \(^1\)H NMR (300 MHz, DMSO-d\(_6\)) δ ppm: 7.69-7.67 (d, 1H, J = 8Hz, Ar), 7.53-7.47 (m, 1H, Ar), 7.44-7.37 (m, 2H, Ar), 7.34-7.18 (m, 6H, Ar, NH\(_2\)), 5.44 (s, 1H). \(^1^C\) NMR (75 MHz, DMSO-d\(_6\)) δ ppm: 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. calcld. For C\(_{20}\)H\(_{11}\)BrN\(_2\)O\(_5\): 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 establish molecular structures by quantum mechanical methods. All calculations were performed using DFT. All geometries were optimized with respect to internal coordinates, using the B3LYP method and 6-311++G (d,p) basis set. Theoretical and experimental investigations into the structural, electronic, and molecular properties of 1,5-dihydropyrano[2,3-c]chromene derivatives.

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-hydroxy coumarin (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 substituent, 4b-4e structures have a substituent on C\(_2\) or C\(_3\) and 4f-4i structures have a substitute on C\(_3\) which we name them R\(_2\)-DHPc, R\(_3\)-DHPc and R\(_4\)-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 R\(_2\)-DHPc structures are more stable than R\(_3\)-DHPc ones. Fig. 1 shows optimized structures. Also, according to the total energies, as expected, locating substitutes on R\(_4\)-DHPc towards R\(_2\)-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 derivatives. Meanwhile, the dipole moments of molecule systems increase in solvent media. In the following, we study R\(_2\)-DHPc structures and compare them with R\(_4\)-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 R\(_2\)-DHPc structures in comparison to R\(_4\)-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.

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 R₂ and R₄ positions except MeO, R₂-DHPC structures are covered by the negative charge and R₄-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.

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 (E₉) 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 E₉ 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, E₉, hardness, softness, chemical potential, electrophilicity and Fermi level energy (E_f). As seen from Table 2, difference E₈ between R₂ and R₄ 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 R₂ and R₄ positions and this difference is so slight in Me-DHPC and MeO-DHPC compounds. According to chemical hardness and softness values both positions (R₂ and R₄) are the same in Br-DHPC and Cl-DHPC compounds and in Me-DHPC and MeO-DHPC compounds, R₂ and R₄ 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
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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.

Also, gap energy of DHPC molecule is more than other compounds and therefore has more hardness and less softness towards them; so, R$_1$ and R$_4$ DHPC structures have higher chemical activity. Meanwhile, the results show the value of hardness and less softness for R$_2$ and R$_3$ DHPC structures are very similar. So, in human body there is no much difference between their activity values.

### 3.5. NMR analysis

$^1$H and $^{13}$C NMR of the investigated compounds were estimated experimentally in DMSO solvent and TMS as an internal standard. We calculated $^1$H and $^{13}$C NMR in similar media (DMSO) using GIAO method at the same level of optimization [25-30]. Table 3 displays experimental and theoretical results of $^1$H and $^{13}$C NMR data of R$_2$ and R$_4$(Cl)-DHPC compounds. NMR data of other compounds are presented in supplementary data section. The experimental results of R$_4$ position are in references [14-17]. Experimental and theoretical $^{13}$C 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 R$_4$ position is higher than R$_2$ 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, $^1$H NMR revealed the presence of 11 or 14 protons, that which 10 protons correspond to aromatic ring and NH$_2$ 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 5.03-5.29 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 | E(eV) | Dipole Moment | E(eV) | Dipole Moment |
|--------------|----------------------|-----------|-------|---------------|-------|---------------|
| Br-DHPC      | R$_1$                | -99056.513 | 3.025  | -99057.091    | 4.2382|               |
|              | R$_2$                | -99056.436 | 3.282  | -99056.989    | 4.4018|               |
|              | R$_3$                | -99056.343 | 3.9756 | —              | —     |               |
| Cl-DHPC      | R$_1$                | -41533.377 | 3.0273 | -41533.954    | 4.2467|               |
|              | R$_2$                | -41533.322 | 3.3100 | -41533.875    | 4.4175|               |
|              | R$_3$                | -41533.247 | 3.8694 | —              | —     |               |
| Me-DHPC      | R$_1$                | -30096.495 | 3.5111 | -30097.055    | 4.6424|               |
|              | R$_2$                | -30096.403 | 3.3557 | -30096.944    | 4.6722|               |
|              | R$_3$                | -30096.335 | 3.1940 | —              | —     |               |
| MeO-DHPC     | R$_1$                | -32143.591 | 4.1847 | -32144.205    | 5.6884|               |
|              | R$_2$                | -32143.602 | 4.4624 | -32144.190    | 6.0619|               |
|              | R$_3$                | -32143.573 | 3.5145 | —              | —     |               |
| DHPC         | R$_1$                | —         | -29026.320 | 3.2791 | -29026.882 | 4.4034|               |

### Table 2. Orbital energies (HOMO and LUMO), energy gap (E$_g$), difference between gap energies (DE$_g$), Fermi level energy (E$_f$), hardness (\(\eta\)), softness (\(S\)), chemical potential (\(\mu\)), and electrophilicity index (\(\omega\)) of the titled compounds in the DMSO solvent. Energies are in eV.

| Compound     | substitute position | HOMO | LUMO | E$_g$ | DE$_g$ | E$_f$ | \(\eta\) | \(S\) | \(\mu\) | \(\omega\) |
|--------------|---------------------|------|------|-------|--------|-------|---------|-------|--------|---------|
| Br-DHPC      | R$_1$               | -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  | 0.00   | -4.49 | 2.01    | 0.25  | -4.49  | 5.01    |
| Cl-DHPC      | R$_1$               | -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  | 0.00   | -4.50 | 2.03    | 0.25  | -4.50  | 5.00    |
| Me-DHPC      | R$_1$               | -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  | 0.00   | -4.42 | 2.00    | 0.25  | -4.42  | 4.89    |
| MeO-DHPC     | R$_1$               | -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  | 0.00   | -4.31 | 2.00    | 0.25  | -4.31  | 4.65    |
4. CONCLUSIONS

In conclusion, the 1,5-dihydropyran[3,2-c]chormene 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 R₃ 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 Eₛ 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.

5. REFERENCES

1. Brahmachari, G.; Nurjamal, K. Facile and chemically sustainable catalyst-free synthesis of diverse 2-aryl-4-alkyl/aryl-pyra[n][3,2-c]chromen-5(4H)-ones by one-pot multicomponent reactions at room temperature. ChemistrySelect. 2017, 2, 3695-3702. https://doi.org/10.1002/slct.201700687.

2. Raj, T.; Bhattacharjee, R.K.; Kapur, A.; Sharma, M.; Saxena, A.K.; Ishar, M.P.S. Cytotoxic activity of 3-(5-phenyl-3H-[1,2,4]thiazol-3-yl)chromen-4-ones and 4-oxo-4H-chromene-3-carboxthioic acid N-phenylamides. Eur. J. Med. Chem. 2010, 45, 790-794. https://doi.org/10.1016/j.ejmech.2009.11.001.

3. Kalitsakis, M.G.; Carotti, A.; Catto, M.; Peperidou, A.; Hadjipavlou-Litina, D.J.; Litinas, K.E. Synthesis and Biological Evaluation of novel hybrid molecules containing purine, coumarin and isoxazoline or isoxazole moieties. Open J. Med. Chem. 2017, 7, 196-211. https://doi.org/10.2174/1874104501711010196.

4. El-Sayed, T.H.; Aboelmaga, A.; El-Atawy, M.A.; Hagar, M. Ball milling promoted N-heterocycles synthesis. Molecules 2018, 23, 1348-1369. https://doi.org/10.3390/molecules23061348.

5. Zhang, K.; Chen, D.; Ma, K.; Wu, X.; Hao, H.; Jiang, S. NAD(P)H:Quinone Oxidoreductase 1 (NOQ1) as a Therapeutic and Diagnostic Target in Cancer. J. Med. Chem. 2018, 61, 6983–7003. https://doi.org/10.1021/acs.jmedchem.8b00124.

6. Ferguson, S.A.; Menorca, A.; Van Zuylen, E.M.; Cheung, C.Y.; McConnell, M.A.; Remniss, D.; Brimble, M.A.; Bodle, K.; McDougall, S.; Cook, G.M.; Heikal, A. Microtiter screening reveals oxygen-dependent antimicrobial activity of natural products against mastitis-causing bacteria. Front. Microbiol. 2019, 10, 1955. https://doi.org/10.3389/fmicb.2019.01995.

7. Ellis G.P. The Chemistry of Heterocyclic Compounds: Chromones, Chromanones and Chromones. John Wiley and Sons, New York and London. 1977. https://doi.org/10.1002/9780470187012.ch1.

8. Haiez, E.A.A.; Elagnidi, M.H.; Elagamey, A.G.A.; El-Taweel, F.M.A.A. Nitriles in heterocyclic synthesis: novel synthesis of benzo[c]coumarin and of benzo[c]pyran[3,2-c]quinoline derivatives. Heterocycles. 1987, 26, 903-907. https://doi.org/10.3987/R-1987-04-0903.
Theoretical and experimental investigations into the structural, electronic, and molecular properties of 1,5-dihydropyrazino[2,3- c]chromene derivatives

9. Yoosefian, M.; Mola, A.; Hajiabadi, H.; Amiri Delouei, R.; Mahdavi Shahri, S.M. Theoretical prediction of chloroform, ethanol, water and DMSO effects on electronic characteristics of Capecitabine different conformers as an antinecancer chemotherapy drug. J. Mol. Liq. 2018, 264, 115-118, https://doi.org/10.1016/j.molliq.2018.04.115.

10. Fathi Azarbayjani, A.; Aliasgharlou, N.; Khoshbakht, S.; Ghanbarpouri, P.; Rahimpour, E.; Barzegar-Jalali, M.; Jouyban, A. Experimental Solubility and Density Functional Theory Studies of Deferasirox in Binary Solvent Mixtures Performance of Polarizable Continuum Model andJouyban–Acree Model. J. Chem. Eng. Data. 2019, 64, 2273-2279, https://doi.org/10.1021/acs.jced.8b01001.

11. Kohanoff, J.J. Electronic structure calculations for solids and molecules: theory and computational methods. Cambridge University Press. 2006; https://doi.org/10.1017/CBO9780511755613.

12. Fukui, K. Role of frontier orbitals in chemical reactions. Science 1982, 218, 747-754, https://doi.org/10.1126/science.218.4574.747.

13. Koopmans, T. Über die Zuordnung von Wellenfunktionen und Eigenwerten zu den einzelnen Elektronen eines. Physica 1934, 1, 104-113, https://doi.org/10.1016/S0031-8914(34)90011-2.

14. Patra, A.; Mahapatra, T. Synthesis of Dihydromelanato[c]chromenes from Hydroxycoumarins Using Aliquat® 336 Catalyzed Condensation in Aqueous Medium. J. Indian Chem. Soc. 2012, 89, 925-933, https://doi.org/10.1002/chin.201313122.

15. Paul, S.; Bhattacharyya, P.; Das, A.R. One-pot synthesis of dihydropyrazino[2,3-c]chromenes via a three component coupling of aromatic aldehydes, malonitrile, and 3-hydroxycoumarin catalyzed by nano-structured ZnO in water: a green protocol. Tetrahedron Lett. 2011, 52, 4636-4641, https://doi.org/10.1016/j.tetlet.2011.06.101.

16. Das, P.; Dutta, A.; Bhaumik, A.; Mukhopadhyay, C. Heterogeneous ditopic ZnFeO4 catalyzed synthesis of 4H-pyran: further conversion to 1,4-DHPs and report of functional group interconversion from amide to ester. Green Chem. 2014, 16, 1426-1435, https://doi.org/10.1039/C3GC42095G.

17. Paul, S.; Ghosh, S.; Bhattacharyya, P.; Das, A.R. Synthesis of a SO3H-bearing carbonaceous solid catalyst, PEG–SAC: application for the easy access to a diversified library of pyran derivatives. RSC Adv. 2013, 3, 14254-14262, https://doi.org/10.1039/C3RA24352B.

18. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scallan, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; Nakatsuji, H. Gaussian 09, Revision B.01, Gaussian Inc.: Wallingford, CT. 6492, 2010.

19. Barone, V.; Cossi, M.; Tomasi, J. A new definition of cavities for the computation of solvation free energies by the polarizable continuum model. J. Chem. Phys. 1997, 107, 3210-3221, https://doi.org/10.1063/1.474671.

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