Synthesis and quantum chemical studies of methyl 2-(4-methyl-2-oxo-2h-chromen-7-yloxy) acetate derivatives

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Abstract, derivatives of coumarin were synthesised in worthy yields. Their purity and chemical structures have been described using TLC, IR and ¹H-NMR, ¹³C-NMR spectra. The Density Functional Theory DFT measurements of the coumarins synthesised were made using standardized molecular structure geometry. Molecular orbital calculations defined the orbitals in detail, including spatial properties, patterns, and contributions of the nodal to the individual atoms.

Keywords: 7-Hydroxy 4-methyl coumarin, Hydrazin hydrate, HOMO, LUMO.

1. Introduction
Coumarins are a major class of natural as well as synthetic compounds. Several compounds containing coumarin have good and various pharmaceutical and bio-activities; sometimes according to the parent benzopyrene substituents they carry [1,2] and their synthesis has gained increasing interest [3]. Some of these coumarin derivatives were found to be effective in photochemotherapy, antitumor [4], anti-HIV therapy [5, 6] as a CNS-stimulant [7], antibacterial [8–10], anticoagulant [11–13], antifungal [14, 15], antioxidant [16] agent and as a colorant [17]. The azomethine group (> C= N-) which contains compounds traditionally it's classified as the Schiff bases have been synthesized with active carbonyls by condensing primary amines. Schiff bases form an essential class of medicinal products and pharmaceuticals chemical compounds with various biological uses including antibacterial [18-23], antifungal [20-23] and antitumor activity [24, 25]. The ligand class was extensively studied as in [26-28] which are known to coordinate, via the azomethine nitrogen atom with metal ions. Therefore, those Schiff-based coumarins would have increased antitumor and other biological activity. Biological activity related to hydrazone compounds is well known to be due to Pharmacophore action (-CONH-N = C-). Thus, a lot of hydrazone compounds contain this active motherhood exhibit significant bioactivity of anticancer [29-30]. This study aimed at extending the applications of coumarins, several of substituted coumarin derivatives were synthesized and shown in the following scheme:
2. Experimental work

Spectra from Infrared (IR) were captured with KBr pellets at room temperature from 4000-400 cm\(^{-1}\), using DTGS detector-equipped Avatar 330. The 1H NMR was measured at room temperature on a Bruker AMX-400 instrument; the \(^1\)H NMR was measured in DMSO-d6 makes use of TMS as an internal guide. For open capillaries melting points have been determined and are uncorrected. Aldrich ordered both of the reagents.

2.1 General procedure with Spectral data, preparation of:

A. Methyl 2-Acetate (2) [(4-methyl-2-oxo-2H-chromen-7-yl) oxy] methyl bromoacetate (1.528 g, 9.15 mmol) and (4.69 g, 33.91 mmol) potassium carbonate K\(_2\)CO\(_3\) were reflux for 12 hours with (1.086 g, 6.17 mmol) 7-hydroxy-4-methylcoumarin in acetone (30 ml). The mixture was evaporated after cooling, to remove the moisture. The residue was then split into chloroform (50 ml) and H\(_2\)O (50 ml); the crud was purified by crystallization from ethanol [31]. Yield 80 % [lit. 40 %][32], m.p. 93-95 ºC [lit. 88-90 ºC] [33]; IR (KBr, cm\(^{-1}\)): 3001, 2917, 1742, 1700, 1613, 1390, 1195, 1473, 1075; \(^1\)H NMR(400 MHz, DMSO, ppm), \(\delta\) = 7.71 (2H, d - d, 5,6-H), 6.97 (H, s, 8-H), 6.23 (1H, s, 3-H), 4.93 (2H, s, OCH\(_2\)), 3.68 (3H, s, CH\(_3\)), 2.41 (3H, s, CH\(_3\)).

B. 2-((4-Methyl-2-oxo-2H-chromen-7-yl) oxy) acetohydrazide (3) hydrazine hydrate (7.5 g, 15 mmol) refluxed with (2.48 g, 10 mmol) compound (2) in 25 ml C\(_2\)H\(_5\)OH for 4 hr. The residue was then desiccated and dried to provide a crystalline powder. Chloroform / methanol recrystallized the material, and gave colorless needles. Product yield was 88 to 90 per cent. [34], of m.p. 198-200 ºC,[35]; IR (KBr, \(\pi_{\text{max}}, \text{cm}\(^{-1}\)): 3330, 3265, 3082, 2955, 1685, 1670, 1508, 1439, 1153, 1074; \(^1\)H NMR (400 MHz, DMSO, ppm), \(\delta\) = 8.5 (1H, s, NH), 7.73 (1H, dd, 5,6-H), 6.91 (1H, s, 8-H), 6.23 (1H, s, 3-H), 6.21 (1H, s, 3-H),4.51(2H,s,NH\(_2\)),4.45(2H,s,NH\(_2\)),4.45(2H,s,CH\(_3\)).

B. (E)-2-((4-Methyl-2-oxo-2H-chromen-6-yloxy)N'-(4-(E)-(2-(4-(methyl-2-oxo-2H-chromen-7-yloxy)acetyl)hydrazono)methyl)benzylidene)acetohydrazide (4), A mixture of the chloroform methanol compound (4)(0.01 mol) (1:1 v / v) mixture (30 mL), terephthalaldehyde (0.005 mol) and 1 mL of glacial acetic acid was reflux one per 3 hour water bath. The mixture was cool and the isolated

\[ \text{Reagents and Conditions: } a= \text{Hydrazine hydrate; } b= \text{Terephthalaldehyde.} \]

Scheme 1. Synthesized compounds \' reaction sequences
solid was drained, washed with waste CH₃OH [36]. Chemical yield for compound (4) was 45%, m.p. 251–253 the solid is separated, washed with excess methanol °C

Spectral data of compound (4) IR (KBr, vmax, cm⁻¹): 3170,3079, 2908, 1717, 1670, 1512, 1423, 1145, 1086; ¹H- NMR (400 MHz, DMSO, ppm), δ = 8.0 (1H, s, NH), 8.05-8.12 (2H, d-d, aromatic), 8.50 (1H, s, CH=N), 6.93-7.71 (2H, d-d, 5,6H), 6.95 (1H, S,8-H), 6.21 (1H, s, 3-H), 4.51 (2H, s, OCH₂), 2.41(3H, s, CH₃).

2.2. DFE (what does DFE stand for in your study?)

With Visualization Materials Studio 5.5 molecular drawings of compounds synthesized were plotted. All calculations of the quantum chemical were carried out using Density Functional Theory (DFT), as implemented in the Materials Studio 5.5 program. DMol3 model was used to obtain and optimize quantum chemical parameters molecular structure. These equations employed an ab initio; General gradient approximation (GGA) based on functional Lee-Yang-Parr correlation (BLYP) and dual number d-functions (DND). Known for producing suitable geometries for a wide variety of structures, this technique. The following quantum chemical indices have been Calculated: energy from the highest molecular orbital occupation. (HOMO), the energy of the lowest unoccupied orbital molecules (LUMO), and the dipole moment.

3. Computational Studies

3.1. Atomic stabilities and charges

The experimental tests for compound 3 showed that the nuclear charges were affected by the presence of a substitute ring. (Additional file) and the 3d-geometric this molecule is not planar in structure suggested. From Figure 1 it can be shown the maximum atomic charge is at [O (16) −0.916] the value [O (3) −0.636] is the next charge, these findings clearly show these two atoms are the most reactive installations to the reactions and bond with the metals. This molecule is not planarly indicated by the bond and twist angles calculated (additional file) and the 3d-geometric structure.

![Figure 1. 3D-Geometric compound form (3).](image-url)
Figure 2 is shown the compound minimum geometry (4). The figure also expresses the atomic charges calculated for the material. The findings showed $[O(3) - 0.517]$ is the highest atomic charge, and the value $[O(17) - 0.455]$ is the next load. These results demonstrated that those two atoms are the most reactive reaction sites and metal-binding sites. The angles of the determining bond, twist angles, and 3d-geometric structure suggest that this molecule is not planar, and stereochemistry C(2)-C(3) is (Z).

![Figure 2. 3D-Geometric compound form (4).](image)

### 3.2. Density Functional Theory (DFT)

Compounds 3 and 4 were measured using DFT. Figure 3 displays streamlined molecular frameworks of the stables forms. Their measured Table 1 shows the energies and their relative energies. Molecular orbital calculations give a complete info overview of orbitals, including spatial characteristics, nodal patterns and individual atomic contributions. Figure 4 displays border orbital contour plots for ground-state 3 and 4, these include (HOMO) and (LUMO). It is important to note that there is a significant distribution of both orbitals over the conjugation plane. Figure 4 shows that the orbitals of HOMO are on the substituted molecule, whereas the orbitals of LUMO are similar to those of the replaced molecule and therefore replacement has an impact on the ability to donate electrons, but only a small impact on the ability to accept electrons [39]. Compounds 3 and 4 were measured using DFT. Figures 3 and 4 demonstrate streamlined molecular structures of the stables forms. Their measured Table 1 shows the energies and their relative energies include a thorough explanation of orbitals including spatial properties, nodal patterns and the contributions of individual atoms. Figures 3 and 4 display the contour plots of the ground state frontier orbitals 3 and 4, (HOMO) and (LUMO), among others. It is important to note that both orbitals are considerably spread over the conjugation plane. Figures 1 and 2 show (HOMO) orbitals are centered on the molecule replaced while the (LUMO) orbitals are similar to those obtained for the replaced molecule and Substitution hence it influences the ability to donate an electron, but just slightly impacting the ability to accept an electron. HOMO and LUMO orbital energy levels of compounds 3 and 4 are listed in Table 1. The energy differences between HOMO and LUMO can be shown to be about 4.4564 and 3.8249 eV. For the 3 and 4 compounds, accordingly. The smallest interest in the energy difference between HOMO and LUMO describes the subsequent interaction of the movement of charges within the molecules.
Table 1. Total Energy (a.u), HOMO, LUMO energies of 3 and 4 (eV)

| Total energy | HOMO     | LUMO     | ΔE     |
|--------------|----------|----------|--------|
| -874.619582  | -6.4363  | -1.9799  | 4.4564 |
| -2055.21731  | -6.0654  | -2.2405  | 3.8249 |
| HOMO-1       | LUMO+1   | ΔE       |
| -7.0132      | -0.6329  | 6.3803   |
| -6.4926      | -2.2033  | 4.2893   |

Figure 3. HOMO and LUMO orbitals of Compound 3 by DFT
4. Conclusions

The compounds 1–4 were synthesized in this study and distinguished by various methods of spectroscopy and an analysis basic. The compounds synthesized were analyzed theoretically, estimating the atomic charges, heat output and stereochemistry compounds 3, 4 were found not to be planar.

Reference

[1] Musa MA, Badisa VL, Latinwo LM, Cooperwood J, Sinclair A, Abdullah A. 2011, Cytotoxic activity of new acetoxycoumarin derivatives in cancer cell lines. Anticancer Res., 31, 2017–2022.

[2] Pallabi Borah, P. Seetham Naidu, Pulak J. Bhuyan 2012 , Synthesis of some tetrazole fused pyrido(2,3-c] coumarin derivatives from a one-pot three-component reaction via intra molecular 1,3-dipolar cyclo addition reaction of azide to nitriles. Tetrah`edron Lett.  53, 5034–5037.

[3] El-Ansary, S.L.; Abbas, S.E.; Mikhail, A.N.; El-Banna, H.A.1992, Synthesis and biological activity of some new coumarins. Egypt. J. Pharm. Sci. 33, 639–650.

[4] Stefano M, Daniele S, Roberto F, Rita Bi, Sigrid H, , Erik D 1997, retinoic acid conjugates as potential antitumor agents: synthesis and biological activity of conjugates with Ara-A, Ara-C, 3(2H)-furanone, and aniline mustard moieties. J. Med. Chem.  40, 3851–3857.
[5] Wattenberg, L.W., Lam, K.T., Fladmoe, A.V., 1979, Inhibition of chemical carcinogen-induced neoplasia by coumarins and a-angelica lactone. Cancer Res. 39, 1651–1654.

[6] Kashman, K R Gustafson, 1992, The cardenolides, a novel HIV-inhibitory class of coumarin derivatives from the tropical rainforest tree, Calophyllum lanigerum. J. Med. Chem. 35, 2735–2743.

[7] Mckee T C, Fuller R W, Covington C D, J.H Cardellina J H 1996, New pyranocoumarins isolated from Calophyllum lanigerum and Calophyllum teysmannii. J. Nat. Prod. 59, 754–758.

[8] Anjum N F, Aleem A, Nayeem N, Asdaq S M 2011, Synthesis and antibacterial activity of substituted 2-phenyl-4-chromones. Der Pharma Chem. 3.

[9] Simone M de Souza, Franco D M, Artur S Jr 2005, Jr. Antibacterial activity of coumarins. Z. Naturforsch. C, 60, 693–700.

[10] Aziz Behrami 2014, Antibacterial activity of coumarine derivatives synthesized from 4-chloro-chromen-2-one. The comparison with standard drug. Orient. J. Chem.30, 1747–1752.

[11] Walter M. Barker, Mark A. Hermodson, K. P. Link 1971, 4-Hydroxycoumarins. Synthesis of the metabolites and some other derivatives of warfarin. J. Med. Chem. 14, 167–169.

[12] Mike G 2005, Pharmacogenetics in the management of coumarin anticoagulant therapy: The way forward or an expensive diversion, PLoS Med.,2, e342.

[13] Cristina M, Simone M. de Souzaa, Cla’udia G , Franco Delle M , Elza F. A. Sma’niaa , Artur Sma’nia Jr. 2008, Jr. Antifungal activity of coumarins. Z. Naturforsch. C 63, 21–28.

[14] Rodrigo S A de Araújo, Felipe Q S Guerra, Edeltrudes de O Lima, Carlos A de Simone, Josean F Tavares, Luciana Scotti, Marcus T Scotti, Thiago M de Aquino, Ricardo O de Moura, Francisco J B Mendonça, José M Barbosa-Filho 2013, Synthesis, structure-activity relationships (SAR) and in silico studies of coumarin derivatives with antifungal activity. Int. J. Mol. Sci. 14, 1293–1309.

[15] Gloria M, Naim M, Annia G, Nino R , Marirosa T 2015, Antioxidant properties of several coumarin–chalcone hybrids from theoretical insights. RSC Adv. 5, 565–575.

[16] Raboin, J, Beley, M,Kirsch, G 2000, G. Pyridine-fused coumarins: A new class of ligands for ruthenium complexes with enhanced spectral absorption. Tetrahedron Lett. 4, 1175–1177.

[17] Azza A.Abou-Hussein, WolfgangLinert 2006 Synthesis, spectroscopic, coordination and biological activities of some organometallic complexes derived from thio-Schiff base ligands , J. Coord. Chem., 59, 157.

[18] Mari S K, Dasappa J P, Boja P, Subrahmanyana B, Bantwal Sh H, Nalilu S K 2006, Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety B. Poojary and K.S. Bhat, Bioorg. Med. Chem., 14, 7482.
[20] Kiran S, Manjeet S B, Parikshit T 2006, Synthesis, characterization and biological studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes with bidentate Schiff bases derived by heterocyclic ketone Eur. J. Med. Chem., 41, 1.

[21] Perumal P, Rajasree RN, Gudaparthi V, Ekambararam H S, Seshaiyah K S 2005, Synthesis of Schiff bases of 4-(4-aminophenyl)-morpholine as potential antimicrobial agents Eur. J. Med. Chem., 40, 225.

[22] S K Sridhar, M Saravanan, A Ramesh2001, Synthesis and antibacterial screening of hydrazones, Schiff and Mannich bases of isatin derivatives Eur. J. Med. Chem., 36, 615.

[23] S N Pandeya, D Sriram, G Nath, E DeClercq 1999, E Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and N-[4-(4'-chlorophenyl)thiazol-2-yl] thiosemicarbazide ur. J. Pharmacol., 9, 25.

[24] V. S. V. Satyanarayana; P. Sreevani; Amaravadi Sivakumar; V. Vijayakumar2002, Synthesis and antimicrobial activity of new Schiff bases containing coumarin moiety and their spectral characterization Eur. Polym. J., 38, 989.

[25] OM Walsh, MJ Meegan, RM Prendergast, T Al Nakib1996, Synthesis of 3-acetoxyazetidin-2-ones and 3-hydroxyazetidin-2-ones with antifungal and antibacterial activity Eur. J. Med. Chem., 31, 989.

[26] Erdal C, Mehmet K 2005, Studies on Mononuclear Chelates Derived from Substituted Schiff Base Ligands (Part 4): Synthesis and Characterization of a New 5-Hydroxysalicyliden-P-Aminoacetophenoneoxime and Its Complexes with Co(II), Ni(II), Cu(II) and Zn(II), Turk J Chem 29, 409–415

[27] A. D. Garnovskii, I. S. Vasil’chenko, D. A. Garnovskii, A. S. Burlov, A. I. Uraev 2010, Binuclear and polynuclear complexes of Schiff bases Russian Journal of General Chemistry volume 79, pages2776–2786.

[28] Katsuki T 1995, Catalytic asymmetric oxidations using optically active (salen) manganese (III) complexes as catalysts Coord. Chem. Rev., 140, 189.

[29] Jin L, Chen J, Song B, Chen Z, Yang S 2006, Synthesis, structure, and bioactivity of N'-substituted benzylidene-3,4,5-trimethoxybenzohydrazide and 3-acetyl-2-substituted phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives Med. Chem. Lett., 16, 5036.

[30] Hiba H. Ibraheem 2019, New derivative of 1,2-Dihydropyridine-3-Carbonitrile as Corrosion Inhibitor; Mater. Sci. Eng. 579 012052.

[31] Kotla V V, V.R. Chunduri 2013, Synthesis and Antimicrobial Activity of Novel 1, 2, 4-Triazole Derivatives. Der Pharmacia Sinica 4(3): 103.

[32] Khanum S A, Shashikanth S and Deepak A V 2004, Synthesis and anti-inflammatory activity of benzophenone analogues. Bioorg. Chem., 32, 211.

[33] Kotla VV, Chunduri 2014, Synthesis and Antimicrobial Activity of Novel 1, 2, 4-Triazole Derivatives. Der Pharmacia Sinica 4(3): 103.
[34] S.A. Khanum, S. Shashikanth and A.V. Deepak, Bioorg 2004, Synthesis and anti-inflammatory activity of benzophenone analogues Chem., 32, 211.

[35] Vsatyanarayana, Madhumita Rakshit and A. Sivakumar 2011: Microwave-Assisted Synthesis of 2,4,5-Triphenyl-1H-imidazole Containing Schiff Base Derivatives with Potential Antioxidant and Anticancer Activities; Asian Journal of Chemistry; Vol. 23, No. 3 1212-1218.

[36] Zou X J , Lai LH, Jin GY, Zhang ZX 2002, Synthesis, fungicidal activity, and 3D-QSAR of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles, J Agric Food Chem. Jun 19;50(13):3757-60.

[37] Bushra B A, Mohammed Al-Ghorbani, Suresh ShVivek K. Guptaband Sh, Ara K 2003, 2-Benzoyl-4-chlorophenyl benzoate; Indian J. Chem., 42B, 900.

[38] Yasameen K Al-Majedy, Hiba H I, Marwa S F , Ahmed Al-Amiery 2019, New coumain derivatives as corrosion inhibitor; Materials Science and Engineering 579,012051.

[39] Musa A Y, Kadhum AAH, Mohamad AB, Rahoma, A.A.B, Mesmari, H 2010, Electrochemical and quantum chemical calculations on 4,4-dimethylloxazolidine-2-thione as inhibitor for mild steel corrosion in hydrochloric acid. J. Mol. Struct. 969, 233-237.

[40] Ahmed Al-Amiery, Yasameen K Al-Majedy, Amer A K, Abo B M 2015, New coumarin derivative as an eco-friendly inhibitor of corrosion of mild steel in acid medium. Molecules.;20(1), 366-83.

[41] Yasameen K Al-Majedy., Amer A K, Ahmed Al-Amiery, Abo B M 2014 , Synthesis and characterization of some new 4-hydroxycoumarin derivatives. Molecules.,19(8):11791-9.

[42] Ahmed Al-Amiery, Amer A K, Yasameen K AL-Majedy, Hiba H I , Al-Temimi AA, Al-BayatiRI 2013, The legend of 4-aminocoumarin: Use of the Delépine reaction for synthesis of 4-iminocoumarin. Res Chem Intermed. ,39(3):1385-91.

[43] Ahmed Al-Amiery, Yasameen K AL-Majedy, Al-Duhaidahawi D , Amer A K, , Mohamad AB 2016, Green Antioxidants: Synthesis and Scavenging Activity of Coumarin-Thiadiazoles as Potential Antioxidants Complemented by Molecular Modeling Studies. Free Radicals and Antioxidants. 6(2):173-7.