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# SYNTHESIS, ANTIOXIDANT AND DFT STUDY OF SOME 4-METHYL-2H- CHROMEN-2-ONE DERIVATIVES

Souad BOUASLA,[a,b,*] Chafia SOBHI,[b,c] Hamza ALLAL,[d,e] Wahiba MECIBAH,[d] Mouna CHERIFI[f] and Issam BOUGDAH[c]

[a]Department of chemistry & physics, Normal High School of Technology Education (ENSET) SKIKDA, Brother Bousseta. City 21300. Azzaba, Algeria
[b]Laboratory of Materials and Energy Engineering, Faculty of Technology, University August 20,1955 Skikda, BP 26, 21000, Skikda, Algeria
[c]Department of Petrochemistry and Process Engineering, Faculty of Technology, University August 20, 1955 Skikda, BP 26, route El-Hadaiek, 21000, Skikda, Algeria
[d]Department of Technology, Faculty of Technology, University August 20, 1955, Skikda, 21000, Algeria
[e]Environmental, Molecular and Structural Chemistry Research Unit, University of Constantine-1, 25000, Constantine, Algeria
[f]Laboratory of Water Treatment and Valorization of Industrial Wastes, Department of Chemistry, Badji-Mokhtar University, Annaba, Algeria

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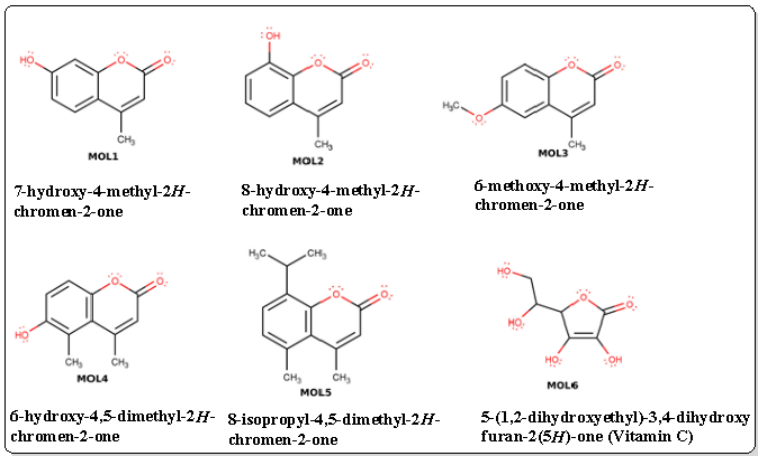
A series of 4-methyl-2H-chromen-2-ones (Mol 1-Mol 5) were synthesized via Von Pechmann condensation and characterized using spectroscopic techniques. Their antioxidant activity was investigated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay. The latter study showed that all the examined compounds (Mol 1-Mol 5), have a moderate to significant antioxidant capacity (IP % > 50%) compared to the reference vitamin C (Mol 6). In order to correlate molecular structure-antioxidant activity, DFT based molecular descriptors, such as $E_{HOMO}$, $\Delta E_{gap}$, Ionization potential (IP), Electron affinity (EA), Hardness (η), Softness (S), and Electronegativity (μ), global electrophilicity (ω) were computed for Mol 3, Mol 5 and the reference Vitamin C (Mol 6).




## INTRODUCTION

Oxidative stress is produced by a surplus formation of free radicals like, reactive oxygen species (ROS), reactive nitrogenous species (RNS) and reactive sulfur species (RSS), that are generated as by-products from enzymatic and non-enzymatic biological processes.[1] They are highly reactive species, with an unpaired electron, that can interact with a variety of molecules to achieve their stability.[2] Consequently, they cause harm to biomolecules like nucleic acids, amino acids, proteins, lipids and carbohydrates.[3] Their oxidative effect on cellular components, causes damage and

* Corresponding author: souad2004_chem@yahoo.fr or bouasla.souad@enset-skikda.dz

are implicated into the pathogenesis of many diseases such as hypertension,[4] thrombosis,[5] cancer,[6] cardiovascular,[7] atherosclerosis,[8] Alzheimer's and aging.[9] As a result, elimination of free radicals and similar species has become an essential research topic in recent years. Antioxidants, are compounds that provide biomolecules protection.[10]

Coumarins are a well-known family of oxygen heterocycles with a 1,2-benzopyrone ring. They are naturally occurring secondary metabolites, isolated for the first time from the Tonka beans by Vogel in 1882,[11] they can be found also in many other species including lavender, sweet woodruff, strawberry, cherry, cinnamon and vanilla grass.[12]

Chromene is one of the privileged pharmacophores, it is the basic structure of various types of natural polyphenols such as alkaloids, tocopherols, flavonoids and anthocyanins, which are endowed with a large spectrum of biological activities such as: platelet aggregation inhibition,[13] antibacterial,[14] anticancer,[15] antioxidant and many more.[16,17]

There is a close relationship between antioxidant activity and structural properties. Global reactivity descriptors have been extensively used to study molecules reactivity and reactions, and have been effectively carried out using DFT method. DFT calculations has been performed for the investigation of the antioxidant activity of a variety of compounds such as flavonoids and dihydrochalcones.[18,19] However, only limited works were dedicated to 4-methyl-coumarin derivatives.

The present study aims to prepare five 4-methyl-coumarins, labelled **Mol1-Mol5** (Fig. 1), according to Pechmann protocol, and examine their antioxidant capacity by DPPH radical scavenging test and to understand the structure-antioxidant activity relationship through quantum chemical calculations using the DFT method.

## EXPERIMENTAL

### Chemicals

Ethyl acetoacetate (≥99%), resorcinol (≥99%), catechol (≥99%), methyl hydroquinone (≥99.8%), thymol (≥99%), 4-methoxy phenol (≥99%) DPPH (≥99%) and Amberlyst-15 were purchased from Sigma-Aldrich chemical supplier. Absolute methanol was provided by ACROS.

### General Protocol for The Synthesis of 4-Methylcoumarin Derivatives[20]

In a 100 mL flask, introduce 1 equivalent of a phenol derivative with 1 equivalent of ethyl acetoacetate and 0.25 g of the Amberlyst A15, leave the mixture stirring at 110 ° C until the complete consumption of ethyl acetoacetate as indicated by TLC. Add 10 ml of ethanol and keep stirring for 10 min, then filter the catalyst and evaporate the solvent in the rotary evaporator. The crude solid was crystallized from ethanol-water to give a pure products **Mol 1-Mol 5**. All reactions were followed by thin layer chromatography carried out on Merck silica gel 60 F254 sheets with a fluorescent indicator, they were visualized under UV light (254 nm-365 nm). Melting points were recorded on Stuart Electrothermal Capillary melting point apparatus «Stuart SMP 30 » and are uncorrected. $^{1}$H and $^{13}$C NMR were recorded on a Bruker-DPX 300 MHz spectrometer and are reported in ppm (δ), using DMSO-$d_6$ as a solvent and TMS as an internal standard. IR spectra were recorded on a Shimadzu FTIR-8201 as KBr pellets for all compounds and wave numbers are expressed in $cm^{-1}$. CG-MS analysis were recorded on GC-varian (CP 3800) coupled to a Varian 3900 mass spectrometer.

UV-Visible measurements were recorded in methanol on a "T90 + UV / VIS" Spectrophotometer equipped with UVWIN 5.05 software, in quartz cells containing 4 ml of solutions.

**7-Hydroxy-4-methyl-2H-chromen-2-one (Mol 1):**[21] white solid (90%, 20 min), $\mathbf{M_P}$ = 185°C. **IR** (pastille KBr, υ $cm^{-1}$), 1700.00; 1675.00; 2215.14. **$^{1}$H NMR:** δ = 2.33 (s, 3H, $CH_3$), 6.09(s, 1H, CH=C), 6.67 (s, $1H_{Arom}$), 6.77 (d, $1H_{Arom}$), 7.55 (d, $1H_{Arom}$), 10.51 (1H, OH). **$^{13}$C NMR:** δ =161.58, 160.72, 155.26, 153.96, 127.03, 113.28, 112.44,110.68, 102.60, 18.54. **GC/MS**: t = 11,104 min and m/z = 177/ 149/ 65 /50.

**8-Hydroxy-4-methyl-2H-chromen-2-one (Mol 2):** white needles (48%, 113 min), $\mathbf{M_P}$ = 98°C. **IR** (pastille KBr, υ $cm^{-1}$): 3437.5; 3051.18; 2981.7; 1762.00; 1280.65; 1508.23-1625.00. **$^{1}$H NMR**: δ= 2.34 (s, 3H, $CH_3$), 6.20 (s, 1H, CH=C), 6.60-7.82(m, $3H_{Arom}$), 10.45 (1H, OH). **$^{13}$C NMR**: δ = 162.28, 159.15, 155.50, 152.53, 127.40, 113.80, 112.44,112.26, 102.58, 20.16. **GC/MS**: t = 11.082 min and m/z = 177/149/105/65/50.

**6-Methoxy-4-méthyl-2H-chromen-2-one (Mol 3):** white crystals (40%, 120 min), $\mathbf{M_P}$ = 162-164°C. **IR** (KBr, υ $cm^{-1}$): 2935, 1683, 1626, 1485, 1238, 1187, 804. **$^{1}$H NMR:** δ 2.41 (s, 3H, $CH_3$), 3.89 (s,3H, O-$CH_3$), 6.36 (s, 1H, CH=C), 7.15 (d, $1H_{Arom}$), 7.26 (s, $1H_{Arom}$), 7.35 ($1H_{Arom}$, d). **$^{13}$C NMR:** δ = 18.4, 56.1, 108.3, 115.3, 117.4, 119.7, 120.2, 146.9, 153.2, 155.4, 160.1. **GC/MS:** t = 12.016 min and m/z = 190/ 162/147/119/91/65/50.

**6-Hydroxy-4, 5-dimethyl-2H-chromen-2-one (Mol 4):** beige solid (80%, 37 min), $\mathbf{M_P}$ = 195-197°C, **IR** (KBr, υ $cm^{-1}$): 3421.48; 3066.61; 2920.03; 1687.50; 1280.55; 1558.39-1627.81. **$^{1}$H NMR:** δ = 2.38 (s, 3H, $CH_3$),2.47 (s, 3H, $CH_3$), 6.12 (s, 1H, CH=C), 6.88 (d, $1H_{Arom}$), 6.93 (d, $1H_{Arom}$),10.20 (1H, OH). **$^{13}$C NMR**: δ = 162.15, 159.80, 155.30, 154.61, 128.10, 112.90, 112.10,111.26, 104.40, 20.12, 18.90. **C/MS**: t = 11.073 min and m/z = 191/177/149/105/65/50.

**8-Isopropyl-4,5-dimethyl-2H-chromen-2-one (Mol 5):** brown solid (75%, 10 min), $\mathbf{M_P}$ = 107°C, **IR** (KBr, υ $cm^{-1}$): 3043.46; 2923.88; 1687.50; 1265.22; 1577.66-1620.09. **$^{1}$H NMR**: δ = 3.49 (m, 1H, CH), 1.34 (d, 6H, 2 * $CH_3$) 2.49 (S, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 6.10 (s, $1H_{Arom}$), 7.06 (dd, $1H_{Arom}$), 7.36 (dd, $1H_{Arom}$). **$^{13}$C NMR:** δ = 162.5, 152.69, 152.34, 134.34, 132.48, 126.25, 123.53, 116.2, 26.93, 22.94, 20.03. **GC/MS:** t = 11.094 min and m/z = 215/ 177/149/121/105/93/77/65/50.

### DPPH Radical Scavenging Assay

DPPH free radical trapping test is extensively used to investigate the antioxidant capacity. It relies on the measurement of the reduction of this radical induced by Substances capable of donating electrons/hydrogen atoms. This reduction is accompanied by its discoloration transition from the purple color ($DPPH^{\bullet}$) to the yellow color (DPPH-H). The intensity of the color is inversely proportional to the antioxidant activity.

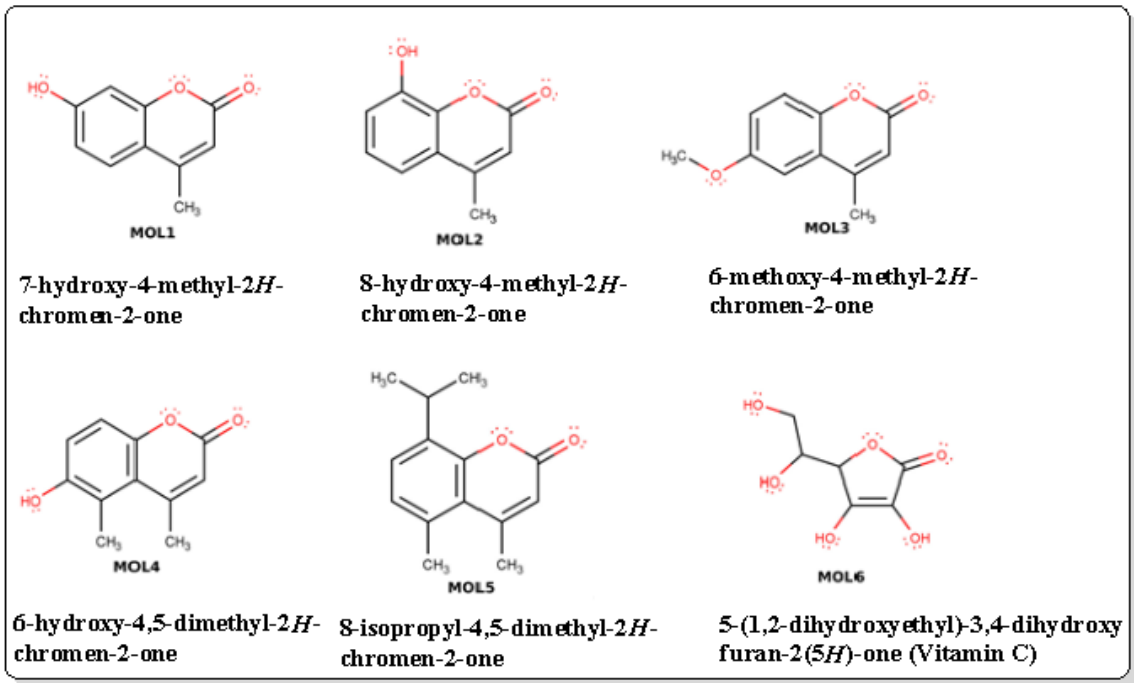



Fig. 1 – 2D Coumarins molecular structures.

The DPPH scavenging activity of all synthesized compounds (**Mol1-Mol5**) was measured as previously reported by Shen *et al.*, 2010.[22] Briefly, a 1mL of 0.1mM DPPH methanolic solution was added to 3ml of the solution of all compounds in methanol at different concentrations 4-0.25mg/mL. The mixtures were shaken vigorously and allowed to stand in the dark at room temperature for 30 minutes. Then the absorbance decrease was measured at 517 nm using a UV-VIS spectrophotometer. Lower absorbance values of the tested products solutions, caused by the pairing of the free electrons, indicate higher free radical scavenging activity (IP%). Ascorbic acid was used as a positive control. The capability to scavenging the DPPH radical was calculated using the equation bellow.

$$IP\% = \frac{A_{Control} - A_{Tested\ molecule}}{A_{Control}} \quad (1)$$

$A_{Tested\ molecule}$: absorbance of the tested molecules or Vitamin C.
$A_{Control}$: absorbance of the DPPH solution without the product.

The results obtained are expressed as 50% inhibition concentration ($IC_{50}$). The sample concentration, which provides 50% antioxidant activity. $IC_{50}$, values were calculated from the Excel plotted graphs of IP % activity versus sample concentrations.

### Density Functional Theory (DFT) Calculations

In order to investigate the experimental-theoretical consistency, quantum chemical calculations were performed utilizing ORCA program (version 4.1.2).[23] The geometries of the molecules were fully optimized with DFT/CAM-B3LYP[24] and combined with def2-TZVPP[25] basis set. Quantum chemical parameters such as highest occupied molecular orbital energy ($E_{HOMO}$), lowest unoccupied molecular orbital energy ($E_{LUMO}$), energy gap (ΔE) and dipole moment (μ), electronegativity (χ), hardness (η), softness (S), global electrophilicity index (ω), electron affinity (EA), potential ionisation (IP), electron acceptor power ($\omega^+$), and electron donor power ($\omega^-$) have been calculated as in Eqs (2)-(10).[26-29] Theses parameters were calculated for the most active antioxidant compound **Mol 3** and the least one **Mol 5** and the positive standard Vit C (**Mol 6**).

$$I = -E_{HOMO} \quad (2)$$

$$A = -E_{LUMO} \quad (3)$$

$$\Delta E_{gap} = E_{LUMO} - E_{HOMO} \quad (4)$$

$$\chi = \frac{I + A}{2} \quad (5)$$

$$\eta = \frac{I - A}{2} \quad (6)$$

$$S = \frac{1}{\eta} = \frac{2}{I - A} \quad (7)$$

$$\omega = -\frac{\mu^2}{2\eta} \quad (8)$$

$$\omega^- = -\frac{(3I + A)^2}{16(I - A)} \quad (9)$$

$$\omega^+ = -\frac{(I + 3A)^2}{16(I - A)} \quad (10)$$

## RESULTS AND DISCUSSION

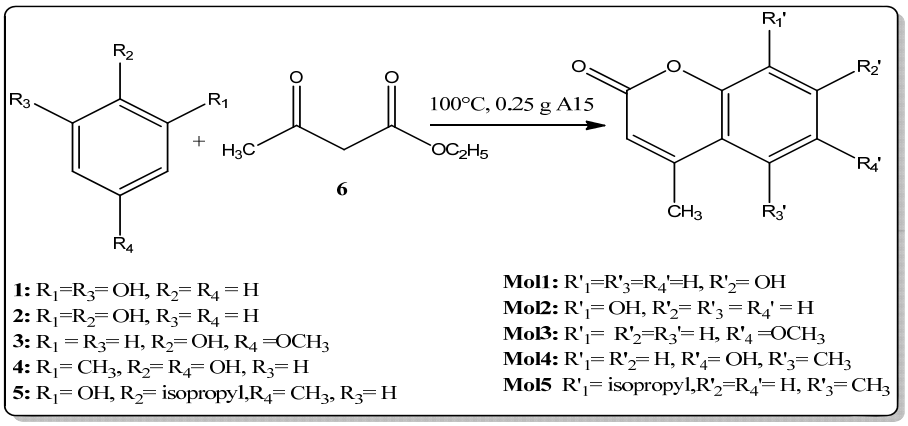
### 4-Methyl-2H-Chromen-2-Ones derivatives Synthesis (Mol 1-Mol 5)

The solvent-free condensation of phenol derivatives **1-5** with ethyl acetoacetate **6** catalyzed by amberlyst A15 at 100 ° C is outlined in **Scheme 1** has given the expected coumarins **Mol 1-Mol 5**.

The reaction time and yield depend on the substituent on the phenol starting substrate. *m*-Hydroxy phenol substrate gave the highest yield in a relatively short time (20 min), followed by methyl hydroquinone and thymol which also gave quantitative yields of 80% and 75% respectively. 4-Methoxy phenol and 2-hydroxy phenol are the least reactive substrates, they gave low yields 40% and 48% respectively, associated with the longest reaction times 120 min and 113 min respectively.

### DPPH Test

The obtained results for the antioxidant activity study of the synthesized compounds **Mol 1-Mol 5**, along with the reference Vit C (**Mol 6**), are depicted in Fig. 2 and Table 1.




Scheme 1 – Pechmannn condensation of phenol derivatives (**1-5**) with ethyl acetoacetate (**6**) to produce 4-methyl-2H-chromen-2-ones **(Mol 1-Mol 5)**.

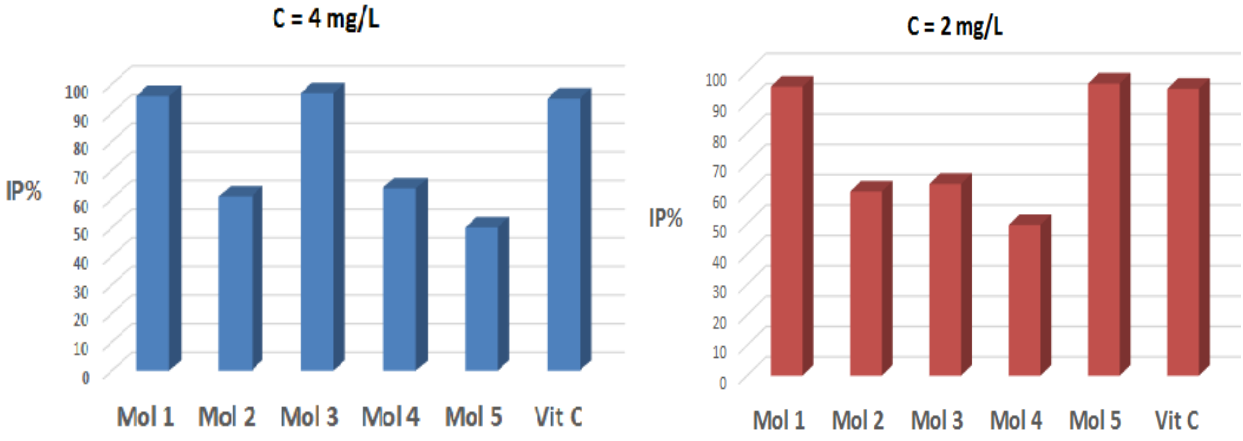



Fig. 2 – DPPH Inhibition % of the tested compounds Mol 1-Mol 5 against the reference Vit C (**Mol 6**).

*Table 1*

The $IC_{50}$ antioxidant activity results of compounds Mol 1-Mol 5 and the ascorbic acid (**Mol 6**) reference.

| Compound | Mol 1 | Mol 2 | Mol 3 | Mol 4 | Mol 5 | Mol6 (VitC) |
|---|---|---|---|---|---|---|
| **$IC_{50}$ (mg/mL)** | 191.57 | 74.63 | 37.48 | 51.18 | 165.02 | 285.71 |

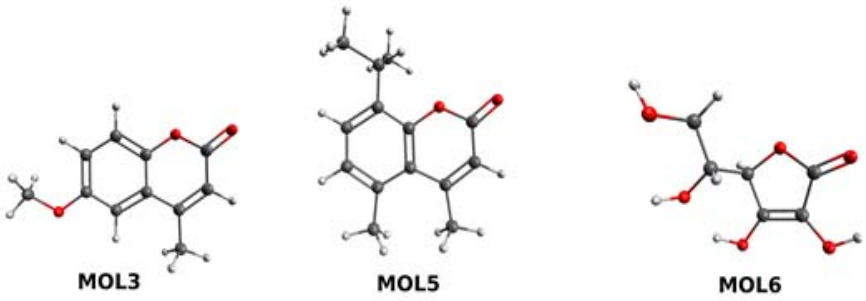



Fig. 3 – Optimized molecular structures of compounds **Mol 3**, **Mol 5** and **Mol 6**.

*Table 2*

The calculated chemical descriptors of compounds Mol 3, Mol 5 and Mol 6

| | **MOL 3** | **MOL 5** | **MOL 6 (Vit C)** |
|---|---|---|---|
| **HOMO (eV)** | -7,6013 | -7,9393 | -7,9879 |
| **LUMO (eV)** | -0,7638 | -0,6444 | 0,3463 |
| **$\Delta E_{gap}$ (eV)** | 6,8375 | 7,2949 | 8,3342 |
| **IP (eV)** | 7,6013 | 7,9393 | 7,9879 |
| **EA (eV)** | 0,7638 | 0,6444 | -0,3463 |
| **χ** | 4,1826 | 4,2919 | 3,8208 |
| **μ** | -4,18255 | -4,29185 | -3,8208 |
| **h** | 3,41875 | 3,64745 | 4,1671 |
| **S** | 0,29250457 | 0,27416414 | 0,23997504 |
| **ω** | 2,55849719 | 2,52504852 | 1,75163935 |
| **$\omega^-$** | 5,07711594 | 5,12690477 | 4,18292685 |
| **$\omega^+$** | 0,89456594 | 0,83505477 | 0,36212685 |

As can be seen from the results presented in Fig. 2 and Table 1, the radical scavenging activities increases (IP%) with the compound concentration increase. All the synthesized products demonstrated medium to high antioxidant activity with an IP % values greater than 50%, except for the compound 8-hydroxy-4-methyl-2H-chromen-2-one which has a low inhibition percentage of 48.87%. Mol 3 exhibited the highest antioxidant capacity (IP% 96.87, $IC_{50}$ 37.48 mg/mL) among all the tested molecules, higher than the standard Vitamin C (IP% 94.94, $IC_{50}$ 285.71 mg/mL).

## Computational Calculations

### *Molecular Descriptors*

The optimized molecular structures of the three studied compounds using DFT/CAM-B3LYP method combined with def2-TZVPP basis set are shown in Fig. 3. The calculated quantum indices, $E_{HOMO}$, $E_{LUMO}$, $\Delta E_{gap}$ and dipole moment (μ), ectronegativity (χ), hardness (η), softness (S), global electrophilicity (ω), electron affinity (EA), potential ionisation (IP), electron-donating ($\omega^-$) and electron-accepting ($\omega^+$) powers are listed in Table 2.

An inspection of the results summarized in Table 2, reveals that almost all the calculated quantum descriptors gave results that are concordant with the experimental $IC_{50}$ data, **Mol 3** > **Mol 5** > **Mol 6** (VitC). HOMO energy is a valuable reactivity descriptor in evaluating electron-donating ability of an antioxidant.[30] Another parameter of outmost importance in determining the chemical reactivity, is the energy gap $\Delta E_{gap}$. As $\Delta E_{gap}$ increases, hard/less reactive will be the molecule and vice versa. The lower $\Delta E_{gap}$, the easier electrons donation, and the more antioxidant effect.[31] The estimated ionisation potential IP, provides an understanding of the

initial energy required to release an electron from a compound, which implies an inverse relation between the antioxidant capacity and IP. Therefore, the lower the energy required to remove an electron, the higher is the compound's antioxidant activity. Higher electron affinities EA values allow a compound to easily absorb electrons. Thus, higher values are related to a better antioxidant activity.[32] The electronegativity χ is a measure of the tendency to attract electrons in a chemical bond and is defined as the negative of the chemical potential μ in DFT. Thus, a compound with a lower χ value is expected to have a higher antioxidant activity.[33] The greater the electronic chemical potential μ, the less stable/more reactive is the compound.

The chemical hardness η, is associated with the stability of a chemical species, it measures the resistance to charge transfer,[34] whereas, softness (S) provides a measure of its reactivity. Electrophilicity index ω, measures the propensity or capacity of a species to accept electrons. It is a measure of the stabilization in energy after a system accepts an additional amount of electronic charge from the environment. Recently Gázquez *et al.*,[35] introduced two new chemical reactivity indicators ($\omega^-$) and ($\omega^+$), to measure the capacity of a molecule to give and to accept a charge fraction, respectively.

### *Frontier Molecular Orbital Analysis*

Frontier molecular orbitals are important parameters that characterise the antiradical activity of organic compounds.[36-37] Fig. 4 reveals that, the distribution of HOMOs and LUMOs for the two molecules, **Mol 3** and **Mol 5** is mainly concentrated on the 2H-chromen-2-one nucleus. Whereas, for Vitamin C (**Mol 6**), HOMOs and LUMOs are localised over the entire molecule.

### *Molecular Electrostatic Potential Analysis*

Molecular electrostatic potential (MEP) mapping Fig. 5, is another useful tool for analyzing and predicting antioxidant activity,[38] it helps visualize electrophilic and nucleophilic sites. [39] The regions of positive, negative, and neutral potentials are indicated by different colors.

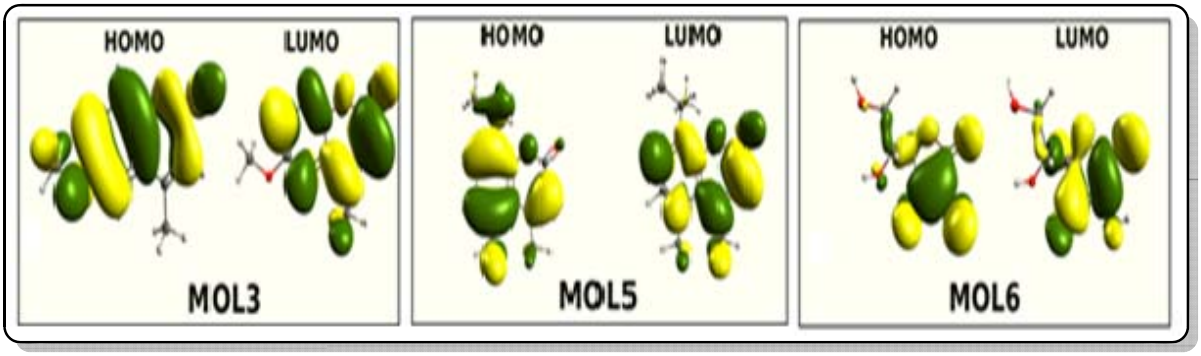



Fig. 4 – Frontier molecular orbitals of compounds **Mol 3**, **Mol 5** and **Mol 6**.

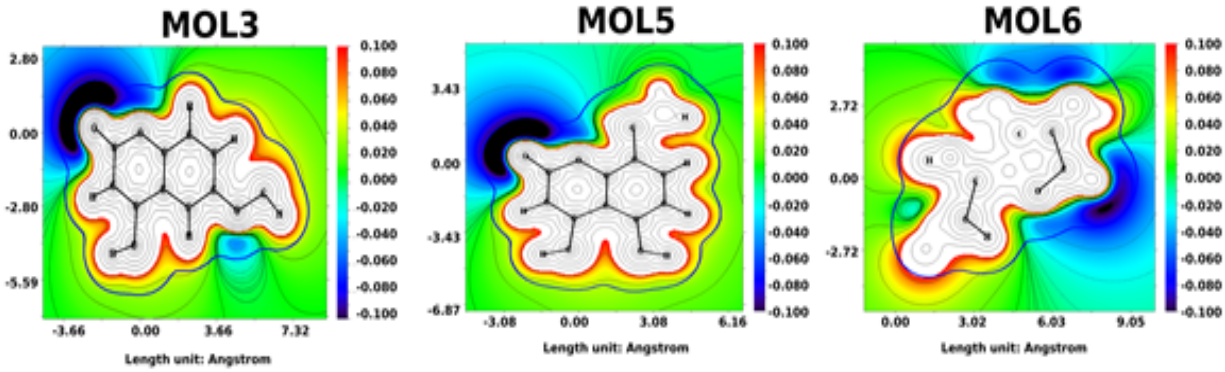



Fig. 5 – Mapping of the electrostatic potential (MEP) surface of molecules, Mol 3, Mol 5 and Mol 6 (VitC).

The red and yellow regions in the ESP plot refer to the region of high electron density and are associated with electrophilic reactivity. while, the blue parts represent low electron density and are susceptible to nucleophilic reactivity. The negative electrostatic potential (blue regions) are concentrated at the oxygen atom O11 of the carbonyl group at the C1 position for the studied molecules **Mol 3** and **Mol 5**, indicating thus, the primary site for electrophilic attacks.

## CONCLUSIONS

Acoording to the results of the present study, the following conclusions can be drawn:

The Von Pechmannn solventless condensation between phenol derivatives and ethyl acetoacetate catalyzed by amberlyst A15, has been performed to prepare five coumarin compounds, with simple, inexpensive reagents and a respectful protocol towards the environment. The yields thus obtained are moderate to excellent. *m*-Hydroxyphenol is the most reactive substrate with 90% yield in 20 min reaction time.

The evaluation of the antioxidant activity by DPPH radical scavenging assay, revealed that all the synthesized coumarins exhibited a good to moderate antioxidant activity.

Among the prepared compounds, **Mol 3** showed the highest inhibition activity (IP % = 96.87%, $IC_{50}$ = 37.48 mg/mL), better than the reference Vitamin C (94.94%, $IC_{50}$= 285.71 mg/mL).

DFT based quantum chemical calculations were performed, on the highest **Mol 3**, the weakest **Mol 5** coumarins and on the reference Vitamin C (**Mol 6**), in order to correlate the observed antioxidant potential to their molecular structures. Molecular descriptors like $E_{HOMO}$, ΔE gap, chemical potential (μ), hardness (η), softness (S), global electrophilicity index (ω), electron affinity (EA), potential ionisation (IP), electron acceptor power ($\omega^+$), and electron donor power ($\omega^-$), were computed. These descriptors reveal perfect correlation with the experimental $IC_{50}$ trend: **Mol 3** > **Mol 5** > **Mol 6** (Vit C).

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