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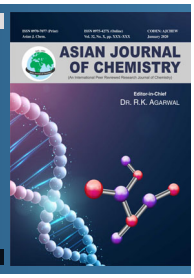


# Density Functional Theory Calculation of Molecular Descriptors for Simple Coumarins in Gas and Different Solvents

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The primary aim of this study is to show the importance of molecular structure analysis of pharmaceutical active coumarins compounds using quantum chemistry methods based on density functional theory. To explore the theoretical calculations for global descriptors, the standard Gaussian 09W program was used for coumarins compounds. The full geometry optimization was carried out by the B3LYP/6-311G level of theory. The octanol-water and air-water partition coefficients were also estimated using functional density theory. The order of the HOMO-LUMO energy gap for studied coumarins in the gas phase is umbelliferone (UBA) < (herniarin) HNR ~ (crenulatin) CNT < (scopoletin) SCT < (scoparone) SCO < (isoscopoletin) IST < (4-methylesculetin) MST < (umbelliferone-2-carboxylic acid) UCA < (isofraxidin) IFD < (fraxetin) FXT < (aesculetine) ACT < (dapnetine) DPT. Therefore, UBA molecule in gas phase is less stable. Compared to the measured index of electrophilicity (DE). The MST molecule is stronger, more reactive, nucleophile electrophile at the gas phase and in solvents. In all solvent phases, CNT and UCA molecules have lower values, which mean they are strong nucleophiles. From the log P values of ACT and MST coumarins are in between 1.35-1.8, so ACT and MST coumarins use oral and intestinal absorptions.

**Keywords: Coumarins, DFT method, HOMO-LUMO energies, Global descriptors, Partition coefficients.**

## INTRODUCTION

Phytochemicals are chemical compounds naturally found in the kingdom of plants. Some are responsible for the organoleptic properties of the natural sources. The term is commonly used to refer to those chemicals, for example carotenoids, flavonoids, coumarins or chromones, that may have biological significance, but not all of them are considered important. There may be up to 4,000 different phytochemicals with possible action in various conditions such as cancer and metabolic or degenerative diseases. Coumarins are of the form of the benzopyrone family (1,2-benzopyrones, or 2*H*-1-benzopyrane-2-ones) [1] and/or synthetic oxygen-containing heterocycles.

Coumarin compounds are the structural class of lactones developed with a benzene ring, fused into an α-pyrone ring and have basically a combined structure with rich electron and strong load-carrying characteristics [2,3]. The simplicity and flexibility of coumarin scaffold make it an interesting starting point for several different applications [4-6]. Coumarins are used as perfumes, cosmetics and industrial additives. Any of its derivatives have been used in tobacco and other alcoholic beverages as taste enhancers [7,8]. In addition, several coumarin compounds as drug candidates with good pharmacological activity, low toxicities and side effects, decreased drug resistance, high bioavailability, broad range, stronger curative effects, *etc*. are being actively researched for the treatment of various types of diseases [9]. A number of attempts were made mainly in the production of coumarin based anticoagulants, antioxidants [10], antimicrobials (antivirals, antifungals and antiparasitics) [8,11], anticancer [12-14] and antidiabetic, anti-antimicrobial and anti-inflammatory agents [8,15].

Studies on coumarins as bioactive agents [16] as well as supramolecular medicinal agents, diagnostic agents and pathologic samples and biological stubble were also carried out [17]. Especially an interaction between this scaffold with molecules and ions is a broad conjugated system in the coumarin ring, with electron rich and charging transporting properties. Coumarin based ion receptors, fluorescent samples and biological stains are increasing rapidly and extensively monitored in living cells for timely enzyme activity, complex biological effects and reli-

able pharmaceutical and pharmacokinetic properties [18,19]. Coumarin compounds as pharmaceutical goods are gradually attracted by their excellent contribution to disease prevention and therapy and the associated research and development are becoming an extremely attractive highlight.

The prediction of chemical properties by computational tools has been a useful and easy way of analyzing and comparing large libraries of compounds aimed at creating and developing new molecules with greater biological activity and/or better controlled chemical behavior. In modern scientific approaches, molecular design and prediction of molecular parameters using *ab initio* methods and the physical and chemical properties, mathematical modeling are important steps in the development of new drugs or advanced materials. Density functional theory (DFT) was approved for the measurement of molecular structure, vibration rates, and chemical reaction energy [20-23]. It offers an effective method in electronic calculations for inclusion of correlation energy [24]. Furthermore, it provides a good basis for reactivity models [25]. The molecule reactivity also depends on its electronic characteristics and its kinetic and thermodynamic stability. Moreover, DFT [26,27] has succeeded considerably in providing theoretical context for popular qualitative chemical concepts. Several descriptors of reactivity were suggested for the of chemical reactivity and site selectivity. The global reactivity descriptors are hardness, global softness, electronegativity and polarity, widely used to understand the global existence of molecules in terms of their stability and knowledge of molecular reactivity can be established.

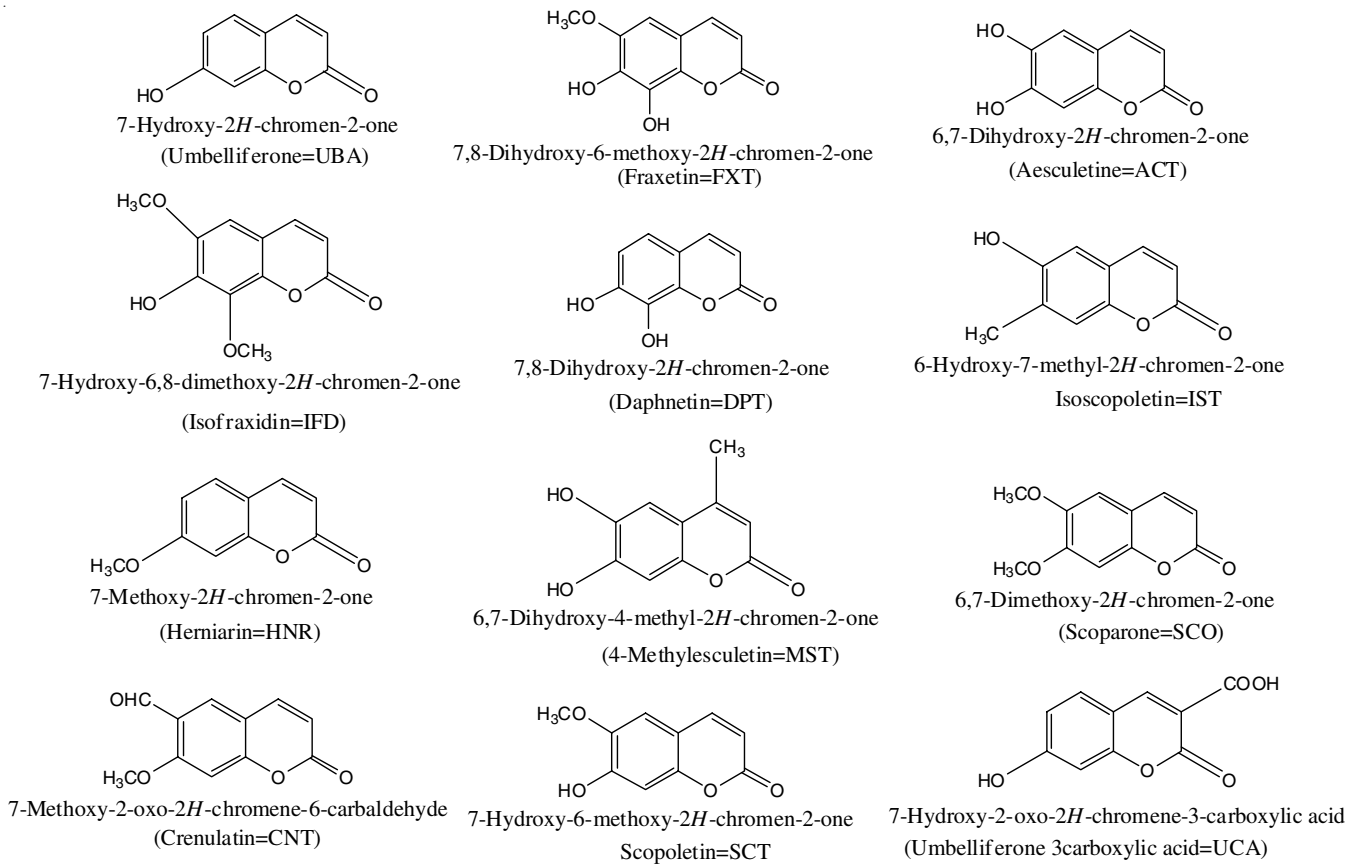
## COMPUTATIONAL METHODS

All the calculations in this work were performed using the Gaussian 09W quantum chemistry package [28]. Molecular structures were generated in the more extended conformation using GaussView 5.0 [29]. The geometries of all studied coumarins (**Scheme-I**) were optimized using the three density functionals B3LYP [30] with the 6-311 basis set. Hessian analysis indicated no existence of imaginary frequencies, proving that all of the optimized structures were true minima. Following the geometry optimizations, analytical frequency calculations were preceded following the standard procedures to obtain the thermochemical properties.

Furthermore, the effects of solvents on the structural properties were analyzed using the self-cohesive reaction field (SCRF) method on a PCM basis developed by Tomasi *et al.* [28,31]. In this model, the solution is treated inside a cavity and the solvent as a less medium structure distinguished by certain parameters such as dielectric constant, volume of the molar, and polarization. This aspect will significantly boost the simul-ation results of real molecular systems for electronic or vibra-tional spectroscopy. In this analysis, the solvents chosen were water, benzene, tetrahydrofuran and octanol.

## RESULTS AND DISCUSSION

All the geometries of the studied coumarins have been fully optimized using the B3LYP method within the framework of density functional theory in conjunction with the 6-311 basis




**Scheme-I:** Studied coumarins with IUPAC names, in brackets common names with code

set. The molecular structures of the compounds with an atom numbering scheme adopted in the computations are shown in Fig. 1. By using of the optimized geometries, the quantum chemical descriptors in gas and different solvents were calculated.

**HOMO-LUMO energies:** The energy of HOMO is directly linked to the ionizing potential (A) and characterizes the molecule′s susceptibility to electrophilic attack. The LUMO energy is directly related to the affinity of electrons (I) and characterizes the molecule′s susceptibility to nucleophile attack. The values A and I are shown in Table-1 and Fig 2. In radical reactions, the HOMO and LUMO energies are both important [32,33]. The principle of soft and hard nucleophiles and electrophiles also has a direct connection with the relative energy of orbits HOMO/LUMO. Hards nucleophiles have low-energy HOMO; soft nucleophiles have high-energy HOMO; high-energy LUMO hard electrophiles and low-energy LUMO soft electrophiles [34]. For this analysis, UCA demonstrates soft nucleophilic and hard electrophilic substances in gas and other solvents tested.

**HOMO-LUMO energy gap ($\Delta E_g$):** The measured HOMO-LUMO energy level and the HOMO-LUMO energy difference in different solvents and gas phase are summarized in Table-1. Frontier orbital diagrams of the studied molecules in Fig. 3

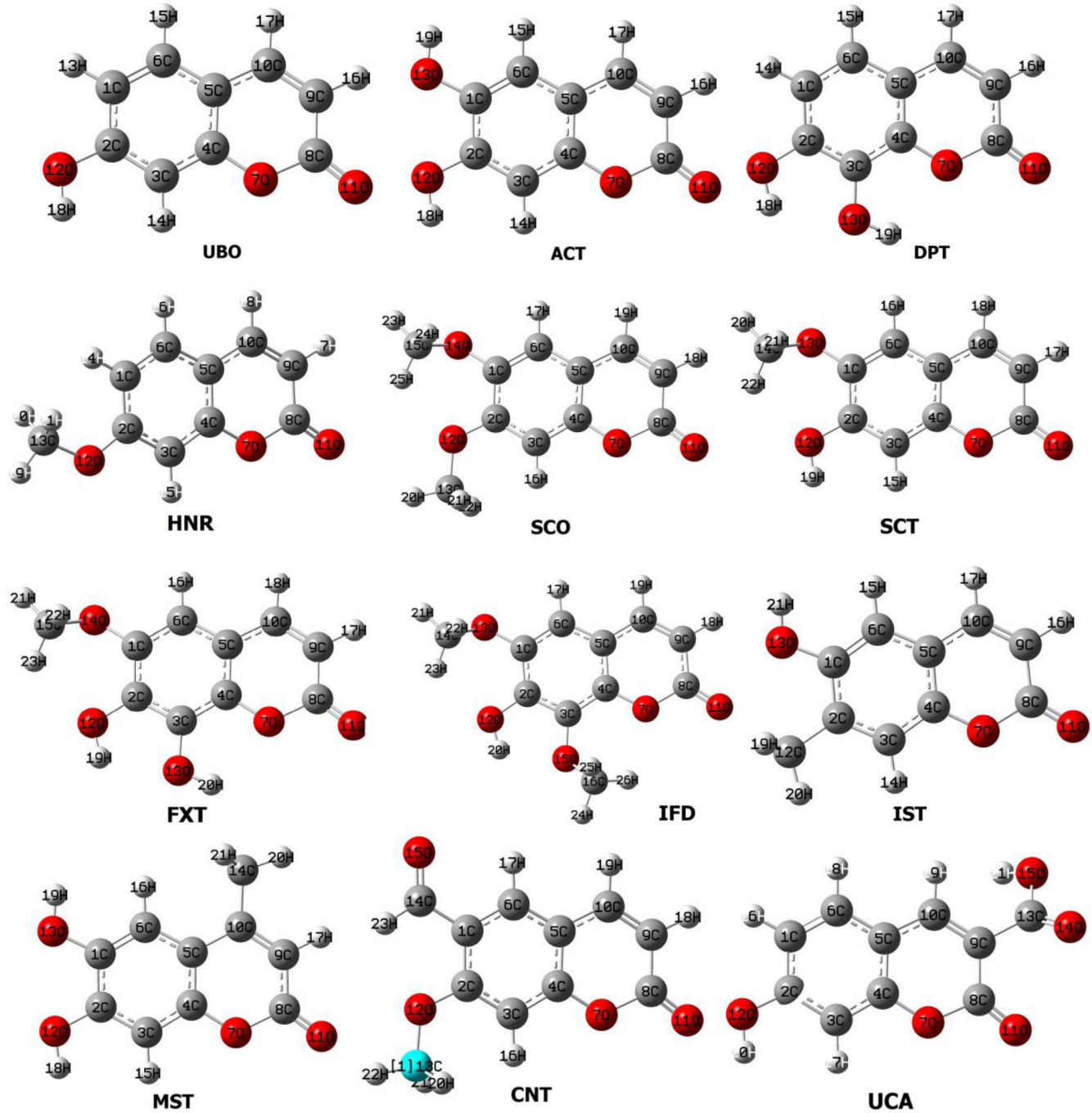



Fig. 1. Optimized structures of studied coumarins in gas phase at DFT/B3LYP/6-311 level

TABLE-1
THEORETICAL ELECTRONIC PROPERTIES (HOMO, LUMO) AND ENERGY GAP ($E_g$) AND REACTIVE DESCRIPTORS IONIZATION POTENTIAL (I), ELECTRON AFFINITY (A), ELECTRONEGATIVITY ($\chi$), HARDNESS ($\eta$), SOFTNESS (s), CHEMICAL POTENTIAL ($\mu$), SOFTNESS (S), ELECTROPHILICITY INDEX ($\omega$), CHARGE TRANSFER ($\Delta N_{max}$), NUCLEOFUGALITY ($\Delta E_n$) AND ELECTROFUGALITY ($\Delta E_e$) OF CYANURIC ACID TAUTOMERS CALCULATED BY B3LYP/6-311 IN GAS PHASE AND DIFFERENT SOLVENTS

| Molecule | HOMO | LUMO | I | A | $\chi$ | $\eta$ | $\mu$ | S | $\omega$ | $\Delta N_{max}$ | $\Delta E_n$ | $\Delta E_e$ | $\Delta E_g$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gas | | | | | | | | | | | | | |
| UBO | -6.5835 | -2.2017 | 6.5835 | 2.2017 | 4.3926 | 2.1909 | -4.3926 | 0.4564 | 4.4034 | 2.0049 | 2.2017 | 10.9869 | 4.3819 |
| ACT | -6.2831 | -2.2245 | 6.2831 | 2.2245 | 4.2538 | 2.0293 | -4.2538 | 0.4928 | 4.4585 | 2.0962 | 2.2339 | 10.7416 | 4.0586 |
| DPT | -6.2749 | -2.2319 | 6.2749 | 2.2319 | 4.2534 | 2.0215 | -4.2534 | 0.4947 | 4.4747 | 2.1041 | 2.2428 | 10.7497 | 4.0431 |
| HNR | -6.4777 | -2.1279 | 6.4777 | 2.1279 | 4.3028 | 2.1749 | -4.3028 | 0.4598 | 4.2564 | 1.9784 | 2.1284 | 10.7340 | 4.3497 |
| SCO | -6.2496 | -2.1073 | 6.2496 | 2.1073 | 4.1784 | 2.0712 | -4.1784 | 0.4828 | 4.2148 | 2.0174 | 2.1076 | 10.4645 | 4.1424 |
| SCT | -6.3721 | -2.1979 | 6.3721 | 2.1979 | 4.2850 | 2.0871 | -4.2850 | 0.4791 | 4.3987 | 2.0531 | 2.2008 | 10.7708 | 4.1742 |
| FXT | -6.4047 | -2.3271 | 6.4047 | 2.3271 | 4.3659 | 2.0388 | -4.3659 | 0.4905 | 4.6746 | 2.1414 | 2.3475 | 11.0794 | 4.0776 |
| IFD | -6.3019 | -2.2161 | 6.3019 | 2.2161 | 4.2590 | 2.0429 | -4.2590 | 0.4895 | 4.4395 | 2.0848 | 2.2234 | 10.7414 | 4.0858 |
| IST | -6.3800 | -2.2362 | 6.3800 | 2.2362 | 4.3081 | 2.0719 | -4.3081 | 0.4827 | 4.4790 | 2.0793 | 2.2428 | 10.8590 | 4.1438 |
| MST | -6.2151 | -2.0966 | 6.2151 | 2.0966 | 4.1559 | 2.0592 | -4.1559 | 0.4856 | 4.1936 | 2.0182 | 2.0970 | 10.4087 | 4.1184 |
| CNT | -6.8491 | -2.4972 | 6.8491 | 2.4972 | 4.6731 | 2.1760 | -4.6731 | 0.4596 | 5.0181 | 2.1476 | 2.5209 | 11.8672 | 4.3519 |
| UCA | -7.0725 | -2.9587 | 7.0725 | 2.9587 | 5.0156 | 2.0569 | -5.0156 | 0.4862 | 6.1151 | 2.4384 | 3.1564 | 13.1876 | 4.1138 |
| Water | | | | | | | | | | | | | |
| UBO | -6.5471 | -2.2180 | 6.5471 | 2.2180 | 4.3825 | 2.1645 | -4.3825 | 0.4620 | 4.4367 | 2.0247 | 2.2187 | 10.9837 | 4.3291 |
| ACT | -6.2788 | -2.2335 | 6.2788 | 2.2335 | 4.2561 | 2.0226 | -4.2561 | 0.4944 | 4.4780 | 2.1043 | 2.2445 | 10.7568 | 4.0452 |
| DPT | -6.4350 | -2.2888 | 6.4350 | 2.2888 | 4.3619 | 2.0731 | -4.3619 | 0.4824 | 4.5887 | 2.1040 | 2.3000 | 11.0237 | 4.1462 |
| HNR | -6.4758 | -2.2226 | 6.4758 | 2.2226 | 4.3492 | 2.1266 | -4.3492 | 0.4702 | 4.4474 | 2.0452 | 2.2248 | 10.9232 | 4.2531 |
| SCO | -6.3683 | -2.2251 | 6.3683 | 2.2251 | 4.2967 | 2.0716 | -4.2967 | 0.4827 | 4.4558 | 2.0741 | 2.2308 | 10.8241 | 4.1432 |
| SCT | -6.4513 | -2.2509 | 6.4513 | 2.2509 | 4.3511 | 2.1002 | -4.3511 | 0.4762 | 4.5073 | 2.0718 | 2.2563 | 10.9585 | 4.2004 |
| FXT | -6.4600 | -2.3192 | 6.4600 | 2.3192 | 4.3896 | 2.0704 | -4.3896 | 0.4830 | 4.6534 | 2.1202 | 2.3342 | 11.1134 | 4.1408 |
| IFD | -6.4535 | -2.2934 | 6.4535 | 2.2934 | 4.3734 | 2.0800 | -4.3734 | 0.4808 | 4.5977 | 2.1026 | 2.3043 | 11.0511 | 4.1601 |
| IST | -6.3862 | -2.2779 | 6.3862 | 2.2779 | 4.3321 | 2.0542 | -4.3321 | 0.4868 | 4.5679 | 2.1089 | 2.2900 | 10.9542 | 4.1084 |
| MST | -6.2477 | -2.1315 | 6.2477 | 2.1315 | 4.1896 | 2.0581 | -4.1896 | 0.4859 | 4.2642 | 2.0356 | 2.1328 | 10.5120 | 4.1163 |
| CNT | -6.6597 | -2.4882 | 6.6597 | 2.4882 | 4.5740 | 2.0858 | -4.5740 | 0.4794 | 5.0152 | 2.1930 | 2.5270 | 11.6750 | 4.1715 |
| UCA | -6.8581 | -2.8493 | 6.8581 | 2.8493 | 4.8537 | 2.0044 | -4.8537 | 0.4989 | 5.8767 | 2.4215 | 3.0274 | 12.7348 | 4.0088 |
| Benzene | | | | | | | | | | | | | |
| UBO | -6.5607 | -2.2022 | 6.5607 | 2.2022 | 4.3814 | 2.1792 | -4.3814 | 0.4589 | 4.4046 | 2.0106 | 2.2023 | 10.9652 | 4.3584 |
| ACT | -6.2730 | -2.2248 | 6.2730 | 2.2248 | 4.2489 | 2.0241 | -4.2489 | 0.4940 | 4.4596 | 2.0991 | 2.2348 | 10.7326 | 4.0482 |
| DPT | -6.4665 | -2.3081 | 6.4665 | 2.3081 | 4.3873 | 2.0792 | -4.3873 | 0.4809 | 4.6287 | 2.1101 | 2.3207 | 11.0953 | 4.1584 |
| HNR | -6.4698 | -2.1628 | 6.4698 | 2.1628 | 4.3163 | 2.1535 | -4.3163 | 0.4644 | 4.3255 | 2.0043 | 2.1628 | 10.7953 | 4.3070 |
| SCO | -6.3005 | -2.1603 | 6.3005 | 2.1603 | 4.2304 | 2.0701 | -4.2304 | 0.4831 | 4.3226 | 2.0436 | 2.1623 | 10.6231 | 4.1402 |
| SCT | -6.4306 | -2.2387 | 6.4306 | 2.2387 | 4.3346 | 2.0960 | -4.3346 | 0.4771 | 4.4822 | 2.0681 | 2.2435 | 10.9128 | 4.1919 |
| FXT | -6.4268 | -2.3200 | 6.4268 | 2.3200 | 4.3734 | 2.0534 | -4.3734 | 0.4870 | 4.6574 | 2.1299 | 2.3374 | 11.0842 | 4.1067 |
| IFD | -6.3604 | -2.2474 | 6.3604 | 2.2474 | 4.3039 | 2.0565 | -4.3039 | 0.4863 | 4.5036 | 2.0928 | 2.2562 | 10.8640 | 4.1130 |
| IST | -6.3770 | -2.2482 | 6.3770 | 2.2482 | 4.3126 | 2.0644 | -4.3126 | 0.4844 | 4.5046 | 2.0890 | 2.2564 | 10.8816 | 4.1288 |
| MST | -6.5000 | -2.1040 | 6.5000 | 2.1040 | 4.3020 | 2.1980 | -4.3020 | 0.4550 | 4.2100 | 1.9572 | 2.1060 | 10.7100 | 4.3960 |
| CNT | -6.7969 | -2.4890 | 6.7969 | 2.4890 | 4.6429 | 2.1539 | -4.6429 | 0.4643 | 5.0041 | 2.1556 | 2.5151 | 11.8010 | 4.3078 |
| UCA | -6.9688 | -2.8912 | 6.9688 | 2.8912 | 4.9300 | 2.0388 | -4.9300 | 0.4905 | 5.9606 | 2.4181 | 3.0694 | 12.9294 | 4.0776 |
| Tetrahydrofuran | | | | | | | | | | | | | |
| UBO | -6.5506 | -2.2101 | 6.5506 | 2.2101 | 4.3804 | 2.1702 | -4.3804 | 0.4608 | 4.4206 | 2.0184 | 2.2105 | 10.9712 | 4.3405 |
| ACT | -6.2749 | -2.2319 | 6.2749 | 2.2319 | 4.2534 | 2.0215 | -4.2534 | 0.4947 | 4.4747 | 2.1041 | 2.2428 | 10.7497 | 4.0431 |
| DPT | -6.4437 | -2.2931 | 6.4437 | 2.2931 | 4.3684 | 2.0753 | -4.3684 | 0.4819 | 4.5976 | 2.1050 | 2.3045 | 11.0413 | 4.1506 |
| HNR | -6.4720 | -2.2009 | 6.4720 | 2.2009 | 4.3364 | 2.1356 | -4.3364 | 0.4683 | 4.4027 | 2.0306 | 2.2019 | 10.8747 | 4.2711 |
| SCO | -6.3454 | -2.2044 | 6.3454 | 2.2044 | 4.2749 | 2.0705 | -4.2749 | 0.4830 | 4.4131 | 2.0647 | 2.2087 | 10.7585 | 4.1410 |
| SCT | -6.3985 | -2.2158 | 6.3985 | 2.2158 | 4.3072 | 2.0913 | -4.3072 | 0.4782 | 4.4354 | 2.0595 | 2.2195 | 10.8338 | 4.1827 |
| FXT | -6.4518 | -2.3209 | 6.4518 | 2.3209 | 4.3863 | 2.0655 | -4.3863 | 0.4841 | 4.6575 | 2.1236 | 2.3366 | 11.1093 | 4.1310 |
| IFD | -6.4222 | -2.2749 | 6.4222 | 2.2749 | 4.3485 | 2.0736 | -4.3485 | 0.4822 | 4.5595 | 2.0970 | 2.2846 | 10.9817 | 4.1473 |
| IST | -6.3824 | -2.2664 | 6.3824 | 2.2664 | 4.3244 | 2.0580 | -4.3244 | 0.4859 | 4.5434 | 2.1013 | 2.2770 | 10.9259 | 4.1160 |
| MST | -6.2360 | -2.1219 | 6.2360 | 2.1219 | 4.1790 | 2.0570 | -4.1790 | 0.4861 | 4.2449 | 2.0315 | 2.1230 | 10.4810 | 4.1141 |
| CNT | -6.7544 | -2.4877 | 6.7544 | 2.4877 | 4.6210 | 2.1334 | -4.6210 | 0.4687 | 5.0048 | 2.1661 | 2.5171 | 11.7592 | 4.2667 |
| UCA | -6.8965 | -2.8577 | 6.8965 | 2.8577 | 4.8771 | 2.0194 | -4.8771 | 0.4952 | 5.8895 | 2.4152 | 3.0318 | 12.7860 | 4.0387 |
| Octanol | | | | | | | | | | | | | |
| UBO | -6.5471 | -2.2096 | 6.5471 | 2.2096 | 4.3783 | 2.1687 | -4.3783 | 0.4611 | 4.4195 | 2.0188 | 2.2099 | 10.9666 | 4.3375 |
| ACT | -6.2749 | -2.2313 | 6.2749 | 2.2313 | 4.2531 | 2.0218 | -4.2531 | 0.4946 | 4.4735 | 2.1036 | 2.2422 | 10.7485 | 4.0436 |
| DPT | -6.4409 | -2.2912 | 6.4409 | 2.2912 | 4.3661 | 2.0749 | -4.3661 | 0.4820 | 4.5937 | 2.1043 | 2.3025 | 11.0346 | 4.1497 |
| HNR | -6.4709 | -2.2041 | 6.4709 | 2.2041 | 4.3375 | 2.1334 | -4.3375 | 0.4687 | 4.4094 | 2.0332 | 2.2053 | 10.8803 | 4.2667 |
| SCO | -6.3511 | -2.2096 | 6.3511 | 2.2096 | 4.2804 | 2.0708 | -4.2804 | 0.4829 | 4.4238 | 2.0670 | 2.2142 | 10.7749 | 4.1416 |
| SCT | -6.4355 | -2.2395 | 6.4355 | 2.2395 | 4.3375 | 2.0980 | -4.3375 | 0.4766 | 4.4838 | 2.0674 | 2.2443 | 10.9193 | 4.1960 |
| FXT | -6.4518 | -2.3184 | 6.4518 | 2.3184 | 4.3851 | 2.0667 | -4.3851 | 0.4839 | 4.6522 | 2.1218 | 2.3337 | 11.1040 | 4.1334 |
| IFD | -6.4301 | -2.2830 | 6.4301 | 2.2830 | 4.3565 | 2.0735 | -4.3565 | 0.4823 | 4.5767 | 2.1010 | 2.2936 | 11.0067 | 4.1470 |
| IST | -6.3811 | -2.2667 | 6.3811 | 2.2667 | 4.3239 | 2.0572 | -4.3239 | 0.4861 | 4.5441 | 2.1019 | 2.2774 | 10.9252 | 4.1144 |
| MST | -6.2369 | -2.1198 | 6.2369 | 2.1198 | 4.1783 | 2.0585 | -4.1783 | 0.4858 | 4.2404 | 2.0297 | 2.1207 | 10.4773 | 4.1171 |
| CNT | -6.7484 | -2.4871 | 6.7484 | 2.4871 | 4.6178 | 2.1307 | -4.6178 | 0.4693 | 5.0041 | 2.1673 | 2.5169 | 11.7525 | 4.2613 |
| UCA | -6.8845 | -2.8490 | 6.8845 | 2.8490 | 4.8668 | 2.0177 | -4.8668 | 0.4956 | 5.8693 | 2.4120 | 3.0203 | 12.7538 | 4.0355 |

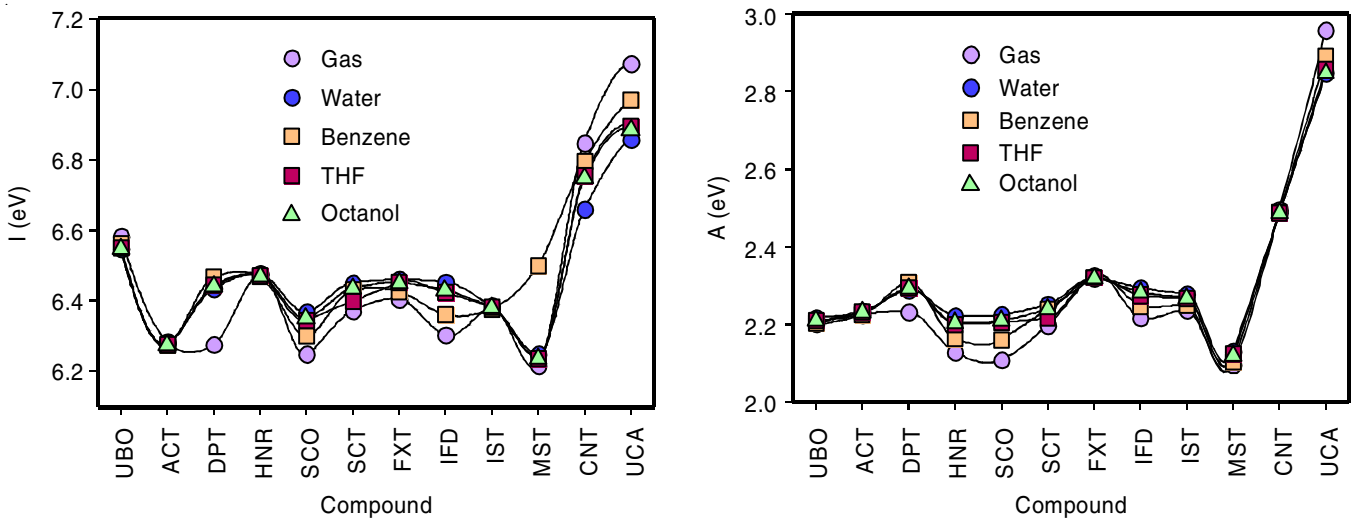



Fig. 2. Calculated ionization potential (A) and electron affinity (I) for studied molecules at DFT/B3LYP/ 6-311 level in gas phase and different solvents

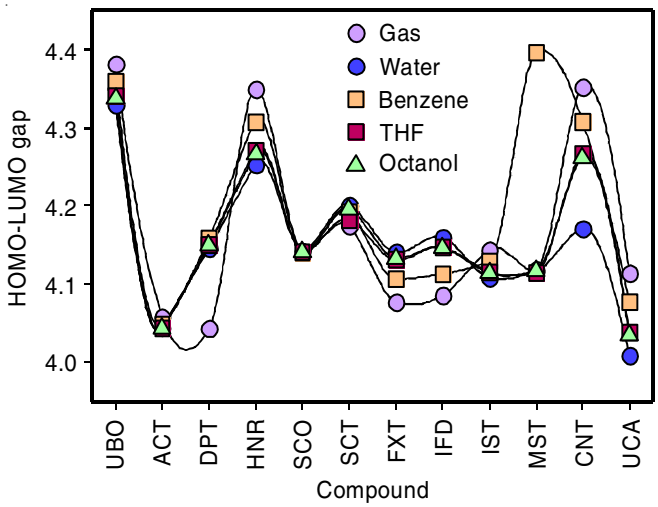



Fig. 3. HOMO-LUMo energy gap for studied molecules at DFT/B3LYP/ 6-311 level in gas phase and different solvents

shows that the UBA, HNR and CNT tests are totally stable as there is a large HOMO-LUMO distance between other compounds during the gas phase and in different solvents. Gas-phase stability: UBA < HNR ~ CNT < SCT < SCO < IST < MST < UCA < IFD < ACT < DPT.

**Frontier orbital densities:** According to the theory of frontier electron reactivity, a majority of chemical reactions occur at and in the place where the HOMO and LUMO overlap of the respective reactants can be optimum. In the case of a donor molecule, the HOMO density is crucial for the transfer of charges (electrophilic electron density) and the LUMO density (nucleophilic electron density) is essential for an acceptor molecule. Such indices were used in QSAR studies to identify interaction sites between drugs and receptors. The electron density diagrams in HOMO and LUMO shown in Fig. 4 in the gas phase.

**Chemical hardness (η):** Chemical hardness using eqn. 1 has been calculated and its values are shown in Table-1. Fig. 5 shows the chemical hardness of studied coumarins in the gas and different solvents. The chemical hardness (η) of cyano coumarins were showed a similar trend to the ΔEg.

$$\chi = \frac{I+A}{2};\ \eta = \frac{I-A}{2};\ \mu = -\frac{(I+A)}{2};\ S = \frac{1}{\eta} \qquad (1)$$

**Electrophilicity index (ω):** The electrophilicity index (ω) has been used for the study of the chemical reactivity of the molecule as a structural represented. The index value for electrophilicity has been determined by eqn. 2 and its value is shown in Table-1. Fig. 6 demonstrates the influence of solvents on the electrophilicity index of the coumarins tested. In the gas phase and solvents. It is observed that MST compound is a stronger electrophile, while UCA and CNT coumarins have lower values in all the solvents phase, so considered as good nucleophiles.

$$\omega = \frac{\mu^2}{2\eta} \qquad (3)$$

**Chemical potential (μ):** The chemical potential (μ) theoretically represents the electrons′ escape tendency from an equilibrium environment. In the gas phase and in all solvents, the MST is less stable and reactive (Fig. 7).

**Nucleofugality ($\Delta E_n$):** Nucleophugality is defined as the tendency of an atom or group of molecules to withdraw with the connecting electron pair in a heterolytic cleavage process. Among the coumarins, the most nucleofugal were UCA, CNT and FXT in gas and various solvents. Similarly, electrofugality ($\Delta E_e$) describes the properties of a molecule atom or group of atoms for the movement of electrons in adjacent bonds. The values are tabulated in Table-1.

**Partition coefficients:** The SMD solvation model was applied to 12 studied coumarins molecules with B3LYP/ 6-311 as basis sets in order to test the methodology used for further calculations. Geometry optimizations frequency calculations were carried out for all molecules in the gas phase, in water and in octanol. The octanol/water partition coefficients values were estimated from solvation free energies (eqn. 3) for coumarins molecules and the values are listed in Table-2.

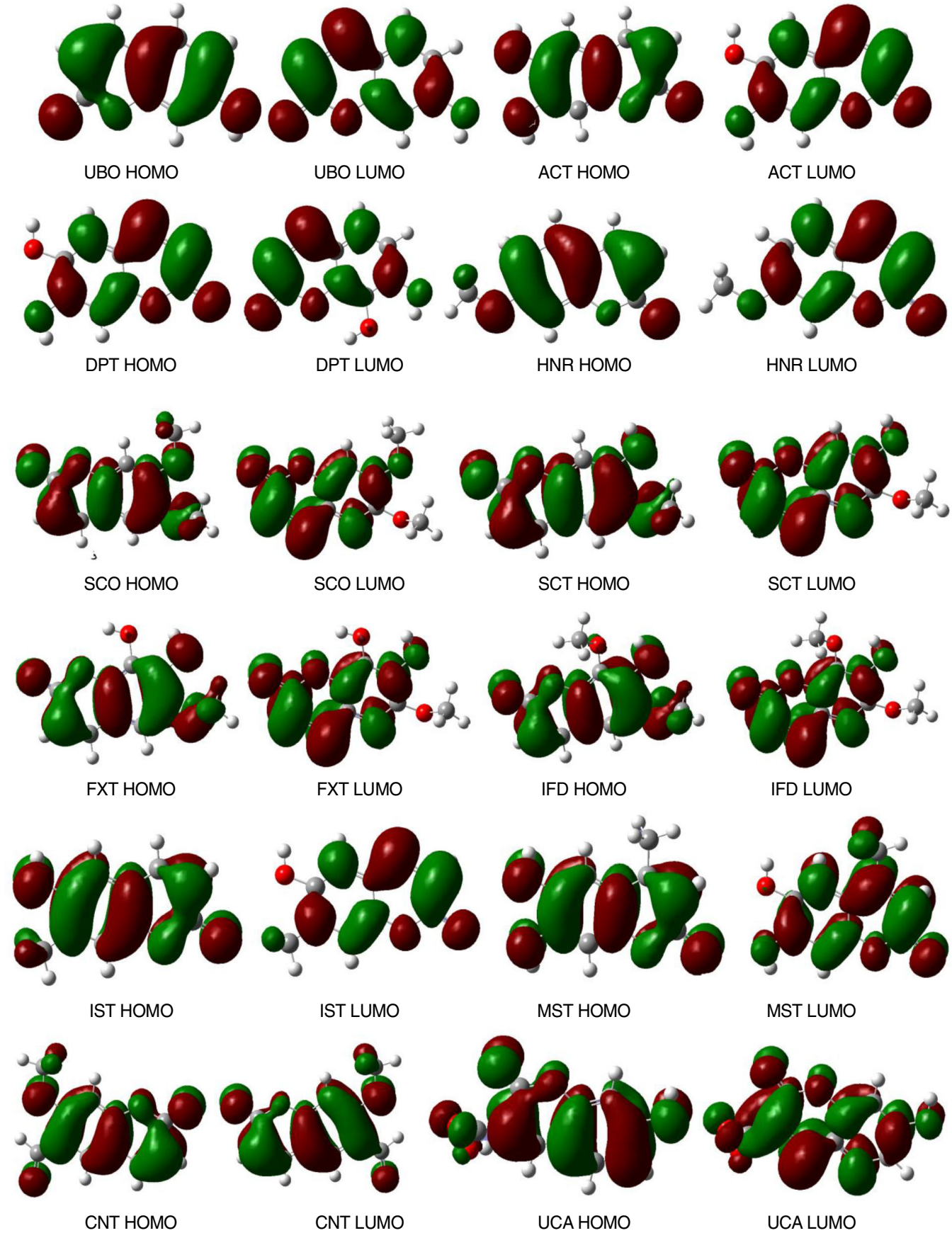



Fig. 4. HOMO and LUMO frontier molecular orbitals of studied molecules at at B3LYP/6-311 level in gas phase. In surface box, grey= available; red = displayed

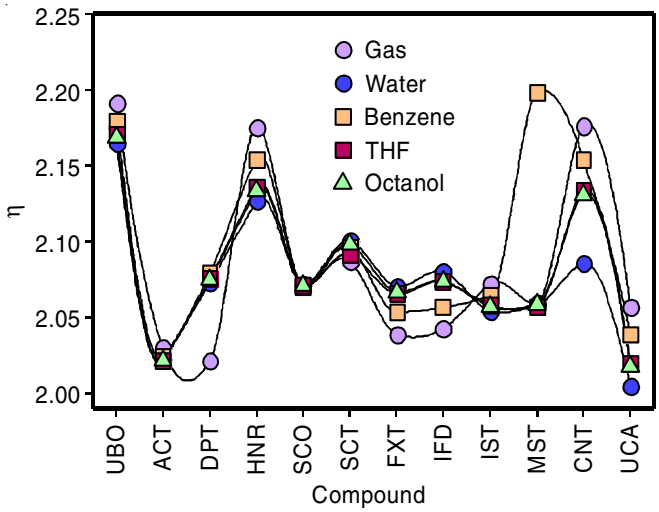



Fig. 5. Chemical hardness (η) for studied molecules at DFT/B3LYP/6-311 level in gas phase and different solvents

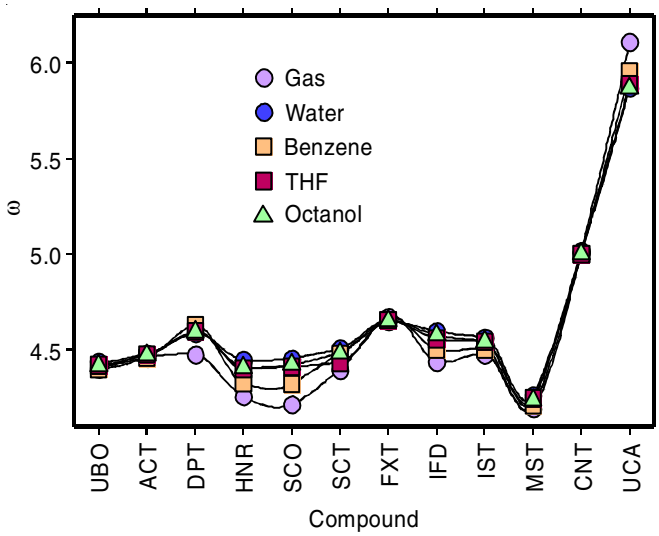



Fig. 6. electrophilicity index (ω) of coumarins at DFT/B3LYP/6-311 level in gas phase and different solvents

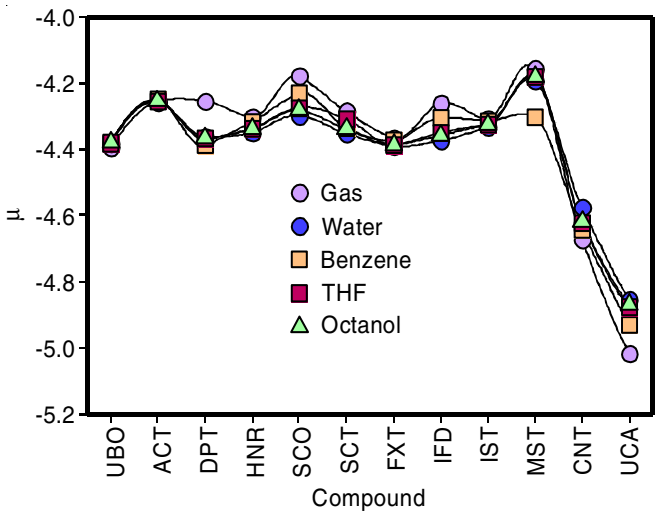



Fig. 7. Chemical potential (μ) for studied molecules at DFT/B3LYP/6-311 level in gas phase and different solvents

TABLE-2
CALCULATED SOLVATION FREE ENERGY CHANGE OF TRANSFER FROM THE GAS PHASE TO WATER PHASE ($\Delta G_{solv(water)}$, kcal mol$^{-1}$) AND OCTANOL PHASE ($\Delta G_{solv(octanol)}$, kcal mol$^{-1}$) UNDER STANDARD STATE CONDITIONS, AND CORRESPONDING log P VALUES OF EXAMINED B3LYP/6-311 LEVEL OF THEORY

| Molecule | $\Delta G_{sol.w}$ | $\Delta G_{sol.o}$ | $\Delta G_{o/w}$ |
|---|---|---|---|
| UBO | -10.44 | -8.93 | 1.1034 |
| ACT | -15.16 | -12.97 | 1.6076 |
| DPT | -9.15 | -7.86 | 0.9443 |
| HNR | -9.66 | -8.28 | 1.0095 |
| SCO | -10.57 | -9.11 | 1.0722 |
| SCT | -12.05 | -10.30 | 1.2813 |
| FXT | -10.37 | -8.76 | 1.1827 |
| IFD | -10.44 | -8.83 | 1.1811 |
| IST | -10.69 | -9.12 | 1.1482 |
| MST | -15.34 | -13.22 | 1.5546 |
| CNT | -11.15 | -9.61 | 1.1285 |
| UCA | -19.21 | -16.09 | 2.2880 |

$$\log P = -\frac{\Delta G^{o}_{o/w}}{2.303RT} \quad (3)$$

The log P of a compound intended for oral administration should be < 5, according to 'Lipinski's rule of 5'. An ideal CNS-oriented drug should have a log P value of approximately 2 [35] the ideal value for oral and intestinal absorption is 1.35-1.8, while a drug intended for sub-lingual absorption should have a log P value > 5. A certain material is distinguished by a low octanol-water partitioning coefficient, which can be mainly found in body fluid (intracellular fluid, transcellular fluid or blood plasma) [36,37].

It is evident from Table-2 that DPT is very hydrophilic (low for log P = 0.94) and also high-lipophilic (high for log P = 2.2): instead, the LP-value coumarins of between 1.35-1.8 are the indication of oral and intestinal absorption of ACT and MST coumarins.

## Conclusion

Molecular geometries of studied coumarins were fully optimized by using the Gaussian quantum chemistry software package Gaussian 09 at DFT/B3LYP level of theory, using the 6-311 basis set. The HOMO and LUMO energies were calculated in order to determine, the usefulness of global reactivity descriptors *viz*. electrophilicity, chemical hardness (η), chemical potential (μ), polarizability (α), electrophilicity index (ω), softness (S), nucleofugality and electrofugality, values for the prediction of the reactivity of the coumarins. Solvents effect on coumarins in four different solvents. In addition, octanol/water partition coefficients were predicted within the framework of DFT using three density functionals B3LYP. The order of the stability of coumarins in gas phase based on HOMO-LUMO energy gap: UBA < HNR ~ CNT < SCT < SCO ~ IST < MST ~ UCA < IFD < FXT < ACT < DPT in both gas and solvents. Therefore, UBA compound is least stable in gas phase, while compound MST is a good electrophile in both gas phase and solvents. From partition coefficients values, DPT is extremely hydrophilic (low value for log P = 0.94) as well as UCA that are highly lipophilic (high value for log P = 2.2); the log P value between 1.35-1.8, indicate ACT and MST compounds are using oral and intestinal absorption.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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