Original Article

MOLECULAR ELECTROSTATIC POTENTIAL AND CHEMOMETRIC STUDIES OF SIMPLE COUMARINS

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Abstract

The primary aim of this study is applying Chemometric techniques and Molecular Electrostatic Potential (MEP) to analyse and designing of pharmaceutical active coumarin compounds. By measuring and analysing MEP on molecular surfaces, the both positive $V_{s,\,max}$, negative $V_{s,\,min}$ values are determined based on Gauss view 5.0 program. The order of $V_{s,\,min}$ in kcal/mole : UCA < IST ≈ SCT < IST < MST ≈ ACT < UBO < HNR < SCO < IFD < FXT ≈ DPT. UCA is the most active compound. The hierarchical cluster analysis (HCA) and principle component analysis (PCA) was also applied to complete set of global descriptors of studied coumarins data and analysed the data matrix. The two coumarins UCA and CNT constituted different unique groups, SCT, HNR and UBO constituted second group, and remaining coumarins constituted third group.

Keywords: MEP, PCA, HCA, Coumarins.

INTRODUCTION

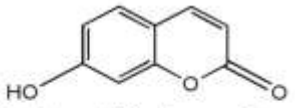
Phytochemicals are natural compounds produced by plants like carotenoids, flavonoids, coumarins and chromones. Coumarin (1, 2-benzopyron or 2H-1 benzopyron-2-one) is close relative of benzopyrene [1] with good pharmacological properties. Coumarins have biological activity with possible antioxidant [2], antimicrobial [3&4], anti-cancer [5&6], anti-inflammatory [7], and anti-coagulant [8] properties using as medicines.

Coumarins have integrated structure with rich electron and load-carrying properties [9&10] created by a benzene ring attached to the pyron ring. In particular oxygen-containing heterocyclic structure[11&12] also plays a important role in medicinal chemistry. These scaffolds molecules and ions have good interactions supported by a broad, electron-rich and load-carrying structure in the coumarin ring. Due to the disease prevention ability, Coumarin compounds as pharmaceutical goods [13,14&15] are making interest to do reaserach in this area of molecules to serve the mankind. Earlier the author studied the various computational studies on coumarins [16&17]

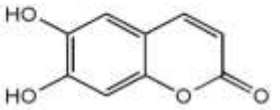
COMPUTATIONAL METHODS AND CHEMOMETRIC METHODS

The Gaussian 09W software package [18] is used for all quantum-chemical calculations. In the gas phase at the DFT level, the molecular geometries of the coumarin molecules studied were optimized entirely using the B3LYP function, a combination of functionally correct hybrid exchange of three parameters (B3) in the Becke gradient [19] with functionally dynamically correlated LYP [20]. The 6-311G basis set included a sufficient number of essential functions that can replicate the experimental observations and describe all atoms. Gauss View 5.0 [21] has been used to show the MEP maps and all the data. Chemometrics is a field that collects tools for complex chemical data from mathematical, statistical, information science [22,23,24&25]. The two multivariate analytical technologies used for analysing data that corresponds to more than one variable are the principal component (PCA) [26,27] and hierarchical cluster (HCA) (27&32). With these techniques how the variable are interrelated and how they can differentiated multiple observational events were studied.

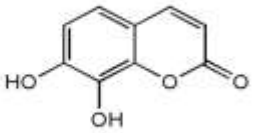
Scheme 1 The structures of simple coumarins



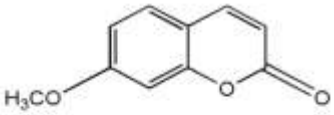
7-hydroxy-2*H*-chromen-2-one
(Umbelliferone=UBO)



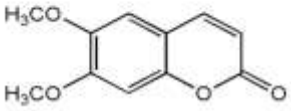
6,7-dihydroxy-2*H*-chromen-2-one
(Aesculetine=ACT)



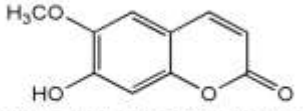
7,8-dihydroxy-2*H*-chromen-2-one
(Daphnetin=DPT)



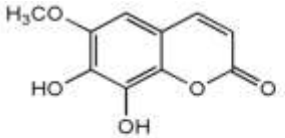
7-methoxy-2*H*-chromen-2-one
(Herniarin=HNR)



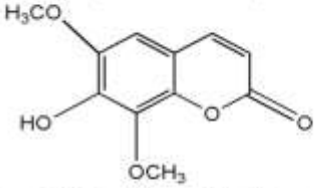
6,7-dimethoxy-2*H*-chromen-2-one
(Scoparone=SCO)



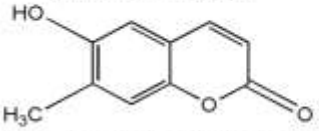
7-hydroxy-6-methoxy-2*H*-chromen-2-one
(Scopoletin=SCT)



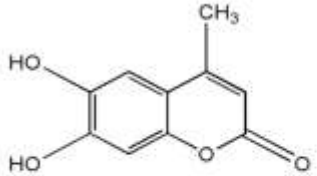
7,8-dihydroxy-6-methoxy-2*H*-chromen-2-one
(Fraxetin=FXT)



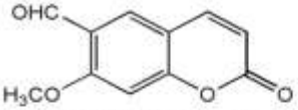
7-hydroxy-6,8-dimethoxy-2*H*-chromen-2-one
(Isofraxidin=IFD)



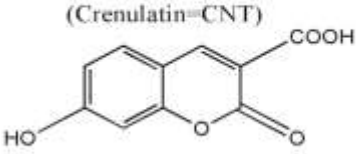
6-hydroxy-7-methyl-2*H*-chromen-2-one
(Isoscopoletin=IST)



6,7-dihydroxy-4-methyl-2*H*-chromen-2-one
(4-Methylesculetin=MST)



7-methoxy-2-oxo-2*H*-chromene-6-carbaldehyde
(Crenulatin=CNT)



7-hydroxy-2-oxo-2*H*-chromene-3-carboxylic acid
(Umbelliferone 3carboxylic acid=UCA)

RESULTS AND DISCUSSION

Geometry optimization was performed using relative steps to determine the true values of global minima present on potential energy surface (PES) with preselected convergence variables. In a constatnt frequency estimation accomplished at same level of theory, lack of an imaginary frequency means the geometry is a genuinely global minimum for PES.

Molecular electrostatic potential maps

The MEP is related to the electronic density on molecule surface [28&29] and is an extremely useful descriptor to determine locations for electrical, nuclear reactors and exchanges with hydrogen [30]. The measured both positive $V_{s,\,max}$, negative $V_{s,\,min}$ and electrostatic maps for the studied coumarins given in Table 1 and figure 1 display 3D representation on gas and solvents.

Analysis of these maps showed red colour reflects a maximum adverse region, which is an electrophilic attack site and the blue colour reflects the maximum positive area that represents the zero-potential area, a desirable nuclear attack site reflected by green colour. [31]The MEP map shown negative areas of −48.82 to −54.86 kcal/mol and positive areas in the range 48.82 to 54.86 kcal/mol values of these compounds. The central adverse values are, oxygen atoms in the carbonyl group in the most active compound UCA (- 54.86 kcal/mole). The $V_{s,\,max}$ is correlated with the most favourable values with covalently bound carbon atom hydrogens

Table 1 The $V_{s,\,max,}$ and $V_{s,\,min}$ (kcal/mol) of molecular surface electrostatic potentials of studied coumarins calculated by DFT/ B3LYP/ 6-311G level of basis set in gas and other solvents.

Molecule	**Gas**		**water**		**benzene**		**THF**		**Octanol**	
	Red	**Blue**	**Red**	**Blue**	**Red**	**Blue**	**Red**	**Blue**	**Red**	**Blue**
UBO	-48.82	48.82	-56.27	56.27	-52.30	52.30	-54.98	54.98	-55.31	55.31
ACT	-48.34	48.34	-58.44	58.44	-52.42	52.42	-56.31	56.31	-56.85	56.85
DPT	-36.09	36.09	-44.76	44.76	-39.94	39.94	-43.12	43.12	-43.53	43.53
HNR	-43.25	43.25	-54.81	54.81	-48.21	48.21	-52.54	52.54	-53.11	53.11
SCO	-42.02	42.02	-51.81	51.81	-46.49	46.49	-49.43	49.43	-50.45	50.45
SCT	-50.60	50.60	-59.75	59.75	-54.56	54.56	-57.91	57.91	-58.34	58.34
FXT	-36.45	36.45	-44.37	44.37	-40.09	40.09	-42.93	42.93	-43.31	43.31
IFD	-37.94	37.94	-47.69	47.69	-41.96	41.96	-45.64	45.64	-46.14	46.14
IST	-48.95	48.95	-59.82	59.82	-53.47	53.47	-57.60	57.60	-58.16	58.16
MST	-48.89	48.89	-58.71	58.71	-52.89	52.89	-56.62	56.62	-57.13	57.13
CNT	-36.79	36.79	-45.31	45.31	-40.56	40.56	-43.72	43.72	-49.71	49.71
UCA	-54.86	54.86	-68.81	68.81	-59.50	59.50	-64.43	64.43	-65.05	65.05

Figure 1 3D-imaging of the electrostatic potential on the molecular surface of 0.001 and in the studied coumarin molecules, computed at the DFT/ B3LYP/ 6-311G level in the phase of gas . In kcal/mole blue colour ranges are more positive and red is more negative.

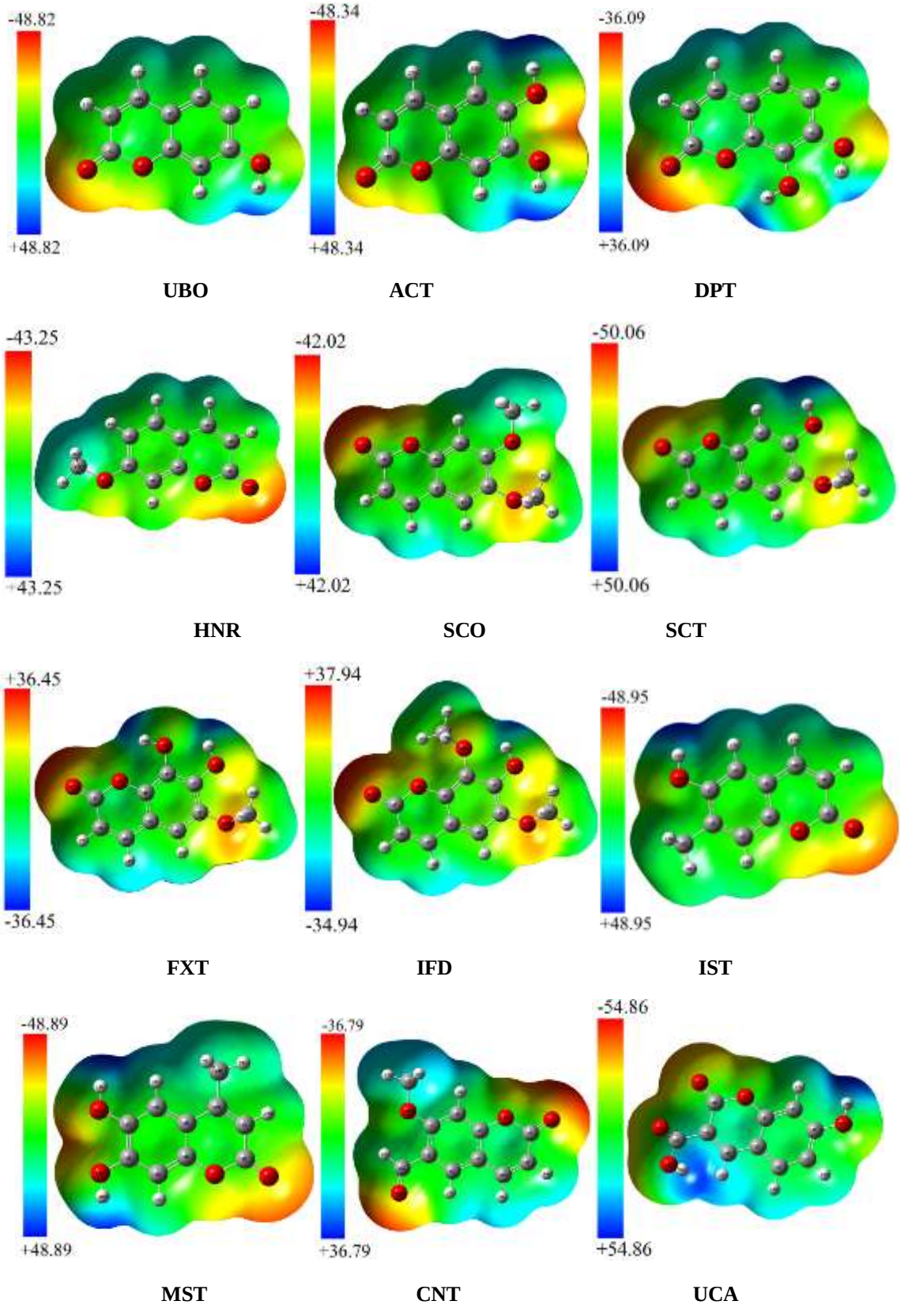


Figure 2 3D-imaging of the electrostatic potential on the molecular surface of 0.001 and in the studied coumarin molecules, calculated in water at the DFT/B3LYP/6-311G level. Colour ranges, in kcal/mole blue is more positive and red is more negative.

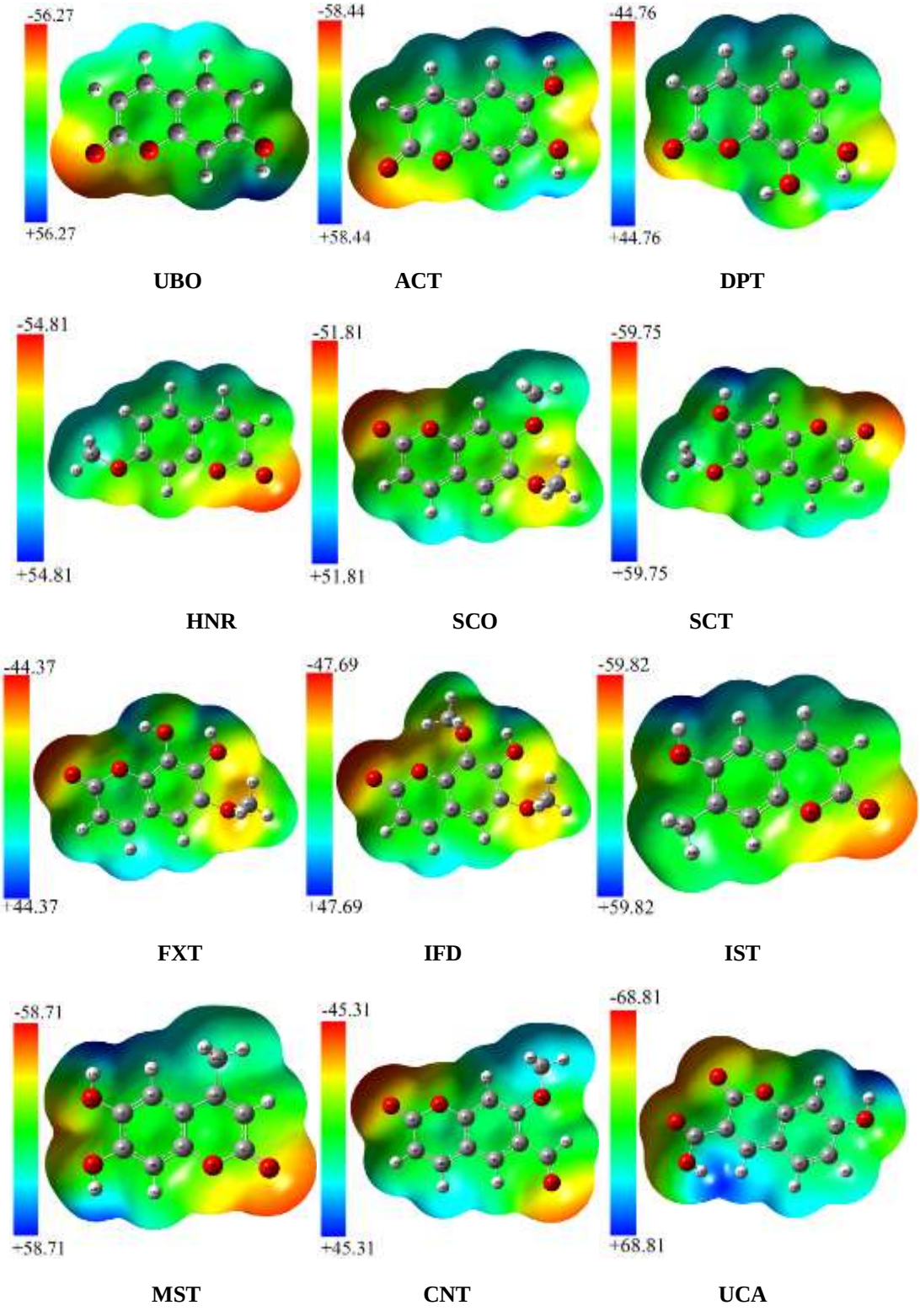


Figure 3 3D-imaging of the electrostatic potential on the molecular surface of 0.001 and in the studied coumarin molecules, calculated values in benzene at the DFT/B3LYP/6-311G level. Colour ranges, in kcal/mole, blue is more positive and red is more negative.

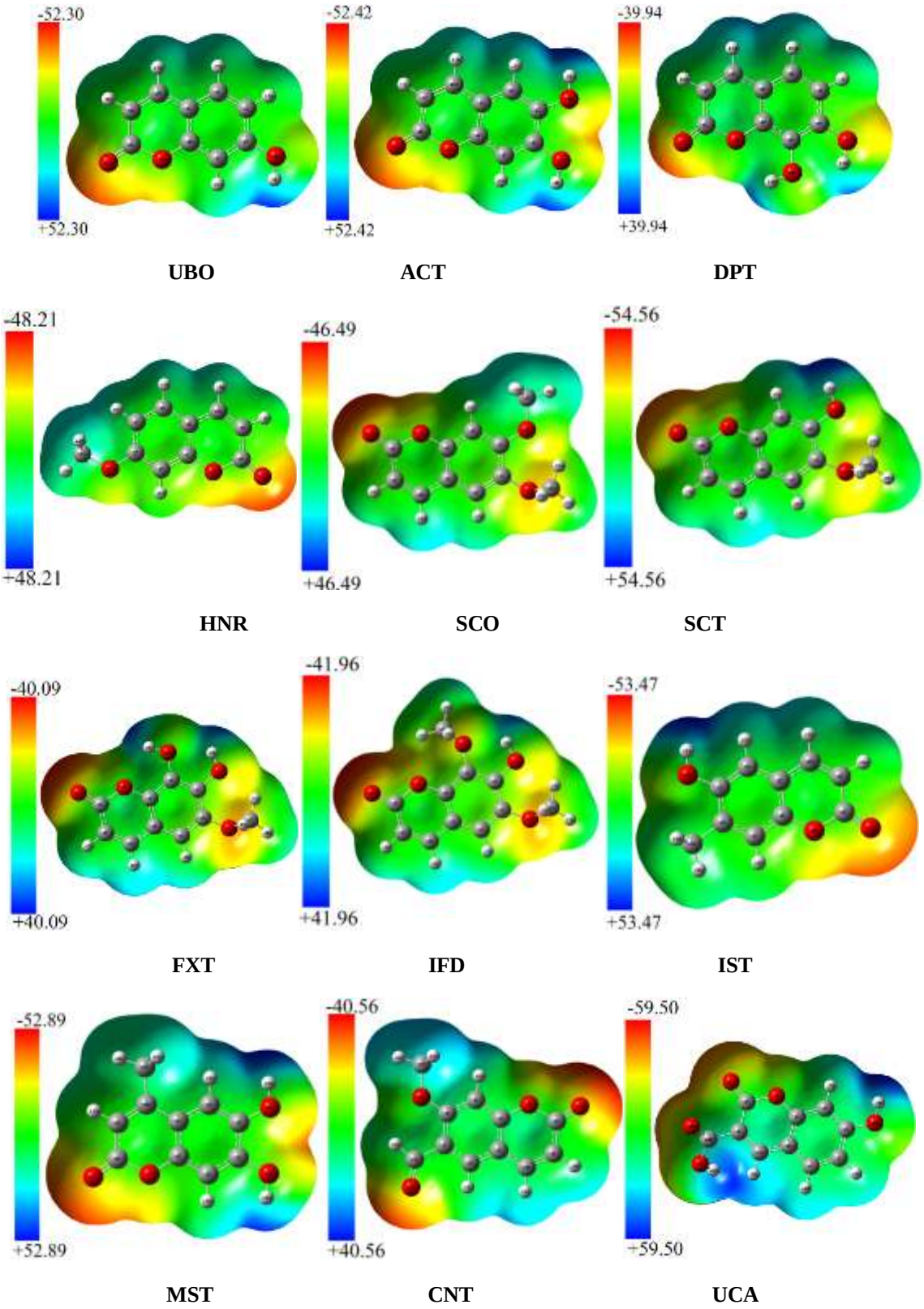


Figure 4 3D-imaging of the electrostatic potential on the molecular surface of 0.001 and in the studied coumarin molecules, calculated in the THF at the DFT/B3LYP/6-311G level. Colour ranges, in kcal/mole, blue is more positive and red is more negative.

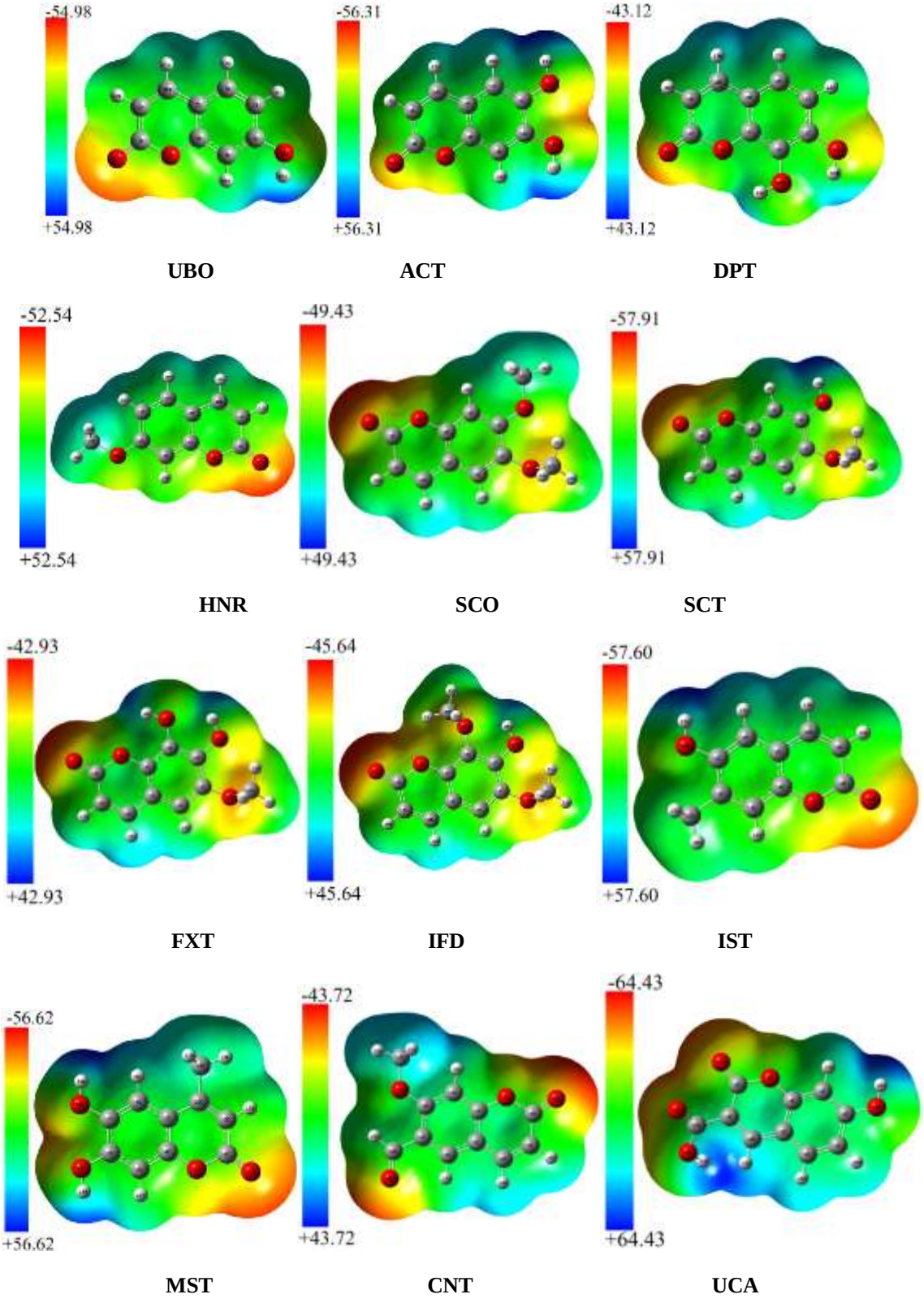


Figure 5 3D-imaging of the electrostatic potential on the molecular surface of 0.001 and in the studied coumarin molecules, calculated in Octanol solvent at the DFT/B3LYP/6-311G level. Colour ranges, in kcal/mole, blue is more positive and red is more negative.

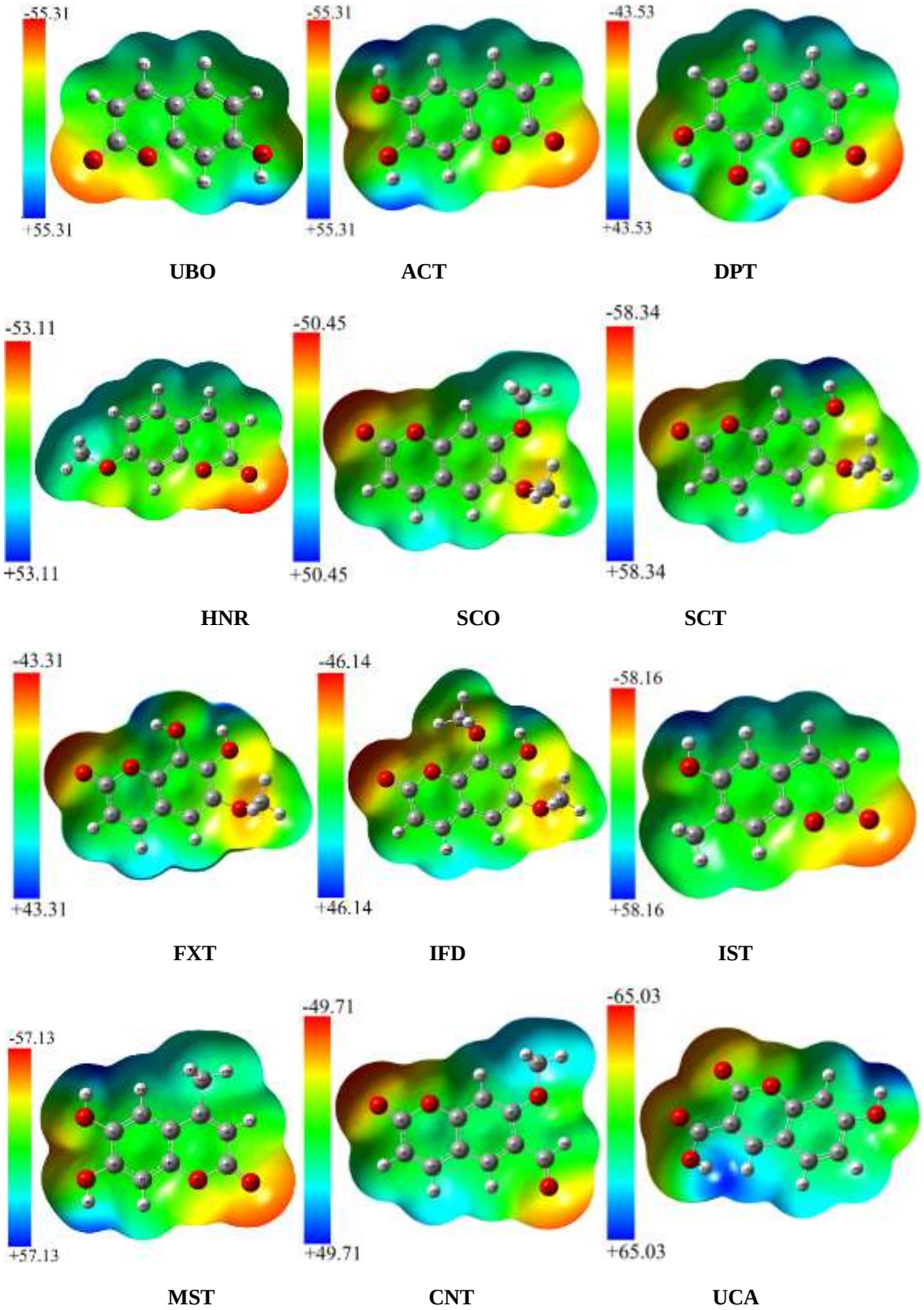
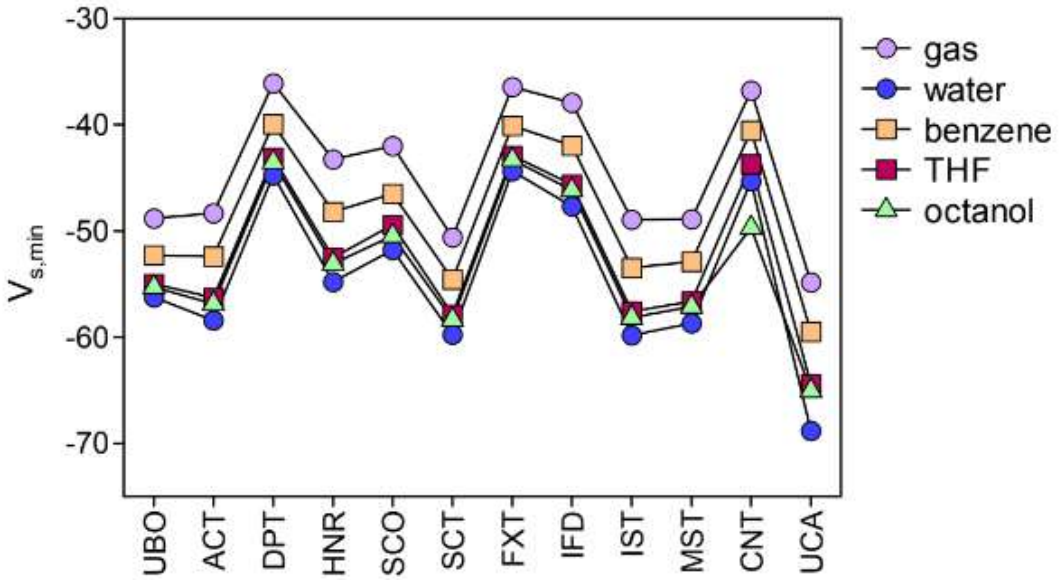


Figure 6 The $V_{s,\ min}$ that has been cited are local minima only on the molecular surface; calculated in the gas phase and different solvents at the DFT/B3LYP with 6-311G level.



$V_{s,\ min}$ values are determined based on Gauss view 5.0 program and referenced in Figure 6 in the gaseous phase and different solvents as local minima only on molecular surfaces. The order of $V_{s,\ min}$ in kcal/mole: UCA < IST ≈ SCT < IST < MST ≈ ACT < UBO < HNR < SCO < IFD < FXT ≈ DPT. Thus, C-H, O-H bonds build positive regions that can be called barriers to electrophilic reaction channels due to variations in atomic electricity. The electrostatic potentials in areas near 'O' atoms are profoundly negative. The aromatic rings also found negative potential values above and below.

Principle component analysis (PCA)

This techniques described the eigenvalues and eigenvectors for two variables having performed data, 12 coumarins, 13 variables PCA results stated in Table 1. Among the 13 variables first two principle components are accounted nearly 98% of complete variance. Fig. 1 shown scatter design of first two of the essential constituents scores and sample patterns. The two coumarins UCA & CNT constituted different unique groups from the remaining coumarins. SCT, HNR & UBO constituted a different group and remaining coumarins are formed in the 3rd group in the gas phase.

Most regularly vectors are score (Figure 1) and loading plots (Figure 12) envisage actual interpretation and variables in novel organised methods. The essential variables are weighed to cover the novel alliance represented by loading values, while their place in a novel coordinate system explained by sample scores. These designs are interactive and thus interpreted.

Table 2 Results of principal components analysis on the global descriptors data

Eigenvalues													
Gas-phase													
	PC 1	**PC 2**	**PC 3**	**PC 4**	**PC 5**	**PC 6**	**PC 7**	**PC 8**	**PC 9**	**PC 10**	**PC 11**	**PC 12**	**PC 13**
Variance	9.5408	3.4553	0.0036	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0000	-0.0000

% Variance	73.4	26.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cumulative	73.4	100	100	100	100	100	100	100	100	100	100	100	100
Water													
	PC 1	**PC 2**	**PC 3**	**PC 4**	**PC 5**	**PC 6**	**PC 7**	**PC 8**	**PC 9**	**PC 10**	**PC 11**	**PC 12**	**PC 13**
Variance	10.160	2.837	0.0175	0.0003	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0000
% Variance	78.2	21.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cumulative	78.2	100	100	100	100	100	100	100	100	100	100	100	100
Benzene													
	PC 1	**PC 2**	**PC 3**	**PC 4**	**PC 5**	**PC 6**	**PC 7**	**PC 8**	**PC 9**	**PC 10**	**PC 11**	**PC 12**	**PC 13**
Variance	9.557	3.4398	0.0042	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
% Variance	73.5	26.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cumulative	73.5	100	100	100	100	100	100	100	100	100	100	100	100
THF													
	PC 1	**PC 2**	**PC 3**	**PC 4**	**PC 5**	**PC 6**	**PC 7**	**PC 8**	**PC 9**	**PC 10**	**PC 11**	**PC 12**	**PC 13**
Variance	9.6845	3.3122	0.0030	0.0003	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
% Variance	74.5	25.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cumulative	74.5	100	100	100	100	100	100	100	100	100	100	100	100
Octanol													
	PC 1	**PC 2**	**PC 3**	**PC 4**	**PC 5**	**PC 6**	**PC 7**	**PC 8**	**PC 9**	**PC 10**	**PC 11**	**PC 12**	**PC 13**
Variance	9.7047	3.2920	0.0030	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0000	-0.0000	-0.0000
% Variance	74.7	25.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.0	-0.0	-0.0
Cumulative	74.7	100	100	100	100	100	100	100	100	100	100	100	100

The coumarins constituted groups are different in different solvents, namely water, benzene, THF and octanol. In two solvents THF and octanol, are similar trend followed compression of other solvents. In all solvents, CNT and UCA are constituted different groups and well distinguished from the rest. In water, four coumarins, UBO, HNR, SCT and IFD, included one group, but DPT, SCO, IST, MST and ACT constituted another different group and also in benzene, three coumarins, UBO, MST and HNR, constituted one group, but DPT, SCO, SCT, IST, MST, IFD and ACT constituted another different group.

Figure 7 The global descriptors Score plots for the studied coumarins in the gas phase at DFT/B3LYP/6-311G level of theory.

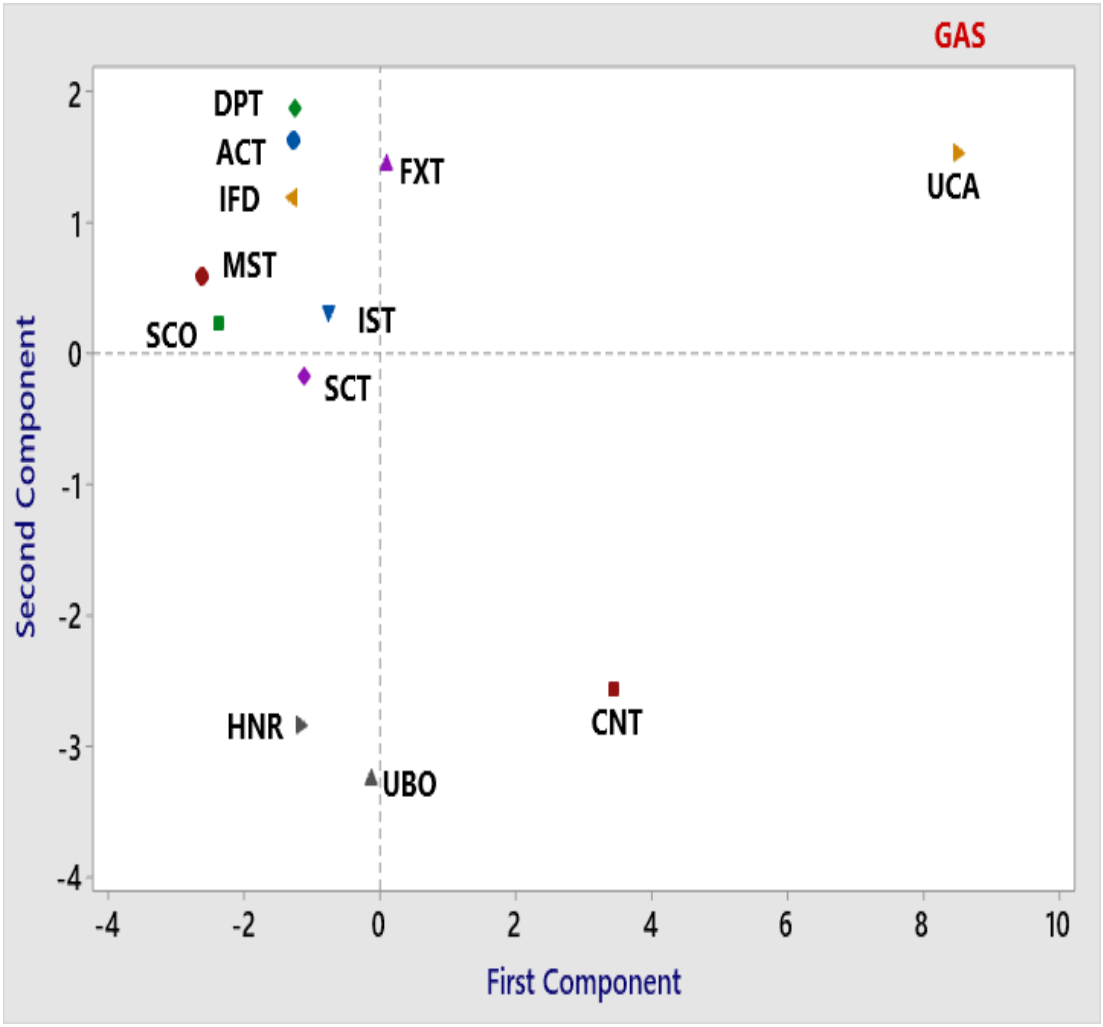


Figure 8 The global descriptors Score plots for the studied coumarins in water at DFT/B3LYP/6-311G level of theory.

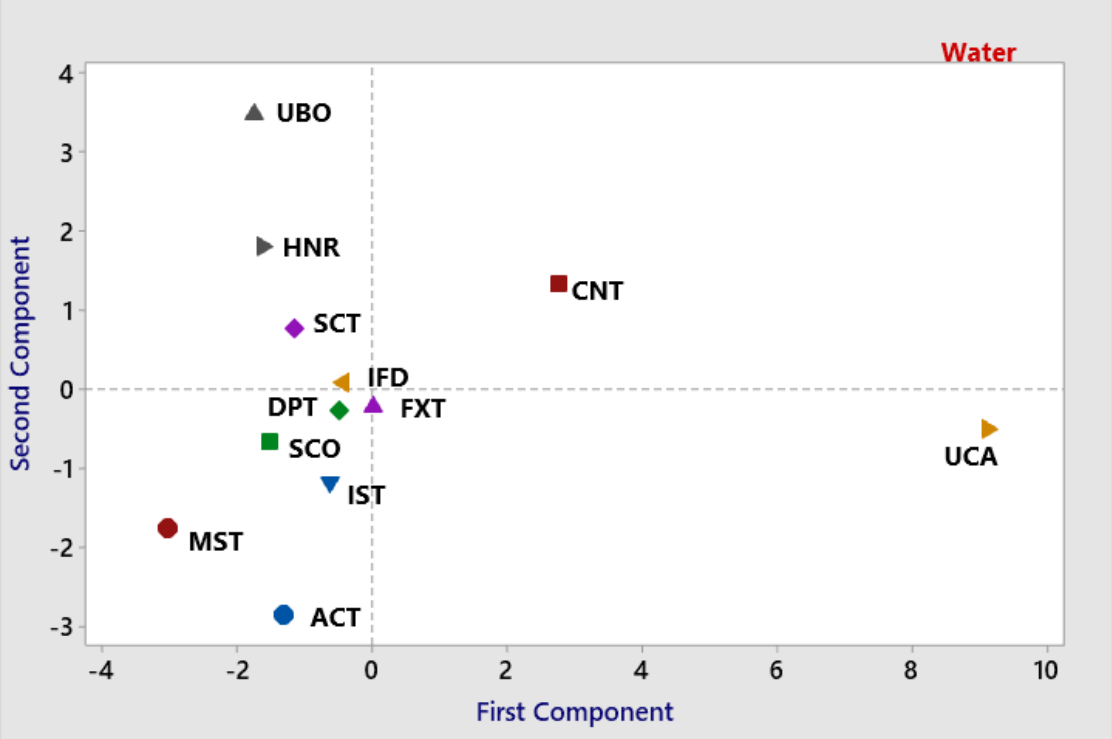


Figure 9 The global descriptors Score plots for the studied coumarins in benzene at DFT/B3LYP/6-311G level of theory.

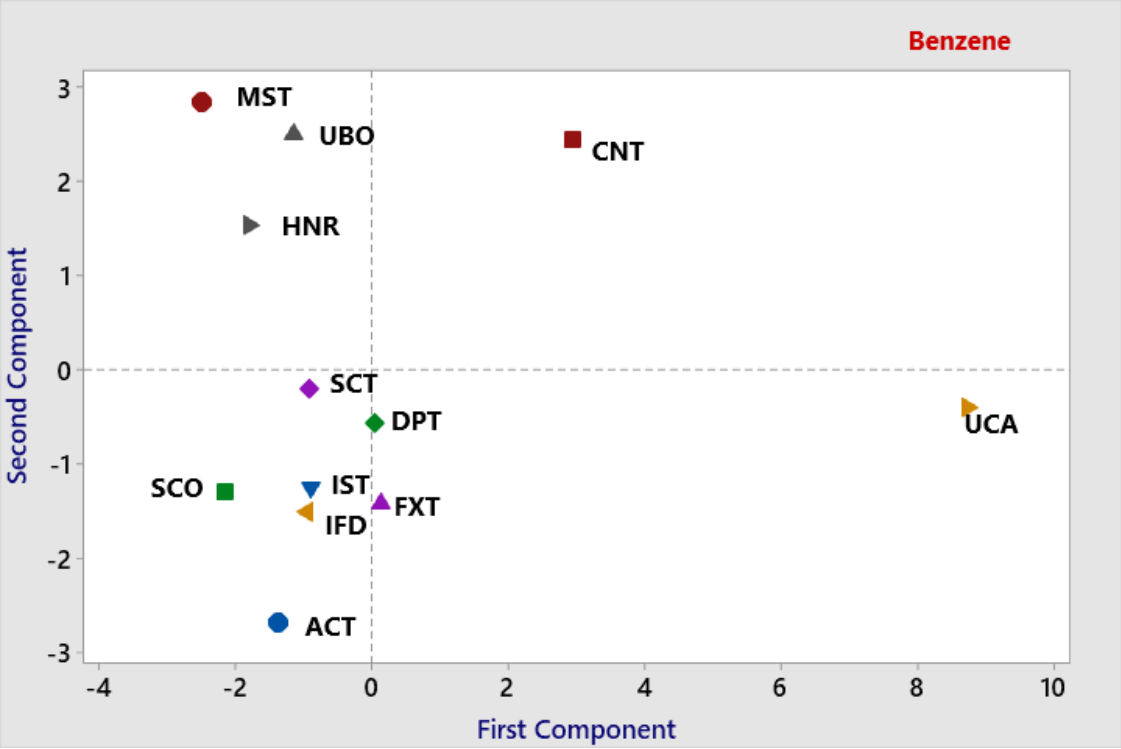


Figure 10 The global descriptors Score plots for the studied coumarins in THF at DFT/B3LYP/6-311G level of theory.

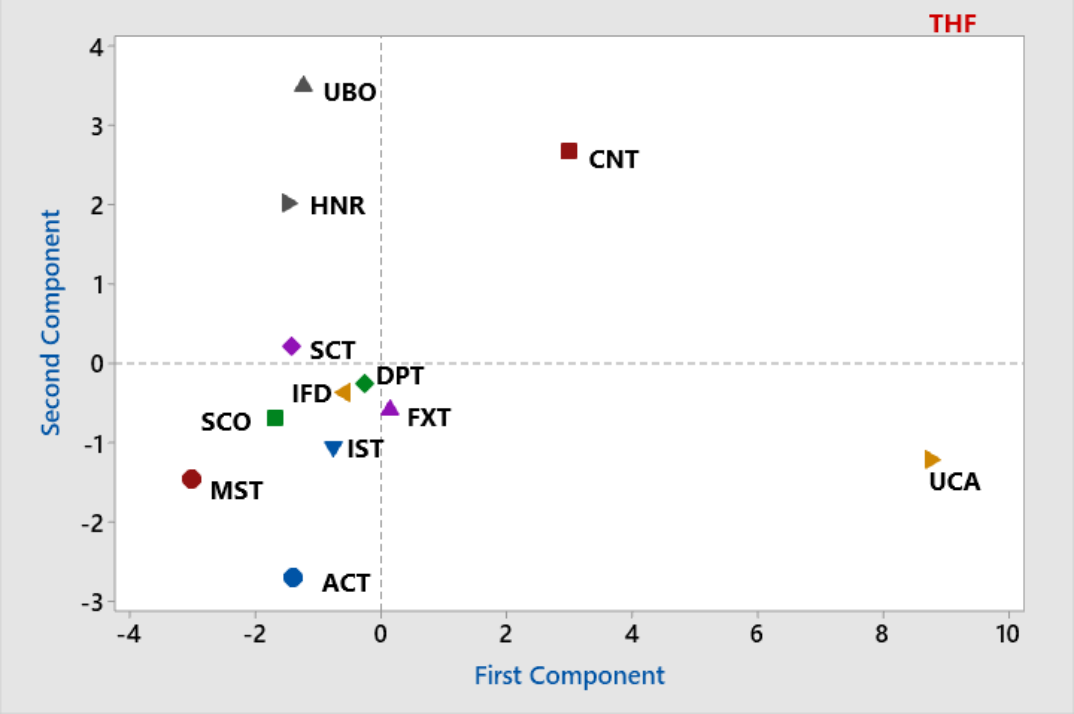


Figure 11 The global descriptors Score plots for the studied coumarins in octanol at DFT/B3LYP/6-311G level of theory.

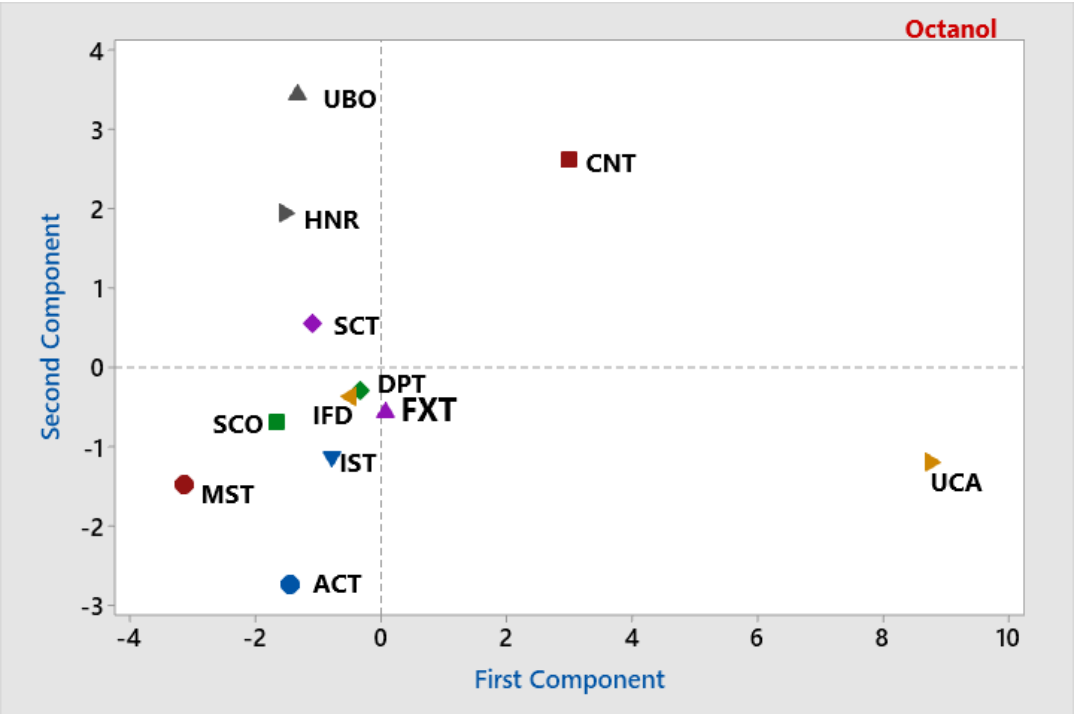


Figure 12 The global descriptors loading plots of studied coumarins in the gas phase at DFT/B3LYP/6-311G level of theory.

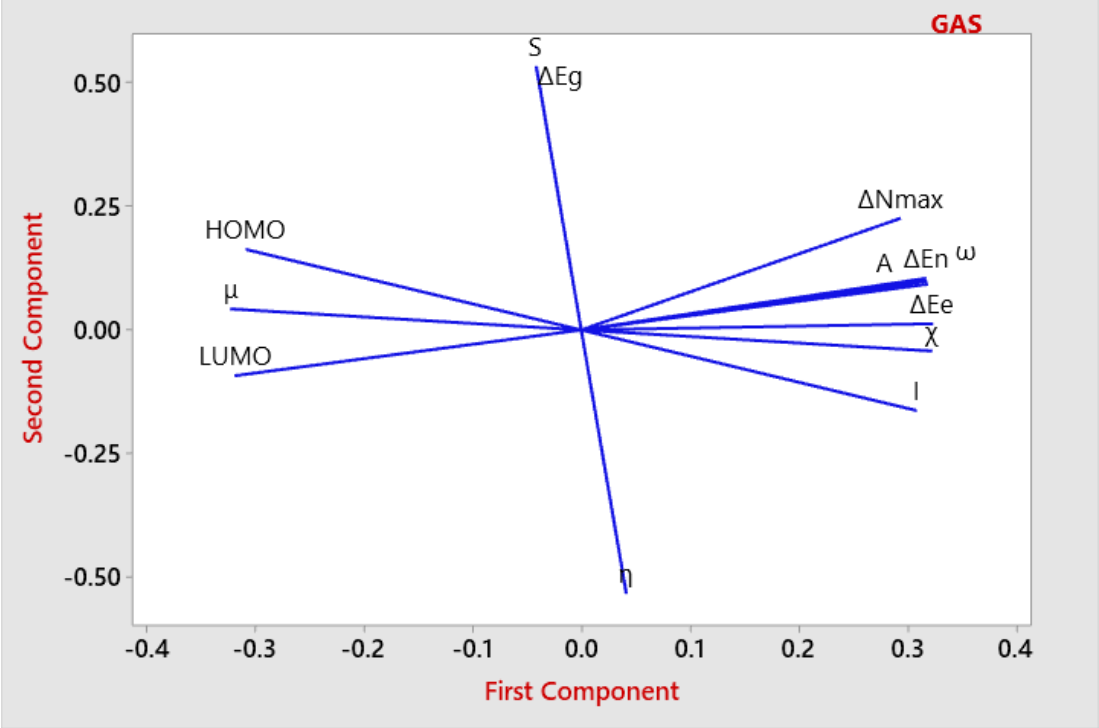


Figure 13 The global descriptors loading plots of studied coumarins in water at DFT/B3LYP/6-311G level of theory.

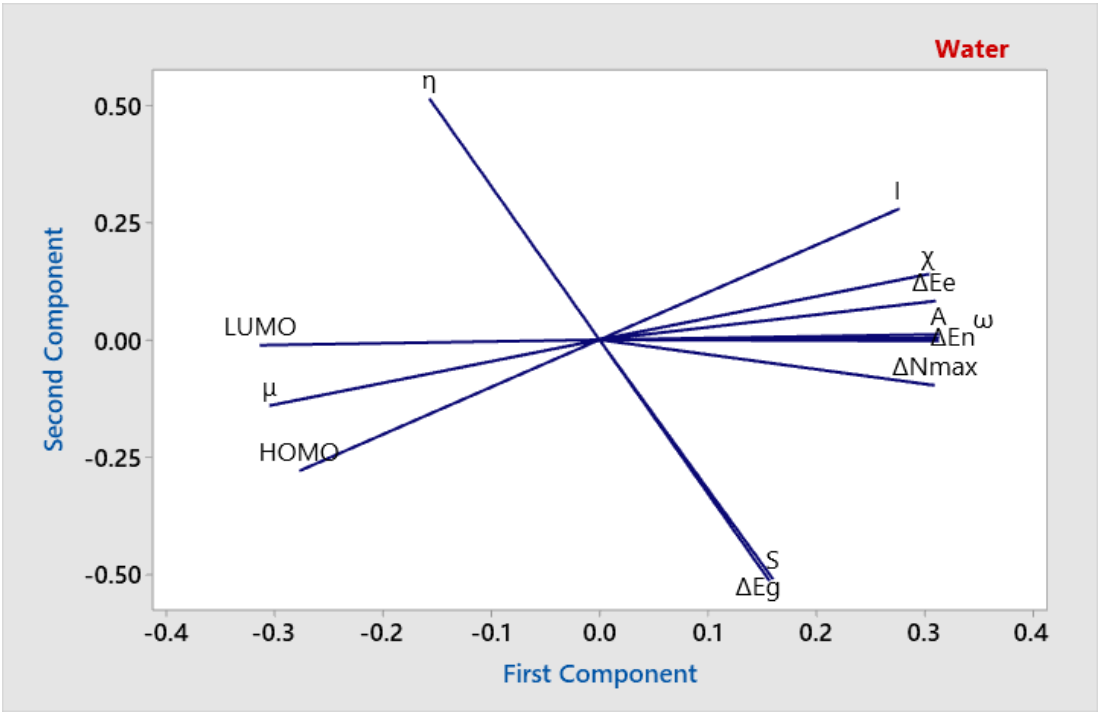


Figure 14 The global descriptors loading plots of studied coumarins in benzene at DFT/B3LYP/6-311G level of theory.

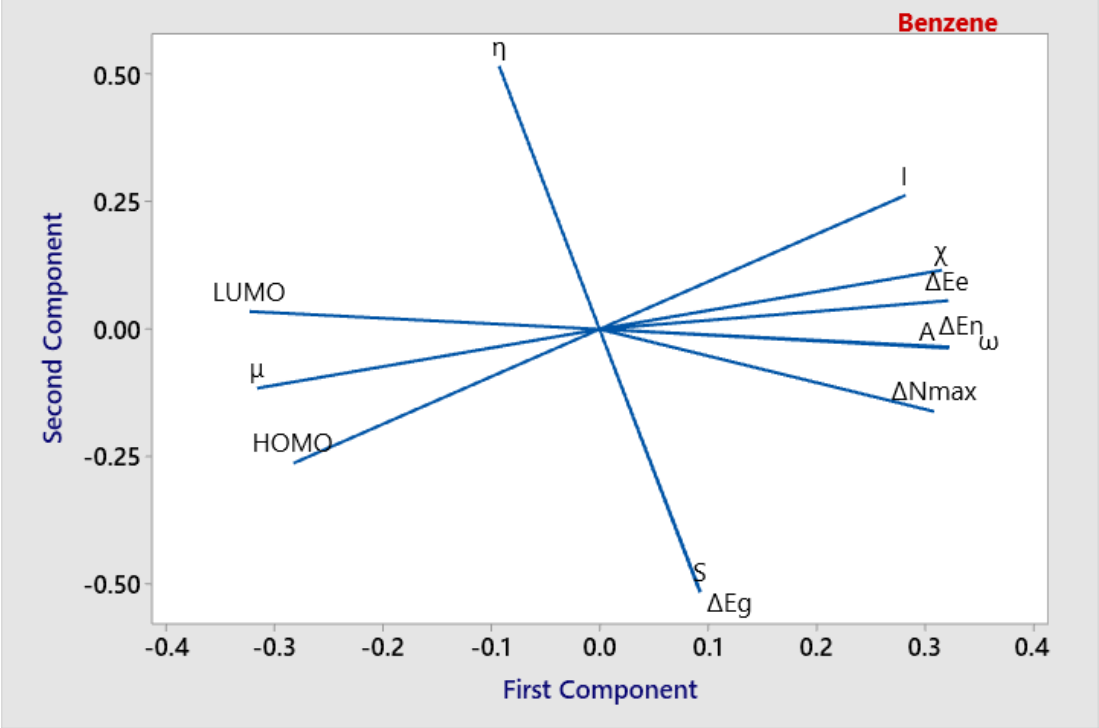


Figure 15 The global descriptors loading plots of studied coumarins in THF at DFT/B3LYP/6-311G level of theory.

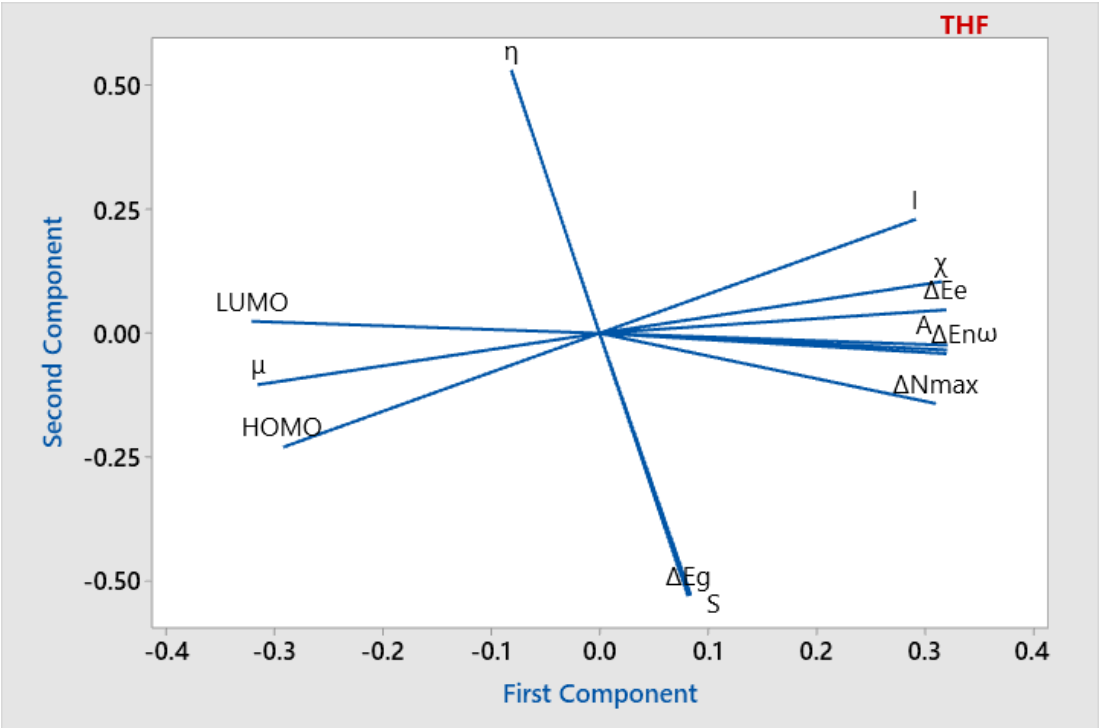
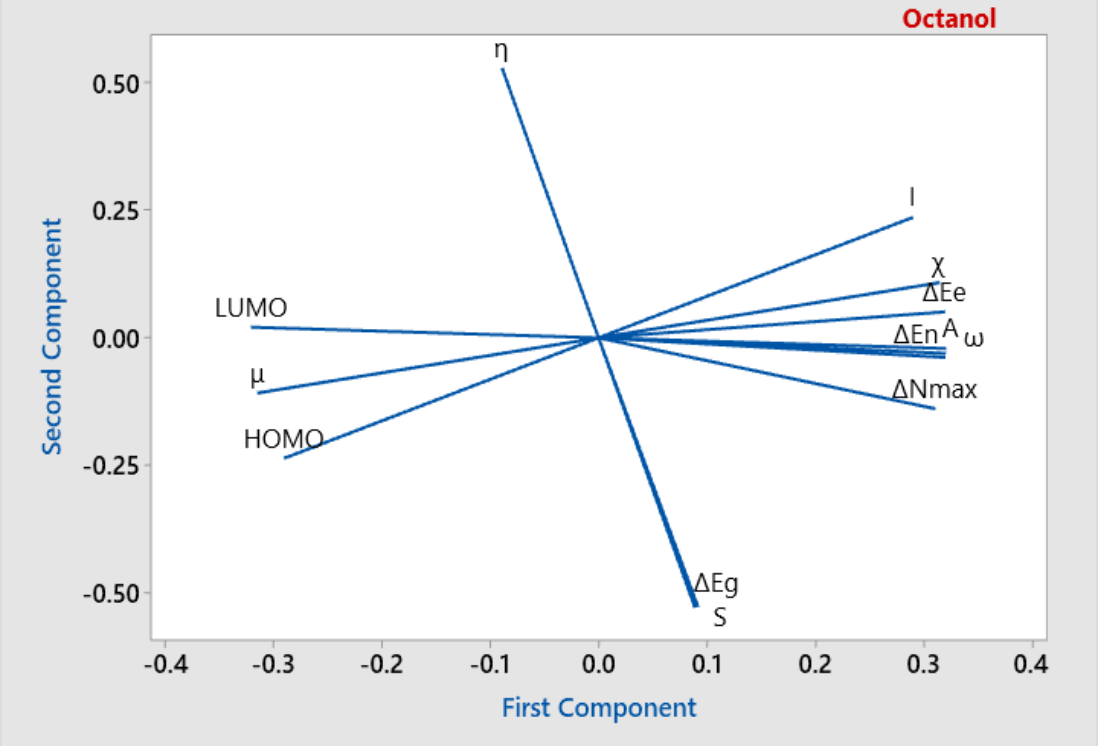


Figure 16 The global descriptors loading plots of studied coumarins in octanol at DFT/B3LYP/6-311G level of theory.



HIERARCHICAL CLUSTER ANALYSIS (HCA)

HCA along with the PCA is an important technique to recognise patterns [30] It gives dendrogram in the result. In dendrogram the difference between variables calculates and computes with similarity index. The range starts with zero. In Figure 17 complete dendrogram shown for the values in the table 1. The dendrogram was computed using the HCA in various solvents. In graph, method represented by the horizontal line and resemblance values among the processes pairs, process and processes set, amongst the group of procedures are represented by the vertical line. Conclusion drawn from the Figure 17 is PCA results and HCA results are similar.

Figure 17 The global descriptors Dendrogram obtained for studied coumarins in the gas phase.

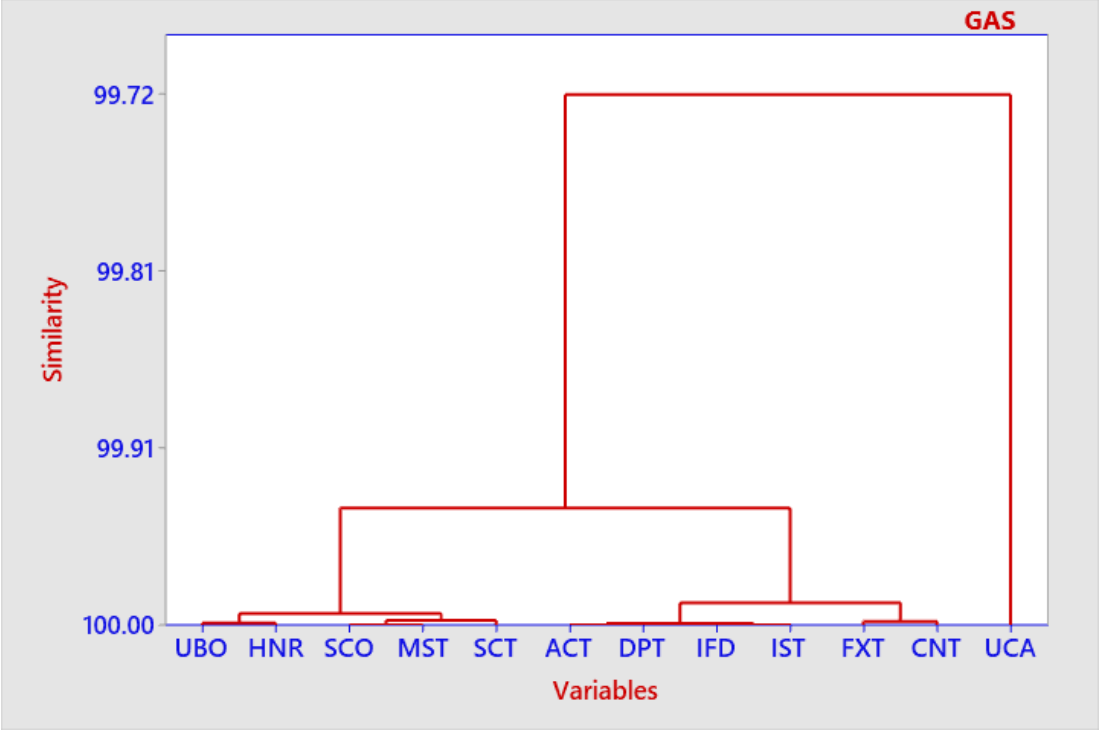


Figure 18 The global descriptors Dendrogram obtained for studied coumarins in water.

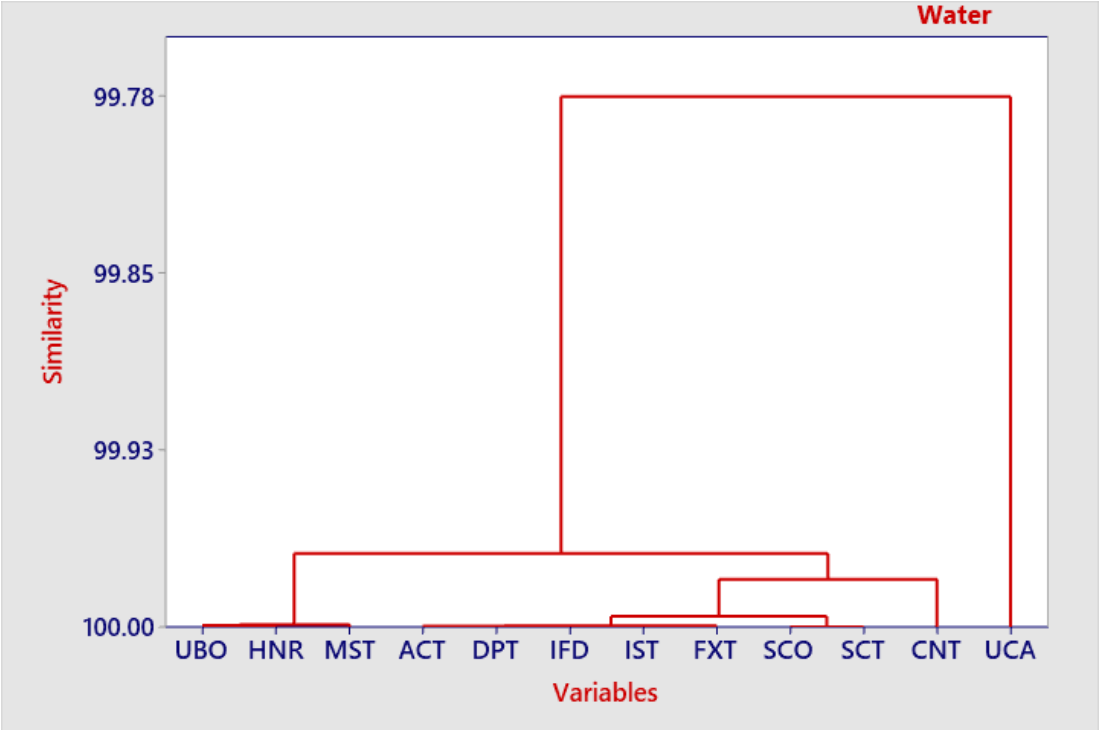


Figure 19 The global descriptors Dendrogram obtained for studied coumarins in benzene.

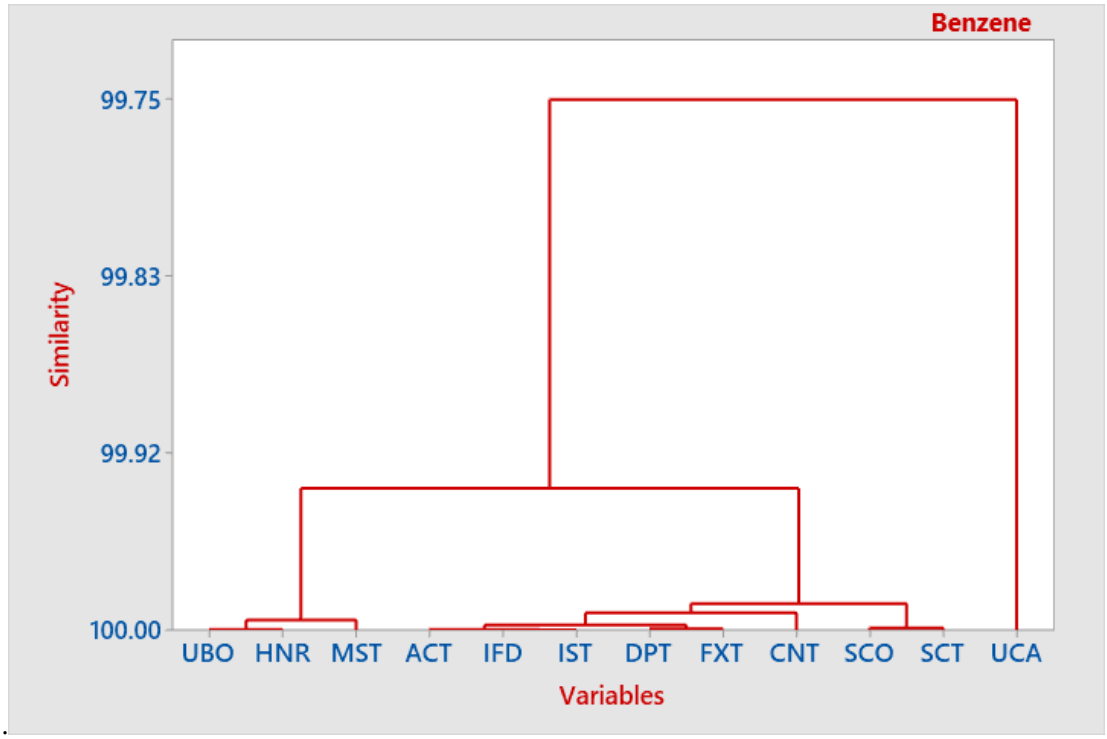


Figure 20 The global descriptors Dendrogram obtained for studied coumarins in THF.

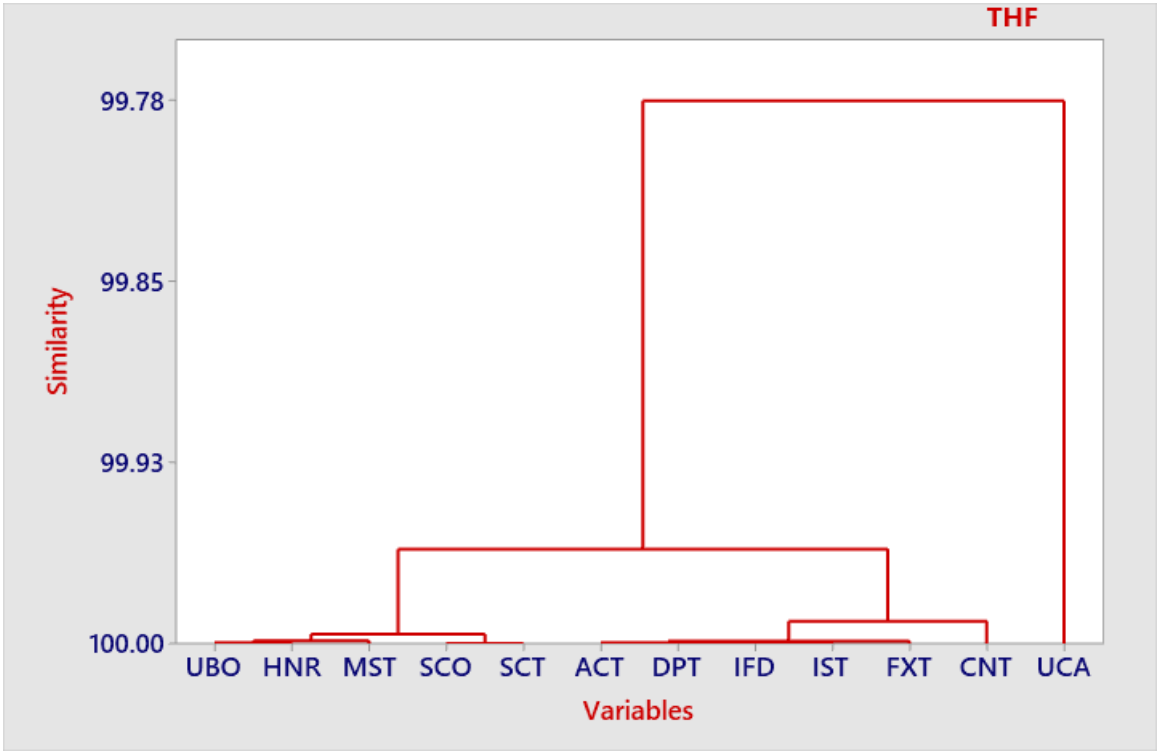
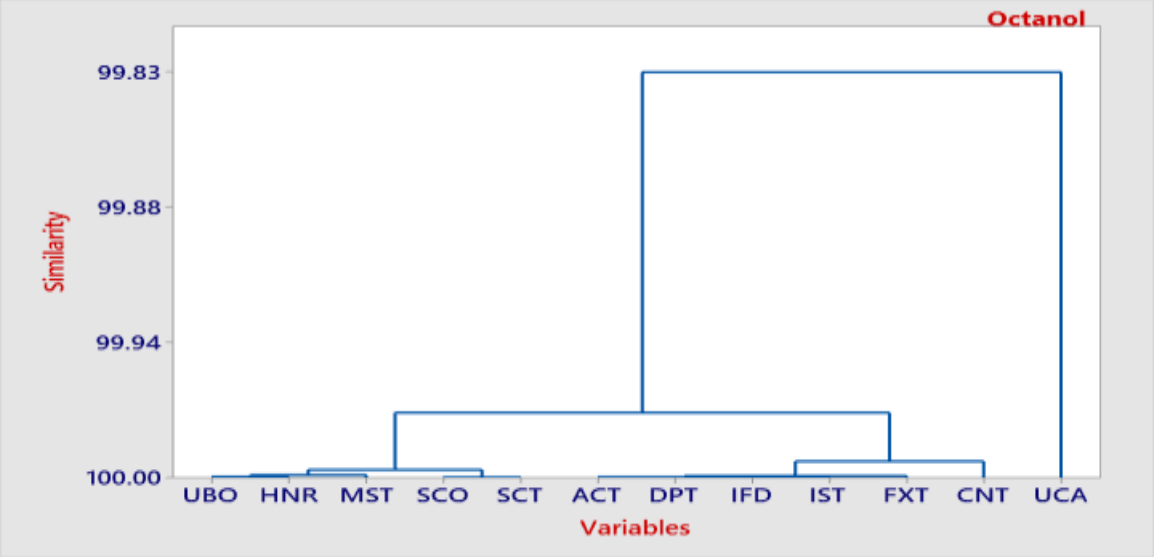


Figure21 The global descriptors Dendrogram obtained for studied coumarins in octanol.



CONCLUSIONS

MEP maps for 12 coumarins were constructed using the B3LYP functional DFT method on a 6-311G basis in various media. The primary structural characteristics of compounds contain unsaturation and present a greater electron density in the 'O' atom next to the carbonyl group in the ring. The MEP map shown negative areas of −48.82 to −54.86 kcal/mol and positive regions in the range of 48.82 to 54.86 kcal/mol of these compounds. The central adverse values are oxygen atoms in the carbonyl group in the most active compound UCA (- 54.86 kcal/mole). The electronic density increases with the increase of the regions with compounds with a double carbonyl group.

Principle component analysis (PCA) and hierarchical cluster analysis (HCA) in several solvents were used to evaluate coumarin global and reactivity descriptors. The coumarins forming groups vary in the gas phase, water, benzene, THF and octanol in various solvents. Similar trends followed by compression of other solvents occur in two solvents (THF and octanol). The results of HCA are highly linked to the results of the PCA.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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