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Monomethoxy Isomers of Psoralen - DFT Treatment

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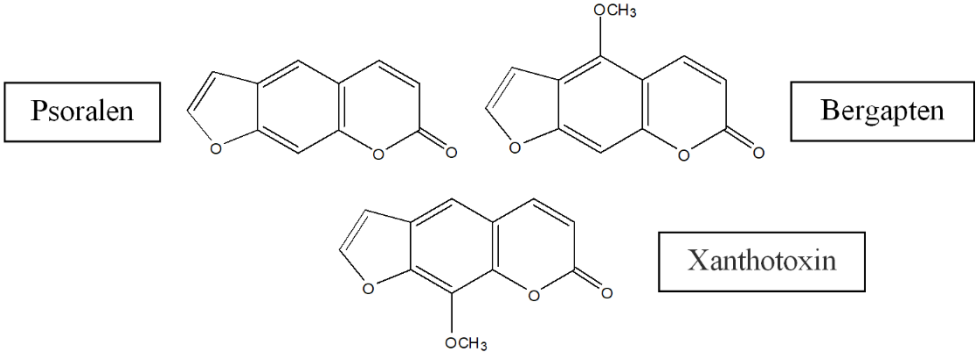
Abstract

The present study considers psoralen isomers having a methoxy substituent at different positions of the psoralen backbone. Density functional approach has been adopted at the level of B3LYP/6-311++G(d,p) to obtain various geometrical, physicochemical, spectral and quantum chemical properties of the isomers of concern including bergapten and xanthotoxin. Also local aromaticities of the benzenoid and furanoid rings have been obtained by calculating the nucleolus independent chemical shift values.

1. Introduction

Psoralen (also called psoralene) is the parent compound in a family of naturally occurring organic compounds known as the linear furanocoumarins [1]. It is structurally



related to coumarin by the addition of a fused furan ring, and may be considered as a derivative of umbelliferone [1,2]. The psoralens are secondary metabolites in plants, including many fruits and vegetables. An important member of the furanocoumarin

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family is bergapten (5-methoxypsoralen,5-mop) which is a naturally-occurring organic chemical compound produced by numerous plant species, especially from the carrot family *Apiaceae* and the citrus family *Rutaceae*. It was the first furanocoumarin isolated and identified.

Psoralen naturally occurs in the seeds of *Psoralea corylifolia*, as well as in the common fig, celery, parsley, West Indian satinwood, and in all citrus fruits. Furanocoumarins derived from citrus and herbal extracts were reported acting as antibacterial, antioxidant, immunomodulator, apoptotic, and selective anticancer agents, prompting a biological investigation to determine and predict their clinical therapeutic significance [1-15]. Psoralen is widely used in PUVA (psoralen+ UVA) treatment for psoriasis, eczema, vitiligo, and cutaneous T-cell lymphoma. All these therapeutic applications are typically through the use of medications such as methoxsalen. Synthetic forms of xanthotoxin and 5-methoxypsoralen (bergapten) are widely used as drugs in skin photochemotherapy, for example, with long wave ultraviolet (UV) light in the treatment of psoriasis, vitiligo, and mycosis fungoides. On the other hand, the development of nonmelanocytic skin cancer (basal- and squamous-cell skin cancers) has been reported in patients treated with 8-methoxypsoralen and long-wave ultraviolet light (UVA) (PUVA) for psoriasis or mycosis fungoides. Many furanocoumarins are found to be extremely toxic to fish. Bergapten and other linear furanocoumarins induce a loss of template activity for RNA synthesis. 5-Methoxypsoralen has also been noted for its mutagenic effects as well as its capacity for being a very potent agent for inducing chromosome aberrations. With a high enough concentration, complete mitotic inhibition was observed [16].

In the literature, also various quantum chemical research exist on psoralen and analogous compounds, beside some biological and medical investigations mentioned above [10,12,15,17,18]. In the present density functional study, monomethoxy isomers of psoralen including (bergapten and xanthotoxin) have been investigated in the realm of density functional theory.

2. Method of Calculations

All the structures presently considered have been subjected to the geometry optimizations leading to energy minima. The optimizations have been achieved first by using MM2 method which is followed by semi-empirical PM3 self consistent fields molecular orbital (SCF MO) method [19,20] at the restricted level [21,22]. Subsequent

optimizations were performed at Hartree-Fock level employing various basis sets. Afterwards, geometry optimizations were managed within the framework of density functional theory [23,24] at the level of B3LYP/6-311++G(d,p) [21,25]. Note that the exchange term of B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange [24,26]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [27] and Lee, Yang, Parr (LYP) correlation correction functional [28]. Also, vibrational analyses have been done on the optimized structures. The total electronic energies are corrected for the zero point vibrational energy (ZPE). Moreover, the normal mode analysis for each structure yielded no imaginary frequencies for the $3N–6$ vibrational degrees of freedom, where N stands for the number of atoms in the system. This has indicated that the structure of each molecule corresponds to at least a local minimum on the potential energy surface. All these calculations have been done by using the Spartan 06 package program [29]. Whereas the NICS(0) calculations were performed by using Gaussian 03 program [30].

3. Results and Discussion

Furanocoumarins are therapeutically important molecules which have various clinical applications. The most outstanding property of furanocoumarins is their great ability to sensitize cells to visible light, sunlight, and, especially, near-ultraviolet light. Therefore, this results in strong toxicity, mutagenicity, and possibly carcinogenicity. The mechanism of action is well known. After intercalation into the double helix of the DNA and molecular complexing, the light-activated furanocoumarins react with the pyrimidine bases, especially with thymine [31]. Since furanocoumarins are strong phototoxic compounds, their presence in a plant has been demonstrated to be a protective mechanism against phytopathogenic microorganisms and herbivores.

Figure 1 shows the optimized structures as well as the direction of the dipole moment vectors of the isomeric molecules (methoxy psoralens) considered. Note that structures C and F stand for bergapten and xanthotoxin, respectively which are therapeutically important molecules. As seen in the figures, in all the cases the dipole moment vectors are directed to the lactone moiety and originating from somewhere around the benzenoid ring of the structures.

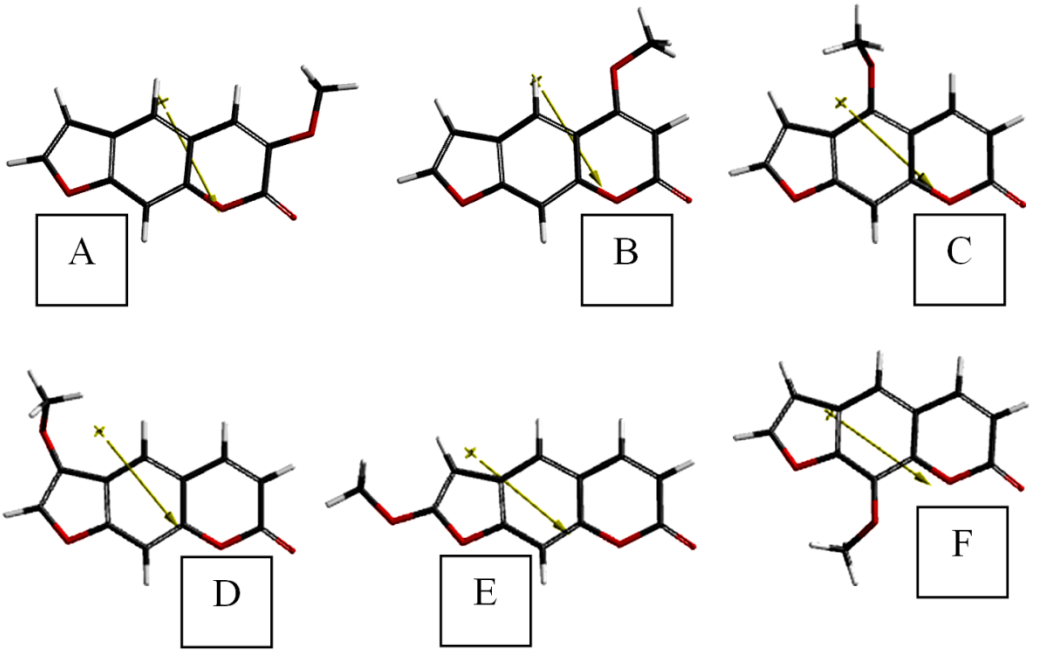


Figure 1. Optimized structures of the molecules considered.

Figure 2 shows the electrostatic potential (ESP) charges on the atoms of the isomers considered. It is worth noting that the ESP charges are obtained by the program based on a numerical method that generates charges that reproduce the electrostatic potential field from the entire wavefunction [29].

Negative partial charge residing on the methoxy oxygen atom follows the algebraic order of D<A<E<B<C<F. This order reflects the flow of electron population from the methoxy group to the rest of the molecule. It is worth mentioning that mesomeric and inductive effects of oxygen atom is opposing to each other. Also note that the heteroatoms in the rings have different extent of opposing and assisting effects on to the net electron flow effect from the methoxy group. On the other hand, the lactone carbonyl moiety embedded in to the psoralen backbone attracts electrons mesomerically. So, the whole system in each isomer is under the influence of electron donor and attractor groups/atoms that the effect is mainly dictated by the topology of the conjugated skeleton. Note that in some of the isomers considered, the methoxy group and the lactone carbonyl are crossly conjugated with each other so that there is no conjugative interaction between them.

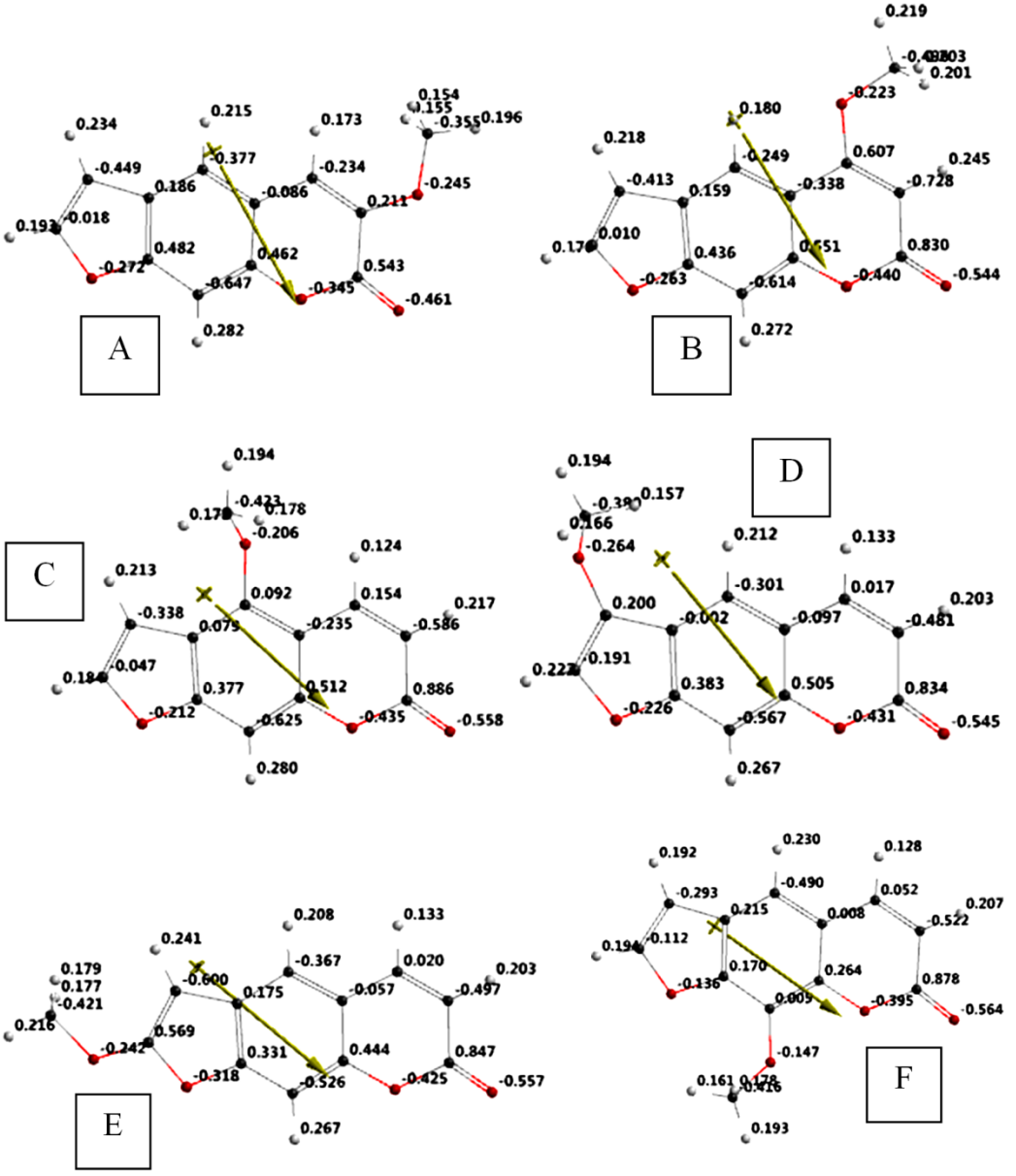


Figure 2. The ESP charges on the atoms of the isomers considered.

Figure 3 displays the electrostatic potential maps of the isomers considered. In all the isomers considered, as seen in Figure 3, the most negative potential region coincides with the oxygen atom of lactone moiety of the structures. The negative potential region in the isomers spreads over the adjacent sides depending on the position of the methoxy

substituent. The methoxy substituent perturbs the electrostatic potential of the parent structure, psoralen, mainly by mesomeric effect it exerts and partly by inductive and field effects. Note that the oxygen atom of the substituent possesses opposing mesomeric and inductive effects like the other oxygen atoms present.

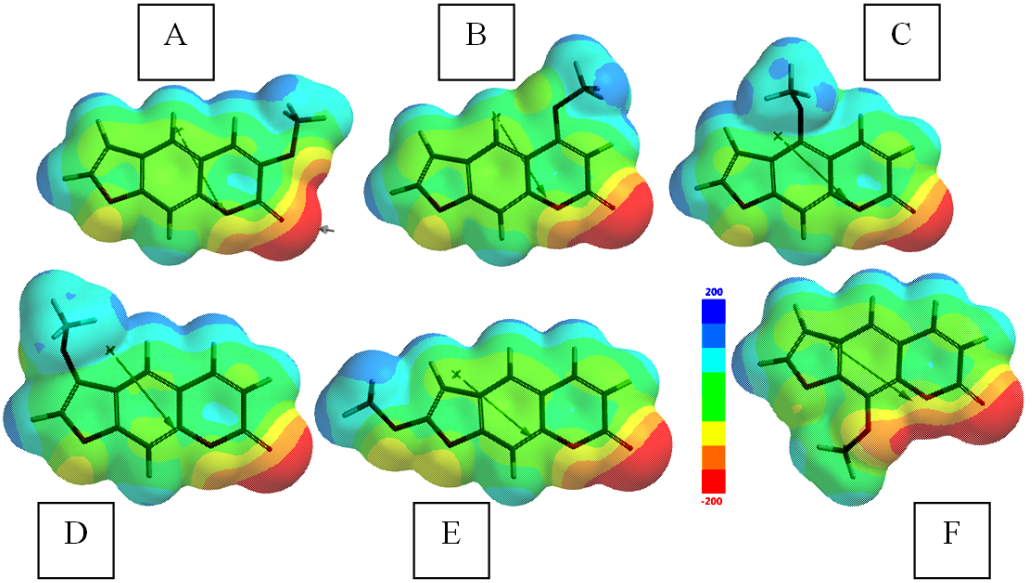


Figure 3. The electrostatic potential maps of the isomers considered.

Table 1 lists some properties of the isomers considered. The order of dipole moment values follows the sequence of E>C>F>A>B>D. In the structures considered, the lactone moiety acts as an electron attracting whereas the methoxy group acts as the electron donating one. Consequently, depending on the position of the substituent, variations result in the magnitude of the dipole moments in the series. On the other hand, the polarizability is defined according to the formula [29].

$$\text{Polarizability} = 0.08*V - 13.0353*h + 0.979920*h^2 + 41.3791$$

where V and h are the Van der Waals volume and hardness, respectively. Hardness is defined as,

$$\text{Hardness} = -(\varepsilon_{HOMO} - \varepsilon_{LUMO})/2$$

Partition coefficients are important property and useful in estimating the distribution of drugs within the body. Hydrophobic drugs with high octanol-water partition coefficients are mainly distributed to hydrophobic areas such as lipid bilayers of

cells. Conversely, hydrophilic drugs (low octanol/water partition coefficients) are found primarily in aqueous regions such as blood serum. Note that the log P value of isomer-E is very different from the others.

Table 1. Some properties of the isomers considered.

	A	B	C	D	E	F
Dipole moment	6.49	6.30	6.92	6.06	8.25	6.63
Polarizability	57.00	56.95	57.04	57.08	57.08	57.07
Log P	-1.65	-1.65	-1.65	-1.65	-0.49	-1.65

Dipole moments and polarizabilities are in debye and 10^{-30} m^3 units, respectively.

Table 2 lists the aqueous energies of the isomers considered. The order is B<E<A<C<D<F. So, isomer-B should be aquated more favorably. It should be noted that the "energy aqueous (E_{aq})" is the sum of the base energy and the energy of solvation. The program calculates the solvation energy using SM54A method (Ghose-Crippen method) [29,32].

Table 2. Aqueous energies of the isomers considered.

Structures	**E_{aq}**
A	-2003728.55
B	-2003761.68
C	-2003728.38
D	-2003719.23
E	-2003754.10
F	-2003716.84

Energies in kJ/mol.

Table 3 lists some energies of the isomers considered where E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. According to the data presented in the table, the electronic stability order of the isomers is B>E>A>C>D>F. Namely, isomers B and F, respectively stand for

the most and least stable ones. Note that isomers C and F are known as bergapten and xanthotoxin, respectively.

Table 3. Some energies of the isomers considered.

Structures	E	ZPE	E_C
A	-2003704.37	460.66	-2003243.71
B	-2003734.86	461.60	-2003273.26
C	-2003701.16	459.19	-2003241.97
D	-2003689.00	459.62	-2003229.38
E	-2003724.46	460.57	-2003263.89
F	-2003684.90	459.94	-2003224.96

Energies in kJ/mol.

Table 4 lists some thermodynamic properties of the isomers considered. As the data indicate, all the isomers have exothermic heat of formation and thermodynamically favorable Gº values. The order of Gº values is B<E<A<C<D<F, namely B is the most favorable isomer in terms of Gibbs free energy of formation.

Table 4. Some thermodynamic properties of the isomers considered.

Structures	Hº (kJ/mol)	Sº (J/molº)	Gº (kJ/mol)
A	-2003231.022	427.92	-2003358.609
B	-2003260.672	428.65	-2003388.474
C	-2003229.063	430.38	-2003357.380
D	-2003216.670	429.68	-2003344.780
E	-2003251.225	428.63	-2003379.022
F	-2003212.120	430.34	-2003340.427

Since, the light-activated furanocoumarins react with the pyrimidine bases, after intercalation into the double helix of the DNA and molecular complexing, the frontier molecular orbitals, in the ground and the exited states get primary importance.

The HOMO, LUMO energies and the interfrontier molecular orbital energy gaps, Δε ($\Delta\varepsilon = \varepsilon_{LUMO} - \varepsilon_{HOMO}$), of the isomers are listed in Table 5. The HOMO energies follow the order of D<C<B<F<A<E whereas D<C<F<E<B<A stands for the LUMO energy order. Consequently, Δε values constitute the order of E<F<D<C<A<B. Thus, isomer-E has the narrowest interfrontier energy gap and possesses the hardness value of 193.18 kJ/mol. Note that isomers C and F are bergapten and xanthotoxin, respectively.

The substituent, methoxy group, is an electron donating group due to the presence of oxygen atom which is mesomerically electron donor but inductively electron attractor. However, the mesomeric effect is the overwhelming contributor to the overall effect. In general, electron donors attached to a conjugated system raises up both the frontier orbitals, HOMO and LUMO [33]. In that respect, the methoxy substituent in isomer-E is more effective in raising the HOMO energy level than it is in the others whereas in the case of LUMO levels the raising effect is more pronounced in isomer-A.

Table 5. The HOMO, LUMO energies and Δε values of the isomers.

Structures	HOMO	LUMO	Δε
A	-602.95	-182.28	420.67
B	-616.68	-182.64	434.04
C	-622.17	-208.99	413.18
D	-622.82	-219.39	403.43
E	-585.91	-199.55	386.36
F	-603.52	-203.09	400.43

Energies in kJ/mol.

Figure 4 displays some of the molecular orbital energy levels of the isomers considered. The spacing and energies of the inner lying occupied molecular orbitals are generally accepted as the factor which dictates the thermal stability of a molecule.

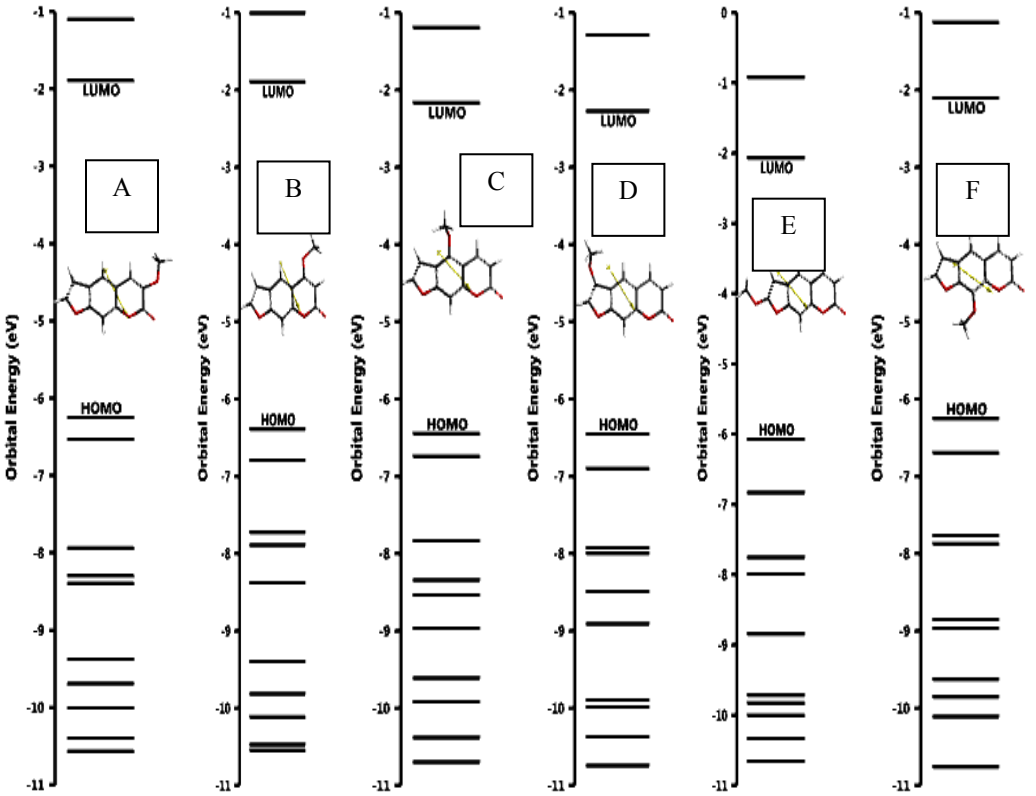
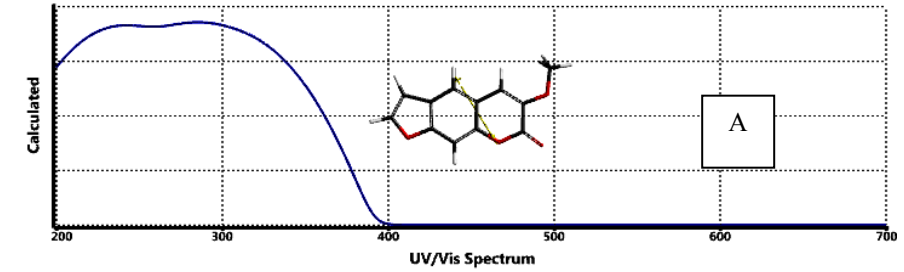


Figure 4. Some molecular orbital energy levels of the isomers considered.

Figure 5 shows the calculated (time-dependent DFT) UV-VIS spectra of the isomers considered. As seen in the spectra all the isomers of present concern absorb mainly in the ultraviolet region. In the cases of E and F some slight shift to the visible region occurs.

Figure 6 shows the local ionization maps of the isomers considered. In the local ionization potential map, conventionally red/reddish regions (if any exists) on the density surface indicate areas from which electron removal is relatively easy, meaning that they are subject to electrophilic attack.

Figure 7 shows the LUMO maps of the isomers considered. A LUMO map displays the absolute value of the LUMO on the electron density surface. The blue color stands for the maximum value of the LUMO and the color red, the minimum value. As seen in the figure, in most of the cases the lactone moiety is the most potent site to undergo nucleophilic type additions including the conjugate types.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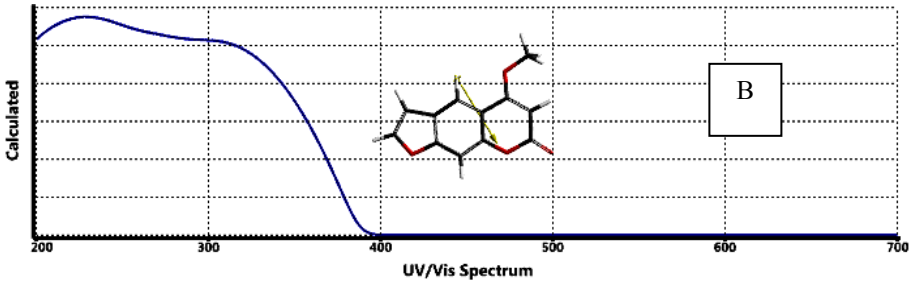
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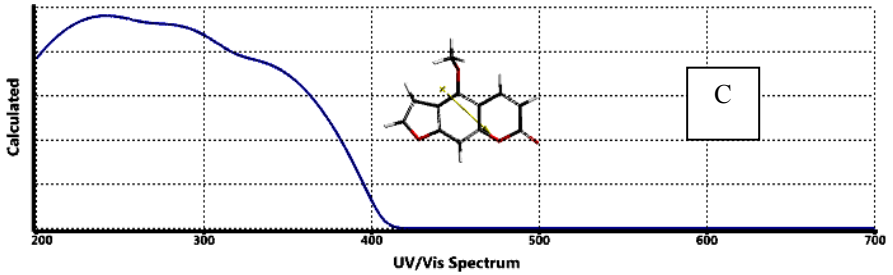
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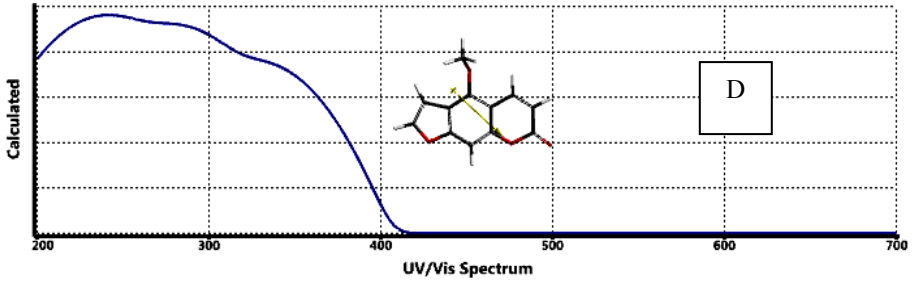
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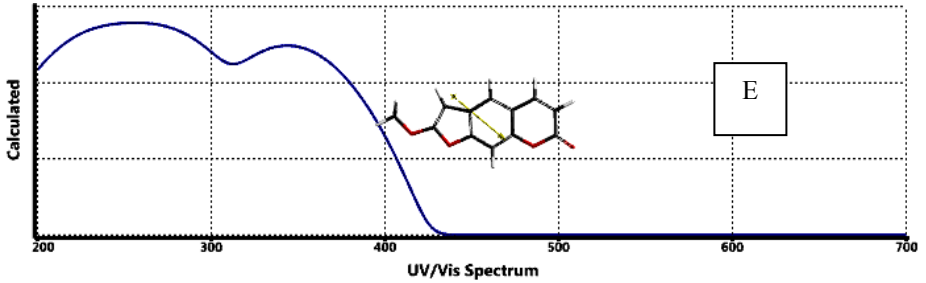
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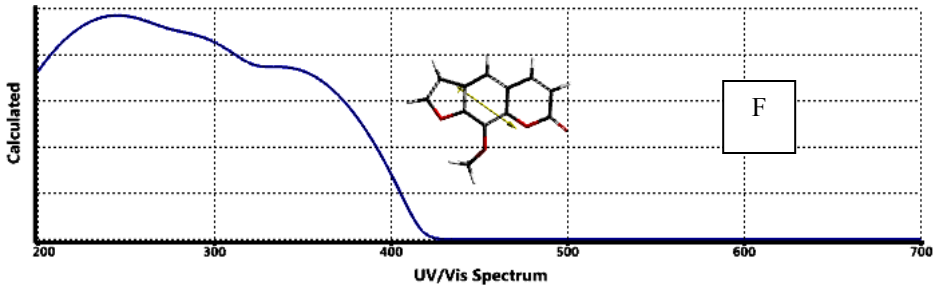

Figure 5. The calculated UV-VIS spectra of the isomers considered.

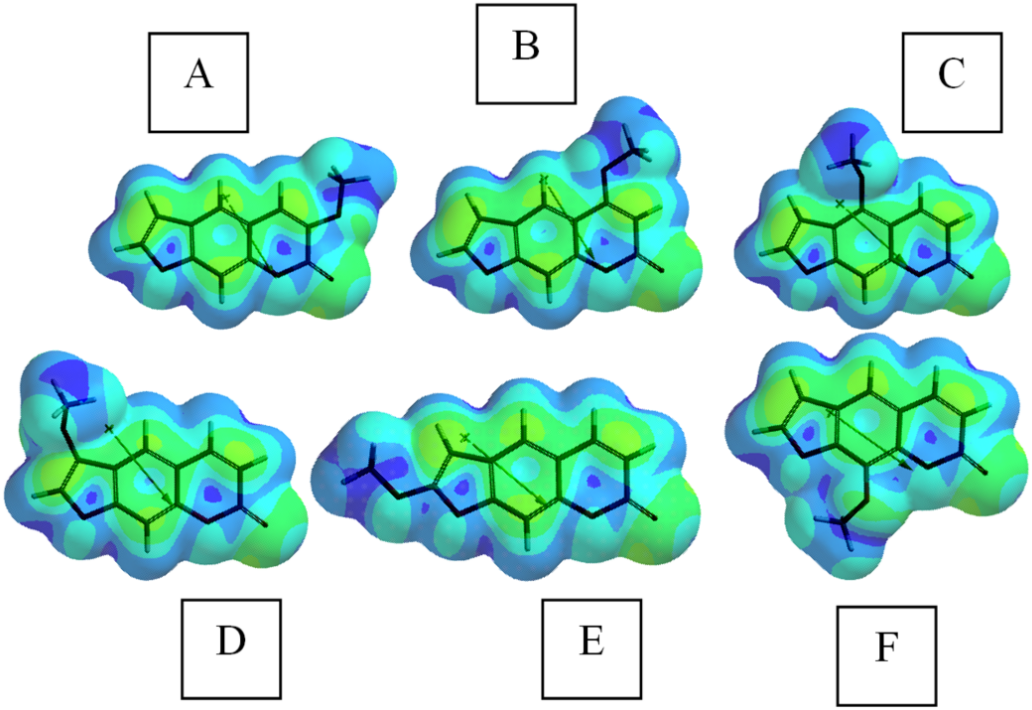

Figure 6. The local ionization potential maps of the isomers considered.

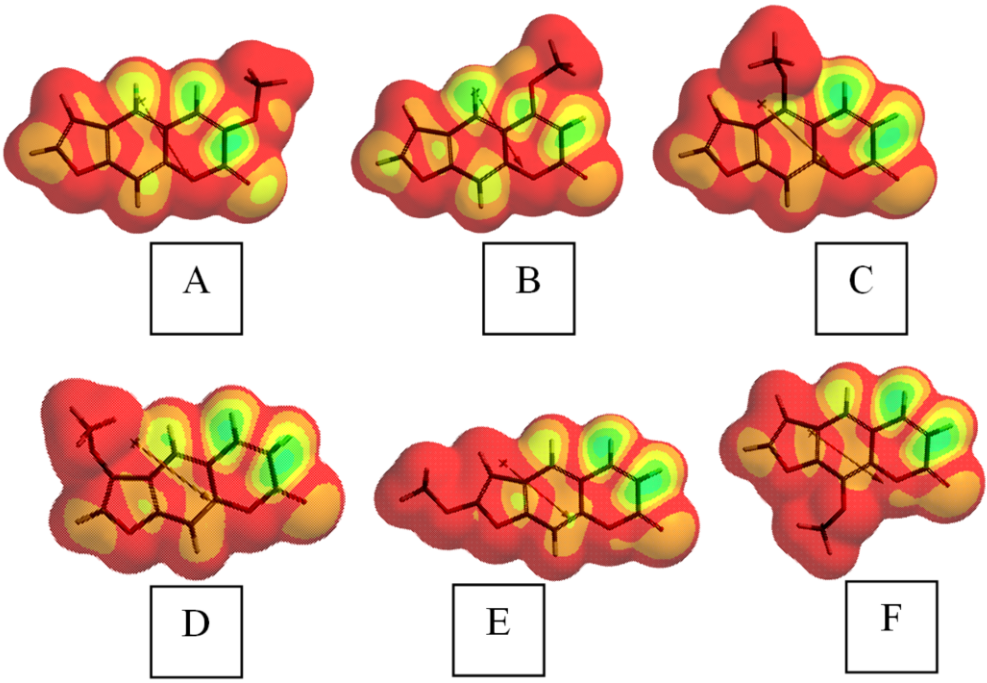

Figure 7. The LUMO maps of the isomers considered.

NICS

There exist numerous articles in the literature, discussing aromaticity in terms of energetic, structural and magnetic criteria [34-39]. An efficient probe has been introduced for aromaticity which is called "nucleus-independent chemical shift" (NICS) [40]. It is the computed value of the negative magnetic shielding at some selected point in space, generally at a ring or cage center. The calculated data piled in the literature through the years indicate that negative NICS values denote aromaticity such as -11.5 for benzene, -11.4 for naphthalene. On the other hand, positive NICS values stand for antiaromaticity (28.8 for cyclobutadiene) while small NICS values indicate non-aromaticity (-2.1 for cyclohexane, -1.1 for adamantine). Although NICS has been proved to be an effective probe for local aromaticity of individual rings of polycyclic systems a couple of contradictory results exist [40].

Table 6 lists the nucleolus independent chemical shift (NICS) values at the center of furanoid and benzenoid rings of the isomers. The table indicates that the order of NICS(0) values for the benzenoid ring is F<C<A<B<D<E whereas for the furanoid rings it is D<C<F<A<B<E. Note that the local aromaticity gets bigger and bigger as the NICS

values become more and more negative. Also note that in isomers F and C, the methoxy substituent is on the benzenoid ring and they exhibit high local aromaticity whereas in D and E it is attached to the furanoid ring. In all the cases, except isomer-D, the local aromaticity value of the benzenoid ring is greater than the furanoid ring of the same isomer.

Table 6. NICS(0) values of the isomers considered.

	Isomers					
	A	B	C	D	E	F
Furanoid ring	-9.3895	-9.2854	-10.1464	-11.2179	-8.8641	-9.7109
Benzenoid ring	-11.2654	-10.9322	-11.4669	-10.9158	-10.8753	-12.1109

Rationalization of the calculated NICS values can be done up to a certain extents by valence bond structures. The electron donating effect of the methoxy group may assist or not to the ring current in the furanoid ring depending on its position. However, the conjugative effects dictated by the lactone moiety also has some influence on the NICS values of the benzenoid and furanoid rings, depending on whether the methoxy group and the lactone moiety are in conjugation or they are crossly conjugated.

4. Conclusion

The present density functional treatment, within the restrictions of the theory and the basis set employed, has indicated that the positional variations of the methoxy substituent in psoralen backbone result in electronically stable as well as thermally favorable isomers in all the cases. They all have exothermic heat of formation values and the rings are highly aromatic. Note that furanocoumarins (include psoralen) are therapeutically important compounds which have various clinical applications. In the present study, positional effect of an electron donating substituent (methoxy group) on various properties of the isomeric structures have been investigated. It would be equally interesting to investigate the effect of an electron attracting substituent systematically.

References

[1] Mirzaei, S.A., Dehkordi, N.G., Ghamghami, M., Amiri, A.H., Abdolahinia, E.D., & Elahian, F. (2017). ABC-transporter blockage mediated by xanthotoxin and bergapten is the major pathway for chemosensitization of multidrug-resistant cancer cells. *Toxicology and Applied Pharmacology*, *337*, 22-29. https://doi.org/10.1016/j.taap.2017.10.018

[2] Diawara, M.M., & Kulkosky, P.J. (2003). Reproductive toxicity of the psoralens. *Pediatric Pathology & Molecular Medicine*, *22*(3), 247-258. https://doi.org/10.1080/pdp.22.3.247.258

[3] Hearst, J.E. (1989). Photochemistry of the psoralens. *Chem. Res. Toxicol.*, *2*(2), 69-75. https://doi.org/10.1021/tx00008a001

[4] Hearst, J., Isaacs, S.T., Kanne, D., Rapoport, H., & Straub, K. (1984). The reaction of the psoralens with deoxyribonucleic acid. *Quarterly Reviews of Biophysics*, *17*(1), 1-44. https://doi.org/10.1017/S0033583500005242

[5] Kanne, D., Straub, K., Rapoport, H., & Hearst, J.E. (1982). The psoralen-DNA photoreaction. Characterization of the monoaddition products from 8-methoxypsoralen and 4,5',8-trimethylpsoralen. *Biochemistry*, *21*(5), 861-871. https://doi.org/10.1021/bi00534a008

[6] Fitzpatrick, T.B., Arndt, K.A., El Mofty, A.M., & Pathak, M.A. (1966). Hydroquinone and psoralens in the therapy of hypermelanosis and vitiligo. *Arch Dermatol.*, *93*(5), 589-600. https://doi.org/10.1001/archderm.1966.01600230093025

[7] Hanson, C.V. (1992). Photochemical inactivation of viruses with psoralens: an overview. *Blood Cells*, *18*(1), 7-25. PMID: 1617194

[8] Marumoto, S., & Miyazawa, M. (2010). Biotransformation of bergapten and xanthotoxin by Glomerella cingulata. *J. Agric. Food Chem.*, *58*(13), 7777-7781. https://doi.org/10.1021/jf101064v

[9] Schimmer, O. (1981). Comparison of photomutagenic activities of 5-mop (bergapten) and 8-mop (xanthotoxin) in *chlamydomonas reinhardii* (ger). *Mutation Research*, *89*(4), 283-296. https://doi.org/10.1016/0165-1218(81)90109-9

[10] Tatchen, J., & Marian, C.M. (2006). Vibronic absorption, fluorescence, and phosphorescence spectra of psoralen: a quantum chemical investigation. *Phys. Chem. Chem. Phys., 8*(18), 2133-2144. https://doi.org/10.1039/B518436C

[11] Wood, P.D., Mnyusiwalla, A., Chen, L., & Johnston, L.J., (2000). Reactions of psoralen radical cations with biological substrates. *Photochemistry and Photobiology*, *72*(2) 155-162. https://doi.org/10.1562/0031-8655(2000)0720155ROPRCW2.0.CO2

[12] Serrano-Perez, J.J., Merchán, M., & Serrano-Andrés, L. (2007). Quantum chemical study on the population of the lowest triplet state of psoralen. *Chemical Physics Letters, 434*(1-3), 107-110. https://doi.org/10.1016/j.cplett.2006.11.086

[13] Zhou, Y. Peng, J., Shen, W., & Li, X. (2020). Psoralen as an interstrand DNA crosslinker in the selection of DNA-encoded dynamic chemical library. *Biochemical and Biophysical Research Communications*, *533*(2), 215-222. https://doi.org/10.1016/j.bbrc.2020.04.033

[14] Gao, W., Cao, P., Li, B., Zhao, L., Sun, W., & Zhou, W. (2022). Unraveling the role of chemistry and topology of MOFs in psoralen adsorption. *Ind. Eng. Chem. Res.*, *61*(20), 7172-7182. https://doi.org/10.1021/acs.iecr.1c04121

[15] Tatchen, J., Gilka, N., & Marian, C.M. (2007). Intersystem crossing driven by vibronic spin-orbit coupling: a case study on psoralen. *Phys. Chem. Chem. Phys.*, *9*(38), 5209-5221. https://doi.org/10.1039/B706410A

[16] Scott, B.R., Pathak, M.A., & Mohn, G.R. (1976). Molecular and genetic basis of furocoumarin reactions. *Mutat Res*. *39*(1), 29-74. https://doi.org/10.1016/0165-1110(76)90012-9

[17] Serrano-Pérez, J.J., Serrano-Andrés, L., & Merchán, M. (2006). A theoretical insight into the photophysics of psoralen. *J. Chem. Phys*., *124*, 124502. https://doi.org/10.1063/1.2178794

[18] Koval'skaya, N.E., & Sokolova, I.V. (2002). The nature of electronically excited states and photoprocesses in psoralen molecules and their complexes. *High Energy Chemistry, 36*, 193-196. https://doi.org/10.1023/A:1015333119535

[19] Stewart, J.J.P. (1989). Optimization of parameters for semiempirical methods I. Method. *J. Comput. Chem*., *10*, 209-220. https://doi.org/10.1002/jcc.540100208

[20] Stewart, J.J.P. (1989). Optimization of parameters for semiempirical methods II. Application. *J. Comput. Chem*., *10*, 221-264. https://doi.org/10.1002/jcc.540100209

[21] Leach, A.R. (1997). *Molecular modeling*. Essex: Longman.

[22] Fletcher, P. (1990). *Practical methods of optimization*. New York: Wiley.

[23] Kohn, W., & Sham, L. (1965). Self-consistent equations including exchange and correlation effects. *J. Phys. Rev.*, *140*, A1133-A1138. https://doi.org/10.1103/PhysRev.140.A1133

[24] Parr R.G., & Yang, W. (1989). *Density functional theory of atoms and molecules*. London: Oxford University Press.

[25] Cramer, C.J. (2004). *Essentials of computational chemistry*. Chichester, West Sussex: Wiley.

[26] Becke, A.D. (1988). Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev. A*, *38*, 3098-3100. https://doi.org/10.1103/PhysRevA.38.3098

[27] Vosko, S.H., Wilk, L., & Nusair, M. (1980). Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis. *Can. J. Phys.*, *58*, 1200-1211. https://doi.org/10.1139/p80-159

[28] Lee, C., Yang, W., & Parr, R.G. (1988). Development of the Colle-Salvetti correlation energy formula into a functional of the electron density. *Phys. Rev. B*, *37*, 785-789. https://doi.org/10.1103/PhysRevB.37.785

[29] SPARTAN 06 (2006). Wavefunction Inc., Irvine CA, USA.

[30] Gaussian 03, Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Montgomery, Jr., J.A., Vreven, T., Kudin, K.N., Burant, J.C., Millam, J.M., Iyengar, S.S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G.A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J.E., Hratchian, H.P., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Ayala, P.Y., Morokuma, K., Voth, G.A., Salvador, P., Dannenberg, J. J., Zakrzewski, V.G., Dapprich, S., Daniels, A.D., Strain, M.C., Farkas, O., Malick, D. K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Ortiz, J.V., Cui, Q., Baboul, A.G., Clifford, S., Cioslowski, J., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M. W., Gonzalez, C., & Pople, J.A., Gaussian, Inc., Wallingford CT, 2004.

[31] Del Río, J.A., Díaz, L., García-Bernal, D., Blanquer, M., Ortuño, A., Correal, E., Moraleda, J.M. (2014). Furanocoumarins: Biomolecules of Therapeutic Interest, *Studies in Natural Products Chemistry*, *43*, 145-195. https://doi.org/10.1016/B978-0-444-63430-6.00005-9

[32] Ghose, A.K., Pritchett, A., & Crippen, G.M. (1988). Atomic physicochemical parameters for three dimensional structure directed quantitative structure-activity relationships III: Modeling hydrophobic interactions. *J. Computational Chemistry*, *9*(1), 80-90. https://doi.org/10.1002/jcc.540090111

[33] Fleming, I. (1973). *Frontier orbitals and organic reactions*. London: Wiley.

[34] Minkin, V.I., Glukhovtsev, M.N., & Simkin, B.Y. (1994). *Aromaticity and antiaromaticity: Electronic and structural aspects*. New York: Wiley.

[35] Schleyer, P.R., & Jiao, H. (1996). What is aromaticity?. *Pure Appl. Chem*., *68*, 209-218. https://doi.org/10.1351/pac199668020209

[36] Glukhovtsev, M.N. (1997). Aromaticity today: energetic and structural criteria. *J. Chem. Educ*., *74*, 132-136. https://doi.org/10.1021/ed074p132

[37] Krygowski, T.M., Cyranski, M.K., Czarnocki, Z., Hafelinger, G., & Katritzky, A.R. (2000). Aromaticity: a theoretical concept of immense practical importance. *Tetrahedron, 56*, 1783-1796. https://doi.org/10.1016/S0040-4020(99)00979-5

[38] Schleyer, P.R. (2001). Introduction: aromaticity. *Chem. Rev*., *101*, 1115-1118. https://doi.org/10.1021/cr0103221

[39] Cyranski, M.K., Krygowski, T.M., Katritzky, A.R., & Schleyer, P.R. (2002). To what extent can aromaticity be defined uniquely?. *J. Org. Chem*., *67*, 1333-1338. https://doi.org/10.1021/jo016255s

[40] Schleyer, P.R., Maerker, C., Dransfeld, A., Jiao, H., & Hommes, N.J.R.E. (1996). Nucleus independent chemical shifts: a simple and efficient aromaticity probe. *J. Am. Chem. Soc*., *118*, 6317-6318. https://doi.org/10.1021/ja960582d