Egypt. J. Chem. **Vol.64**, No. 7, pp. 3457 - 3463 (2021)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Molecular Docking, Electronica, Structural Characterization of Xanthanolides Derivative A: PM3 Model and ADMET

Zaheda Ahmed Najim

Department of Chemistry, College of Education for Pure Science, Mosul University, Mosul, Iraq

Abstract

This piece of work is concerned with characterization and studying the overgrown natural products known as Xanthananolide derivatives, by applying quantum mechanical model represented by PM3 (Parametric Method) as a semi-empirical method. Energy minimization was first carried out. The molecular structure with minimized energy was indemnified and assigned as the most stable conformation.

The molecular orbital energy HOMO and LUMO are determined and they were used as descriptor for the estimation of the reactivity of the nucleophilic cite.Simulation of ADMET (Absorption Distribution Metabolism Excretion Toxicity) was performed related to skin permeability, blood brain barriers (BBB), binding of protein CYP2D6(cytochrome p4502D6), absorption of gastrointestinal binding.

Good oral bioavailability was noted by compound 5.

Key words: Docking, PM3, ADMET

1. Introduction

The determination of molecular structure and related activity can be achieved by molecular modeling program [1]. Many software and other sustainable tools are available now days for studying molecular geometry and modeling can give a clear picture and visualizing the structure of the compound to be considered in such analysis. Generation of a structure with stable geometry become possible by computation chemistry. Addition parameters related to drug activity such as heat of formation, steric energy and energies of the molecular orbitals (HOMO and LUMO) can facilitate the simulation ADMET behavior inside the human body [2-4].The process of ADMET simulation normally spotlighting on the discovery and designing new drugs. Such drug are employed in the early stage of the process of the research giving preference in terms of financial cost and helps to develop a new drugs by using animals for such study [5-7].

In the development of inhibitors of cytochrome CYP450 type 2D6 of Xanthanolides derivatives that is an active inflammatory in the traditional Chines medicine having a fused system could be synthesized from the reaction of compound(1) with a nucleophile (malonate)via the rearrangement reaction of Kom Blum DeLaMar[8].Such studies can be performed by using the result of standard study molecule docking and design of drugs. Docking examination was accomplished for the considered goal molecules to CYP4502D6 online using mcule.com/apps/1-click docking.

Material and Methods

1- Computational specifications

The computational are achieved on NVidia/ GEFORCE GTX-670MX personal computer Intel core i7-3630, 24GB RAM, hard 1 tera os :win 8 , the operating system consisted used card and Microsoft windows 8.1.The codes used are belonging to free license of academic use. Calculations were performed using Gaussian 09 program [9].

1-1 Energy minimization of molecular structure

The energy minimizations of the compounds under consideration is carried out by using geometry optimization technique in which the system is taken into a near local minimize energy by moving over the potential surfers toward the direction of the decrease of energy (10,11).

In this work all compounds (12) were achieved by employing the PM3 (Parametric Method) as a semi-empirical method base on quantum mechanical method with Hamiltonian. A number of molecular properties were determined by using

*Corresponding author e-mail: zahedahmed@uomosul.edu.iq

Receive Date: 17 February 2021, Revise Date: 23 February 2021, Accept Date: 14 March 2021

DOI: 10.21608/EJCHEM.2021.63311.3364

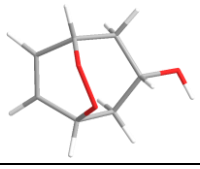
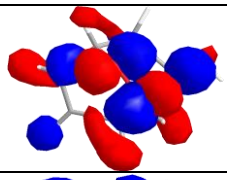
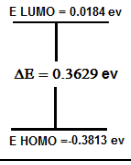
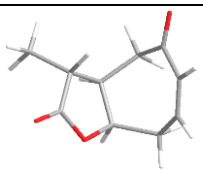
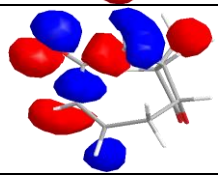
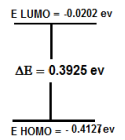
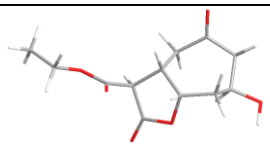
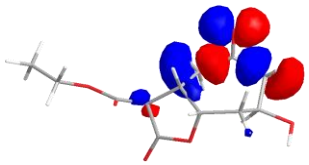
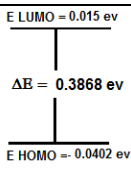
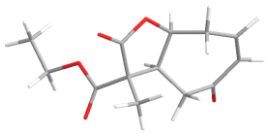
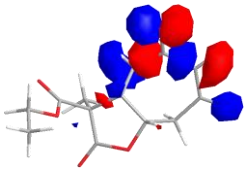
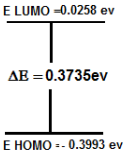
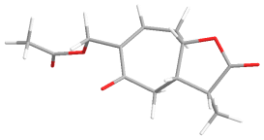
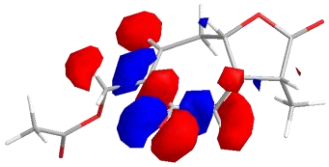
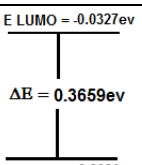
MOE program to find a reliable and exact image of biologically energetic compounds.

1-2 Frontier Molecular Orbitals (FMOs), MESP and Descriptors Reactivity

The mean orbital in quantum chemistry are the frontier molecular orbitals (FMOs) which is represented by the (HOMO) and (LUMO) orbital these orbitals are very important when chemical stability is considered [13]. LUMO represents the electron affinity, HOMO as an ionization potential [14].The different between HOMO - LUMO molecular orbital known as energy gap which is an important and give indicator to the stability of the compound under consideration [15]. The HOMO and LUMO energies of compounds calculated by MP3 methods are listed in Table (1) closed to the pictures represented by their HOMO-LUMO dispensing and their related negative and positive region listed in Table (1).

Negative and positive field indicate by red and blue colour respectively.

Table 1: HOMO-LUMO structure with the energy level diagram of compounds

Code	Formula M.wt	Structure	HOMO-LUMO	Energy level diagram
1	$C_7H_{10}O_3$ 142.15			
2	$C_{10}H_{12}O_3$ 180.20			
3	$C_{12}H_{16}O_6$ 256.25			
4	$C_{13}H_{16}O_5$ 252.27			
5	$C_{13}H_{16}O_5$ 252.25			

1-3 Global Reactivity Descriptions

Descriptors representing global chemical reactivity for the compounds selected for this study such as hardness (η) and softness (S) were evaluated by using the data of HOMO & LUMO as frontier molecular orbitals by applying the explanation Parr and Person as well as the Koopmans theorem [15,16]. The energies of the HOMO and LUMO (ε) are representative of the ionization potential (I) and electron affinity (A). Equation (1) and (2) were used to calculate these values.

$$\Delta E = \left|\varepsilon_{HOMO} - \varepsilon_{LUMO}\right| \quad \text{.....(1)}$$

$$\eta \approx \frac{1}{2}(\varepsilon_{LUMO} - \varepsilon_{HOMO}) \approx \frac{1}{2}(I - A) \quad \text{.....(2)}$$

Where ΔE = is gap, I is ionization potential, A is the LUMO orbital ability of compounds to accept electrons and called as electron affinity. This refers the softness as measure the extend of chemical activity. This is equal to the invers of the hardness [17].

1-4 In Silico ADMET and Molecular Docking Screening

The properties of absorption, metabolism and carcinogenicity of all compounds were predicted by utilizing ADMET SAR online database [18]. These data are derived from different experiments for various compounds with proximally chemical structure [19, 20].

Analysis was carried out in order to know whether the compounds are a cytochrome of family as isoform inhibitor (p450cyp) as like cup2D6. Finally molecular docking simulation was performed by mucle.com, 1-click docking online for all compounds to obtain binding energy for them. Table 2 shows binding energy and pharmacokinetic parameters of all compounds.

Table 2: Binding energy and pharmacokinetic parameters of all compounds

Comp. no	Binding energy kcal/mol	Blood brain barrier (BBB)	Human intestinal absorption	p-glyco-protein inhibitor	Carcinogen binary	Actual oral toxicity	Cyp2D inhibitor
1	-4.8	+0.9522	+0.8771	-0.9776	-0.9000	III 0.4273	-0.9231
2	-6.8	+0.9248	+0.9990	-0.9717	-0.9714	III 0.6118	-0.9674
3	-5.7	+0.9486	+0.9530	-0.9273	-0.9571	III 0.5085	-0.9500
4	-5.4	+0.9735	+0.9857	-0.8920	-0.8714	III 0.5323	-0.9566
5	-5.7	+0.9643	+0.9911	-0.8938	-0.8857	III 0.4342	-0.9324

Result & Discussions

In order to determine the initial structure for the considered compounds (Table 1) with minimum energy conformation, free Gaussian (09) was used. The semi-empirical (PM3) method a good selection for modeling a medium size molecules . Experimentally, a pre-established of parameters was achieved for reducing the integrals when solving the SchrÖdinger equation (equation 3) [21,22].

$$-\frac{\hbar^2}{2m}\Delta^2\psi + E_p\psi = i\hbar\frac{\partial\psi}{\partial t} \ldots\ldots (3)$$

Where E_p is the potential energy in the considered region, m is the mass of the particle accompanied with the wave function $\psi/\partial t$. This function representing a partial derivative of the wave function in time order, 2 ψ in a mathematical operator of ψ named as Laplacian .The electronic and nuclear movement were decouples using Born-Oppenheimer approximation and by assuming a certain distance of fix position between the electrons and nuclei in the compound to be solved by SchrÖdinger equation. The state of global energy where screening is obtained after conformational analysis. The conformation that could be considered as more stable thermodynamically. The more stable geometries resulted from energy of minimization is taken to estimate the global chemical reactivity descriptors of compounds.

The value of calculated parameters such as potential energy (IP= -HOMO), electron affinity EA = (– LUMO), hardness and softness are listed Table (3).

As can be seen in Table(3), the compound with lowest gab energy is compound (1) which has (ΔE_{gab} = 0.3626 ev) this gab of lower energy indicates to the softest molecules. Compound No. (3) has the largest gab (ΔE_{gab} = 0.3868 ev). The compound that with the highest energy of molecular orbital (HOMO)(lowest IP) (E_{HOMO}= -0.8132 ev). The higher value of HOMO energy increases its ability to donate electron. Meanwhile compound (3) has the lowest energy of LUMO (highest EA) among the studied compounds (E_{LUMO}=-0.0152 ev) indicating to the ability as electron acceptor.

Table 3:Quantum Chemical Descriptors of Compounds

Comp. no	IP = -HOMO	EA = -LUMO	η = (I-A)/2	S= 1/ η	ΔE_{gap} Ev
1	0.3813	-0.0184	0.1998	5.0037	0.3629
2	0.3927	-0.0202	0.2364	4.8449	0.3725
3	0.4020	-0.0152	0.2086	4.7938	0.3868
4	0.3993	-0.0258	0.2125	4.7040	0.3732
5	0.3986	-0.0327	0.2156	4.6380	0.3659

To obtain the initial structure (structure with minimize energy) with easily visible conformations, the Gaussian program was used .

The PM3 method (semi-empirical method) has become a vital disband for modeling molecules of medium sizes, experimentally, they employ a pre-stabilized parameters. These parameters working introducing the number of integrals used for solving the schrodenger equation.

$$-\frac{\hbar^2}{2m}\Delta^2\psi + E_p\psi = i\hbar\frac{\partial\psi}{\partial t} \ldots\ldots (3)$$

Where E_p is the potential energy in the considered region m is the mass of the particles

As shown in Table 3, the compound which have the lowest energetic gap is the compound (1) (ΔE_{gap}= 0.3626 ev).this lower gap allows it to be softest molecule. The compound that have the highest gap is compound (3) (ΔE_{gap}= 0.3868 ev),

the compound that has the highest HOMO energy (lowest IP) compound (1) (E_{HOMO} = -3.813 ev) this higher value allows it to be the best electron donor. The compound that has lowest LUMO energy (highest EA) is the compound (3) (E_{LUMO} = 0.0152 ev) which signifies that it can be best electron acceptor. The two properties like IP (ionization potential) and EA (electron affinity) are so important these allow us to calculate the hardness and softness.

The values of IP and EA proved to be very important in calculating the values of softness and hardness employing the data generated during the structural optimization of modeling techniques helping in understanding the type of interaction through the studying the surface map electrostatic potential (MESP) [23]. Three type of charge distribution were very important for the analysis and determination of the region representing the higher and lower electronic density. These regions of the highest and lowest electron density forming a good indicator for the behavior of the different site being either electrophile or nucleophile. The descriptor analysis could assess the understanding of the molecular interactions by illustrating the behaviors of molecule in which can interact with other one with different charge [24]. Sometime the red color is used as an indication to the lowest energy of electrostatic potential, which determinate the higher electron density region. The blue color marking the high region of electrostatic energy potential into a relative loss of electron density. The green color representing an intermediate value of electrostatic potential. The map shows the distribution of the electrostatic potential of molecules can be used to identify the region of high electron density (nucleophile), indicated by red color and located close to the oxygen atom (figure1). The region indicate to the position of high electron density, which give a due to the location of possible electrostatic interaction due to hydrogen bond [25].

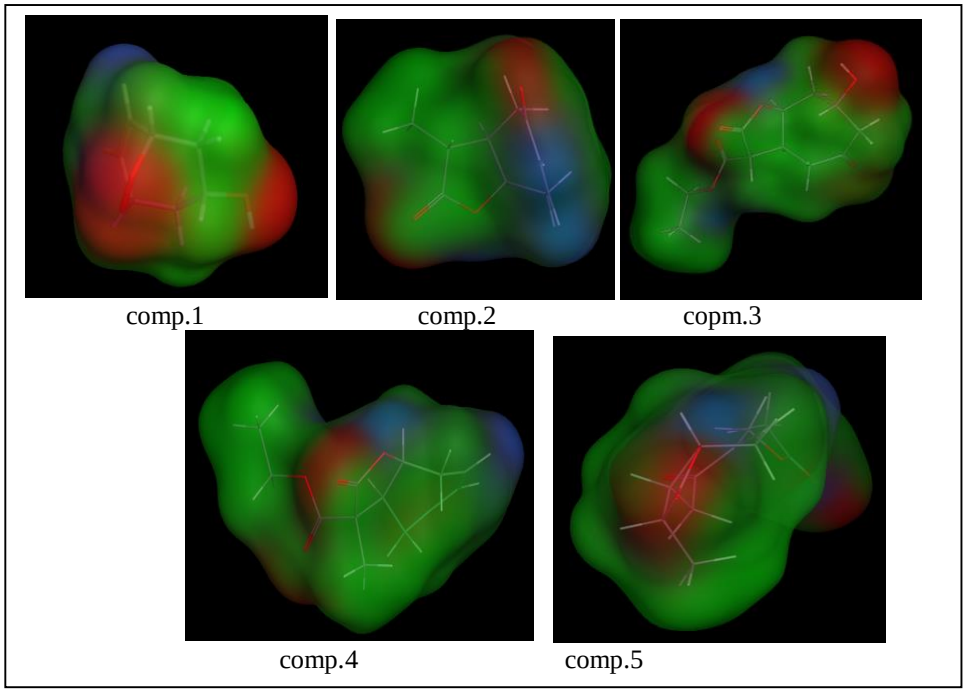


Fig.1. Map of the distribution of electrostatic potential obtained by MP3 method

A positive response was noticed for all compounds blood brain barrier (BBB) when applying ADMET SAR2 as criteria for predicting whether compounds, can get through the BBB. All compounds show III category harmless for oral administration. AdemtSAR2 measurement indicated that all compounds are not-carcinogenic. So the compounds should be topically saved to use.

P-glycoprotein compounds are not-inhibitor, whereas the p-glycoprotein inhibition can block the absorption. permeability and retention of the compounds(26).

Docking estimation of the compounds was achieved by http://www.Mcule.com . Docking was done against the active site of the cytochrome P450 2D6 (Quinoprotien Methanol Dehydrogenase 1G72), Figure(3) show contact sites of compounds with cytochrome amino acids.

Table (2) show binding energy of compounds, compound (2) showed highest value of binding energy compare with other compounds (-6.8 kcal/mol) and there is contact

between two oxygen atoms with three amino acid (three hydrogen bonds) of Arg(109) , Thr (153) and Ser(108), compound (1) display binding energy (-4.8 kcal/mol) and it's contact by forming hydrogen bonds between carbonyl group with NH group of Arg(109), Ter(153) and Asp(175) amino acids.

The values of the binding energy revealed by compound (3) (-5.7 kcal/mol) indicate to (hydrogen bond type) happened between hydroxyl group on the cycloheptane ring and cys (123) amino acid.

The energy of the binding revealed by compound (4) equal to (-5.4 kcal/mol) representing a single hydrogen bond existing between oxygen of carbonyl group in furan ring with Gly(546) amino acid.

Compound (5) display binding energy (-5.7 kcal/mol) and there is no hydrogen bond with amino acid.

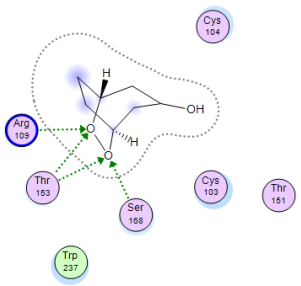
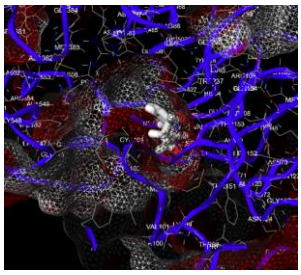
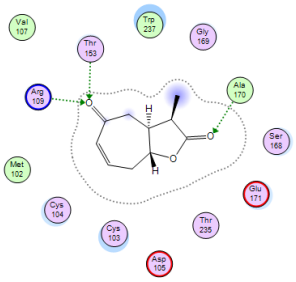
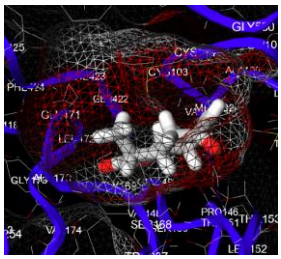
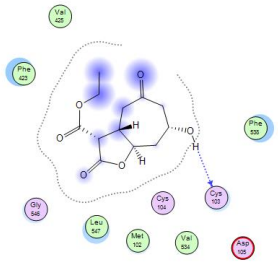
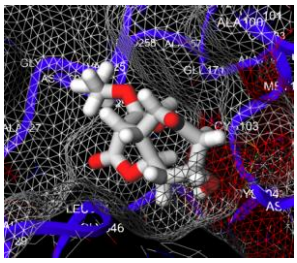
The result of the calculation carried out by employing ADMET SAR and listed in Table2, for all the compounds are positively responded exhibiting three type of verbal acute toxicity, so it can be predicted. The ADMET SAR results can also predict compounds one relating harmless for oral academic institution, also the ADMET SAR calculation can indicate that the compounds are not carcinogenic and be safety used.

In addition the p-glycoprotein is non-inhibitor. The p-glycoprotein as disincentive can block the permeability, absorption and retaining the compounds.

All molecules showed non-inhibiting properties for known cyp2D6 inhibitor.

Pharmacokinetic Investigation

From ADMET SAR calculation shown in Table (2), it is found that all compounds show positive response for blood brain barrier (BBB), show (III) category acute oral toxicity so it can be predicted that they are relatively harmless for oral administration admetSAR calculation predicts, all compounds are non-carcinogenic, so the compounds are expected to be safer for topical use, also they are p-glycoprotien non-inhibitor. p-glycoprotien inhibition can block the absorption, permeability and retention of the compounds(27). However, all, molecules showed non- inhibitory properties for human cyp2 D6 inhibitor.

Comp.no	**Bonding interaction**	**Docked Conformation**
1		
2		
3		

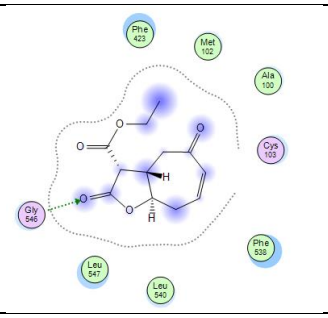
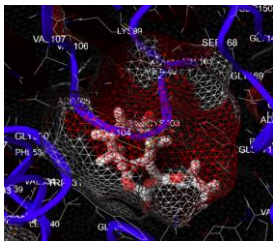
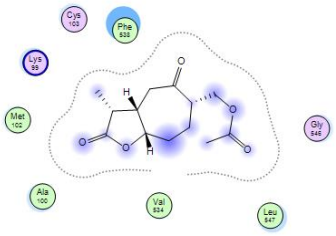
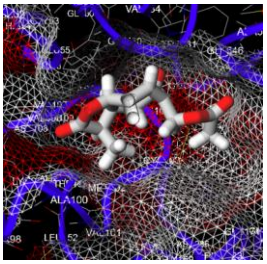
4		
5		

Fig.2.Docking of compounds into active site of CYT450 2D6

Acknowledgment

I thank Dr.Yassir Al Jawaheri for helping to choose important compound from his PhD thesis additionally, Prof. Dr. Emad Al Hyali for doing prof reading.

References

[1] Lima A.R., Silva J., Bezerra L.L., Marinho M.M., Marinho E.S. 2017 . Molecular docking of potential curcuminoids inhibitors of the NS1 protein of dengue virus. Int J Sci Eng Res. **8**(4).

[2] Carneiro, S.S., Lima, A.R., Marinho, M.M., Marinho, E.S. In silico Study Of The Therapeutic Agent In The Treatment Of Non-Hodgkin's Lymphomas, 2016. Peripheral T- Cell Belinostat , A SemiEmpirical Approach. Imp J Interdiscip Res. 8,1645–8 .

[3] Oliveira, V.M. De, Marinho, M.M., Marinho, E.S.,2019. Semi-Empirical Quantum Characterization of the Drug Selexipag: HOMO and LUMO and Reactivity Descriptors. Int J Recent Res Rev.**XII** (2),15–20.

[4] Henrique, C., Roberto, A., Marinho, E.S., Campos, O.S., Nithael,. F, Lucio M, 2019. Characterization of the natural insecticide methylcytisine: An in silico study using classic force field. Int J Recent Res Rev.; **XII** (2):15–20.

[5] Cheng, F., Li, W., Zhou, Y., Shen, J., Wu, Z., Liu, G., et al. 2012. AdmetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. J Chem Inf

a. Model. 52(11):3099-3105 .

[6] Tareq-Hassan Khan, M., 2010. Predictions of the ADMET Properties of Candidate Drug Molecules Utilizing Different QSAR/QSPR Modelling Approaches. Curr Drug Metab. **11**(4):285-95.

[7] Chinthala Y., Thakure S., Tirunagari S., Chinde S., Domatti A., Arigari N., et al 2015. "Synthesis docking and ADMET studies of novel chalcone trizoles for anti-cancer and anti diabetic activity", Eur J Med Chem , **93**,564-73.

[8] Steven T., Xin Linghu and Dean F.,2006."Enantioselective synthesis of γ-hydroxyenones by chiral base- catalyzed kornblum deLaMare rearrangement, J.AM.CHEM.SOC.,**128**,12658-12659 .

[9] Frisch J., Trucks W., Schlegel H., Scuseria G., Robb M., Cheeseman J., et al. 2010. Gaussian 09,Revision C.,Gaussian Inc Wallingford. CT, USA

[10] Atkins,. P, De Paula, Atkins J., 2010. '' physical chemistry / Peter Atkins, Julio de Paula. Physical chemistry'' Publisher: Oxford University Press; 10th edition .

[11] Csizmadia P,2019 ."Molecule Applets for the Word Wide Web.In", MarvinSketh and Marvin View.

[12] Yassir AL-Jawaheri,(2019), "An Efficient synthesis of natural products using singlet oxygen", Ph.D. thesis.

[13] Gece C.,2008. The use of quantum chemical methods in corrosion inhibitor studies. Corros.Sci, 50(11),2981-2992,.

[14] Fukui.K.,(1975-1987),"Theory of Orientation and Steroselection", Vol.281 spring Ver.1, Berlin, 747.

[15] Ding E, Ying N, Zhou Y, Lei T. 2010. Polycyclic imide derivative synthesis and effective tuning of Lowes unoccupied molecular orbitals levels through molecular. Engineering Org.Lettt, 12(23), 55222-5525.

[16] Pearson R.G.,(1995),"The HSAB principle – more quantitative aspects ", Inorganic Chimica Acta , 240,93-98.

[17] Pearson R , 1986. ”Absolute electro-negativity and hardness correlated with molecular orbital theory. National Academy of Science , 83, 8440-8441.

[18] Hanae T., Taher A., Amel B. 2017. “ Theoretical investigations on the molecular structure HOMO-LUMO. Fukui function, NBO analysis and NLO of amino methyl tetrathiofulvalenes compounds by DFT method, International Journal of Chemical Studies , 5(6),1368-1375.

[19] Cheng F.,Liw,Zhou Y., 2019. “ADMET SAR Comprehensive source and free tool for assessment of chemical information and modeling , 52,3092-3105.

[20] Okoli P.T., Nzute V.C., Durogaye O.A., Chielo O.H.,Rjibo Q.C., Udu S.I., et al .2019. ” An In-Silico pharmacokinetics study on cis. A Nutraceutical compound with anticancer properties, 7(3), 1-17.

[21] Silva A.B., Maiinho M.M., Mendes F.R.D.S., 2019. “In-silico study of phytochemical chlorogenic acid :A semi-empirical quantum study and adme”. Int. J Recent Res Rev, XIII(2): 34-9 .

[22] Lewars E.G.,2016. “Computational chemistry : Introduction to the theory and applications of molecular and quantum mechanics”, third edition .

[23] Sandy P.E., Froucisco R. D., Emaonauelle M.M..2019. International Journal of Research Granthaalayall, (Vol 7) 15510, 429-445 .

[24] Marino E.S.,2016. ADET study of synthetic drug topiroxostat , MEP, HOMO,LUMO. Int. J.Sci Eng Res,(7), 1264-1270 .

[25] Lai T.Y, Guo J.D., Fettinger J.C., Nagase S., Power P.P. , 2019. ” Facile insertion of ethylene into a group 14 element-carbon bond: effects of the HOMO-LUMO energy gap on reactivity”. Chem Commun.55,405-407 .

[26] Rottschäfer D., Sharma M.K., Neumann B., Stammle H.G., Andrada D.M., Ghadwal R.S. 2019 “A Modular Access to Divinyldiphosphenes with a Strikingly Small HOMO–LUMO Energy Gap”. Chem - A Eur J. 25(34), 8127-8134 .

[27] Amin M.L.,2013 . ” p- glycoprotein inhibitor for optimal drug delivery”. Drug target insights , 7, 27 .