Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2019, 11(8):1-8

Research Article

ISSN: 0975-7384
CODEN(USA): JCPRC5

DFT and Docking Studies on Anti-Leukemia Activities of Selected Flavonoids

Erazua Ehimen A[1], Folorunso Aderonke S[2], Akintelu Sunday A[3], Semire Banjo[3] and Oyebamiji Abel Kolawole[3,4*]

[1]*Department of Chemistry, University of Ibadan, Ibadan, Nigeria*

[2]*Department of Chemistry, Louisiana State University, Louisiana, USA*

[3]*Computational Chemistry Laboratory, Department of Pure and Applied Chemistry, LadokeAkintola University of Technology, P.M.B 4000, Ogbomoso, Oyo State, Nigeria*

[4]*Department of Basic Sciences, Adeleke University, P.M.B. 250, Ede, Osun State, Nigeria*

ABSTRACT

*Flavonoids are polyphenolic compounds which have beneficial effects for health and might be considered as potential therapeutic agents. Anticancer activities of some selected flavonoids against leukemia cell line were studied using quantum chemical method through density functional theory (DFT) and molecular docking approach. These Flavonoids were docked against leukemia cell line (protein code: **1aol**) and the correlation between the calculated descriptors and their binding affinity with leukemia cell line were examined. The obtained binding energy showed that taxifolin has the highest inhibition efficiency against **1aol** than other studied compounds, while Daidzein has the least inhibition efficiency. It was observed that molecular weight, polar surface area (PSA), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD) and lipohilicity (log p) influenced the binding ability of the studied flavonoids in the active gouge of the protein.*

Keywords: Molecular docking; DFT; Anticancer; Novel drugs; Flavonoids

---

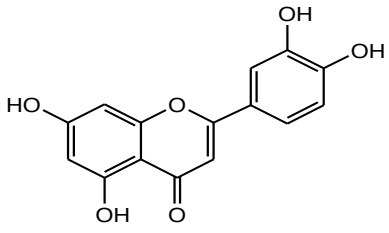
INTRODUCTION

Leukemia is a common malignant tumor that occurs when alterations in normal cell regulatory processes cause uncontrolled proliferation of hematopoietic stem cells in the bone marrow [1]. It affects millions of people yearly leading to almost one-third of all cancer deaths [2-3]. This disease can affect all age groups; it causes about 30% of all cancer-related deaths in children and adolescents under the age of 14 years [3-6]. Leukemia is of four different types namely; acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) [1,4]. It is usually treated by chemotherapy, radiotherapy, immuno-therapy and bone marrow transplantation. Treatment failure may occur because standard

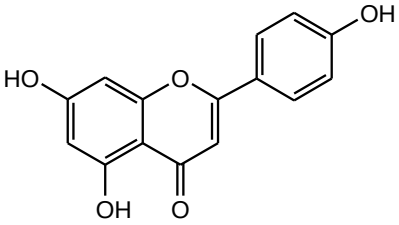
chemotherapy agents are often associated with toxicity towards normal cells resulting in severe side effects, high cost of chemotherapy agents and also because of increased occurrence of drug resistance [7-9]. Hence there is a need to find newer agent with lower toxicity and higher efficacy that can improve patient survival rates.

Several bioactive components from natural products have been used as curing agents with few side effect against various chronic diseases including cancer [10]; among these are Flavonoids which are polyphenolic phytochemicals of low molecular weight that posses benzopyrone structure, a versatile class of natural compounds that represent secondary metabolites [11,12]. Flavonoids consist of C6-C3-C6 ring as basic structure, with different substitutes to create various subclasses such as flavones, flavanol, flavonol, isoflavones, anthocyanins [12]. They are naturally present in fruits, vegetables as well as in beverages, such as red wine and tea [13,14]. Over the years, flavoniods have been evaluated in the prevention and treatment of different diseases with lower side effect, such as antioxidant, anti-cancer, anti-inflammatory, antibacterial and antiviral effects [15-19]. As a result of the diversity of flavonoids, the use of computational designs and molecular information on flavonoid compounds is necessary to enables the selection of the optimum compounds which are aimed at identifying alternative drugs with greater impact. Docking of small molecules in the receptor binding site and estimation of binding affinity of the complex is a vital part of structure based drug design.

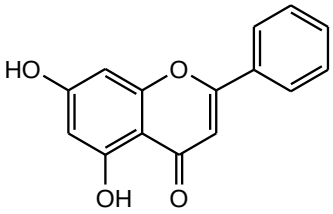
In this study, eleven flavoniods namely; Luteolin, apigenin, chrysin, quercetin, galangin, hesperetin, naringenin, taxifolin, daidzein, kaempferol, and genistein were investigated by using density functional theory (DFT) [20,21] and docking methods. The objectives of this work are (i) to use quantum chemical method via density functional theory methods for the calculation of molecular parameters that may explain the bioactivities of the flavoniods used in this work, (ii) to study the link that exist between the studied molecules (ligands) and leukemia cell line (protein code:**1aol**) and (iii) to observe the correlation between the calculated descriptors and the binding affinities of the ligands.



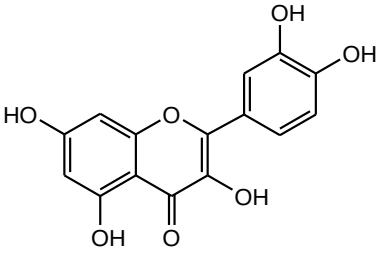
Luteolin



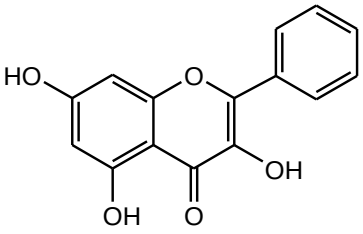
Apigenin



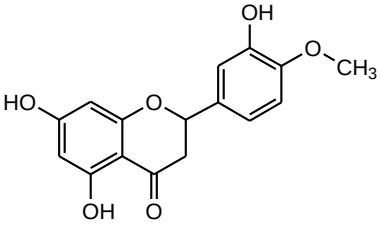
Chrysin



Quercetin



Galangin



Hesperetin

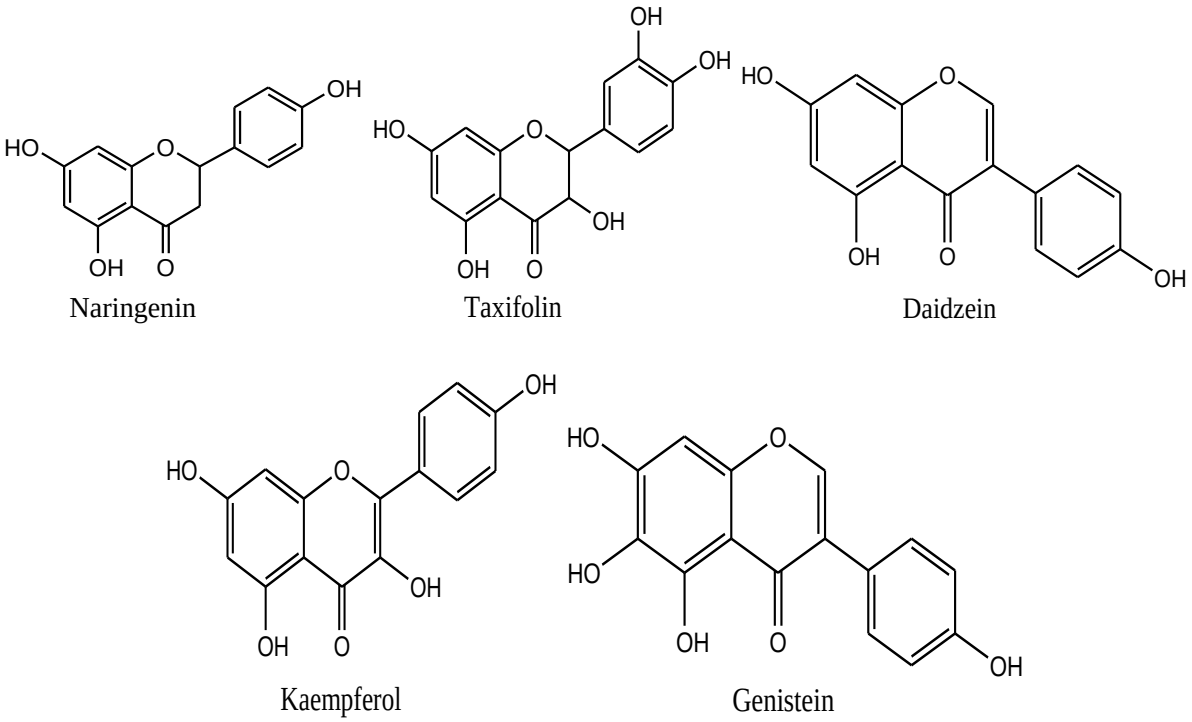


Figure 1. The Schematic Structure of the Studied Flavonoids

METHODS

Quantum Chemical Methods

Eleven flavonoids as shown in Figure 1 were obtained from literature [22]. These Flavoniods were optimized via density functional theory via 6-31G* basis set and this was accomplished with B3LYP density functionals. This theory comprises of Becke's gradient exchange [23] and Lee, Yang and Parr correlation [24]. The software used for this optimization was Spartan '14 software by wavefunction Inc [25].

Molecular Docking Study

All compounds were docked to catalytic binding sites of leukemia cell lines (PDB:**1aol**) [26] downloaded from protein data bank to predict their binding modes and approximate binding free energies. The receptor protein was prepared using Discovery Studio 4.1 visualizer. Autodock tool was used to locate the binding site and convert the optimized ligands and the receptor to pdbqt format. Computational docking was executed with the AutoDockVina software [27]. BioviaDiscovery Studio visualizer 2017 [28] was used to analyze the output of docking process. The grid dimensions used for **1aol** using AutoDock Vina Programme are 54 × 40 × 40 Å (grid size) and the grid point spacing is 1.000Å. Also, the grid centres were specified at 52.074Å, 39.233Å and 44.389Å for X, Y and Z respectively. Default value (8) for exhaustiveness was used for the docking runs and nine (9) conformations each were observed for the docking study with their respective affinity.

RESULTS AND DISCUSSION

Molecular Docking Study

The correlation between the calculated molecular descriptors and the binding affinities of the flavonoids are

explained in this work. Calculated molecular descriptors namely; E_{HOMO} (highest occupied molecular orbital energy), E_{LUMO} (lowest unoccupied molecular orbital energy),dipole moment (DM), Band gap (BG), molecular weight (MW), Chemical potential (CP), area, volume (VOL), polarizability (POL), polar surface area (PSA), partition coefficient (Log P), hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) for the studied flavonoids are shown in Table 1. The binding affinity for each complex formed by the flavonoids (ligand) with the protein (**1aol**) is also shown in Table 1. The value of binding affinity obtained are -6.6Kcal/mol for luteolin, Apigenin, chrysin and Naringenin, -6.8 Kcal/mol for quercetin, -6.3 Kcal/mol for Galangin, -6.5 Kcal/mol forHesperetin, -6.9 Kcal/mol for Taxifolin, -6.1 Kcal/mol for Daidzein, -6.7 Kcal/mol for Kaempferol and -6.2 Kcal/mol for Genistein. This showed that taxifolin possesses the highest inhibiting efficiency than other studied flavonoids. Hence it has the highest ability to inhibit the active gouge of the protein (**1aol**) and form the most stable complex. On the other hand daidzein will have the least inhibiting efficiency than other studied flavonoids as a result of it having the highest binding affinity. Hence it will have the least ability to inhibit the active gouge of the protein (**1aol**) and form the least stable complex.

Table 1. The Selected Molecular Descriptors Generated by B3LYP/6-31G*

Flavonoids	Homo (eV)	Lumo (eV)	BG (eV)	DM (Deby)	CH	MW(amu)	AREA (A2)	VOL (A3)	POL	PSA (Å2)	LOGP	HBD	HBA	AFFINITY(kcal/mol)
Luteolin	-5.85	-1.64	4.21	7.55	2.11	286.24	273.5	259.2	61.4	92.64	1.01	4	6	-6.6
Apigenin	-6.06	-1.6	4.46	5.76	2.23	270.24	266.06	252.4	60.79	74.86	1.4	3	5	-6.6
Chrysin	-6.18	-1.7	4.48	4.29	2.24	254.24	257.33	245.38	60.22	55.22	1.79	2	4	-6.6
Quercetin	-5.69	-1.72	3.97	1.89	1.96	302.24	280.81	266.42	62.05	109.98	-0.07	5	7	-6.8
Galangin	-5.94	-1.77	4.17	2.4	2.09	270.24	264.74	252.6	60.88	72.617	0.71	3	5	-6.3
Hesperetin	-5.71	-1.44	4.27	5.05	2.14	302.28	299.23	283.43	63.36	79.99	1.5	3	6	-6.5
Naringe	-6	-	4.	2.99	2.	272.26	270.	256.	61.	75.0	1.6	3	5	-6.6

nin		1.44	46		23		8	56	11	2	3			
Taxifolin	-5.74	-1.65	4.09	2.51	2.05	304.25	286.49	271.06	62.39	110.92	0.58	4	7	-6.9
Daidzein	-5.86	-1.46	4.4	3.17	2.2	254.24	259.71	246.31	60.31	59.87	2.13	2	4	-6.1
Kaempferol,	-5.8	-1.69	4.11	2.16	2.06	286.24	273.45	259.61	61.46	92.25	0.32	4	6	-6.7
Genistein	-5.85	-1.5	4.35	2.05	2.18	270.24	264.66	252.23	60.81	74.35	1.74	3	5	-6.2

HOMO and LUMO energy characterizes the ability to give out and accept electron respectively. They provide information about excitation characteristics of a molecule [29,30]. A higher E_{HOMO} signifies greater tendency to donate electrons and better reactivity, while a lower E_{LUMO} signifies greater tendency to accept electron and a better reactivity. The calculated E_{HOMO} for the studied flavonoids ranges from -6.18eV for chrysin to -5.69 eV for quercetin, while E_{LUMO} ranges -1.77eV for galangin to -1.50eV for genistein.

The energy gap between the HOMOs and LUMOs is also a measure of reactivity and it is important to drug-receptor interactions. Molecules with narrower energy gap have higher chemical reactivity and better ability to inhibit the active site of protein [31,32]. For the studied flavonoids based on band gap value the order of reactivity is quercetin > Taxifolin > Kaempferol > Galangin > luteolin > Hesperetin > Genistein > Daidzein > Apigenin > Naringenin > chrysin. Therefore, there is no correlation between the calculated band-gap and the binding affinity since a lower band-gap enhanced inhibition efficiency of a molecule.

The distribution of a molecule between aqueous and non-aqueous phase is measured by its log p value. Log P is the total estimation of a molecule's overall lipophilicity and has a major effect on solubility, absorption, distribution, metabolism and the biological activity of ligands [33-35]. In this study, daidzein has the highest value of log p (2.13) and also have the lowest binding affinity (-6.1 Kcal/mol).

Polar surface area (PSA) is a sum of surfaces of polar atoms in a molecule and it allows prediction of transport properties of drugs. Molecules with a PSA greater than 140 $Å^2$ are usually believed to be poor at permeating cell membranes [36,37]. The PSA value for studied flavonoids ranges form (55.216 $Å^2$-110.920 $Å^2$), hence they will effectively penetrate cell membranes. However Taxifolin has the highest value of PSA, this may also contribute to its higher inhibiting ability.

This study also revealed that daidzein with lowest calculated molecular weight has the highest binding energy and hence has the lowest tendency to inhibit the studied protein, while Taxifolin with highest molecular weight and lowest binding energy, inhibited most among the studied flavonoids. Therefore, it may be suggested that larger

molecular weight compounds tend to have stronger binding affinity. Moreso, taxifolin has the highest number of HBA (7) while daidzein has the least number of HBA this may also suggest that the higher the number of HBA the greater the inhibition efficiency of a molecule and hence the stronger the ligand-protein interaction. It was also observed that daidzein has the lowest number of HBD; hence lower number of HBD may contribute to weaker ligand protein interaction.

Interaction between Flavoniods (Ligand) and Receptor (1aol)

The interaction between the ligand and the receptor are shown in Table 2. Figure 2 shows the interaction between the taxifolin and the receptor. several interactions were observed between the studied flavoniods (ligand) and the receptor such as van der waal, Pi-Anion, Amide Pi-Stacked, Pi Alkyl, Pi-Sulfur, Unfavorable Donor-Donor, Pi-Sigma, Pi-Pi T-shaped, Pi-Cation, Pi-Donor Hydrogen bond, Conventional Hydrogen bond and Carbon Hydrogen bond. The presence of Hydrogen bond interaction in taxifolin enhanced its grip onto the active site of leukemia cell line (**1aol**) resulting into lower binding affinity.

Table 2. Interactions between Ligands and 1aol receptor

Ligands	Interactions between Ligands and protein.
Luteolin	(i) TYR-64 (ii) SER-66 (iii) SER-65, LIG: H, (iv) PRO-286 (v)TRP-183 (vi) MET-47 (vii) ASN-185 (viii) ASP-44 (ix) CYS-184 (x)VAL-177 (xi) LEU-169 (xii) THR-42, LIG:O (xiii) TRP-26, LIG:O
Apigenin	(i) PRO-186 (ii) THR-42 (iii) TRP-26, LIG: H, O (iv) MET-47 (v) TYR-64, LIG: H (vi) SER-65, LIG: H (vii) SER-66 (viii) TRP-183, LIG: O (ix) ASP-44, LIG: H (x) ASN-185 (xi) CYS-184
Chrysin	(i) LYS-182 (ii) PRO-67 (iii) TRP-183 (iv) ASP-44 (v) TRP-26 (vi) MET-47, LIG: H (vii) PRO-43 (viii) THR-42 (ix) PRO-186 (x) CYS-184 (xi) LEU-169 (xii) VAL-177
Quercetin	(i) ASN-185 (ii) CYS-184 (iii) LEU-169 (iv) VAL-177 (v) ASP-44 (vi) PRO-186 (vii) MET-47 (viii) TYR-64, LIG: H (ix) SER-66 (x) LEU-50 (xi) SER-65, LIG: H (xii) TRP-183, LIG: H,O (xiii) TRP-26 LIG: O (xiv) THR-42, LIG: O
Galangin	(i) TYR-64 (ii) TRP-26, LIG: O (iii) THR-42 (iv) PRO-186 (v) ASN-185 (vi) CYS-184 (vii) ASP-44 (viii) MET-47 (ix) TRP-183, LIG: O (x) SER-65
Hesperetin	(i) PRO-54 (ii) PRO-53 (iii) GLY-52 (iv) SER-51 (v) ASP-21 (vi) GLY-20 (vii) THR-221 (viii) PRO-136 (ix) ASP-137 (x) PHE-139
Naringenin	(i) ASP-137 (ii) PRO-53 (iii) ASP-21, LIG: H (iv) SER-51, LIG: H (v) GLY-52 (vi) GLY-20 (vii) LEU-220 (viii) THR-221, LIG: H, O (ix) PHE-139 (x) PRO-136
Taxifolin	(i) HIS-55 (ii) ARG-216 (iii) PRO-218 (iv) THR-95 (v) PRO-96 (vi) SER-214, LIG:O (vii) VAL-110 (viii) VAL-213 (ix) GLU-116, LIG: H (x) GLN-109 (xi) LYS-113 (xii) LYS-106 (xiii) THR-92 (xiv) SER-93 (xv) LEU-94
Daidzein	(i) THR-171 (ii) GLN-109, LIG: O (iii) LEU-91 (iv) LYS 179 (v) CYS-87, LIG: H (vi) ASP-88 (vii) GLU-89 (viii) LEU-105 (ix) VAL-175
Kaempferol	(i) THR-42, LIG: H (ii) TRP-26, LIG: O (iii) TYR-64 (iv) PRO-67 (v) SER-65, LIG: H (vi) SER-66 (vii) PRO-186 (viii) TRP-183, LIG: O (ix) MET-47 (x) ASP-44 (xi) ASN-185 (xii) CYS-184 (xiii) VAL-177 (xiv) LEU-169
Genistein	(i) LEU-105 (ii) GLU-89 (iii) ASP-88 (iv) CYS-87, LIG: H (v) LYS-179 (vi) LEU-91 (vii) GLN-109, LIG: O (viii) VAL-175 (ix) THR-171

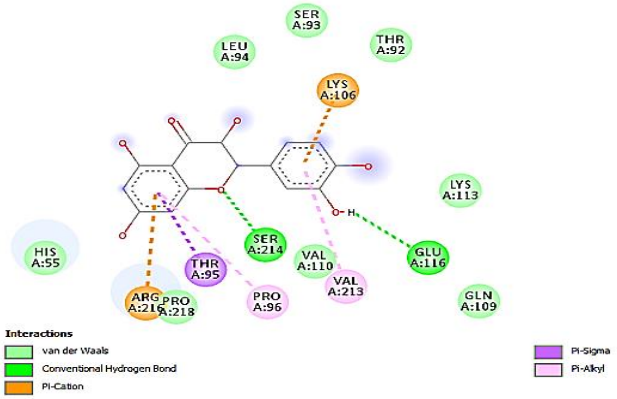


Figure 2. Binding Interactions between ligand (Taxifolin) and Receptor (1aol).

CONCLUSIONS

Some selected flavonoids were studied by Density functional theory calculation and molecular docking approach. These flavonoids were docked to the active site of leukemia cell line (protein code:**1aol**) and from the binding energies obtained taxifolin inhibited effectively more than other studied flavonoids. The correlation between the molecular descriptors and calculated binding affinity showed that higher value of PSA, higher molecular weight and higher number of HBA enhanced the inhibiting strength of the ligand (taxifolin) thereby resulting to lower binding affinity.

REFRENCES

[1] AS Davis; AJ Viera; MD Mead. *Am Fam Physician.* **2014**, 89(9), 731-738.

[2] D Zhang; Y Zhuang; J Pan; H Wang; H Li; Y Yu; D Wang; D. Oxid. *Med Cell Longev*. **2012**, 2012, 1-5

[3] AA Mahbub; CL Le Maitre; SL Haywood-Small; GJ McDougall; NA Cross; N Jordan-Mahy. *Med Chem*. **2013**, 13(10), 1601–1613

[4] S Zhong; Z Chen; X Yu; W Chen; M Lv; T Ma, J Zhao. *Tumour Biol*. **2014**, 35(6), 5205-5212.

[5] H Chang; H Lin; L Yi; J Zhu; Y Zhou; M Mi; Q Zhang. *Eur J Pharmacol*. **2010**, 648(1-3), 31–38.

[6] X Liu; F Ye; J Wu; B How; W Li; DY Zhang. *Nutr Cancer*. **2015**, 67(2), 238-249.

[7] DEI Gerber. *Am Fam Physician*. **2008**, 77(3), 311-319.

[8] A Davenport; M Frezza; M Shen; Y Ge; C Huo; TH Chan; QP Dou. *Int J Mol Med.* **2010**, 25(3), 465-470

[9] RF Li; YQ Feng; JH Chen; LT Ge, SY Xiao; XL Zuo. *Ther Med*. **2015**, 9(3), 697-706.

[10]. AD Panche; AD Diwan; SR Chandra. *J Nutr Sci.* **2016**, 5(47), 1-15.

[11] A Wasim; V Garima; KM Faraz; S Mohammad; A Mymoona; A Ozair1; A Mohammad; T Sarwat; AM Mumtaz. *Int J Drug Dev Res*. **2017**, 9(2), 26-32.

[12] B Yang; H Liu; J Yang; VK Gupta; Y Jiang. *Trends Food Sci. Technol*. **2018**, 79, 116–124.

[13] KC Maheep; S Neelu; PD Mahabeer; CJ Yogesh. Pharmacogn Rev. **2011**, 5(9), 1-12.

[14] RL Nagula; S Wairkar. *J Control Release*. **2019**, 296, 190-201

[15] SK Katiyar; M Athar. *Cancer Prevention Research.* **2013**, 6, 617-621.

[16] Y Bandaruk; R Mukai; J Terao. *Toxicol Rep*. **2014**, 1, 639-649

[17] MA Alam; N Subhan; MM Rahman; SJ Uddin; HM Reza; SD Sarker. *Adv Nutr*. **2014**, 5, 404–417.

[18] P Karak. *International Journal of Pharmaceutical Sciences and Research*, **2019,** 10(4), 1567-1574.

[19] C Rodríguez-García; C Sánchez-Quesada; JJ Gaforio. *Antioxidants*. **2019**, 137(8), 1-25.

[20] RG Parr; W Yang. *J Am Chem Soc*. **1984**, 106 (14), 4049-4050.

[21] MK Awad. *J Electroanal Chem*. **2004,** 567(2), 219-225.

[22] S Kumar; AK Pandey. *The Scientific World Journal*, **2013**, 1-16.

[23] AD Becke. *J Phy Chem.* **1993,** 98, 5648 -5652.

[24] C Lee; W Yang; RG Parr. *Phys Rev B*. **1988**, 37, 785-789.

[25] Spartan 14, Wavefunction, INC, Irvine CA 92612, USA.

[26] D Fass; RA Davey; CA Hamson; PS Kim; JM Cunningham; JM Berger. 1997,

[27] O Trott; AJ Olson. *Journal of Computational Chemistry*. **2010**, 31, 455-461.

[28] Biovia, Wateridge vista drive, San Diego, CA 92121, USA 2005.

[29] JX Mu; MY Yang; ZH Sun; CX Tan; JQ Weng; HK Wu; XH Liu. *Crystals.* **2015**, 5(4), 491-500.

[30] AK Oyebamiji; B Semire. *Bulletin of Pharmaceutical Research.* **2017**, 7(3),148.

[31] PT Taslı; A Bayrakdar; OO Karakus; HH Kart; Y Koc. *Optics and Spectroscopy*. **2015**, 119(3), 467-484.

[32] DF Lewis. *Toxicol Model*. **1995**. 1, 85-97.

[33] JD Hughes; B Julian; P David; B Simon; AD Gary, D Rajesh; Bioorg. *Med Chem Lett.* **2008,** 18(17), 4872-4875.

[34] A Khaled; R Petri; M Sampo; P Olavi. *Xenobiotica*. **2011**, 41,101-111.

[35] Z Almi; B Salah; L Touhami; T Noureddine. *International Letters of Chemistry, Physics and Astronomy*. **2014**, 37,113-124

[36] P Ertl; B Rohde; P Selzer. *Journal of Medicinal Chemistry*. **2000**, 43, 3714-3717.

[37] M Bouachrine; M Hamidi; SM Bouzzine; H Taoufik. *Journal of Chemical Research.* **2009**, 10, 29-37.