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Theoretical Approach on the Structural aspects of 2,2'-[5-(1,2,4-triazolidin-1-ylmethyl)benzene-1,3-diyl]bis(2-methylpropaneniti le) (Anastrozole) and its Molecular Docking Studies with Promyelocytic Leukemia Protein

Igwe Kalu Kalu [1], Amaku Friday James [2] and Otuokere Ifeanyi Edozie [3]

[1] Department of Vet. Biochemistry and Pharmacology,Michael Okpara University of Agriculture, Umudike, Abia +234 / Nigeria

[2] Department of Chemistry, Michael Okpara University of Agriculture, Umudike, Abia ,+234 / Nigeria

[3] Department of Chemistry, Michael Okpara University of Agriculture, Umudike, Abia ,+234 / Nigeria

Abstract

2,2'-[5-(1,2,4-triazolidin-1-ylmethyl)benzene-1,3-diyl]bis (2-methylpropanenitrile) also known as anastrozole or arimidex is an aromatase inhibitor approved worldwide for an effective primary adjuvant treatment for postmenopausal women with early-stage breast cancer . Theoritical studies were based on molecular mechanics. The universal force field (UFF) molecular mechanics method have been used to calculate the steric energy of 2,2'-[5-(1,2,4-triazolidin-1-ylmethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile) anastrozole using Argus lab software. Molecular mechanics calculations were based on specific interactions within the molecule. These interactions included stretching or compressing of bond beyond their equilibrium lengths and angles, torsional effects of twisting about single bonds, the Van der Waals attractions or repulsions of atoms that came close together, and the electrostatic interactions between partial charges in a anastrozole due to polar bonds. The steric energy calculated for anastrozole was 470.05kcal/mol. It was concluded that the lowest energy and most stable conformation of anastrozole was 470.05 kcal/mol. The most energetically favourable conformation of anastrozole was found to have a heat of formation of 113249.91 kcal/mol. Molecular docking was performed using Patchdock and firedock online docking server. Molecular docking result showed the global energies and their ranks. The global binding energy value -26.85 Kcal/mole was ranked first because it had the least energy. The most feasible position for anastrozole to inhibit promyelocytic leukemia protein was found to be -26.85 kcal/mol.

Keywords: Anastrazole, molecular mechanics, Arguslab software, global energy.

1. Introduction

2,2'-[5-(1,2,4-triazolidin-1-ylmethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile also known as anastrozole or arimidex is an aromatase inhibitor approved worldwide for an effective primary adjuvant treatment for postmenopausal women with early-stage breast cancer [1]. Aromatase is an enzyme that synthesizes estrogen. Breast and ovarian cancer require estrogen to grow [2]. Aromatase inhibitors are taken to either block the production of estrogen or block the action of estrogen on receptors [2].The class of compounds known as aromatase inhibitors offers potential benefits in the management of breast carcinoma, particularly for postmenopausal patients with advanced disease [3-5]. Since the development of aminoglutethimide, new generations of aromatase inhibitors have been synthesized; all these compounds are substantially more potent than aminoglutethimide as inhibitors of the aromatase enzyme [6]. One of the new aromatase inhibitors is anastrozole, an achiral benzytriazole derivative, which has highly effective and selective activity for the aromatase enzyme[7].

Argus Lab is an electronic structure program that is based on the quantum mechanics, it predicts the potential energies, molecular structures, geometry optimization of structure, vibration frequencies of coordinates of atoms, bond length, bond angle and reactions pathway [8]. Conformational analysis of molecule is based on molecular mechanics, it is method for the calculation of molecular structures, conformational energies and other molecular properties using concept from classical mechanics. A molecule is considered as a collection of atoms held

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together by classical forces. These forces are described by potential energy function of structural features like bond lengths, bond angles and torsion angles etc. The energy (E) of the molecule is calculated as a sum of terms as in equation (1).

$E = E_{stretching} + E_{bending} + E_{torsion} + E_{Vander\ Waals} + E_{electrostatic} + E_{hydrogen\ bond}$ + cross term

These terms are of importance for the accurate calculation of geometric properties of molecules. The set of energy functions and the corresponding parameters are called a force field [9].

Acute promyelocytic leukemia (APL) is a cancer of the white blood cells 1. In APL, there is an abnormal accumulation of immature granulocytes called promyelocytes. Currently it is one of the most treatable forms of leukemia with a 12-year progression-free survival rate that is estimated to be approximately 70% [10,11]. In line with this progressive treatment trend we have decided to dock anastrozole with promyelocytic leukemia and determine its binding free energy, geometry optimization and excited state properties.

2. Materials and Method

Increase in quest for a high level of accuracy in computational studies created tools to construct models, minimization and representations of molecular structure [12,13]. All conformational analysis (geometry optimization) study was performed on a window based computer using Argus Lab 4.0.1 [14,15] and ACD Lab Chem Sketch software. Anastrozole structure was sketched with ACD Lab Chem Sketch software and saved as MDL molfiles (*mol). The Anastrozole structure was generated by Argus lab, and minimization was performed with UFF molecular mechanics method [16 – 18]. The minimum potential energy was calculated by using geometry convergence function in Argus lab software. Surfaces created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potentials (ESP) spin densities and generated the grid data used to make molecular orbital surfaces to visualize the molecular orbital and making an electro static potential mapped on electron density surface [19]. The minimum potential energy was calculated for anastrozole through the geometry convergence map.

Retrieval of promyelocytic leukemia protein

Crystal structure of promyelocytic leukemia protein from the organism *Homo sapiens* with the PDB ID 1BOR was retrieved from the Protein Data Bank (PDB)

Molecular docking

Molecular docking was performed using patchdock online server [20]. Patchdock is a molecular docking algorithm based on shape complementarity principles**.** The Receptor (promyelocytic leukemia protein) and ligand molecule (anastrozole) were uploaded in PDB format in Patchdock server, an automatic server for molecular docking. Clustering RMSD was chosen as 1.5 Å. E-mail address to retrieve the result was given. Complex type was chosen as enzyme – inhibitor type. The docking job was submitted to the Patchdock server , refined in firedock online server [21,22] and opened with swissPDB viewer [23,24].

3. Results and Discussion

The molecule 2,2'-[5-(1,2,4-triazolidin-1-ylmethyl)benzene-1,3-diyl]bis(2-methylpropane nitrile) Anastrozole was built using molecule builder of Argus lab. The "Molecule Settings of 2,2'-[5-(1,2,4-triazolidin-1-ylmethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile) anastrozole was atoms 45, net charge +1 and valence electrons 92. The Prospective view , electron density clouds, prospective view of active conformation, highest occupied molecular orbital, lowest unoccupied molecular orbital, electrostatic potential mapped density of anastrozole, crystal structure of promyelocytic leukemia protein and anastrozole - promyelocytic leukemia protein complex care shown in Figures 1 – 8 respectively. The atomic coordinates, bond length, bond angles, dihedral angles , improper torsions, molecular mechanics final energy evaluation of anastrozole and molecular docking result of anastrozole - promyelocytic leukemia protein are shown in Tables 1 – 7 respectively.

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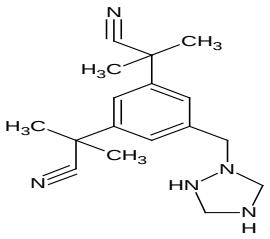

Molecular Formula	= $C_{17}H_{23}N_5$
Formula Weight	= 297.39802
Composition	= C(68.66%) H(7.80%) N(23.55%)
Molar Refractivity	= 85.25 ± 0.3 cm^3
Molar Volume	= 270.2 ± 3.0 cm^3
Parachor	= 705.4 ± 6.0 cm^3
Index of Refraction	= 1.543 ± 0.02
Surface Tension	= 46.4 ± 3.0 dyne/cm
Density	= 1.100 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 33.79 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 297.195346 Da
Nominal Mass	= 297 Da
Average Mass	= 297.398 Da

Figure 1: Prospective view of 2,2'-[5-(1,2,4-triazolidin-1-ylmethyl)benzene-1,3-diyl]bis(2-methyl propanenitrile), anastrozole by ACD/Chemsketch

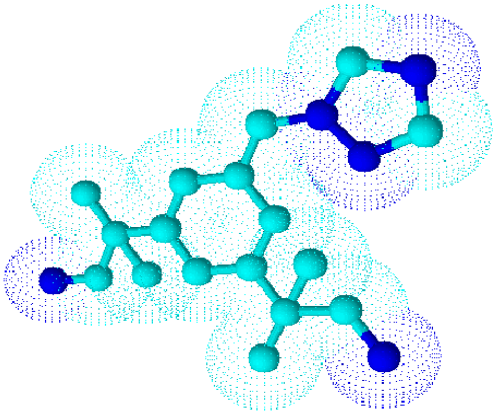

Fig. 2: Electron density clouds of Anastrozole by ACD Labs. 3D viewer

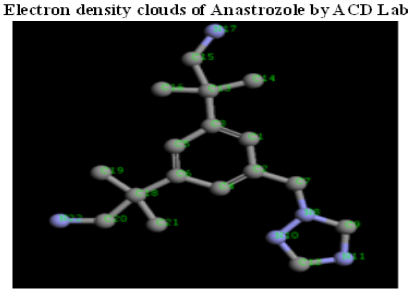

Figure 3: Prospective view of active confor of anastrozole by Arguslab software.

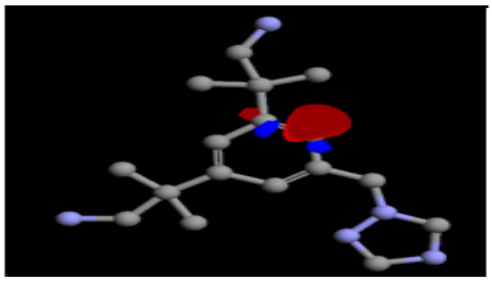

Figure 4: Highest Occupied Molecu Orbital of anastrozole.

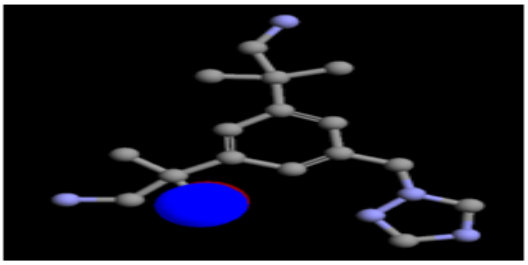

Figure 5: Lowest Unoccupied Molecular Orbital of anastrozole.

Figure 6: Electrostatic potential mapped density of anastrozole.

Figure 7: Crystal structure of promyelocytic leukemia protein in ribbon shape (1BOR PDB)

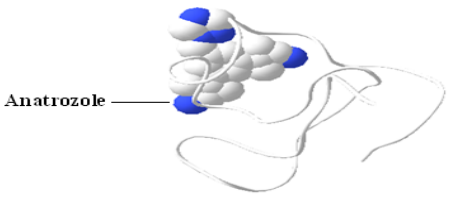

Figure 8: Anatrozole in complex with promyelocytic leukemia protein

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Table 1: Atomic coordinates of anastrozole.

S/NO	Atoms	X	Y	Z
1	C	22.047300	-11.641500	0.000000
2	C	22.047300	-12.971500	0.000000
3	C	20.895400	-10.976500	0.000000
4	C	20.895400	-13.636500	0.000000
5	C	19.743600	-11.641500	0.000000
6	C	19.743600	-12.971500	0.000000
7	C	23.199100	-13.636500	0.000000
8	N	23.199000	-14.966500	0.000000
9	C	24.275000	-15.748300	0.000000
10	N	22.123000	-15.748300	0.000000
11	N	23.864000	-17.013200	0.000000
12	C	22.534100	-17.013400	0.000000
13	C	20.895300	-9.646500	0.000000
14	C	22.047100	-8.981500	0.000000
15	C	19.743500	-8.981500	0.000000
16	C	19.743500	-10.311500	0.000000
17	N	19.743500	-7.651500	0.000000
18	C	18.591800	-13.636500	0.000000
19	C	17.440000	-12.971500	0.000000
20	C	18.591700	-14.966500	0.000000
21	C	19.743600	-14.301500	0.000000
22	N	17.439900	-15.631500	0.000000

Table 2: Bond length of anastrozole.

Atoms	Bond Length
(C1)-(C2)	1.458000
(C1)-(C3)	1.323387
(C2)-(C4)	1.323387
(C2)-(C7)	1.461000
(C3)-(C5)	1.458000
(C3)-(C13)	1.486000
(C4)-(C6)	1.458000
(C5)-(C6)	1.323387
(C6)-(C18)	1.486000
(C7)-(N8)	1.436817
(N8)-(C9)	1.433804
(N8)-(N10)	1.398000
(C9)-(N11)	1.433804
(N10)-(C12)	1.433804
(N11)-(C12)	1.433804
(C13)-(C14)	1.489000
(C13)-(C15)	1.489000
(C13)-(C16)	1.489000
(C15)-(N17)	1.437821
(C18)-(C19)	1.489000
(C18)-(C20)	1.489000
(C18)-(C21)	1.489000
(C20)-(N22)	1.437821

Table 3: Bond angles of anastrozole.

Atoms	Angles	Alternate angles
(C2)-(C1)-(C3)	120.000000	216.488007
(C1)-(C2)-(C4)	120.000000	216.488007
(C1)-(C2)-(C7)	120.000000	187.861407
(C1)-(C3)-(C5)	120.000000	216.488007
(C1)-(C3)-(C13)	120.000000	209.804299
(C4)-(C2)-(C7)	120.000000	215.760874
(C2)-(C4)-(C6)	120.000000	216.488007
(C2)-(C7)-(N8)	120.000000	255.456798
(C5)-(C3)-(C13)	120.000000	183.094781
(C3)-(C5)-(C6)	120.000000	216.488007
(C3)-(C13)-(C14)	109.470000	225.865192
(C3)-(C13)-(C15)	109.470000	225.865192
(C3)-(C13)-(C16)	109.470000	225.865192
(C4)-(C6)-(C5)	120.000000	216.488007
(C4)-(C6)-(C18)	120.000000	183.094781
(C5)-(C6)-(C18)	120.000000	209.804299
(C6)-(C18)-(C19)	109.470000	225.865192
(C6)-(C18)-(C20)	109.470000	225.865192
(C6)-(C18)-(C21)	109.470000	225.865192
(C7)-(N8)-(C9)	120.000000	197.520556
(C7)-(N8)-(N10)	120.000000	272.827854
(C9)-(N8)-(N10)	120.000000	273.709525
(N8)-(C9)-(N11)	120.000000	350.783913
(N8)-(N10)-(C12)	120.000000	273.709525
(C9)-(N11)-(C12)	120.000000	198.144139
(N10)-(C12)-(N11)	120.000000	350.783913
(C14)-(C13)-(C15)	109.470000	225.183707
(C14)-(C13)-(C16)	109.470000	225.183707
(C15)-(C13)-(C16)	109.470000	225.183707
(C13)-(C15)-(N17)	120.000000	247.861261
(C19)-(C18)-(C20)	109.470000	225.183707
(C19)-(C18)-(C21)	109.470000	225.183707
(C20)-(C18)-(C21)	109.470000	225.183707
(C18)-(C20)-(N22)	120.000000	247.861261

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Table 4: Dihedral angles of anastrozole.

Atoms	Dihedral Angles
(C4)-(C2)-(C1)-(C3)	5.000000
(C7)-(C2)-(C1)-(C3)	5.000000
(C2)-(C1)-(C3)-(C5)	19.486776
(C2)-(1C)-(C3)-(C13)	19.486776
(C1)-(C2)-(C4)-(C6)	19.486776
(C1)-(C2)-(C7)-(N8)	5.000000
(C1)-(C3)-(C5)-(C6)	5.000000
(C1)-(C3)-(C13)-(C14)	0.333333
(C1)-(C3)-(C13)-(C15)	0.333333
(C1)-(C3)-(C13)-(C16)	0.333333
(C6)-(C4)-(C2)-(C7)	19.486776
(C4)-(C2)-(C7)-(N8)	5.000000
(C2)-(C4)-(C6)-(C5)	5.000000
(C2)-(C4)-(C6)-(C18)	5.000000
(C2)-(C7)-(N8)-(C9)	5.000000
(C2)-(C7)-(N8)-(N10)	5.000000
(C6)-(C5)-(C3)-(C13)	5.000000
(C5)-(C3)-(C13)-(C14)	0.333333
(C5)-(C3)-(C13)-(C15)	0.333333
(C5)-(C3)-(C13)-(C16)	0.333333
(C3)-(C5)-(C6)-(C4)	19.486776
(C3)-(C5)-(C6)-(C18)	19.486776
(C3)-(C13)-(C15)-(N17)	0.333333
(C4)-(C6)-(C18)-(C19)	0.333333
(C4)-(C6)-(C18)-(C20)	0.333333
(C4)-(C6)-(C18)-(C21)	0.333333
(C5)-(C6)-(C18)-(C19)	0.333333
(C5)-(C6)-(C18)-(C20)	0.333333
(C5)-(C6)-(C18)-(C21)	0.333333
(C6)-(C18)-(C20)-(N22)	0.333333
(C7)-(N8)-(C9)-(N11)	5.000000
(C7)-(N8)-(N10)-(C12)	5.000000
(N11)-(C9)-(N8)-(N10)	5.000000
(C9)-(N8)-(N10)-(C12)	5.000000
(N8)-(C9)-(N11)-(C12)	10.000000
(N8)-(N10)-(C12)-(N11)	10.000000
(C9)-(N11)-(C12)-(N10)	10.000000
(C14)-(C13)-(C15)-(N17)	0.333333
(N17)-(C15)-(C13)-(C16)	0.333333
(C19)-(C18)-(C20)-(N22)	0.333333
(N22)-(C20)-(C18)-(C21)	0.333333

Table 5: Improper torsions of anastrozole

S.NO	Atoms	Improper tortions
1	(C4)-(C7)-(C2)-(C1)	2.000000 0
2	(C5)-(C13)-(C3)-(C1)	2.000000 0
3	(C5)-(C18)-(C6)-(C4)	2.000000 0
4	(C9)-(N10)-(N8)-(C2)	2.000000 0

Table 6: Molecular mechanics final energy evaluation.

S.No.	Force field	Energy components (au)
1	Molecular mechanics bond (Estr)	0.021450
2	Molecular mechanics angle (Ebend)+ (Estr-bend)	0.644789
3	Molecular mechanics dihedral (Etor)	0.003187
4	Molecular mechanics ImpTor (Eoop)	0.000000
5	Molecular mechanics vdW (EVdW)	0.079659
6	Molecular mechanics coulomb (Eqq)	0.000000
	Total	0.749087a.u. (470.059759 kcal/mol)

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Table 7: Molecular docking result of anastrozole - promyelocytic leukemia protein

Rank	Solution Number	Global Energy	Attractive VdW	Repulsive VdW	ACE	HB
Kcal/mol						
1	6	-26.85	-14.14	2.44	-9.54	0.00
2	1	-24.05	-13.46	6.09	-9.06	0.00
3	8	-22.64	-12.56	5.37	-9.34	0.00
4	4	-19.83	-11.98	4.22	-7.11	0.00
5	7	-15.13	-9.36	6.38	-8.02	0.00
6	3	-10.70	-9.98	5.40	-4.43	0.00
7	10	-9.51	-9.09	4.92	-4.44	0.00
8	5	-5.34	-7.42	1.79	-0.96	0.00
9	2	-2.88	-4.98	0.55	-0.91	0.00
10	9	3.17	-2.88	1.75	-0.52	0.00

Excited state properties: ArgusLab was used to see what happened to the electrons in anastrozole when it absorbed light. Surfaces were made to explore this fascinating phenomenon. When anastrozole absorbsed energy in the form of UV/visible light, it made a transition from the ground electronic state to an excited electronic state. The excited and ground states have different distributions of electron density. This property is often valuable and sought after by chemists who are interested in molecules that are useful as dyes, sunscreens, etc [14, 15]. The HOMO is localized to the plane of the molecule and is a non-bonding molecular orbital (Figure 4). The LUMO is perpendicular to the plane of the molecule and is a combination of the p_z atomic orbitals (Figure 5). The n->π^* transition is dominated by the excitation from the HOMO to the LUMO. The positive and negative phases of the orbital are represented by the two colors, the red regions represent an increase in electron density and the blue regions a decrease in electron density. However, these calculations were examined in the ground state and also in vacuum [14,15]. The electrostatic potential is a physical property of a molecule that relates to how a molecule is first “seen” or “felt” by a positive "test" charge at a particular point in space. A distribution of electric charge creates an electric potential in the surrounding space. A positive electric potential means that a positive charge will be repelled in that region of space. A negative electric potential means that a positive charge will be attracted. A portion of a molecule that has a negative electrostatic potential will be susceptible to electrophilic attack – the more negative the better [14,15]. QuickPlot ESP mapped density generates an electrostatic potential map on the total electron density contour of the molecule (Figure 6). The electron density surface depicts locations around the molecule where the electron probability density is equal [14,15]. This gives an idea of the size of the molecule and its susceptibility to electrophilic attack. Figure 6 is an electron density surface of anastrozole using PM3 geometry which shows the complete surface of anastrozole with the color map. The surface color reflects the magnitude and polarity of the electrostatic potential. The color map shows the ESP energy (in hartrees) for the various colors. The red end of the spectrum shows regions of highest stability for a positive test charge, magenta/ blue show the regions of least stability for a positive test charge [14,15]. These images show that the triple and double bonded end of the molecule is electron rich relative to the single bonded end [14,15].

Heat of Formation: The standard heat of formation of a compound is the enthalpy change for the formation of 1 mole of the compound from its constituent elements in their standard states at 1 atmosphere. Its symbol is ΔH_f^0. The most energetically favourable conformation of anastrozole was found to have a heat of formation of 113249.91 kcal/mol via use of the Argus Lab software [14].The steric energy calculated for anastrozole (Table 6) was 0.74a.u.(470.05 kcal/mol)

Crystal structure of promyelocytic leukemia protein from the organism *Homo sapiens* with the PDB ID 1BOR retrieved from the Protein Data Bank (PDB) is shown in Figure 7. The ouput of PatchDock and firedock was a list of candidate complexes between receptor (promyelocytic leukemia protein) and anastrozole. The list is presented in Tables 8. The table contains rank, solution number, global energy, attractive VanderWaal energy, repulsive VanderWaals energy, atomic contact energy and hydrogen bond energy. PDB file of the complex denotes the predicted complex structure in PDB format. The lowest global binding energy solution was downloaded. Global binding energy value -26.85 Kcal/mole was ranked first because it had the least energy.

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4. Conclusion

The universal force field (UFF) molecular mechanics method have been used to calculate the steric energy of 2,2'-[5-(1,2,4-triazolidin-1-ylmethyl)benzene-1,3-diyl]bis (2-methylpropane nitrile) anastrozole using Arguslab software. Molecular mechanics calculations were based on specific interactions within the molecule. These interactions included stretching or compressing of bond beyond their equilibrium lengths and angles, torsional effects of twisting about single bonds, the Vander Waals attractions or repulsions of atoms that came close together, and the electrostatic interactions between partial charges in a anatrozole due to polar bonds. The steric energy calculated for anastrozole was 470.05 kcal/mol. It was concluded that the lowest energy and most stable conformation of anatrozole was 470.05 kcal/mol. Molecular docking result revealed the lowest global energy. The global binding energy value -26.85 Kcal/mole was ranked first because it had the least energy. The most feasible position for anastrozole to inhibit promyelocytic leukemia protein was found to be -26.85 kcal/mol.

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First Author: Igwe Kalu Kalu bagged the degree of Doctor of Vet. Medicine in 1990, M.Sc in Biochemistry (2008) and a Ph.D degree in Biochemistry (2015). He is a lecturer in the department of Vet. Biochemistry and Pharmacology in Michael Okpara University of Agriculture, Umudike, Nigeria.

Second Author: Amaku James Friday is a specialist in adsorption and computational chemistry. He is a menber of the Chemical Society of Nigeria. He is a lecturer in the department of Chemistry, Michael Okpara University of Agriculture, Umudike, Nigeria.

Third Author : Otuokere Ifeanyi Edozie (Ph.D). He bagged his Ph.D degree in 2008 in the field of Inorganic Chemistry. He is a menber of Chemical Society of Nigeria. He is a lecturer in the department of Chemistry, Michael Okpara University of Agriculture, Umudike, Nigeria. He is a menber of the Chemical Society of Nigeria