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Journal of Medicinal Research and Biological Studies

RESEARCH ARTICLE

ISSN: 2641-8843

Molecular Docking of New Alpha-Glucosidase Inhibiting Anthracenone used Against Some Selected Type Ii Diabetes Receptors

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Citation: Adejoro IA, Fayemi OS, Adeboye OO (2023) Molecular Docking of New Alpha-Glucosidase Inhibiting Anthracenone used Against Some Selected Type Ii Diabetes Receptors. J Med Res Biol Stud 2: 103

Abstract

Type II diabetes is a chronic metabolic disorder characterized by an impaired insulin action, early insulin resistance, and a decline and ultimate failure of beta cell function. In addition, both fasting and postprandial glucose levels in the blood are high. Compared to controls, type II diabetics have reduced insulin stimulated glucose disposal in all insulin sensitive tissues, particularly skeletal muscle, liver, and fat. Improving tissue sensitivity to insulin is a major clinical goal to help ameliorate not only abnormal glucose metabolism, but also some of the cardiovascular risk factors that accompany this syndrome. Treatment of diabetes include: enhancement of the action of insulin at the target tissues, with the use of sensitizers like thiozolidinediones; stimulation of endogenous insulin secretion with the use of sulfonylureas and reduction of the demand for insulin using specific enzyme inhibitors like acarbose, miglitol. However, there is a burden of unwanted side effects like diarrhea, dyspepsia, nausea, myocardial infarction, peripheral edema and dizziness with the use of these drugs. Type II diabetes is expected to reduce ten-year-shorter life expectancy. To this effect, Plants have been an exemplary source of drugs due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output, inhibiting the intestinal absorption of glucose or facilitating metabolites in insulin dependent processes.

The inhibitors used was a new alpha-glucosidase inhibiting anthracenone isolated from the barks of Harunganamadagascariensis Lam. The new anthracenonecompounds were designed using Chemoffice 2004.

The binding free energy for the ligand-receptor interactions as well as important amino acid residues responsible for the stabilization of the ligand in the active site of the receptor was reported using Auto Dock Vina, Pymol viewer and Discovery Studio Visualizer.

Keywords: Molecular Docking; DFT; Molecular Descriptors; Type-2 diabetes; Discovery Studio Visualizer; Binding affinity.

Introduction

Diabetes is a major health problem affecting major populations worldwide. It is a chronic disorder in metabolism of carbohydrates, proteins and fat due to absolute or relative deficiency of insulin secretion with/without varying degree of insulin resistance. Diabetes is being projected as the world's main disabler and killer in the next 25 years [1]. The incidence of diabetes has increased worldwide in recent years. The estimated number of people with diabetes was 30 million in 1985, 150 million in 2000 and then 246 million in 2007, according to the International Diabetes Foundation. It expects the number to hit 380 million by 2025 [2]. This deranged metabolism results in abnormally high blood sugar level (hyperglycemia). Hyperglycemia in diabetes results either from an absolute deficiency in insulin secretion (type 1 diabetes mellitus) or insulin action (type 2 diabetes mellitus) or both.

Epidemiological studies and clinical trials strongly support the notion that hyperglycemia is the principal cause of complications. Effective blood glucose control is the key for preventing or reversing diabetic complications and improving quality of life in patients with diabetes. Thus sustained reduction in hyperglycemia will decrease the risk of developing microvascular complications and most likely reduce the risk of macrovascular complications [3].

Patients suffering from type 2 diabetes (insulin independent) are unable to respond to insulin after food intake and can be treated with dietary changes, exercise and medication. The effective treatment for type 2 is to inhibit or delay intestinal carbohydrate digestion.

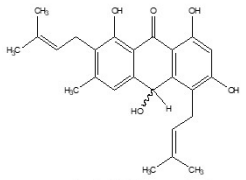
The α-glucosidase, an enzyme secreted from the epithelium of intestine, catalyses the hydrolysisof polysaccharides to monosaccharide. Inhibition of α-glucosidase interferes in thedigestion of carbohydrate and ultimately decreases the risk of postprandial hyperglycemiain diabetic patients. Moreover, this α-glucosidase inhibitors are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates: specifically α-glucosidase enzymes in the brush border of the small intestine. The membrane bound intestinal α-glucosidases hydrolyze oligosaccharides, trisaccharides and disaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzyme systems reduces the rate of digestion of carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. In diabetic patients, the short-term effect of these drugs therapies is to decrease current blood glucose levels: the long term effect is a small reduction in haemoglobin level [4]. 1-Deoxynojirimycin, acarbose and miglitol have been developedas α-glucosidase inhibitors for clinical use. However, use of acarbose cause gastrointestinaltract disturbance and there is a need to develop the safe and effective compounds to managehyperglycaemia of the diabetes [5]. However, many natural products have been reported as α-glucosidase inhibitors [6], and many other secondary metabolites showed excellent α-glucosidase inhibition activity [7,8].

GSK-3β is a serine/threonine kinase that plays a key role in the regulation of numerous signaling pathways. As GSK-3β plays a crucial role in several human diseases, it is being considered as one of the potential therapeutic targets for diseases such as cancer, diabetes, cardiac, Alzheimer's and other central nervous system disorders [9].

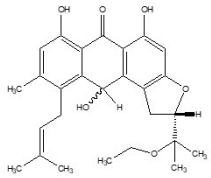
Inactivation of GSK-3β appears to be the major route by which insulin activates glycogen synthesis [10, 11], elimination of GSK-3β is more effective at promoting neuronal survival than is elimination elimination of GSK-3α [12].GSK-3 activity has been shown to be increased in peripheral tissues in diabetic animals and patients [13,14,15], and diabetes was reversed in obese diabetic animal treated with GSK-3 inhibitors [16,17,18].

The compounds madagascenone A and B isolated from Harunganamadagascariensis Lam isolated by Onajobi and co-workers [19] are considered in this present paper. In this work, the use of DFT method is considered to calculate molecular descriptors that describe bioactivity of these compounds since nothing of this molecular mechanism has been done. The optimized structures of these compounds are docked with alpha-glucosidase (PDB ID: 3WY1) and Glycogen Synthase Kinase 3Beta (PDB ID: 5HLN) for the estimation of free energy of binding as well as predicting suitable formation of the compounds in the binding purse of the receptor

which may assist in understanding in the inhibitory mechanism of type 2 diabetes. The bioactivities of these compounds are correlated to the free energy of interactions between the compounds and the receptor. The receptors used have resolutions of 2.15Å and 3.10Å for 3WY1 and 5HLN respectively.



Madagascenone A: 1,3.8,10-tetrahydroxy-6-methyl-4,7-bis(3-methyl-2-butenyl)-9(10H)-anthracenone



Madagascenone B: 2-(2-ethoxypropan-2-yl)-1,8,10-trihydroxy-6-methyl-5-(3-methyl-2-butenyl)-3,4-dihydro [2, 1-b] furan-9(10H)-anthrone

Figure 1: The structures of the studied molecules [19]

Computational Procedures

Docking Studies

The files 3WY1 and 5HLN generated from the Protein Data Bank (http://www.rcsb.org) were prepared by deleting native ligands, water molecules, co-factors and other non-protein parts using Discovery Studio 4.1 Visualizer, AutoDock Tool 1.5.6 and AutoDockVina version for docking process (downloaded from http://autodock.scripps.edu), Spartan '14 version was used for geometry optimization and geometric analyses of the ligands and Pymolviewer from DeLanoScientific LLC was used for docking results analysis. The comprehensiveness of the software search for the best binding mode was set to the default value of 8Å. The grid boxes were generated to envelope the active site using autogrid. The number of grid points in the x, y, z axes are 40 x 40 x 40 (mm) each separated by 1.000 Angstrom (grid-point spacing). The grid centre in x, y, z, were also specified and it varied from one receptor to another (Table 1). The receptors were prepared by adding Gasteiger charges.AutodockVina was used to compute the binding affinity of the ligand to the protein by searching Algorithm and Pymol viewer was used to view the result of the receptor in the pdbqt file format, also, the different binding modes of the ligandobtained after calculation was opened to check the best modes that fitted accurately with the protein binding site. Also, the various atomic distances of the protein-ligand interactions were viewed and measured. The converted structures were minimized and geometrically optimized in Spartan '14.

$$\Delta G = RT\ln K_i$$

$$K_i = e\Delta G/RT$$

Where ΔG is the binding affinity in kcal/mol

R is gas constant in 1.987 cal/mol/K and

T is absolute temperature, assumed to be room temperature in 298.15K [20]

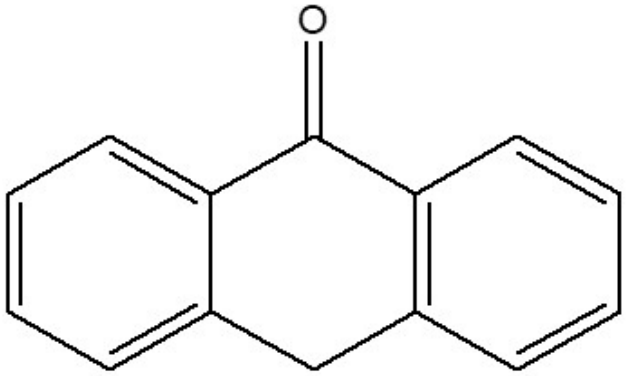


Figure 2: Structure of Anthracen-9(10H)-one moiety

RECEPTORS	Centre X (Å)	Centre Y (Å)	Centre Z (Å)
3WY1	5.594	2.030	1.284
5HLN	40.062	-23.761	0.385

Table 1: The grid centres of X, Y and Z coordinates used for docking analysis for MA

RECEPTORS	Centre X (Å)	Centre Y (Å)	Centre Z (Å)
3WY1	0.327	-3.394	2.654
5HLN	36.469	-32.447	2.130

Table 2: The grid centres of X, Y and Z coordinates used for docking analysis for MB

Quantum Chemical Parameters

The equilibrium geometries for the inhibiting anthracenones considered in this research work were optimized at Density Functional Theory (DFT) with the standard 6-31G* basis set at the level of B3LYP methods which uses the exchange functional proposal by Becke [21] and all the correlations functional given by Lee, Yang and Parr [22]. The selection of the preferred functional and basis sets was attributed to the accuracy of DFT calculations. The 6-31G* basis set has been used in conjunction with DFT method because it has the advantage of being flexible enough to guarantee reliable theoretical results and being small enough for rapid calculations. It represents an excellent compromise between completeness and economy.

The geometry of the ligands used was optimized to calculate the molecular descriptors that described the bioactivity. These optimized structures were considered to be appropriate for the docking process of the studied molecules with receptors.

The following quantum chemical indices were considered in the calculation: the energy of the lowest unoccupied molecular orbital (E_{LUMO}), the energy of the highest occupied molecular orbital (E_{HOMO}), separation energy (Koopman's*in silico* LUMO-HOMO energetic gap), dipole moment (μ), polarizability, ovality, log P, hydrogen bond donor, hydrogen bond acceptor and global molecular descriptors such as chemical hardness, softness and chemical potential. All quantum chemical calculations were performed using Spartan '14 by Wavefunction Inc.

Global Reactivity Descriptors

Several global chemical reactivity descriptors of molecules such as hardness (η), chemical potential (μ), softness (S), electronegativity (χ) and electrophilicity index (ω) were calculateed based on the density functional theory

(DFT). The global hardness (η), and chemical potential (μ) [22,23,24,25] is defined as the second and first derivative of the energy (E), with respect to the number of electrons (N), at constant external potential, v($\hat{r}$), captures the resistance of a chemical species to changing its electronic number.

$$\eta = \frac{1}{2}\left(\partial^2 \mathrm{E}/(\partial \mathrm{N}^2\right)_{V(\hat{r})}$$

$$\mu = \left(\partial \mathrm{E}/\partial \mathrm{N}\right)_{V(\hat{r})}$$

Ionization Potential, IP = - E_{HOMO}

Electron Affinity, EA = - E_{LUMO}

$$Chemical\ hardness, \eta = \frac{\mathrm{E}_{LUMO} - \mathrm{E}_{HOMO}}{2}$$

Softness, S = 1/ η

$$Electronic\ chemical\ potential, \mu = \frac{\mathrm{E}_{Homo} + \mathrm{E}_{LUMO}}{2}$$

$$Electrophilicindex, \omega = \frac{\mu^2}{\eta}$$

Global hardness and global softness are the basic chemical concepts, called global reactivity descriptors which have been theoretically justified within the framework of DFT. A hard molecule is characterized by a large energy gap and a soft molecule with a small energy gap [26]. Soft molecules show a more reactivity when compared with hard molecules due to the easy donation of electrons to an acceptor.

Results and Discussion

Docking and Scoring Results

The docking simulation of each ligand produced nine conformations while the best one is assumed to be the one with highest binding energy since the more negative value assumes the best conformation in any docking. The energies of interaction for the compounds are represented in the Table 3. Hence, the calculated binding energies/affinites of MA with 3WY1 and 5HLN are -9.40 Kcal/mol and -10.10 Kcal/mol respectively while MB with 3WY1 and 5HLN are -9.70 Kcal/mol and -10.80 Kcal/mol respectively. The result shows that MB (Madagascenone B) gave better binding interactions than MA (Madagascenone B) which implies that MB will be more effective that MA in the treatment of the disease.

Molecular Descriptors

Molecular descriptors like molecular weight, solvation energy, Log P, volume, Area, dipole moment, ovality, polar surface area, HOMO and LUMO energies were calculated. The HOMO and LUMO energies playimportant roles in the qualitative description of the excitation properties of molecules. For MA ligand, the calculated E_{HOMO} is -5.730 eV and for MB, it is -5.530 eV while for MA, the calculated E_{LUMO} is -1.860 eV and for MB, it is -1.610 eV. The energetic band gaps for MA and MB are 3.870 eV and 3.920 eV respectively (Table 4). Hence, MB < MA, i.e. MA ligand due to its lower value will be easier to be excited.

Receptors	MA		MB	
	ΔG	K_i	ΔG	K_i
3WY1	-9.40	0.128	-9.70	0.077
5HLN	-10.10	0.039	-10.80	0.012

Table 3: Score results for Type II diabetes receptors

ΔG = Binding Affinity (kcal/mol)

K_i= Inhibition constant (μM)

Properties	MA	MB
Molecular Formula	$C_{25}H_{28}O_5$	$C_{27}H_{32}O_6$
E_{HOMO}(eV)	-5.73	-5.53
E_{LUMO}(eV)	-1.86	-1.61
Band Gap	3.87	3.92
Dipole Moment (debye)	4.60	7.45
Molecular Weight	408.494	452.547
Log P	4.755	4.660
Ovality	1.58	1.63
Area ($Å^2$)	433.21	476.39
Volume ($Å^3$)	425.17	468.38
PSA ($Å^2$)	72.242	76.238
Molar Refractivity	118.964	127.723
Number of Atoms	58	65
Electrophilic Index (ω)	3.721	3.251
Chemical Potential (μ)	-3.795	-3.570
Hardness (⊠)	1.935	1.960
Softness (S)	0.517	0.510
HBA	5	6
HBD	4	3
Solvation Energy (kJ/mol)	-92.25	-92.47

Table 4: The calculated properties from the ligands MA and MB for T2D inhibition

The Lipinski[28] properties (Table 4) such as molecular weight (408.494 for MA ligand and 452.547 for MB ligand), Partition coefficient value, Log P – which signifies the lipophilicity of the ligand (4.76 for MA ligand and 4.66 for MB ligand), Hydrogen Bond Donor (4 for MA ligand and 3 for MB ligand), Hydrogen Bond Acceptor (5 for MA ligand and 6 for MB ligand) and Molar Refractivity, MORF (118.964 for MA ligand and 127.723 for MB ligand). For the Lipinski's rule of five, drugs must have the molecular weight ≤ 500, Hydrogen Bond Donor ≤ 5, Hydrogen Bond Acceptor ≤ 10, Partition coefficient, Log P ≤ 5 and Molar refractivity between 40–130.

The Vebers rule holds that properties such as rotatable bonds, ROTB ≤ 10 (for MA it is 4 and MB it is 5), Polar Surface Area, PSA

≤ 140 (MA has 72.242 and MB has 76.238).

Other rules like Ghose Filter, MDDR-like for drug-like compounds include other important additional properties like Number of Atoms, NAT between 20-70 (MA contains total of 58 atoms and MB contains total of 65 atoms) and Aromatic Rings, AROM ≥ 3 (MA has 3 and MB has 4). The synthesized ligands passed the Lipinski's rule of five and the Vebers rule[27]

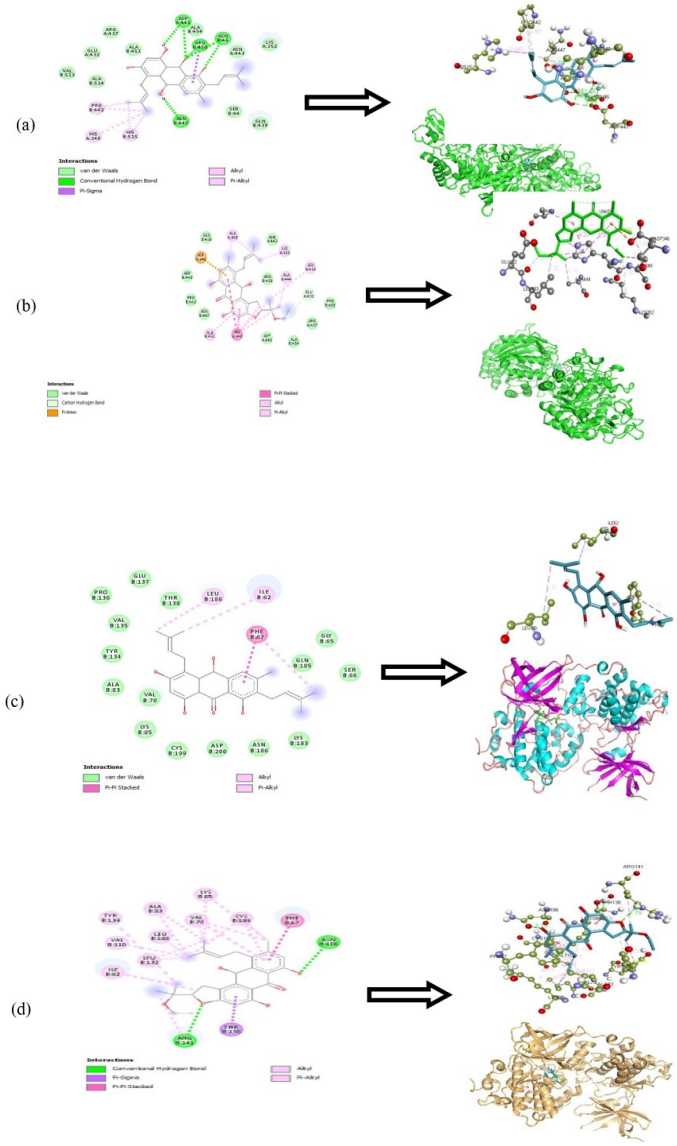


Figure 3: Interaction mappings: (a) 3WY1 receptor vs MA ligand, (b) 3WY1 receptor vs MB ligand, (c) 5HLN receptor vs MA ligand, (d) 5HLN receptor vs MB ligand

Conclusion

The quantum chemical approach using Density Functional Theory (DFT) method, QSAR properties and molecular docking were performed on the ligands, Madagascenone A (MA) and Madagascenone B (MB) and the results confirmed that the calculated descriptors using quantum chemical procedure correlate to the electronic properties of the molecules to their biological activities. The ligands docked effectively with the T2D receptors and this suggests the efficacious treatment of T2D with the synthesized ligands. Therefore, the simulation results predicted stable conformations of the drug-like molecules inside the purse of the receptors as well as the free energy of interactions thus providing useful parameters that aids the potency of the drug.

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