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Research Article

Binding Energy Predictions and Molecular Docking Studies of Acetohexamide with Some Bacterial Species

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Abstract

Acetohexamide belongsto the class of drug known as sulfonylurea. It is a first generation sulfonylurea drug that is used in the treatment of type 2 diabetes mellitus expecially in patients whose diabetes cannot be managedwith diet. Molecular docking studies of acetohexamide with *Candida albicans, Klebsiella pneumonia, Proteusmirabilis, Staphylococcus aureus* and *E.Coli* were carried out using Patchdock and Firedock online server. The predicted binding energies are -54.35, -22.44, -38.38, -37.84and -50.12 Kcal/mol respectively. The negative values of the binding energy suggest that acetohexamide would inhibit these bacterial species. The molecular interactions were hydrogen bonding and steric interactions.

Keywords: Acetohexamide; diabetes mellitus; molecular docking; binding energy; bacteria

Abbreviations

PDB: Protein Data Bank

Introduction

Acetohexamide belongsto the class of drug known as sulfonylurea. It is a first generation sulfonylurea drug that is used in the treatment of type 2 diabetes mellitus expecially in patients whose diabetes cannot be managed w ith diet. It works by stimulating the pancreas to effectively produce and use insulin [1]. This drug cannot be used for pateints suffering from type 1 diabetes mellitus. The discovery of sulfonylurea was made in 1942 by Marcel Janbon and Co-workers [2] during their research work on sulfonamide antibiotics.

Sulfonylurea drugs are group of compounds that are used in medicine and agriculture. These class of drug helps the beta cells of the pancreas to secrete insulin [1]. This class of drug can also act as herbicide because they disrupt plant biosynthesis [3]. Acetohexamide may lead to excess secretion of insulin which might cause hypoglycemia. It may also induce weight gain, headache, gastrointestinal upset and hypersensitivity reactions. It was reported [4] that patients treated with sulfonylurea drugs have fewer non-fatal cardiovascular events than those treated with metformin.The interaction of acetohexamide with some drugs may increase the risk of hyperglycemia and worsen glucose tolerance. These drugs are acetylsalicyclic acid, allopurinol, sulfonamide, fibrates, corticosteroids, isoniazid, oral contraceptives and estrogens [5,6]. The mechanism of action of sulfonylurea drug is through the blockage of ATP-sensitive $K^+(K_{ATP})$ channels in the pancreatic beta cells. The pancreatic beta cells becomes depolarized and limit the existence of K^+. The depolarization opens voltage-gated Ca^{2+} channels. The increase in intracellular calcium causes an increase in insulin [7]. The structure of acetohexamide is shown in (Figure 1).

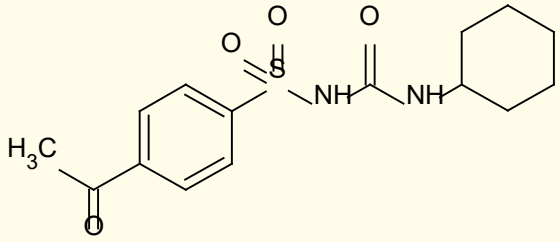


Figure 1: Structure of Acetohexamide.

Molecular docking is used in structure-based drug design to predict the binding energy and conformation of ligands complexed to

target receptors. Molecular docking can be seen as "*lock-and-key*". The receptor is seen as the lock while the ligand is the key. It tries to explain the best conformation of the ligand when it binds to the receptor. During molecular docking, the ligand and the protein try to achieve the "best-fit". This type of geometry adjustment resulting in the overall binding energy is known as "induced-fit" [8].

Candida a genus of yeast commonly called normal flora of the mouth, skin, intestinal tract and vagina can cause variety of diseases.Most infections are associated with predisposing factors especially immune suppression. Only *C. albicans* is commonly associated with the mouth, crop, proventricular in the gizzard of birds.Candidiasis occurs as complications secondary to other systemic disease such as diabetes mellitus or hyperadrenocortism [9]. *Klebsiella* is a gram-negativebacteria in the tribe *Klebsiella* family Enterobacteriaceae. *K. pneumonia* is carried in the vestibule of the vagina, urethra and clitoridean fossa of the mare as normal flora but invasion causes metritis and infertility. It also causes hematogenous osteomyelitis from pulmonary leisions in cattle, *bronchio pneumoniain* dogs and pyro thorax in horses [9]. *Proteus* is a genus of gram negative bacteria, member of the family Enterobacteriaceae found in putrefying matter. Associated with infections of the external ear and skin and in *pyometra* and *pyelonephritis. P. mirabilis* is a common inhabitant of animal faucal material and in the infections of the eye, skin, urinary and respiratory tract [9]. *Staphylococcusaureus* is a genus of spherical gram-positive bacteria occurring in grapelike clusters. *S. aureusis* common cause disease in animal and man including abscesses, dermatitis, furunculous, meningitis, osteomyelitis, food poisoning and wound suppurations [9].

E.coli is a specie of bacteria in the genus *Escherichia* of normal flora of animals. Pathogenic strains cause respiratory tract infections, epidemic diarrheal disease especially in new born animals, pyometra in dogs or respiratory diseases in broiler chickens. *E. coli* a shiga-like toxin (verodoxin) producing *E. coli* that has been responsible for outbreaks of hemorrhagic colitis especially in children, but also in all ages [9]. Diabetes is a disease of carbohydrate, protein and fat metabolism resulting from an imbalance between availability and insulin need which can present an absolute insulin deficiency or impaired release of insulin by the pancreatic beta cells [10]. It is characterized by destruction of the pancreatic beta cells [11].

We hereby present the binding energy predictions and molecular docking studies of acetohexamide with *Candida albicans, Klebsiella pneumonia, Proteus mirabilis, Staphylococcus aureus* and *E. coli*.

Materials and Methods

Protein Preparation

The three-dimensional structure of *Candida albicans, Klebsiella pneumonia, Proteus mirabilis, Staphylococcus aureus* and *E.coli* were obtained from the Protein Data Bank, PDB 1IYK, 40R7, 4GW3, 7AHL and 4CKL respectively. The protein structures were subjected to a refinement protocol using Monegro Molecular Viewer [12].

Designing of Acetohexamide

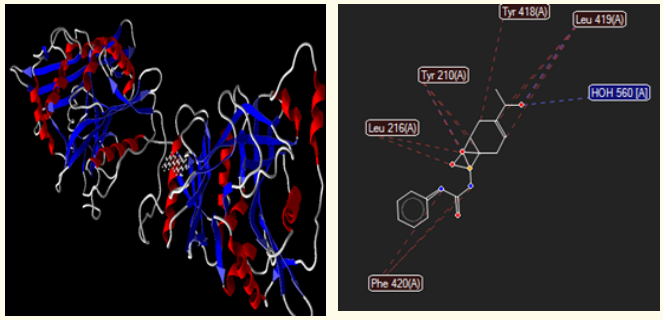
The structure of acetohexamide (Figure 1) was drawn with ACD/ ChemSketch software [13] and minimized with Argus lab software [14].

Molecular Docking

Molecular docking was performed using Patch dock [15]. Patch dock is a molecular docking algorithm based on shape complementarity principles. Refinement was done in Fire dock [16] and processed with Monegro molecular viewer [12].

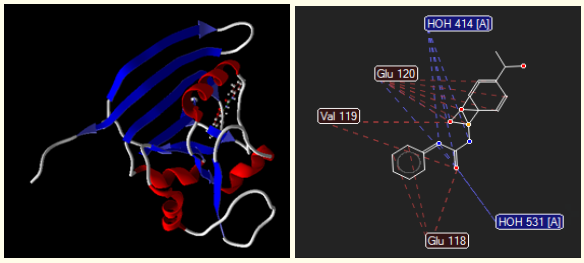
Results and Discussion

The molecular docking and molecular interactions of acetohexamide with *Candida albicans, Klebsiella pneumonia, Proteus mirabilis, Staphylococcus aureus* and *E. Coli* are presented in (Figures 2-6) respectively. The solutions Table of the molecular docking are shown in (Tables 1-5) respectively.



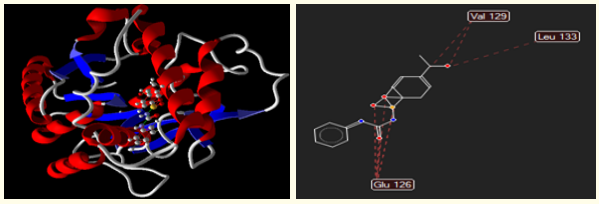
(a) ***(b)***

Figure 2: (a) Acetohexamide docked with Candida albicans (b) Molecular interactions of acetohexamide with Candida albicans



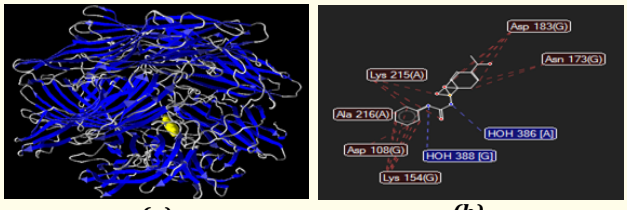
(a) *(b)*

Figure 3: l(a) Acetohexamide docked with Klebsiella pneumoniae dihydrofolate reductase (b) Molecular interactions of acetohexamide with Klebsiella pneumoniae dihydrofolate reductase.



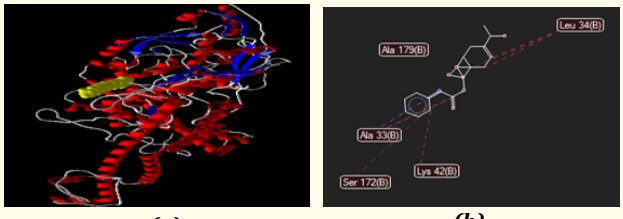
(a) *(b)*

Figure 4: (a) Acetohexamide docked with Lipase from Proteus mirabilis (b) Molecular interactions of acetohexamide with Lipase from Proteus mirabilis.



(a) *(b)*

Figure 5: (a) Acetohexamide docked with alpha-hemolysin from Staphylococcus aureus (b) Molecular interactions of acetohexamide with alpha-hemolysin from Staphylococcus aureus.



(a) *(b)*

Figure 6: (a) Acetohexamide docked with E. coli DNA gyrase A subunit (b) Molecular interactions of acetohexamide with E. coli DNA gyrase A subunit.

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
		↓			
1	4	-54.35	-19.00	4.29	-18.99
2	7	-46.91	-15.62	2.92	-16.69
3	10	-40.61	-14.69	1.92	-13.39
4	1	-37.71	-14.43	7.97	-14.36
5	8	-37.24	-18.37	11.79	-13.17
6	2	-36.65	-14.95	5.87	-13.22
7	3	-31.03	-16.61	5.96	-7.96
8	9	-27.60	-11.87	3.55	-10.15
9	5	-27.15	-13.11	2.20	-6.76
10	6	-14.82	-12.73	6.29	-3.59

Table 1: Solution Table of Acetohexamide in Complex with Candida Albicans.

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
		↓			
1	3	-22.44	-9.61	1.43	-6.77
2	7	-20.61	-9.84	4.35	-7.11
3	6	-18.38	-10.41	3.62	-6.64
4	9	-10.63	-7.26	3.10	-3.30
5	8	-9.30	-5.61	0.91	-3.04
6	10	-9.24	-6.96	2.39	-2.41
7	2	-7.47	-6.99	2.08	-1.15
8	5	-7.26	-5.49	0.65	-1.99
9	1	-6.17	-6.66	3.79	-2.81
10	4	-2.78	-3.53	1.74	-1.76

Table 2: Solution Table of Acetohexamide in Complex with Klebsiella Pneumonia.

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
		↓			
1	7	-38.38	-16.51	5.25	-12.53
2	4	-23.79	-12.07	2.45	-7.98
3	10	-20.40	-10.95	1.57	-5.49
4	9	-10.88	-9.24	6.80	-2.94

5	1	-10.69	-11.48	9.04	-2.93
6	3	-10.12	-7.60	3.13	-5.69
7	8	-7.59	-6.86	0.42	-0.93
8	5	-6.39	-5.79	3.23	-3.34
9	6	-5.42	-9.93	2.51	1.95
10	2	-2.99	-6.26	1.02	2.07

Table 3: Solution Table of acetohexamide in complex with Proteus mirabilis.

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol)
		↓			
1	3	-37.84	-17.85	1.07	-7.57
2	8	-25.94	-14.85	3.99	-4.49
3	6	-23.73	-14.49	2.53	-2.54
4	4	-22.78	-16.17	2.74	-0.74
5	5	-22.77	-15.20	5.46	-2.75
6	2	-14.56	-15.72	24.42	-6.72
7	9	-8.42	-14.59	22.54	-2.92
8	1	-4.79	-11.33	0.50	6.77
9	10	16.17	-20.02	56.84	-0.26
10	7	19.33	-17.59	75.22	-9.25

Table 4: Solution Table of Acetohexamide in Complex with Staphylococcus Aureus.

Rank	Solution Number	Global Energy (Kcal/mol)	Attractive VdW (Kcal/mol)	Repulsive VdW (Kcal/mol)	ACE (Kcal/mol l)
		↓			
1	8	-50.12	-16.91	2.32	-17.31
2	1	-43.42	-13.23	2.14	-16.62
3	7	-40.74	-13.03	3.71	-15.83
4	10	-37.31	-12.55	2.18	-13.25
5	5	-35.80	-12.65	1.40	-11.51
6	3	-24.16	-12.64	2.50	-5.28
7	6	-21.77	-12.73	5.06	-5.06
8	2	-19.84	-7.72	1.40	-6.68
9	4	14.63	-14.07	62.32	-9.81
10	9	61.09	-11.63	104.89	-3.54

Table 5: Solution Table of acetohexamide in complex with E.coli.

The best ranking in Table 1 is solution 4 with global energy -54.35 Kcal/mol. This suggests that acetohexamide has the ability to inhibit *Candida albicans*. The attractive Vander waals, repulsive Vander waals and atomic contact energy (ACE) were also predicted. The molecular interactions (Figure 2b) shows that *Candida albicans* formed hydrogen bonding with acetohexamide using Tyr 210(A), Leu 419(A) and H2O 560(A). Steric interaction between *Candida albicans* and acetohexamide were observed with Phe 420(A), Leu 216(A), Tyr 210(A), Tyr 418(A) and Leu 419 (A).

The best global energy in (Table 2) is -22.44 Kcal/mol (solution 3). This suggests that acetohexamide has the ability to inhibit *Klebsiella pneumonia*. The attractive Vander waals, repulsive Vander waals and atomic contactenergy (ACE) were also predicted. The molecular interactions (Figure 3b) show that *Klebsiella pneumonia* formed hydrogen bonding with acetohexamide using H_2O 414(A), Glu 120 and H_2O 531(A). Steric interaction between *Klebsiella pneumonia* and acetohexamide were observed with Val 119, Glu 120 and Glu 118.

The minimum global energy for the complex of acetohexamide -*Proteus mirabilis* is -38.38 Kcal/mol (solution 7) (Table 3). The negative value of the binding energy indicates that acetohexamide can be used in the treatment of *Proteus mirabilis* diseases. The attractive Vander waals, repulsive Vander waals and atomic contact energy (ACE) were also predicted. The molecular interactions (Figure 4b) show steric interaction between *Proteusmirabilis* and acetohexamide. Steric interactions were observed with Val 129, Leu 133 and Glu 126.

In Table 4, the best ranking was solution 3 with global energy -37.84 Kcal/mol. The inhibitory effect of acetohexamide against *Staphylococcus aureus* is assured.The attractive Vander waals, repulsive Vander waals and atomic contact energy (ACE) were also predicted. The molecular interactions (Figure 5b) show that *Staphylococcus aureus* formed hydrogen bonding with acetohexamide using H_2O 388(G) and H_2O 386(G).

Steric interaction between *Staphylococcus aureus* and acetohexamide were observed with Lys 215(A), Ala 216(A), Asp 108(G), Lys 154(G), Asn 173(G) and Asp 183(G).

The minimum global energy for acetohexamide -*E.coli* complex-is -50.12 Kcal/mol (solution 8) (Table 5). The negative value of the binding energy indicates that acetohexamide has the ability to inhibit *E.coli*. The attractive Vander waals, repulsive Vander waals and atomic contact energy (ACE) were also predicted. The molecular interactions (Figure 6b) shows steric interaction between *E.coli* and acetohexamide. Steric interactions were observed with Ser 172(B), Lys 42(B),

Leu 34(B) and Ala 179(B). Hydrogen bonding was observed between the drug and *E.coli* through Ala 33(B).

Conclusion

Acetohexamide is a first generation sulfonylurea drug that is used in the treatment of type 2 diabetes mellitus expecially in patients whose diabetes cannot be managed w ith diet. Aside from the hypoglycemic activity of acetohexamide, the molecular docking studies also suggest that it can act as an antibacterial agent.

Acknowledgements

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Conflict of interest

There is no conflict of interest.

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