BINDING FREE ENERGY PREDICTIONS OF SOME OXOVANADIUM (IV) POLYPYRAZOLYLBORATE MIXED CHELATES INHIBITING ALPHA-GLUCOSIDASE ENZYME

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ABSTRACT: Alpha-glucosidase inhibitors are oral anti-diabetic drugs used for diabetes mellitus type II that work by preventing the digestion of carbohydrates. Carbohydrates are normally converted into simple sugars (monosaccharides), which can be absorbed through the intestine. Hence, alpha-glucosidase inhibitors reduce the impact of carbohydrates on blood sugar. Enzyme-inhibitor docking was performed between alpha-glucosidase and tripyrazolylborate/dipyrazolylborateoxovanadium(IV), trifluoroacetylacetonate/tripyrazolyl borateoxovanadium(IV) and dimethyldithiocarbamate/tripyrazolylborateoxovanadium(IV) chelates using the Patchdock online server. The docking study provided a quantitative energetic measure (Atomic Contact Energy) of -349.56, -189.99 and -296.69 Kcal/mole for alpha-glucosidase inhibition by tripyrazolylborate/ dipyrazolylborateoxovanadium (IV), trifluoroacetylacetonate/ tripyrazolyl borate oxovanadium (IV) and dimethyldithiocarbamate / tripyrazolylborateoxovanadium (IV) chelates respectively. These negative values of binding free energy indicated that the oxovanadium chelates were able to inhibit the activity of alpha-glucosidasewhich in turn can reduce the impact of carbohydrates on blood sugar in diabetic mellitus type II patients.

Keywords: Oxovanadium (IV), polypyrazolylborate, chetates, molecular docking, alpha-glucosidase

INTRODUCTION

Vanadium is an essential element for biological systems. Vanadium is reported to participate in some enzymatic reactions such as nitrogen fixation [1, 2]. Vanadium is found naturally in soil and water as trace metal. “Accumulated” vanadium in the form of ores such as vanadinite or patronite is rare. Vanadium is actually the second most abundant transition metal in sea water, only surpassed by molybdenum as molybdate [3]. Vanadium compounds with oxidation state IV and V exist in the biological systems [3]. Vanadium is actually known as a trace element, essential for higher organisms although deficiency symptoms in humans have not yet been clearly identified [4]. The coordination chemistry of vanadium is of great current interest because of the discovery of its presence in abiotic as well as biotic systems [5, 6]. Vanadium(V) complexes are known as potential inhibitors of various enzymes. Recent advances in catalytic and medicinal properties of vanadium complexes have stimulated their design and synthesis. Another important impetus to the coordination chemistry of vanadium in the context of medical application has arisen from the ability of vanadium complexes to promote the insulin mimetic activity in pathophysiological state of diabetes mellitus in humans [7-10]. This biological and catalytic relevance of vanadium has promoted the synthesis of model vanadium compounds containing O, N donor ligands. Potential medicinal application of vanadium compounds in the reduction of hyperlipidemia, hypertension, anticancer, anticancer, antitumor [11, 12], insulin deficiency and insulin resistance [13] has stimulated research in vanadium coordination. Oxovanadium complexes as one group of transition metal compounds have aroused great interestamong biochemists and pharmacologists owing to diverse biologic and pharmacological activities such as antiproliferative [14], antibacterial [15], biocatalytic oxidation [16, 17],

insulin-enhancing effects [18], apoptosis-inducing activity [19, 20], potential capabilities as DNA structural probes and DNA dependent electron transfer likewise [21, 22]. In recent years, mixed-ligand oxovanadium complexes have demonstrated both *in vitro* antibacterial and antifungal properties [23] as well as intense interactions with DNA [24, 25].

Alpha-glucosidase (maltase, glucoinvertase, glucosidosucrase, maltase-glucoamylase, alpha-glucopyranosidase, glucosidoinvertase, alpha-D-glucosidase, alpha-glucoside hydrolase, alpha-1,4-glucosidase, alpha-D-glucosideglucohydrolase) is a glucosidase located in the brush border of the small intestine that acts upon 1,4-alpha bonds. [26 – 31]. This is in contrast to beta-glucosidase. Alpha-glucosidase breaks down starch and disaccharides to glucose. Alpha-glucosidase hydrolyzes terminal non-reducing 1-4 linked alpha- glucose residues to release a single alpha-glucose molecule [32]. Alpha-glucosidase is a carbohydrate-hydrolase that releases alpha-glucose as opposed to beta-glucose. Beta-glucose residues can be released by glucoamylase, a functionally similar enzyme. The substrate selectivity of alpha-glucosidase is due to subsite affinities of the enzyme's active site [33]. Two proposed mechanisms include a nucleophilic displacement and an oxocarbenium ion intermediate [33]. Alpha-glucosidase inhibitors are oral anti-diabetic drugs used for diabetes mellitus type II that work by preventing the digestion of carbohydrates (such as starch and table sugar). Carbohydrates are normally converted into simple sugars (monosaccharides), which can be absorbed through the intestine. Hence, alpha-glucosidase inhibitors reduce the impact of carbohydrates on blood sugar [34].

Tripyrazolylborate/dipyrazolylborateoxovanadium(IV), trifluoroacetylacetonate/tripyrazolylborate oxovanadium(IV), and dimethyldithiocarbamate/ tripyrazolylborateoxovanadium (IV) chelate complexes have been synthesized and characterized in previous publication [35]. Their structures are shown in Figures 1 – 3 repectively.

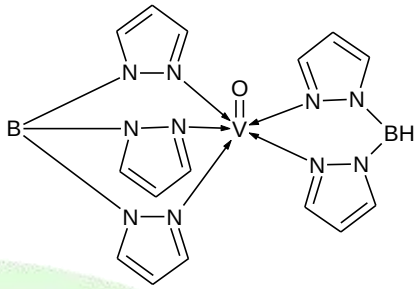

Figure 1: Tripyrazolylborate /dipyrazolylborate oxovanadium (IV) complex

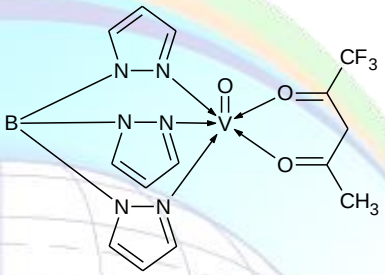

Figure 2: Hexafluoroacetylacetonate/ tripyrazolyl borate oxovanadium (IV) chelate complex

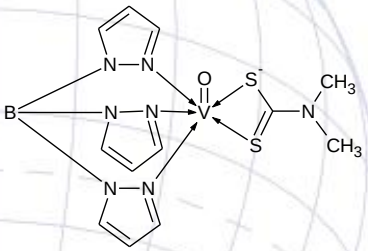

Figure 3: Dimethyldithiocarbamate / tripyrazolylborate oxovanadium (IV) complex

We hereby present binding free energy predictions of some oxovanadium (IV) mxedchetates containing polypyrazolylborate ligands inhibiting alpha-glucosidase enzyme.

EXPERIMENTAL

The complexes were drawn using ACDLab/ChemSketch software [36], saved in MOL format and converted to PDB format using Arguslab 4.0.1 software [37]. PDB is one of the repositories for 3-D structural data of proteins and nucleic acids. The PDB database is operated by the research collaboratory for structural bioinformatics (RCSB). As at March 3, 2009 PDB had 56217 macromolecular structure data entries [38].

Retrieval of alpha-glucosidase

Crystal structure of alpha-glucosidase from the organism *Homo sapiens* with the PDB ID 1R46 was retrieved from the Protein Data Bank (PDB).

Molecular docking

Molecular docking was performed using patchdock online server [39]. Patchdock is a molecular docking algorithm based on shape complementarity principles. Receptor (alpha-glucosidase) and ligand molecule (oxovanadium polypyrazolylborate complexes) 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 theresults was given. Complex type was chosen as enzyme – inhibitor type. Then the docking job was submitted to the Patchdock server.

RESULTS AND DISCUSSION

Crystal structure of alpha-glucosidase from the organism *Homo sapiens* with the PDB ID 1R46 retrieved from the Protein Data Bank (PDB) is shown in Figure 4.

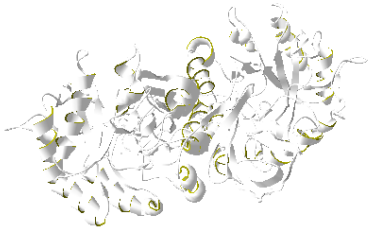

Figure 4: Crystal structure of alpha-glucosidase PDB ID 1R46

The ouput of PatchDock is a list of candidate complexes between receptor (alpha-glucosidase) and ligands: tripyrazolylborate/dipyrazolylborate oxovanadium(IV), trifluoroacetylacetonate/tripy razolylborateoxovanadium(IV) and dimethyldithio carbamate/tripyrazolylborateoxovanadium(IV) chelate complexes. The lists are presented in Tables 1 – 3 respectively.

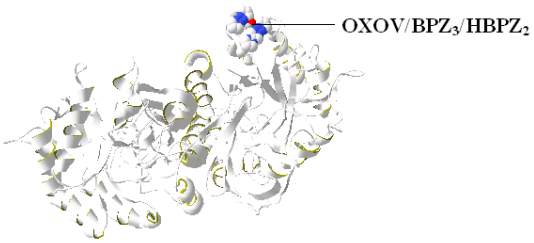

Figure 5: Crystal structure of docked alpha-glucosidase OXOV/BPZ_3/$HBPZ_2$
Atomic Contact Energy = -349.56 Kcal/mole

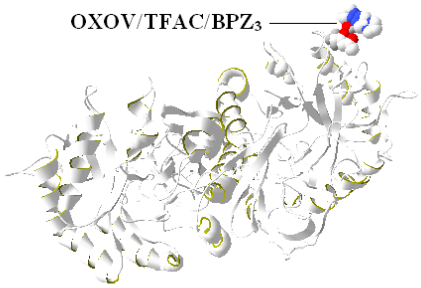

Figure 6: Crystal structure of docked alpha-glucosidase OXOV/TFAC/BPZ_3
Atomic Contact Energy = -189.99

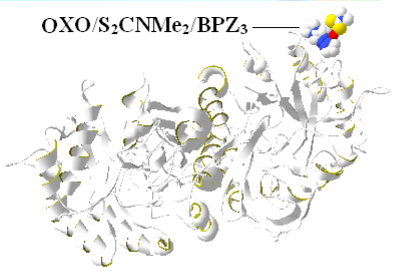

Figure 7: Crystal structure of docked alpha-glucosidase OXO/S_2CNMe_2/BPZ_3
Atomic Contact Energy = -296.69

Each table contains one candidate complex. Solution No. represents the number of the solution. Score correspond to geometric shape complementarity score [39]. The solutions are sorted according to this score. Area stands for the approximate interface area of the complex. ACE indicates Atomic Contact Energy [40]. Transformations represented are 3D transformations that include 3 rotational angles and 3 translational parameters. These transformations are applied on the ligand molecule. PDB file of the complex denotes the predicted complex structure in PDB format.The Lowest Atomic Contact Energy solutions were downloaded.

Alpha-glucosidase-tripyrazolylborate/dipyrazolyl borateoxovanadium(IV) complex structure (Figure 5), has a complementarity score value of 535.70 with an Atomic Contact Energy (ACE) of -349.56 Kcal/mol. Alpha-glucosidase-trifluoro acetylacetonate/tripyrazolyl borate oxovanadium (IV) complex structure (Figure 6) has a comple-mentarity score value of 509.50 with an Atomic Contact Energy (ACE) of -189.99 Kcal/mol. Alpha-

glucosidase-dimethyldithiocarbamate/tripyrazolylborate oxovanadium (IV) complex structure (Figure 7) has a complementarity score value of 526.60 with an Atomic Contact Energy (ACE) of -296.69 Kcal/mol.

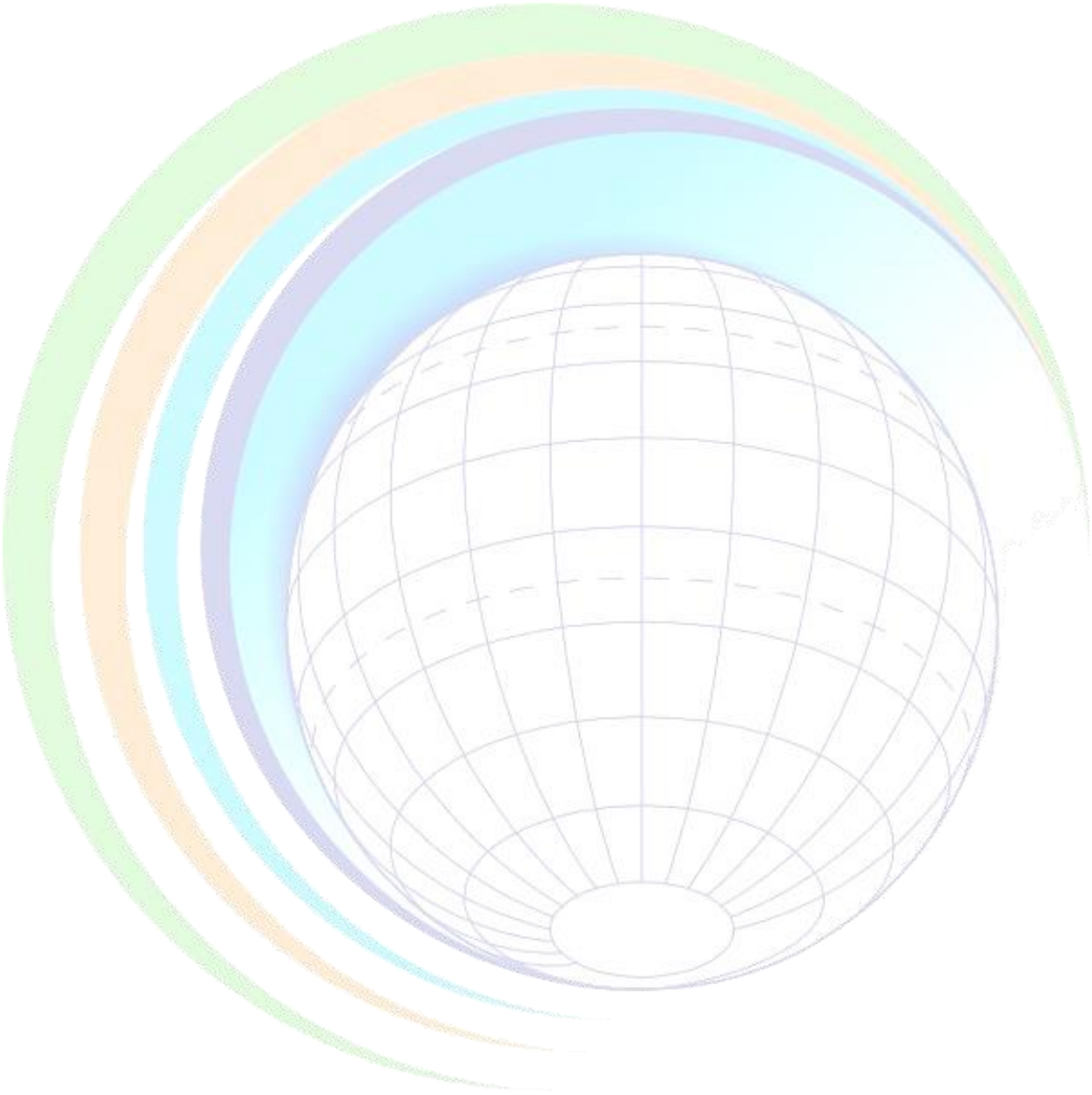

Table 1: Molecular docking result of alpha-glucosidase-tripyrazolylborate/dipyrazolylborate oxovanadium (IV) complex

Molecular Docking Algorithm Based on Shape Complementarity Principles

[About PatchDock] [Web Server] [Download] [Help] [FAQ] [References]

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
1R46.pdb	OXOVBPZ$_3$HBPZ$_2$.pdb	EI	1.5	ifeanyiotuokere@gmail.com	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	4576	555.70	-162.96	-1.56 0.17 -2.06 3.18 86.47 61.83	result.1.pdb
2	4564	605.50	-198.92	-0.01 -0.18 0.26 -14.97 54.26 94.87	result.2.pdb
3	4422	548.40	-138.05	-1.01 0.32 0.42 -31.28 46.79 71.87	result.3.pdb
4	4422	494.20	-254.95	1.21 -0.95 0.76 6.97 85.60 86.78	result.4.pdb
5	4410	564.30	-143.14	0.33 0.02 0.51 -17.00 48.33 96.05	result.5.pdb
6	4362	507.10	-266.54	-1.28 0.78 -2.24 13.65 80.39 46.79	result.6.pdb
7	4360	577.00	-133.79	-0.33 0.27 3.00 14.83 30.64 83.45	result.7.pdb
8	4308	530.90	-169.53	3.09 -0.10 -1.90 -0.15 64.14 94.37	result.8.pdb
9	4284	516.40	-274.04	-2.66 -0.26 -2.26 31.73 106.14 86.40	result.9.pdb
10	4278	535.70	-349.56	-2.74 0.02 2.47 35.87 81.66 79.05	result.10.pdb
11	4278	519.40	-125.02	2.32 -0.08 -2.54 40.52 64.99 102.05	result.11.pdb
12	4260	504.70	-158.34	2.36 -0.32 -2.39 38.87 66.81 106.62	result.12.pdb
13	4238	497.00	-109.55	-1.34 -0.39 0.15 -1.23 48.02 93.10	result.13.pdb
14	4236	517.50	-140.31	3.13 -0.04 1.71 20.70 30.84 92.89	result.14.pdb
15	4236	536.80	-106.13	-2.21 0.38 0.63 27.43 35.25 75.69	result.15.pdb
16	4226	508.00	-40.95	0.80 -0.15 0.21 4.12 92.06 84.61	result.16.pdb
17	4226	506.80	-56.08	-2.69 0.21 -2.99 -8.35 84.17 115.19	result.17.pdb
18	4226	516.20	-173.48	-1.87 -0.25 2.31 18.81 56.12 108.64	result.18.pdb
19	4216	552.50	-178.86	-1.59 0.37 -2.13 1.67 82.57 60.61	result.19.pdb
20	4210	523.50	-175.33	3.07 -0.02 -2.43 10.83 65.41 93.24	result.20.pdb

Table 2: Molecular docking result of alpha-glucosidase - trifluoroacetylacetonate/tripyrazolylborate oxovanadium (IV) complex

PATCHDOCK + = ?

Molecular Docking Algorithm Based on Shape Complementarity Principles

[About PatchDock] [Web Server] [Download] [Help] [FAQ] [References]

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
1R46.pdb	OXOVTFACBPZ3.pdb	EI	1.5	ifeanyiotuokere@gmail.com	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	5030	629.30	-106.26	0.13 0.08 2.92 21.00 30.40 92.32	result.1.pdb
2	4980	589.30	-30.43	0.18 0.00 0.29 -20.23 50.47 94.31	result.2.pdb
3	4808	608.90	-74.49	-1.48 0.14 -2.15 8.42 90.09 61.95	result.3.pdb
4	4628	552.20	-112.06	-0.18 0.10 2.44 16.98 23.26 87.72	result.4.pdb
5	4608	582.70	-105.35	-2.97 0.07 0.44 -7.20 26.83 88.66	result.5.pdb
6	4588	550.20	-131.31	-2.93 0.16 0.03 -10.69 33.40 86.30	result.6.pdb
7	4558	494.70	2.72	1.14 0.99 -2.52 37.00 54.74 87.73	result.7.pdb
8	4534	592.50	-23.34	0.27 0.05 2.78 19.43 26.95 94.40	result.8.pdb
9	4514	524.30	-167.16	1.15 -0.78 0.70 0.27 79.92 89.51	result.9.pdb
10	4512	559.50	-129.44	-2.99 -0.04 -0.10 -14.43 36.13 90.89	result.10.pdb
11	4480	540.60	-41.31	2.38 -0.11 -2.50 44.97 68.69 101.54	result.11.pdb
12	4432	519.00	-143.75	-1.29 0.77 -2.14 15.79 85.10 43.14	result.12.pdb
13	4422	543.50	-98.23	-2.98 -0.05 0.35 -7.47 27.13 91.52	result.13.pdb
14	4412	545.10	-39.83	0.38 -0.02 0.06 -19.56 54.26 96.93	result.14.pdb
15	4410	507.00	-35.10	1.39 -0.69 -3.03 24.31 46.31 119.64	result.15.pdb
16	4396	552.20	-51.98	2.88 0.95 0.83 -11.51 26.79 63.54	result.16.pdb
17	4392	530.90	-46.96	-2.22 -0.55 0.06 11.55 40.46 93.36	result.17.pdb
18	4380	466.90	-2.56	-1.25 -0.97 0.34 -32.26 42.56 96.65	result.18.pdb
19	4378	509.50	-189.99	-2.79 -0.01 -2.12 32.54 109.11 84.69	result.19.pdb
20	4374	552.10	-62.14	2.35 0.15 -2.77 51.34 65.43 95.40	result.20.pdb

Table 3: Molecualar docking result of alpha-glucosidase - dimethyldithiocarbamate/tripyrazolylborate oxovanadium (IV) complex

PATCHDOCK + = ?

Molecular Docking Algorithm Based on Shape Complementarity Principles

[About PatchDock] [Web Server] [Download] [Help] [FAQ] [References]

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
1R46.pdb	$OXOVS_2CNMe_2BPZ_3$.pdb	EI	1.5	ifeanyiotuokere@gmail.com	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	4746	567.00	-202.33	0.39 -0.06 0.57 -19.36 50.26 99.39	result.1.pdb
2	4712	572.50	-215.44	0.17 -0.03 2.89 13.40 25.85 96.04	result.2.pdb
3	4692	555.60	-141.61	-0.00 0.07 2.92 15.37 25.49 91.15	result.3.pdb
4	4408	532.90	-268.85	0.36 -0.11 2.99 16.98 29.39 100.38	result.4.pdb
5	4356	492.90	-187.96	2.94 -0.85 -1.56 15.62 55.49 103.74	result.5.pdb
6	4282	518.80	-170.79	2.26 0.08 -2.69 44.67 67.44 103.52	result.6.pdb
7	4250	526.60	-296.69	2.95 0.18 0.82 31.41 61.44 88.88	result.7.pdb
8	4240	508.40	-180.74	-2.90 0.06 0.33 -2.73 25.02 86.85	result.8.pdb
9	4228	510.30	-213.06	0.27 -0.17 2.71 11.27 24.95 100.38	result.9.pdb
10	4228	484.30	-120.89	2.58 0.06 -0.54 -41.64 66.20 131.69	result.10.pdb
11	4224	507.90	-137.84	2.73 0.92 1.02 -4.50 24.39 70.09	result.11.pdb
12	4204	495.10	-128.04	0.63 -0.28 -0.13 9.27 100.02 86.46	result.12.pdb
13	4174	477.40	-192.10	-3.13 0.41 0.37 2.63 25.42 86.16	result.13.pdb
14	4168	486.60	-256.19	1.46 -0.15 -3.11 -1.56 40.10 138.62	result.14.pdb
15	4154	465.40	-169.89	2.29 0.92 2.37 25.54 37.13 71.36	result.15.pdb
16	4140	511.40	-190.62	3.00 0.13 -2.54 11.22 67.54 92.64	result.16.pdb
17	4126	465.50	-131.57	-1.07 -0.64 0.42 -3.78 45.61 99.56	result.17.pdb
18	4120	520.20	-191.24	-1.50 0.02 -2.12 5.88 86.75 57.88	result.18.pdb
19	4118	480.60	-284.43	0.93 -0.93 0.56 5.49 91.33 88.35	result.19.pdb
20	4112	443.90	-130.12	2.82 1.40 -0.27 -30.79 43.46 68.67	result.20.pdb

CONCLUSION

Enzyme-inhibitor docking was performed between alpha-glucosidase and tripyrazolylborate/dipyrazolylborate oxovanadium (IV), trifluoroacetylacetonate/ tripyrazolyl borate oxovanadium (IV) and dimethyldithiocarbamate / tripyrazolylborate oxovanadium (IV) chelates using the Patchdock online server. The docking study provided a quantitative energetic measure (Atomic Contact Energy) of -349.56, -189.99 and -296.69 Kcal/mole for alpha-glucosidase inhibition by tripyrazolylborate/ dipyrazolylborate oxovanadium (IV), trifluoroacetylacetonate/ tripyrazolyl borate oxovanadium (IV) and dimethyldithiocarbamate / tripyrazolylborate oxovanadium (IV) chelates respectively. This indicated that the oxovanadium chelates were able to inhibit the activity of alpha-glucosidase which in turn can reduce the impact of carbohydrates on blood sugar in diabetic mellitus type 2 patients.

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