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IDENTIFICATION OF NOVEL DRUG/LEAD MOLECULE FOR SCHIZOPHRENIA TARGETING RGS4 GENE THROUGH IN-SILICO ANALYSIS

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Schizophrenia is a neuropsychiatric disorder that is caused by many factors including changes in the chemistry of the brain, structure of the brain, and genetic factors. The neuropathology of the disorder has been identified morphologically and physiologically through a number of parameters from a reduction in brain size and abnormalities in the neurotransmitter network affecting the brain to changes in the molecular composition of specific cell populations in the brain. Over a long period of time, clinicians and researchers have identified schizophrenia as a complex neurological genetic disorder as a result of the functionality of several susceptible genes. Various scientists are of the opinion that there are about 20 candidate genes that cause schizophrenia. Several genes like Dysbindin, Neuregulin, DAAO, G72, PRODH, COMT, and RGS4 have been proven to be the risk factors for schizophrenia disease. RGS4 was identified as a target gene for schizophrenia. Hence the present study was taken up to identify a Novel Drug/Lead Molecule from 12 selected drugs based on a bioinformatics approach for schizophrenia targeting the RGS4 gene. The genomics and proteomics approach of the RGS4 gene was carried out for nucleotide and protein sequences and the protein was modeled using SPDBV with 80% accuracy. The potential active site amino acids were predicted using molecular cavities based on energy and surface area and the protein was targeted using the best active site amino acids. The protein-ligand interactions were also performed using the Argus Lab engine with flexible docking. The data of the present study reveals that ziprasidone is showing maximum inhibition of the RGS4 gene among the 12 drugs selected

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for screening. It is thus concluded that ziprasidone with the lowest free energy and high affinity is the best inhibitor for the schizophrenia protein and hence it can be suggested for the treatment of schizophrenia.

Keywords: Schizophrenia; RGS4; novel drug/lead molecule.

1. INTRODUCTION

"Schizophrenia (MIM 181500; http:// www.ncbi.nlm.nih.gov/omim/) is a common psychiatric disorder with a lifetime prevalence of ~1% which presents with psychotic symptoms. Schizophrenia is often described in terms of positive and negative symptoms. Positive symptoms are those that most individuals do not normally experience but are present in people with schizophrenia. They include delusions, disordered thoughts and speech, tactile, auditory, visual, olfactory, and gustatory hallucinations" [1]. Positive symptoms generally respond well to medication [2].

"Negative symptoms include flat expressions or little emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation" [3-5]. "Negative symptoms appear to contribute more to poor quality of life, functional ability and the burden on others than do positive symptoms [6]. People with greater negative symptoms often have a history of poor adjustment before the onset of illness and response to medication is often limited" [3-7]. "Late adolescence and early adulthood are the peak period for the onset of schizophrenia" [8].

"The etiology of the disease remains elusive with studies implicating the effect of both genetic and environmental factors on neurodevelopmental processes" [9-11]. "Identifying susceptibility genes for complex disorders has proved difficult but a recent meta-analysis of linkage data supports a number of schizophrenia susceptibility loci" [12]. "More recently a series of studies have reported association between several candidate genes and schizophrenia" reviewed by Harrison and Owen, [13], such as Dysbindin, Neuregulin, D-aminoacid oxidase (DAAO), G72gene, proline dehydrogenase (PRODH), Catehol–o–methyl transferase (COMT) and Regulator of G-protein signaling 4 (RGS4).

RGS4 maps to chromosome (1q21-q22) or 1q21-22 (NCBI accession number U 27768, UniGene cluster Hs-227571), a chromosome region strongly linked to schizophrenia [14], and thus is a candidate for a major schizophrenia susceptibility gene on this locus. A number of studies associate the RGS4 gene with schizophrenia [15-18]. Chowdari and colleagues [19] identified association at this locus in a number of distinct and ethnically diverse samples suffering from schizophrenia. This is further supported by Morris et al. [20] who succeeded in detecting evidence of association at the RGS4 locus and schizophrenia in the Irish population.

"In addition to the genetic evidence described, RGS4 is a potentially interesting functional candidate gene. RGS4 regulates G-Protein coupled receptors by rapidly turning them off [21]. This regulation appears to be selective to specific neural systems and has been implicated in modulating the function of dopamine and glutamate receptors" [22]. "RGS4 is highly expressed in specific brain regions such as the neocortex, caudate and putamen regions of the brain implicated in the pathophysiology of schizophrenia. Further, it has also been reported that a decrease in RGS4 expression is a common and specific feature of schizophrenia which could affect neuronal signaling" [23]. Considering the implication of the RGS4 gene in the prevalence of schizophrenia disease, the current study was taken up. The present study is based on a bioinformatics approach to identify a new drug/lead molecule for schizophrenia disease targeting the RGS4 gene.

2. MATERIALS AND METHODS

The nucleotide and the protein sequences of the RGS4 gene were collected in Fasta Format from the Gene bank and protein data bank and a sequence alignment of RGS4 from Homosapiens was constructed using a multiple sequence alignment program, clustal w. The nucleotide composition, open reading frame, predicted peptide region, and primers were known through genomics whereas the stability of the protein sequence, various structures of the protein molecule, and its physicochemical nature were studied through proteomics. The protein was modeled using SPDBV software and the final protein model was evaluated using prochek. The potential active site amino acids were predicted using molecular cavities and a Q-site finder based on energy and surface area and the protein was targeted using the best active site amino acid. Once the target site has been selected, the search for the chemicals was performed. The chemicals were collected from the pubchem database, screened, and finally selected for docking studies.

The 12 chemicals selected after screening include

1. 7-Hydroxy-nor2-chlorpromazine.
2. Aripiprazole.

3. Chlorpromazine Hydrochloride.
4. Chlorpromazine; Largactil.
5. d-Deoxyephedrine-Methamphetamine.
6. Ectasy-MDMA
7. Hexythiazox
8. Methamphetamine pfp.
9. Methamphetamine.
10. Perphenazine-trilafon.
11. Risperidone
12. Ziprasidone.

Then the protein-ligand interaction was performed using the Argus lab engine with flexible docking. Based on the docking energy values, the best ligand-receptor pair can be finalized.

3. RESULTS

The results of the present study are divided into 3 phases. Homology Modeling, Active Site analysis, and Docking studies are shown in Figs. 1-10.

The general information of the RGS4 gene is shown in Table 1 and Fig. 1.

Table 1. General information on the RGS4 gene

Official Symbol – RGS4
Name:-Regulator of G-protein signaling 4
Other Aliases (Names) – MGC 2124, MGC 60244, RGP4, SCZD9.
Chromosome:-1; Location :1q23.3.
MIM: 602516
Gene ID:5999
NP_005604.1 NM_005613.3

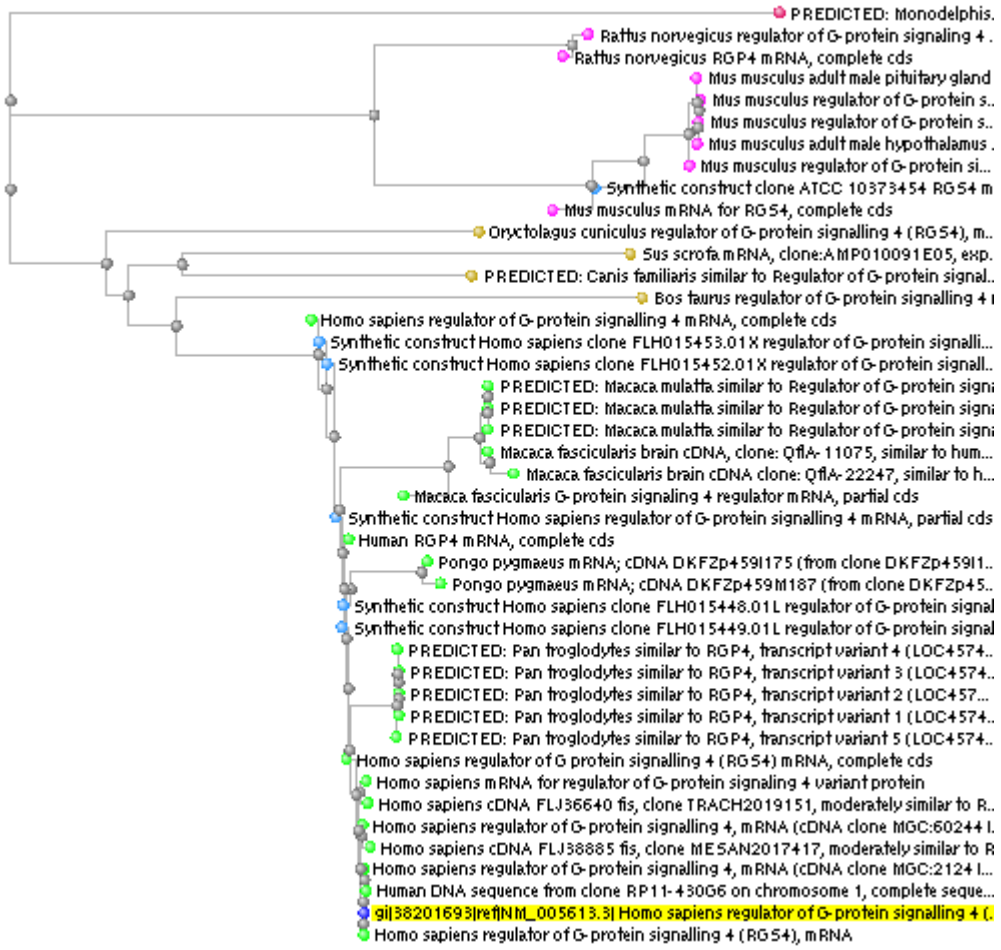

Fig. 1. Showing the evolutionary tree view of RGS4 protein

3.1 Homology Modeling

The homology modeling performed using the crystallographic structure of RGS-4 from Homosapien's by different templates is obtained from a protein data bank with SPDBV software. The final model later was evaluated using prochek. Analysis of the Ramachandran plot of the RGS-4 model shows that 78.5% of residues lie in the most favored regions and the remaining 3.5% in the additional allowed regions. Thus overall it can be said that 82% of the residues are in the allowed portions of the plot.

ClustalW Results

Results of search	
Number of sequences	5
Alignment score	162404
Sequence format	Pearson
Sequence type	nt
ClustalW version	1.83
JalView	
Output file	clustalw-20070707-10381001.output
Alignment file	clustalw-20070707-10381001.aln
Guide tree file	clustalw-20070707-10381001.dnd
Your input file	clustalw-20070707-10381001.input

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Fig. 2. Showing results of Clustal W

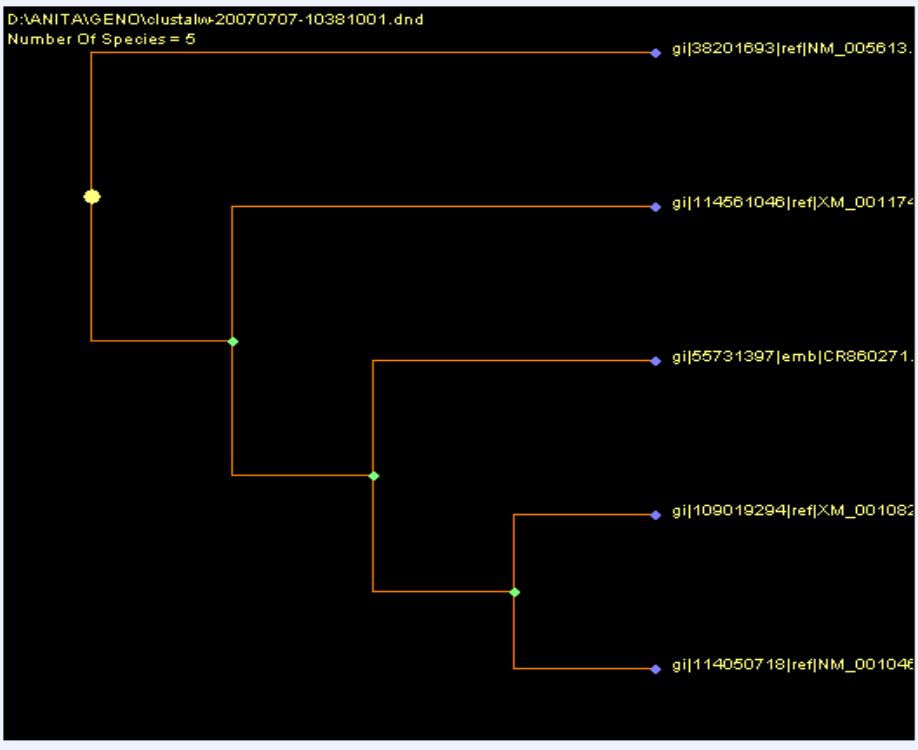

Fig. 3. Showing phylogenetic analysis using Clustal W

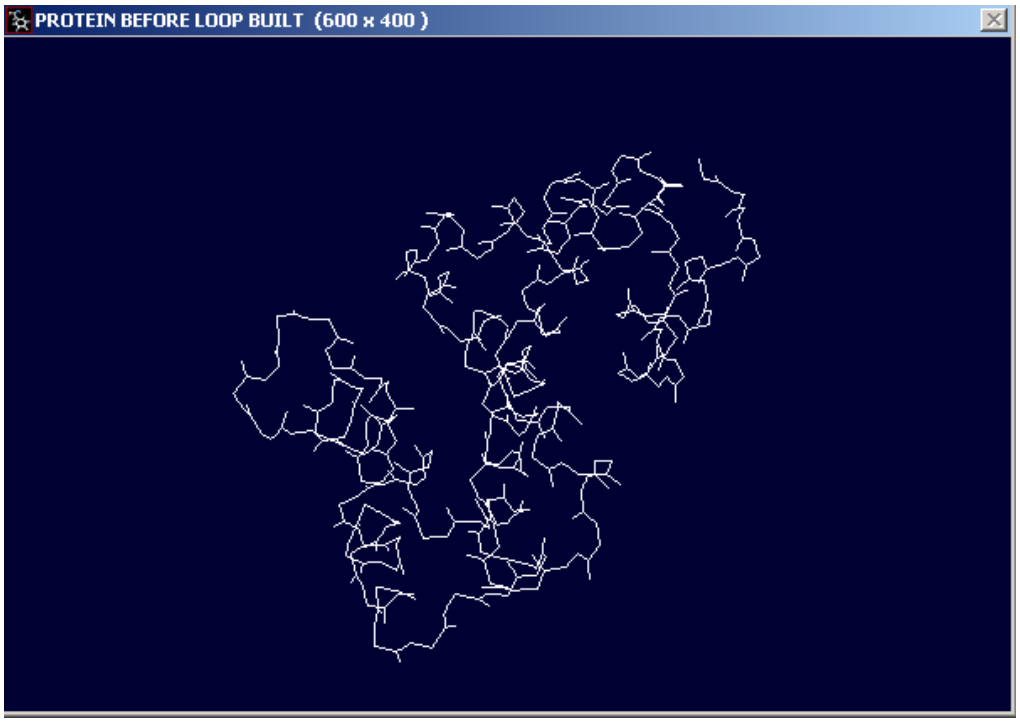

Fig. 4. Showing the protein before Loop Built

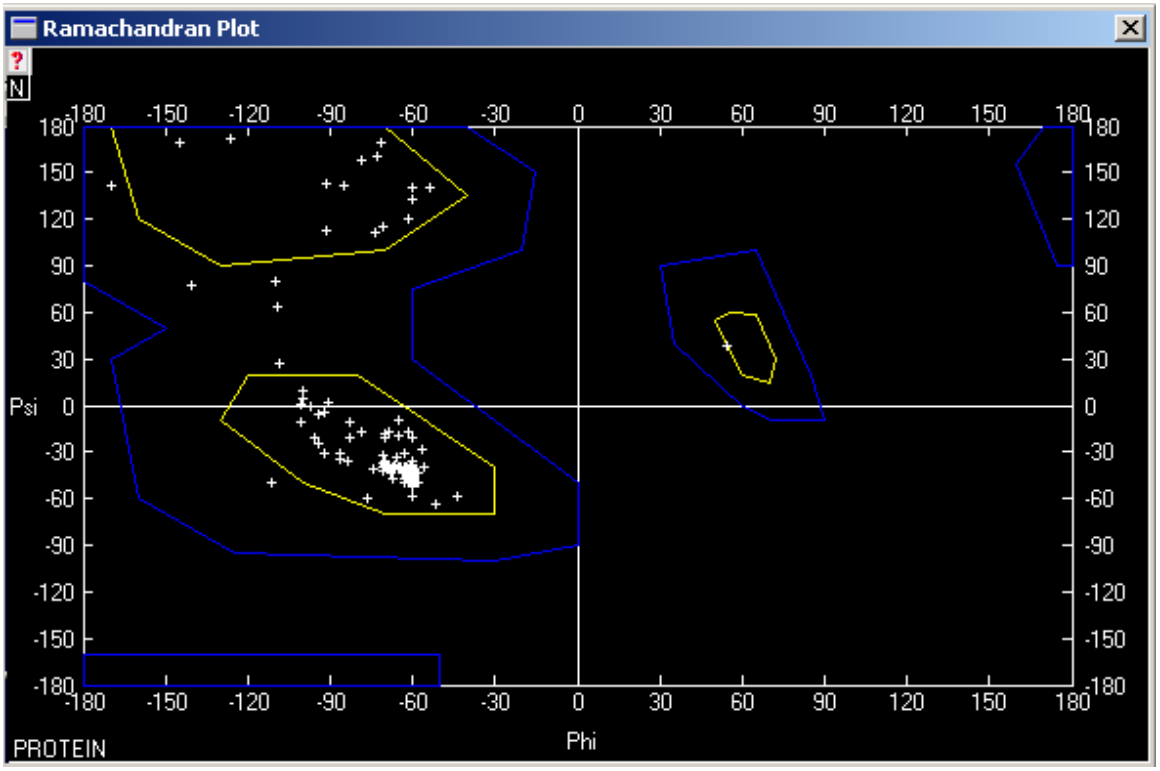

Fig. 5. Showing the Ramachandran Plot

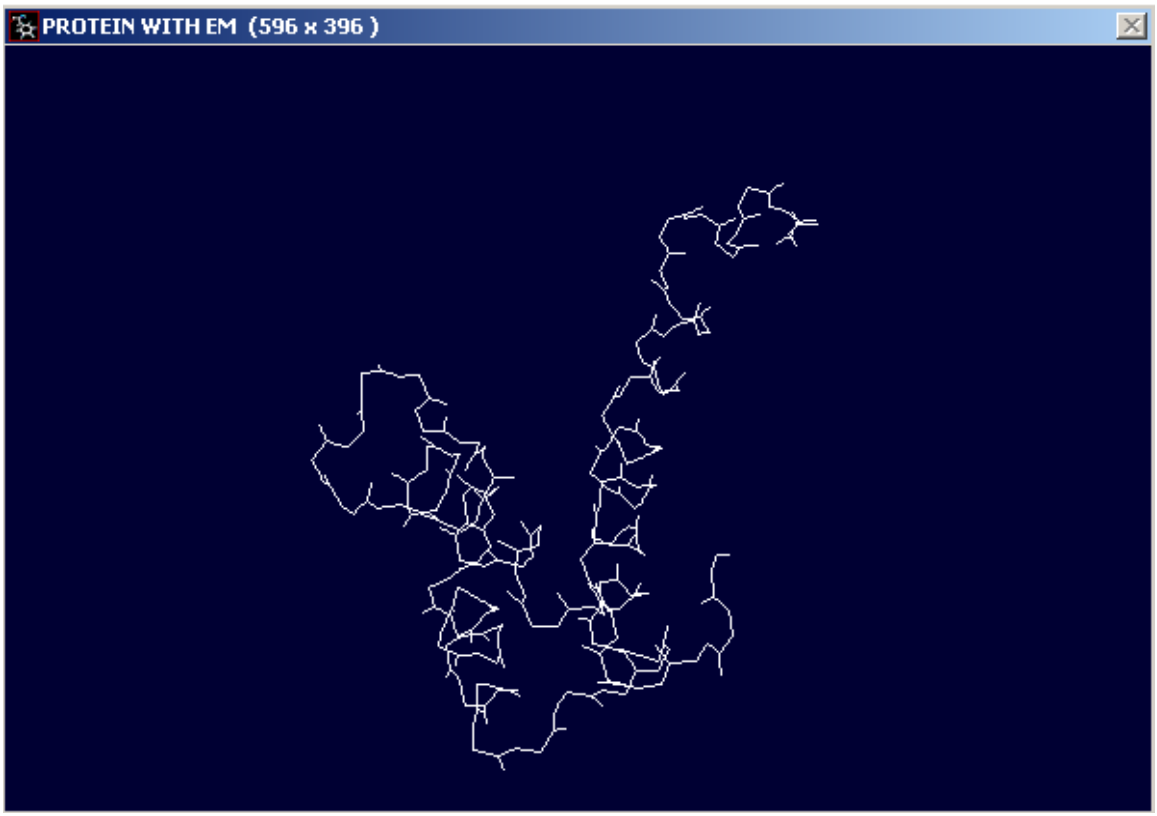

Fig. 6. Showing the Protein with energy minimization

Table 2. Results of the predicted site 2 using Q-site finder

Predicted site 2:
Site volume: 128 Cubic Angstroms.
Protein volume: 12832 Cubic Angstroms.

Residues			
202	CE1	PHE	76
204	CZ	PHE	76
226	CD2	PHE	79
228	CE2	PHE	79
235	CG	LEU	80
237	CD2	LEU	80
254	CA	GLU	83
255	C	GLU	83
256	O	GLU	83
257	CB	GLU	83
258	CG	GLU	83
259	CD	GLU	83
260	OE1	GLU	83
261	OE2	GLU	83
275	CA	SER	85
277	O	SER	85
278	CB	SER	85
279	OG	SER	85
302	CB	ASN	88
303	CG	ASN	88
305	ND2	ASN	88
633	CG	ASN	128

Residues			
635	ND2	ASN	128
880	CA	LEU	159
881	C	LEU	159
882	O	LEU	159
883	CB	LEU	159
884	CG	LEU	159
885	CD1	LEU	159
886	CD2	LEU	159
887	N	MET	160
888	CA	MET	160
889	C	MET	160
890	O	MET	160
891	CB	MET	160
892	CG	MET	160
913	N	ASP	163
914	CA	ASP	163
915	C	ASP	163
916	O	ASP	163
917	CB	ASP	163
918	CG	ASP	163
919	OD1	ASP	163
920	OD2	ASP	163
921	N	SER	164
922	CA	SER	164
925	CB	SER	164
926	OG	SER	164

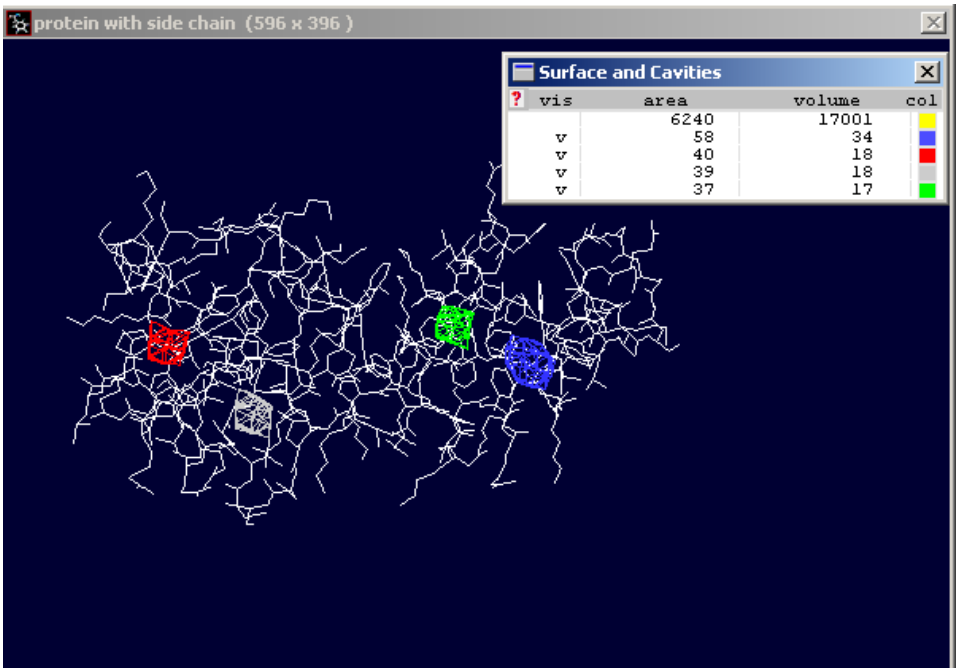

Fig. 7. Showing the protein with molecular surface and cavities

The plot can be exploited for drug designing after further energy-minimizing the model and performing molecular dynamics simulations. Thus, the initial structure of modeling was revised by means of refining loops and rotamers, checking bonds, and adding hydrogen atoms and then molecular dynamics simulations optimized the initial modeling structure. The refined model structure thus obtained after energy

minimization and molecular dynamics simulations were used for docking studies.

3.2 Active Site Analysis

The active site analysis was performed using both molecular cavities and a Q-site finder. From among the 10 sites predicted for active amino acids, site 2 was found to be the best active site by both the above-mentioned methods based on energy and surface area and thus the protein was targeted using site 2. The results of the predicted site 2 using the Q-site finder are shown in Table 2.

Table 3. Summary of results in order of docking score

Docking result of site II **Summary of results in order of docking score (Kcal/mol)**
PHE 76
1. Ziprasidone – -11.7084
2. Hexythiazox - -9.23056
3. 7-hydroxy-nor 2-chlorpromazine - -8.51496
4. Chlorpromazine; Largactil - -8.02016
LEU 80
1. Ziprasidone - -9.65712
2. Hexythiazox - -9.47776
3. Chlorpromazine; Largactil - -8.93693
4. 7-hydroxy-nor 2-chlorpromazine - -8.42105
GLU 83
1. Ziprasidone - -9.82127
2. Hexythiazox - -9.24332
3. Chlorpromazine; Largactil - -8.6733
4. 7-hydroxy-nor 2-chlorpromazine - -8.45991
SER 85
1. Ziprasidone - -10.314
2. Hexythiazox - -9.39959
3. Chlorpromazine; Largactil - -8.768
4. 7-hydroxy-nor 2-chlorpromazine - -8.3468
ASN 88
1. Chlorpromazine; Largactil - -10.6708
2. 7-hydroxy-nor 2-chlorpromazine - -8.23873
3. Ziprasidone - -5.17507
4. Hexythiazox - -3.6273
LEU 159
1. Ziprasidone - -10.7757
2. Hexythiazox - -9.74265
3. 7-hydroxy-nor 2-chlorpromazine - -8.76431
4. Chlorpromazine; Largactil - -6.20349
MET 160
1. Ziprasidone - -10.5407
2. Hexythiazox - -9.4249
3. Chlorpromazine; Largactil - -8.88438
4. 7-hydroxy-nor 2-chlorpromazine - -8.25365
ASP 163
1. Hexythiazox - -6.8811
2. Chlorpromazine; Largactil - -6.15126
3. 7-hydroxy-nor 2-chlorpromazine - -5.43999
4. Ziprasidone - -5.29744
SER 164
1. Ziprasidone - -9.65543
2. Chlorpromazine; Largactil - -7.85114
3. 7-hydroxy-nor 2-chlorpromazine - -7.70876
4. Hexythiazox - -6.60547

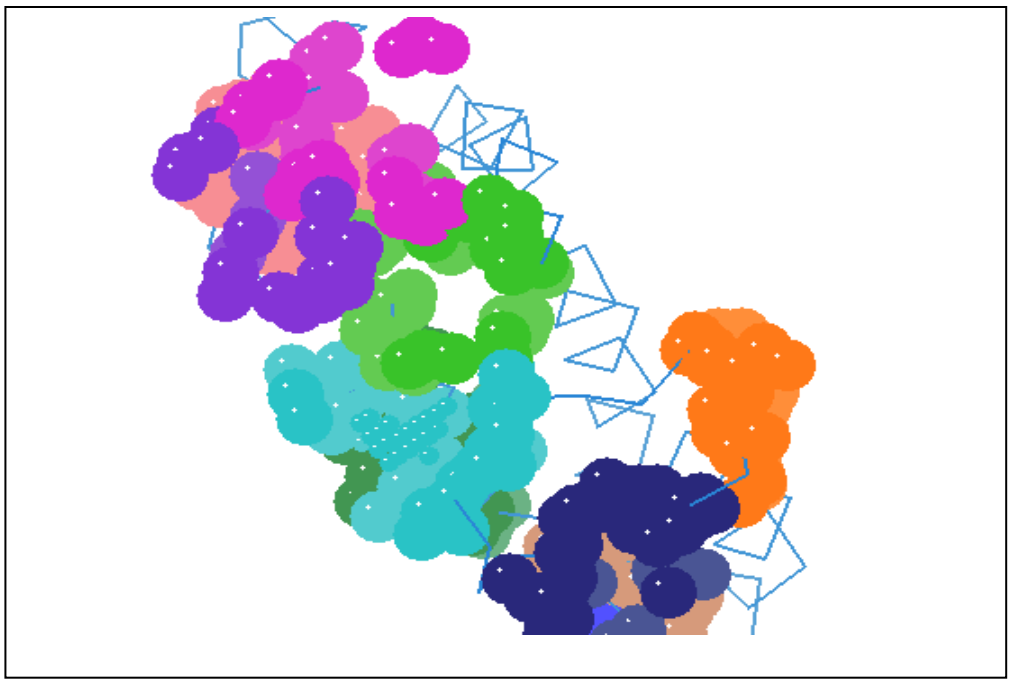

Fig. 8. Showing the protein with all sites and residues

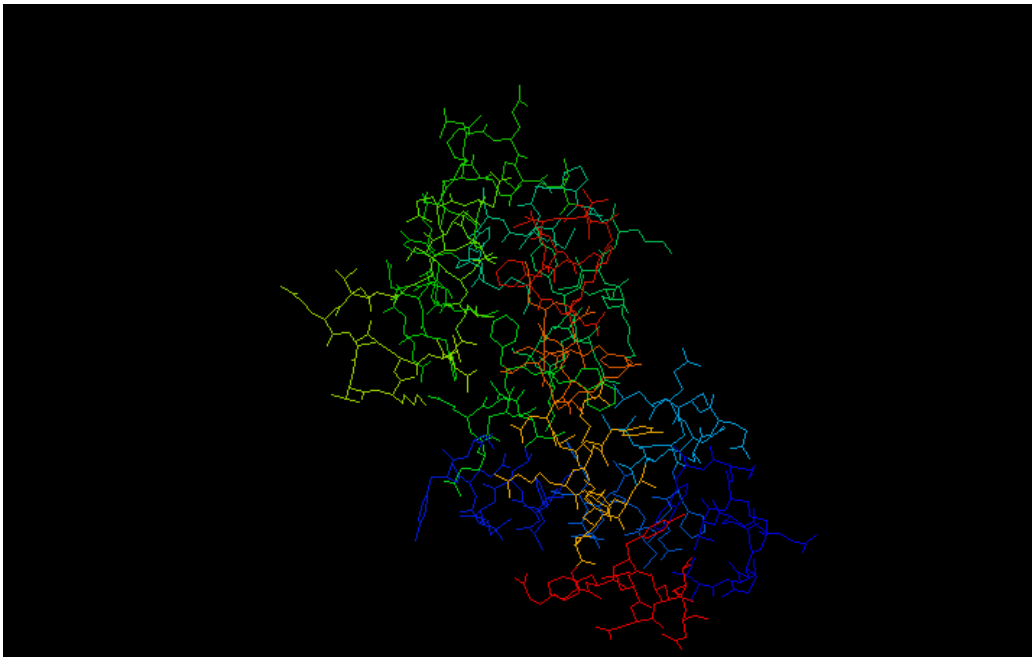

Fig. 9. Showing the final Refined Model Structure of RGS4 Protein used for Docking.

3.3 Docking Studies

Docking studies with Argus Lab Engine gave an insight into the binding modes of the various inhibitors.

Out of the 12 drugs that were selected only 4 drugs i.e., Ziprasidone, Hexythiazox, Chlorpromazine-Largactil, 7 hydroxynor – 2 – chlorpromazine represented a novel set of leads against the RGS4 gene and showed significant results. The results of these 4 drugs in order of docking score are shown in Table 3. Through Argus lab, it was found that the Ziprasidone compound has the best docking score (minimum energy interaction) of – 11.7084 from the 12 drugs selected for screening.

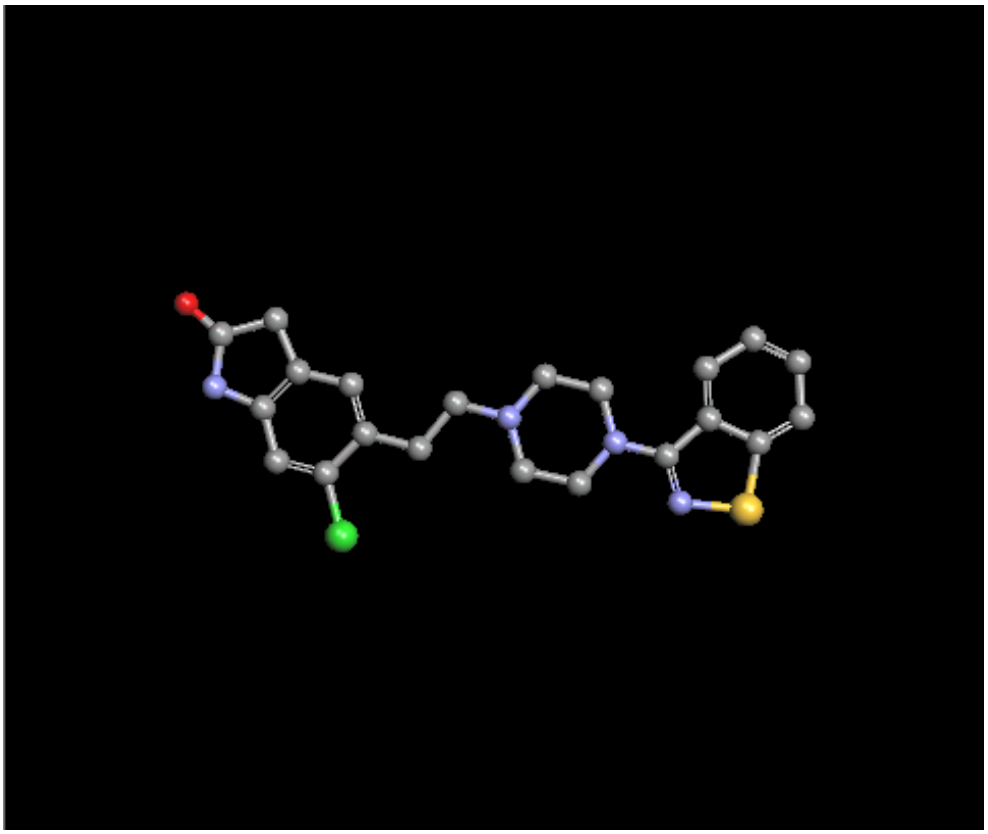

Fig. 10. Showing the final Ziprazidone Molecule in Argus Lab

4. DISCUSSION

Ziprasidone (Marketed as Geodon, Zeldox) is the fifth atypical and unique anti-psychotic drug to gain FDA approval in February 2001. It is an oral and injectable drug that is used for treating schizophrenia which is characterized by distorted thoughts, perceptions, and emotions. Ziprasidone helps manage schizophrenia's positive symptoms (visual and auditory hallucinations and delusions) and may also help in treating the negative symptoms of schizophrenia. (social withdrawal, apathy, lack of motivation, and an inability to experience a pleasure.

Ziprasidone inhibits communication between nerves of the brain by blocking receptors on the nerves for several neurotransmitters such as dopamine and serotonin. It also inhibits the synaptic re-uptake of serotonin and norepinephrine. The mechanism of the action of ziprasidone having efficacy in schizophrenia is unknown. However, it has been proposed that its efficacy in treating the positive symptoms of schizophrenia is mediated primarily via antagonism of the dopamine receptors specifically D_2, and blockade of the 5-HT_{2A} receptor [24]. "Blockade of 5-HT_{2A} and 5-HT_{2c} and activation of $5HT_{1A}$, as well as inhibition of the reuptake of serotonin and nor-epinephrine all, contribute to its ability to alleviate negative symptoms" [25].

"The absolute bioavailability of a 20mg dose of ziprasidone is 100% when administered intravenously and 60% orally without food" [26]. However pharmacokinetic studies have demonstrated that the bioavailability of ziprasidone is significantly increased by up to 100% in the presence of food. It is therefore recommended that ziprasidone should be taken with food as maximum absorption of Ziprasidone is achieved when administered with food. Ziprasidone is greater than 99% protein bound, binding primarily to albumin and □α_1-acid glycoprotein. Twice daily dosing generally leads to the attainment of a steady state within one to three days. Systemic exposures at steady state are related to dose. Ziprasidone has a volume of distribution of approximately 1.1 to 1.5 L/Kg when administered intravenously. Ziprasidone is extensively metabolized in the liver by aldehyde oxidase and via cytochrome P_{450} $3A_4$ (CYP_3A_4) [27], after oral administration with only a small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, i.e., benzisothiazole piperazine (BITP) sulphoxide, BITP

sulphone, ziprasidone sulphoxide, and S-methyl 2-hydroziprasidone.

Approximately 20% of the dose is excreted in the urine with 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of the total drug-related concentration in serum.

The mean terminal phase half-life after multiple dosing in normal volunteers and schizophrenic patients is between 6 and 10 hours [28], with a range of individual values from 3 to 18 hours. The mean systemic clearance of ziprasidone administered intravenously is approximately 5 – 7.5 ml/min/kg. However, very little evidence is available on the toxicity of ziprasidone.

The present study was investigated to identify a Novel Drug/Lead Molecule from 12 selected drugs based on a bioinformatics approach for schizophrenia targeting the RGS4 gene. The results demonstrate that ziprasidone is showing maximum inhibition of the RGS4 gene among the 12 drugs selected for screening.

5. CONCLUSION

It is thus concluded from the present study that the molecule with the lowest free energy (minimum energy inactivation) and high affinity as revealed by Ziprasidone is the best drug to inhibit the action of RGS4 protein. Thus inhibition of the RGS-4 gene may protect the body against schizophrenia disease and hence it can be suggested for the treatment of schizophrenia.

DISCLAIMER

Some part of this manuscript was previously presented in the conference (poster): Thirteenth International Symposium on Recent Advances in Environmental Health Research on September 11-14, 2016 in Jackson State University, Jackson, MS, USA. Web Link of the proceeding: http://ehr.cset.jsums.edu/13cd/pdfs/Faculty%2038.pdf.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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