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COMPUTATIONAL ANALYSIS ON ZINC DATABASE AGAINST ALDOSE REDUCTASE AS ANTI DIABETIC

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ABSTRACT

Effort to apply computational power to the combined chemical and biological space in order to streamline computer aided drug discovery and development is the spirit of scientific method. India is a world capital of diabetes. Immediate attention is required for the development of a novel drug for diabetes. Though Type 2 Diabetes has many drugs, it lacks 100% effective cure. The drug design is mainly based on target identification, protein-ligand interactions and the active site residues. An investigation has been carried out to study the mode of binding as well as the affinities of drug-like compounds for 1AH3(aldose reductase)from ZINC database(a free database for virtual screening) as anti-diabetic agents by performing protein – ligand interactions using various docking software.

Keywords: *Computer Science, Bioinfomratics, Diabetes, Aldose Reductase, Zinc Database, Anti Diabetic Agents*

1. INTRODUCTION

A mutation in a protein may leads to malfunction which result in causing disease. A Protein may cause more diseases, a disease can caused by many proteins. There are many proteins which causes diabetes, all the proteins are not having ligands to correct the sequence. Designing drug using conventional process is time consuming and expensive, but using in-silico can be minimized and also cheaper. Virtual screening (VS), or in silico screening, is a new approach attracting increasing levels of interest in the pharmaceutical industry as a productive and cost-effective technology in the search for novel lead compounds[1].

Protein coding genes related to Diabetes are figured out from the gene cards website [2]. Many of them are screened as they don't have PDB id, and some doesn't have ligands. All those are eliminated and only the closely linked proteins with ligand are selected and the best suited protein Aldose Reductaseis filtered finally as it exihibts more consenus from the remaining. The average docking score of the ligands, inhibitors is -126.048 kcal/mol. .

2. METHODOLOGY

In order to find the best ligand having affinity/docking score more than the average -126.048 kcal/mol. For this we are considering the ZINC database.
ZINC, an acronym for 'ZINC is not commercial, a free database for virtual screening' contains over 4.6 million compounds in ready-to-dock, 3D formats, available at the URL http://zinc.docking.org. ZINC is different from other chemical databases because it aims to represent the biologically relevant, three dimensional form of the molecule. ZINC database currently has a library of 727, 842 molecules, and can be searched each with 3D structure, using catalogs of compounds from vendors (the size of this library continues to grow) [3].

Molecules in ZINC are annotated by molecular property that include molecular weight, number of rotatable bonds, calculated LogP, number of hydrogen-bond donors, hydrogen-bond acceptors, chiral centers, chiral double bonds [E/Z isomerism], polar and apolar desolvation energy [in kcal/mol], net charge and rigid fragments. The database contains 494,915 Lipinski compliant molecules and 202,134 'lead-like' molecules, having molecular weight in the range 150 to 350 with calculated LogP < 4, number of hydrogen-bond donors ≤ 3 and number of hydrogen-bond acceptors ≤ 6. ZINC

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provides several search criteria such as molecular property constraint, ZINC codes, vendor based, and molecular substructure search [4].

The inhibitors which are co-crystallized with the protein structures in PDB and the inhibitors from the literature [5-7] were taken.

Two types of ZINC Database searches were done.

First Search_Range:

The ZINC Database was searched giving the range of the ligand properties as lower and higher limits in search window as shown below in figure 1.

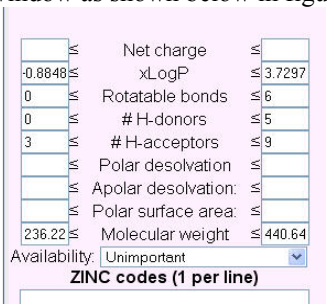

Figure 1: Image showing the first search parameters in ZINC search.

Second Search_Average

The ZINC Database was searched giving the average of the above properties as the lower limit and the upper limits were giving as per the Lipinski rule of 5 i.e., Log P<5, Molecular weight<500, Rotatable bonds<10, Hydrogen bond acceptors<10, Hydrogen bond donors<5 as shown below

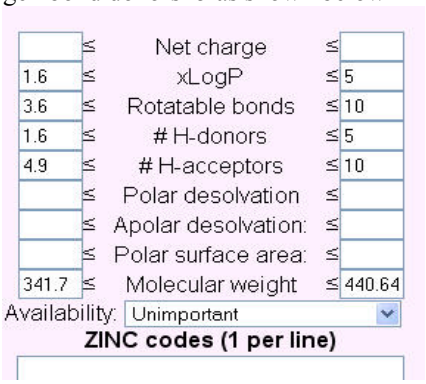

Figure 2: Image showing the second search parameters in ZINC search.

3. RESULTS

3.1 Compounds from ZINC Database:

To search the ZINC Database, we have considered the properties of the 15 co-crystallized ligands of the protein aldose reductase(pdb id: 1AH3). The properties are given in the Table 1.

First search_Range:

The ZINC Database was searched giving the range of the above properties as lower and higher limits. This resulted in 1001 hits. We have performed docking of all these ligands with 1AH3 protein and docking scorings are recorded.

Second search_Average:

The ZINC Database was searched giving the average of the above properties as the lower limit and the upper limits were giving as per the Lipinski rule of 5 i.e., Log P<5, Molecular weight<500, Rotatable bonds<10, Hydrogen bond acceptors<10, Hydrogen bond donors<5. This resulted in 837 hits. We have performed docking of these ligands with 1AH3 protein and the results of all these 837 ligands are recorded.

3.2 Best compounds from ZINC Database

First search_Range

The dock scores of the top 10 compounds taken from 1001 hits resulted in the first search of ZINC Database are shown in the Table 2

Second search Average

The dock scores of the top 10 compounds taken from 837 hits resulted in the second search of ZINC Database are shown in the Table 3

Ranking was done individually by clustering best scored compounds into equally split four classes using Tsar software[8], of which compounds in Class4 represents the highest class or top rank. Classes were generated for all scoring functions and instead of taking an average, rank-sum technique [9] was employed to retrieve best compounds. For ZINC first search range, the docking scores of different tools for top 10 ligands is given in Table 4 and result of rank sum technique is given in Table 5.

For ZINC second search average, the docking scores of different tools for top 10 ligands is given in Table 6 and result of rank sum technique is given in Table 7.

Further filtering of the best compounds:

Further filtering of the top 10 compounds from each section through consensus scoring and rank-sum technique resulted in the following compounds.

1. ZINC first search_Range: ZINC00844930
2. ZINC second search_Average: ZINC00702953

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4. CONCLUSION

In the conventional process customization process is tedious work because the process of what follows is more economical in terms of resources. Once you fall in computer-aided design of personalized medicine is more effective and provides immediate service to the needy.

A total of 1001 and 837 (search result based on range and average physico-chemical properties of co-crystallized aldose reductase ligands)

compounds from ZINC database docked with 1AH3 resulted in ZINC00447821 (-150.707 kcal/mol) and ZINC06075556 (-186.887 kcal/mol) as best compounds from 1001 and 837 hits of ZINC database.

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Mr. M Naresh Babu is a doctoral student of Prof Allam Appa Rao, who is working on investigation of anti diabetic agents using bioinformatic tools. He is a graduate of Andhra University. He published 6 research papers in the area of bioinformatics. Currently he is working as Associate Professor and Head of the department of Computer Science & Engineering in Avanthi's Research & Technological Academy.

Dr Allam Appa Rao was the first Computer Engineering scholar from Andhra University to receive Ph.D in Computer Engineering in the year 1984.

19 scholars were awarded Ph. D degrees under his tutelage and another 12 have submitted their PhD theses. "Best Academician Award" and "Best Researcher Award" were bestowed on him by Andhra University. Andhra Pradesh Government accorded him "Best Teacher" award.

Dr Allam proposed new computing methods, and showed the way to better treatments of disease and better understanding of healthy life. Perhaps even more intriguing, his work may enable the design of entirely novel systems that could prove useful in applications ranging from medicines to environmental cleanup and more. He has published in PubMed http://www.ncbi.nlm.nih.gov/pubmed/

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Table 1. Table showing the properties of the above said ligands.

S.No.	Ligand	Mol. Wt.	HBA	HBD
1	Sorbinil	236.2002	3	2
2	Tolrestat	357.3495	4	3
3	Fidarestat	279.2251	5	2
4	IDD384	390.4557	4	0
5	Zenarestat	441.6375	5	1
6	62P	324.7415	4	1
7	BTO	277.2341	6	1
8	Nitrofuryl-oxadizol	271.2082	9	0
9	IDD388	416.6280	4	0
10	IDD393	364.7390	4	2
11	ITA	393.3270	6	2
12	47D	351.7670	3	2
13	IDD-393	364.7390	4	1
14	53N	277.2975	5	5
15	IDD740	377.3425	7	2
	Average	341.5927	4.8667	1.6

Table 2 Table showing the docking scores of the best compounds from ZINC first search.

S.No.	ZINC ID	Affinity(kcal/mol)
1	ZINC00447821	-150.707
2	ZINC00005258	-147.748
3	ZINC00844930	-146.974
4	ZINC00712672	-139.608
5	ZINC00225101	-139.243
6	ZINC20357853	-139.185
7	ZINC00156572	-138.731
8	ZINC02138728	-138.431
9	ZINC20357855	-138.292
10	ZINC13298260	-138.085

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Table 3 Table showing the docking scores of the best compounds from ZINC second search.

S.No.	ZINC ID	Affinity(kcal/mol)
1	ZINC06075556	-186.887
2	ZINC00702980	-184.345
3	ZINC04019626	-181.231
4	ZINC00702964	-180.314
5	ZINC00702957	-179.491
6	ZINC00703016	-179.19
7	ZINC00702960	-177.675
8	ZINC00702959	-176.621
9	ZINC00702953	-176.479
10	ZINC00702951	-176.149

*Table 4 Scores of the top 10 ligands from **ZINC first search_Range** obtained from different docking softwares.*

S.No.	ZINC ID	Molegro (kcal/mol)	Ehits (kcal/mol	Vina (kcal/mol	Gold (kcal/mol	MEDock (kcal/mol	Patchdock (kcal/mol)
1	ZINC00447821	-150.707	-6.7087	-9.3	71.74	-10.52	4610
2	ZINC00005258	-147.748	-5.898	-8.5	56.43	-39.56	4822
3	**ZINC00844930**	**-146.974**	**-5.8752**	**-8.9**	**65.41**	**-57.93**	**5100**
4	ZINC00712672	-139.608	-5.2235	-8.6	54.35	-10.74	4914
5	ZINC00225101	-139.243	-5.8125	-8.3	52.52	-10.47	4288
6	ZINC20357853	-139.185	-5.648	-8.2	64.78	-61.43	4298
7	ZINC00156572	-138.731	-6.0916	-9.5	58.37	-11.19	4456
8	ZINC02138728	-138.431	-4.1219	-7.9	55.87	-55.51	4302
9	ZINC20357855	-138.292	-6.5123	-7.9	63.48	-57.48	4128
10	ZINC13298260	-138.085	-5.329	-11.6	66.25	-12.4	5304

Table 5 Classes generated using Tsar software.

S.No.	ZINC ID	Molegro	Ehits	Vina	Gold	MEDock	Patchdock	Sum
1	ZINC00447821	4	4	2	4	1	2	17
2	ZINC00005258	4	3	1	1	3	3	15
3	**ZINC00844930**	**3**	**3**	**2**	**3**	**4**	**4**	**19**
4	ZINC00712672	1	2	1	1	1	3	9
5	ZINC00225101	1	3	1	1	1	1	8
6	ZINC20357853	1	3	1	3	4	1	13
7	ZINC00156572	1	4	2	2	1	2	12
8	ZINC02138728	1	1	1	1	4	1	9
9	ZINC20357855	1	4	1	3	4	1	14
10	ZINC13298260	1	2	4	3	1	4	15

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Table 6 Scores of the top 10 ligands from ZINC second search_Average obtained from different docking software.

S.No.	ZINC ID	Molegro (kcal/mol)	Ehits (kcal/mol)	Vina (kcal/mol)	Gold (kcal/mol)	MEDock (kcal/mol)	Patchdock (kcal/mol)
1	ZINC06075556	-186.887	-3.9293	-8.3	65.46	-10.22	6052
2	ZINC00702980	-184.345	-4.8846	-9.5	67.42	-11.21	5642
3	ZINC04019626	-181.231	-5.9268	-9.3	83.89	-10.34	5246
4	ZINC00702964	-180.314	-6.3608	-9.6	60.37	-9.3	5832
5	ZINC00702957	-179.491	-5.0898	-9	87.79	-11.65	5386
6	ZINC00703016	-179.19	-6.1432	-9	53.8	-11.96	5296
7	ZINC00702960	-177.675	-5.477	-9.6	66.81	-10.67	5468
8	ZINC00702959	-176.621	-4.8692	-9.5	87.22	-10.44	5280
9	**ZINC00702953**	**-176.479**	**-6.0522**	**-9.5**	**84.35**	**-11.66**	**5256**
10	ZINC00702951	-176.149	-4.9741	-9.5	86.68	-10.96	5576

Table 7 Classes generated using Tsar software.

S.No.	ZINC ID	Molegro	Ehits	Vina	Gold	MEDock	Patchdock	Sum
1	ZINC06075556	4	1	1	2	2	4	14
2	ZINC00702980	4	2	4	2	3	2	17
3	ZINC04019626	2	4	4	4	2	1	17
4	ZINC00702964	2	4	4	1	1	3	15
5	ZINC00702957	2	2	3	4	4	1	16
6	ZINC00703016	2	4	3	1	4	1	15
7	ZINC00702960	1	3	4	2	3	2	15
8	ZINC00702959	1	2	4	4	2	1	14
9	**ZINC00702953**	**1**	**4**	**4**	**4**	**4**	**1**	**18**
10	ZINC00702951	1	2	4	4	3	2	16