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Successful challenge: A key step in infectious diseases treatment using computer-aided drug design

Hioual K. S*, Chikhi A, Bensegueni A, Merzoug A, Boucherit H, Mokrani El H, Teniou S, Merabti B

Department of Biochemistry and Microbiology, Faculty of natural and life Sciences , Mentouri University, Constantine, Algeria

Email address
didjasoulef@yahoo.fr (Hioual K. S)

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Abstract
The design molecules of therapeutic interest has benefited in recent decades developments from various scientific disciplines such as biology, medicinal chemistry and computer science and research, which once was to synthesize and test compounds selected on the basis of intuition and experience of the chemist medicinal, has radically changed. The development of computers has changed the particular given, leading to the emergence of a new discipline can participate in step initials of pharmaceutical research in addition to experimental methods already recognized. This is referred to in silico drug design - that is to say, assisted by computer - which corresponds to a specific set of information technology often designated by the acronym CADD (for "Computer Aided Drug Design") . Although, these tools have a wide scope in the process of searching for new drugs, we limit ourselves to the description of the methods used for this work, namely molecular docking, or " docking". The in silico molecular docking aims to predict the structure of a molecular complex from the isolated molecules, which is easier to implement, cheaper and faster than the use of experimental methods. Our goal is first to test the reliability of the docking software FlexX1.3.0 via RMSD (Root Mean Square Deviation), then to search for new inhibitors of neuraminidase (NA) which is one of the therapeutic targets of the influenza virus using zanamivir similars; one of the NA inhibitors, obtained from the PubChem.

1. Introduction

The research for new drugs was always the major concern of health researchers this is why docking small-molecular-weight ligands to the appropriate macromolecules has become a major computational method for predicting protein–ligand interactions and for drug design [1].

Computing the RMSD or the criterion deflection of the structure obtained by docking with respect to the structure given by X-ray diffraction of 153 complexes from the Protein Data Bank is used to test the reliability of the software FlexX, then zanamivir and its similar at the percentage of 90% meeting the criteria of the rule of Lipinski were docked by FlexX were looking for that which interacts better with neuraminidase.

2. Methodology

FlexX [2] uses an incremental reconstruction algorithm. In this latter, base fragments are identified first, after that the selected fragment is placed into the active site of the receptor using a hashing technique. The complete ligand is constructed by adding the remaining components one after the other. At each time of reconstruction a specified number of optimal partial solutions are selected for the next extension time. In FlexX the scoring is done using a modified Böhm scoring function, which includes the following terms: entropic; hydrogen bonding; ionic; aromatic; and lipophilic.

All values of RMSD ≤ 2 Å are considered positives; FlexX reproduced the experimental data at a rate of 60.78% of RMSD values ≤ 2 Å, similar CID 10038864 has interaction energy with the NA a bit less than zanamivir.

3. Results

Since each docking tool requires combining a docking engine with function quick score, the recent literature is full of pins match possible three issues: the ability of a docking algorithm to reproduce the pose crystallographic ligands selected low molecular weight [3, 4] [5] [6] [7]; rend functions quick score to predict the binding free energy from the best pose classified [8] [9] [10] [11, 12, 13], discrimination of known binders from molecules randomly selected from virtual screening experiments [14] [15] [16] [17].

The main criterion of a qualified docking program is its ability to reproduce the experimental binding modes of ligands. To test this, a ligand is taken out of the X-ray structure of its protein– ligand complex and docked back into its binding site. The docked binding mode is then compared with the experimental binding mode, and a root-mean-square distance (RMSD) between the two is calculated; a prediction of a binding mode is considered successful if the RMSD is below a certain value (usually 2.0 Å) [8]. Recently, Nissink et al. pointed out that to establish the success rate of a docking program, a large and carefully constructed set of protein–ligand complexes is required. [9] From here on, the "best pose" is defined as the docking solution that is the nearest to the experimental binding mode, whereas the "top pose" is defined as the docking solution that is ranked first. The ability to predict the correct binding of a ligand into its active site was thus evaluated by comparing the best pose and the experimentally determined solution. The ability to predict the correct binding of a ligand into its active site was thus evaluated by comparing the best pose and the experimentally determined solution.

Here are the results in diagrams:

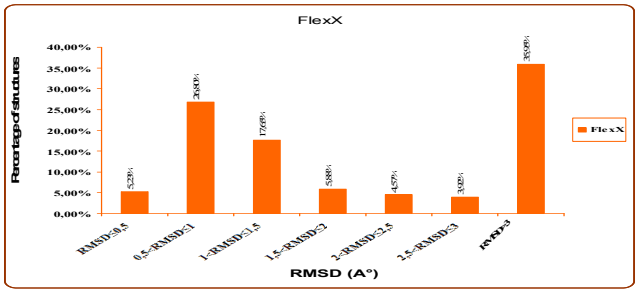

Fig 1. *The performance of Flex X according to the best docking pose generated.*

Docking results are discussed in the light of one major issue in the application of docking programs to virtual screening: docking accuracy. This criteria was assessed on a data set of 153 diverse protein–ligand complexes from the PDB.

Most good RMSD is in the range] 0.5 Å-1, 0A] for FlexX (see Fig1). Fig 1 shows also that within 2 Å of the X-ray pose, docking is successful for 55.56% of the cases using FlexX. Our result confirms the results obtained by Zaheer et al. In 2010 [19] where six docking programs were used: FRED, GOLD, MOE, AutoDock, and FlexX SURFLEX-Dock for a comparative study to determine their ability to reproduce poses via the experimental RMSD using 26 complex of Acetyl cholinesterase, FRED was the best followed SURFLEX-Dock and GOLD, other programs such as FlexX, AutoDock and MOE showed a slightly lower performance in the generation of poses. Michael et al. [18] evaluated in the same year the performance of the four programs GOLD, AutoDock, Dock-SURFLEX FRED by calculating the RMSD using inhibitors of the sarcoplasmic endoplasmic reticulum calcium ATPase, the best results were obtained by GOLD and FRED.

We all had a day flu and would not have it again, a high fever, headache, fatigue and other symptoms. Unfortunately, we can not be sure of escaping the next season (5 to 15% of population suffering from upper respiratory infections each winter). Described since ancient times and the middle Ages, annual influenza epidemics are also a cause significant mortality, especially among the elderly and those with illnesses chronic (3 to 5 million cases of severe illness and 250 000 to 500 000 deaths per year worldwide). Finally, severe influenza pandemics - three in the last century: the Spanish flu 918 (40 million dead), Asian flu in 1957 and Hong Kong flu in 1968 – have laimed the lives of many people over a short period of time, affecting even more resistant [20].

The NA was chosen as antiviral target, because of its important role in the propagation of influenza virus [21] due to the conservation of amino acid residues of the active site which interact directly or indirectly with the substrate in the virus influenza A and B [22]. due to the conservation of amino acid residues of the active site which interact directly or indirectly with the substrate in the virus

influenza A and B [22].

The crystal structure of the NA is downloaded from the PDB [23]; the choice fell on the 3CKZ complex has the cavity 150 adjacent to the binding site, which is a typical characteristic of the N1 subtype NA. It was shown in previous research [24] that viral replication was significantly inhibited by the binding of a compound to the cavity 150 of the NA of N1.

Docking by FlexX these similar and our original inhibitor gave the results in Table; Tab1

Tab 1. *Results docking zanamivir and 90% similar to the neuraminidase N1.*

	Ligand	Score	Match	Lipo	Ambig	Clash	Rot	Match
	3CKZ	-74,9698	-78,1127	-5,787	-11,9453	2,8751	12,6000	16
1	CID 44574175	-67.0328	-71.7204	-6.3155	-12.4883	2.6914	15.4000	15
2	CID 10112455	-38.1617	-45.5758	-6.1217	-10.9531	6.4889	12.6000	15
3	CID 5270784	-39.7879	-52.8120	-2.8300	-5.4216	4.6756	11.2000	13
4	CID 5273235	-45.4008	-57.7234	-2.8738	-6.8157	5.4122	11.2000	10
5	CID 10041431	-49.0993	-57.6054	-2.2210	-7.2202	1.3473	11.2000	11
6	CID14802591	-55.8186	-63.2724	-2.1901	-7.4754	0.5194	11.2000	12
7	CID14802593	-49.0904	-57.9034	-2.4892	-6.8011	1.5032	11.2000	10
8	CID 21157879	-48.4832	-59.6385	-3.0475	-6.6192	4.2220	11.2000	13
9	CID 5273237	-38.7517	-52.6517	-3.3567	-8.4927	9.1494	11.2000	11
10	CID 44371716	--49.1148	-56.5160	-4.3498	-6.8784	3.4294	9.8000	11
11	CID 16095341	-66.7145	-74.4605	-6.8622	-12.6514	2.2596	19.6000	17
12	CID 10180973	-37.5495	-45.1258	-6.9662	-12.6318	7.7743	14.0000	14
13	CID 10181866	-37.5329	-45.2882	-7.7349	-12.6514	7.3416	15.4000	14
14	CID 10205443	-39.6282	-51.5136	-8.5857	-10.7491	7.6201	18.2000	15
15	CID 10300514	-38.3600	-51.5424	-10.1696	-10.6770	7.6290	21.0000	15
16	CID 46215567	-21.1643	-33.9521	-3.2307	-6.3054	4.3239	12.6000	11
17	CID 23380404	-57.3460	-64.1054	-3.3540	-7.7486	1.2621	11.2000	14
18	CID 502292	-68.0551	-67.8805	-6.4697	-10.8048	3.2999	8.4000	13
19	CID 502293	-69.3773	-66.6381	-8.2999	-12.8015	3.1623	9.8000	14
20	CID 10088846	-58.0467	-66.1309	-5.9218	-10.8032	6.8092	12.6000	14
21	CID 5273230	-44.1653	-57.4363	-4.9959	-8.8595	4.9264	16.8000	12
22	CID 10740676	-73.7973	-81.6385	-6.4655	-11.7167	3.8234	16.8000	16
23	CID 10740677	-61.1877	-70.9431	-6.8893	-11.1366	8.3813	14.0000	13
24	CID 11724157	-26.3543	-39.8034	-3.4699	-6.7579	5.6769	12.6000	13
25	CID 502295	-66.3935	-69.0091	-8.4919	-14.4196	3.3271	16.8000	14
26	CID 5278155	-74.4958	-68.7768	-6.7076	-10.9616	2.3502	4.2000	14
27	CID 10781794	-37.1979	-47.1481	-5.7340	-8.2900	5.9742	12.6000	14
28	CID 502294	-67.4514	-68.1714	-8.6600	-14.1970	5.5770	12.6000	14
29	CID 10038864	-69.2587	-66.4422	-4.7206	-10.9010	1.8051	5.6000	14
30	CID 10264569	-68.1993	-70.6802	-4.8834	-8.2759	3.2403	7.0000	14
31	CID 10265401	-44.2669	-57.0326	-2.7569	-5.8545	6.1771	9.8000	14
32	CID 10497603	-25.6356	-36.2767	-5.4260	-9.2352	5.9023	14.0000	12

Of the 32 tested similar, the similar No. 29 (see Table) established an interaction similar to that of our original inhibitor zanamivir (3CKZ) like this has the same interesting than zanamivir pharmacokinetics: low weight molecular, less rotable bond and a good hydrophilicity (LogP).

So we can offer the similar No. 29 as another neuraminidase inhibitor N1 seen 3 good criteria previously mentioned it is interesting to make substitutions on it to increase the interaction energy more, in addition to in vitro and in vivo tests are recommended to confirm the efficiency of our program FlexX.

4. Conclusion

FlexX can be considered sufficiently effective since it reproduces quite well the experimental results, we can suggest the similar CID 10038864 as a new potent neuraminidase inhibitor with an interaction energy a bit less to that of zanamivir but with interesting pharmacokinetic properties.

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