International Journal of Scientific Research in Biological Sciences
Vol.10, Issue.5, pp.50-53, October 2023
E-ISSN: 2347-7520
Available online at: www.isroset.org

Research Paper

Computational analysis of Probable inhibitors of Serine/Threonine-protein kinase PIM-1/PIM-2 and of Proto-oncogene Tyrosine-protein kinase LCK

Ivan Vito Ferrari[1]

[1]Institute of clinical physiology of CNR, Massa, Italy

Author's Mail Id: ivanvitoferrari@gmail.com

Received: 13/Aug/2023; **Accepted**: 15/Sept/2023; **Published**: 31/Oct/2023

Abstract—In this short communication, it has been carried several computational studies of Probable inhibitors of Serine/Threonine-protein kinase Pim-1/Pim-2 and Proto-oncogene Tyrosine-protein kinase LCK. The method applied was Molecular Docking by Autodock Vina with the Pyrx program, comparing hundreds of drugs and natural molecules based on their binding energies calculated in the active site of Serine/Threonine-protein kinases PIM-1/PIM-2. From these Silico analyses, Imatinib and Hypericin showed theoretically the most binding affinity with both Serine/Threonine-protein kinase PIM-1 (Imatinib with binding energy of -10.8 kcal/mol and Hypericin with binding energy of -11.8 kcal/mol) and Serine/Threonine-protein kinase PIM-2 (Imatinib with binding energy of -11.4 kcal/mol and Hypericin with binding energy of -13.7 kcal/mol), compared to all other drugs and natural molecules examined. Although these results are an important first step to better understand what their biological action is with the enzymes studied, it will require many computational analyses and in vitro and in vivo biological tests to come to an actual conclusion about their mechanism.

Keywords— Autodock Vina, Autodock 4, Docking program, Hypericin

1. Introduction

PIM-1 is a proto-oncogene that encodes for the serine/threonine kinase of the same name, a gene that has the potential to cause cancer [1,2]. In tumor cells, these genes are often mutated, or expressed at high levels [1,2]. General speaking, a serine/threonine protein kinase (EC 2.7.11.-) is a kinase enzyme, in particular a protein kinase, which phosphorylates the OH group of the amino acid residues serine or threonine, which have similar side chains. At least 350 of the 500+ human protein kinases are serine/threonine kinases (STK) [3]. PIM-1 is primarily involved in cell cycle progression, apoptosis, and transcriptional activation, as well as more general signal transduction pathways [4-6]. Pim-1's role in oncogenic signaling has led it to become a widely studied target in cancer research, with numerous drug candidates under investigation that target it [4-6]. PIM-1 is primarily involved in cytokine signaling and has been implicated in many signal transduction pathways and humans, murine, and rats. Pim-1 contains 313 amino acids and has an amino acid identity of 94-97%. [4-6] Serine/threonine-protein kinase Pim-2 is an enzyme that in humans is encoded by the PIM2 [7,8]. Currently, the family of serine/threonine protein kinases are critically important, yet poorly understood [8]. In this short communication, we performed Autodock Vina and Autodock-4 Algorithms for natural compounds and drugs with protein apoptotic protease activating factor 1 to which of the drugs and natural substances binds better to this protein and which chemical bonds are involved. The first analysis, by Autodock Vina Polydatin, Ergotamine, and Dydro-Ergotamine are potential compounds to be bound in the Acitive site of APFA-1. With the second method that is more accurate in terms of binding energies, only Dydroergotamine showed excellent binding energy scores of about -12.5 kcal/molt, concerning crystal ligand ADP of about -10.9 kcal/mol. This means that Dihydro-ergotamine, used in the acute treatment of migraine, could be involved in the apoptosis process. It should be underlined that the natural molecule called Polydatin showed excellent results only with Autodock Vina, partially demonstrating that it could also play an important role with APFA-1.

2. Related Work

The goal of this short communication is to try to better understand the biological role of serine/threonine protein kinases, through fast and accurate computational methods. The In Silico method used was that of Molecular Docking [9,10], a powerful technique which with extreme precision allows hundreds of drugs and natural substances to be analyzed in a short time. Molecular Docking based on

Autodock Vina was applied in the active sites of serine/threonine protein kinases.

3. Calculation

Serine/threonine protein kinases PIM-1-PIM-2 are performed with several drugs and several natural compounds by Autodock Vina Algorithm with Pyrx program [9], which assigns a binding energy score value (kcal/mol) for each target molecule detected in The Binding Site pocked of Serine/threonine protein kinases PIM-1-PIM-2 respectively .

4. Experimental Method

Serine/threonine protein kinases PIM-1-PIM-2 are were downloaded from Protein Data Bank (PDB 4dtk) [10] and (PDB 2iwi) [7] respectively [1] and were accurate prepared before to perform Docking analysis by Autodock Vina [11]. All drugs and natural compounds were downloaded from Pubchem Database and manually prepared before to perform Docking analysis by Autodock Vina [11]. Virtual Screening approach by Pyrx [9] are used to detect about 150 small molecules with Serine/threonine protein kinases PIM-1-PIM-2 respectively.

5. Results and Discussion

The goal of this paper is to perform docking calculations of binding energy scores of drugs and natural compounds with the structure of the PIM-1 and PIM-2 kinase respectively [1,2]. The 3D crystal structures of these enzymes are shown in Fig. 1 and Fig. 2 respectively. After performing a Virtual Screening by Autodock Vina [9,11] with the Pyrx program [9] few compounds obtained significant binding energy values with PIM1 and PIM2 respectively. They are mainly Imatinib and Hypericin respectively. This paper aims to perform docking calculations of binding energy scores of drugs and natural compounds with the structure of the PIM-1 and PIM-2 kinase respectively [1,2]. The 3D crystal structures of these enzymes are shown in Fig. 1 and Fig. 2 respectively. After performing a Virtual Screening by Autodock Vina [9,11] with the Pyrx program [9] a few compounds obtained significant binding energies values with PIM-1 and PIM-2 respectively. They are mainly Imatinib and Hypericin respectively, as shown in Table 1 and Table 2.

The main docking results by Autodock Vina with Serine/Threonine-protein kinase Pim-1 are Imatinib with a binding energy of -11.8 kcal/mol, Ergosterol with a binding energy of -9.8 kcal /mol, Daidzin with a binding energy of -9.8 kcal/mol, Chloresterol with a binding energy of -10.1 kcal/mol, Naringenin with a binding energy of -9.9 kcal/mol, Hypericin -11.8 kcal/mol and 7- with a binding energy of dehydrocholestol -10.1.

The main docking results by Autodock Vina with Serine/Threonine-protein kinase Pim-2 are: Imatinib with a binding energy of -11.4 kcal/mol, Silibinin with a binding energy of -10.3 kcal/mol, Sylimarin with a binding energy of -10.4 kcal/mol, Ergosterol with a binding energy of- 11.0 kcal/mol, Hypericin with a binding energy of -13.7 kcal/mol, Stigmasterol with a binding energy of -11.0 kcal/mol Mocetinostat -10.2 kcal/mol, Lathosterol -10.3 kcal/mol.

The main docking results by Autodock Vina with Proto-oncogene Tyrosine-protein kinase LCK are: Hypericin with a binding energy of -12.4 kcal/mol, Imatinib with a binding energy of -11.7 and Mocetinostat with a binding energy of -10.5 kcal/mol.The possible conclusions that can be drawn from these computational results are different, for example, Imatinib and Hypericin would seem to have a greater binding affinity with Serine/Threonine-protein kinase Pim-2 than Serine/Threonine-protein kinase Pim-1 after having made a comparison of their energy binding (Hypericin has a value of binding energy of -11.8 kcal/mol with PIM-1, while Hypericin has a value of binding energy of -13.7 kcal/mol). The same observation applies to the case of the drug Imatinib (Imatinib has a value of binding energy of -10.8 kcal/mol with PIM1, while Imatinib has a value of binding energy of -11.4 kcal/mol with PIM-2.

Another possible observation can be seen that some sterols that have a chemical structure similar to cholesterol, such as Ergosterol, Cerebrostero, Stigmasterol, beta-Sitosterol, Zymosterol and Stigmasterol show an excellent ability to bind with both Serine/Threonine-protein kinase PIM-1 that Serine/Threonine-protein kinase PIM2

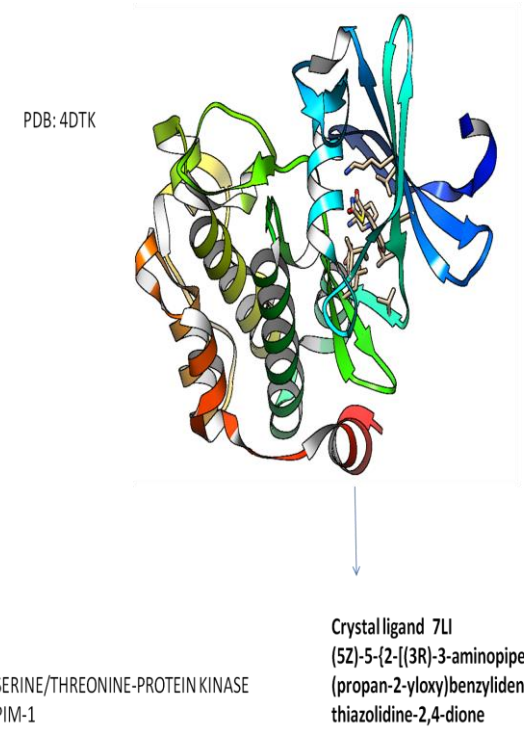

Figure 1. Crystal structure of the PIM-1 kinase in complex with an (5Z)-5-{2-[(3R)-3-aminopiperidin-1-yl]-3-(propan-2-yloxy)benzylidene}-1,3-thiazolidine-2,4-dione inhibitor. This figure was reproduced by Chimera program

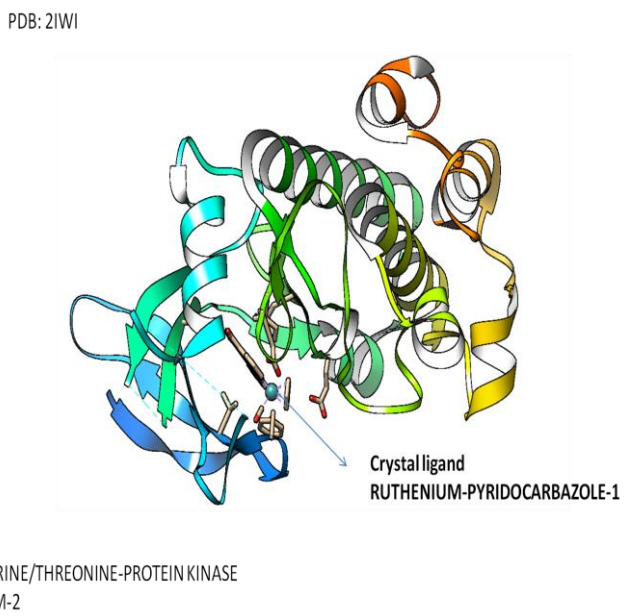

Figure 2. Crystal structure of the PIM2 kinase in complex with an organoruthenium inhibitor. This figure was reproduced by Chimera program

Table 1. Comparison best first poses of binding energies of drugs and natural compounds respectively with Serine/threonine protein kinases PIM-1 by Autodock Vina with Pyrx program

Compounds	Binding Energies (kcal mol^{-1})
7-Dehydrocholesterol	-10.1
Imatinib	**-10.8**
Naringin	-9.9
Hypericin	**-11.8**
Daidzin	-9.8
Ergosterol	-9.8
Camptothecin	-10.7
Cholesterol	-10.1
Cerebrosterol	-9.9

Table 2. Comparison best first poses of binding energies of drugs and natural compounres respectively with Serine/threonine protein kinases PIM-2 by Autodock Vina with Pyrx program

Compounds	Binding Energies (kcal mol^{1})
7 Dehydrocholesterol	-10.2
Androstenediol	-9.7
Campesterol	-10.3
Silibinin	-10.3
Silymarin	-10.4
Stigmasterol	-11.0
Zymosterol	-11.0
beta-Sitosterol	-10.1
Imatinib	**-11.4**
Ergosterol	-11.0
Hypericin	**-13.7**
Silibinin	-10.3
Kaempferitrin	-10.2
Lathosterol	-10.3
Mocetinostat	-10.2
Naringin	-9.8

Table3. Comparison best first poses of binding energies of drugs and natural compounds respectively with 2PL0 (Proto-oncogene tyrosine-protein kinase LCK) by Autodock Vina with Pyrx program

Compounds	Binding Energies (kcal mol^{1})
Mocetinostat	-10.5
Hypericin	**-12.4**
Imatinib	**-11.7**

6. Conclusion and Future Scope

The aim of this short paper was to study the Serine/Threonine-protein kinases PIM -1/PIM-2 and Proto-oncogene Tyrosine-protein kinase LCK respectively both drugs and natural compounds through Molecular docking, comparing their binding energies scores. From these docking results, Hypericin and Imatinib showed the best docking results in terms binding energies. Another possible observation can be seen that some sterols that have a chemical structure similar to cholesterol, such as Ergosterol, Cerebrostero, Stigmasterol, beta-Sitosterol, Zymosterol and Stigmasterol have showed theoretically an excellent ability to bind with both Serine/Threonine-protein kinase PIM-1 that Serine/Threonine-protein kinase PIM-2.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

Authors' Contributions

Ivan Vito Ferrari researched literature , involved in protocol development conceived the study. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

References

[1]. Chiang, W. F., Yen, C. Y., Lin, C. N., Liaw, G. A., Chiu, C. T., Hsia, Y. J., & Liu, S. Y.Up-regulation of a serine–threonine kinase proto-oncogene Pim-1 in oral squamous cell carcinoma. *International journal of oral and maxillofacial surgery*, Vol**.35**, Issue. (**8**), pp.**740-745**,**2006**.

[2]. Dakin, L. A., Block, M. H., Chen, H., Code, E., Dowling, J. E., Feng, X., & Zheng, X. Discovery of novel benzylidene-1, 3-thiazolidine-2, 4-diones as potent and selective inhibitors of the PIM-1, PIM-2, and PIM-3 protein kinases. *Bioorganic & medicinal chemistry letters*, Vol.22, Issue. (**14**), pp.4599-4604,2012.

[3]. Modi, V., & Dunbrack Jr, R. L. A structurally-validated multiple sequence alignment of 497 human protein kinase domains. Scientific reports, Vol.**9**, Issue. (**1**), pp.**19790**,**2019**.

[4]. Wang, Z., Bhattacharya, N., Weaver, M., Petersen, K., Meyer, M., Gapter, L., & Magnuson, N. S. Pim-1: a serine/threonine kinase with a role in cell survival, proliferation, differentiation and tumorigenesis. *Journal of veterinary science*, Vol.**2**, Issue. (**3**), pp.**167-179**,**2001**.

[5]. Bachmann, M., & Möröy, T. The serine/threonine kinase Pim-1. *The international journal of biochemistry* & cell biology, Vol.**37**(**4**), pp.**726-730**.**2005**.

[6]. Malone, T., Schäfer, L., Simon, N., Heavey, S., Cuffe, S., Finn, S., & Gately, K. Current perspectives on targeting PIM kinases to overcome mechanisms of drug resistance and immune evasion in cancer. Pharmacology & Therapeutics, Vol.**207**, pp.**107454**,**2020**.

[7]. Baytel, D., Shalom, S., Madgar, I., Weissenberg, R., & Don, J.

The human Pim-2 proto-oncogene and its testicular expression. Biochimica et Biophysica Acta (BBA)-Gene *Structure and Expression*, Vol.1442, Issue. (**2-3**), pp.**274-285**,**1998**.

[8]. Bullock, A. N., Russo, S., Amos, A., Pagano, N., Bregman, H., Debreczeni, J. E., & Knapp, S. Crystal structure of the PIM2 kinase in complex with an organoruthenium inhibitor. *PloS one*, Vol.**4**, Issue. (**10**), pp.**e7112**,**2009**.

[9]. Fulcher, L. J., & Sapkota, G. P. Functions and regulation of the serine/threonine protein kinase CK1 family: moving beyond promiscuity. *Biochemical Journal*, Vol.**477**, Issue.(**23**), pp.**4603-4621**,**2020**.

[10]. Dallakyan, S., & Olson, A. J. Small-molecule library screening by docking with PyRx. *Chemical biology: methods and protocols*, pp.**243-250**,**2015**.

[11]. Dakin, L. A., Block, M. H., Chen, H., Code, E., Dowling, J. E., Feng, X., & Zheng, X. Discovery of novel benzylidene-1, 3-thiazolidine-2, 4-diones as potent and selective inhibitors of the PIM-1, PIM-2, and PIM-3 protein kinases. *Bioorganic & medicinal chemistry letters*, Vol.**22**, Issue. (**14**), pp.**4599-4604**,**2012**.

[12]. Trott, O., & Olson, A. J. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of computational chemistry*, Vol.**31**, Issue. (**2**), pp.**455-461**,**2010**.

AUTHORS PROFILE

Ivan Vito Ferrari earned his Master degree in Industrial Biotechnology at University of Rome Tor Vergata in 2014., and Double Ph.D. in Industrial Engineering and material Science in 2017. He is currently working as Researcher in at the Institute of Clinical Physiology (C.N.R.) - Section of Massa Hospital Plant of Massa (Italy).

Call for Papers:
Authors are cordially invited to submit their original research papers, based on theoretical or experimental works for publication in the journal.

Make a Submission

All submissions:
- must be **original**
- must be **previously unpublished research results**
- must be **experimental or theoretical**
- must be in **the journal's prescribed Word template**
- and will be **peer-reviewed**
- may not be **considered for publication elsewhere at any time during the review period**