Lead-like compounds for inhibiting Methionine amino peptidase 2 (MetAP2)

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Abstract: This research aims to find a new approach to deal with cancer, by targeting a protein that controls the growth and increases the size of the tumour. The approach uses computer-aid drug designed to find the best drug for inhibiting f Methionine Aminopeptidase (Metap2) which is an enzyme that is responsible for starting the synthesis of new protein. The inhibition of the enzyme was found to be crucial in stopping the growth of the tumour and its development. In this research, an in-silico approach was conducted to obtain compounds that are capable of inhibiting the enzyme with non-toxic features. This is done by using Ligand-Based. The Zinc15 and National Institute of Cancer Data (NCI) Databases were screened to attain a variety of manufactured Compounds. Then, molecular docking filtration process was carried out using PyRx, and Autodock4. Finally, SwissADME protocol was used to show the ADMET properties and that compounds can permit the blood barriers and validate better pharmacokinetic properties than the Fumagillin.

Keywords: Cancer, Protein, Tumour, drug design, Computational Drug design.

1. Introduction

Cancer is an illness that effects the body's cells and make them produce wildly and spread in the effected organ. Cancer can initiate and spread in any parts of the human body. Cancer requires enormous amount of nutrition for its abnormal growth to be continued in the cell, by which the process of angiogenesis take a place. Angiogenesis take a serious part in the progression of cancer as the tumours normally required a blood vessel in order for them to grow and spread. these tumours can arouse the cell to start the angiogenesis process which forms a new blood vessel that nurtures that tumour [1].

MetAP2 plays a very important role in human cell propagation by removing methionine from newly synthesised protein by which starting the protein function. It found to be critical to the growth of the angiogenesis process and by sequencel the growth of cancer[2].

Over years many compounds have been developed to inhibit this protein (Methionine amino peptidase2). Fumagillin a natural irreversible inhibitor of MetAp2 and its derivatives have been showing an excellent potential therapy [3]. Methionine aminopeptidase (MetAP) is a metalloprotease enzyme that is responsible for eliminating the N-terminal methionine throughout protein synthesis as removing it is necessary for the protein to start its action. Methionine aminopeptidase 2, a member of the (MetAP) family. MetAP2 is located in all creatures and is particularly important because of its significant function in tissue reconstruction and protein decline. MetAP2 is very important precisely because of its key role in angiogenesis process, which is the development of freshly grown blood vessels, that are critical for the growth and nourishment of malady tumour such as cancer. MetAP2 is a pharmaceutical target for anti-angiogenic natural compounds such as fumagillin [4]. It's a key ligand that is used to inhibit the MetAP2

which was discovered in the earlier 20th century. Unfortunately, their toxicity and poor pharmacokinetic characteristics have denied them in both clinical trials and FDA approval [5].

2. Method and procedure

This research was made by using computer-aid drug designed tools (In silico) method to find the optimal drug (lead) of Metap2. All leads already has been manufactured and set for virtual screening in the Zinc database and are available online .

2.1 Data set preparation

The new innovative platform of Zinc15 called "Tranches" delivered a beneficial feature of picking according to Lipinski's rule of five which is very important in the drug industry that ensures the drug capability to be consumed by human body [6]. Accordingly, the leads like choice was set to the following standards: logp from 1 to 5 [5], molecular wight Mw from 250 to 500, figure of Hydrogen-donor from 0 to 5, figure of Hydrogen- acceptors from 0 to 9 a drug like a subset[7] as its showing in, the leads like that were chosen are consistent with this rules. The following Table 1 shows the compounds and there's calculated properties that's obey these rules.

Table 1 Lead-like ID and Lipinski's rule of five of the top four potential selective inhibitors of Methionine Amino peptidase (Metap2)

ZINC ID	logp	Mw	H-bond donors	H-bond acceptors	Rotatable bonds	Molecular Formula
ZINC000014235069	2.61	320.201	0	4	4	C11H11Cl2N3O2S
ZINC000534675358	2.0	308.407	3	4	6	C14H20N4O2S
ZINC000020653311	3.357	307.434	1	3	10	C18H29NO3
ZINC000065474804	0.606	323.441	2	6	7	C16H29N5O2

2.2 Protein Preparation

The selection of the Protein data bank PDB structure of MetAP2 that was chosen in this research was obtained from the literature as the best to resemble the MetAP2. It was selected from protein data bank in certain criteria to ensure its validity and accuracy. The protein of human methionine aminopeptidase-2 PDB code identified by the code 1BOA was selected according to the following criteria: Resolution 1.80 Å less than 3 for the best accuracy, No Alteration in the protein were found, the creature that was obtained from is Homo sapiens, the technique of obtaining the protein: X-Ray Diffraction [8]. After selecting the inhibitor, a protocol of cleaning the protein and preparing it was carried using Biovia discovery studio 2016. They were set for the upcoming step by eliminating all water particles from all structure.

2.3 Docking

The docking used the tools and software that's shown in Figure1; show the research work path which followed to obtain the results. The first tool PyRX used as primary filtration to minimize the huge database that was obtained from Zinc database [9]. Binding energy is the force of binding interactivity between one lead like to the inhibitor. The smaller the value, the greater the binding affinity of the ligand to its target. The threshold was set to -5 Free Energy of Binding. all compounds that failed to reach this threshold were excluded. Furthermore, Autodock4 software was used to obtain precise and accurate manual one by one docking [10]. The threshold was set to -7 Binding energy between the protein and the ligand. The lead like that were implement into the binding location of the receptor to assure its accuracy. The boundary was used for the (GPF) for each and all lead like 60, 60, 60 and the grid centres were 627848, 521848, and 942788 were used as x, y, and z coordinated sequentially [11]. The Estimated Inhibition Constant ki inhibitor constant, Ki, is a manifestation of how strong a lead is; it is the dose essential to yield half-maximum inhibition. The least the Ki, the better the binding energy and the smaller the quantity of drug necessary to stop the activity of that protein ___ was also taking into consideration within this research [12].

2.4 ADMET predication

ADMET Predictor is an online tool that can rapidly and perfectly anticipate and evaluate the chemical drug-likeness. The website SwissADME was used to find the results of the used compounds [13][9].

The risk of the drug toxicity was taken into consideration as we studied it through an online algorithm tool called ADMET predication that studies the lead like toxicity through its weight, physicochemical properties and its water solubility. The water solubility is one of the necessary factors to achieve the required dose of the drug in systemic circulation to fulfil the necessary pharmacological response. Poor water-soluble drugs usually need a high amount of drug so they can reach the medicinal plasma level after taking it orally [8]. Physicochemical properties include Lipinski's role of five that was mentioned before also verified within this tool, and other factors, which are also going to be tested in further study in pharmaceutical laboratory.

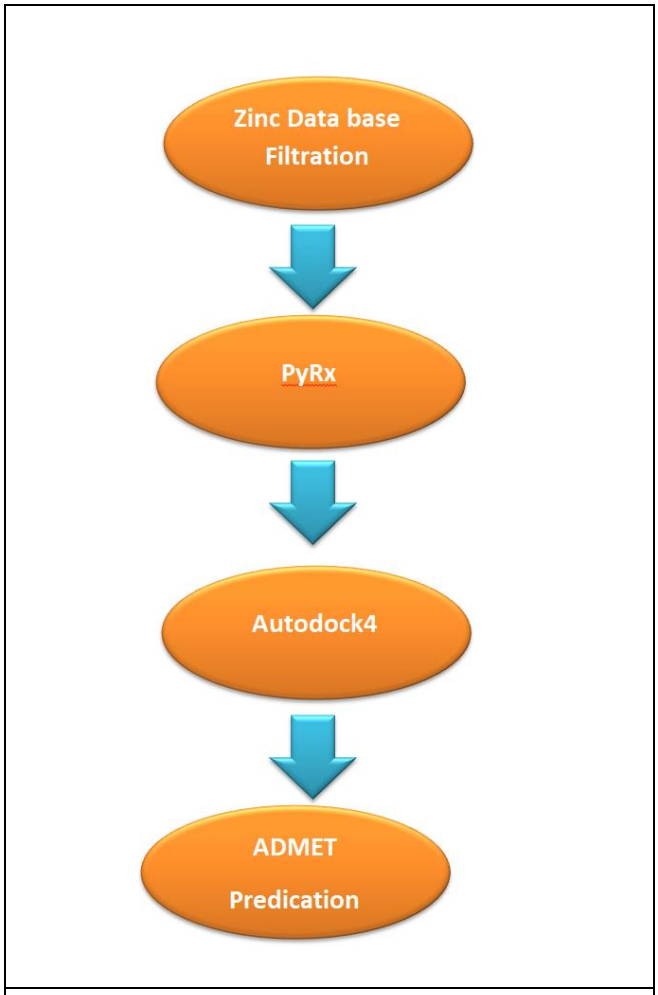

Figure 1. Shows the way that was taking in to the consideration in this research**.**

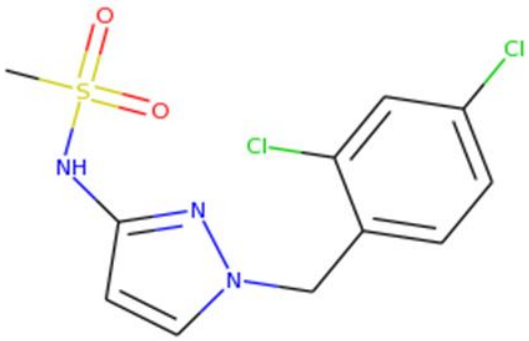

Figure 2a ZINC000014235069

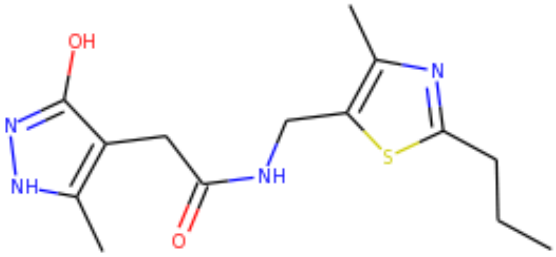

Figure 2b. ZINC000534675358

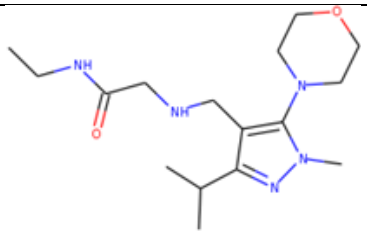

Figure 2c. ZINC000065474804

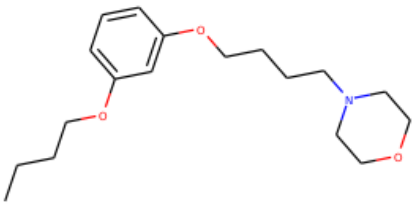

Figure 2d. ZINC000020653311

Figure 2 The lead like from zinc database showing 2d format.

3. Results and discussion

The present work is to find a new approach to deal with the cancer, by targeting a protein that controls the growth and the increment in the tumour size. The approach uses computer-aid technique, this approach will help the pharmaceutical companies to develop the best lead without spending too much on developing the assay. Till this very moment, the science community has failed to find the best drug that replaces Fumagillin. This work will provide compounds that will replace it and hopefully cure the cancer.

The result that is showing in Table 2 shows the Ki in macromolecule indicating a good drug characteristic. Also, the binding energy were showing a favourable interaction that can be further demonstrated in Figure 2,3 (2d and 3d). It clearly clarified that there is no bombe or unfavourable interaction between the ligand and the drug. The interaction between the amino acids of the protein with the ligand clearly states the successes of this lead-like compound. Furthermore, the solubility and lead liken from the ADMET predication website show the good drug quality of the compound.

Table 2 Binding energy and inhibition constant (Ki) and ademt predication values of the lead like inhibitors virtual screening using PyRx and molecular docking using AutoDock 4 and swissadme tool.

ZINC ID	Estimated Inhibition Constant, Ki micromolar	Estimated Free Energy of Binding	Water Solubility	**Drug likeness**
ZINC000014235069	1.97 uM	-7.78 kcal/mol	Yes	Yes
ZINC000534675358	5.91 uM	-7.13 kcal/mol	Yes	Yes
ZINC000020653311	4.86 uM	-7.25 kcal/mol	Yes	Yes
ZINC000065474804	5.13 uM	-7.22 kcal/mol	Yes	Yes

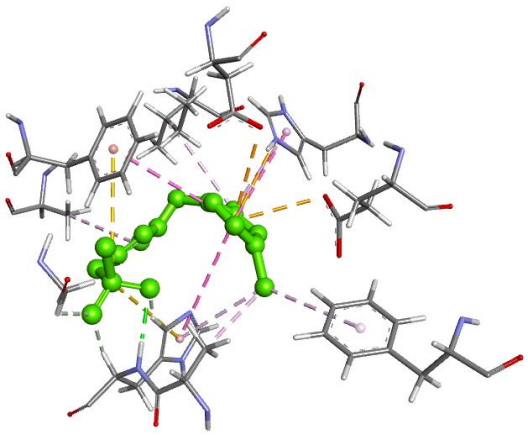

Figure 3a. 3D image shows the binding pocket between the protein (1BOA) and the Lead like ZINC000014235069

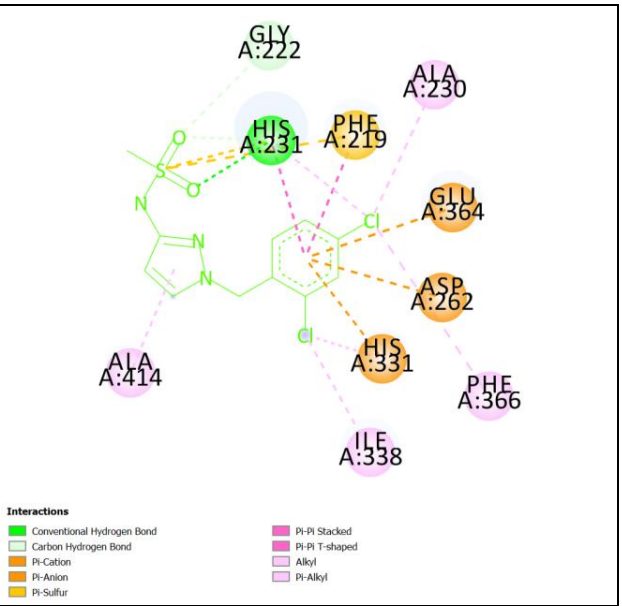

Figure 3b. 2D schematic shows the binding pocket between the protein (1BOA) and the Lead like ZINC000014235069

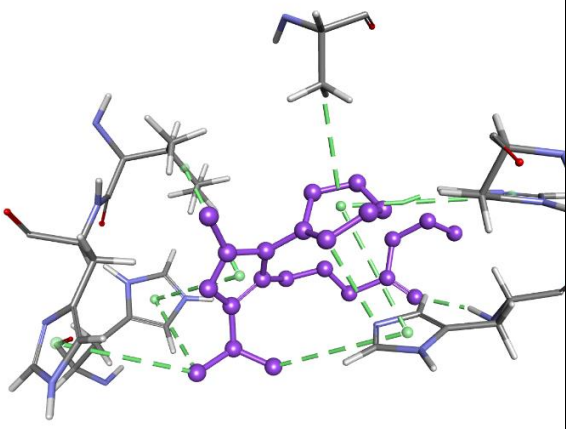

Figure 3c. 3D image shows the binding pocket between the protein (1BOA) and the Lead like ZINC000065474804

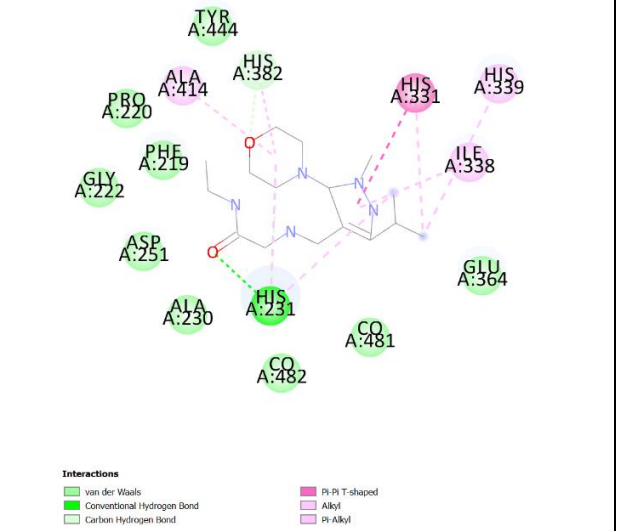

Figure 3d. 2D schematic shows the binding pocket between the protein (1BOA) and the Lead like ZINC000065474804

Figure 3 interactivity among MetAP2 and lead like ZINC000014235069, ZINC000065474804. 3D and 2D interactivity are shown in the left and right diagrams, respectively.

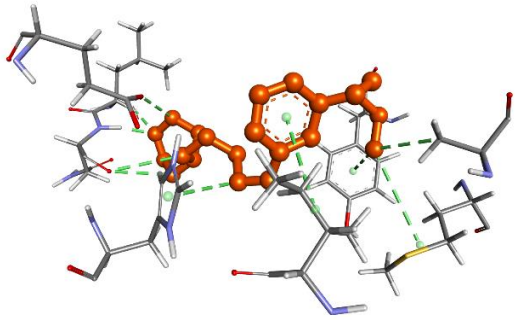

Figure 3e. 3D image shows the binding pocket between the protein (1BOA) and the Lead like ZINC000020653311

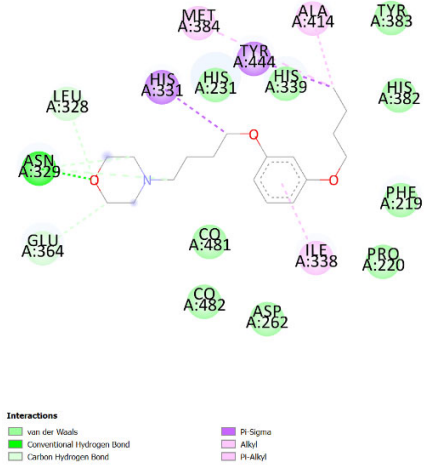

Figure 3f. 2D schematic shows the binding pocket between the protein (1BOA) and the Lead like ZINC000020653311

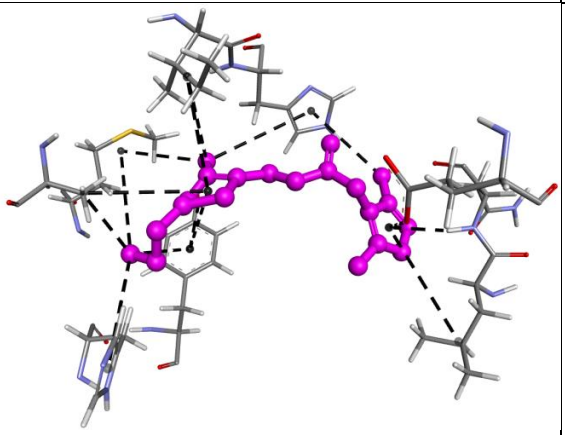

Figure 3g. 3D image shows the binding pocket between the protein (1BOA) and the Lead like ZINC000534675358

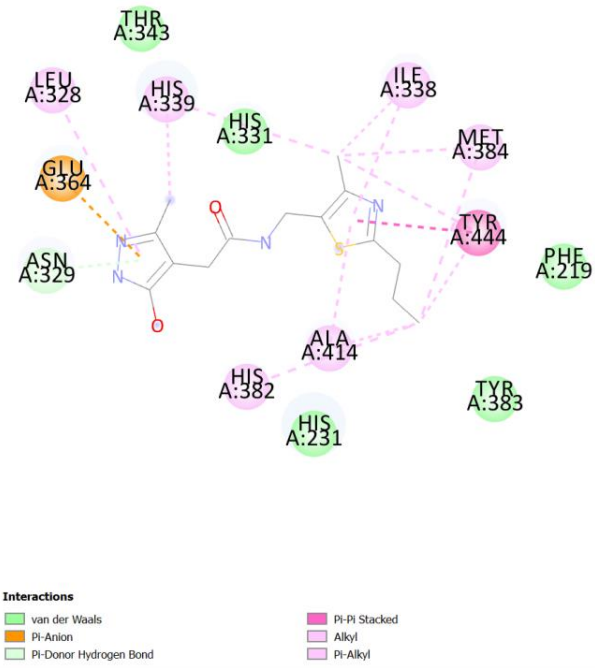

Figure 3h. 2D schematic shows the binding pocket between the protein (1BOA) and the Lead like ZINC000534675358

Figure 3 interactivity among MetAP2 and lead like ZINC000020653311, ZINC000534675358. 3D and 2D interactivity are shown in the left and right diagrams, respectively.

4. Conclusion

Cancer is a fatal disease that's kills millions every year. In this project we try to approach this disease by in silico methods to find the best drug to stop its growth and spreading. The in-silico method that was conducted screened thousands of compounds from zinc 15 database trying to find the best lead like. The project also tries to find the best lead like by following the ADMET predication procedure. These procedures ensure our lead like to be safe for the human consumption. Here in Maarif school Baghdad we hope that we can be a solider in the fight against this disease.

5. Acknowledgments

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6.Refrences

[1] Michael M, Christian J, Mona M, Robert J, Dierk N, Christian D K, Nikolas G, Aubry K M 2016 *ACS Chem. Biol* 10.1021/acschembio.5b00755.

[2] Liu S, Widom J, Kemp CW, Crews CM, Clardy J 1998 Science 13:1324-7. doi: 10.1126/science.282.5392.1324. PMID: 9812898.

[3] Augustine S S, Kemal Y, Abdullahi I U 2019 *Journal of Biomolecular Structure and Dynamics* 10.1080/07391102.2018.1557559

[4] Christopher A.L, Franco L, Beryl W.D, Paul J.F 1997 *Adv. Drug Deliv. Rev.*, 46:3–26 doi: 10.1016/S0169-409X(00)00129-0.

[5] Albert L, Corwin H, David E 1971 *Chem. Rev* 71 6:525-616 DOI: 10.1021/cr60274a001

[6] Jung W P, Sung-Wha H, 2019 *IEEE International Conference on Bioinformatics and Biomedicine*, pp. 1235-1236, doi: 10.1109/BIBM47256.2019.8983013.

[7] SHENPING L, JOANNE W, CHRISTOPHER W. K, CRAIG M. C , JON C 1998 *Science* 282:1324–1327 doi: 10.1126/SCIENCE.282.5392.1324.

[8] Antoine D, Olivier M, Vincent Z 2014 Journal *of Chemical Information and Modeling 54* 12:3284-3301 DOI: 10.1021/ci500467k

[9] Garrett M. M,Ruth H,William L,Michel F. S,Richard K. B,David S. G,Arthur J. O 2009 *J. Comput. Chem* 30: 2785-2791. https://doi.org/10.1002/jcc.21256

[10] Peruze A E, Özlem S, Gülüzar E, Gamze B T , Didem D E, Kemal Y, Hayat Y, Ayhan Sıtkı D 2014 *Turkish J. Chem* doi: 10.3906/kim-1305-56.

[11] Xing D, Yi L, Yang-Ling X. Shi-meng A, Jing L, Peng S, Xing-Lai J, Shu-Qun L 2016 *Int. J. Mol. Sci.*, 17:144 doi: 10.3390/IJMS17020144.

[12] A Antoine D, Olivier M, Vincent Z 2017 *Sci. Reports* 7:1–13, doi: 10.1038/srep42717.