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Research Article

Molecular docking analysis of pyruvate kinase M2 with a potential inhibitor from the ZINC database

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Abstract:
The pyruvate kinase M2 isoform (PKM2) is linked with cancer. Therefore, it is of interest to document the molecular docking analysis of Pyruvate Kinase M2 (PDB ID: 4G1N) with potential activators from the ZINC database. Thus, we document the optimal molecular docking features of a compound having ID ZINC000034285235 with PKM2 for further consideration.

Keywords: Pyruvate Kinase M2; Cancer; MTiAutoDock; MTiOpenScreen; ADMET/Tox.

Background:
Metabolism of cancer cells varies greatly from that in healthy cells **[1,2,3]**. Glycolysis is used in normal cells to generate energy, but glucose metabolism is transferred to aerobic glycolysis in tumour cells, and this process is called the Warburg effect **[4,5]**. A modern approach to targeted anti-cancer therapies is tumour glycolysis interventions **[6,7,8]**. Pyruvate kinase (PK) is the last rate-limiting enzyme in the glycolytic pathway, which catalyses the transfer of a phosphate group from phosphoenolpyruvate to ADP to obtain pyruvate and ATP **[9, 10,11]**. Pyruvate kinase has four distinct subtypes **[12]**. In the liver, kidney and red blood cells, PKL isoforms occur mainly, whereas PKR is primarily present in red blood cells. In myocardium, skeletal muscle and brain tissue, PKM1 is distributed, and in tissues such as the brain and liver, PKM2 is distributed **[13]**. PKM2 is important for cancer metabolism and tumour growth, yet tetramer and dimer of PKM2 consist of the same monomer **[14, 15]**. Between the tetramer and dimer form, biological effects are considerably different **[16]**. The tetramer mainly plays the role of pyruvate kinase in the sense of glucose metabolism and regulates glycolysis and dimer PKM2 as a switch for energy metabolism and material synthesis **[17]**. Therefore, it is of interest to document the molecular docking **[18-19]** analysis of

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Pyruvate Kinase M2 (PDB ID: 4G1N) with a potential activator from the ZINC database.

Materials and Methods:

Preparation of PKM2 structure:

The 3D crystal structure of Pyruvate kinase isoform M2 in complex with an activator was retrieved from the Protein Data Bank with PDB ID: 4G1N **[20]**. All the water molecules, Oxalate, Magnesium ions and N- (4-{[4-(pyrazin-2-yl) piperazin-1-yl] carbonyl} phenyl) quinoline-8-sulfonamide (NZT) were removed and polar hydrogen added to PKM2 protein for structure based virtual screening. Small-molecule activator NZT bind Pyruvate kinase isoform M2 at the subunit interaction interface, a site different from fructose-1, 6-bisphosphate (FBP) was used as activators binding site for molecular docking studies **[20]**.

Virtual screening:

The Drugs-lib library was used to conduct the virtual screening. The compound library contained 7173 approved drugs from the RPBS Web portal's in-house Drugs-lib database. The compound library was filtered by using the criteria such as molecular weight <500 Dalton; hydrogen bond donor <5, hydrogen bond acceptor <10, octanol–water partition coefficient logP <5; Number of rotatable bonds <8, polar surface area <140 Å. Docking was carried out on the MTiOpenScreen server with AutoDock Vina and with AutoDock on MTiAutoDock server **[21]**. To create a consensus list of compounds with both techniques that scored well, the rankings of AutoDock Vina and AutoDock were combined.

ADME/Tox prediction:

In the drug design process, the prediction of the ADMET properties plays an important role because these properties account for the failure in the clinical phases of about 60% of all drugs. Best predicted compounds on the basis of molecular docking had been processed by PreADMET **[18]** tool and cross reference by Swiss ADME tool **[19]**, which are web-based application for predicting absorption, distribution; metabolism, elimination and toxicity.

Visualization of protein-ligand interaction

Docking results were visualised using Python Molecular Viewer software to display docked pose of activator with PKM2 protein **[22]**.

Results and Discussion:

At the subunit interaction interface, the small molecule activator ZINC000034285235 binds PKM2, a site distinct from that of the endogenous activator fructose-1, 6-bisphosphate (FBP). PKM2 activator binding sites include 8 residues on chain A, such as TYR390, ASP354, GLN393, ILE389, PHE26, GLU397, LEU353, LEU394 and 7 residues on chain B as MET30, PHE26, TYR390, LYS311, LEU394, LEU353, ASP354. A constitutively active enzyme state (tetramer form) is promoted by PKM2 activator binding. 1500 small molecules were screened after applying filter criteria in compound library. AutoDock Vina employs a gradient-based conformational search method. The grid box parameters were set to values of 3.743 Å, -12.72, and 48.977 Å for the grid box center and 34Å ×28Å ×32Å for the box dimensions. We use 10 binding modes in total and 8 for exhaustiveness. The scoring of the generated docking poses and the ranking of the ligands is based on Vina 's empirical scoring function approximating the binding affinity in kcal / mol. Based on their lowest binding energy, the top 100 compounds were selected and further docked with the activator binding site of PKM2 using AutoDock. Docking results of both were shown in **Table 1**. Eight compounds with ZINC000006069082, ZINC000034285235, ZINC000051951668, ZINC000000000623, ZINC000034842284, ZINC000100029945, ZINC000100031653, ZINC000064033452 were selected based on binding energy of compound with PKM2 protein having >-9.0 kcal/mol in AutoDock Vina and >-11.0 kcal/mol in AutoDock, which is even lower than control NZT compound (binding energy: -7.95 kcal/mol with PKM2 protein). Human intestinal absorption properties are essential for the production of drugs that are meant to be administered orally **[23, 24]**. Human intestinal absorption (%HIA) values of eight drug compounds with ZINC000006069082, ZINC000034285235, ZINC000051951668, ZINC000000000623, ZINC000034842284, ZINC000100029945, ZINC000100031653 and ZINC000064033452 were shown in **Table 2**. These compounds have been identified in the category of well-absorbed compounds (HIA: 70 ~ 100 %) **[25]**. In vitro cell permeability Caco-2 is an important test that measures drug intestinal absorption **[26]**. In the MDCK method, the cell permeability in vitro use canine kidney cells and has a shorter growth rate than the Caco-2 cells were used as a tool for the rapid analysis of permeability **[27]**. Skin permeability is used in the pharmaceutical industry to assess the toxicity of chemical products in the event of accidental skin contact **[28]**. The blood-brain barrier (BBB) is essential for drug pharmacology. P_{Caco-2}, MDCK, Skin Permeability, PPB and BBB of eight compounds were shown in **Table 2**. Compound ZINC000034285235 had a BBB value in range 2.0~0.1 and was graded in the central nervous system with middle absorption **[29]**. Carcinogenicity is the toxicity in the body that causes cancer. Compound ZINC000051951668 and ZINC000100031653 had positive carcinogenicity value in mouse and rat, respectively. Compounds ZINC000006069082, ZINC000034842284 and ZINC000100031653 had a BBB value less than 0.1 and were graded in the central nervous system with poor absorption **[29]**. Further, ADME properties of compounds

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ZINC000006069082, ZINC000034285235, ZINC000051951668, ZINC000000000623, ZINC000034842284, ZINC000100029945, ZINC000100031653 and ZINC000064033452 were analysed by SwissADME tool **[19]**. ZINC000051951668, ZINC000034842284, ZINC000100029945 and ZINC000100031653 were not qualified all the five different rule-based filters such as Lipinski filter implemented rule-of-five **[30],** Ghose **[31]**, Veber **[32]**, Egan **[33]** and Muegge **[34]** shown in **Table 3**. The result provided in **Table 3** shows that all the compounds investigated have high gastrointestinal absorption except ZINC000100031653. All the compounds had good skin permeation and bioavailability score. Compounds ZINC000034285235, ZINC000000000623 and ZINC000100029945 indicate positive result in blood-brain barrier (BBB) permeation. The SwissADME estimates for passive human gastrointestinal absorption (GI) and permeation to the blood-brain barrier (BBB) consists of the BOILED-Egg model reading **[35]**. Therefore, only one compound ZINC000034285235 qualifies all parameters of ADME /Tox on analysis of eight best-predicted compounds using PreADMET and SwissADME tools. Best-docked complex was analyzed through Python Molecular Viewer for their interaction study shown in **Figure 1**. It is evident from this analysis that compound ZINC000034285235 is located at the subunit interaction interface of protein and is stabilized by hydrogen bonding.

Table 1: Docking results of compounds with PKM2 using Autodock Vina and Autodock tools.

Sl. No.	Compound Name	Compound ZINC Id	Binding Energy (AutoDock Vina)	Binding Energy (AutoDock)
1	Ditercalinium	ZINC000004215707	-10.2	-4.3
2	Reglitazar	ZINC000006069082	-10.1	-13.52
3	Bolazine	ZINC000008214506	-9.9	49.13
4	Amg-208	ZINC000034285235	-9.8	-12.91
5	Sanguinarium	ZINC000000000706	-9.6	-8.69
6	R428	ZINC000051951668	-9.4	-14.52
7	Acitazanolast	ZINC000001532937	-9.4	-8.34
8	Granisetron	ZINC000100018852	-9.3	-8.98
9	Vidarabine-phosphoric-acid	ZINC000504744048	-9.2	-7.93
10	Piketoprofen	ZINC000000000623	-9.2	-11.91
11	Furalazine	ZINC000004216369	-9.1	-8.10
12	Bagrosin	ZINC000026663185	-9.1	-10.12
13	Mk-2461	ZINC000034842284	-9.1	-11.59
14	Venetoclax	ZINC000150338755	-9.1	-9.84
15	Amg-517	ZINC000014974132	-9.1	19.19
16	Ladarixin	ZINC000084596756	-9.1	-7.95
17	Zosuquidar	ZINC000100029945	-9	-12.97
18	Sulfasalazine	ZINC000100031653	-9	-11.69
19	Lumacaftor	ZINC000064033452	-9	-11.68
20	Dihydroergocristine	ZINC000003947494	-9	1.12
21	Cyclobendazol	ZINC000005387004	-9	-8.31
22	Tazanolast	ZINC000001548561	-9	-9.69
23	Irinotecan	ZINC000001612996	-9	-6.28
24	Prasterone_acetate	ZINC000004063548	-9	-8.66
25	Ledipasvir	ZINC000150338819	-9	1710.00
26	R428	ZINC000051951669	-8.9	-12.44
27	Micinicate	ZINC000013884308	-8.9	-11.44
28	Derquantel	ZINC000056898856	-8.9	40.29
29	Benoxaprofen	ZINC000000000070	-8.9	-8.00
30	Raxatrigine	ZINC000113543589	-8.9	-9.16
31	Panamesine	ZINC000003801505	-8.9	-10.11
32	Bagrosin	ZINC000026663179	-8.9	-9.83
33	Uk432097	ZINC000095539256	-8.9	30.19
34	Xaliproden	ZINC000000577115	-8.9	-11.74
35	Prasterone_acetate	ZINC000253498202	-8.9	-8.45
36	Estriol	ZINC000003881360	-8.9	-9.80
37	Hesperidin	ZINC000008680007	-8.8	-3.52
38	Ci-988	ZINC000014952320	-8.8	-6.13
39	Dihydroergotamine	ZINC000003978005	-8.8	-13.61
40	Talniflumate	ZINC000000601275	-8.8	-11.30
41	Hydroxyestrone_diacetate	ZINC000005228505	-8.8	-9.96

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42	Dihydroergocristine	ZINC000003947496	-8.8	323.86
43	Velpatasvir	ZINC000220902773	-8.8	614.84
44	Mk3207	ZINC000103760981	-8.8	-7.68
45	Metergotamine	ZINC000072266819	-8.7	-12.14
46	Hesperidin	ZINC000038144568	-8.7	-9.60
47	Antrafenine	ZINC000053073961	-8.7	-12.43
48	Cep-32496	ZINC000000000043	-8.7	-9.56
49	Lifitegrast	ZINC000084668739	-8.7	-10.06
50	Elbasvir	ZINC000150588351	-8.7	1810.00
51	Hesperidin	ZINC000008382286	-8.7	-11.91
52	Lixazinone	ZINC000005318265	-8.7	-11.39
53	Proscillaridin	ZINC000038139432	-8.7	17.40
54	Fiduxosin	ZINC000029747110	-8.7	-15.12
55	Teniposide	ZINC000004166028	-8.7	-5.63
56	Golvatinib	ZINC000043195317	-8.7	-10.43
57	Flumatinib	ZINC000068244727	-8.7	-10.45
58	Nicofuranose	ZINC000004217093	-8.7	-11.51
59	Nicotredole	ZINC000000004164	-8.7	-9.78
60	Hesperidin	ZINC000103938998	-8.6	-10.96
61	Asobamast	ZINC000001537504	-8.6	-8.88
62	Setiptiline	ZINC000001482169	-8.6	-9.42
63	Midostaurin	ZINC000100013130	-8.6	4.52
64	Mk-8033	ZINC000068203670	-8.6	-13.40
65	Velpatasvir	ZINC000504665933	-8.6	746.28
66	Hesperidin	ZINC000103939005	-8.6	-11.24
67	Pretomanid	ZINC000003821675	-8.6	-8.81
68	Velpatasvir	ZINC000203686879	-8.6	148.54
69	Taclamine	ZINC000011616858	-8.6	-10.41
70	Ergotamine	ZINC000052955754	-8.6	-2.90
71	Pralnacasan	ZINC000003994903	-8.6	-14.50
72	Hesperidin	ZINC000100204053	-8.6	-10.82
73	Proscillaridin	ZINC000118917543	-8.6	-9.22
74	Ribavirin	ZINC000003831419	-8.6	-6.64
75	Hesperidi	ZINC000238924080	-8.5	-7.80
76	Clidinium	ZINC000000601316	-8.5	-9.92
77	Teniposide	ZINC000202773821	-8.5	5.21
78	Diosmin	ZINC000004098512	-8.5	-12.38
79	Proscillaridin	ZINC000118915484	-8.5	13.20
80	Azumolene	ZINC000005842585	-8.5	-9.84
81	Raxatrigine	ZINC000113543591	-8.5	-9.04
82	Estrone	ZINC000013509425	-8.5	-9.82
83	Isometamidium	ZINC000004216649	-8.5	-15.71
84	Hesperidin	ZINC000067902505	-8.5	-3.08
85	Velpatasvir	ZINC000504665932	-8.5	640.14
86	Mk3207	ZINC000103760984	-8.5	-16.62
87	Abamectin-component-b1a	ZINC000252673976	-8.5	92.47
88	Salazodine	ZINC000003917759	-8.5	-12.24
89	Azatadine	ZINC000000968337	-8.5	-10.30
90	Riociguat	ZINC000003819392	-8.5	-11.20
91	Saperconazole	ZINC000026168046	-8.4	-6.74
92	Glisamuride	ZINC000000537797	-8.4	-13.79
93	Proscillaridin	ZINC000118917543	-8.4	100.74
94	Glisindamide	ZINC000000537799	-8.4	-14.14
95	Mk3207	ZINC000043203371	-8.4	-9.43
96	Dihydroergocristine	ZINC000003995616	-8.4	1320.00
97	Icopezil-maleate	ZINC000000537848	-8.4	-12.20
98	Trazitiline	ZINC000022463350	-8.4	-9.14
99	Mirtazapine	ZINC000000000509	-8.4	-9.15
100	Azacitidine	ZINC000000967756	-8.4	-7.09

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Table 2: ADMET properties of eight best-predicted activators.

Compound ZINC Id	P_{Caco-2} (nm/sec)	MDCK (Nm/sec)	Skin Permeability	%HIA	%PPB	BBB	Carcinogenicity		
							Ames test	Mouse	Rat
ZINC000006069082	27.74	62.64	-3.16	97.14	90.34	0.03	Mutagen	-ve	-ve
ZINC000034285235	45.28	12.86	-3.44	97.57	94.82	0.51	Mutagen	-ve	-ve
ZINC000051951668	15.62	64.94	-3.02	95.87	81.82	0.90	Mutagen	+ve	-ve
ZINC000000000623	25.40	0.23	-2.30	96.13	90.41	0.16	Mutagen	-ve	-ve
ZINC000034842284	18.93	0.36	-3.62	97.74	72.34	0.06	Mutagen	-ve	-ve
ZINC000100029945	55.14	8.74	-2.46	97.22	89.03	0.21	Mutagen	-ve	-ve
ZINC000100031653	38.36	0.32	-2.63	90.00	100.00	0.01	Mutagen	-ve	+ve
ZINC000064033452	21.19	0.05	-2.11	97.60	92.95	0.13	Mutagen	-ve	-ve

PPB: Plasma Protein Binding, BBB: blood brain barrier.

Table 3: The pharmacokinetics and drug likeliness prediction of eight best-predicted compounds

Compound ZINC Id	GI	BBB	Log Kp (skin permeation Coefficient) (cm/s)	Bioavalia-bility Score	Lipinski	Ghose	Veber	Egan	Muegge
ZINC000006069082	High	No	-5.88	0.55	Yes	Yes	Yes	Yes	Yes
ZINC000034285235	High	Yes	-6.41	0.55	Yes	Yes	Yes	Yes	Yes
ZINC000051951668	High	No	-5.45	0.17	No	No	Yes	Yes	No
ZINC000000000623	High	Yes	-5.39	0.55	Yes	Yes	Yes	Yes	Yes
ZINC000034842284	High	No	-8.49	0.55	Yes	No	Yes	Yes	Yes
ZINC000100029945	High	Yes	-6.03	0.55	Yes	No	Yes	Yes	Yes
ZINC000100031653	Low	No	-7.18	0.56	Yes	Yes	No	No	Yes
ZINC000064033452	High	No	-5.91	0.56	Yes	Yes	Yes	Yes	Yes

GI: Gastrointestinal absorption, BBB: Blood Brain Barrier penetration.

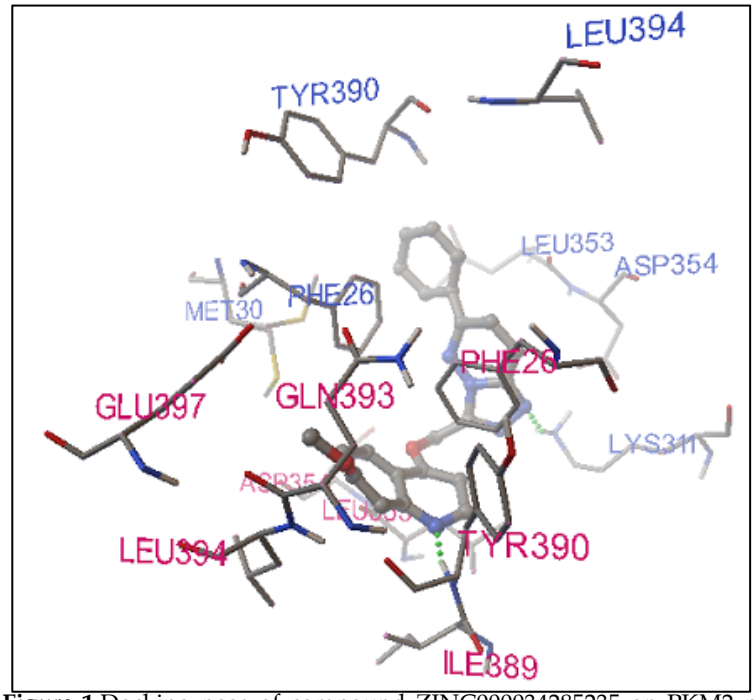

Figure 1:Docking pose of compound ZINC000034285235 on PKM2 protein structure. Two H-bonds were formed between amino acids TYR390, LYS311 of protein chain A and B with compound, respectively. H-Bonds are represented by green dotted spheres. Chain A and B binding residues of PKM2 protein were colored with pink and royal blue, respectively.

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Conclusion:
We document the optimal molecular docking features of a compound having ID ZINC000034285235 with PKM2 for further consideration in combating cancer.

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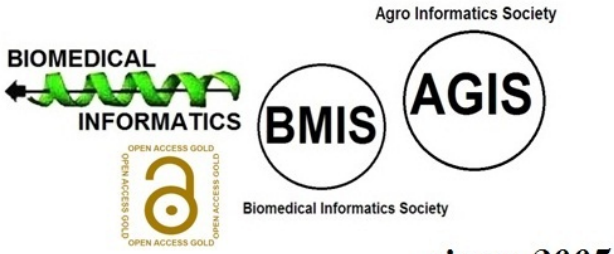

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