

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

Pankaj Sharma<sup>1\*</sup>, Manvender Singh<sup>1</sup> & Sangeeta Sharma<sup>2</sup>

<sup>1</sup>Department of Biotechnology, UIET, Maharshi Dayanand University Rohtak Haryana; <sup>2</sup>School of Life Sciences, IIMT University Meerut, India; Pankaj Sharma - Email: pank\_lko456@rediffmail.com; \*Corresponding author

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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

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 ZINC00006069082, 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 ZINC00006069082, 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<sub>Caco-2</sub>, 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 ZINC00006069082, 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

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	ZINC00000421570	-10.2	-4.3
2	Reglitazar	ZINC00000606908	-10.1	-13.52
3	Bolazine	ZINC00000821450	-9.9	49.13
4	Amg-208	ZINC00003428523	-9.8	-12.91
5	Sanguinarium	ZINC00000000070	-9.6	-8.69
6	R428	ZINC00005195166	-9.4	-14.52
7	Acitazanost	ZINC00000153293	-9.4	-8.34
8	Granisetron	ZINC00010001885	-9.3	-8.98
9	Vidarabine-phosphoric acid	ZINC00050474404	-9.2	-7.93
10	Piketopofen	ZINC00000000062	-9.2	-11.91
11	Furalazine	ZINC00000421636	-9.1	-8.10
12	Bagrosin	ZINC00002666318	-9.1	-10.12
13	Mk-2461	ZINC00003484228	-9.1	-11.59
14	Venetoclax	ZINC00015033875	-9.1	-9.84
15	Amg-517	ZINC00001497413	-9.1	19.19
16	Ladarixin	ZINC00008459675	-9.1	-7.95
17	Zosuquidar	ZINC00010002994	-9	-12.97
18	Sulfasalazine	ZINC00010003165	-9	-11.69
19	Lumacaftor	ZINC00006403345	-9	-11.68
20	Dihydroergocristine	ZINC00000394749	-9	1.12
21	Cyclobendazol	ZINC00000538700	-9	-8.31
22	Tazanolast	ZINC00000154856	-9	-9.69
23	Irinotecan	ZINC00000161299	-9	-6.28
24	Prasterone_acetate	ZINC00000406354	-9	-8.66
25	Ledipasvir	ZINC00015033881	-9	1710.00
26	R428	ZINC00005195166	-8.9	-12.44
27	Micinicat	ZINC00001388430	-8.9	-11.44
28	Derquantel	ZINC00005689885	-8.9	40.29
29	Benoxapofen	ZINC00000000007	-8.9	-8.00
30	Raxatrigine	ZINC00011354358	-8.9	-9.16
31	Panamesine	ZINC00000380150	-8.9	-10.11
32	Bagrosin	ZINC00002666317	-8.9	-9.83
33	Uk432097	ZINC00009553925	-8.9	30.19
34	Xaliproden	ZINC00000057711	-8.9	-11.74
35	Prasterone_acetate	ZINC00025349820	-8.9	-8.45
36	Estriol	ZINC00000388136	-8.9	-9.80
37	Hesperidin	ZINC00000868000	-8.8	-3.52
38	Ci-988	ZINC00001495232	-8.8	-6.13
39	Dihydroergotamine	ZINC00000397800	-8.8	-13.61
40	Talnidflumate	ZINC00000060127	-8.8	-11.30
41	Hydroxyestrone_diacetate	ZINC00000522850	-8.8	-9.96

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42	Dihydroergocristine	ZINC0000394749	-8.8	323.86
		6		
43	Velpatasvir	ZINC00022090277	-8.8	614.84
		3		
44	Mk3207	ZINC00010376098	-8.8	-7.68
		1		
45	Metergotamine	ZINC00007226681	-8.7	-12.14
		9		
46	Hesperidin	ZINC00003814456	-8.7	-9.60
		8		
47	Antrafenine	ZINC00005307396	-8.7	-12.43
		1		
48	Cep-32496	ZINC00000000004	-8.7	-9.56
		3		
49	Lifitegrast	ZINC00008466873	-8.7	-10.06
		9		
50	Elbasvir	ZINC00015058835	-8.7	1810.00
		1		
51	Hesperidin	ZINC00000838228	-8.7	-11.91
		6		
52	Lixazinone	ZINC00000531826	-8.7	-11.39
		5		
53	Proscillaridin	ZINC00003813943	-8.7	17.40
		2		
54	Fiduxosin	ZINC00002974711	-8.7	-15.12
		0		
55	Teniposide	ZINC00000416602	-8.7	-5.63
		8		
56	Golvatinib	ZINC00004319531	-8.7	-10.43
		7		
57	Flumatinib	ZINC00006824472	-8.7	-10.45
		7		
58	Nicofuranose	ZINC00000421709	-8.7	-11.51
		3		
59	Nicotredole	ZINC000000000416	-8.7	-9.78
		4		
60	Hesperidin	ZINC00010393899	-8.6	-10.96
		8		
61	Asobamast	ZINC00000153750	-8.6	-8.88
		4		
62	Setiptiline	ZINC00000148216	-8.6	-9.42
		9		
63	Midostaurin	ZINC00010001313	-8.6	4.52
		0		
64	Mk-8033	ZINC00006820367	-8.6	-13.40
		0		
65	Velpatasvir	ZINC00050466593	-8.6	746.28
		3		
66	Hesperidin	ZINC00010393900	-8.6	-11.24
		5		
67	Pretomanid	ZINC00000382167	-8.6	-8.81
		5		
68	Velpatasvir	ZINC00020368687	-8.6	148.54
		9		
69	Taclamine	ZINC00001161685	-8.6	-10.41
		8		
70	Ergotamine	ZINC00005295575	-8.6	-2.90
		4		
71	Pralnacasan	ZINC00000399490	-8.6	-14.50
		3		
72	Hesperidin	ZINC00010020405	-8.6	-10.82

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				3
73	Proscillaridin	ZINC00011891754	-8.6	-9.22
		4		
74	Ribavirin	ZINC00000383141	-8.6	-6.64
		9		
75	Hesperidi	ZINC00023892408	-8.5	-7.80
		0		
76	Clidinium	ZINC00000060131	-8.5	-9.92
		6		
77	Teniposide	ZINC00020277382	-8.5	5.21
		1		
78	Diosmin	ZINC00000409851	-8.5	-12.38
		2		
79	Proscillaridin	ZINC00011891548	-8.5	13.20
		4		
80	Azumolene	ZINC00000584258	-8.5	-9.84
		5		
81	Raxatrigine	ZINC00011354359	-8.5	-9.04
		1		
82	Estrone	ZINC00001350942	-8.5	-9.82
		5		
83	Isometamidium	ZINC00000421664	-8.5	-15.71
		9		
84	Hesperidin	ZINC00006790250	-8.5	-3.08
		5		
85	Velpatasvir	ZINC00050466593	-8.5	640.14
		2		
86	Mk3207	ZINC00010376098	-8.5	-16.62
		4		
87	Abamectin-component- b1a	ZINC00025267397	-8.5	92.47
		6		
88	Salazodine	ZINC00000391775	-8.5	-12.24
		9		
89	Azatadine	ZINC00000096833	-8.5	-10.30
		7		
90	Riociguat	ZINC00000381939	-8.5	-11.20
		2		
91	Saperconazole	ZINC00002616804	-8.4	-6.74
		6		
92	Glisamuride	ZINC00000053779	-8.4	-13.79
		7		
93	Proscillaridin	ZINC00011891754	-8.4	100.74
		3		
94	Glisindamide	ZINC00000053779	-8.4	-14.14
		9		
95	Mk3207	ZINC00004320337	-8.4	-9.43
		1		
96	Dihydroergocristine	ZINC00000399561	-8.4	1320.00
		6		
97	Icopezil-maleate	ZINC00000053784	-8.4	-12.20
		8		
98	Trazitiline	ZINC00002246335	-8.4	-9.14
		0		
99	Mirtazapine	ZINC00000000050	-8.4	-9.15
		9		
100	Azacitidine	ZINC00000096775	-8.4	-7.09
		6		

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

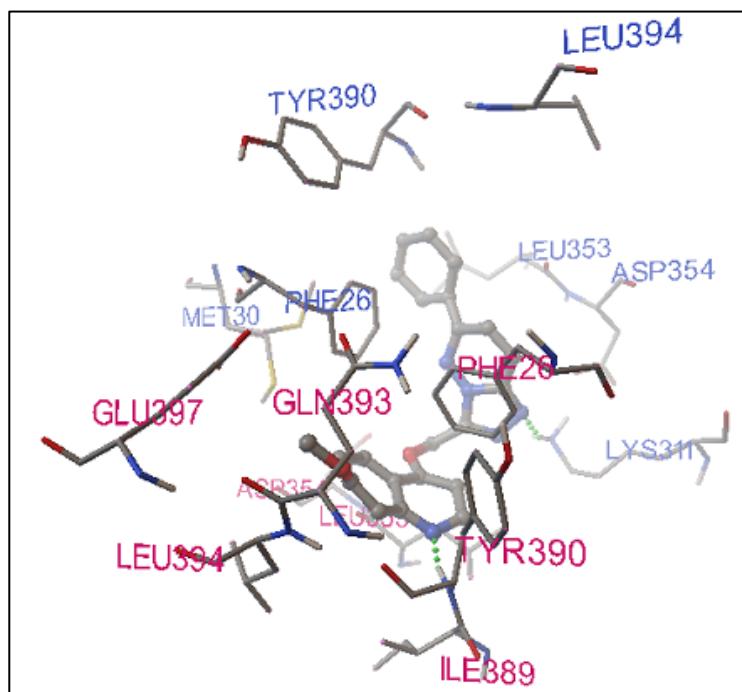
Compound ZINC Id	P <sub>Caco-2</sub> (nm/sec)	MDCK (Nm/sec)	Skin Permeability	%HIA	%PPB	BBB	Carcinogenicity		
							Ames test	Mouse	Rat
ZINC000006069082	27.74	62.64	-3.16	97.14	90.34	0.03	Mutagen	-ve	-ve
ZINC000034285235	45.28	12.86	-3.44	97.57	94.82	0.51	Mutagen	-ve	-ve
ZINC000051951668	15.62	64.94	-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)	Bioavailability 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.

**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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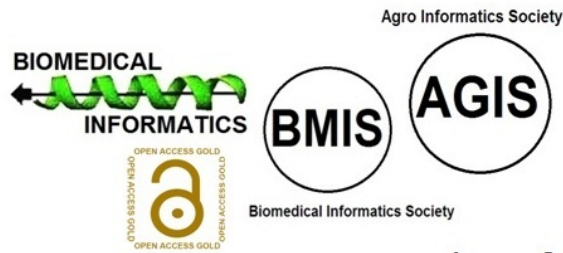
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