A Comparative Docking Studies of Dichloroacetate Analogues on Four Isozymes of Pyruvate Dehydrogenase Kinase in Humans

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ABSTRACT

Introduction: The four Pyruvate dehydrogenase kinases (PDKs) that regulate the mammalian Pyruvate dehydrogenase complex (PDC) are a novel class of kinases that are expressed in most tissues. PDK is a novel therapeutic target in oncology. Recent studies show that various oncogenes or transcription factors essential for cancer development, such as loss of p53 or activation of HIF1α can induce PDK expression and therefor inhibit PDH and glucose oxidation. Dichloroacetate (DCA) is a pyruvate mimetic anti-cancer compound that stimulatethe activity of the enzyme pyruvate dehydrogenase (PDH) through inhibition of PDKs. **Methods:** In this study, More than 200 DCA analogues were designed. Proper docking protocols were presented for the four isoenzymes of PDK using Autodock 4.2 and Vinasoftwares. **Results:** The docking binding energy values were in the order of PDK2>PDK1>PDK4>PDK3. ANOVA studies shows that the P value is significant at the level of 0.05 for PDK2 compared to PDK1, PDK2 and PDK3. **Conclusion:** The results show that the most sensitive to DCA and its analogues was PDK2. The validity of docking procedure was proved by high values of ROC_{AUC} or EF_{max} factor.

Key words: DCA analogues, Molecular docking studies, PDK isozymes, Pyruvate dehydrogenase kinase, Statistical analysis.

INTRODUCTION

Recent evidence in the fields of oncology implies that targeting the cancer-specific metabolic and remodeling of the mitochondria have increased selectivity in cancer treatment.[1] Due to great and essential role of mitochondria for the continuation of life in higher eukaryotic cells, such as cancer cells, mitochondrial enzymes have attracted scientists' interest.[2,3] Pyruvate dehydrogenase kinase (PDK) is one of the mitochondrial enzyme that is activated in a variety of cancers and selectively causes the inhibition of pyruvate dehydrogenase complex (PDC). PDC is a complex of three enzymes that convert cytosolic pyruvate into mitochondrial acetyl-CoA, the substrate for the citric acid cycle, by pyruvate decarboxylation process.[4,5] The activity of PDC is regulated by reversible phosphorylation of three serine residues on the E1α subunit. PDK phosphorylate these sites. Inhibition of PDK with either small drug dichloroacetate (DCA) or the small interfering RNAs (siRNA) shifts the metabolism of cancer cells from glycolysis to glucose oxidation (GO) and reverberate the suppression of mitochondria-dependent apoptosis.[1,4,5]

There are four known isozymes of PDK in humans. These kinases are named on the basis of their order of discovery, PDKs1-4. The primary sequencing between the four isozymes are conserved with 70% identity. The greatest differences exist near the N-terminus. PDK isoform function is apparently ancient and essential as the corresponding isoforms in rodents and humans are at least 94% conserved.[1,5,6]

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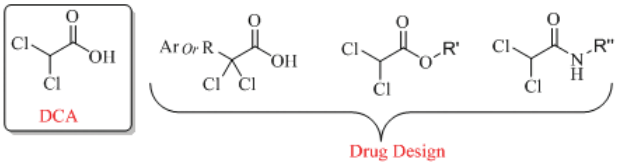
Tissue distribution and kinetic parameters for the four isoenzymes of PDK were analyzed. The expression of these isoenzymes transpires in a tissue-specific manner.[4-6] The mRNA for isoenzyme PDK1 was found mostly in heart. The message for PDK2 was present in all tissues tested but the level was low in spleen and lung. The mRNA for PDK3 was predominantly explicated in testis. The mRNA for PDK4 was predominantly expressed in skeletal muscle and heart. The major factors responsible for tissue-specific regulation of the PDC activity are unique tissue distribution and kinetic characteristics of the isoenzymes of PDK, as described by Melissa M *et al*.[6]

PDK1 is the largest isoform with 436 residues while PDK2, PDK3 and PDK4 have 407, 406, and 411 residues respectively.[7] Theisozymes have different activity and phosphorylation rates at each site. All four PDKs phosphorylated site 1 and site 2 in the subunit of the pyruvate dehydrogenase (E1) component, with different rates. At site 1 in order from fastest to slowest, PDK2 > PDK4 ≈ PDK1 > PDK3. For site 2, PDK3 > PDK4 > PDK2 > PDK1. Site 3 was phosphorylated by PDK1 only.[8] It should be mentioned that slight changes in pH can cause a great change in these rates. Therefore, the microenvironment of the PDK isoforms may change the reaction rates. As it was shown by Melissa M *et al*.[6], the specific activities of the isoenzymes varied 25-fold, from 50 nmol/min per mg for PDK2 to 1250 nmol/min per mg for PDK3. Apparent Ki values of the isoenzymes for DCA, varied 40-fold, from ± 0.2 mM for PDK2 to 8 mM for PDK3.

DCA is a lactate-lowering drug which has been in use for many years to treat various diseases such as lactic acidosis, inborn errors in mitochondrial function.[9,10] DCA prevent cell growth of a large range of tumor cells like endometrial,[11] pancreatic,[12] pediatric,[13] cervical,[14] colorectal,[15] lung, breast, glioblastoma,[16] and prostate[17] cancer cells by promoting mitochondria-regulated apoptosis, inhibit tumor growth and reduce proliferation by shifting the glucose metabolism in cancer cells from anaerobic to aerobic glycolysis.

Here, in this paper, More than 200DCA analogueswere designed and their binding modes toward four PDK isoenzymes have been explored by molecular docking. ANOVA studies of docking binding energies shows that PDK2 is the most sensitive to DCA whereas PDK2 is the less sensitive. Docking validation was also investigated.



Ar= aromatic groups, **R**= aliphatic groups, **R'=R"**=aliphatic and aromatic groups

Scheme 1: Chemical structure of DCA analogues used in molecular docking study

MATERIALS AND METHODS

Drug design

More than 200 DCA analogues were designed based on Scheme 1. The two dimensional structures of the ligands were drawn using ACD chem-sketch software. Then the ligands were subjected to minimization procedures by means of an in house TCL script using Hyperchem (Version 8, Hypercube Inc., Gainesville, FL, USA). Each ligand was optimized with different minimization methods such as molecular mechanics method (MM^+) and then quantum based semi-emprical method (AM1) by using Hyperchem package. The output structures were thereafter converted to PDBQT using MGLtools 1.5.6.[18]

Molecular Preparation of the structures

The 3D crystal structures for four PDK isozymes, PDK1 (2Q8H), PDK2 (2BU8), PDK3 (1Y8O) and PDK4 (3D2R) were retrieved from protein data bank (PDB).[19] Water molecules and the co-crystal ligands were thereafter excluded from the structures and the PDBs were corrected in terms of missing atom types using modeller 9.12.[20] An in house application program interface (MODELFACE) was applied for generation and running of python scripts within modeller software. Subsequently, the enzymes were converted to PDBQT and gasteiger partial charges were added using MGLTOOLS 1.5.6.

For validation of docking protocol, 20 active ligands and 50 inactive decoys were retrieved from ChEMBL database as SMILES format.[21-23] Iterative runs of openbabel 2.3.2 through a shell script provided the primary 3D generation of the structures as mol2 format.[24] The shell script was provided by means of batch scripting in windows operating system.

Docking procedure

The docking simulations were carried out by means of an *in house* batch script (DOCKFACE) for automatic running of AutoDock 4.2 and Vina in parallel mode

Table 1: Gridbox parameters in Autodock 4.2				
Parameter Name	**PDK1**	**PDK2**	**PDK3**	**PDK4**
PDB ID	2Q8H	2BU8	1Y8O	3D2R
No. of points in x	50	50	50	50
No. of points in y	50	50	50	50
No. of points in z	50	50	50	50
Grid spacing	0.375	0.375	0.375	0.375
Box X center	1.439	55.7	63	-25
Box Y center	38.929	46.5	-3.763	-6.8
Box Z center	-9.933	81	75	6

Table 2: Docking binding Energy (kcal/mol) of PDK1-4 isoenzymes by Autodock Vina				
PDK isoforms	**PDK1**	**PDK2**	**PDK3**	**PDK4**
Number of ligands	230	230	230	230
Minimum	-7.940	-9.570	-6.360	-6.890
25% Percentile	-6.270	-6.750	-5.540	-5.610
Median	-5.550	-6.050	-5.080	-4.940
75% Percentile	-4.890	-5.320	-4.320	-4.340
Maximum	-2.540	-3.120	-2.040	-2.740
Mean	-5.531	-6.174	-4.780	-5.029
Minimum	-7.940	-9.570	-6.330	-6.890
Std. Deviation	1.020	1.232	0.8620	0.8875
Std. Error of Mean	0.07229	0.08735	0.06110	0.06292
Lower 95% CI of mean	-5.681	-6.270	-5.020	-5.105
Upper 95% CI of mean	-5.396	-5.926	-4.779	-4.857

using all system resources. DOCKFACE was designed to facilitate the virtual ligand screening in stepwise mode including ligand preparation, receptor preparation, grid maps generation, dpf files preparation and finalization of docking runs. Processing of docking with Vina was also implemented in DOCKFACE. Genetic algorithm search method was used to find the best pose of each ligand in the active site of the target enzyme In all Autodock 4.2 experiments.[20,25-26] The Genetic Algorithm and grid box parameters are listed in Table 1. The exhaustiveness parameter in Vina was set to 100.[27] The receptors was kept rigid. All visualization of protein ligand complexes were analyzed using VMD software,[28] Autodock tools program (ADT, Version 1.5.6), and LigandScout 3.12.[29] All calculations were run on a core i7 personal computer (CPU at 6 MB) with Windows 7 operating system.

Analysis of Docking Results

Hundred docking poses saved for each compound were ranked according to their dock score function. AutoDock gives total binding energies of the compounds as well as steric and electrostatic lowest binding energy (LBE) for individual atoms as an output. For each target, the resulted Autodock dlg files and Vina out. txt files were subjected to an *in house* application implemented in vigual.net and the minimum energies related to the most favourable pose of each ligand were extracted. Then, the two metrics of virtual screening including the area under the curve (AUC) for receiver operating characteristic (ROC) plot and the maximum value of enrichment factor (EF_{max}) were calculated for active ligands and decoys using our ROC application.[30,31]

Analysis of variance (ANOVA)

To the best of our knowledge, ANOVA is a collection of statistical models used in order to analyze the differences among group means and their associated procedures. Data analysis was performed using GraphPad Prism 6 software (La Jolla, CA).[32] Significance was set at $p<0.05$.

RESULTS AND DISCUSSION

The grid box parameters are displayed in Table 1. The grid box dimensions were determined based on two times the length of the largest ligand in the data set for each PDK isozymes to nullify any constrains in docking procedure.

Table 3: ANOVA studies and standard errors of PDK1-4 isoenzymes for Autodock 4.2

	PDK1	PDK2	PDK3	PDK4	S.E
PDK1	-	0.032*	0.011*	0.035*	0.0758
PDK2	0.032*	-	0.003*	0.018*	0.0894
PDK3	0.011*	0.003*	-	0.067	0.0663
PDK4	0.035*	0.018*	0.067	-	0.0685

*The mean difference is significant at the level of 0.05.

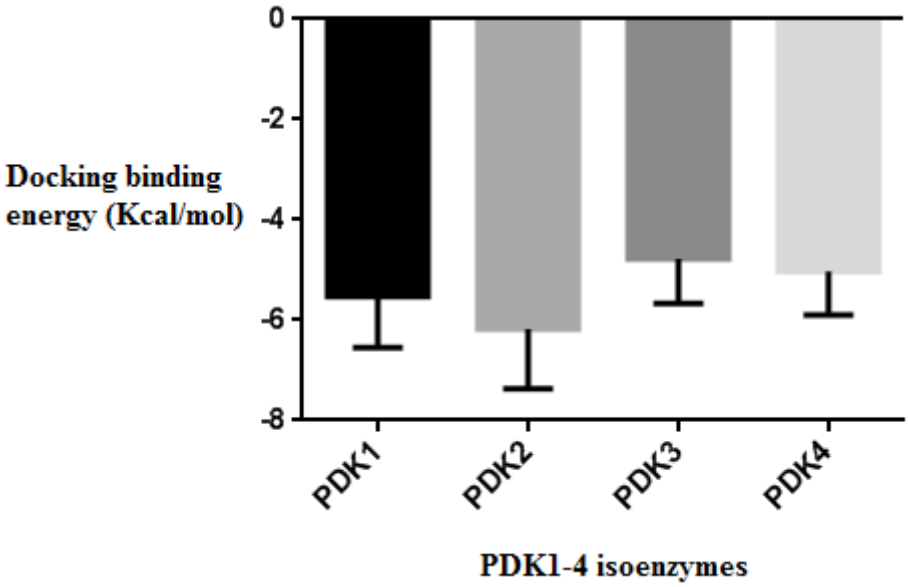


Figure 1: Statistical analysis of docking binding energies (Kcal/mol) of PDK1-4 isoenzymes

As it was shown in Table 2, 230 DCA analogues were docked against four isozymes of PDK. The mean docking binding Energy (kcal/mol) was -5.31, -6.174, -4.780 and -5.029 for PDK1-4 respectively. Statistical analysis of docking binding energies (Kcal/mol) of all 230 ligands shows thatthe most sensitive to DCA and its analogues is PDK2 and the least is PDK3 (Figure 1). All four PDKs isozymes have satisfactory binding energies with the ligands, however, with different valuesin the order of PDK2 > PDK1 > PDK4 > PDK3. As it was shown in Table 3, ANOVA studies of PDK1-4 isoenzymes for Autodock 4.2 shows that the P value is significant at the level of 0.05 for PDK2 compared to PDK1, PDK2 and PDK3.

For validation of docking protocols, the plots of ROC and EF_{max} were provided for PDK2 using Autodock 4.2 are depicted in Figure 2. The application of ROC in computational medicinal chemistry was first reported by Triballeau *et al.*[30] It was widely used as a useful metric in order to evaluate the validity of docking scores in virtual screening studies. So that, the structures must be first classified into two subsets of actives and decoys based on their experimental activities (20 active ligands and 50 inactive from ChEMBL database). The screening method should be therefore able to discriminate between active ligands and decoys. ROC value is the area under the curve (AUC) for the plot of selectivity versus specificity in a screening method. ROC curves were obtained by plotting (Se) versus (1-Sp) for all docking scores. The area under the curve for ROC is computed by trapezoidal integration method as implemented in our *in house* application. The more ROC_{AUC} value means that the docking protocol is more capableto distinguish between active ligands and decoys. Another tool to evaluate the efficiency of docking protocol in virtual screening studies is Enrichment Factor. Compared to ROC curves, EF_{max} factor is highly dependent to the number of actives in a data set.[31] It means that early enrichment can be easily obtained if the number of active ligands is increasing in a dataset. High values of ROC_{AUC} or EF_{max} are good criterion to prove the validity of our docking procedure. The best poses of ligands and decoys were merely used during analysis and other generated poses were ignored. This finding was exten-

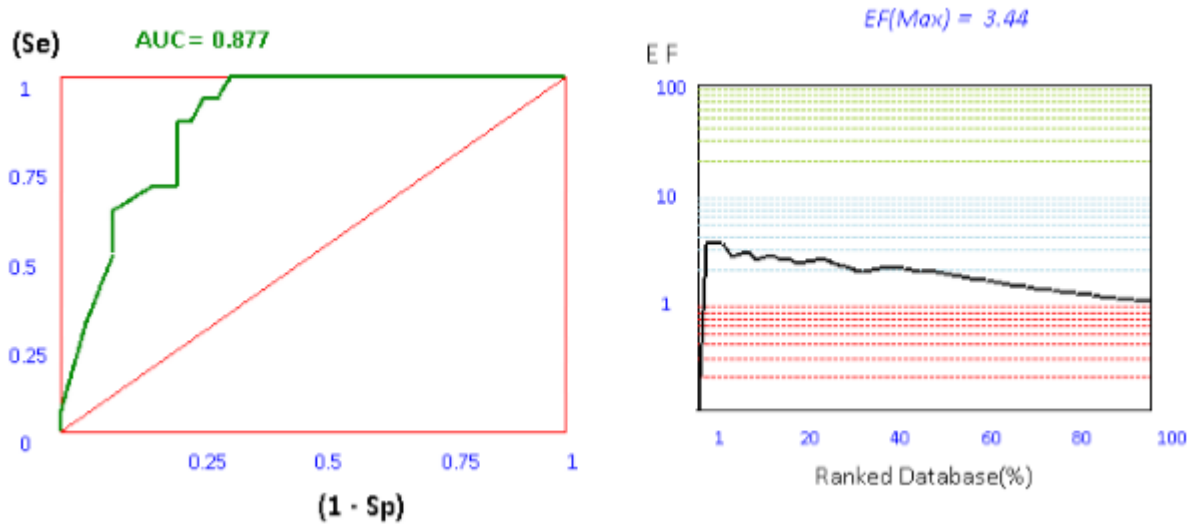


Figure 2: ROC and enrichment factor (EF_{max}) diagrams for PDK2 receptor using Autodock 4.2

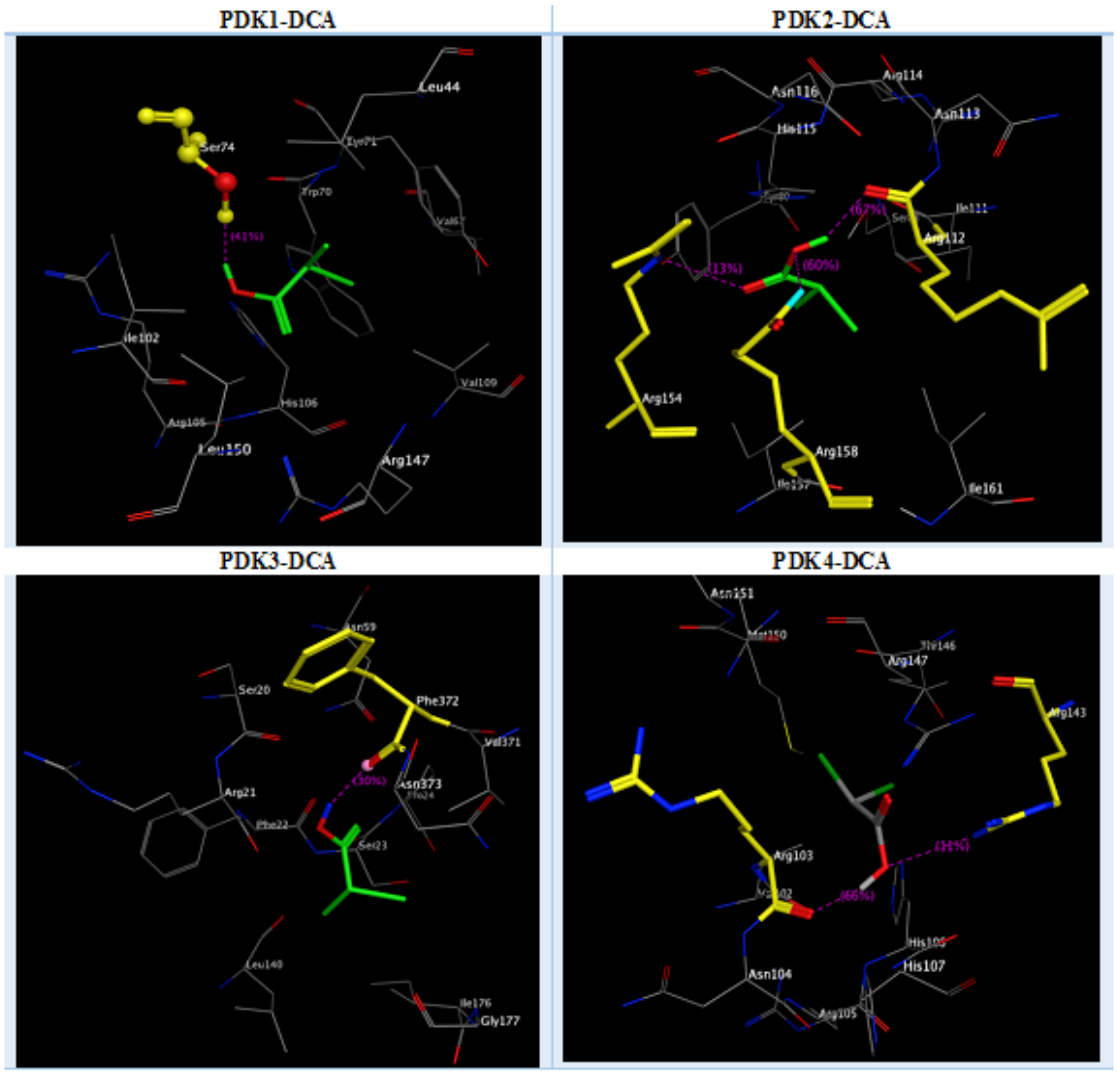


Figure 3: Interaction of DCA with PDK1-4 isoenzymes

sively similar in case of both softwares used in this study.

The interactions of DCA with four isozymes of PDK were investigated. As it was depicted in Figure 3, a hydrogen bond donor interaction exists between oxygen of hydroxyl group of DCA withSer74 in 2Q8H (PDK1) receptor. Meanwhile, two hydrogen bond acceptor interactions exist between oxygen of carbonyl group with Arg154 and oxygen of hydroxyl group with Arg158 in 2BU8 (PDK2) receptor. There is also exists a hydrogen bond donor interaction exists between oxygen of hydroxyl group of DCA with Arg112. The most important residues for 1Y8O (PDK3) target was a hydrogen bond donor interaction between oxygen of hydroxyl group of DCA with Phe A372. Whereas a hydrogen bond acceptor interaction exist between oxygen of carbonyl group with Ser A23 and a hydrogen bond donor interaction between oxygen of hydroxyl group of DCA with Gly B177 in D2R (PDK4) target.

CONCLUSION

PDK as a novel therapeutic target in oncology is one of the mitochondrial enzyme that is activated in a variety of cancers and selectively causes the inhibition of PDC. In this paper, more than 200 DCA analogues were designed and molecular docking studies of them for the four isoenzymes of PDK were carried out using Autodock4.2 and Vina softwares. The docking binding energy values were in the order of PDK2 > PDK1 > PDK4 > PDK3. ANOVA studies shows that the P value is significant at the level of 0.05 for PDK2 compared to PDK1, PDK2 and PDK3. The results show that the most sensitive to DCA and its analogues was PDK2. The validity of docking procedure was proved by high values of ROC_{AUC} or EF_{max} factor.

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CONFILCTS OF INTEREST

The authors declare that they have no conflicts of interest.

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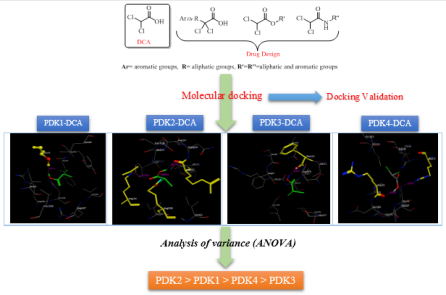
PICTORIAL ABSTRACT



ABBREVIATIONS USED

PDKs: Pyruvate dehydrogenase kinases; **PDC:** Pyruvate dehydrogenase complex; **PDH:** pyruvate dehydrogenase; **DCA:** Dichloroacetate; **GO:** glucose oxidation; **VMD:** Visual Molecular Dynamics; **ROC:** Receiver operating characteristic; **EFmax:** maximum enrichment factor; **AUC:** area under curve.

SUMMARY

- Proper docking protocols on the four isoenzymes of PDK using Autodock 4.2 and Vina softwares.
- PDK as a novel therapeutic target in oncology is one of the mitochondrial enzyme that is activated in a variety of cancers and selectively causes the inhibition of PDC.
- Designing more than 200 DCA analogues.
- The docking binding energy values were in the order of PDK2 > PDK1 > PDK4 > PDK3.
- The validity of docking procedure was proved by high values of ROCAUC or EFmax factor.
- ANOVA studies shows that the P value is significant at the level of 0.05 for PDK2 compared to PDK1, PDK2 and PDK3.

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