In Silico Insights into the Inhibitory Activity of Prodigiosin against Tumour Cells Targeting the Tyrosine Kinases Receptors

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INTRODUCTION

Prodigiosin (PDG) is a linear derivative of pyrrolyl dipyrromethene with a 4-methoxy,2-2-bi-pyrrole ring system. It is produced by some species of bacteria and eubacteria and is reputed for its anticancer activity against breast, colon and lung cancers via induced cellular stress. The study investigated the PDG binding interaction with several co-crystallized receptor tyrosine kinases (rTKs) to estimate the binding energies (E) and inhibition constants (Ki) of PDG.

METHODS

Prodigiosin was docked using AutoDockTools-1.5.6 against 20 co-crystallized rTKs selected from the protein data bank, PDB. The E, Ki, RMSD, the number of H-bonds and the amino acids involved in the interactions of their best conformational poses were estimated and compared with those of doxorubicin, a potent cytotoxin

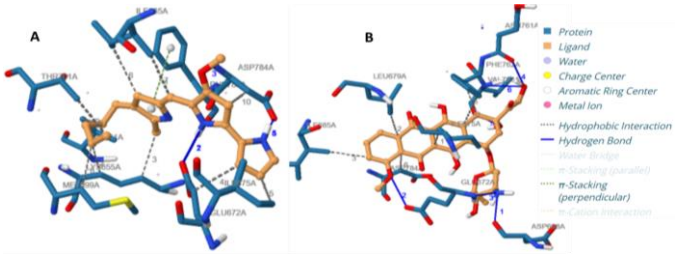

Figure 1: Theoretical 3D binding poses for DDR1 type II kinase protein- (A) PDG and (B) doxorubicin. The protein residue and ligand are represented in thick line format. Various interactions are color coded as shown on the right panel. The background represents the protein's molecular surface

RESULTS

PDG interacted more efficiently with the collagen discoidin domain receptor subfamily 1 (DDR1) type II kinase protein (PDB: 4BKJ). A total of 16 amino acid residues were involved in hydrophobic (Val624, 2 Lys655, Glu672, Ile675, 2 Ile685, Met699, Thr701 and Asp784), hydrogen (2 Glu672, 3 Asp784) and π-stacking (Phe785) interactions with the DDR1 type II tyrosine kinase protein. A significant RMSD, E, Ki of 60.071 A, -10.04 Kcal/mol and 43.90 nM respectively for the binding of PDG to the rTK were obtained vis-a-viz native ligand, imatinib (78.961 A, -14.20 Kcal/mol and 39.11 ρM) and doxorubicin control (52.52 A, -8.65 Kcal/mol and 457.29 nM) respectivelv.

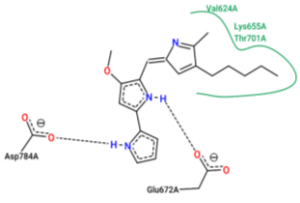

Figure 2. 2D representation of some hydrogen and hydrophobic interaction of PDG

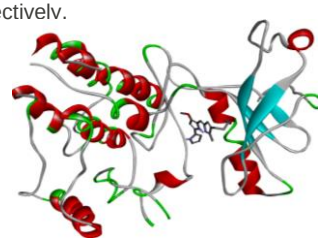

Figure 3. PDG dockied pose in DDR1 protein

Table 1. Binding parameters of PDG to DDR1 type II kinase protein

Ligands	RMSD	E (Kcal/mol	K_i (nM)	H-bonds	Amino acids involved
Imatinib	78.96	-14.20	0.0391	4	Val624, Lys655, Met676, Ile685, Thr701, Tyr703, Leu773, Leu773, Leu679, Asp784 & Phe785
PDG	60.07	-10.04	43.80	5	Val624, Lys655, Lys655, Glu672, Ile675, Ile685, Ile685, Met699, Thr701 & Asp784
Doxo	52.52	-8.65	457.2	6	Ile 675, Ile685, Leu679, Phe762, Phe762, Asp784

Doxorubicin (doxo); root mean square deviation (RMSD); number of hydrogen, drug-enzyme (H-bond); Prodigiosin (PDG); binding energy (E); inhibition constant (Ki)

CONCLUSION

The significantly higher inhibition of the DDR1 type II kinase protein by PDG compared with doxorubicin provides vital insights into understanding the molecular basis of the mechanism of anticancer activity and its clinical application in the treatment of breast, colon and lung cancers

REFERENCES

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2. Valiathan RR, Marco M, Leitinger B, Kleer CG, Fridman R. Discoidin domain receptor tyrosine kinases: new players in cancer progression.CancerMetastasisRev 2012, 31, 295–321.