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PRDX1 Inhibition Based on Molecular Docking and ADME-TOX Study Using New Anti-Colorectal Cancer Compounds †

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Abstract: Colorectal cancer ranks as the third most prevalent form of cancer on a global scale. The abnormal expression of Peroxiredoxin 1, or PRDX1, plays an important role in cancer progression and tumor cell survival. This makes inhibiting this protein a promising target for colorectal cancer treatment. In order to develop effective PRDX1 inhibitors, a drug design investigation based on computational methods was applied using a collection of recently synthesized compounds derived from two main chemical base structures: C-5 sulfenylated amino uracils and 1,2,3-triazole benzothiazole derivatives. Towards the PRDX1 protein PDB ID: 7WET, a molecular docking was performed on the studied compounds in complex with PRDX1. The 1,2,3-triazole benzothiazole derivatives show interesting docking results. In which nine top hits were distinguished by their formation of better stable complexes with PRDX1 in terms of E (binding) from −7.0 to −7.3 kcal/mol, namely, 7WET-L18, 7WET-L17, 7WET-L25, 7WET-L19, 7WET-L20, 7WET-L26, 7WET-L22, 7WET-L23, and 7WET-L24. And E of −6.8 kcal/mol for Celastrol as a known PRDX1 inhibitor, Moreover, an extensive evaluation of ADME-TOX was performed to predict the pharmacokinetic, pharmacodynamic, and toxicological properties of the compounds being studied. The findings acquired offer significant support for the prospective application of these analogues in the fight against colorectal cancer.

Keywords: PRDX1; colorectal cancer; molecular docking; ADME-TOX ; 1,2,3-triazole benzothiazole; C-5 sulfenylated amino uracils

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1. Introduction

Colorectal cancer (CRC) plays a major role in the worldwide cancer burden, standing out as one of the most frequently occurring cancers across the globe [1,2]. Among the factors involved in the pathogenesis of CRC and their initiation and development is oxidative stress [3], which is the imbalance between Reactive oxygen species (ROS) [4], and antioxidants such as Peroxiredoxins (Prxs) [5], that leads to cell damage [2].

Peroxiredoxin 1 (PRX1) is a transcriptional factor expressed during early limb bud mesoderm development [6], belongs to the Prxs family. PRRX1 significantly enhances the growth, survival, and stem cell-like characteristics of CRC via the JAK2/STAT3 pathway by affecting IL-6 as a major transcriptional factor for regulating its transcription in CRC [7]. Studies show that PRRX1 plays a crucial role in cell growth, and it has been suggested as a dependable biomarker for evaluating the probability of tumor metastasis in CRC [8]. Moreover, it was discovered that chemotherapy may improve the outlook exclusively for

CRC patients with diminished PRRX1 expression. This nominates PRX1 as a pivotal target for advancements in anti-CRC therapies [7].

In order to develop effective PRDX1 inhibitors, a drug design investigation based on computational methods was applied using a collection of recently synthesized compounds, derived from two main chemical base structures; thiol-linked pyrimidine derivatives [9], and 1,2,3-triazole benzothiazole derivatives [10], toward PRDX1 protein PDB ID: 7WET, a molecular docking was performed to the studied compounds in complex with PRDX1.Furthermore, an extensive evaluation of ADME-TOX was performed to predict the pharmacokinetic, pharmacodynamic, and toxicological properties of the compounds being studied. The findings acquired offer significant support for the prospective application of these analogues in the fight against colorectal cancer.

2. Materials and Methods

Twenty-seven compounds belonging to thiol-linked pyrimidine and 1,2,3-triazole benzothiazole derivatives were optimized by HyperChem software [11]. The compounds were docked by Autodock Vina [12] using PyRx—Virtual Screening Tool (https://pyrx.sourceforge.io/). ADME-T prediction of the selected best compounds was conducted using some wed tool such as SwissADME (http://www.swissadme.ch/), and PKCSM (https://biosig.lab.uq.edu.au/pkcsm/).

3. Results and Discussion

3.1. Molecular Docking

A molecular docking study was conducted for the Twenty-seven derivatives with the PRDX1 in the 7WET protein PDB structure. L18 gives the best energy score compared to the other compounds (−9.4 kcal/mol), Figure 1 indicates the 2D and 3D interaction diagrams between the active site of 7WET and L18.

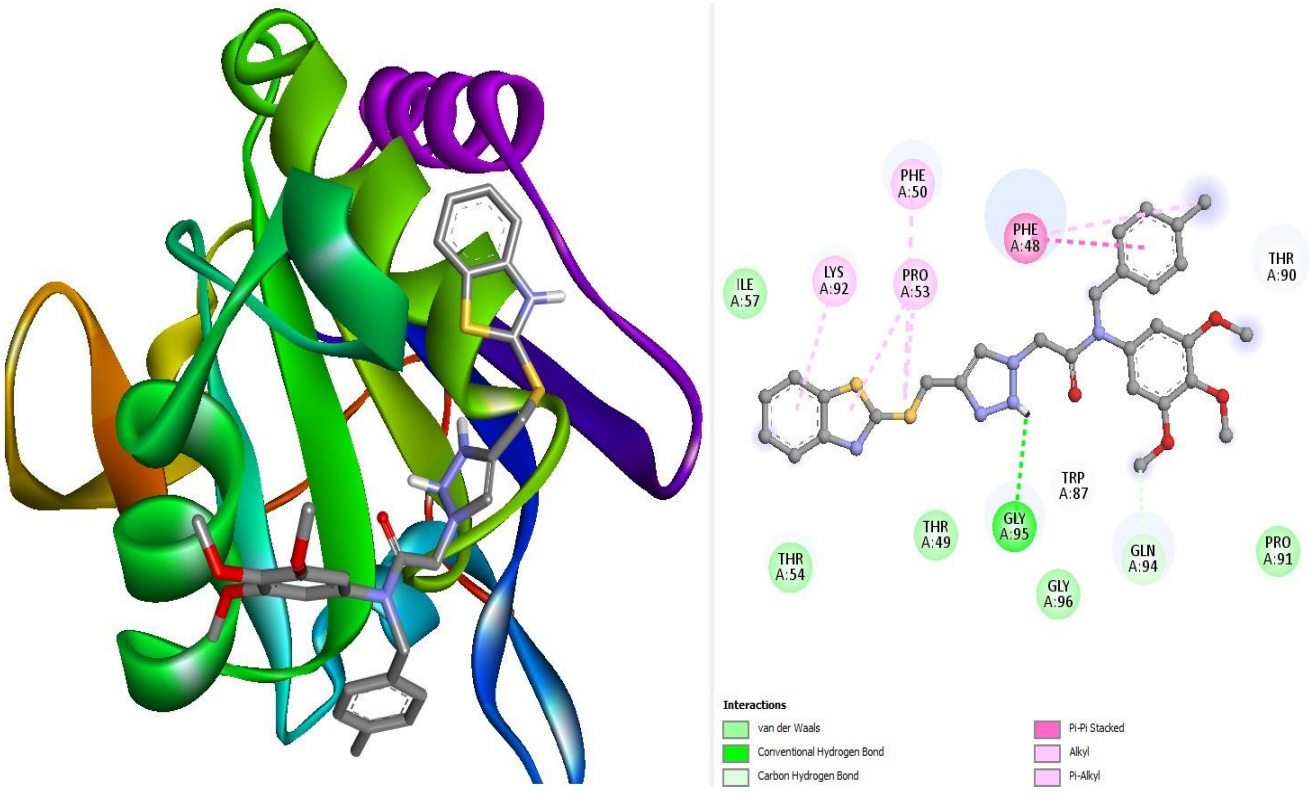

Figure 1. 2D interactions and 3D illustration of 7WET-active site and L18.

The total score energy results of the docked complexes with their distances, types of interactions, key residues, and atoms involved in the compounds and the receptor for the 7WETtarget, are summarized in Table 1.

The reference molecule has score energy of −6.8 Kcal/mol, without formation of H-Bonds, but Pi-Pi interactions type with PHE50 residue.

The nine best compounds are ordered according to their affinity for the formation of stable complexes with the 7WET Protein as follows: 7WET-L18 < 7WET-L17, 7WET-L25 < 7WET-L19, 7WET-L20, 7WET-L26 < 7WET-L22, 7WET-L23, 7WET-L24. With energy scores −7.4, −7.3, −7.2, and (kcal/mol) respectively.

Table 1. Docking score and interactions between compounds and 7WET active site.

Complex	Binding Affinity (kcal/Mol)	Bonds between the Compounds Atoms and the Active Site Residues (Chain A)				
		Interactions Type	Receptor Residues	Receptor Atoms	Compound Atoms	Distance (*A*°)
Ref1	−6.8	Pi-Pi stacked	Phe50	6-ring	6-ring	4.4
L18	−7.4	H-Bond	Gly95	O	NH	2.28
		H-Bond	Gln94	O	H5	2.97
L17	−7.3	H-Bond	Gly95	O	NH	2.28
		H-Bond	Thr49	O	NH	2.59
L25	−7.3	H-Bond	Gly95	O	NH	2.22
		H-Bond	Thr49	O	NH	2.65
L19	−7.2	H-Bond	Gly95	O	NH	2.19
		H-Bond	Gly94	O	C	3.5
L20	−7.2	H-Bond	Gly95	O	NH	2.1
L26	−7.2	H-Bond	Gly95	O	NH	2.07
L22	−7.0	H-Bond	Gly95	O	NH	2.13
L23	−7.0	H-Bond	Gly95	O	NH	2.24
L24	−7.0	H-Bond	Gly95	O	NH	2.18

3.2. Evaluation ADME-TOX

The (ADME-T) properties play a significant role in drug development [13]. Table 2 summarize the best profiles of pharmacological properties and of ligands 25, 20, and 26. According to the presented results, all selected compounds have high human intestinal absorption, and they are P-gp substrates. It is worth nothing that all of these compounds cannot pass through the BBB. These molecules have a similar metabolic profile; they are all metabolized by CYP3A4. The total clearance (CLtot) value of the molecules ranges from 0.73 to 0.78 mL/min/kg. And a T1/2 (h) value between (0.7–1.14). All compounds have not AMES toxicity, Hepatotoxicity, and Skin sensitization. The LD50 value of studied molecules ranges from 1.75 to 2.4 mol/kg.

Table 2. ADME-T properties of candidate compounds.

Category	Model Name	L25	L20	L26
Absorption	Water solubility	−5.57	−4.91	−5.57
	Caco-2 permeability	0.75	0.98	0.75
	HIA (% Absorbed)	83.3	90.3	83.6
	P-gp substrate	Yes	Yes	Yes
	P-gp I inhibitor	Yes	Yes	Yes
Distribution	VDss	−0.25	−0.34	−0.28
	BBB permeability	−2.01	−1.39	−1.99
Metabolism	CYP2D6 substrate	No	No	No

	CYP3A4 substrate	Yes	Yes	Yes
	CYP1A2 inhibitor	No	No	No
	CYP2C19 inhibitor	Yes	Yes	Yes
	CYP2C9 inhibitor	Yes	Yes	Yes
	CYP2D6 inhibitor	No	No	No
	CYP3A4 inhibitor	Yes	Yes	Yes
Excretion	Total clearance	0.76	0.73	0.78
	T1/2 (h)	1.14	0.72	1.06
	AMES toxicity	No	No	No
	Max tolerated dose (log mg/kg/day)	0.69	0.68	0.69
	HERG I inhibitor	No	No	No
Toxicity	HERG II inhibitor	Yes	Yes	Yes
	Oral Rat Acute Toxicity (LD50) (mol/kg)	2.41	1.75	2.41
	Hepatotoxicity	No	No	No
	Skin sensitization	No	No	No

3. Conclusions

According to these findings we revealed that these three selected cytotoxic molecules L25, L20, and, L26 have a very important structures without toxicity to pay attention to future studies in order to improve their properties and direct them to be effective PRDX1 inhibitors against colorectal cancer.

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