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# Insilico design, ADMET screening, MM-GBSA binding free energy of novel 1,3,4 oxadiazoles linked Schiff bases as PARP-1 inhibitors targeting breast cancer

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## Abstract

**Background:** Poly(ADP-ribose) polymerases (PARPs), a nuclear protein belongs to a new class of drugs, which mainly target tumours with DNA repair defects. They are mainly involved in the multiple cellular processes in addition to the DNA repair process. They act directly on the base excision repair, which is considered as one of the important pathway for cell survival in breast cancer. These belong to the active members of DNA repair assembly and evolved as a key target in the anti-cancer drug discovery. 1,3,4-Oxadiazoles are also well known anticancer agents.

**Results:** A novel series of 1,3,4-oxadiazoles linked to Schiff bases (T1-21) were designed and subjected to In-silico analysis against PARP-1 (PDB ID:5DS3) enzyme targeting against breast cancer. Molecular docking study for the designed compounds (T1-21) was performed by In-silico ADMET screening by QikProp module, Glide module and MM-GBSA binding free energy calculations by using Schrodinger suit 2019–2. The PARP-1 enzyme shows the binding affinity against the newly designed molecules (T1-21) based on the glide scores. Compounds T21, T12 showed very good glide score by the molecular docking studies and compared with the standard Tamoxifen. The binding free energies by the MM-GBSA assay were found to be consistent. The pharmacokinetic (ADMET) parameters of all the newly designed compounds were found to be in the acceptable range.

**Conclusion:** The selected 1,3,4-oxadiazole-schiff base conjugates seems to be one of the potential source for the further development of anticancer agents against PARP-1 enzyme. The results revealed that some of the compounds T21, T17, T14, T13, T12, T8 with good glide scores showed very significant activity against breast cancer

**Keywords:** Cancer, PARP-1, Breast cancer, 1,3,4 oxadiazoles, In-silico ADMET screening, MM-GBSA assay

## Background

Cancer is a large group of diseases. According to WHO, cancer causes the second highest mortality rate after the cardiac disease in humans [1]. The number of new cases of cancer escalated to 19.3 million and caused 10.0 million deaths in the year 2020 Males are primarily affected by cancers of liver, prostrate, lung, stomach, colon and rectum while females are primarily affected by breast, cervix, colorectal, lung, and thyroid cancer. Treatment of cancer treatment has spawned an entirely new field of research involving both conventional and modern technologies. The global surge in the spread of cancer has led to 70% of the cancer mortality rate all over the world [2].

Breast cancer constitutes one of the most frequently occurring cancer in females around the world, with 3,50,000 deaths each year. Chemotherapy can be used to

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treat many malignant tumours, so looking for new chemotherapeutic drugs is still important [3]. The fact that, one out of every five women is diagnosed with breast cancer, necessitates the development of new compounds to treat the disease [4]. Over the years, scientists have collaborated with specific remedial experts to develop a target for bosom malignant growths. Human Epidermal development factor Receptor-2 (HER2) [5–7], Estrogen Receptor (ER) [8, 9], & vascular endothelial development factor (VEGF) [10, 11] are some of the targets for breast malignant growth. Epidermal Growth Factor Receptor (EGFR) [12, 13], Poly ADP ribose polymerase (PARP) [14–16], BRCA1 (Breast disease type 1 helplessness protein) [17, 18], TKI (tyrosine kinase inhibitor) [19, 20], CDK4/6 (cyclin subordinate kinase) inhibitors [21] etc. and so on.

The PARP-1 enzyme has recently gained a great deal of attention as a potential anti-cancer agent because it belongs to the PARP family of proteins that are essential to the single-stranded DNA repair process [22]. These are the group of enzymes and a type of targeted therapy, which plays a key role in transcriptional regulation, cell death and DNA repair. Since they are involved in the DNA repair they are called as *guardian angel* of DNA. PARP-1 also plays a crucial role in a variety of cell-based processes, including cell differentiation and cell division. PARP-1 inhibitors inhibit mitosis, inflammation, gene transcription, and finally cause cell death, all of which result in cytotoxic potential. PARP-1 inhibitions are based on the existence of BRC A 1/2 mutations, which are essential protein for DNA, breaks in homologous recombination (HR) double-stranded breaks [23], since the mutated cancer cells use PARP-1 in order to remedy and cellular survival [24, 25]. As a result, PARP-1 inhibitors have the potential to cause cell death selectively, especially in breast and ovarian cancers [26]. The FDA has already licenced many PARP-1 inhibitors, including BMN673 (Talazoparib), AZD2281 (Olaparib), AG014699 (Rucaparib), MK4827 (Niraparib) [27–29]. It is found that PARP-1 easily catalyses the required division of NAD + (nicotinamide adenine dinucleotide) into ADP and nicotinamide ribose units. In response to DNA damage [30], these are transferred to various acceptor proteins involved in the DNA damage repair process such as ADP-ribose polymers (PAR) and histones. The enzyme PARP-1 is basically composed of two active binding sites, namely adenine-ribose binding site (AD site) and nicotinamide-ribose (NI site) [31].

The proposed PARP inhibitors (1,3,4-oxadiazole derivatives), in the presence of DNA damage, the PARP inhibitors prohibit PARylation from occurring and these PARP-1 will remains very tightly bound to the damaged sites [32]. The later action, is due to the binding affinity of PARP-1 to the damaged DNA is very much increased and this process is called as PARP trapping [33]. The cell death is due to the homologous recombination deficiency (HRD) and the synthetic lethality mediated by the PARP inhibition. Some of the previous studies very efficiently demonstrated, the cells which are deficient in BRCA1 or BRCA2, will display an increased sensitivity towards the PARP inhibitors at least by about 1000 fold times [34]. Based on the above observations, the PARP inhibition is found to be a one of the promising therapeutic strategy for homologous recombination-deficient tumours, which are mainly associated with BRCA mutations. Thus the use of PARP inhibitors can potentially be expanded to tumours without BRCA mutations [35].

1,3,4-Oxadiazoles are found to be an one of the important class of heterocyclic compounds with very large diversified activities and good bio-isosteres of amide and ester, participate with the receptor through hydrogen bonding and increase the biological profile to a large extent [36]. Five membered 1,3,4-oxadizole analogues are rich in potential activities [37]. The central ring of the 1,3,4-oxadiazole moiety contains toxophoric –N=C–O– linkage [38] and considered as one of the important group, which might be responsible for their potent pharmacological activities including anticancer activity. In the recent time lot of interest is created over the synthesis of these compounds due to their higher antitumor activity [39]. Similarly, the Schiff bases are also reported for various pharmacological actions due to its >C=N group, and found to possess the antitumor activity [40]. Based on the above facts, the present work was designed to report a new series of 1,3,4-oxadiazole derivatives clubbed with Schiff bases containing the active C=N group at its second position.

The present work is aimed at targeting PARP-1 enzyme against breast cancer, by the new class of hybrids of 1,3,4-oxadiazoles and Schiff bases by the *In-silico* approach.

## Methods

### In silico studies

#### *Protein preparation*

The protein data bank yielded PARP-1 inhibitors with co-crystalline ligand (PDB ID: 5DS3 2.3A0). The protein was established using the Schrodinger suite 2019–2 protein preparation wizard module. Water atoms which are more than 5 A0 and do not have hydrogen bonds are evacuated. The primary module of the Schrodinger suite 2019–2 is used to fill missing chain iotas. For the heteroatoms in the protein, all possible ionisation states were formed, and the state with the highest degree of stability was chosen. Following that, the OPLS3 force field was used to conduct a controlled energy minimization of

the protein structure in order to reorient the side-chain hydroxyl groups and reduce the probability of steric clashes [41].

#### *Receptor grid set to generation*

The co-crystallized ligand was housed in the crystal structure of the protein, which was developed using the protein preparation wizard. To describe the centroid of the dynamic site used for docking, a Gride box (14Ao × 14Ao × 14Ao) was generated using the Glide grid generation wizard [41].

#### *Ligand preparation*

The required ligands T1-21is showed in Fig. 1 and docked onto the pocket of PARP-1 protein. (PDB ID: 5DS3). Chemsketch software was used to build the ligand structures, which were then subjected to the LigPrep module of the Schrodinger suite 2019. Ligands were converted to 3D structures through stereo concoction, ionisation, and tautomerism, as well as vitality minimization and geometry optimization, and they were also dissolved and rectified for the absence of hydrogen atoms and chiralities. Finally, the mixes were limited using the optimized potentials for liquid simulations-3 (OPLS-3) power field in the Schrodinger Impact package until a root mean square deviation of 1.8Ao was achieved. A single low-energy ring confirmation was made for each ligand, and the streamlined ligands were used for docking studies.

#### *Glide ligand docking*

The ligands are located in the synergist pocket of the PARP-1 protein with the Schrodinger suite 2019–2's Glide module (PDB ID: 5DS3). The Glide score is used to select the ligands that are best covered. The Glide ligand docking module was used to test active relationships between ligands and receptors. Docking was done in a versatile docking mode that automatically generates conformations for each input ligand, using extra precision (XP) mode and the OPLS-3 power field. Positive interactions such as lipophilia, hydrogen bonding, and metal-linking are rewarded, while steric conflicts are punished. Finally, re-scoring of a few positions was done via glide score's ability to score. The docking results were analysed using the Glide module's XP visualizer. The Glide score of the standard compounds containing Olaparib & compounds with hostile to bosom malignancy tranquillize, tamoxifen was condensed and contrasted. Glide score capability is primarily determined by docking parameters, such as lipophilic perseverance, wherein the compounds are secured in the lipophilic pocket, which is important for action control. The Schrodinger suit-2019 QikProp module was used to detect the ligands' ADMET properties [41].

#### *Calculation of bind free energy using MM-GBSA*

MM-GBSA assay helps to know the binding free energy of protein–ligand complexes. The Schrodinger suite 2019–2 Prime module (the OPLS3 power field and the dissolvable model VSGB) is used to process the drug-receptor complex's binding free energy using the MM-GBSA assay process [42].

## Results

The affinity of the compounds (T1-T21) with receptor PARP-1 (PDB ID: 5DS3) is given Table 1 in terms of Glide scores. The docking studies were carried out in order to know the binding mode of all the designed analogues into the active site of PARP-1 at atomic levels. The compounds Glide docking score were in the range from − 6.357 to − 3.723 kcal/mol. Trp 861, His 862, Gly 863, Ser 864, Arg 865, Asn 868, Gly 876, Leu 877, Arg 878, Phe 891, Ile 895, Tyr 896, Phe 897, Ala 898, Lys 903, Ser 904, Tyr 907, Asn 987, Glu 988, Tyr 989 are the active residues in 5DS3. Compound T21 has the highest Gscore of 6.357 kcal/mol, followed by compound T12 with a G score of 5.938 kcal/mol. represents the structures of the designed compounds and Figs. 2, 3, 4 and 5 represents the 2D docking of these compounds with PDB ID: 5DS3, respectively. These compounds demonstrate pi-pi stacking with Tyr 907. Compound T21 forms hydrogen bonds with Phe 897, Gly 863 and Ser 904. Compound T12 forms hydrogen bonds with Met 890 and Ser 904. Some of the other designed compounds T8, T10, T13, T17 also showed very good G scores when compared to the standard drugs.

The ADMET properties of all the designed compounds are predicted by qikprop module of Schrödinger suite 2019.2 Table 2. The molecular weight of all the compounds found below 500 and also the dipole moments showed zero. All the compounds obeyed Lipinski's rule of five as the molecular weight, the number of hydrogen bond donors and acceptors, and Log P values were all within the acceptable limits. Qikprop also helps to know #metab, the number of probable metabolic reactions. It aids to predict the ease with which the drug might approach the target. All the designed compounds lie within the recommended range of 1–8. Owing to the fact that the % human oral absorption of all the compounds were > 80%, there would be no effect on the bioavailability of the compounds, in case of deviation from the Lipinski's rule of five. Among the designed compounds T10, T17 and so many others also displayed 100% human oral absorption.

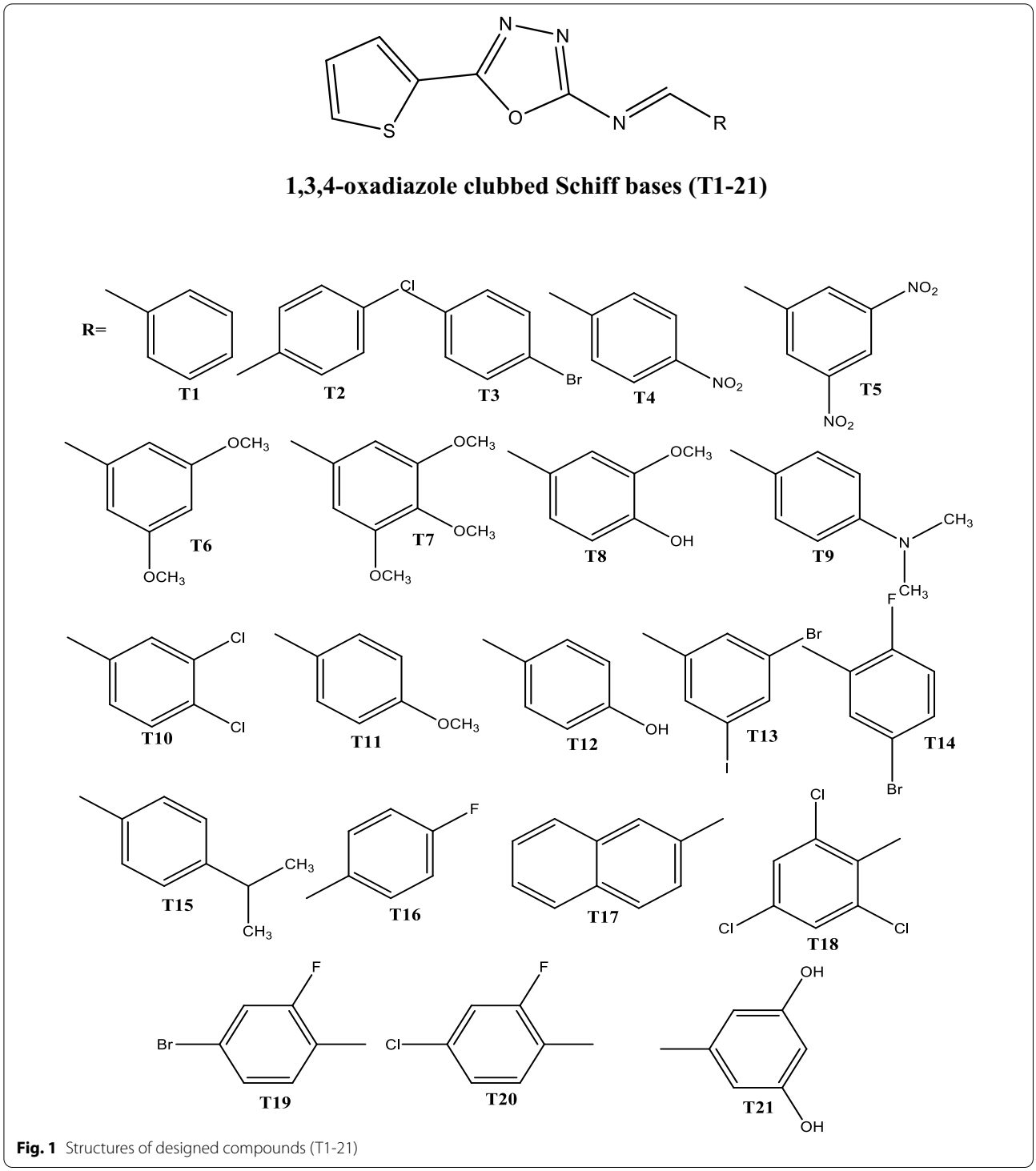


**Fig. 1** Structures of designed compounds (T1-21)

### MM-GBSA assay

The target protein and the respective protein were prepared as per the depicted structure Fig. 1. All the proposed analogues, showed good free binding energy, which will fit well into the PARP-1 receptor Table 3. The binding free energies of the Compound T17 has the highest ΔG binding energy to 5DS3 with a value of -73.9 kcal/mol when compared to the known standard drug, Tamoxifen having a ΔG binding energy of − 65.62 kcal/mol.

**Table 1** Docking studies for compounds (T1-21) with PARP-1 (5DS3)

| Comp | Glide score | Glide EvdW | XP H Bond | Glide emodel | G Rotatable bonds | Glide ecoul |
|---|---|---|---|---|---|---|
| T1 | − 3.723 | − 30.679 | 0 | − 43.735 | 1 | − 1.373 |
| T2 | − 4.355 | − 33.583 | 0 | − 47.977 | 3 | − 2.751 |
| T3 | − 4.187 | − 39.2 | 0 | − 48.686 | 3 | 0.462 |
| T4 | − 4.112 | − 38.044 | 0 | − 53.766 | 4 | − 1.604 |
| T5 | − 4.323 | − 41.715 | 0 | − 66.406 | 5 | − 3.925 |
| T6 | − 4.045 | − 38.565 | 0 | − 52.939 | 5 | 0.707 |
| T7 | − 4.342 | − 40.712 | 0 | − 56.312 | 6 | − 0.095 |
| T8 | − 5.873 | − 44.333 | − 0.539 | − 66.103 | 5 | − 3.091 |
| T9 | − 4.192 | − 37.756 | 0 | − 51.971 | 4 | 0.225 |
| T10 | − 4.674 | − 37.194 | 0 | − 51.666 | 3 | − 3.082 |
| T11 | − 3.909 | − 32.69 | 0 | − 49.102 | 4 | − 2.995 |
| T12 | − 5.938 | − 34.531 | − 0.539 | − 55.861 | 4 | − 4.798 |
| T13 | − 5.343 | − 40.198 | − 0.971 | − 63.475 | 4 | − 6.149 |
| T14 | − 4.585 | − 39.039 | 0 | − 53.036 | 3 | 0.27 |
| T15 | − 3.828 | − 33.566 | 0 | − 45.797 | 4 | − 1.594 |
| T16 | − 4.291 | − 33.122 | 0 | − 46.571 | 3 | 0.024 |
| T17 | − 4.944 | − 38.34 | 0 | − 56.241 | 3 | − 1.871 |
| T18 | − 4.004 | − 39.049 | 0 | − 53.025 | 3 | 1.283 |
| T19 | − 4.355 | − 36.235 | 0 | − 47.701 | 3 | − 0.252 |
| T20 | − 4.556 | − 33.874 | 0 | − 50.684 | 3 | − 1.825 |
| T21 | − 6.357 | − 35.848 | − 1.571 | − 64.252 | 5 | − 8.412 |
| Olaparib (Std) | − 13.523 | − 54.374 | − 2.8 | − 114.487 | 6 | − 16.488 |
| Tamoxifen (Std) | − 5.045 | − 36.865 | 0 | − 56.406 | 8 | − 2.306 |

Glide score, glide score; Glide EvdW, glide van der Waals energy; XP H Bond, extra precision hydrogen bonding; Glide emodel, glide model energy; G Rotatable bonds, Glide Rotatable bonds; Glide ecoul, glide Coulomb energy

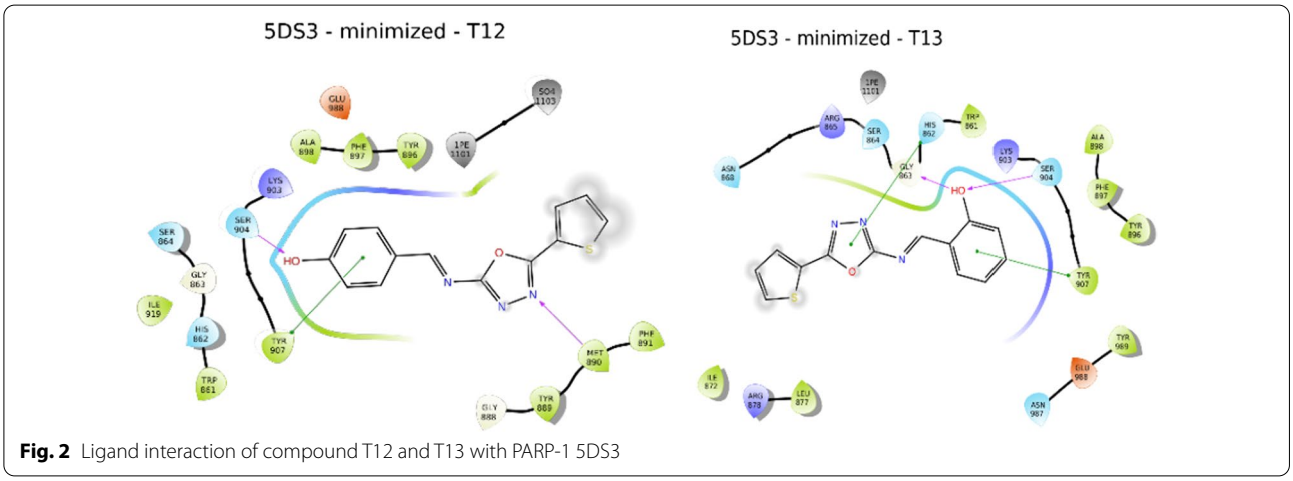


**Fig. 2** Ligand interaction of compound T12 and T13 with PARP-1 5DS3

## Discussion

Molecular docking studies assessments were performed to understand the interactions of compound (T1-T21) (Fig. 1, Table 1) with Poly [ADP-ribose] polymerase-1(PARP-1). The binding modes of the designed compounds were investigated by using Molecular docking tools [42]. The coordinates and structure factors for the reported X-ray crystal structures have been deposited in the PDB: ID: 5DS3, the latter is responsible for PARP-1 inhibitory activity [43]. The docking studies of the newly designed compounds involve several molecular interactions, in order to bind into the active site of target. These

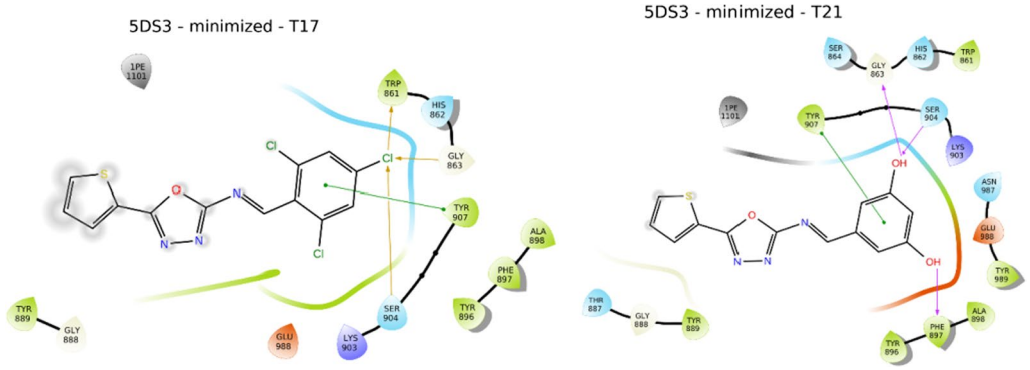


**Fig. 3** Ligand interaction of compound T17 and T21 with PARP-1 5DS3

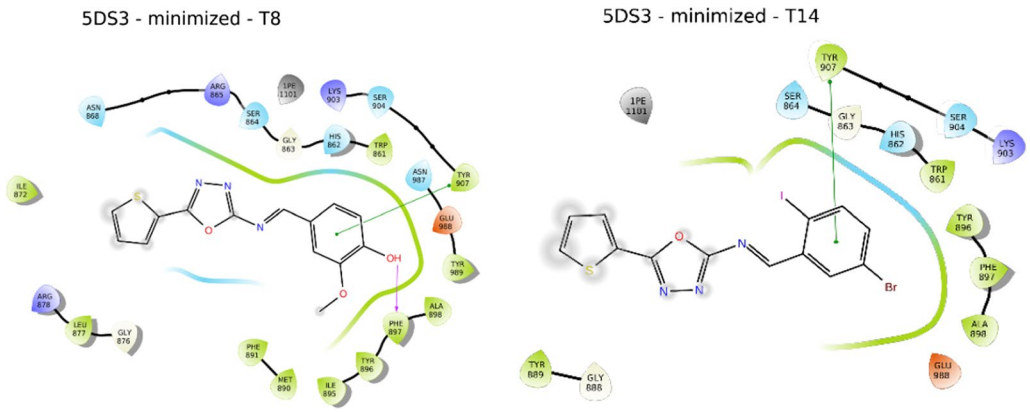


**Fig. 4** Ligand interaction of compound T8 and T14 with PARP-1 5DS3

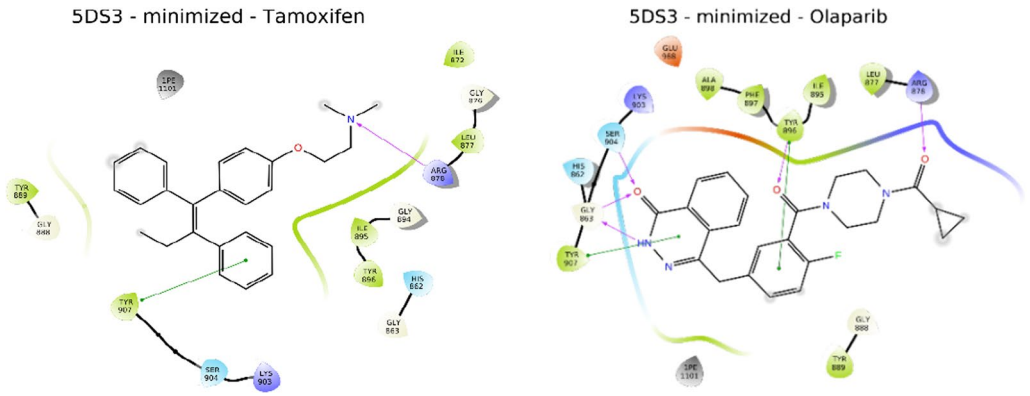


**Fig. 5** Ligand interaction of Standard Tamoxifen and Olaparib with PARP-1 5DS3

interactions will be responsible for the profound affinity to these compounds. The glide scores which are obtained from the docking studies against PDB: 5DS3 were showed in Table 1 and the results were compared with standard Olaparib and Tamoxifen. The binding affinity is due to the lipophilic factors and it is due to the presence of five membered heterocyclic ring and 1,3,4-oxadiazole moiety.

In accordance to the Lipinski's RO5, the molecular weight of the molecule should be $\leq 500$, partition coefficient $\leq 5$, the number of hydrogen bond donors and

**Table 2** Insilico ADMET screening for proposed compounds (T1-21)

| Comp | Mol. Wt | Dipole | Donar HB | Accept HB | Q Plog o/w | # Met abolism | RO5 | % Human Oral Absorption |
|---|---|---|---|---|---|---|---|---|
| Acceptable range- Acceptable range | ≤ 500 | (0.0–0.13) | ≤ 5 | ≤ 10 | (− 2.0 to 6.5) | (1–8) | < 5 | > 80% High, < 25% low |
| T1 | 255.294 | 0 | 0 | 3.5 | 3.191 | 2 | 0 | 100 |
| T2 | 289.739 | 0 | 0 | 3.5 | 3.711 | 2 | 0 | 100 |
| T3 | 334.19 | 0 | 0 | 3.5 | 3.79 | 2 | 0 | 100 |
| T4 | 300.291 | 0 | 0 | 4.5 | 2.453 | 3 | 0 | 85.318 |
| T5 | 345.289 | 0 | 0 | 5.5 | 1.854 | 4 | 0 | 68.545 |
| T6 | 315.346 | 0 | 0 | 5 | 3.298 | 4 | 0 | 100 |
| T7 | 345.372 | 0 | 0 | 5.75 | 3.467 | 5 | 0 | 100 |
| T8 | 301.319 | 0 | 1 | 5 | 2.741 | 4 | 0 | 94.853 |
| T9 | 298.362 | 0 | 0 | 4.5 | 3.956 | 3 | 0 | 100 |
| T10 | 324.184 | 0 | 0 | 3.5 | 4.148 | 2 | 0 | 100 |
| T11 | 285.32 | 0 | 0 | 4.25 | 3.269 | 3 | 0 | 100 |
| T12 | 271.293 | 0 | 1 | 4.25 | 2.62 | 3 | 0 | 93.546 |
| T13 | 271.293 | 0 | 1 | 4.25 | 2.675 | 3 | 0 | 95.445 |
| T14 | 460.086 | 0 | 0 | 3.5 | 4.4 | 2 | 0 | 100 |
| T15 | 297.374 | 0 | 0 | 3.5 | 4.221 | 3 | 0 | 100 |
| T16 | 273.284 | 0 | 0 | 3.5 | 3.446 | 2 | 0 | 100 |
| T17 | 358.629 | 0 | 0 | 3.5 | 4.619 | 2 | 0 | 100 |
| T18 | 305.353 | 0 | 0 | 3.5 | 4.193 | 2 | 0 | 100 |
| T19 | 352.18 | 0 | 0 | 3.5 | 3.199 | 2 | 0 | 100 |
| T20 | 307.729 | 0 | 0 | 3.5 | 3.912 | 2 | 0 | 100 |
| T21 | 287.292 | 0 | 2 | 5 | 1.9 | 4 | 0 | 80.1 |
| Olaparib | 434.469 | 0 | 1 | 8 | 2.504 | 1 | 0 | 81.826 |
| Tamoxifen | 371.521 | 0 | 0 | 2.75 | 6.393 | 3 | 1 | 100 |

MW, Molecular weight of the molecule; Dipole, Computed dipole moment; Donor HB, Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution; Accept HB, Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution; QP logPo/w, Predicted octanol/water partition coefficient; # metab, Number of likely metabolic reactions; Rule of Five Number of violations of Lipinski's rule of five; %Human- Oral absorption, Predicted human oral absorption on 0 to 100% scale

acceptors should be ≤ 5 and ≤ 10, respectively. All these properties along with molecular flexibility are regarded as essential determinants of oral bioavailability. Hence, the compounds ability to obey this rule was evaluated and all the designed compounds obey's Lipinski's RO5. The results from the In-silico ADMET screening, most of the designed compounds are within the recommended values. The results are shown in Table 2.

Prime MM-GSBA analysis (Table 3) depicts the relative energies of binding of each compound with that of the receptor. It is a culmination of numerous drug-receptor interactions including polar interaction, hydrophobic interaction, covalent bond interactions etc. The results of MM-GBSA assay showcase that the energies which strongly ligand binding in the binding pocket of 5DS3 are Van der Waals energy (ΔGvdW) and non-polar solvation (ΔGLipo) owing to the high negative values displayed by all the compounds. The other energies, namely covalent energy (ΔGCov) and electrostatic solvation (ΔGSolv) energy do not strongly favour receptor binding. Further, the higher values of ΔGVdW and ΔGLipo in the negative range show remarkable hydrophobic interaction with 5DS3 and ligands T1-21. Highly favoured ligand binding was observed in compounds T7, T10, T13, T14 and T21. This result can be correlated to the G score as well since compound T21 displayed highest docking score implying that columb energy (ΔGCoul- 39.94 to -18.95 kcal mol-1). plays a vital role in the drug-receptor interaction. It can be observed through the MM-GSBA assay, that strong binding affinities of the compounds T5, T8, T18, T20 and the receptor are visible.

## Conclusions

1,3,4-oxadiazoles have gained a lot of medicinal importance due to their varied pharmacological and biological profile, thereby making an unique molecule for various studies. Similarly, Schiff bases are well known compounds in the organic chemistry field. The hybrids of these moieties, was explored for possible anticancerous activity by In-silico studies. The study reveals, the presence of Schiff

**Table 3** Binding free energy calculation using Prime/MM-GBSA approach of compounds (T1-T21)

| Comp | ΔG bind (Kcal/ mol) | ΔG bind Coulomb | ΔG bind covalent | ΔG bind Vander | ΔG bind H Bond | ΔG bind Lipophilic |
|---|---|---|---|---|---|---|
| T1 | − 43.97 | − 5.28 | 1.75 | − 31.2 | − 0.2 | − 22.82 |
| T2 | − 58.34 | − 9.01 | 2.8 | − 35.81 | − 0.36 | − 25.53 |
| T3 | − 54.8 | − 0.21 | 1.96 | − 40.82 | 0 | − 26.21 |
| T4 | − 55.42 | 4 | 3.8 | − 44.71 | − 0.02 | − 25 |
| T5 | − 60.29 | 7.07 | 2.45 | − 45.31 | − 0.93 | − 15.34 |
| T6 | − 59.22 | 1.06 | 2.36 | − 41.45 | − 0.03 | − 27.87 |
| T7 | − 65.31 | − 2.54 | 2.82 | − 44.32 | − 0.12 | − 29.21 |
| T8 | − 60.19 | − 11.51 | 5.2 | − 48.44 | − 0.28 | − 26.06 |
| T9 | − 51.63 | 1.08 | 0.86 | − 38.85 | 0 | − 25.07 |
| T10 | − 69.72 | − 9.66 | 2.35 | − 38.92 | − 0.39 | − 30.5 |
| T11 | − 48.36 | − 7.72 | 5.26 | − 34.34 | − 0.34 | − 23.76 |
| T12 | − 55.56 | − 18.95 | 2.13 | − 34.92 | − 0.81 | − 20.33 |
| T13 | − 63.76 | − 16.4 | 6.17 | − 43.65 | − 0.62 | − 23.41 |
| T14 | − 65.17 | − 6.53 | 3.71 | − 42.61 | 0 | − 30.64 |
| T15 | − 47.29 | − 5.33 | 2.73 | − 33.65 | − 0.16 | − 27.19 |
| T16 | − 49.25 | − 5.55 | 1.61 | − 32.61 | − 0.02 | − 19.01 |
| T17 | − 73.9 | − 7.23 | 0.92 | − 40.09 | 0 | − 35.43 |
| T18 | − 60.45 | 0.05 | 2.16 | − 40.93 | − 0.04 | − 28.36 |
| T19 | − 49.74 | − 2.56 | 5.46 | − 40.19 | − 0.13 | − 25.94 |
| T20 | − 61.98 | − 9.91 | 1.2 | − 37.41 | − 0.31 | − 26.98 |
| T21 | − 64.32 | − 20.33 | 3.66 | − 38.8 | − 0.84 | − 20.33 |
| Olaparib | − 121.53 | − 39.94 | 3.54 | − 61.19 | − 1.23 | − 37.94 |
| Tamoxifen | − 65.62 | − 11.83 | 7.01 | − 44.73 | − 0.25 | − 41.83 |

Δ G bind, free energy of binding; ΔG bind Coulomb, Coulomb energy; ΔG bind covalent, covalent energy (internal energy); ΔG bind Vander, van der Waals energy; ΔG bind H Bond, hydrogen bonding energy; ΔG bind Lipophilic, hydrophobic energy (non-polar contribution estimated by solvent accessible surface area)

bases, which is linked to the 1,3,4-oxadiazole moiety, showed very good binding energy and G score. The selection of PARP-1 enzyme has showed promising activity by these hybrid molecules. However still it requires further In-vitro and In-vivo studies to confirm their further SAR. The In-silico studies, have greatly exhibited anticancer property, in the designed molecules. The compounds T21, T17, T14, T13, T12, T8 showed a significant anti-breast cancer activity and these analogues are found to be one of the promising molecules and requires further modifications in the structural requirement.

#### Abbreviations

PARP: Poly ADP ribose polymerase; ADMET: Absorption, distribution, metabolism, excretion, and toxicity; SAR: Structural activity relationship; MM-GBSA: Molecular mechanics/Generalized born surface area 3D Qsar; PDB: Protein data bank; XP: Extra precision; MW: Molecular weight; Δ G bind: Free energy of binding; BRCA: Breast cancer gene.

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#### Authors' contributions

BCR did the conception of work, design of the work, experimental work and the interpretation of data and drafting of the manuscript. GSM, SD contributed in the design of work, experimental work done, results analysis. NNA, BFDG helped in carrying out the designed work, interpretation of data and critical revision of the manuscript. BCR reviewed the manuscript. All authors read and approved the final manuscript.

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#### Availability of data and materials

All data and materials are available upon request

### Declarations

#### Ethics approval and consent of participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no conflict of interests.

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