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Research Article

Selection the Drug Efficacy of Oroidin Derivatives as Hsp90 Inhibitors by Computer Aided Drug Design Method

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ABSTRACT

Heat shock protein 90 (Hsp90) is a conserved molecular chaperone associated with the regulation of hundreds of client proteins that are key drivers, regulators and promoters of numerous refractory diseases, including cancer. Consequently, Hsp90 is a significant target for the development of harmless anticancer therapies. Marine organisms are a rich source of pharmacologically important compounds, especially oroidin. Oroidin, a pyrrole-2-aminoimidazole alkaloid, isolated from the marine sponge *Agelas oroides*, binds ATP pocket of Hsp90 and suppresses the ATPase activity of the protein. Natural product oroidin was selected as potent inhibitor of Hsp90, and its drug candidature was accordingly improved by substituting various functional groups. Virtual screenings were done through in silico studies, carried out on 39 derivatives of oroidin. DFT study was performed with Gaussian16, UB3LYP/6-311G++ (d, p) basis set to investigate the quantum mechanical parameters such as HOMO-LUMO energies, dipole moments. Derived parameters like ionization potential, electron affinity, softness-hardness, chemical potential, and electrophilicity index were also calculated. Using AutoDock 4.0 program, we studied docking of the thirty-nine designed derivatives with macromolecule Hsp90 and recorded the best conformation's binding energy values out of nine in each docked compound. Absorption, distribution, metabolism and excretion (ADME) predictions, molecular descriptor properties, and theoretical toxicity tests were evaluated using preADMET, molinspiration, and OSIRIS property explorer web tools, respectively. We found 28 derived compounds, each docked at the same region of Hsp90, possessing higher binding energies compare to the precursor oroidin. Seven of them qualified all the rules of drug candidature and could be safe in using as effective drugs for cancer treatment. This study suggests that these compounds could be synthesized for in vitro test and may lead to novel anticancer therapeutics.

INTRODUCTION

Cancer is a collection of related diseases that initiate the uncontrolled growth of abnormal cells with the ability to spread to adjoining or other parts of the body. According to a world health organization (WHO) report, it was estimated that cancer, 2nd leading cause of death globally, accounting for over 9.6 million deaths in 2018.^[1] Nowadays, research on alternative or combined therapies has received wide interest as traditional chemotherapy has a severe adverse effect during and after treatment.^[2] Hsp90 (heat shock protein 90) involves a significant role in cancer and presently, Hsp90 inhibitors have become intense research attention.^[3] Hsp90 is a molecular

chaperone protein that stabilizes proteins against heat stress, assists other proteins' incorrect folding, promotes protein degradation, prevents protein aggregation, and regulates apoptosis through interaction with mediators of apoptotic pathways.^[4-6] Functional human genes encoding, cystolic Hsp90 α/β are two isoforms of Hsp90, largely non-polar on the inside and polar on the outside nine helices and eight antiparallel beta-pleated sheets.^[7-9] The protein (Hsp90) regulates gene expression, proliferation, cellular signal transduction, and transcription networks, but dysregulation causes cell homeostasis. misfolding and overexpression of client proteins, which are responsible factors for the development of refractory diseases

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including cancer, inflammation, neurodegeneration, and viral infection like hepatitis C and Chikungunya.^[10-12] Heat shock protein and its co-chaperones, stabilizing numerous growth factors receptors and signaling molecules, including PI3K/AKT proteins, inhibit both apoptotic and necrotic pathways.^[13,14] ATP binding is the basis of the Hsp90 chaperone cycle. Inhibition of this protein by ATPase inhibitors weakens the client proteins and may induce apoptosis, the programmed cell death, which maintains the healthy survival death balance in metazoan cells.^[15,16] The ATPase-binding site is the principal binding region of drugs targeting Hsp90.^[17] Protein kinase A (PKA) phosphorylates a single residue Thr90 of Hsp90 α and stimulates its secretion and thus tumor metastasis.^[18] On the other hand, the inhibition of serine-threonine acidophilic kinase phosphorylates two serine residues Ser226 and Ser255, resulting in stabilization of Hsp90 β -apoptosome interaction, may contribute to chemo-resistance in leukemias.^[19] Upregulation of Hsp90 β protein leads to lung cancer with the highest mortality rate among carcinogens and autoimmune ovarian failure disease, causing infertility.^[20,21]

It is reported that some natural products and their derivatives target Hsp90-ATP binding sites and exhibit antitumor activity.^[22] Marine sponges are an abundant source of natural products and their varieties of chemical compounds escalated the development of pharmaceuticals.^[23,24] Oroidin (ODN), a pyrrole-2-aminoimidazole alkaloid (Fig. 1), derived from a marine sponge *Agelas oroides*, has significant biological activities, including antitumor, immunosuppressive and adrenoceptor-related activities.^[25-29] It displayed potency against breast, ovarian, colon, pancreas, liver carcinoma, and leukemia.^[30-33] An experimental study^[12] reported that some synthesized oroidin analogs, screened against replicon models of two ribonucleic acid (RNA) viruses, hepatitis C virus (genus *Hepacivirus*) and Chikungunya virus (genus *Alphavirus*), could inhibit bacterial deoxyribonucleic acid (DNA) gyrase. This bacterial protein's ATP-binding site shows high structural similarity to the ATP-binding site of heat-shock protein 90 (Hsp90). Based on these remarkable pharmacological properties we have chosen oroidin as a ligand to inhibit Hsp90.

Currently, drug design technique demands a suitable screening of the compounds to measure pharmacophore activity, using the theoretical and computational

approaches, before real-time experiments. Prediction of bioavailability, in vitro, and in vivo findings are enumerated by using the numerous physicochemical parameters. These properties are the basis of the idiosyncratic biological and physicochemical parameters of the compounds. Nevertheless, the complex structure of the whole drug compound faces difficulties in correlating with these parameters.^[34] The molecular docking method reveals the detailed possibilities of drug-receptor binding interactions. Thus the initial studies of receptor-ligand interaction have been gaining immense interest among logical drug designers.^[35]

Based on these studies, we have modified oroidin to set up a library of 39 derivatives, undergoing molecular docking interaction with Hsp90 β (PDB ID: 3NMQ), to improve the drug-like properties of the inhibitor ODN. In silico ADME predictions characterizing drug-likeness features were performed to screen the active biochemical derivatives. Our study's main goal was to find new chemical compounds, possessing better drug candidature than the natural oroidin, being potentially good inhibitors of Hsp90.

METHODS AND MATERIALS

Preparation of Protein

The 3-dimensional X-ray crystal structure of Hsp90 was collected from the Protein Data Bank (PDB ID: 3NMQ). Water and other chemical compounds were removed from the crystal structure before docking using Molegro Molecular viewer (MMV) program (CLC Bio, Qiagen Inc.).^[36]

Preparation of Ligand

The software Chemdraw was used to draw the standard drug ODN and all its derivative ligands.^[37] The selected molecules obtained by various substitutions were shown in Table 1. All the explicit hydrogen was added at the time of preparation of ligands, including 2D-3D structure conversion. The compounds were optimized using DFT.^[38,39] Original structures and as well as the optimized structures of the four best derivatives of ODN are shown in Fig. 2, and the remaining are displayed in the supplementary Fig. S1.

Density Function Theory (DFT)

Gaussian16W^[40] suite of software was made to involve minimizing the compounds' energy content leading to geometrical optimization. Total energy, highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), corresponding energy-gap, and dipole moment were calculated (Table 2) using DFT model constrained to work under unrestricted Becke's three-parameter exchange potential and Lee-Yang-Parr correlation functional (UB3LYP) method with 6-311++G(d,p) basis set.^[41,42]

Fig 1: Structure of oroidin (ODN).

Table 1: Binding energy of compounds having different substituents of oroidin.

Compounds	Substituted groups	Substituted by	$\Delta G_{\text{Binding}}$ (kcal/mol)
ODN1	7-H	7- NH ₂	-12.07
ODN2	6-H,7-H	6- NH ₂ ,7- NH ₂	-11.94
ODN3	7-H	7-CONH ₂	-12.63
ODN4	6-H,7-H	6- CONH ₂ ,7- CONH ₂	-12.33
ODN5	7-H	7-OH	-12.54
ODN6	6-H,7-H	6-OH,7-OH	-10.97
ODN7	7-H	7-COOH	-12.60
ODN8	6-H,7-H	6-COOH,7-COOH	-11.04
ODN9	7-H	7-F	-11.26
ODN10	7-H	7-CF ₃	-9.87
ODN11	7-H	7-NO ₂	-11.37
ODN12	13-Br	13-PO ₃ H ₂	-12.34
ODN13	8-H, 13-Br	8- PO ₃ H ₂ , 13- PO ₃ H ₂	-11.60
ODN14	7-H	7-CN	-10.42
ODN15	6-H	6-F	-11.85
ODN16	6-H	6-CF ₃	-10.17
ODN17	13-Br	13-CONH ₂	-12.68
ODN18	2-NH ₂ , 13-Br	2-CONH ₂ ,13-CONH ₂	-13.18
ODN19	12-Br	12-OH	-11.78
ODN20	12-Br,13-Br	12-OH,13-OH	-11.53
ODN21	13-Br	13-OCH ₃	-11.63
ODN22	7-H,13-Br	7-OCH ₃ ,13-OCH ₃	-11.72
ODN23	13-Br	13-COOH	-12.25
ODN24	2-NH ₂ ,13-Br	2-COOH,13-COOH	-12.23
ODN25	13-Br	13-F	-11.50
ODN26	13-Br	13-NO ₂	-11.60
ODN27	13-Br,14-H	13-H,14-Br	-11.56
ODN28	13-Br,14-H	13-H,14-OH	-11.28
ODN29	13-Br,14-H	13-H,14-OCH ₃	-12.08
ODN30	2-NH ₂ ,4-H	2-C,4-NH ₂	-12.39
ODN31	2-NH ₂ ,4-H,7-H	2-C,4-NH ₂ ,7-OH	-11.83
ODN32	2-NH ₂ ,4-H,13-Br	2-H,4-NH ₂ ,13-NH ₂	-11.66
ODN33	10-C=O	10-C(OH)	-10.88
ODN34	10-C=O	10-C(COOH)	-9.91
ODN35	10-C=O	10-C(OCH ₃)	-9.50
ODN36	10-C=O	10-C(CONH ₂)	-11.89
ODN37	6-H	6-CN	-11.41
ODN38	10-C=O	10-C(CF ₃)	-11.88
ODN39	7-H	7-CH(OH)COOH	-9.88

Fig 2: Compounds having, (a) normal structures and (b) optimized structures.

Toxicity and ADME Parameters

The overall toxicity of active derivative compounds was predicted by OSIRIS property explorer (<http://www.organic-chemistry.org/prog/peo/>). which indicates mutagenic, tumorigenic, irritant, and reproductive effect. Smiles were generated by SWISS ADME explorer.

Pre-ADMET (<http://preadmet.bmdrc.org/>) server was being exercised to explore drug-likeness properties and ADME profile (Absorption, distribution, metabolism, and excretion) of all the designed compounds. The extensive studies of logP, solubility, topological polar surface area (TPSA), molecular weight (MW), drug-likeness, drug-score, and the number of violations to Lipinski's rule had been carried out by Molinspiration (<http://www.molinspiration.com>) and OSIRIS program.

Docking Method

Auto dock tools 4.0 (ADT),^[43] interface program was used to predict the binding mode of ODN and its derivatives into the binding site of the receptor protein Hsp90 β (PDB ID: 3NMQ). The protein was made ready by checking, repairing missing atoms, adding all the missing hydrogen with no bond order, and using the ADT's graphical interface. To continue with the rigid docking process, the ligands were prepared as PDB files from all the optimized Gaussian output. Active torsions were kept to the maximum number of atoms. The grid box was so constructed that active sites of the receptor based on amino acid residues, were covered. The grid box size was maintained at 94, 94, 94 Å (x, y, and z respectively) and center at 0.076,15.013,20.513

Fig S1: Compounds having, (a) normal structure and (b) optimized structure.

Fig S1: Compounds having, (a) normal structure and (b) optimized structure.

(x, y, and z respectively) with grid point spacing 0.525 Å. Thirty-nine separate molecular docking experiments were performed, keeping the Lamarckian genetic algorithm (LGA) and other parameters in default mode. Nine conformations were generated for each ligand and the docked compounds with maximum cluster size as well as maximum binding energy were considered for advanced studies. The docking output results were transformed into .pdb format from .dlg, using python script (PMV 1.5.6).^[44]

RESULTS

The results (Table 1) executed by molecular docking revealed that the docked complex of twenty-eight derived compounds has higher binding energy (docked with PDB: 3NMJ) than ODN (-11.58 Kcal/mol). HOMO-LUMO energies and dipole moments of all forty molecules were listed in Table (2) from DFT analysis. The derived physical parameters like ionization potential (I), electron affinity (A), global hardness (η), softness

Table 2: Calculated energy values of oroidin and different derived compounds using UB3LYP/6-311++G(d,p).

Compounds	E_{HOMO} (eV)	E_{LUMO} (eV)	Band gap (ΔE_{HL}) (eV)	$E_{TOTAL} \times 10^4$ (eV)	Dipole moment (Debye)
ODN	-5.67	-1.38	4.29	-16.12	2.24
ODN1	-5.05	-1.59	3.46	-16.27	2.04
ODN2	-5.26	-1.23	4.03	-16.42	3.81
ODN3	-6.07	-2.02	4.05	-16.58	6.01
ODN4	-5.85	-1.86	3.99	-17.04	7.40
ODN5	-5.20	-1.66	3.54	-16.32	2.82
ODN6	-5.27	-1.53	3.74	-16.53	4.19
ODN7	-6.25	-2.34	3.91	-16.63	7.95
ODN8	-6.32	-2.68	3.64	-17.14	7.06
ODN9	-5.54	-1.41	4.13	-16.39	3.15
ODN10	-6.03	-1.92	4.11	-17.04	7.52
ODN11	-6.21	-2.84	3.37	-16.67	7.74
ODN12	-5.67	-1.45	4.22	-10.66	8.48
ODN13	-5.66	-1.56	4.10	-12.21	4.45
ODN14	-6.03	-2.19	3.84	-16.37	3.62
ODN15	-5.82	-1.38	4.44	-16.39	4.57
ODN16	-5.90	-1.66	4.24	-17.04	2.92
ODN17	-5.66	-1.39	4.27	-9.57	8.30
ODN18	-6.47	-1.88	4.59	-9.88	3.82
ODN19	-5.53	-1.16	4.37	-9.32	4.69
ODN20	-5.48	-1.08	4.40	-2.52	5.12
ODN21	-5.57	-1.20	4.37	-9.43	6.20
ODN22	-5.21	-1.19	4.02	-9.74	5.07
ODN23	-5.73	-1.61	4.12	-9.63	8.18
ODN24	-6.61	-2.15	4.46	-9.99	4.08
ODN25	-5.62	-1.35	4.27	-9.38	5.35
ODN26	-5.72	-2.65	3.07	-9.67	6.87
ODN27	-5.56	-1.32	4.24	-16.12	7.57
ODN28	-5.45	-1.00	4.45	-9.32	5.07
ODN29	5.44	-1.01	4.43	-9.43	5.91
ODN30	-5.10	-1.21	3.89	-16.27	5.41
ODN31	-5.31	-1.10	4.21	-16.47	5.61
ODN32	-5.00	-0.96	4.04	-9.42	5.65
ODN33	-5.54	-1.03	4.51	-16.12	5.79
ODN34	-5.54	-1.12	4.42	-16.43	6.36
ODN35	-5.44	-0.97	4.47	-16.23	5.65
ODN36	-5.47	-1.04	4.43	-16.38	6.75
ODN37	-5.92	-2.20	3.72	-16.37	4.25
ODN38	-5.57	-1.17	4.40	-16.83	3.09
ODN39	-5.97	-1.47	4.50	-16.94	8.43

(S), chemical potential (μ), electronegativity (σ), and electrophilicity (ω) had an important role to predict the activity of the thirty-nine derived compounds of oroidin (Table 3).

In this study we have found that all the compounds obey Lipinski's rule of five,^[45] majority of them qualified CMC like rule (except ODN2, ODN13) and WDI like rule (Table 4). As per Table 5, most of the compounds, with

Table 3: Global reactivity descriptors of oroidin and derived compounds.

Compounds	I (eV)	A (eV)	μ (eV)	η (eV)	S (eV ⁻¹)	σ (eV)	ω (eV)
ODN	5.67	1.38	-3.53	2.15	0.47	3.53	2.90
ODN1	5.05	1.59	-3.32	1.73	0.58	3.32	3.19
ODN2	5.26	1.23	-3.25	2.02	0.50	3.25	2.61
ODN3	6.07	2.02	-4.05	2.03	0.49	4.05	4.04
ODN4	5.85	1.86	-3.86	2.00	0.50	3.86	3.72
ODN5	5.20	1.66	-3.43	1.77	0.56	3.43	3.32
ODN6	5.27	1.53	-3.40	1.87	0.53	3.40	3.09
ODN7	6.25	2.34	-4.30	1.96	0.51	4.30	4.72
ODN8	6.32	2.68	-4.50	1.82	0.55	4.50	5.56
ODN9	5.54	1.41	-3.48	2.07	0.48	3.48	2.92
ODN10	6.03	1.92	-3.98	2.06	0.49	3.98	3.84
ODN11	6.21	2.84	-4.53	1.69	0.59	4.53	6.08
ODN12	5.67	1.45	-3.56	2.11	0.47	3.56	3.00
ODN13	5.66	1.56	-3.61	2.05	0.49	3.61	3.18
ODN14	6.03	2.19	-4.11	1.92	0.52	4.11	4.40
ODN15	5.82	1.38	-3.60	2.22	0.45	3.60	2.92
ODN16	5.90	1.66	-3.78	2.12	0.47	3.78	3.37
ODN17	5.66	1.39	-3.53	2.14	0.47	3.53	2.91
ODN18	6.47	1.88	-4.18	2.30	0.44	4.18	3.80
ODN19	5.53	1.16	-3.35	2.19	0.46	3.35	2.56
ODN20	5.48	1.08	-3.28	2.20	0.45	3.28	2.45
ODN21	5.57	1.20	-3.39	2.19	0.46	3.39	2.62
ODN22	5.21	1.19	-3.20	2.01	0.50	3.20	2.55
ODN23	5.73	1.61	-3.67	2.06	0.49	3.67	3.27
ODN24	6.61	2.15	-4.38	2.23	0.45	4.38	4.30
ODN25	5.62	1.35	-4.39	2.14	0.47	3.49	2.84
ODN26	5.72	2.65	-4.19	1.54	0.65	4.19	5.70
ODN27	5.56	1.32	-3.44	2.12	0.47	3.44	2.79
ODN28	5.45	1.00	-3.23	2.23	0.45	3.23	2.34
ODN29	5.44	1.01	-3.23	2.22	0.45	3.23	2.35
ODN30	5.10	1.21	-3.16	1.95	0.51	3.16	2.56
ODN31	5.31	1.10	-3.21	2.11	0.48	3.21	2.44
ODN32	5.00	0.96	-2.98	2.02	0.50	2.98	2.20
ODN33	5.54	1.03	-3.29	2.26	0.44	3.29	2.39
ODN34	5.54	1.12	-3.33	2.21	0.45	3.33	2.51
ODN35	5.44	0.97	-3.21	2.24	0.45	3.21	2.30
ODN36	5.47	1.58	-3.26	2.22	0.45	3.26	2.39
ODN37	5.92	2.20	-4.06	1.86	0.54	4.06	4.43
ODN38	5.57	1.17	-3.37	2.20	0.45	3.37	2.58
ODN39	5.97	1.47	-3.72	2.25	0.44	3.72	3.08

a few exceptions were appeared to have healthy oral bioavailability. Except for a few, all the ligands indicated excellent permeability (Table 6). The drug score and drug-likeness values of the ligands were also evaluated

(Table 7) and the result predicted that twenty-two compounds have better drug score value, in the range of 0.45-0.94 than that of ODN (0.45). Toxicity plays a key role in the selection of a promising drug. Numerous studies

Table 4: Drug-likeness properties of oroidin and derived compounds.

<i>Compounds</i>	<i>CMC[†] like rule</i>	<i>MDDR[‡] like rule</i>	<i>Rule of five</i>	<i>WDF[§] like rule</i>
ODN	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN1	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN2	Not qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN3	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN4	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN5	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN6	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN7	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN8	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN9	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN10	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN11	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN12	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN13	Not qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN14	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN15	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN16	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN17	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN18	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN19	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN20	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN21	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN22	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN23	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN24	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN25	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN26	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN27	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN28	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN29	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN30	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN31	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN32	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN33	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN34	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN35	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN36	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN37	Qualified	Mid-structure	Suitable	In 90% cutoff
ODN38	Qualified	Mid-structure	Suitable	Out of 90% cutoff
ODN39	Qualified	Mid-structure	Suitable	Out of 90% cutoff

[†]Comprehensive medicinal chemistry[‡]Molecular Detection of Drug Resistance[§] World drug index

reported that the molecule with low toxicity showed a high order of the therapeutic index. OSIRIS Property

Explorer was used to perform the toxicity prediction of all the derived compounds. The toxicity parameters were

Table 5: Molecular descriptor properties of oroidin and derived compounds.

Compounds	miLogP	TPSA ^a	natoms ^b	nON ^c	nOHNH ^d	nviolations ^e	nrotb ^f	volume
ODN	2.16	99.59	19	6	5	0	4	243.93
ODN1	1.68	125.62	20	7	7	1	4	255.22
ODN2	0.76	151.64	21	8	9	1	4	266.51
ODN3	0.83	142.69	22	8	7	1	5	274.20
ODN4	-0.76	185.78	25	10	9	1	6	304.48
ODN5	1.82	119.82	20	7	6	1	4	251.95
ODN6	2.26	140.05	21	8	7	1	4	259.97
ODN7	1.34	136.89	22	8	6	1	5	270.93
ODN8	0.27	174.19	25	10	7	1	6	297.93
ODN9	2.19	99.59	20	6	5	0	4	248.86
ODN10	3.02	99.59	23	6	5	0	5	275.23
ODN11	2.05	145.42	22	9	5	0	5	267.26
ODN12	0.16	157.12	22	9	7	1	5	270.43
ODN13	-1.12	214.65	26	12	9	2	6	314.84
ODN14	1.88	123.39	21	7	5	0	4	260.79
ODN15	2.13	99.59	20	6	5	0	4	248.86
ODN16	2.77	99.59	23	6	5	0	5	275.23
ODN17	0.17	142.69	21	8	7	1	5	256.32
ODN18	-0.71	159.76	23	9	7	1	6	275.30
ODN19	1.13	119.82	19	7	6	1	4	234.06
ODN20	0.10	140.05	19	8	7	1	4	224.20
ODN21	1.41	108.83	20	7	5	0	5	251.59
ODN22	0.40	118.06	22	8	5	0	6	277.14
ODN23	0.92	136.89	21	8	6	1	5	253.05
ODN24	0.80	148.17	23	9	5	0	6	268.76
ODN25	1.51	99.59	19	6	5	0	4	230.98
ODN26	1.31	145.42	21	9	5	0	5	249.38
ODN27	2.16	99.59	19	6	5	0	4	243.93
ODN28	1.13	119.82	19	7	6	1	4	234.06
ODN29	1.41	108.83	20	7	5	0	5	251.59
ODN30	1.76	125.62	20	7	7	1	4	255.22
ODN31	1.43	145.85	21	8	8	1	4	263.24
ODN32	0.44	151.64	20	8	9	1	4	248.62
ODN33	2.06	102.75	19	6	6	1	5	249.79
ODN34	1.95	119.82	21	7	6	1	6	268.78
ODN35	2.68	91.76	20	6	5	0	6	267.32
ODN36	1.44	125.62	21	7	7	1	6	272.05
ODN37	1.63	123.39	21	7	5	0	4	260.79
ODN38	3.63	82.52	22	5	5	0	6	273.07
ODN39	0.70	157.12	24	9	7	1	6	295.78

^aTopological polar surface area^bNumber of heavy atoms present in the compound^cNumber of hydrogen bond acceptors^dNumber of hydrogen bond donors^eNumber of violations made by proposed drug^fNumber of rotatable bonds

Table 6: Pre-ADMET prediction of oroidin and derived compounds

<i>Compound</i>	<i>HIA^a%</i>	<i>Caco2^b (nm/sec)</i>	<i>MDCK^c (nm/sec)</i>	<i>In vitro PPB^d %</i>	<i>BBB^e</i>	<i>Skin permeability</i>
ODN	86.55	11.15	0.34	41.90	0.27	-4.60
ODN1	79.84	9.56	0.47	20.86	0.07	-4.81
ODN2	67.99	13.03	0.51	17.57	0.04	-4.96
ODN3	74.33	10.89	0.48	23.86	0.06	-4.81
ODN4	48.96	14.88	0.51	31.41	0.04	-4.92
ODN5	80.40	10.52	0.44	39.71	0.12	-4.79
ODN6	69.34	13.19	0.51	31.85	0.07	-4.91
ODN7	74.64	10.23	0.45	48.50	0.07	-4.81
ODN8	51.84	14.12	0.49	58.07	0.05	-4.89
ODN9	86.56	11.35	0.39	60.84	0.25	-4.81
ODN10	87.10	9.94	0.36	88.02	0.60	-3.70
ODN11	69.58	11.90	0.43	64.72	0.09	-4.62
ODN12	36.36	0.93	0.27	61.76	0.03	-4.43
ODN13	4.46	0.61	0.43	71.40	0.03	-3.63
ODN14	81.49	8.03	0.40	48.85	0.12	-4.57
ODN15	86.56	12.08	0.37	48.01	0.27	-4.79
ODN16	87.10	14.99	0.34	88.52	0.94	-3.60
ODN17	55.87	17.20	0.34	18.61	0.05	-4.90
ODN18	45.19	17.49	0.20	27.17	0.04	-4.94
ODN19	66.10	15.36	0.39	24.57	0.12	-4.80
ODN20	18.43	6.26	1.85	32.03	0.06	-4.95
ODN21	75.64	14.89	0.32	24.41	0.13	-4.84
ODN22	72.09	15.21	0.44	26.61	0.08	-4.99
ODN23	56.49	16.93	0.26	32.76	0.06	-4.89
ODN24	47.25	17.04	0.07	66.10	0.05	-4.89
ODN25	78.91	15.11	0.27	33.94	0.18	-4.86
ODN26	48.72	17.09	0.26	50.51	0.05	-4.72
ODN27	86.55	11.15	0.27	48.20	0.37	-4.59
ODN28	66.11	16.34	0.20	23.11	0.12	-4.84
ODN29	75.64	14.89	0.18	23.66	0.12	-4.83
ODN30	80.16	14.08	0.13	30.77	0.13	-4.63
ODN31	69.24	13.73	0.25	34.45	0.07	-4.81
ODN32	47.39	17.99	0.20	13.37	0.05	-4.87
ODN33	83.92	11.34	0.34	15.41	0.19	-4.53
ODN34	79.01	13.35	0.43	64.49	0.11	-4.54
ODN35	87.34	12.45	0.31	26.51	0.34	-4.49
ODN36	79.11	13.84	0.47	40.95	0.09	-4.53
ODN37	81.49	13.67	0.39	50.99	0.15	-4.56
ODN38	88.97	15.71	0.30	94.56	1.38	-3.19
ODN39	62.06	12.97	0.50	43.92	0.06	-4.81

^aHuman intestinal absorption^bHuman colon carcinoma cell line^cMadin-Darby canine kidney^dPlasma protein binding^eBlood brain barrier

Table 7: Drug-likeness of oroidin and derived compounds using OSIRIS

<i>Compounds</i>	<i>clogP</i>	<i>Solubility</i>	<i>Molecular weight (MW)</i>	<i>TPSA[†]</i>	<i>Drug-likeness</i>	<i>Drug-score</i>
ODN	1.51	-3.13	387	99.59	-2.24	0.45
ODN1	0.94	-3.13	402	125.6	-1.93	0.46
ODN2	-0.16	-2.74	417	151.6	-1.93	0.46
ODN3	0.44	-2.80	430	142.6	-0.63	0.54
ODN4	-1.01	-2.08	473	185.7	-0.63	0.52
ODN5	1.34	-3.06	403	119.8	-1.72	0.47
ODN6	0.64	-2.59	419	140.0	-1.81	0.47
ODN7	0.67	-2.72	431	136.8	-1.21	0.49
ODN8	-0.39	-1.93	475	174.1	-1.21	0.38
ODN9	2.04	-3.64	405	99.59	-3.61	0.39
ODN10	2.60	-3.99	455	99.59	-8.83	0.34
ODN11	0.57	-3.48	432	145.4	-7.33	0.38
ODN12	-3.13	-0.69	389	166.9	-10.30	0.44
ODN13	-6.92	0.33	469	234.2	-10.32	0.40
ODN14	1.36	-3.40	412	123.3	-6.05	0.39
ODN15	1.5	-3.24	405	99.59	-3.61	0.41
ODN16	2.21	-3.59	455	99.59	-9.27	0.36
ODN17	-0.13	-2.38	352	142.6	1.06	0.78
ODN18	-0.84	-1.41	380	159.7	1.30	0.80
ODN19	0.69	-2.76	325	119.8	-1.96	0.50
ODN20	-0.38	-1.63	263	140.0	3.32	0.94
ODN21	0.71	-2.31	339	108.8	-0.16	0.66
ODN22	0.97	-2.37	369	118.0	-0.21	0.63
ODN23	0.10	-2.31	353	136.8	0.49	0.72
ODN24	-0.22	-1.25	382	148.1	0.69	0.74
ODN25	0.88	-2.61	327	99.59	-1.51	0.53
ODN26	-0.31	-2.75	354	145.4	-5.22	0.44
ODN27	1.51	-3.13	387	99.59	-2.41	0.45
ODN28	0.44	-2.00	325	119.8	-0.25	0.66
ODN29	0.71	-2.31	339	108.8	-0.33	0.64
ODN30	1.18	-3.73	402	125.6	-1.96	0.44
ODN31	1.02	-3.66	418	145.8	-1.45	0.46
ODN32	-0.22	-2.97	339	151.6	-1.08	0.55
ODN33	1.32	-2.68	389	102.7	-3.48	0.44
ODN34	-1.13	-2.54	417	119.8	-2.97	0.44
ODN35	1.75	-2.81	403	91.75	-3.50	0.42
ODN36	0.04	-2.62	416	125.6	-1.87	0.47
ODN37	0.97	-3.00	412	123.3	-6.49	0.41
ODN38	2.20	-3.81	441	82.5	-10.92	0.36
ODN39	0.10	-2.60	461	157.1	-0.71	0.51

[†]Topological polar surface area

displayed in OSIRIS as color codes where green indicated for low, yellow for mediocre, and red for high toxicity. Table (8) showed that all but merely two compounds had

a low toxicity. Amino acid residues that interacted with corresponding derived molecules, participated in protein-ligand interaction into the binding site of the receptor and

Table 8: Toxicity prediction of oroidin and derived compounds using OSIRIS

Compounds	Mutagenic	Tumorigenic	Irritant	Reproductive affective
ODN	Green	Green	Green	Green
ODN1	Green	Green	Green	Green
ODN2	Green	Green	Green	Green
ODN3	Green	Green	Green	Green
ODN4	Green	Green	Green	Green
ODN5	Green	Green	Green	Green
ODN6	Green	Green	Green	Green
ODN7	Green	Green	Green	Green
ODN8	Green	Red	Green	Green
ODN9	Green	Green	Green	Green
ODN10	Green	Green	Green	Green
ODN11	Green	Green	Green	Green
ODN12	Green	Green	Green	Green
ODN13	Green	Green	Green	Green
ODN14	Green	Green	Green	Green
ODN15	Green	Green	Green	Green
ODN16	Green	Green	Green	Green
ODN17	Green	Green	Green	Green
ODN18	Green	Green	Red	Green
ODN19	Green	Green	Green	Green
ODN20	Green	Green	Green	Green
ODN21	Green	Green	Green	Green
ODN22	Green	Green	Green	Green
ODN23	Green	Green	Green	Green
ODN24	Green	Green	Green	Green
ODN25	Green	Green	Green	Green
ODN26	Green	Green	Green	Green
ODN27	Green	Green	Green	Green
ODN28	Green	Green	Green	Green
ODN29	Green	Green	Green	Green
ODN30	Green	Green	Green	Green
ODN31	Green	Green	Green	Green
ODN32	Green	Green	Green	Green
ODN33	Green	Green	Green	Green
ODN34	Green	Green	Green	Green
ODN35	Green	Green	Green	Green
ODN36	Green	Green	Green	Green
ODN37	Green	Green	Green	Green
ODN38	Green	Green	Green	Green
ODN39	Green	Green	Green	Green

the number of hydrogen bonds formed during interactions were enlisted in Table 9.

DISCUSSION

HOMO-LUMO Analysis

A compound's reactivity depends upon the difference of energy between the HOMO and LUMO of a system.^[46] HOMO-LUMO energies were calculated by DFT-UB3LYP using the basis set 6-311++G(d,p) and the contour diagrams were displayed in Fig. 3 where positive and negative lobes were represented by red and green color, respectively. Homo has a tendency to give away its electron and behaves as nucleophile whereas LUMO, due to its electron-accepting tendency, behaves as an electrophile.^[47]

The knowledge of HOMO-LUMO band gap energy (ΔE_{HL}) is useful in determining various molecular properties like chemical reactivity, kinetic stability, optical polarizability, and chemical hardness-softness of molecules. The smaller the ΔE_{HL} value, the greater the chemical reactivity and polarizability, which corresponds to less stability.^[48,49] On the contrary higher, the value of ΔE_{HL} points out greater chemical stability and low reactivity. Moreover, molecules that possess a higher dipole moment show a tendency towards strong intermolecular interaction. The degree of chemical reactivity determines the nature of chemical hardness and softness.^[50]

Fig 3: Contours of the occupied and unoccupied molecular orbitals of the ligands.

Table 9: List of amino acids of oroidin and derived compounds, participating in protein-ligand interaction into binding site, with receptor and the number of hydrogen bonds.

Compounds	$\Delta G_{\text{Binding}}$ (kcal/mol)	Key protein-ligand interaction	H-bond
ODN	-11.31	Asn51, Leu107, Gly108, Phe138, Tyr139, Ala111, Val136, Ile26, Gln23, Phe22, Ala21, Phe170, Ile104, Leu103, Trp162	5
ODN1	-12.07	Asn105, Ile104, Leu103, Gln23, Ala21, Phe170, Phe22, Trp162, Thr109, Leu107, Gly108, Ile26, Tyr139, Phe138, Val150	3
ODN2	-11.94	Phe138, Tyr139, Leu103, Trp162, Phe22, Phe170, Ile104, Gln23, Ile26, Gly108, Leu107, Ala111, Val136, Ala21	4
ODN3	-12.63	Asn105, Ile104, Leu103, Met98, Val150, Trp162, Leu107, Phe170, Gly108, Thr109, Ala21, Gln23, Phe22, Ile25, Tyr138, Phe138	3
ODN4	-12.33	Leu48, Asn51, Thr184, Phe138, Tyr139, Val150, Trp162, Phe22, Phe170, Leu103, Leu107, Met98, Gly97, Ala55	4
ODN5	-12.54	Val150, Trp162, Leu103, Phe138, Met98, Tyr139, Leu107, Phe170, Ile104, Phe22, Phe20, Ala21, Gln23, Asn105, Ile26, Gly108	4
ODN6	-10.97	Asn51, Met98, Phe138, Leu107, Tyr139, Ala111, Val136, Gly135, Leu103, Trp162, Ile104, Phe170, Phe22,	5
ODN7	-12.60	Asn105, Ile104, Phe170, Phe22, Ile26, Gly108, Thr109, Gln23, Leu103, Trp162, Phe138, Asn51, Val136, Tyr139	5
ODN8	-11.04	Ala111, Leu107, Met98, Tyr139, Val136, Gly135, Gly137, Phe138, Thr184, Val186, Ala55, Asn51, Leu48, Ala52, Asp93, Lys185, Val92, Leu91	6
ODN9	-11.26	Ala21, Gln23, Phe22, Ile26, Phe170, Trp162, Tyr139, Val150, Phe138, Leu107, Leu103, Gly108, Thr109, Asn105, Ile104	2
ODN10	-9.87	Lys185, Val92, Asp93, Thr184, Leu91, Val186, Ala52, Ala55, Met98, Leu48, Asn51, Phe138, Leu107, Tyr139, Gly137, Val136, Gly135, Ala111	3
ODN11	-11.37	Leu107, Leu103, Phe138, Trp162, Tyr139, Phe170, Phe22, Gln23, Ile104, Gly108, Asn105, Thr109, Asn51	6
ODN12	-12.34	Gly135, Val136, Gly137, Ala111, Ile110, Ile26, Gly108, Gln23, Leu107, Phe138, Tyr139, Asn51, Phe22, Asn105, Ile104, Phe170, Trp162, Leu103	8
ODN13	-11.60	Ala55, Ala52, Gly97, Ile49, Asn51, Ile78, Asp93, Met98, Leu48, Thr184, Leu91, Val186, Val150, Trp162, Leu103, Tyr139, Phe138, Leu107	5
ODN14	-10.42	Asn51, Ala52, Ala55, Leu48, Leu91, Asp93, Val92, Lys185, Thr184, Val186, Val150, Trp162, Leu103, Leu107, Tyr139, Phe138, Met98	4
ODN15	-11.85	Gly135, Val136, Asn51, Tyr139, Phe138, Ile26, Thr109, Gly108, Leu107, Phe22, Trp162, Asn105, Phe170, Leu103, Ile104, Gln23	5
ODN16	-10.17	Val136, Gly135, Tyr139, Ala111, Phe138, Phe22, Ile110, Gly108, Phe170, Trp162, Leu107, Leu103, Asn105, Asp102, Ile104	3
ODN17	-12.68	Val136, Gly135, Gly137, Ile26, Tyr139, Ala111, Phe138, Gln23, Phe22, Asn51, Gly108, Ala21, Leu107, Trp162, Phe170, Leu103, Ile104	8
ODN18	-13.18	Val136, Gly135, Ile26, Tyr139, Ala111, Gln23, Phe22, Phe138, Asn51, Gly108, Ala21, Thr109, Leu107, Phe170, Trp162, Leu103, Asn105, Ile104	7
ODN19	-11.78	Val136, Gly135, Ile26, Tyr139, Ala111, Gln23, Phe22, Phe138, Asn51, Gly108, Ala21, Leu107, Phe170, Leu103, Ile104	7
ODN20	-11.53	Gly135, Asn51, Gly137, Val136, Phe138, Leu107, Tyr139, Gly108, Ile26, Leu103, Trp162, Phe22, Gln23, Phe170, Ile104	6
ODN21	-11.63	Phe138, Tyr139, Leu107, Gly108, Trp162, Leu103, Phe22, Gln23, Phe170, Ile104, Asn105, Thr109, Asn51,	5
ODN22	-11.72	Asp102, Asn51, Gly135, Leu107, Thr109, Leu103, Val136, Gly108, Phe138, Trp162, Tyr139, Gln23, Phe170, Phe22, Asn105, Ile104	8
ODN23	-12.25	Asn51, Leu107, Leu103, Asn105, Gly135, Thr109, Ile104, Gly108, Trp162, Tyr139, Val136, Phe138, Gly137, Phe170, Gln23, Phe22	8
ODN24	-12.23	Gly135, Ala111, Val135, Gly108, Leu107, Asn51, Gly137, Gln23, Ile26, Tyr139, Phe138, Ile104, Leu103, Phe22, Trp162, Phe20, Phe170, Ala21	6

Compounds	$\Delta G_{\text{Binding}}$ (kcal/mol)	Key protein-ligand interaction	H-bond
ODN25	-11.50	Thr109, Asn106, Ala111, Val136, Leu107, Gly108, Asn105, Gln23, Phe138, Tyr139, Leu103, Ile104, Phe22, Trp162, Phe170	4
ODN26	-11.60	Asn51, Val136, Ala111, Leu107, Gly108, Phe138, Tyr139, Ile26, Gln23, Asn105, Leu103, Phe22, Ile104, Trp162, Phe170	6
ODN27	-11.56	Thr109, Ala111, Asn105, Leu107, Gly108, Gln23, Met98, Ile104, Leu103, Tyr139, Phe22, Phe138, Phe170, Trp162	4
ODN28	-11.28	Thr109, Asn105, Leu107, Gly108, Gln23, Asn51, Ile104, Leu103, Tyr139, Phe138, Phe22, Phe170, Trp162	6
ODN29	-12.08	Gly108, Val136, Leu107, Gln23, Ile26, Ile104, Tyr139, Phe22, Leu103, Ala21, Phe138, Phe170, Trp162, Val150	5
ODN30	-12.39	Thr109, Gln23, Ile26, Gly108, Asn105, Leu107, Ala21, Tyr139, Phe22, Ile104, Phe20, Phe138, Phe170, Lu103, Met98, Trp162, Val150	8
ODN31	-11.83	Gln23, Ile26, Ala21, Thr109, Phe22, Gly108, Asn105, Tyr139, Phe170, Ile104, Leu107, Trp162	9
ODN32	-11.66	Thr109, Leu107, Met98, Gly108, Tyr139, Ile26, Asn105, Leu103, Gln23, Ile104, Trp162, Phe22, Phe170, Phe20, Ala21	7
ODN33	-10.88	Gly108, Leu107, Ile26, Gln23, Tyr139, Phe138, Phe22, Leu103, Val150, Ile104, Trp162, Phe170, Ala21	6
ODN34	-9.91	Thr109, Leu107, Gly108, Asp102, Phe138, Tyr139, Gln23, Asn105, Leu103, Phe22, Ile104, Trp162, Phe170, Ala21	6
ODN35	-9.50	Asn51, Ile49, Ala52, Ile78, Leu48, Leu107, Asp93, Phe138, Leu91, Met98, Thr184, Val92, Val186, Leu103, Val150	2
ODN36	-11.89	Thr109, Ala111, Val136, Leu107, Met98, Phe138, Tyr139, Gly108, Asn105, Gln23, Leu103, Val150, Trp162, Ile104, Phe22, Phe170	5
ODN37	-11.41	Thr109, Leu107, Gly108, Met98, Phe138, Tyr139, Ile26, Asn105, Gln23, Leu103, Val150, Trp162, Ile104, Phe22, Phe170, Ala21	2
ODN38	-11.88	Asn51, Ala111, Leu107, Phe138, Tyr139, Ile26, Gly108, Gln23, Asn105, Leu103, Phe22, Val150, Trp162, Ile104, Phe170	4
ODN39	-9.88	Asp54, Ala55, Ile96, Gly95, Ala52, Gly97, Asp93, Gly183, Asn51, Met98, Thr184, Leu107, Leu103, Phe138, Val150, Tyr139, Trp162	4

Amino acids with bold letters are the participators in forming H-bonds.

Here we observed that twenty-eight derived compounds possessed lower ΔE_{HL} value than that of precursor

ODN (4.29 eV) (Table 2). Among all, ODN18 contained the highest energy gap (4.59 eV) and was considered as least reactive. On the other hand, ODN26 with the lowest value (3.07eV) was highly polarizable, reactive, and behaved as a soft species. Analyzing the dipole moment values it had been found that ODN12, ODN17, ODN23, and ODN39 derived molecules had a higher tendency to take part in strong intermolecular interaction (Table 2).

Global Reactivity Descriptors

Several new chemical descriptor parameters have been suggested to understand some important pharmacological properties and the eco-toxicological character of drug molecules. Conceptual DFT based parameters are being used to understand the reactivity of molecules by calculating the chemical potential, global hardness, softness, and electrophilicity index. Ionization potential (I) and electron affinity (A). Expressions of them are as follows:

$$I = -E_{\text{HOMO}} \quad (1)$$

$$A = -E_{\text{LUMO}} \quad (2)$$

Using the above other descriptor properties such as chemical potential (μ), global hardness (η), global softness (S), electronegativity (σ), and electrophilicity index (ω) can be calculated.

$$\mu = (E_{\text{LUMO}} + E_{\text{HOMO}})/2 \quad (3)$$

$$\eta = (E_{\text{LUMO}} - E_{\text{HOMO}})/2 \quad (4)$$

$$S = 1/\eta \quad (5)$$

$$\sigma = -\mu \quad (6)$$

$$\omega = \mu^2/2\eta \quad (7)$$

Global hardness predicts the chemical stability and measures the resistance to change the electronic charge distribution in a molecule.^[48,49] Electrophilicity index (ω) is the measure of electron acceptance capacity of a molecule.^[50] The higher value of chemical softness of ODN1, ODN11, and ODN26 suited them to act as a soft molecule with high polarizability while the higher value of global hardness of ODN18, ODN33, and ODN39 were considered as electron-withdrawing species and could be treated as electrophiles (Table 3).

Toxicity and Molecular Descriptor Properties

In this study, we tested *silico* toxicity parameters by using the OSIRIS property explorer that indicates mutagenic, tumorigenic, irritant, and reproductive index of the designed ligands. All the compounds, except ODN8 and ODN18, qualified the above-desired parameters (Table 8). Solubility, drug-likeness and drug-score values were also evaluated from this web application.^[51] Molinspiration web toolkit predicted the bioactive scores which help us to screen best inhibitors of Hsp90 and we calculated valuable parameters such that *miLogP*, topological polar surface area (TPSA), number of rotatable bonds (*nrotb*), number of hydrogen bond acceptors (*nON*) and donors (*nOHNH*). Permeability through cell membrane depends on the *miLogP* parameter and TPSA provides the tendency of generating hydrogen bonds. The number of rotatable bonds represents the flexibility of the compound. Molecular properties and structural features, irrespective of known drugs were scrutinized based on the drug-likeness data of molecules.^[51] The excellent results listed in (Table 5, 7) indicate that most of the derived compounds have good potential to qualify as future drugs.

Rule of five states that compounds having some violations ≤ 1 shows good bioavailability and the obtained results confirmed that all the derived compounds may behave as good bioavailable drugs. High probability of solubility in cellular membranes requires $nOHNH \leq 5$ and sixteen of the derived compounds followed this rule.^[52] Apart from this, all the derived molecules have a molecular weight (MW) < 500, $nON \leq 10$ (except ODN13), $cLogP \leq 5$ and $nrotb \leq 6$ and qualified oral route of newly designed drugs.^[53] Molecules with $TPSA > 140$ exhibit poor permeability through the cell membrane and $TPSA < 90$ is required to penetrate the blood-brain barrier in the central nervous system. Twenty-one of the derived compounds have the desired TPSA range (90 Å²-140 Å²) and could be considered as candidate drugs.

ADME Prediction and Drug-likeness Properties

The ADME is an abbreviation used in the pharmacokinetics for absorption, distribution, metabolism, and excretion and affects the compound's performance and pharmacological activity as a drug.^[54] Most of the derived compounds have shown satisfactory in *silico* ADME properties (Table 6) Six derived compounds showed better results as intestinal absorption (HIA) than standard ODN closed to 86.55%. ODN38 secured the highest HIA (88.97%); hence, it showed maximum absorption. All the compounds exhibited low or moderate in vitro Caco2 and MDCK cell permeability. In vivo blood-brain barrier (BBB) penetration discovered that most of the compounds (except ODN38) had no or low ($BBB < 1$) absorption into the central nervous system (CNS), causing no or less adverse effect towards CNS. Plasma protein binding refers to the degree of binding of a drug to proteins within the blood. The less is the binding of the more efficient drug causes more penetration through

the cell membrane. All the compounds recorded $PPB < 90\%$ (except ODN38), possessing better diffusion into the cell. Skin permeability data indicated that they could have a transdermal application. Moreover, except ODN2 and ODN13 all the derived molecules obeyed CMC, MDDR, and WDI like rules as displayed in Table 4. Based on these observations, we may conclude that most of these derived molecules have the capability of good drug-likeness and ADME properties.

Molecular Docking and Pharmacophore Studies

Molecular docking is the most sound and significant method to realize the foundation of protein-ligand interaction.^[55] We have studied this method to ascertain the binding affinity of the ligands with the active sites of Hsp90 (PDB: 3NMQ). The standard structure of ODN was marked into three subsections, two 5-member rings (A, B) and linker (C) (Fig. 1). Molecular docking was done to demonstrate the recognition mode between derived ODN derivatives with Hsp90 and a graphical illustration of best results displayed in Fig. 4.

Katja-Emilia Lillsunde and his co-workers found that oroidin derivatives (imidazole ring substituted by the thiazole ring isosterically) could be used as potent DNA gyrase inhibitors targeting ATP-binding site of Hsp90 required for viral replication.^[12] Based on their experimental work we followed a theoretical approach to design oroidin derivatives based on functionalisation

Fig 4: Bar graph represents compound with higher binding energies than oroidin (ODN).

in the native oroidin compound. We got better binding values when substitution at various positions of oroidin (Fig. 2) was done by amide, amine, phosphate, hydroxyl, fluorine, methoxy, and carboxylic acid groups but the groups like trifluoromethyl, cyanide, and nitro failed to exhibit better result.

The docking results revealed that 28 derived compounds had a better result of binding energy than the standard ODN (-11.31 Kcal/mol) (Table 1). A 2D and 3D ligand-receptor docking interactions of the four best derivatives are shown in Figs. 5 and Fig. 6) while the rest are shown in the supplementary file. The residues of the active site of Hsp90 were found to be *Asn51, Leu107, Gly108, Phe138, Tyr139, Ala111, Val136, Ile26, Gln23, Phe22, Ala21, Phe170, Ile104, Leu103* and *Trp162* (Fig. 7). From the analysis of the molecular alignment of docked complexes, it was found that all the derived compounds docked at the same region of Hsp90 as in the case of ODN (Fig. 8). Out of them, 5 derivatives indicated considerably higher binding energy (<-12.5Kcal/mol), whereas the rest 23 compounds have moderately higher binding energy (<-11.31 Kcal/mol) compared to precursor ODN.

Fig 5: 2-D docking model of the ligands (a) ODN1, (b) ODN7, (c) ODN22, (d) ODN37 with Hsp90 (PDB: 3NMQ) protein (Hydrogen bonds are represented as blue line and steric interactions are represented as red or no line).

Fig. 6: 3D docking model of ligands (a) ODN1, (b) ODN7, (c) ODN22, (d) ODN37, with Hsp90 (PDB: 3NMQ) protein. (Dark lines indicate the hydrogen bond interaction).

Incorporation of one or more amide groups either at the side ring (B) or at linker (C) as designed in ODN3, ODN17, ODN4, ODN18, resulted in a better binding score. ODN18 achieved maximum binding energy (-13.18 Kcal/mol) implies maximum stability. Seven strong hydrogen bonds, caused by 2 amide groups incorporated at the side chain of the 5-membered ring (B), have been formed at the binding site. H bonds were found to have interacted with the *Gly135, Gln23, Phe138, Ala21, Ile104* residues (Supplementary Fig. S2), and bond distances lying between 1.97Å to 3.40Å (Supplementary Fig. S3). The amino acids *Val136, Gly135, Ile26, Tyr139, Ala111, Gln23, Phe22, Phe138, Asn51, Gly108, Ala21, Thr109, Leu107, Phe170, Trp162, Leu103, Asn105, Ile104* were found to be connected (Supplementary Fig. S4) with ODN18 through hydrophobic interaction (Table 9). ODN35 showed minimum stability with the lowest binding score (-9.50 Kcal/mol) that might be due to the electrostatic repulsion effect of the methoxy group with the receptor moiety.

Mono substituted amine group at linker (C) in ODN1 exhibited better docking value (-12.07Kcal/mol) than

Fig 7: Pose interaction view of compounds with the target protein Hsp90.

Fig 8: (a) Docking model of the oroidin and other 7 best ligands with Hsp90 (PDB:3NMQ) protein. (b) Zoomed view of the active site showing the docked molecules. (c) Surface view of the ligands into binding site and (d) zoomed view of the ligands into protein surface.

Fig S2: 2-D docking model of the ligands with Hsp90 (PDB: 3NMQ) protein (Hydrogen bonds are represented as blue line and steric interactions are represented as red or no line)

the di-substituted amine groups at the linker in ODN2 (-11.94 Kcal/mol). Surprisingly better results -12.39 Kcal/mol have been found in ODN30 when the position of amine group C-2 at the side ring (A) have been changed to C-4. Strong electrostatic interaction into the binding site is responsible for the better docking results in both cases.

Fig S4: Pose interaction view of compounds with the target protein Hsp90.

and produced higher binding energy (-12.34 Kcal/mol) than ODN13.

The presence of less polar one or more methoxy groups in ODN29, ODN22, ODN21, indicated moderate binding value, following moderate hydrophobic interaction, lying in the range -12.08 Kcal/mol to -11.63 Kcal/mol. The very poor result we got when -O at C-10 position was replaced by a methoxy group, found in ODN35. Introduction of one

highly polar -COOH group in place of -H at the C-7 position in the side chain of linker producing ODN7 and instead of -Br at C-13 position in the side ring (B) producing ODN23, would favor greater electrostatic interaction, Vander Waals interaction, and H-bond interaction into the binding site promoting the excellent value of binding energies of -12.6 Kcal/mol and -12.25 Kcal/mol respectively. But, the incorporation of second -COOH group at C-6, found in

Fig S3: 3D docking model of ligands with Hsp90 (PDB: 3NMQ) protein. (Black lines indicate the hydrogen bond interaction).

ODN8 and replacing $-O$ at C-10 found in ODN34, shown an unfavorable value of binding energies of -11.04 Kcal/mol and -9.91 Kcal/mol respectively, due to some steric hindrance phenomenon existing in the molecules.

We have studied many other groups substituted at different positions into ODN in addition to the above substitutions. We found moderate binding energy values of ODN15 (-11.85 Kcal/mol) and ODN25 (-11.50 Kcal/mol), formed when $-F$ atom was included into the linker (C) and the side ring (B), respectively. Mono substituted cyanide group at C-6 in ODN37 (-11.41 Kcal/mol) reported a much better binding score to compare to $-CN$ group at C-7 in ODN14 (-10.42 Kcal/mol). The molecules ODN26 and ODN11 containing single $-NO_2$ group at C-13 and C-7 position respectively showed better binding affinity (-11.60 Kcal/mol to -11.37 Kcal/mol). Similarly, the molecule ODN16 and ODN10 containing single $-CF_3$ group at C-6 and C-7 position showed unsatisfactory docking scores (-10.17 Kcal/mol to -9.87 Kcal/mol). On the contrary, when $-CF_3$ replaced $-O$ of ODN at C-10 position, a surprisingly very good result was obtained in ODN38 (-11.88 Kcal/mol), probably higher interaction of active moiety (B) with the binding site of the receptor. For the same reason, the ligand ODN36 recorded high docking value (-11.89 Kcal/mol), when the amide group has been used in place of $-CF_3$ following the previous procedure.

Moreover, ODN39 has shown an interesting result. Here, substitution was done by highly polar $-CH(OH)COOH$ and it was supposed to give rise to better docking

with the binding site of Hsp90. But surprisingly, ODN39 with an adequate number of H-bond interactions (four in number) displayed poor performance (-9.88 Kcal/mol) due to steric hindrance.

Selection of Ligands

The compounds ODN1, ODN5, ODN7, ODN22, ODN25, ODN30 and ODN37 displayed binding energies (-11.41 Kcal/mol to -12.60 Kcal/mol) more compared to precursor ODN (-11.31 Kcal/mol) and bandgap energies ΔE_{HL} (3.46 eV to 4.27 eV) also less than that of ODN (4.29 eV). All of them have qualified pharmacophore studies ($HIA > 70\%$, $BBB < 0.2$, $90 \text{ \AA}^2 < TPSA < 140 \text{ \AA}^2$, drug score > 0.4) and in silico toxicity tests. Hence, these seven ligands could be considered as potent molecules, but before that, these compounds have to be synthesized in the wet lab followed by in vivo tests.

Marine natural product oroidin, a viable source of bioactive compounds, has a promising inhibitory effect on Heat shock protein (Hsp90), and that leads us to pursue this study. Here we have designed a library of thirty-nine derivatives by incorporation of various functional groups in the active pharmacophore. We have categorized the whole work into three systemic studies: (1) electronic, quantum mechanical, and thermodynamical behaviors of molecules using DFT at UB3LYP level of basis set 6-311++G(d,p), (2) molecular docking study of each compound in the active site of Hsp90 β , (3) drug-likeness and toxicity prediction and compared the outcomes with the standard drug ODN.

Analysis of all the data available from these studies revealed that seven analogs ODN1, ODN5, ODN7, ODN22, ODN25, ODN30, and ODN37 have better chemical activity and docking capabilities than the precursor molecule (ODN) one. Excellent drug-like behavior and low toxicity studies screened them as more potent inhibitors than the oroidin. These seven computationally designed derivatives may have the advantageous therapeutic strategies for cancer treatment and could be developed as novel effective anticancer drug candidates in the future.

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HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

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