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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 Hsp90α/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 residueThr90 of Hsp90α 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 Hsp90β-apoptosome interaction, may contribute to chemo-resistance in leukemias.[19] Upregulation of Hsp90β 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]

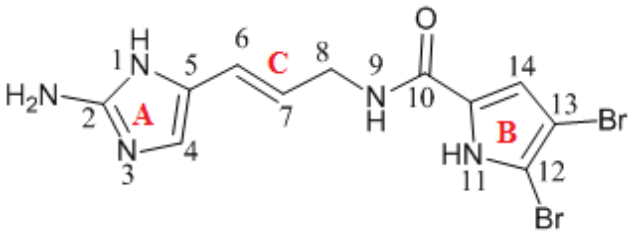

Fig 1: Structure of oroidin (ODN).

Based on these studies, we have modified oroidin to set up a library of 39 derivatives, undergoing molecular docking interaction with Hsp90β (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]

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

Compounds	*Substituted groups*	*Substituted by*	$\Delta G_{Binding}$ *(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_3H_2	-12.34
ODN13	8-H, 13-Br	8- PO_3H_2, 13- PO_3H_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

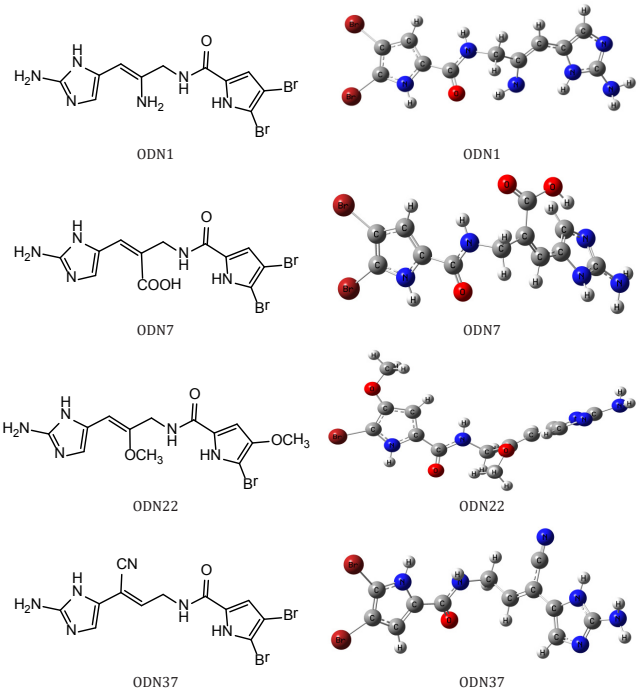

Fig 2: Compounds having, (a) normal structures and (b) optimized structures.

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 Hsp90β (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

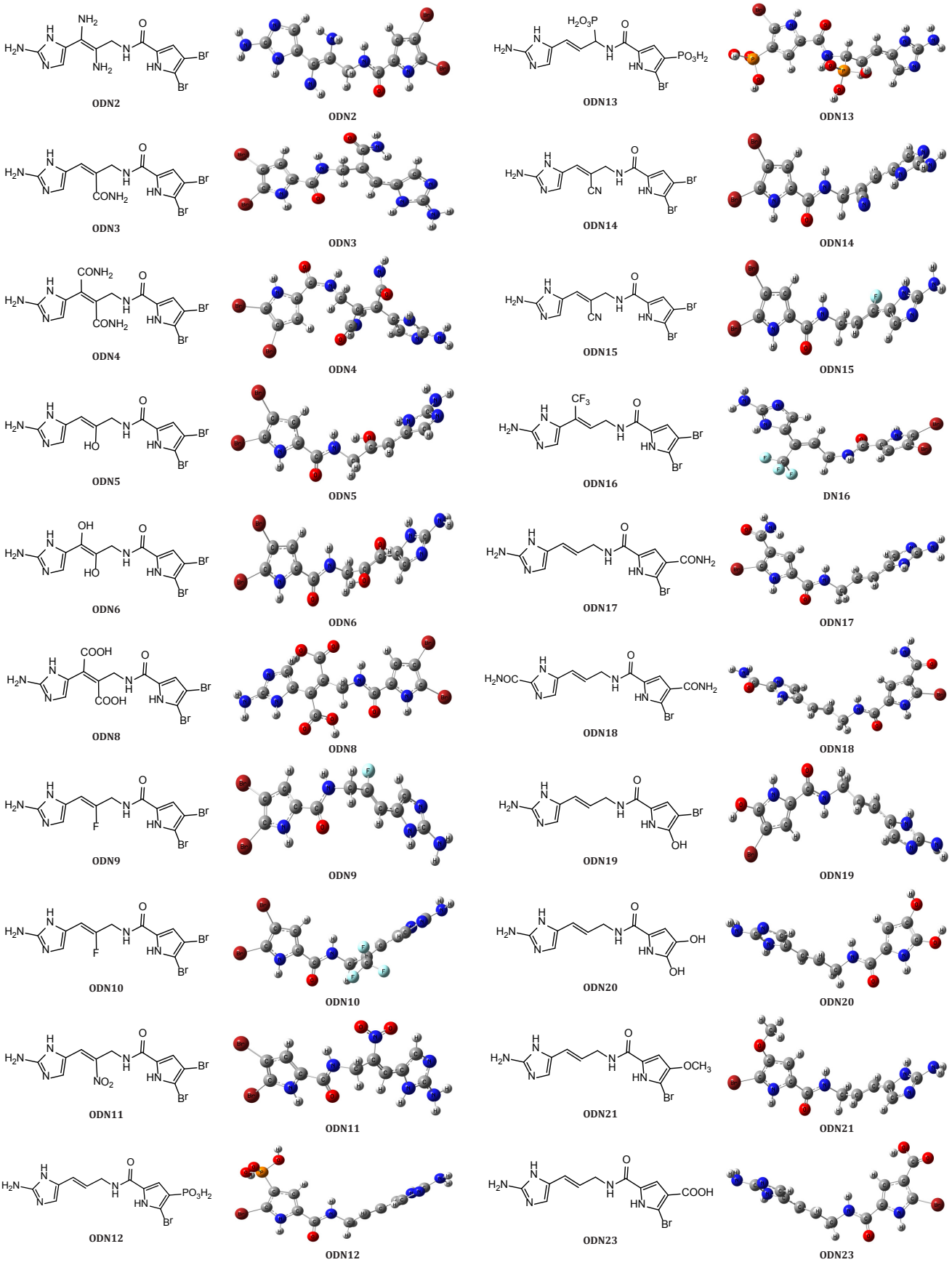

Fig S1: Compounds having, (a) normal structure and (b) optimized structure.

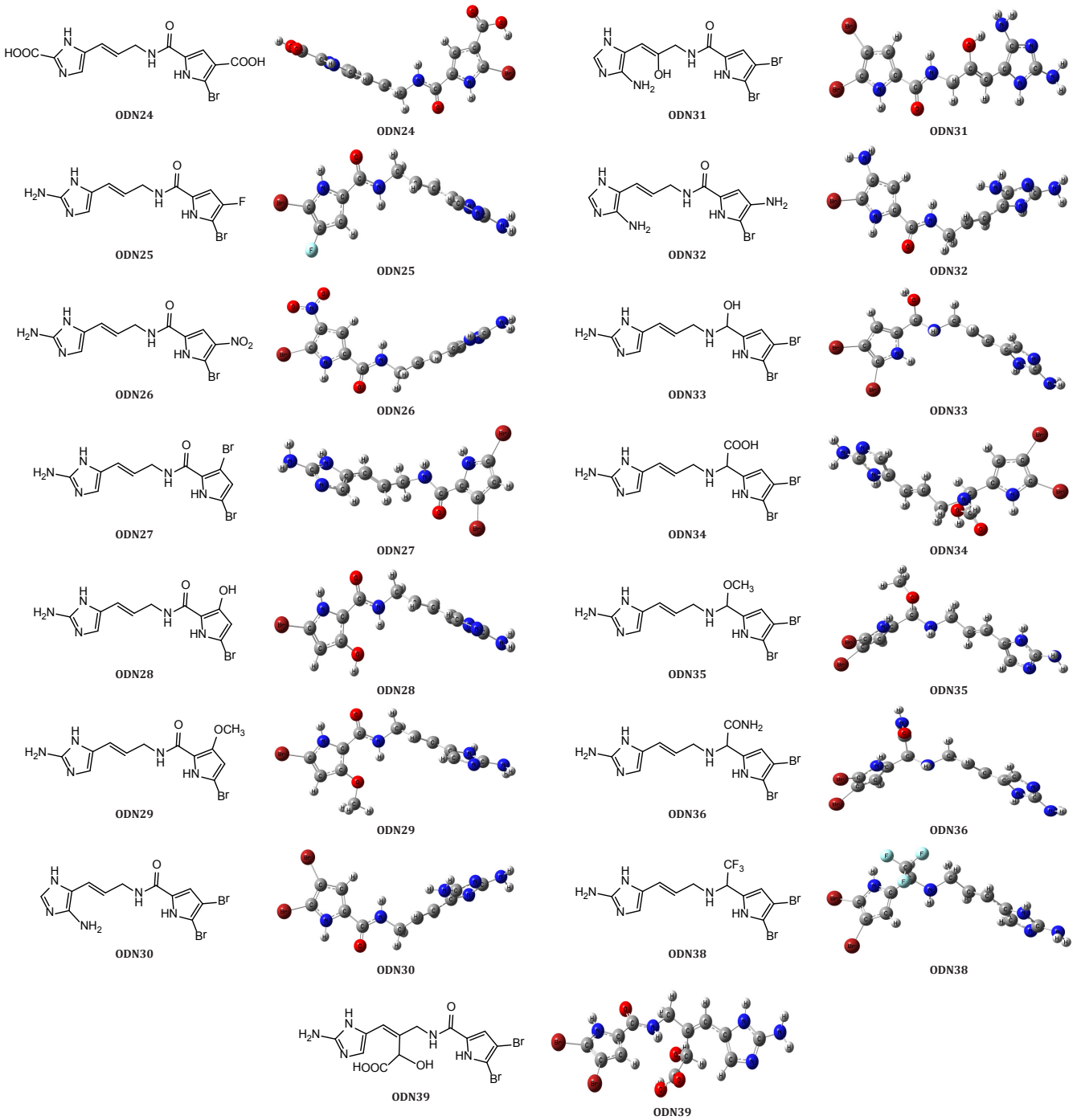

Fig S1: Compounds having, (a) normal structure and (b) optimized structure.

(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: 3NMQ) 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)*	$E_{TOTAL}x10^4$ *(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.

Compounds	*CMC[†] like rule*	*MDDR[‡] like rule*	*Rule of five*	*WDI[§] like rule*
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

[a]Topological polar surface area
[b]Number of heavy atoms present in the compound
[c]Number of hydrogen bond acceptors
[d]Number of hydrogen bond donors
[e]Number of violations made by proposed drug
[f]Number of rotatable bonds

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

Compound	*HIA[a]%*	*Caco2[b] (nm/sec)*	*MDCK[c] (nm/sec)*	*In vitro PPB[d] %*	*BBB[e]*	*Skin permeability*
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

[a]Human intestinal absorption
[b]Human colon carcinoma cell line
[c]Madin-Darby canine kidney
[d] Plasma protein binding
[e] Blood brain barrier