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Original article

Molecular Docking and In vitro Cytotoxic Activity of Novel 1,3,4-thiadiazole Derivatives Against MCF-7 Cell Line

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Abstract
This investigation assesses the cytotoxic profiles and docking properties of twelve newly synthesized 1,3,4-thiadiazole derivatives against the MCF-7 cell line. The results revealed that nine of these compounds displayed noteworthy cytotoxic activity, with the most effective compound recording an IC_{50} value of 17.30 µM. Additionally, docking analyses indicated binding energies ranging from (-7.6 to -12.4 kcal/mol). In silico evaluations confirmed that all compounds are in alignment with Lipinski's Rule of Five. Moreover, the ADMET properties suggest that these synthesized derivatives are suitable for oral administration.
Keywords. 1,3,4-thiadiazole, Docking Studies, Cytotoxic Activity, Breast Cancer.

Introduction

Breast cancer ranks among the most prevalent and clinically significant malignancies worldwide. It is identified as the second leading cause of cancer-related mortality among women globally. It occurs due to the uncontrolled proliferation of cells within the breast tissue. While the precise trigger for this uncontrolled growth is unclear, various risk factors such as age, genetic mutations, family history, hormonal influences, and lifestyle play significant roles in its development [1–5]. About 10% of breast cancers that occur in women are related to genetic predisposition or family history [6]. Estimates from the American Cancer Society for breast cancer in the United States for 2025 indicate that approximately 42,170 women are expected to die from Breast Cancer [7].

Breast cancer treatment in many situations includes surgery (breast-conserving surgery or mastectomy) followed by radiation therapy. Additionally, systematic therapies, depending on the type of breast cancer, different types of drug treatment might be used, including chemotherapy, targeted therapy, hormone therapy, and Immunotherapy [7–11]. Despite the many advances in drugs used to treat cancer, they are inadequate against breast cancer, in addition to the side effects they cause. There is a pressing need for ongoing advancements in the discovery and development of novel compounds that demonstrate both efficacy and safety for prolonged use. Heterocyclic compounds have garnered significant attention in the realm of natural products research and are highly valued by medicinal chemists. Their distinctive biologically active structures present considerable opportunities for pharmacological development [12–16]. Among heterocyclic compounds, thiadiazole is characterized by a five-membered ring that includes one sulfur atom and two nitrogen atoms [17]. It exhibits a broad spectrum of biological activities and is recognized as the most prevalent class of heterocycles commonly employed in drug design and synthetic chemistry [18]. Many broad-spectrum pharmacological activities have been reported for the compounds containing a 1,3,4-thiadiazole ring, such as anti-inflammatory, antituberculosis, antidepressant, anxiolytic, antioxidant, anticonvulsant [19–24], and anticancer activities [25–32] (Figure 1).

Molecular docking is a computational approach designed to estimate the binding affinity of ligands to receptor proteins, playing a crucial role in contemporary drug development methodologies.

In this research, further in silico studies, molecular docking analysis, and the cytotoxic activity of the novel thiadiazole derivatives synthesized in previous literature [33] (Table 1) were predicted in biological studies using the MCF-7 cell line.

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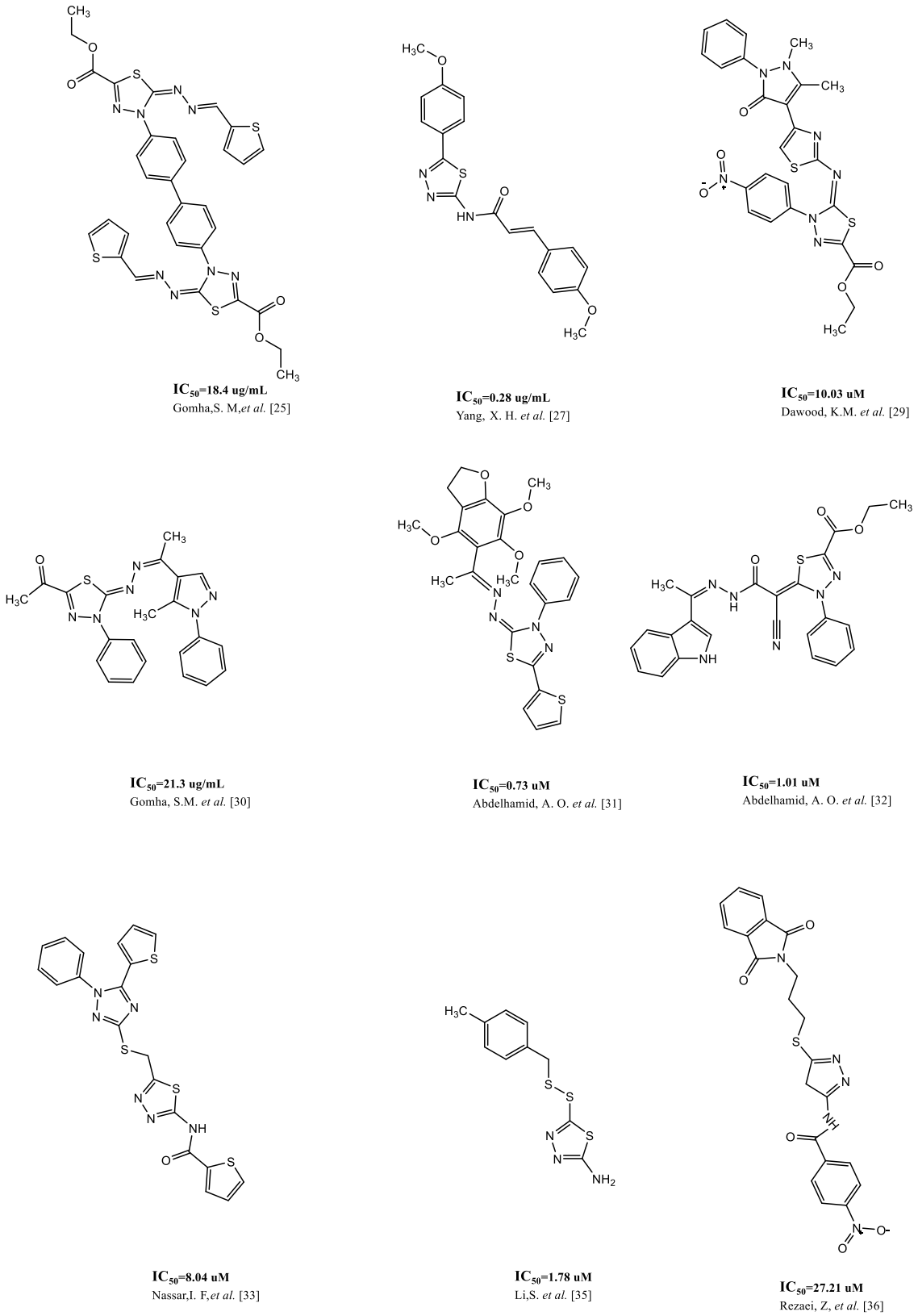

Figure 1. 1,3,4-thiadiazole derivatives recently identified as possessing cytotoxic activity against MCF-7 cancer cell lines.

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Table 1. 1,3,4-thiadiazole derivatives.

Compounds	Structure smiles
1	BrC1=CC(Br)=C(O)C(/C=N/N=C2SC(C(NC3=CC=CC=C3)=O)=NN2C4=CC=C(Cl)C=C4)=C1
2	BrC1=CC(Br)=C(O)C(/C=N/N=C2SC(C3=CC=CO3)=NN2C4=CC=C([N+]([O-])=O)C=C4)=C1
3	BrC1=CC(Br)=C(O)C(/C=N/N=C2SC(C3=CC=CS3)=NN2C4=CC=C([N+]([O-])=O)C=C4)=C1
4	BrC1=CC(Br)=C(O)C(/C=N/N=C2SC(C(OCC)=O)=NN2C3=CC=CC=C3)=C1
5	BrC1=CC(Br)=C(O)C(/C=N/N=C2SC(C(OCC)=O)=NN2C3=CC=C(C)C=C3)=C1
6	BrC1=CC(Br)=C(O)C(/C=N/N=C2SC(C(C)=O)=NN2C3=CC=C(C)C=C3)=C1
7	BrC1=CC(Br)=C(OC(/C(C)=N/NC(SC)=S)=C2)C2=C1
8	O=C(C1=CC=CC=C1)C2=NN(C3=CC=CC=C3)/C(S2)=N\N=C(C)\C4=CC5=CC(Br)=CC(Br)=C5O4
9	O=C(NC1=CC=CC=C1)C2=NN(C3=CC=C(Cl)C=C3)/C(S2)=N/N=C(C)/C4=CC5=CC(Br)=CC(Br)=C5O4
10	CC(C=C1)=CC=C1C2=NN(C3=CC=CC=C3)C(S2)=N/N=C(C)/C4=CC5=CC(Br)=CC(Br)=C5O4
11	BrC1=CC(Br)=C(OC(/C(C)=N/N=C2SC(C3=CC=CO3)=NN/2C4=CC=C([N+]([O-])=O)C=C4)=C5)C5=C1
12	Cl/C(C1=CC=C(C2=NN(C3=CC=CC=C3)/C(S2)=N\N=C(C)\C4=CC5=CC(Br)=CC(Br)=C5O4)C=C1)=N\NC6=CC=CC=C6
DOX	O=C1C2C(C(O)=C(CC(C(CO)=O)(O)CC3OC4CC(N)C(O)C(C)O4)C3=C2O)C(C5=CC=CC(OC)=C51)=O

Methods

Anticancer activities

Cell Line and Culture

The MCF-7 mammary gland breast cancer cell line and WI-38 normal lung fibroblast cell line were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) via the Holding Company for Biological Products and Vaccines (VACSERA) in Cairo, Egypt. Doxorubicin and sorafenib served as the standard chemotherapy agents for comparison.

Cells were cultured in 100 mm plates (Sarstedt, Newton, NC, USA) using RPMI-1640 medium (Sigma Co., St. Louis, USA), enriched with 10% Fetal Bovine Serum (GIBCO, UK) and supplemented with antibiotics, specifically penicillin (100 units/ml) and streptomycin (100 µg/ml). The cultures were maintained under controlled conditions, featuring 5% CO_2, a temperature of 37°C, and humidity levels between 90% and 95%. Afterward, cells were transferred to a 96-well plate at a density of 1.0 x 10^4 cells per well and incubated at 37°C for 48 hours in the presence of 5% CO_2 [34].

MTT Assay

The impact of the newly synthesized derivatives (1–12) on breast cancer cells (MCF-7) was evaluated using the MTT assay, and the normal lung fibroblast cell line (WI-38) was used as a representative non-cancerous control, following the methodology outlined in previous studies [35–37]. Following incubation, the cells were treated with varying concentrations of the compounds (1.56, 3.125, 6.25, 12.5, 25, 50, and 100 µM) for 24 hours. After this treatment period, 20 µl of MTT solution (5 mg/mL) was added, and the cells were incubated for an additional 4 hours. 100 µl of DMSO was added to each well to dissolve the purple formazan crystals formed during this incubation. At 570 nm, the absorbance was measured using a plate reader (EXL 800, USA). Cell viability was calculated using the formula:

$$\text{Cell viability (\%)} = \frac{\text{OD sample}}{\text{OD control}} \times 100$$

In Silico Drug-Likeness Prediction

The assessment of drug-likeness for the synthesized compounds (1–12) involved calculating molecular descriptors via the publicly accessible Swiss ADME web server. Furthermore, the evaluation of ADMET properties was conducted using the admetSAR platform.

Molecular Docking Studies

Molecular docking studies were performed using AutoDock Vina version 1.1.2 (released on May 11, 2011) with grid dimension 60*65*65 Ao and coordinate XYZ (12.550, -0.171, 5.000) to insure include all residues in the binding site and specify run parameter as spaces between grid 0.375 Ao, exhaustiveness 32, and number of modes 100. All synthesized compounds were optimized 3D structures using Avogadro software version 1.2.0 and minimization energy under force field MMFF94s and 10,000 steps, and were prepared as ligand using AutoDock Tool version 1.5.7 to assign Gasteiger charge and add non-polar hydrogens and site torsion. Then, saved as a PDBQT file, doxorubicin, which is used as a drug, was prepared using the previous procedure. The crystal structure of the target protein ERα was obtained from the protein data bank repository (https://www.rcsb.org), PDB ID: 4XO6, with a resolution of 1.20 Å (Figure 2). Imported into AutoDock Tool and prepared by removing water molecules and any non-protein residues. The nonpolar hydrogens and Kollman charges were added. prepared protein saved as PDBQT

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format, the command line of AutoDock Vina included ligand and target protein was used to run docking calculations. The docking procedure was validated by re-docking of the co-crystalized ligand with the receptor, calculating a root mean square deviation (RMSD) of the ligand co-crystalized structure and resulting ligand pose of validated docking (1.623 Aº), which falls within the accepted value (< 2 Ao) (Figure 3). The ligand–protein interactions visualization was utilized using BIOVIA Discovery Studio version 24.1.0.

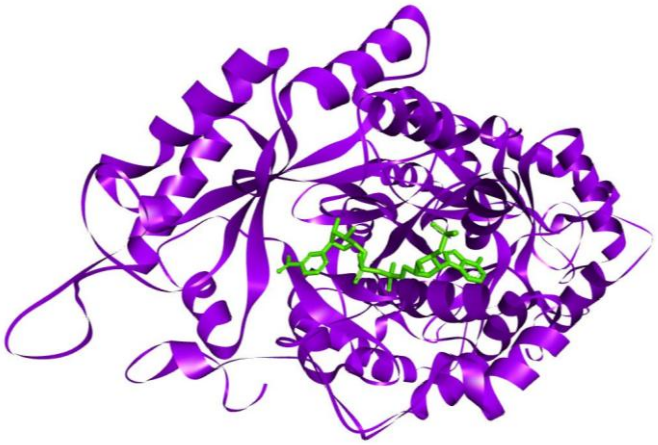

Figure 2. Protein co-crystal structure of protein PDB ID:4XO6.

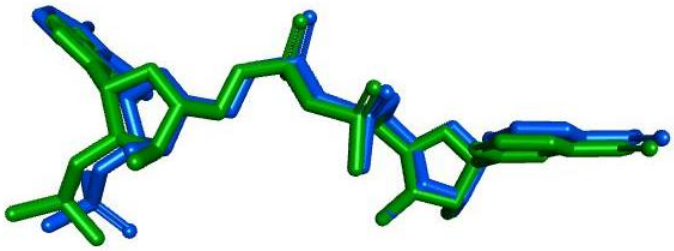

Figure 3. Superposition of re-docked and co-crystalized pose with RMSD value of 1.623 Å (blue= x-ray pose, Green =re-docked pose).

Results

In Vitro Cytotoxic Assay

The cytotoxic effects of twelve newly synthesized 1,3,4-thiadiazole derivatives (compounds 1–12) were assessed using the MTT assay against the MCF-7 cell line, a standard model for in vitro studies. Doxorubicin and sorafenib served as reference drugs, and the normal lung fibroblast cell line (WI-38) was used as a representative non-cancerous control. The IC_{50} values (µM) corresponding to the cytotoxic activity of these derivatives are detailed in (Table 2).

The results demonstrate that all evaluated compounds displayed cytotoxic effects in a concentration-dependent manner against MCF-7 cells, except for compounds 4, 9, and 10, which were found to be non-cytotoxic. Compound 5 demonstrated the strongest anticancer activity, with an IC_{50} value of 17.30 µM. This was followed by compounds 1, 12, and 7, which showed moderate cytotoxic activities with IC50 values of 31.36 µM, 24.53 µM, and 44.05 µM, respectively. In contrast, compounds 2, 3, 6, 8, and 11 demonstrated weak cytotoxic activities, with IC_{50} values of 76.86 µM, 87.94 µM, 74.07 µM, 52.14 µM, and 71.44 µM, respectively. The compound 5 showed cytotoxic activity value IC_{50} = 17.30 µM, which is closest to that of sorafenib (IC_{50} = 7.26 µM), though it was less potent than doxorubicin (IC_{50} = 4.17 µM). Compound 5 showed moderate activity (IC_{50} = 41 µM) against the normal cell line (WI-38). (Figure 4) summarizes the average relative viability of cells (%) for the most potent compounds 1,5 and 12 compared to the reference drugs, doxorubicin and sorafenib, against the human cell line MCF-7. These findings highlight the potential of the newly synthesized 1,3,4-thiadiazole derivatives as candidates for further development in breast cancer therapy, particularly compound 5, which warrants further investigation due to its promising cytotoxic profile.

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Table 2. Cytotoxic activity of synthesized 1,3,4-thiadiazole derivatives against the human cell line MCF-7.

Compound No.	In vitro Cytotoxicity IC_{50} (µM)	
	MCF-7	WI-38
1	31.36±2.0	68.20±3.7
2	76.86±3.8	30.75±1.9
3	87.94±4.4	46.85±2.6
4	>100	60.86±3.5
5	17.30±1.3	41.48±2.4
6	74.07±3.7	39.55±2.2
7	44.05±2.5	>100
8	52.14±3.1	13.18±1.1
9	>100	18.50±1.3
10	>100	>100
11	71.44±3.6	19.69±1.4
12	24.53±1.7	47.39±2.7
Doxorubicin	4.17±0.2	6.72±0.5
Sorafenib	7.26±0.3	10.65±0.8

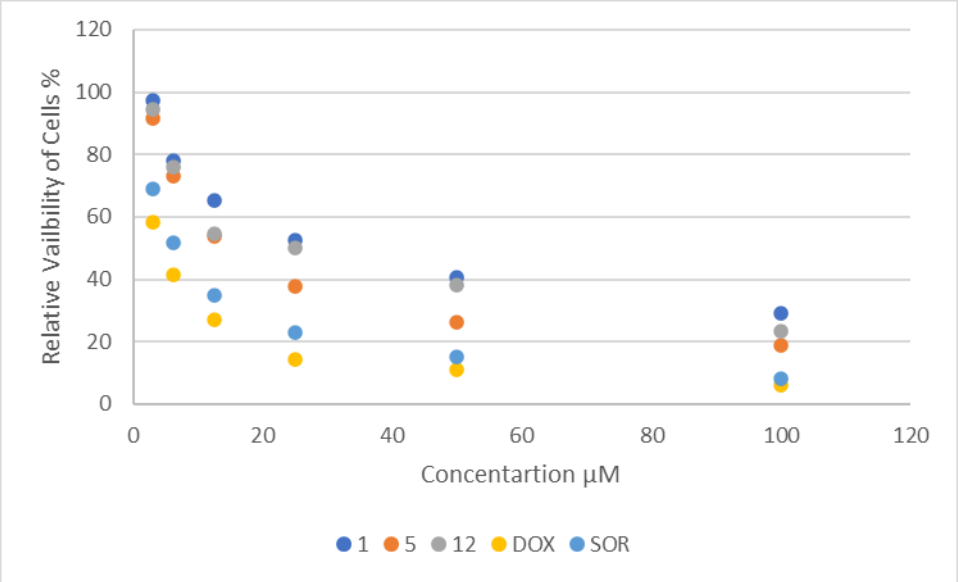

Figure 4. The average of relative viability of cells (%) compounds 1, 5, and 12 with reference drugs doxorubicin and sorafenib against the human cell line MCF-7.

ADMET

The evaluation of drug-likeness acts as a predictive tool to determine if a particular pharmacological agent has properties that make it suitable for use as an orally active medication. This assessment is grounded in the well-established Lipinski's Rule of Five, formulated by Lipinski et al., which predicts molecular characteristics relevant to the pharmacokinetic properties of compounds. As stated in this rule, a compound is expected to demonstrate favorable oral bioavailability if it satisfies the following criteria: cLogP ≤ 5, molecular weight ≤ 500, hydrogen bond acceptors ≤ 10, hydrogen bond donors ≤ 5, and a maximum of 20 rotatable bonds [38]. The results from SwissADME computations indicate that compounds 1–12 comply with Lipinski's Rule of Five without any Infringements. Furthermore, the expected logP values demonstrate optimal lipophilicity, ranging from 4.33 to 8.25 (Table 3). Based on the obtained data, all compounds align with Lipinski's criteria, exhibit high potential for human intestinal absorption, and are unable to penetrate the blood-brain barrier.

In accordance with acquired data, all compounds are appropriate to Lipinski's rule, and this condition supports the classification of compounds 1–12 as drug-like molecules.

ADMET properties for compounds 1–12 was predicted using the admetSAR portal, with the resulting parameters outlined in (Table 4). The findings suggest that all synthesized compounds are appropriate for oral administration. Additionally, each compound shows a considerable level of CYP inhibitory promiscuity. Compounds 1–12 are classified within Category III of toxicity, denoting them as slightly toxic. This category includes substances with LD_{50} values ranging from 500 mg/kg to 5000 mg/kg, and all compounds were determined to be non-carcinogenic according to in silico simulation analyses.

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Table 3. Estimating the molecular descriptors (Lipinski rules of five) for compounds 1–12 by Swissadme.

Compounds	MW [a] g/mol	clog Po/w[b]	RB[c]	HBA[d]	HBD[e]	TPSA[f]	LogS(ESOL)[g]
1	607.7	5.60	6	5	2	12.11	-8.07
2	565.19	4.33	5	7	1	149.97	-7.24
3	581.26	4.91	5	6	1	165.07	-7.73
4	526.2	4.59	6	6	1	117.31	-6.71
5	540.23	4.91	6	6	1	117.31	-7.01
6	510.2	4.62	4	5	1	108.08	-6.51
7	422.16	4.38	4	2	1	94.92	-5.73
8	596.29	6.31	5	5	0	100.99	-8.71
9	645.75	7.24	6	5	1	113.02	−14.62
10	582.31	7.04	4	4	0	83.92	-9.02
11	603.24	5.33	5	7	0	142.88	-8.32
12	720.86	8.25	7	5	1	108.31	-11.11

a: Molecular weight (MW). b: lipophilicity (cLog Po/w). c: number of rotatable bonds (RB). d: number of hydrogen bond acceptor (HBA). e: number of hydrogen bond donors (HBD). f: Topological polar surface area (TPSA). g: estimating aqueous solubility LogS(ESOL).

Table 4. Calculations for the ADMET profile of 1–12.

Compounds	Blood-B.B[a]	HumIn Ab[b]	Caco-2p[c]	CYP Inh Prom[d]	Carcin[e]	AOT[f]	RAT[g]
1	+	+	1.382	High	Non	III	2.3512
2	+	+	1.5185	High	Non	III	2.3704
3	+	+	1.4866	High	Non	III	2.5697
4	+	+	1.1277	High	Non	III	2.388
5	+	+	1.1317	High	Non	III	2.4331
6	+	+	1.5191	High	Non	III	2.355
7	+	+	1.2979	High	Non	III	2.7278
8	+	+	1.599	High	Non	III	2.4438
9	+	+	1.5492	High	Non	III	2.4541
10	+	+	1.4913	High	Non	III	2.4621
11	+	+	1.3067	High	Non	III	2.6209
12	+	+	1.3414	High	Non	III	2.5287

a: Blood-Brain Barrier. b: Human intestinal absorption. c: Caco-2 permeability LogPapp, cm/s. d: CYP inhibitory promiscuity. e: carcinogenicity. f: acute oral toxicity. g: rat acute toxicity LD50 mol/kg.

Molecular docking studies

Molecular docking was implemented for synthesized compounds and doxorubicin, which is an FDA-approved drug [39], to ascertain the most stable ligand-protein complex based on the binding energy [40]. The interactions of synthesized compounds and receptor ERα (PDB ID: 4XO6) and doxorubicin with the same receptor are summarized in (Table 5).

Except for Compound 2, the synthesized compounds exhibited binding energies in the range of −7.9 to −12.4 kcal/mol, which were higher than that of the reference drug doxorubicin (−7.8 kcal/mol), by analyses the docked compounds interactions with receptor, doxorubicin drug had shown two hydrogen bonds with GLU127 and TYR24 and another hydrophobic interaction with TRP86, ILE129, TRP227, LEU308 and PHE311 residues (Figure 5a and 5b). The synthesized compounds were split into two sets: the first set from compounds 1-6, which included Moieties (dibromophenol and thiadiazole), the second set formed hydrogen bonds with TYR24 and TYR55 amino acids, except compound 4, which didn't bind with TYR55. Compound 1 exhibited two additional hydrogen bonds with SER166 and SER217 amino acid residues, and two additional Pi-Sulfur interactions between the S atom in the thiadiazol ring and TYR24 and HIS222 residues, which increase the affinity of the ligand with the backbone (Figure 6a and 6b). Compounds 2 and 4 demonstrated another binding with VAL54, and additional Pi-Sulfur interaction with TYR24 was exhibited by compound 4. Additionally, compounds 3 and 5 showed an extra hydrogen bond with HIS117; furthermore, compound 5 exhibited three additional Pi-Sulfur interactions with TYR55, HIS117, and TYR216 (Figure 7a and 7b). Compound 6 demonstrated a hydrogen bond with the ASN167 residue and the Br atom in the dibromophenol moiety, which serves as an electron acceptor during the formation of the hydrogen bond.

The second set of compounds 7-12 which have Moieties (dibromo substituted benzofuran and thiadiazole), compound 7 which not include thiadiazole moiety exhibited two hydrogen bonds with TYR55 and HIS117

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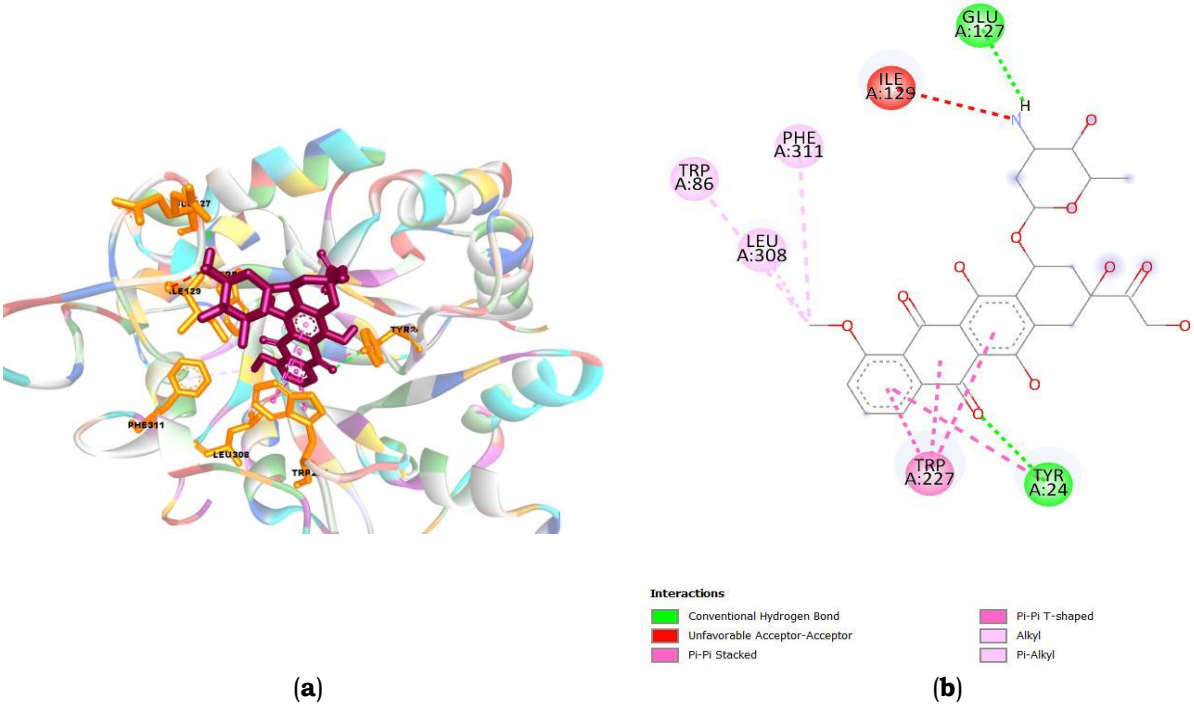
amino acid residues and the rest of compounds exhibited significant binding energies (-8.2 to -12.4 kcal/mol) exhibited different interactions as compound 8 showed one hydrogen bond with TYR24 residue and two Pi-Sulfur interactions with TYR25 and HIS117, compound 9 exhibited two hydrogen bonds with GLY22 and SER217 and also additional electrostatic interaction with LYS270, compound 10 was interacted with LYS270 to formed two hydrogen bonds and additional hydrogen bond with TYR55 also two Pi-Sulfur interactions observed with TYR24 and HIS222, compound 11 exhibited three backbone conventional hydrogen bonds with TYR24,HIS22 and TYR55 and additional hydrogen bond between Br atom in benzofuran moiety and GLN190 amino acid residue, compound 12 which showed the highest binding energy (-12.4 kcal/mol) and exhibfited greatly interactions with four a hydrogen bonds with SER166,SER217,TYR55 and LYS270 residues and extra two Pi-Sulfur interactions with TYR24 and HIS222 (Figure 8a and 8b).

With respect to the MTT assay, compound 12 exhibited the highest binding energy (-12.4 kcal/mol) and moderate cytotoxic value, IC_{50}=24.53 µM. To further understand this phenomenon, studies such as molecular dynamics (MD) simulation should be performed to examine ligand-protein complex stability.

Table 5. Molecular interaction of synthesized 1,3,4-thiadiazole derivatives against MCF-7 protein PDB ID:4XO6.

Compound No.	Binding energy (Kcal/mol)	No. of hydrogen bonds	Residues involved in hydrogen bonding (bond length in Å)
1	-10.30	4	SER166 (2.6), SER217(3.0), TYR24(3.7), TYR55(3.4)
2	-7.4	3	VAL54(2.4), TYR24(3.1), TYR55(4.0)
3	-8.8	3	TYR24(2.8), HIS117(3.7), TYR55(4.1)
4	-8.9	2	VAL54(3.4), TYR24(3.4)
5	-9.0	3	HIS117(3.8), TYR24(3.9), TYR55(4.1)
6	-8.8	3	TYR24(3.0), TYR55(4.1), ASN167(3.3)
7	-7.9	2	HIS117(2.6), TYR55(3.0)
8	-10.50	1	TYR24(3.3)
9	-10.6	2	GLY22(3.3), SER217(4.0)
10	-10.6	3	LYS270(3.2), TYR55(3.9), LYS270(4.0)
11	-9.1	4	TYR24(2.8), HIS222(3.3), GLN190(3.1), TYR55(3.4)
12	-12.4	4	SER166(3.0), SER217(3.3), TYR55(4.0), LYS270(3.8)
Doxorubicin	-7.8	2	GLU127(2.0), TYR24(2.6)



(**a**) (**b**)

Figure 5. Representation binding mode of standard drug Doxorubicin in the active site of protein (PDB ID:4xo6): (a) 3D diagram of interactions of standard drug Doxorubicin with the active site of protein; (b) 2D diagram of interactions of standard drug Doxorubicin with amino acid residues

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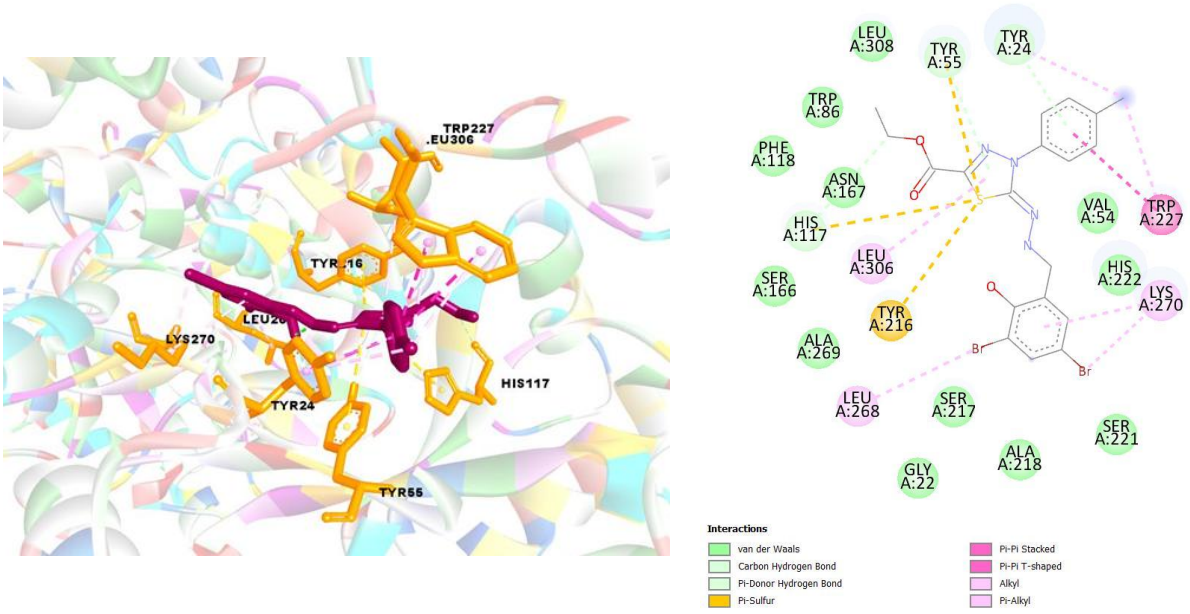
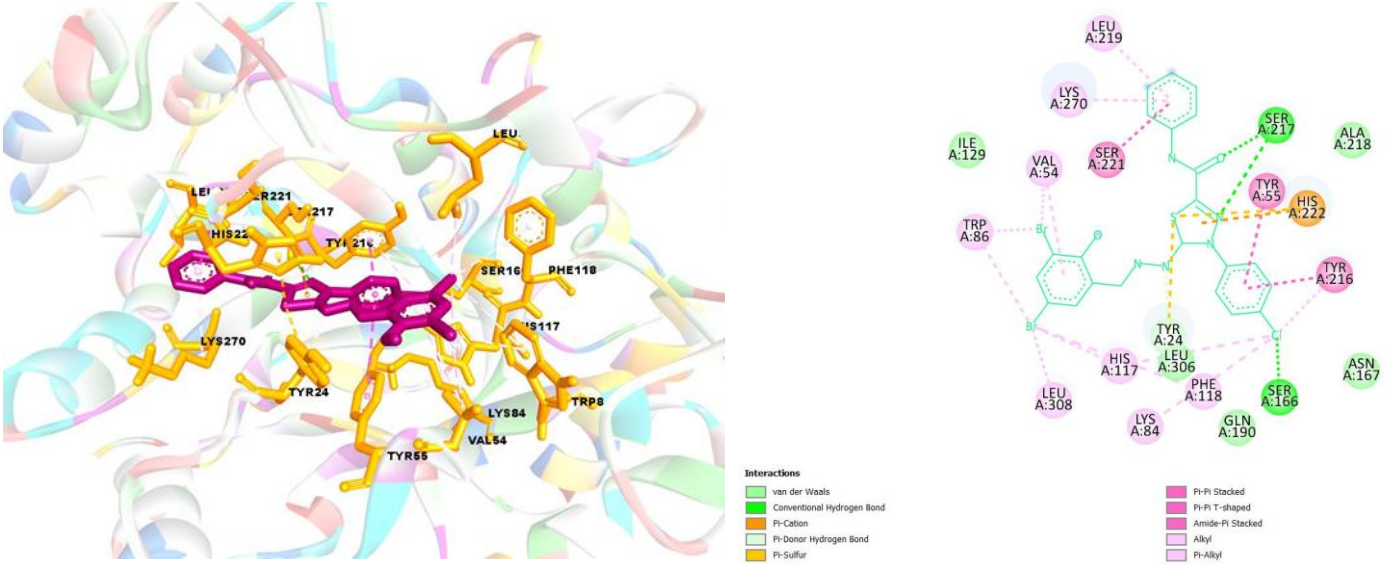


(**a**) (**b**)

Figure 6. Representation binding mode of compound1 in active site of protein (PDB ID:4xo6): (a) 3D diagram of interactions of compound1 with active site of protein; (b) 2D diagram of interactions of compound1 with amino acid residues



(**a**) (**b**)

Figure 7. Representation binding mode of compound 5 in the active site of protein (PDB ID:4xo6): (a) 3D diagram of interactions of compound 5 with the active site of protein; (b) 2D diagram of interactions of compound 5 with amino acid residues

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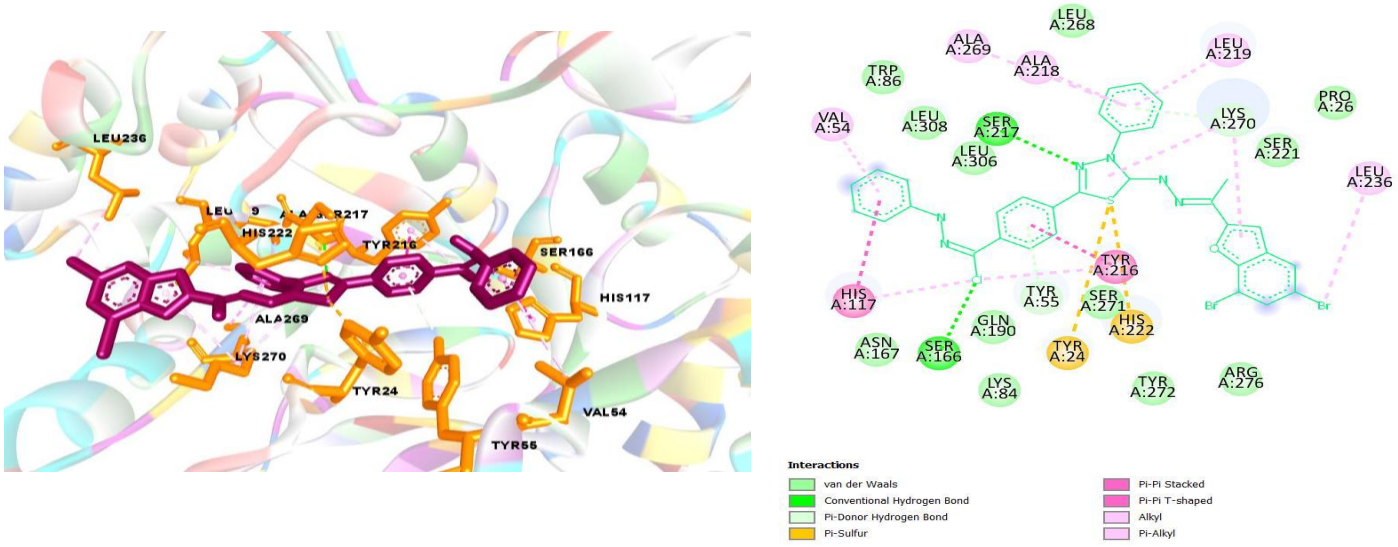

(**a**) (**b**)

Figure 8. Representation binding mode of compound 12 in the active site of protein (PDB ID:4xo6): (a) 3D diagram of interactions of compound 12 with the active site of protein; (b) 2D diagram of interactions of compound 12 with amino acid residues

Conclusion

The newly synthesized 1,3,4-thiadiazole derivatives displayed a range of cytotoxic effects against the MCF-7 cell line, with compounds 4, 9, and 10 demonstrating no cytotoxicity. Compound 5 emerged as the most potent, achieving an IC_{50} value of 17.30 µM. Following it, compounds 1, 7, and 12 exhibited moderate cytotoxic activities, recorded at IC_{50} values of 31.36 µM, 44 .05 µM, and 24.53 µM, respectively. Conversely, compounds 2, 3, 6, 8, and 11 reflected weaker cytotoxic responses. Apart from compounds 8 and 9, the synthesized derivatives broadly demonstrated minimal cytotoxicity against regular cell lines (WI-38). In silico evaluations confirmed that all compounds adhere to Lipinski's Rule of Five, while their ADMET profiles indicate that they are right for oral administration.

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Conflicts of Interest

The authors declare no conflicts of interest.

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