

# Synthesis, Molecular Docking Studies and Anticancer Activity of 1,3,4-Oxadiazole-3(2H)-thione Derivatives

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## Abstract

*1,3,4-oxadiazole derivatives are recognized to possess various biological activities as antiparasitic, antifungal, antimicrobial and antiproliferative. The present work reports the synthesis of four new derivatives under microwave irradiation with the purpose of developing new drugs that present high specificity for tumor cells and low toxicity to the organism. All the newly synthesized compounds 3a-d were further evaluated for anticancer activity against MCF-7 cell lines using MTT assay and compound code 3c could be considered as possible hit as therapeutic agents. The study draws a very good relationship in-silico and in-vitro anticancer activity and the antitumor potential of the cytotoxic compounds.*

**Key words:** *1,3,4-oxadiazole, microwave irradiation, MTT assay, anticancer activity.*

## 1. INTRODUCTION

Cancer is one of the deadlier diseases that accounts for millions of death every year. In 2016, it is estimated that 1,685,210 new cases are diagnosed with cancer and it caused death of 595,690 people in US alone<sup>1</sup>. There are different types of cancer such as, leukemia, melanoma, non-Hodgkin lymphoma, breast cancer, thyroid cancer, lung and bronchus cancer, kidney and renal pelvis cancer, etc., which may all ultimately lead to death. The widely used chemical and radiation therapies are not only ineffective in advanced stages, but also creates additional side effects to the patients. Hence, much efforts are required to develop alternate therapeutic strategies which could effectively treat the disease with no or minimum side effects<sup>2</sup>. A bulk of pharmaceuticals and biologically active compounds are heterocyclic in nature. A remarkable structural feature intrinsic to heterocycles, which continue to be exploited to great benefit by the drug industry, lies in their ability to manifest substituents around a core scaffold<sup>3-4</sup>. Microwave assisted organic synthesis has as a new “lead” in the organic synthesis. The technique offers clean, simple, efficient, fast and economic for the synthesis of a number of organic molecules such reaction has

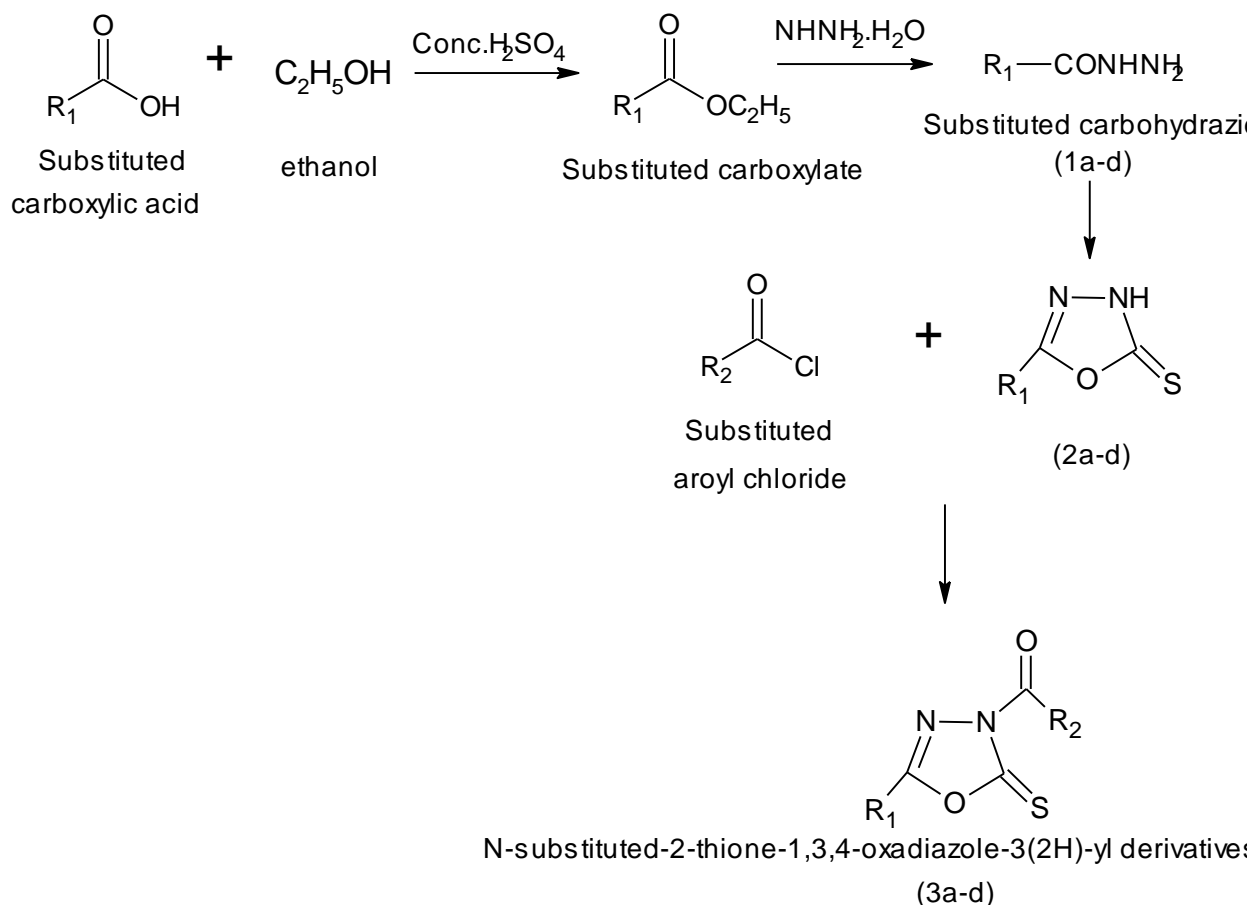
new tool in the organic synthesis<sup>5</sup>. Conventional method of organic synthesis usually requires longer heating time, tedious apparatus setup which result in higher cost of process and the excessive use of solvents or reagents lead to environmental pollution. This technique is considered as important approach toward green chemistry because this technique is more environments friendly and this technology is used in the laboratory and has the potential to have a large impact on the fields of combinatorial chemistry<sup>6-12</sup>. The microwave reactions were performed using microwave assisted synthesis on microwave, the reactions were worked up extensively to obtain a pure form of product which was isolated using literature work-up procedures. This technique is considered as important approach toward green chemistry because this technique is more environments friendly and this technology is used in the laboratory and has the potential to have a large impact on the fields of combinatorial chemistry, screening, medicinal chemistry and drug development<sup>13-20</sup>. Conventional method of organic synthesis usually requires longer heating time, tedious apparatus setup which result in higher cost of process and the excessive use of solvents or reagents lead to environmental pollution<sup>8</sup>. Growth of green chemistry holds necessary potential for the reduction of by product, a reduction in the waste production and a lowering of energy costs<sup>21-26</sup>. Molecular docking is an attractive scaffold to understand drug biomolecular interactions for the rational drug design and discovery, as well as in the mechanistic study by placing a molecule (ligand) into the preferred binding site of the target specific region of the DNA/protein (receptor) mainly in a non-covalent fashion to form a stable complex of potential efficacy and more specificity. The information obtained from the docking technique can be used to suggest the binding energy, free energy and stability of complexes. At present, docking technique is utilized to predict the tentative binding parameters of ligand-receptor complex. In the current study in-silico molecular docking was studied docking tools, VLifeMDS software were used to identify which docking method works better with the target proteins. Here we present synthesis, characterization and anticancer and briefly present results from the docking and screening experiments. In the discovery of effective medicines for prevention and treatment, an outbreak of coronavirus disease (COVID-19) caused by the novel extreme acute respiratory syndrome coronavirus-2 (SARS-CoV-2) poses an unprecedented obstacle. Given the rapid pace of scientific research and clinical data provided by the large number of people who are rapidly infected with SARS-CoV-2, clinicians need reliable evidence of good medical care for this infection, as it is simple to do in-silico analysis in the initial stage with the aid of molecular docking software with help of chemical structure of compound<sup>7</sup>. It is necessary to enhance both enzymatic stability and membrane permeation in the formulating drug delivery system for protein and peptide drugs<sup>27-28</sup>. Soon, someday, you might be making your own drugs at home. That is because researchers have adapted a 3D printer from basic, readily available medicinal active agents fed into a drug delivery system. Due to the high impact of multidrug resistant and

extensively drug-resistant treatment, there is an urgent need for new drugs to treat this disease efficiently. Hence, there is emerging demand for the development of new anticancer agents<sup>29-33</sup>.

## 2. MATERIALS AND METHODS

### Chemistry:

All chemicals and solvents were procured from commercial sources, purified and dried using standard procedures from literature whenever required the reagents were purchased from S.D fine, Research laboratory Mumbai and MARCK laboratory Mumbai, and purchased from store department of Rajarambapu College of Pharmacy, Kasegaon. The melting points ( $^{\circ}\text{C}$ ) of synthesized compound were determined in open capillary tube method and are uncorrected. Thin layer chromatography was used confirmation of reaction and the purity of the intermediate and the final compounds by applying a single spot on TLC plate (silica gel G) using various solvents such as toluene, acetone, ethanol system. TLC plates were visualized under iodine chamber.



Where,

R<sub>1</sub> = p-nitrobenzoic acid

R<sub>2</sub> = 4-methoxy benzoyl chloride

2,4-dichloro benzoyl chloride

4-fluoro benzoyl chloride

4-nitro benzoyl chloride

**Scheme 1:** *Synthetic route for the preparation of the title compound (3a-d)*

### ***General Procedure for the Synthesis of substituted carboxylate***

Substituted benzoic acid (0.01 mol) added in absolute ethanol (0.1 mol) and refluxed in the presence of sulphuric acid (2-3 mL) for 10 to 15 min at 340 watt. After completion of reaction, the reaction mixture was poured into ice-cold water; the oily layer that deposited was extracted with diethyl ether and on evaporation of solvent yielded pure liquid mass, After completion of reaction was checked by TLC.

### ***General Procedure for the Synthesis of substituted carbohydrazide***

A mixture of substituted carboxylate and hydrazine hydrate (0.02 mol) was refluxed in ethanol (25 mL) for 10 to 15 min at 340 watt. After the completion of reaction it was cooled and poured into crushed ice; the solid thus obtained was filtered off, washed with water and recrystallized from ethanol after completion of reaction checked by TLC.

### ***General Procedure for the Synthesis of 1,3,4 oxadiazole-2(3H)-thione***

To a solution containing absolute ethanol (5 mL) and KOH (0.01 mol) was added substituted carbohydrazide (0.01 mol) followed by carbon disulphide (1.5 mol). The reaction mixture was heated under reflux for 10 to 15 min at 340 watt. till the release of hydrogen sulphide gas ceased. After decantation, the supernatant solution was evaporated, diluted with water and acidified with hydrochloric acid. The reaction mixture was allowed to stand at room temperature for 30 min; a solid so obtained was filtered, washed with water and recrystallized from ethanol

### General Procedure for the Synthesis of *N*-substituted 2-thione-1,3,4-Oxadiazole-3(2*H*)-yl derivatives

Take substituted 1,3,4-oxadiazole-2(3*H*)-thione (0.01 mol) and aroyl chloride(0.01 mol) was refluxed for 10 to 15 min at 340 watt. After completion of reaction checked by TLC. The solid product was washed with water and purified by washing with ethanol.

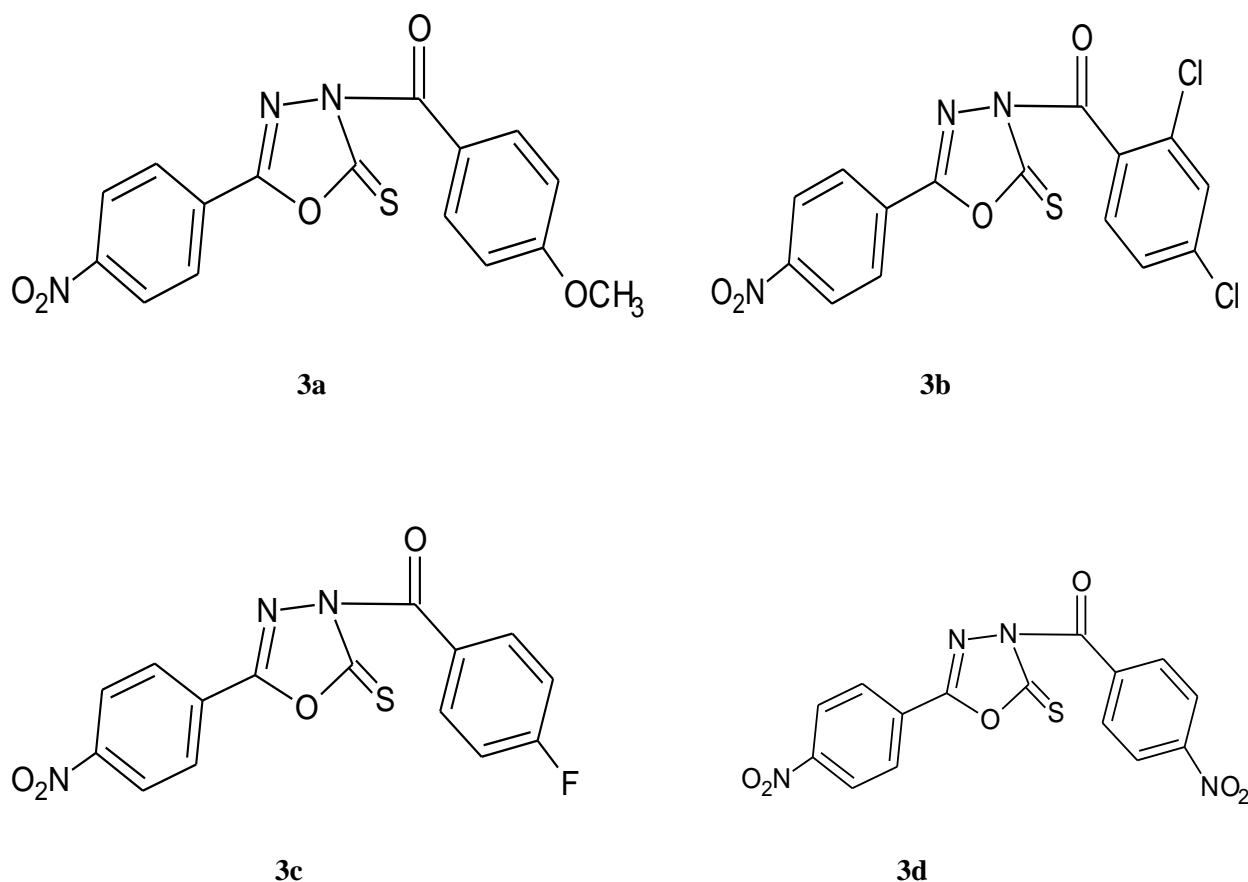


Figure 1. Representative 1,3,4-oxadiazole derivatives as anticancer agents

### Molecular Docking Studies:

All Molecular docking were performed using the molecular modeling software (VLifeMDS) version 4.3. It provided a facility to dock different ligands in protein binding sites chosen by the user. VLifeMDS has provided rigid (no torsional flexibility for a protein as well as a ligand) and flexible (torsional flexibility to a ligand with a rigid protein) docking of the molecules. The target or receptor was either experimentally known or theoretically generated through homology modelling or knowledge-based protein modeling. The molecular docking tool has been developed to obtain a preferred geometry of

interaction of ligand–receptor complexes having minimum interaction energy based on different scoring functions viz. only the dock score, electrostatics and the sum of steric and electrostatic (parameters from the force field). This utility allowed us to screen a set of compounds for the purpose of lead optimization. VLifeMDS uses the Piecewise Linear Pair Wise Potential (PLP), genetic algorithm and Grid algorithms to minimize the interaction energy between the ligand and receptor protein. BioPredicta produces least of inaccurate poses and 85% of binding models from native co-crystallized structure. The docking studies were carried out using The crystal structure potent inhibitors of NUDT5 silence hormone signaling in breast. Ligand preparation 2D structure of 1,3,4-oxadiazole derivatives was drawn using chemsketch software. All structures were cleaned and 3D optimized. All the 3D structures were optimized using Merck molecular force field (MMFF) with distance dependent dielectric function and energy gradient of 0.01 kcal/mol Å with 10000 numbers of cycles. The conformers for all structures were generated and the low energy conformer for each compound was selected and used for further study. The VLifeMDS 4.3 BioPredicta tool was used to evaluate the binding free energy of the inhibitors against the 5NQR receptor to gain insight into the binding modes of 1,3,4-oxadiazole<sup>34-38</sup>.

### ***Selection and preparation of ligands and target protein crystal structures***

The ligands (1,3,4-thiadiazole) were studied for their binding activities. The 2D structures of were drawn using chemsketch software and converted to 3D conformations. The conformers thus obtained, were optimized (MMFF) till they reached a rms gradient energy of 0.001 kcal/mol. Å The crystal structure potent inhibitors of NUDT5 silence hormone signaling in breast (PDB Code-5NQR) from the RCSB Protein Data Bank. All bound water molecules and ligands were removed from the proteins and polar hydrogens were added. The protein structure was energy minimized using Merck molecular force field (MMFF)] with distance dependent dielectric function and energy gradient of 0.01 kcal/mol Å with 10000 numbers of cycles<sup>39-45</sup>.

### ***Identification of cavities***

The cavities in the receptor were mapped to assign an appropriate active site. The basic features used to map the cavities were the surface mapping of the receptor and identifying the geometric voids as well as scaling the void for its hydrophobic characteristics using VLife MDS analyze tool. Hence all the cavities that are present in receptor are identified and ranked based on their size and hydrophobic surface area<sup>46-48</sup>.

### ***Run of docking study***

The genetic algorithm (GA) docking of the conformers of each was done by positioning with the active site of cavity using V Life MDS 4.3 package following the standard operating procedures. The complexes

were energy minimized using the MMFF method, till they reached an rms gradient of 0.1 kcal/mol. The binding energy in kcal/mol or the ligand–receptor interaction energy obtained after docking the ligands into the enzyme active site can be defined as:

$$E = \text{InterEq} + \text{InterEvdW} + \text{IntraEq} + \text{IntravdW} + \text{IntraEtor}$$

Where,

InterEq= Intermolecular electrostatic energy of complex;

InterEvdW= Intermolecular vdW energy of complex;

IntraEq= Intramolecular electrostatic energy of ligand;

IntraEvdW= Intramolecular vdW energy of ligand and

IntraEtor= Intramolecular torsion energy of ligand

The conformers for all structures were generated and the low energy conformer for each compound was selected and used for further study<sup>49-50</sup>.

## **Anticancer Evaluation:**

### ***MTT assay and Anti proliferative activity***

The in-vitro anti-proliferative activity was carried out on three human carcinoma cell lines namely MCF-7. All the cell lines were grown in DMEM-HG supplemented with 10% heat-inactivated FBS, 2% Penicillin-Streptomycin and 2.5 µg/mL Amphotericin-B solutions. Cell lines were incubated at 37°C in a humidified atmosphere of 95% air, 5% CO<sub>2</sub>. Following 24-48 hrs. of incubation period, the adherent cells were detached using Trypsin-EDTA solution. Cell count was determined using the Luna automated cell counter based on trypan blue dye exclusion method. Cytotoxicity of the novel oxadiazole derivatives have been determined using MTT 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay.

### ***Cell Viability Assay (MTT Assay)***

200µL cell suspension was seeded in 96-well microplates at a density of 25,000 cells/well and incubated for 24hrs, all cells were seeded in duplicates with novel compounds 3a-3f having range of concentrations from 50µM-500µM, incubated in a CO<sub>2</sub> incubator at 37°C. Treated cells were thereafter incubated with 10% MTT (5mg/ml) for 3 hrs. The culture medium was then aspirated and 200µL dimethyl sulfoxide

(DMSO; Sigma-Aldrich, India) was added. 5-Fluorouracil (5-FU) was used as standard. Cell viability was determined by measuring the absorbance on a microplate reader at 570nm. Cell viability was calculated as a percentage of viable cells at different test concentrations relative to the control (5-FU) cells [% cell viability = (A570 of treated cells / A570 of control cells)  $\times$  100%]<sup>51-53</sup>.

### 3. RESULTS AND DISCUSSION

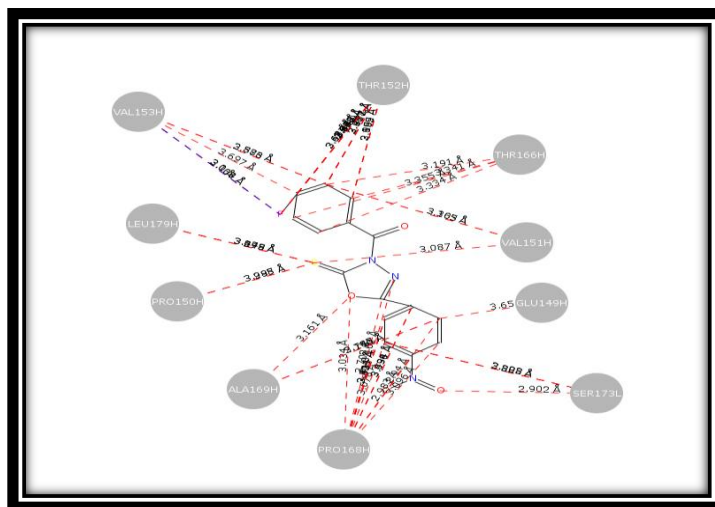
#### *Chemistry*

Substituted carboxylate was prepared by adding solution of an appropriate aromatic acid in absolute ethanol was irradiated in the presence of sulphuric acid for 10 to 15 min at 340 watt. After completion of reaction, the reaction mixture was poured into ice-cold water; the oily layer that deposited was extracted with diethyl ether and on evaporation of solvent yielded pure liquid mass, After completion of reaction checked by TLC. Then substituted carbohydrazide synthesized by adding mixture of substituted carboxylate and hydrazine hydrate was irradiated in microwave by adding in ethanol for 10 to 15 min at 340 watt. After the completion of reaction it was cooled and poured into crushed ice; the solid thus obtained was filtered off, washed with water and recrystallized from ethanol after completion of reaction checked by TLC. In next step, 1,3,4-oxadiazole-2(3H)-Thione was synthesized by adding solution containing absolute ethanol and KOH was added substituted carbohydrazide followed by carbon disulphide. The reaction mixture was irradiated for 10 to 15 min at 340 watt till the release of hydrogen sulphide gas ceased. After decantation, the supernatant solution was evaporated, diluted with water and acidified with hydrochloric acid. The reaction mixture was allowed to stand at room temperature for 30 min; a solid so obtained was filtered, washed with water and recrystallized from ethanol. In next step, for Synthesis of N-substituted 2-thione-1,3,4-oxadiazole-3(2H)-yl derivatives substituted 1,3,4 oxadiazole-2(3H)-thione and aroyl chloride was irradiated for 10 to 15 min at 340 watt. after completion of reaction checked by TLC. The solid product was washed with water and purified by washing with absolute ethanol. The reaction sequence is shown in Scheme 1. Microwave assisted synthesis is faster, better and safer green chemistry approach for the traditional reactions. The time taken for the synthesis of 1,3,4-oxadiazole is drastically reduced by the microwave assisted synthesis. This technique offers clean, simple, efficient, fast and economic for the synthesis of a number of organic molecules such reaction has new tool in the organic synthesis and highly accelerated rate of the reaction time with an improvement in yield and quality of product.

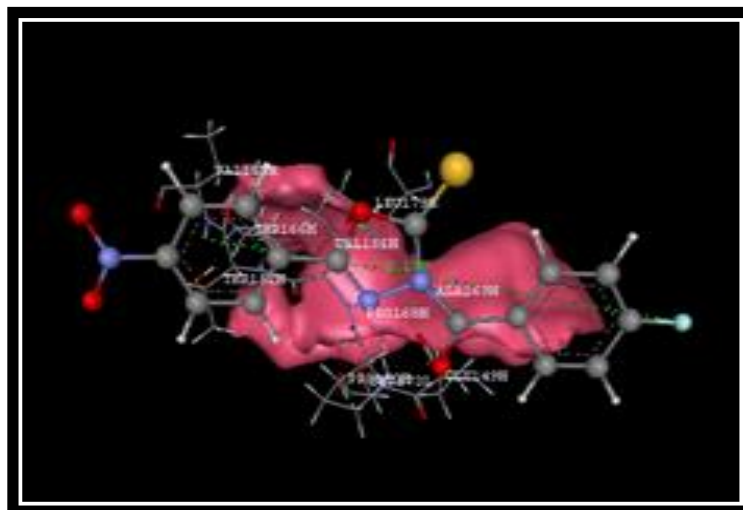


### *Molecular docking study*

The synthesized derivatives 3a-d were evaluated for their antitumor activity against MCF-7 (breast cancer cell line). The dock score of compound 3a-d has shown in table and in that compound 3c dock score found is -52.71 shown minimum dock score than other compounds. As we compared result of compound 3c to the literature this docking score indicate that the designed compounds have good binding affinity for binding to receptor potent inhibitors of NUDTs silence hormone signaling in breast cancer (PDB Code- 5NQR). The best pose obtained by docking results is reported (fig 3) where main interaction between ligand and receptor can be observed. All designed compound adopt a very similar conformation at binding pocket, showing Hydrogen bond interaction with amino acid of VAL153H, Vander Waals binding with amino acid of SER173L, GLU149H, PRO150H, VAL151H, THR152H, PRO168H, LEU179H, ALA169H Which shown by 2D representation diagram (fig 2). Superimpose image of compound 3c with receptor show in diagram (fig 4). The dock score of standard drug 5-fluorouracil was found be -53.65.



**Figure 2:** 2D Representation of Docking Poses of Compound 3c



**Figure 3:** 3D Representation of Docking Poses of Compound 3c



**Figure 4:** Superimpose Image Representation of Docking Poses of Compound 3c

**Table 1:** Anticancer activity result of molecular docking studies by using GRIP batch docking

Sr. no	Compound code	Docking score (Kcal/mol)
1	3a	-44.30
2	3b	-47.59
3	3c	-52.71
4	3d	-45.72
5	5-Fluorouracil	-53.65

### *Anticancer activity*

The synthesized substituted 1,3,4-oxadiazole-2-(3H)-thione (3a-d) were evaluated their anticancer activity on MCF-7 cell lines (50 $\mu$ M-500 $\mu$ M) in order to obtain the effective concentration at 50% of the inhibited cells. The results are expressed as 50% of the total available cells inhibited after 72 hr. of incubation. The compound code 3c showed good cytotoxicity having IC<sub>50</sub> of 5.2  $\mu$ M on MCF-7 cell lines respectively. The results of the MTT assay of these compounds were compared with the results of the standard 5-fluorouracil.

**Table 2:** IC<sub>50</sub> values of the novel of 1,3,4-oxadiazole derivatives for anticancer activity.

Sr. no	Compound code	IC <sub>50</sub> values of 1,3,4-oxadiazole in $\mu$ M
		MCF-7
1	3a	59.21
2	3b	25.14
3	3c	5.2
4	3d	18.9
5	5-fluorouracil	11.4

#### 4. CONCLUSION

The properties of 1,3,4-oxadiazole for anticancer have been tested by IC<sub>50</sub> values estimation. Through this analysis, it can be inferred that oxadiazole compounds may theoretically be transformed into effective anticancer agents that can enable future researchers to synthesize a collection of oxadiazole derivatives comprising a broad range of substituents in order to obtain new heterocyclic systems with enhanced anticancer action. More studies to develop and check related substances for wide variety of biological behavior. All the synthesized derivatives of novel series were synthesized by microwave method. Synthesis of compounds by the microwave method gives more yield and requires less time to complete the reaction. So, the microwave synthesis better method. All the synthesized subjected for anticancer activity among all, the compound code 3c had significant anticancer activity. Electron with drawing groups seemed to be necessary factors in providing higher anticancer activity.

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