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Original Article

Synthesis, Characterization, and Preliminary Evaluation of Ferulic Acid Derivatives Containing Heterocyclic Moiety

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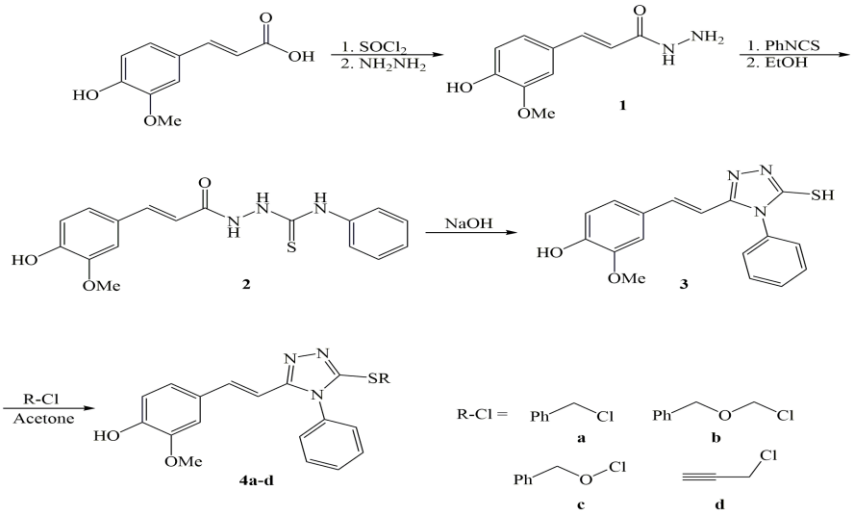
ABSTRACT

This study aimed to synthesize new ferulic acid derivatives through preparing new compounds containing a heterocyclic group that are expected to be biologically effective for diagnosis and studying pharmacological efficacy through these groups. These new compounds are primarily screened (*in vitro*) for their cytotoxic activity against human lung (A549) and breast (MCF-7) cancer cell line, ^{1}H-NMR, ^{13}C-NMR spectroscopy, and FT-IR spectra. Pharm kinetic study by Swiss ADME suite was examined, utilizing molecular docking software (GOLD suite v. 5.7.1), the selectivity for EGFR and ER-receptors, cytotoxicity evaluation tested compounds *in vitro* IC_{50} showed compounds (4a and 4b) are more active anticancer (478.32 and 561.12 µg/mL), respectively than reference erlotinib (582.73), while the compounds **4a**, **4b**, and **4c**, respectively is the more active anticancer than standard tamoxifen (392.3 µg/mL).

GRAPHICAL ABSTRACT



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Introduction

Cancer can be definitely situated by means of the hysterical production of irregular cells in every portion of the body. These atypical cells are mentioned as malignancy cells, tumor cells, or cancer cells. The process of sarcoma cells departure one physical location and rising in another location which called metastasis [1].

Natural plant products have sparked a lot of awareness in the avoidance and cure of prolonged illnesses and normal founded compounds have been for a long time utilized equally medications or drug indications, whether on an experimental or rational basis [2].

Ferulic acid has anti-cancer properties, mostly in vitro and in vivo research condition. It scavenges free radicals, controls cell growing, and spread. Cytoprotective enzymes are promoted and cytotoxic systems are inhibited [3].

Triazole products own a great importance in therapeutic attraction and many heterocyclic triazole chain compounds consuming several biological processes. Triazole is a five-membered basic chemical with the molecular formula $C_2H_3N_3$ that contains two carbon and three nitrogen atoms. It forms a pair of isomers [4, 5].

The 1-2-3 triazole remains measured to be the most constant compound in relationship to other complexes having three neighboring N atoms. Triazole derivatives have an extensive variety of medicinal actions; for example, antifungal, antibacterial, antiviral, antitumor, anti-convulsant, anti-neuropathic, and others [6]. Therefore, new synthesized compound uses ferulic acid as a starting material with heterocyclic moiety and evaluate the cytotoxicity by MTT assay method.

Materials and Methods

2-Chloroacetaphenone, Benzoyl chloride, Propagyl chloride, Ferulic acid, Hyperchem China, Benzyl bromide, Thionyl chloride, CDH India, Phenylisothiocyanate Sigma Aldrich Germany, Sodium hydroxide pellets Spectrum USA. The equipment used in the work are electrical melting point apparatus Stuart UK, FT-IR spectrophotometer 8400s Shimadzu-Bruker Japan, ^{1}H-NMR Jeol-Bruker USA, and ^{13}C-NMR Jeol-Bruker USA.

Chemical synthesis

Scheme 1 shows the Synthesis of ferulic acid derivatives.

*General synthesis of 4 new ferulic acid derivatives (**4a-d**) in the same procedure*

The solution of benzyl/benzoyl/phenacyl/propagyl chloride (0.005 mol) was stirred in acetone (10 mL), and then it was added to the solution of (E)-4-(2-(5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)vinyl)-2-methylphenol (0.96 g, 0.005 mol) in 40 mL acetone containing triethylamine (1.39 mL, and 0.010 mol). The mixture was stirred for 30 hours at 25 °C. After that, it was vaporized under vacuum, and water was added to the precipitate, and then the product compound (**4a-d**) was obtained by filtration [7].

*(E)-4-(2-(5-(benzylthio)-4-phenyl-4H-1,2,4-triazol-3-yl)vinyl)-2-methylphenol (**4a**)*

Yellow green, mp 160-165 °C, yield 50%, IR (KBr) (ν_{max}/ cm^{-1}): 3301 (O-H phenol), 3024 (C-H aromatic ring), 1631 (C=N), 1516-1593 (C=C aromatic ring), 1213 (C-O-CH_3), 1070 (C-S). ^{1}H-NMR (600 MHz, DMSO): δ 3.70 (3H, CH_3 methoxy), 4.39 (2H-Ar ring), 6.35 (1H, CH=CH α, β unsaturated carbonyl), 6.53-755 (13H-Ar ring), 6.82 (1H, CH=CH unsaturated next to aromatic ring), 9.40 (1H, OH phenolic). ^{13}C-NMR (150 MHz, DMSO): δ 39.9 (1C, Ar ring), 56.2 (3C, CH_3 of methoxy group), 108 (1C, CH=CH α, β unsaturated carbonyl), 121-130 (6C, Ar ring), 133.5 1C, CH=CH α, β unsaturated carbonyl), 128-137, (6C-Ar ring), 148.4 (1C ,C-triazole), 111-148.7, (6C, Ar ring), 154.1 (1C, C-S).

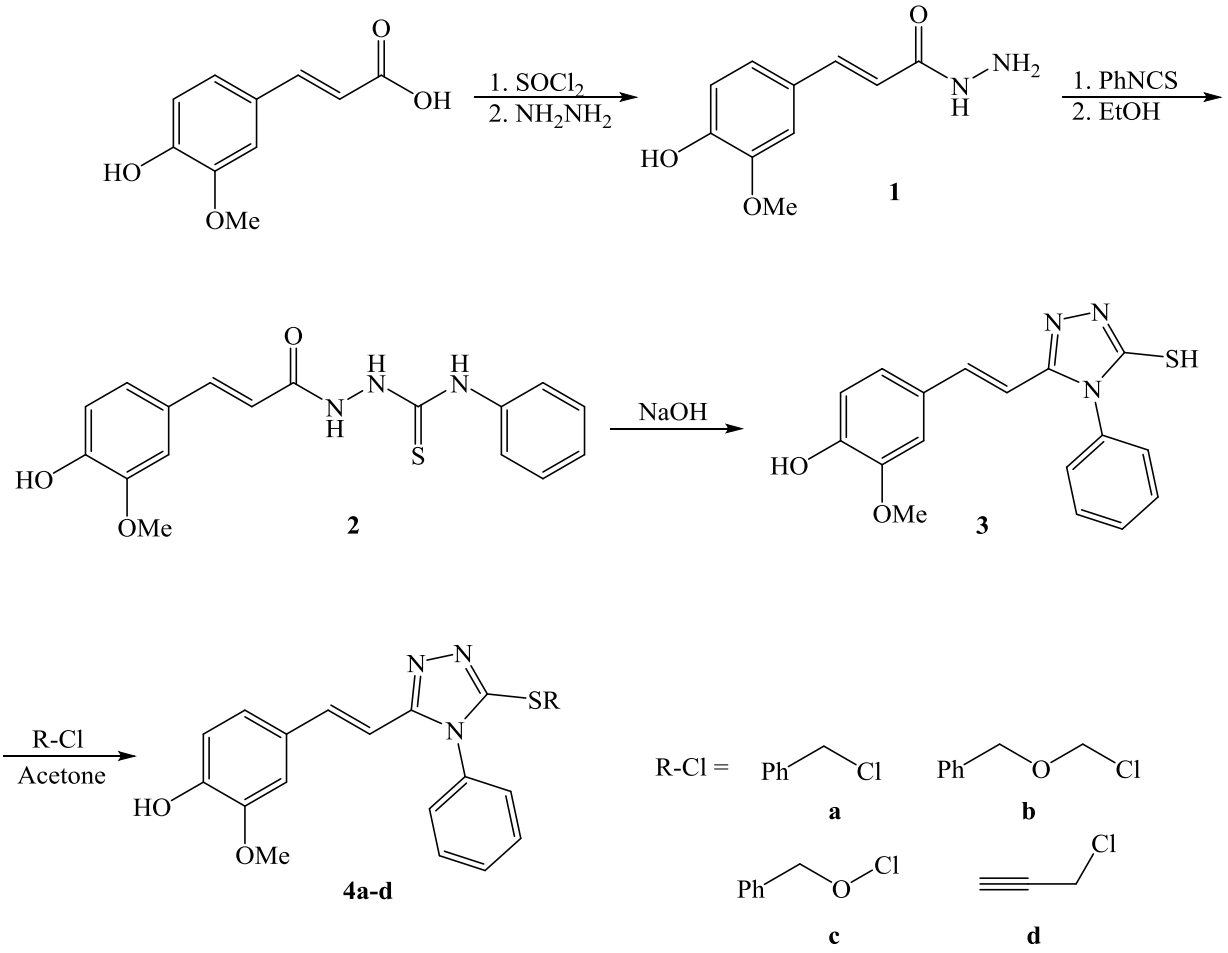
*(E)-2-((5-(4-hydroxy-3-methoxystyryl)-4H-1,2,4-triazol-3-yl)thio)-1-phnylethan-1-one (**4b**)*

Dark brown, mp 180-182 °C, yield 40%, IR (KBr) (ν_{max}/ cm^{-1}): 3273 (O-H phenol), 3059 (C-H aromatic ring), 1676 (C=O ketone), 1635 (C=N), 1524 (C = C aromatic ring), 1128 (C-O-CH_3), 1199 cm^{-1} (C-S). ^{1}H-NMR (600 MHz, DMSO): δ 3.76 (3H, CH_3 methoxy), 4.36 (2H-adjucent to carbonyl),

6.31 (1H, CH=CH α, β unsaturated carbonyl), 6.54-8.30 (13H, Ar ring), 7.07 (1H, CH=CH unsaturated next to aromatic ring), 9.15 (1H, OH phenolic); ^{13}C-NMR (150 MHz, DMSO): δ 39 (1C adjacent to carbonyl), 56.1 (3C, CH_3 of methoxy group), 116 (1C, CH=CH α, β unsaturated carbonyl), 111-128 (6C, Ar ring), 128.7 (1C, CH=CH α, β unsaturated carbonyl), 121-128.9 (6C, Ar ring), 141 (1C ,C- triazole), 129-156 (6C, Ar ring), 148.6 (1C, C-S), 193 (1C carbonyl group).

*(E)-S-(-5-(4-hydroxy-3-methoxystyryl)-4H-1,2,4-triazol-3-yl) benzothioate (**4c**)*

Light brown, mp 175-178 °C, yield 30%, IR (KBr) (ν_{max}/ cm^{-1}): 3254 (O-H phenol), 3115 (C-H aromatic ring), 1703 (C=O ketone), 1595 (C=N), 1545 (C = C aromatic ring), 1220 (C-O-CH_3), 1120 cm^{-1} (C-S). ^{1}H-NMR (600 MHz, DMSO): δ 3.33 (3H, CH_3 methoxy), 6.88-7.97 (13H, Ar ring), 7.39 (1H, CH=CH unsaturated next to the aromatic ring), 7.47 (1H, CH=CH α, β unsaturated carbonyl), 10.15 (1H, OH phenolic). ^{13}C-NMR (150 MHz, DMSO): δ 56 (3C, CH_3 of methoxy group), 112 (1C, CH=CH α, β unsaturated carbonyl), 133 1C, (CH=CH α, β unsaturated carbonyl), 126-131(6C, Ar ring), 128-136 (6C, Ar ring), 144.5 (1C ,C – triazole), 116-149 (6C, Ar ring),162.5 (1C, C-S), 210 (1C carbonyl group).



Scheme 1: Synthesis of ferulic acid derivatives

*(E)-4-(2-(4-cyclohexyl-5-(prop-2-yn-1-ylthio)-4H-1,2,4-triazol-3-yl)vinyl)-2-methoxyphenol (**4d**)*

Black, mp 105-110 °C, yield 15%, R (KBr) (ν_{max}/ cm^{-1}): 3270 (H attach to C triple bond), 3046 (O-H phenol), 2339 (C≡ C), 1703 (C=N), 1515-1596 (C = C aromatic ring), 1234 (C-S), 1157 (C-O-CH_3), ^{1}H-NMR (600 MHz, DMSO): δ 3.38 (2H adjacent to thio), 3.76 (3H, CH_3 methoxy), 4.38 (1H-adjacent to triple bond), 6.31 (1H, CH=CH α, β unsaturated next to aromatic ring), 6.34 (1H, CH=CH unsaturated carbonyl), 6.74-7.32 (8H-Ar ring),

9.16 (1H, OH phenolic). ^{13}C-NMR (150 MHz, DMSO): δ 21 (1C-carbon between triple and thiol), 56.1 (3C, CH_3 of methoxy group), 75-76 (C≡C), 112 (1C, CH=CH α, β unsaturated carbonyl), 133 (1C, CH=CH α, β unsaturated carbonyl), 126-138 (6C-Ar ring), 144.5 (1C, C-triazole), 148.7 (1C, C-S), 111-149 (6C, Ar ring).

Molecular docking studies for the synthesized compounds

The docking research for the produced compounds were carried out by using the Genetic Optimization for Ligand Docking (GOLD) (v 5.7.1). Tool program was obtained from the Cambridge Crystallographic Data Center (CCDC). The Hermes visualizer software (v.1.10.1) was used to show receptors, ligands, active positions, interface modes (hydrogen bonds or brief contacts), posture estimate, bond length assessment, and fold images [8].

Interpretation of the results of ADME studies

The Swiss ADME server examined the physicochemical and ADME properties of the new synthesized compounds to examine which synthesized molecules are subjected to organism given orally, to make known the unharmed, a medication view, and to exclude compounds that inadequate in the phases of drug development deponding on ADME properties [9].

Cytotoxicity assay

It was possible to get the human A459 lung cancer cell line and the human MCF-7 breast cancer cell line. They were in Tissue Culture Research Database Center, Cell Bank in Al-Qahera University, College of Science.

Cell viability by MTT colorimetric assay

The cytotoxic effects of newly developed and manufactured compounds on lung cancer cells and breast cancer cells were determined by using the MTT colorimetric test.

Cell viability was measured by using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells of lung and the breast cancers were seeded in 96-well plates when growth was reaching 70% confluence. Serial indicated concentration of tamoxifen, erlotinib, and newly developed and manufactured compounds were added to culture medium. After 24 hours, twenty microliters of MTT (5 mg/mL) was added to each well, and then the 96-well plates were incubated at 37 °C. After 4 hours, 150 µl of DMSO was added to adherent cells of each well to dissolve crystal. Then, the luminescence of each well was measured by using a microplate reader at a wavelength (570 nm) [10].

Determination of the half-maximal inhibitory concentration (IC_{50})

The IC_{50} of the studied substances may be calculated by using the dose-response curve. The IC_{50} in the MTT experiment (*in vitro*) may be defined as the concentration of produced compounds (**4a**, **4b**, **4c**, and **4d**) required to achieve 50% cell inhibition.

Results and Discussion

Interpretation of ADME result

TPSA or topological polar surface area was considered, this is a useful characteristic for forecasting different ADME features, including drug brain access and bioavailability [11]. The compound with a TPSA > 140 Ao stays likely to be situated weakly absorbed from the GIT.

Bioavailability of all ligands was 0.55 and TPSA for all synthesized compounds was less than 140, indicating that they entered the systemic circulation, as demonstrated in Table 1.

Interpretation of the docking result

Docking study results in the determination of binding energies and specification of the designed compounds to proteins, e.g., EGFR, and ER-α via investigating the molecular interaction between the active binding sites of proteins and designed chemical compounds. The EGFR and ER-α inhibitory effect of developed compounds, erlotinib, and tamoxifen were classified depending on their PLP fitness associated in the complex formation at the active site.

The outcomes of docking analysis of newly created compounds are displayed in Figures 1 to 8 and Tables 2 and 3.

Table 1: ADME result of the final compound

Compound	H bond Accepter	H bond doner	Molar Ritactivity	TPSA A°	GIT Absorpion	BBB permeant	Bioavavailibility	Lipinski
4a	4	1	121.45	85.47	high	no	0.55	0
4b	5	1	128.53	102.54	high	no	0.55	0
4c	5	1	121.87	102.54	high	no	0.55	0
4c	4	1	104.74	85.47	high	no	0.55	0

BBB: Blood Brain Barriar, TPSA: Topological Polar Surface Area

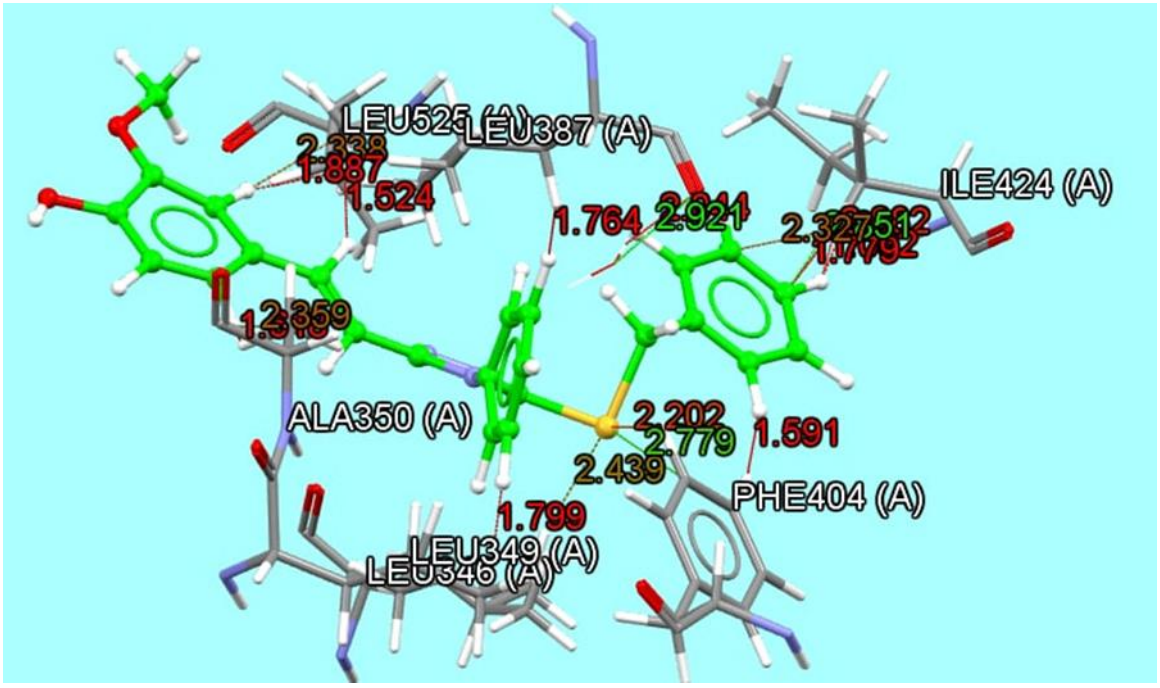


Figure 1: 3-Dimensional binding and orientation of compound **4a** with ER-alpha receptor

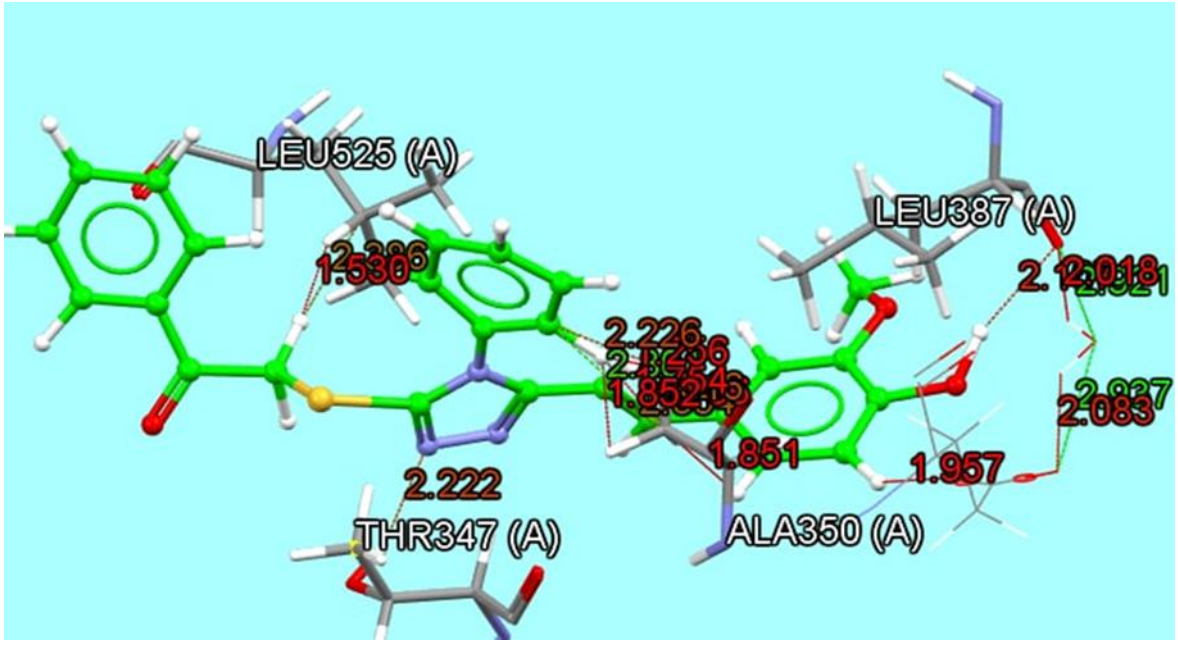


Figure 2: 3-Dimensional binding and orientation of compound **4b** with ER-alpha receptor

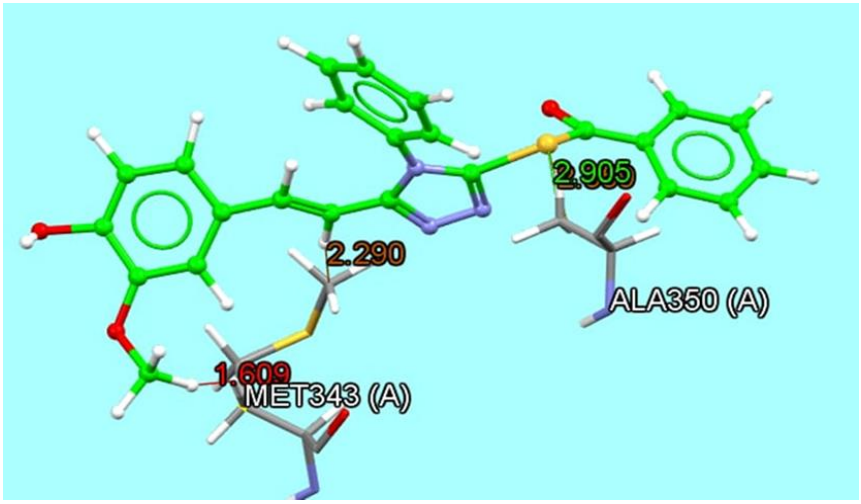


Figure 3: 3-Dimensional binding and orientation of compound **4c** with ER-alpha receptor

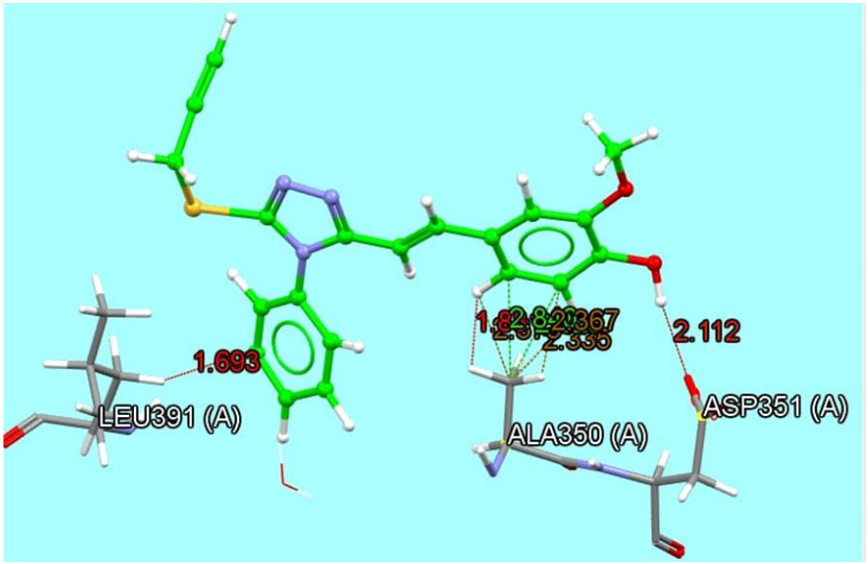


Figure 4: 3-Dimensional binding and orientation of compound **4d** with ER-alpha receptor

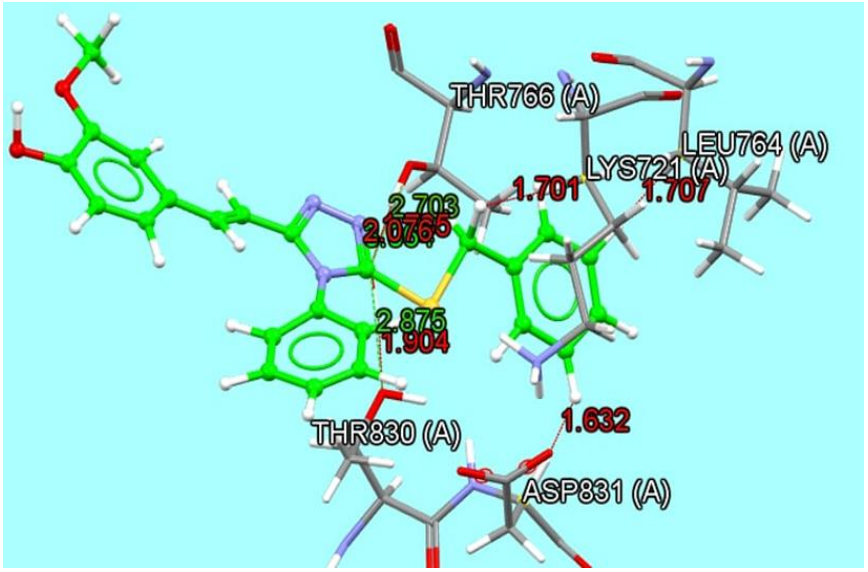


Figure 5: 3-Dimensional binding and orientation of compound **4a** with EGFR receptor

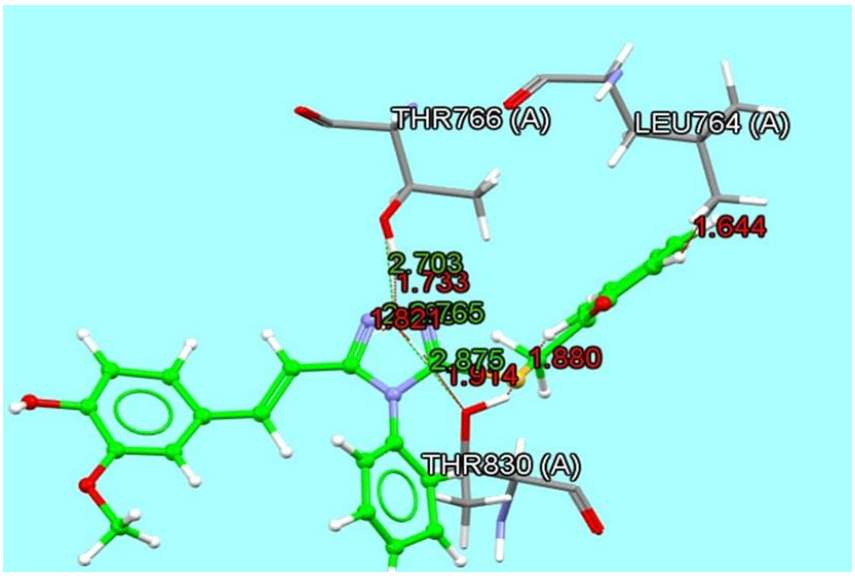


Figure 6: 3-Dimensional binding and orientation of compound **4b** with EGFR receptor

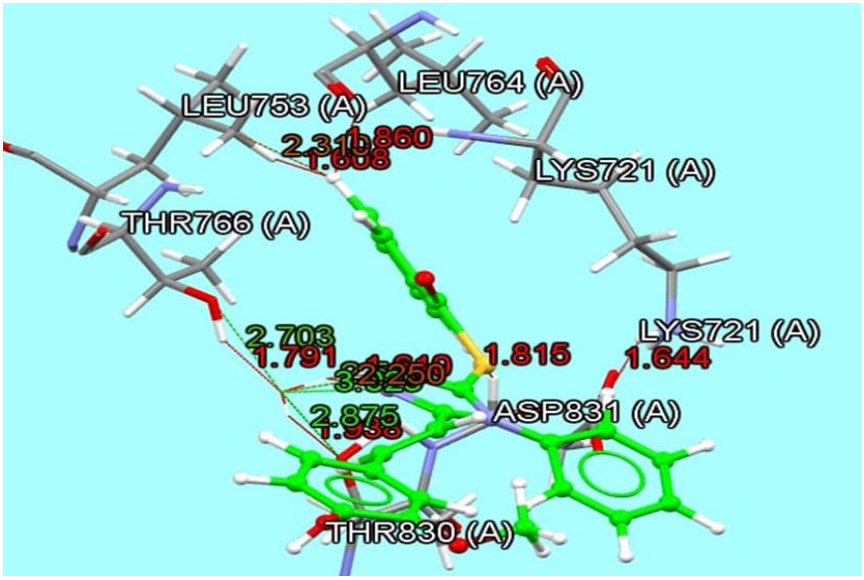


Figure 7: 3-Dimensional binding and orientation of compound **4c** with EGFR receptor

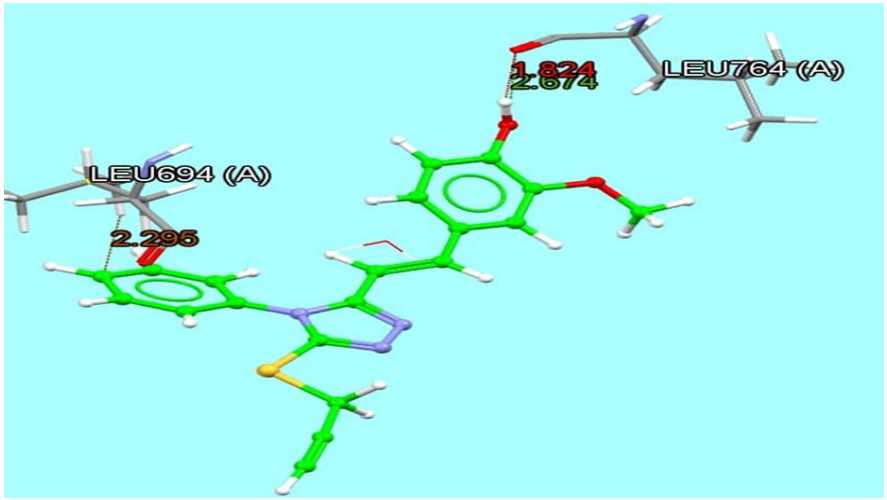


Figure 8: 3-Dimensional binding and orientation of compound **4d** with EGFR receptor

Table 2: New compound and tamoxifen, a predictable drug, docked with ER-α. Binding energies

Compound	Energy binding (PLP fitness)	H-bonding amino acids residues	Amino acids residues in short contact interaction
4a	90.87	-	ALA 350, LEU 387, LEU 346, ILE 424 (5), PHE 404 (4), LEU 349, LEU 525 (3)
4b	88.21	-	ALA 350 (4), LEU 387, GLU 353, LEU 525 (2), THR 347,
4c	80.06	-	MET 343 (2), ALA 350 (2)
4d	84.9	-	LEU 391, ASP 351, ALA 350 (5)
Tamoxifen	92.3	ASP 371	MET 388, LEU 391, HIS 524, THR 347, LEU 525

PLP: Pull Ups, Lunges, and Push Ups

Table 3: The binding energies of new compound and erlotinib, a predictable drug, docked with EGFR

Compound	Energy binding (PLP fitness)	H-bonding amino acids residues	Amino acids in short contact residues interaction
4a	83.92	HOH bridge with THR 766 and THR 830	ASP 831, HOH bridge with THR 766 AND THR 830, LYS 721, LEU 764
4b	92.47	HOH bridge with THR 766 and THR 830 (2)	HOH bridge with THR 766 and THR 830, THR 830, LEU 764
4c	86.06	HOH bridge with THR 766 and THR 830(2)	LYS 721, (2) HOH bridge with THR 766 and THR 830, ASP 831, LEU 753 (2), LEU 764
4d	75.5	LEU 764	LEU 764, LEU 694
Erlotinib	84.51	HOH bridge with THR 766 and THR 830	VAL 702, GLY 695 (2), ASP 776, CYS 773, HOH bridge with THR 766 and THR 830

PLP: Pull Ups, Lunges, and Push Ups, EGFR: Epidermal Growth Factor Receptor

All of the proposed ligands showed binding energies in the active pocket of the receptor, according to docking data, and a positive interaction with EGFR, H-bonds, and other brief contacts was anticipated that strengthen the binding are used by the ER-protein and other proteins to attach to the amino acid residue of the active site.

Results of compounds' cytotoxicity tests on a breast cancer cell line (MCF-7)

By using the MTT assay, the synthesized compounds' IC_{50} values were calculated. The experiment was conducted by using 96-well flat plates with various concentrations of the produced compounds (10000-78.12 µg/mL) of the synthesized compound (**4a**, **4b**, **4c**, and **4d**) compared with the standard anticancer cell, Tamoxifen, the IC_{50} values were obtained after 72 hours of chemical treatment of the cancer cells.

Prism Pad 8.1's nonlinear regression analysis was used to create the dose-response curves for the synthetic substances in MCF-7 cells (12) are demonstrated in Figures 9, 10, 11, and 12. The IC50 of the new synthesized compound was indicated in the Table 4.

From the mentioned result above, we noticed that the new synthesized compounds **4a**, **4b**, and **4c**, respectively are the more active anticancer than standard Tamoxifen as IC_{50} value, which have IC_{50} (89.17, 108.69, and 118.24) lower than standard tamoxifen IC_{50} (392.3).

Serafim *et al*. found that ferulic acid derivatives increase cytotoxicity effect against breast cancer MCF-7 cell line [13]. In the same line, Elkhazendar reported the promising therapeutic effect of ferulic acid in breast cancer treatment [14].

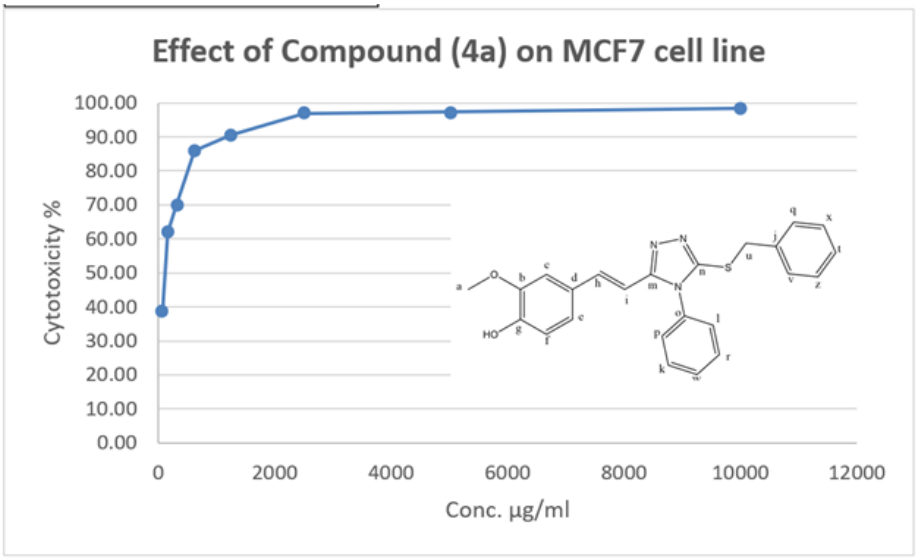


Figure 9: IC_{50} dose-response curve for compound **4a**

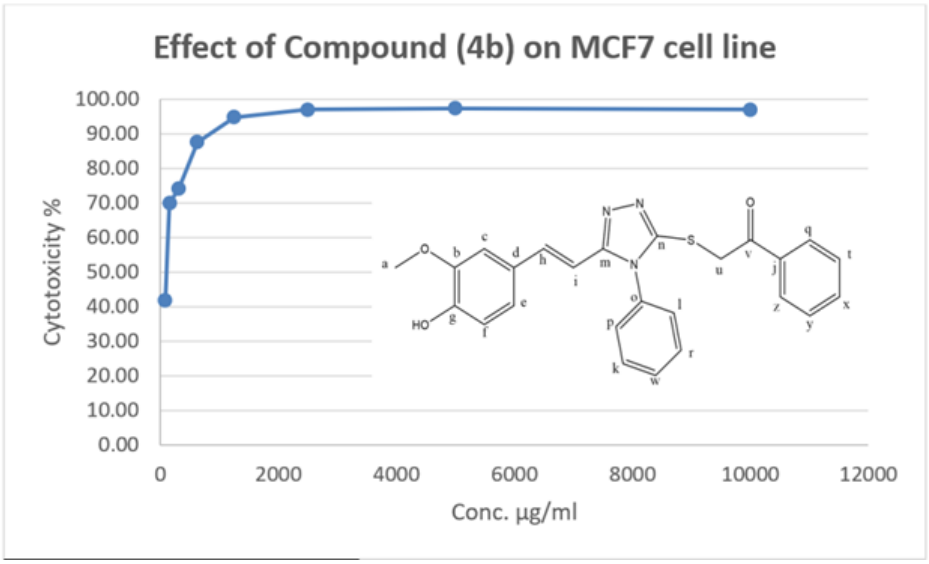


Figure 10: IC_{50} dose-response curve for compound **4b**

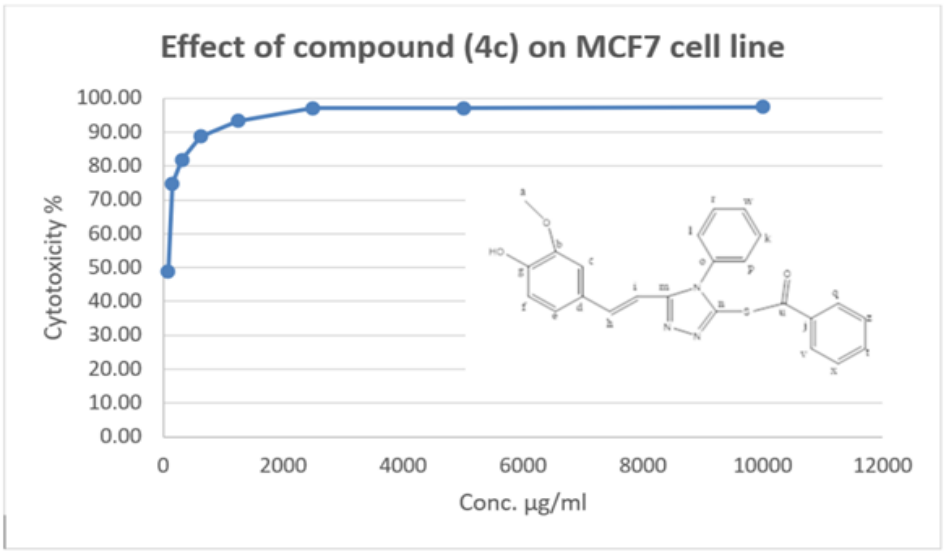


Figure 11: IC_{50} dose-response curve for compound **4c**

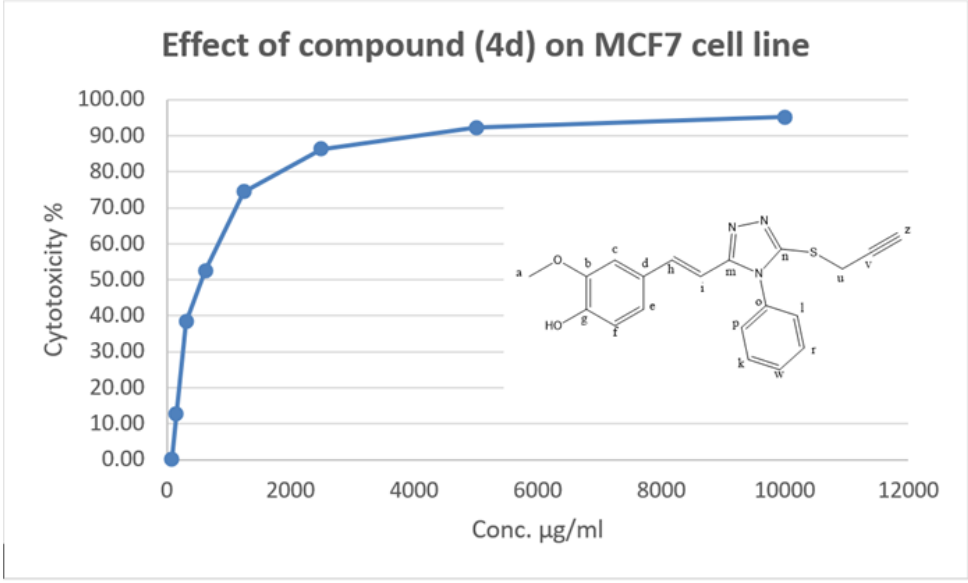


Figure 12: IC_{50} dose-response curve for compound**4d**

Table 4: IC_{50} values for the active chemicals (**4a**, **4b**, **4c**, and **4d**) and Tamoxifen as a standard against breast cancer MCF-7 cell

Compound	IC_{50} ug/ml
4d	562.13
4b	108.69
4C	89.17
4a	118.24
Tamoxifen	392.3

Results of compounds' cytotoxicity tests on a lung cancer cell line (A549)

By using the MTT assay, the synthesized compounds IC_{50} values were calculated. The experiment was conducted by using 96-well flat plates with various concentrations of the produced compounds (10000-78.12 µg/mL) of the synthesized compounds **4a**, **4b**, **4c**, and **4d** compared with standard anticancer cell, erlotinib, the IC_{50} values were obtained after 72 hours of chemical treatment of the cancer cells.

Prism Pad 8.1's nonlinear regression analysis was used to create the dose-response curves for the synthetic substances in A549 cells [15] are indicated in Figures 13, 14, 15, and 16. The IC50 of the new synthesized compound was shown in Table 5.

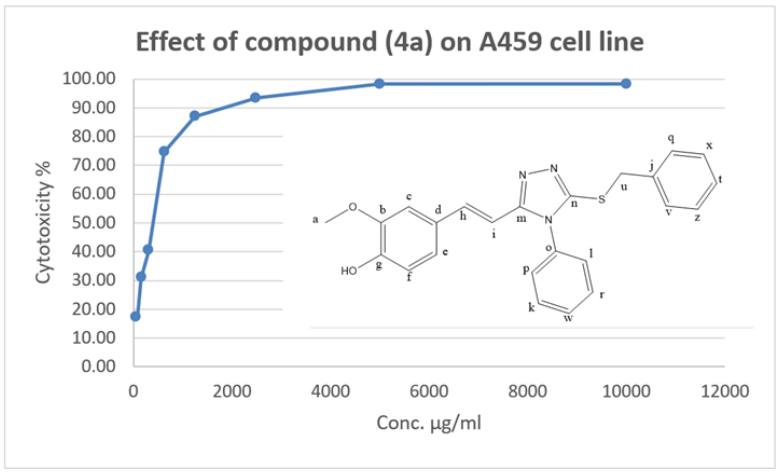


Figure 13: IC_{50} dose-response curve for compound **4a**

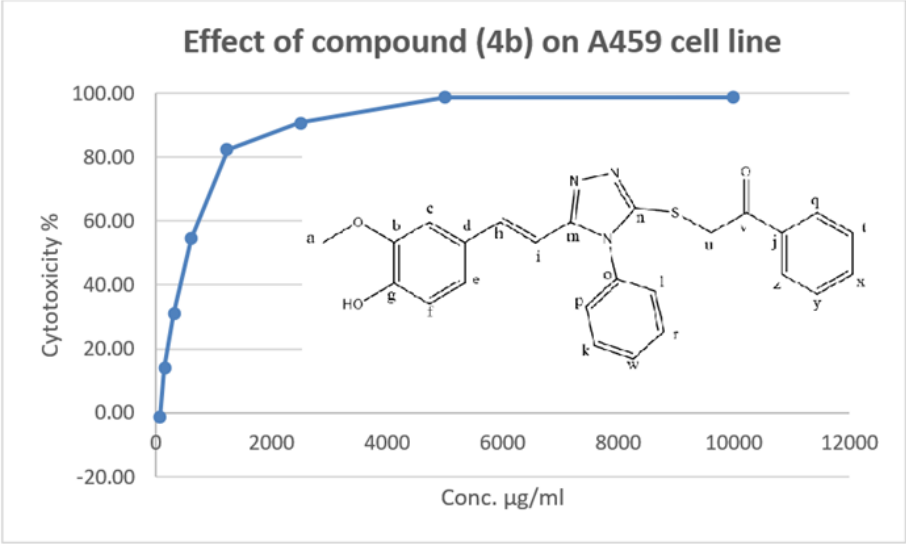


Figure 14: IC_{50} dose-response curve for compound **4b**

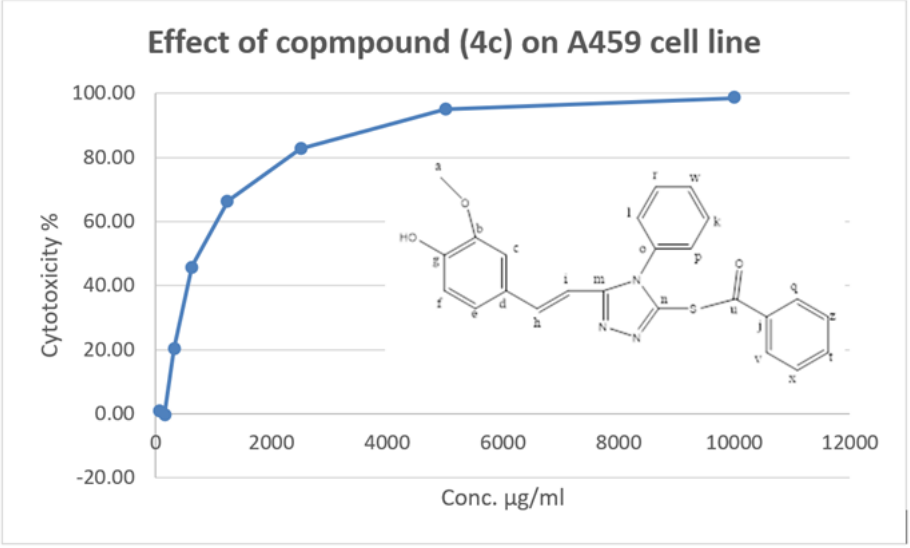


Figure 15: IC_{50} dose-response curve for compound **4c**

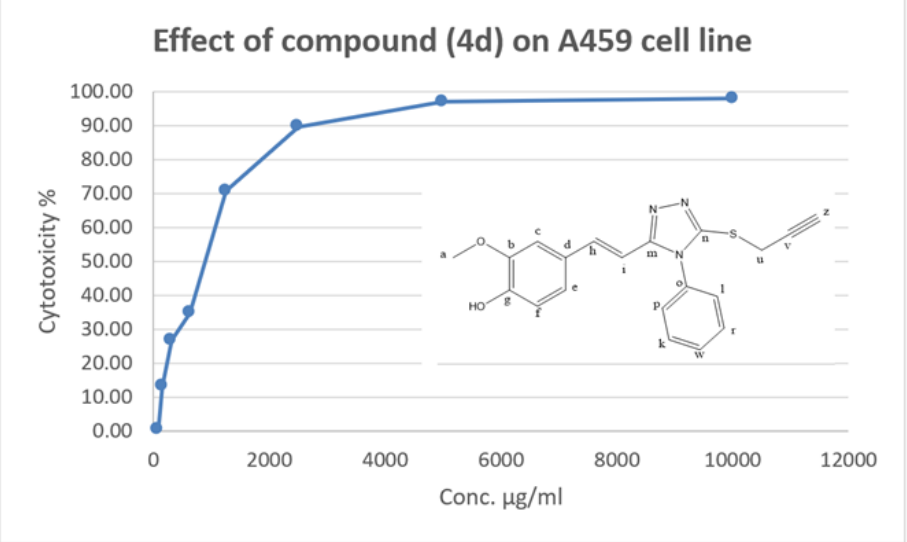


Figure 16: IC_{50} dose-response curve for compound **4d**

Table 5: IC_{50} values for the active chemicals (**4a**, **4b**, **4c**, and **4d**) and erlotinib as a standard drug against lung cancer A 549 cell

Compound	IC_{50} ug,ml
4a	478.32
4b	561.12
4c	712.85
4d	867.92
Erlotinib	582.73

Although erlotinib is important for first line treatment of patients with non-small lung cancer that EGFR mutated, the result of our study noticed the new synthesized compounds **4a** and **4b**, respectively are more active anticancer than standard erlotinib as IC_{50} value, which have IC_{50} (478.32 and 561.12) lower than standard erlotinib IC_{50} (582.73). This finding agrees with Fong *et al.* study indicated inhibitory effect of ferulic acid dervitive against lung cancer by suppressing proliferation and migration of cancer cells [16].

Conclusion

Successful synthesis of a new family of ferulic acid derivatives was accomplished and the anticancer activities of the synthesized compounds were evaluated against the lung cancer cell line A549. Among the examined substances, the most promising compounds **4a** and **4b** which are more active than reference anticancer drug erlotinib. While the others synthesized compound **4d** and **4c** have higher IC_{50} values than standard anticancer drug erlotinib, the anticancer activities of the synthesized compounds were evaluated against the MCF-7 (breast) cancer cell line. We noticed the new synthesized compound **4a**, **4b**, and **4c**, respectively is the more active anticancer than standard tamoxifen as IC_{50} value, which have IC_{50} lower than standard tamoxifen, the results of docking experiments for ligand interactions with the EGFR protein were in agreement with one compound and disagreement with those obtained *in vitro*, the results of docking studies for ligand interactions with the ER-protein were not consistent with those from *in vitro* experiments.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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