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# New heterocyclic derivatives: synthesis, characterization, molecular docking, and their biological activity study as anticancer and antibacterial agents

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## Abstract

This study aimed to prepare a series of novel heterocyclic compounds via the Schiff-Bass cycloaddition reaction of 4-((5-mercapto-1,3,4-thiadiazol-2-yl) imino)methyl)-2-nitrophenol. Schiff bases were used in the synthesis to produce novel Schiff base derivatives, including quinazoline, thiazine, oxazepine, imidazolidine, and tetrazole derivatives. The structures of the derivatives were determined by Fourier transform infrared spectroscopy, 1H NMR, and 13C NMR, and they were evaluated in vitro as antimicrobial and anticancer agents, with several exhibiting useful biological activity. All derivatives were evaluated in vitro for their antimicrobial activity. The new derivatives were studied in vitro against two bacterial species (Escherichia coli and Staphylococcus aureus). The results of the antimicrobial activity study showed encouraging antibacterial activity, with good inhibition rates for some of the studied derivatives compared to the antibiotic amoxicillin. An in vitro study of the product was conducted on the SKGT4 cell line (cancer cells). Cytotoxicity tests showed encouraging results for some of these targeted derivatives against the SKGT4 cell line, with low IC50 values. Theoretically, using a molecular docking program to study the targeted derivative, the cytotoxicity test results were confirmed. The results showed a good low binding energy compared to crizotinib.

**Keywords**: thiazine. Quinazoline . imidazole . tetrazol . molecular docking esophageal cancer

## 1. Introduction

Medicinal chemistry has relied on natural and synthetic heterocyclic organic compounds to discover numerous therapeutic and biological compounds(1-3). Accordingly, heterogeneous organic compounds containing nitrogen atoms in their structures have played an important role in medicinal chemistry, as they include biologically active molecules (4-6). These compounds have played various therapeutic and biological roles, including anticancer (7,8), antiviral (9,10), antimicrobial (11,12), anti-inflammatory, and antioxidant (13,14) activities, as well as other activities (15-16). On the other hand, heterocyclic rings are found in many derivatives used in industrial processing. The activity of the derivatives depends on their molecular structures **(17)**. Such Thiadiazole derivatives are of great importance in preventing corrosion· The diversity of biological activity of these derivatives is attributed to the nature of their molecular structures, reinforced with common aromatic heterocyclic derivatives such as thiazine, Quinazoline, imidazole, oxazepine, and tetrazole, and this work aims to synthesize new derivatives with high biological activity

## 2. EXPERIMENTAL PART

### 2.1 *Materials and Methods*

Chemical materials were purchased from Sigma-Aldrich, Merck, CDH, and BDH. All melting points are uncorrected and determined on a Stuart electric melting point meter. The FT-IR spectra (KBr discs) were recorded with an IRAFFINITY-1CE Shimadzu 400D infrared spectrometer. $H^1$ NMR, $C^{13}$ NMR spectra were recorded on a Broker spectrophotometer - 403.548 fid. All derivatives were monitored by TLC performed on Merck 60 with a 0.25 mm layer of Merck GF254 silica gel. - Use of silica gel plates and purity testing of newly synthesized compounds.

### 2.2 Synthesis of: 4-(((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)-2-nitrophenol (N1)$^{(18)}$

Schiff bases have been synthesized by reaction of compound (N) 5-amino-1,3,4-thiadiazole-2-thiol (2 mmole, 2.6 g) with aromatic aldehyde 3-hydroxy-4-nitrobenzaldehyde (2 mmole, 2.09 gm) in absolute ethanol for (9-10 hours) and add (2–3) drops of glacial acetic acid. The precipitate was filtered, dried, and recrystallized with absolute ethanol. Color: brown crystalline.; Yield: 88%; m.p.244-246°C; IR (v,cm$^{-1}$) ; 3487.22 cm$^{-1}$ (OH), 3095.14 cm$^{-1}$ (CH$_{ar}$),2932.34-2838.10cm$^{-1}$(CH$_{aliph}$),1641.43cm$^{-1}$,(N=CH),1605.80cm$^{-1}$(C=N),1546.37cm$^{-1}$(C=C$_{ar}$), 1337.35 cm$^{-1}$ ($NO_2$),1052.34(C-N), $H^1$NMR δ (ppm) spectra of compound (N1) in DMSO-$d^6$ exhibit anew signals at 13.19 (S, 1H, SH), 9.21 (S, 1H, OH), 8.87 (S, 1H, N=CH), 7.27-8.82 (m, 4H, CHar). $C^{13}$-NMR δ (ppm) for N1 in DMSO exhibits a new signal at 180.58 ($\underline{C}$-SH), 161.95 (N=$\underline{CH}$), 157.24 (N=$\underline{C}$-N$_{ring}$), 154,92(CH-$\underline{C}$-N), 120.15-137.68 (C$_{ar}$). TLC R*f* = 0.7 (ethyl acetate: n-hexane).

### 2.2 Synthesis of 2-(4-hydroxy-3-nitrophenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione (N2)$^{(19)}$

The bottom flask mixing (58 mmol, 1.3 gm.) of compound (N1) and malic anhydride (58 mmole, 0.85 gm.) in dry benzene (25 ml). The mixture was refluxed (25 hours). The reaction was LC, and the precipitate was filtered, dried, and recrystallized with absolute ethanol. Color Crystalline yellow; Yield: 68%; m.p 280-282°C; IR (v, cm-$^1$); 3471.96 cm$^{-1}$ (OH), 3089.37 cm$^{-1}$ (C-H$_{ar}$), 2956.54-2845.05cm$^{-1}$ (C-H$_{aliph}$), 1718.19 cm$^{-1}$ (C=O $_{ester}$), 1665.84 cm$^{-1}$ (C=O $_{amid}$), 1615.88 cm$^{-1}$(C=N), 1581.65 cm$^{-1}$ (C=C$_{ar}$), 1367.53(C-N), 1330.25 cm$^{-1}$ ($NO_2$) ,1064.71cm$^{-1}$ (C-O). The $H^1$ NMR spectra of the compound (N2) in DMSO-$d^6$ show signals at 13.03 (S, 1H, SH), 6.95 (S, 1H, N-$\underline{CH}$-O), 7.13-7.91(m, 5H, CH$_{ar}$), $C^{13}$-NMR in DMSO-$d^6$ exhibits a new signal at 190.79 ($\underline{C}$-SH), 174.70 (C=O$_{ester}$), 166.45 (C=O$_{amid}$), 157.52 (N=$\underline{C}$H), 120.30-137.71 (CH$_{ar}$), and a new signal 75.02(N-$\underline{CH}$-O). TLC R*f* = 0.7 (Ethyl acetate: n-hexane).

### 2.3 Synthesis of: 3-(4-hydroxy-3-nitrophenyl)-4-(5-mercapto-1,3,4-thiadiazol-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione (N3)$^{(19)}$

The bottom flask mixing (50 mmol, 1.6 gm.) of compound (N3) and phthalic anhydride (50 mmol, 0.88 gm.) in dry benzene (25 ml). The mixture was refluxed (25 hours). The reaction was LC, and the precipitate was filtered, dried, and recrystallized with absolute ethanol. Color Crystalline yellow; Yield: 68%; m.p 286-288°C; IR (v, cm-$^{1}$); 3417.86 cm$^{-1}$ (OH), 3174.83 cm$^{-1}$ (C-H$_{ar}$), 2970.54-2822.16cm$^{-1}$ (C-H$_{aliph}$), 1718.58 cm$^{-1}$ (C=O $_{ester}$), 1589.34 cm$^{-1}$ (C=O $_{amid}$), 1558.48 cm$^{-1}$(C=N), 1510.26 cm$^{-1}$ (C=C$_{ar}$), 1373.32 (C-N), 1337.05 cm$^{-1}$ (NO$_2$), 1053.13 cm$^{-1}$ (C-O). The H$^1$ NMR spectra of the compound (N3) in DMSO-$d^6$ show signals at 13.06 (S, 1H, SH), 6.98 (S, 1H, N-CH-O), 7.22-8.36(m, 7H, CH$_{ar}$), C$^{13}$-NMR in DMSO-$d^6$ exhibits a new signal at 190.79 (C-SH), 167.62 (C=O$_{ester}$), 166.36 (C=O$_{amid}$), 154.41 (N=CH), 111.50-132.80 (CH$_{ar}$), and a new signal 68.81 (N-CH-O).TLC R*f* = 0.7 (Ethyl acetate: n-hexane).

### 2.4 Synthesis of: 8-hydroxy-2-(4-hydroxy-3-nitrophenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-2,3-dihydro-4H-benzo[e][1,3]thiazin-4-one (N4)$^{(20)}$

A mixture of Schiff-base (4-(5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)-2-nitrophenol of (56 mmole, 1.5 gm) with 5-hydroxy-2-mercaptobenzoic acid (56 mmole, 0.92 gm) in 30 ml of 1,4-dioxan with a pinch of anhydrous zinc chloride was refluxed (30 hours). This reaction was monitored by TLC. The separated solid crystal was filtered, dried, and recrystallized in absolute ethanol. Color: Crystalline brown; Yield: 66%; m.p. 272-274°C; IR (v, cm-1): 3539.83 cm$^{-1}$ (OH) cm$^{-1}$,3130.77cm$^{-1}$ (C-H$_{ar}$), 2915.75-2884.13 cm$^{-1}$ (CH$_{aliph}$), 1724.36 cm-$^{1}$ (C=O $_{amid}$), 1685.79 cm$^{-1}$ (C=C$_{ar}$), 1614.42 cm-1 (C=N), 1332.35 cm$^{-1}$ (NO$_2$),1159.22 cm$^{-1}$ (C-N). The H$^1$ NMR spectra show signals at 13.16 (S, 1H, SH), 4.27 (N-CH-S), 9.82 (S, 1H, -OH), 6.85-8.37 (m, 6H, CHar). C$^{13}$-NMR exhibits a new signal at 181.24 (C-SH), 172.60 (C=O$_{amide}$), 172.20(COH), 161.67(C-N), 106.20-137.60(CH=CH$_{ar}$), and a new signal 75.08 (N-CH-S). TLC R*f* =0.7 (benzen: n-hexane).

### 2.5 Synthesis of : 5-((1H-indol-3-yl)methyl)-2-(4-hydroxy-3-nitrophenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)imidazolidin-4-one (N5)$^{(21)}$

In the bottom flask, around 7 mmol (1.85 gm) of compound (N1) and 7 mmol (1.42 gm) of Tryptophan in THF (25 ml). The mixture refluxed for 30 hours. The reaction was monitored by TLC, and the precipitate was filtered, dried, and recrystallized from absolute ethanol. Color Crystalline Crystalline yellow; Yield: 71%; m.p. 266-262 °C; IR (v, cm-1):, 3334.92 cm$^{-1}$ (OH),3113.11 cm-$^{1}$ (NH), 3047,53cm-$^{1}$ (CHar), 2891,30-2916,37 cm-$^{1}$ (CHaliph), 1610,55cm-$^{1}$ (C=O amid), 1583,56 cm-$^{1}$ (C=Car), 1556.55cm-$^{1}$ (C=N ring), 13315.45 cm$^{-1}$ (NO$_2$), 1176,58cm-$^{1}$(C-N). The H1 NMR spectra of the compound (N5) show signals at 13.08 (S, 1H, SH), 9.54 (S, 1H, -OH), 6.64 (N-CH-NH), 7.04-7.83 (m, 7H , C-Har), 3.38 (S, 1H, -NH$_{indol}$), 1.78 (S, 1H , NH$_{imidazol}$), 1.78 (t,1H, CH-CH2), 2.39 (d,2H, CH$_2$imidazol). C13-NMR in DMSO-d6 shows a new signal at 184.27 (C-SH), 164.96 (C=O imidazol), 122.98-144.56(CHar), and a new signal at 88.71 (N-CH-NH), 33.87(CH$_{2imidazol}$), 59.47(CH $_{imidazo}$l). TLC Rf =0.7 (DCM: n-hexane).

### 2.6 Synthesis of 2-(4-hydroxy-3-nitrophenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (N6)(22)

A mixture of compound (N1) (56 mmole, 1.5 gm) with 2-aminobenzoic acid (56 mmole, 0.77 gm) in 30 ml of 1,4-dioxan with (0.1) from anhydrous zinc chloride was refluxed (25hours). The separated solid crystal was filtered, dried and recrystallized by absolute ethanol, Color: Crystalline brown; Yield: 68%; m.p. 274-276°C; IR (v, cm-$^1$), 3334.92 cm$^{-1}$ (OH),3122.75 cm$^{-1}$ (NH), 3030.45 cm$^{-1}$ (C-H$_{ar}$), 2877.37-2924.09 cm$^{-1}$ (CH$_{aliph}$), 1683.86 (C=O $_{amide}$), 1608.63 cm$^{-1}$ (C=N), 1543.05 cm$^{-1}$(C=C$_{ar}$), 1311.45 cm$^{-1}$ (NO$_2$),1159.22 cm$^{-1}$ (C-N). The H$^1$ NMR spectra in DMSO-*d*$^6$ show signals at 13.15 (S, 1H, SH), 9.84 (S, 1H, -OH), 6,27 (N-<u>CH</u>-NH), 9.84 (S, 1H, -NH), 6.46-8.61 (m, 7H, CHar). C$^{13}$-NMR spectra exhibit a new signal at 184.35 (-<u>C</u>-SH). 170.06 (<u>C</u>=O), 157,54 (N=<u>C</u>-N), TLC R*f* = 0.6 (benzene: n-hexane).

### 2.7 Synthesis of: 4-(1-(5-mercapto-1,3,4-thiadiazol-2-yl)-4,5-dihydro-1H-tetrazol-5-yl)-2-nitrophenol (N7)(23)

In a round-bottom flask, containing (1mmol, 2.22gm) of compound (N1), was dissolved in (20 ml) of 1,4-dioxane and mixed with (1mmol, 0.56 gm) of sodium azide. The mixture was refluxed for 35 hours, and TLC was used to monitor the reaction. The precipitate was filtered, dried, and recrystallized from absolute ethanol.

Color: Crystalline yellow; Yield: 58%; m.p 270-272°C; IR (v, cm$^{-1}$), 3192.19 (NH), 3008.95 cm$^{-1}$ (CH$_{ar}$), 2914.44- 2850.79 cm$^{-1}$ (C-H$_{aliph}$), 1618.28 cm$^{-1}$ (C=N), 1562.34 cm$^{-1}$ (C=Car),1311.59 cm$^{-1}$ (N-N=N), 1373.32 cm$^{-1}$ (NO$_2$); H$^1$ NMR δ (ppm) spectra of compound (N7) in DMSO-*d*$^6$ exhibit anew signals at 13.08 (S, 1H, SH), 9.45 (S, 1H, -OH), 4.98 (S, 1H, N-CH-NH), 8.21 (S, 1H, NH), 6.46-7.48 (m, 3H, CHar).C$^{13}$-NMR in DMSO-*d*$^6$ exhibits a new signal at 188.72 (<u>C</u>-SH), 164.46 (N=<u>C</u>-S), 118.95-136.76 (CH$_{ar}$), and a new signal, 66.78 (N-<u>CH</u>-NH). TLC R*f* = 0.7 (Ethyl acetate: n-hexane).

## 3. Results and Discussion:

All compounds were synthesized according to the scheme in Figure 1 to give cyclization of the Schiff base, compounds resulting from the reaction of (5-amino-1,3,4-thiadiazol-2-thiol(N) and 3-hydroxy-4-nitrobenzaldehyde to give Schiff base (4-(5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)-2-nitrophenol(N1). After that, Derivative (N1) was entered into a reaction with malic anhydride to form derivative N2, Next, derivative N3 was synthesized by the reaction derivative N1 with Phathalicanhydrid, After that, Derivative (N1) was entered into a reaction with 5-hydroxy-2-mercaptobenzoic acid with presence ZnCl$_2$ as catalytic to form derivative N4, Next, Derivative N5 was synthesized by the reaction derivative N1 with tryptophan to form derivative N2 with presence ZnCl$_2$ as catalytic, After that, Derivative (N1) was entered into a reaction with 2-aminobenzoic acid with presence ZnCl$_2$ as catalytic to form derivative N6, At last, derivative N7 was synthesized by the reaction derivative N1 and sodium azid, as in.

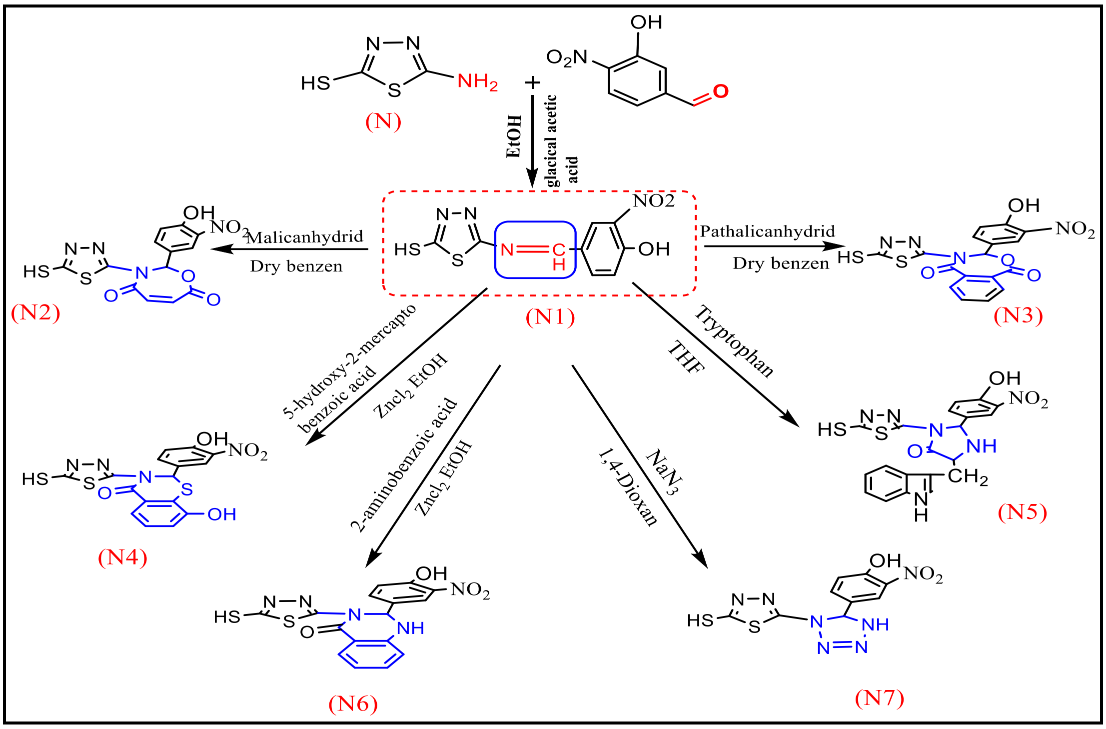


**Figure 1. Scheme of preparation of compounds.**

## 4. Antimicrobial evaluation :[24]

In this research, the biological effectiveness of the derivatives for two pathogenic bacterial strains, Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive), was studied. The bacterial types were cultured on Mueller-Hinton agar, known to cause common diseases. The derivatives were tested, dissolved in solvent (DMSO) at concentrations of 1000 mg/ ml, for two types of bacteria. The aim was to assess the inhibitory effects of the derivatives on the growth of these organisms. The diameter of the inhibitory zone was measured after 24 hours for bacteria. The results indicate an inhibitory effect of the prepared derivatives. Generally, the results in Table 1 showed that the tested derivatives were utilized, with Amoxicillin used as a reference for comparison.

**Table (1):** Antimicrobial activity of the compounds N1-7

| Comp. No. | Anti-bacterial Activity | | | |
|---|---|---|---|---|
| | *Staphylococcus* | size | *E.coli* | size |
| N1 | ++ | 12 mm | + | 7 mm |
| N2 | +++ | 24 mm | ++ | 16 mm |
| N3 | ++ | 13 mm | + | 9 mm |
| N4 | +++ | 20 mm | + | 7 mm |
| N5 | + | 9 mm | ++ | 14 mm |
| N6 | ++ | 12 mm | + | 8 mm |
| N7 | +++ | 21mm | ++ | 14mm |
| **Amoxicillin** | +++ | 22mm | ++ | 18 mm |

(+++): high active > 15 mm;  (++):mild active > 10-15 mm;(+); slowly active = 5-10

## 5. Molecular Docking:(25-26)

This part of the work included the study of the molecular docking of one of the tested derivatives. Molecular docking shows the binding of the prepared derivatives (N7) to the target protein responsible for the esophageal cancer cell line (SKGT4). The newly synthesized derivatives exhibited anticancer activity. The anticancer effects of these derivatives are centered on the C-Met tyrosine kinase receptor. (N7) exhibits binding via multiple mechanisms, including hydrogen bonding, hydrophobic interactions, and electrostatic interactions. Crizotinib was used as a reference, and Table 2 presents the binding energies and interaction types. In addition, the binding conformation of the N7 derivative and crizotinib to the active site of the target protein is visualized in two- and three-dimensional representations, as shown in the accompanying Figure(1,2).

Table (2): Result of molecular fusion with the protein responsible for lung cancer (A549 protein).

| **Compound NO.** | **Lowes Binding Energy** | **Run** |
|---|---|---|
| $N_1$ | -6.00 | 40 |
| $N_2$ | -6.95 | 47 |
| $N_3$ | -6.51 | 21 |
| $N_4$ | -7.49 | 12 |
| $N_5$ | -7.07 | 14 |
| $N_6$ | -7.88 | 22 |
| $N_7$ | -7.95 | 7 |
| Crizotinib | -6.68 | 2 |

According to the molecular docking results shown in Table 2, a comprehensive overview of the interaction parameters for the final products is provided. Compound (N7) has the lowest binding energy ($\Delta G$ = - 7.95 kcal/mole) when compared to the crizotinib drug (-6.68 kcal/mole). Figures (2,3), which provide possible identification of the different affinity interactions between the compound (N7, crizotinib drug) and basic amino acids, and show D2 and D3 dimensional representations of molecular interactions between c-met tyrosine kinase inhibitor and (N7, crizotinib compound). Based on these results, we conclude that the compound (N2) can inhibit cancer cells by targeting the enzyme and disrupting their metabolic processes.

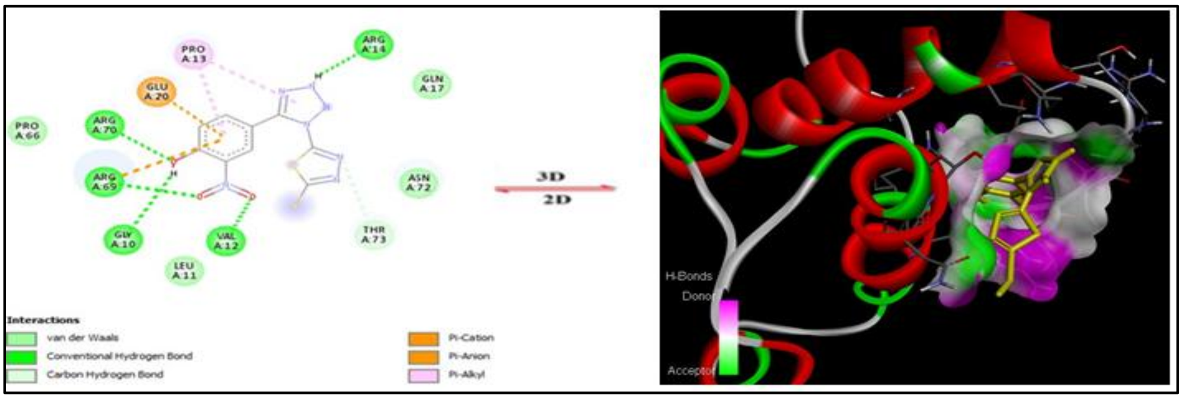


**Fig.2: shows 2D and 3D of molecular interactions between c-met tyrosine kinase inhibitor and derivative (N7)**

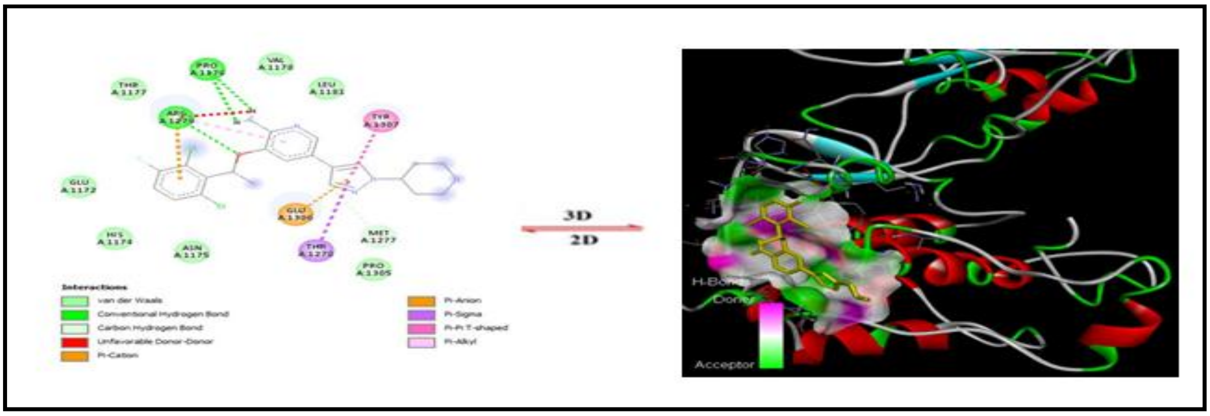


**Fig.3 shows 2D and 3D molecular interactions between the c-met tyrosine inhibitor and the (crizotinib) compound.**

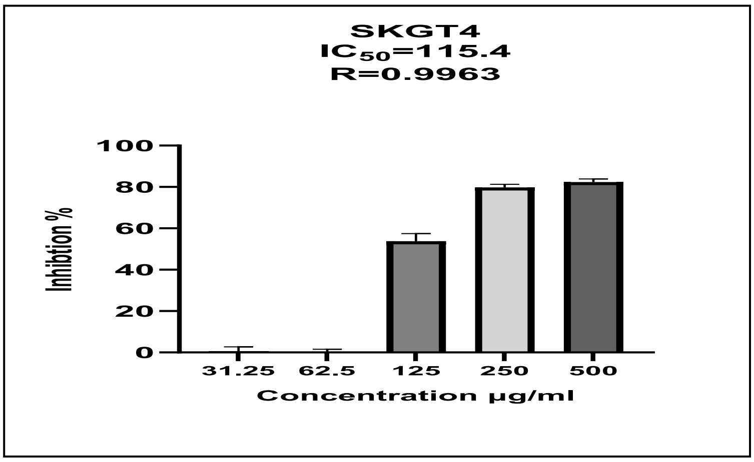
## 5. Cytotoxicity effect: (27-28)

The cytotoxic effect of the newly derived compounds was evaluated against the esophageal cancer cell line (SKGT4). Among the new derivatives (N7), one exhibited promising results as an anticancer agent. The $IC_{50}$ values of (N7) were (115.4) µg/ml. Moreover, the selectivity index specifically states that derivative (N7) is safe. Table 3 showed the lowest inhibition value of cells. Increased anticancer activity was observed at 31 µg/ml, whereas the highest restraint value was observed at 500 µg/ml for the esophageal cancer cell line (SKGT4). The inhibition rates of derivatives (N7) differ depending on the cell line. The number of viable cells after exposure to the tetrazol derivative (N7) ranges from 0.59% to 82.343% in lung cancer cells. The highest rate of inhibition was found at a concentration of 500 µg/ml. These results suggest it could be used as a therapeutic agent to reduce or inhibit the growth of various cancer cell types due to its toxic effects on them. The inhibitory effect can be observed in the presence of the 1,3,4-thiadiazole and tetrazole rings, which have shown activity against cancer cell growth. (26-31)

**Table(4) Anti-cancer activity data of compound (N7)with lung cancer cell line**

| compound | N7 | | | | | 1 |
|---|---|---|---|---|---|---|
| concentration µg/ml | 500 | 250 | 125 | 62 | 31 | 2 |
| technical replicat | 4 | 4 | 4 | 4 | 4 | 3 |
| mean absorbance | 0.06825 | 0.07825 | 0.17875 | 0.3855 | 0.38425 | 4 |
| mean inh% | 82.34381063 | 79.75682318 | 53.75759928 | 0.271633683 | 0.595007114 | 5 |
| SD± | 1.91518303 | 1.84471163 | 4.47533712 | 1.51168778 | 2.53966503 | 6 |
| IC50 | 115.4 | µg/ml | skgt4 | | | 7 |

**Figure (4). Show Cancer activity presentation and IC50 for compound (N7)**



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