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Synthesis of Novel Quinoline containing 1,2,3-Triazole Hybrids: Evaluation of Anticancer Activity and Molecular Docking Studies

SREENIVAS SUNKARA[1,*], DURGA PRASAD BAKA[1], PRAVEEN KUMAR EDIGI[2] and RAVADA KISHORE[1,*]

[1]Department of Chemistry, School of Science, GITAM (Deemed to be University), Visakhapatnam-530045, India
[2]Department of Chemistry, University College of Science, Osmania University, Hyderabad-500007, India

*Corresponding author: E-mail: sreenivassunkara@yahoo.in; kravada@gitam.edu

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Newscaffolds consists of 1,2,3-triazole linked quinoline derivatives (**9a-l**) were synthesized and confirmed by ^{1}H NMR, ^{13}C NMR and ESI-MS spectra. Using the MTT assay and doxorubicin as the standard dugs, all the synthesized compounds were further investigated for their anticancer efficacy against the two cancer cell lines, HT-1080 and A-549. When compared to doxorubicin, compounds **9c**, **9j** and **9d** showed the strongest efficacy against the tested cancer cell lines, HT-1080 and A-549. Using the PyRx tool's Autodock Vina, the molecular docking investigations on enoyl reductase were carried out. It is interesting to note that the interactions and binding energies determined by docking molecules match the data under investigation.

Keywords: 1,2,3-Triazole, Quinoline, Anticancer activity, Molecular docking.

INTRODUCTION

Despite substantial advances in understanding of cancer biology, the disease continues to be a major global source of morbidity and mortality. Each year, cancer kills millions of people throughout the globe, As it originates from a build-up of consecutive changes in normal cell pathways that are both genetic and epigenetic. The ability to maintain proliferative signalling, avoid growth suppressors, withstand cell death, permit replicative immortality, induce angiogenesis and trigger invasion and metastasis are among the characteristics of cancer [1]. Histone alterations and other epigenetic changes, such as DNA methylation, are important factors in the genesis of cancer. These alterations may result in the activation of oncogenes or the silencing of tumour suppressor genes [2]. Ageing, lifestyle, tobacco and alcohol use, a poor diet, physical inactivity and other factors can all raise the risk of developing cancer. So, the robotic-assisted laparoscopic surgery is an evolving method in medicine. Other therapies such as immunotherapy (immune checkpoint inhibitors), exosomes, microbiome and organoids have been used in cancer research, in addition to the development of novel technologies and medications [3].

It is documented that some of the core structures of heterocyclic compounds play an important role in the biological activity of drugs. Among them, the quinoline nucleus is found in many naturally occurring substances and building blocks for more complex natural compounds [4]. The quinoline moiety is important to both chemists and biologists since it is a chemically valuable compound with a variety of biological functions, including anti-inflammatory [5], anti-HCV [6], anti-tubercular [7-9], antimalarial [10,11], anti-HIV [12,13]. Similarly, 1,2,3-triazole derivatives are also one of the most significant classes of nitrogen containing heterocycles, can form a variety of non-covalent interactions with different biological targets, including hydrophobic interactions, hydrogen bonds, van der Waals forces and dipole-dipole bonds, they have a wide range of pharmacological properties, including antioxidant [14], antiviral [15], antidiabetic [16], antifungal [17], anticancer [18,19] and anti-obesity [20] activities. In addition, many naturally occurring and artificially produced small molecules with various biological activities contain the acrylate moiety as a structural scaffold. Such molecules has received great attention for its numerous biological properties including anticancer activity and effective anticancer compounds have been developed that inhibit protein

kinase and α-tubulin [21]. These findings indicated that the acrylate pharmacophore is a viable molecular framework for further modification to produce more effective anticancer drugs candidates.

Based on the literature survey, an effort is going to made to produce excellent therapeutic agents with low perniciousness and more effective drugs as anticancer agents. Therefore, the idea of combination of these two pharmachophores into the novel admirable scaffolds as potent hybrid pharmacophore (1,2,3-triazole tethered quinoline) molecules was developed by utilizing most advisable click reaction and evaluated for their anticancer studies.

EXPERIMENTAL

All chemicals and solvents were obtained from commercial suppliers and underwent additional purification. Using 500 MHz spectrometers (Bruker Avance III 500 MHz), ^{1}H and ^{13}C NMR spectra were acquired in DMSO solvent. Silica gel (60-120 mesh) was purified *via* column chromatography with solvents such as *n*-hexane and ethyl acetate. The Shimadzu FT-IR-8400s mass spectrometer and QSTAR XL GCMS were used to record the mass and infrared spectra, respectively. The melting points were measured using open glass capillary tube and are uncorrected.

The novel quinoline containing 1,2,3-triazole hybrids were synthesized in multi-steps.

Synthesis of 2-chloroquinoline-3-carbaldehyde (2): Formation of 2-chloroquinoline-3-carbaldehyde (**2**) was achieved by using commercially available acetanilide (**1**) by following Vilsmeier-Haack formylation process.

Synthesis of 2-mercaptoquinoline-3-carbaldehyde (3): 2-Mercaptoquinoline-3-carbaldehyde (**3**) was synthesized by reacting 1 mmol of 2-chloroquinoline-3-carbaldehyde (**2**) with 2 mmol of Na_2S and stirring in the presence of DMF for 2 h at room temperature.

Synthesis of 2-(prop-2-yn-1-ylthio)quinoline-3-carbaldehyde (5): 2-(Prop-2-yn-1-ylthio)quinoline-3-carbaldehyde (**5**) was synthesized by reacting compound **3** (1 mmol), which is propargylated using propargyl bromide (**4**) (1.2 mmol) in DMF for 3-4 h at room temperature in the presence of K_2CO_3.

Synthesis of 2-(((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-thio)quinoline-3-carbaldehyde (7a-l): 2-(((Substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinoline-3-carbaldehyde (**7a-l**) was formed from 2-(prop-2-yn-1-ylthio)quinoline-3-carbaldehyde (**5**) (1 mmol) which clicked with substituted aryl azides (**6a-l**).

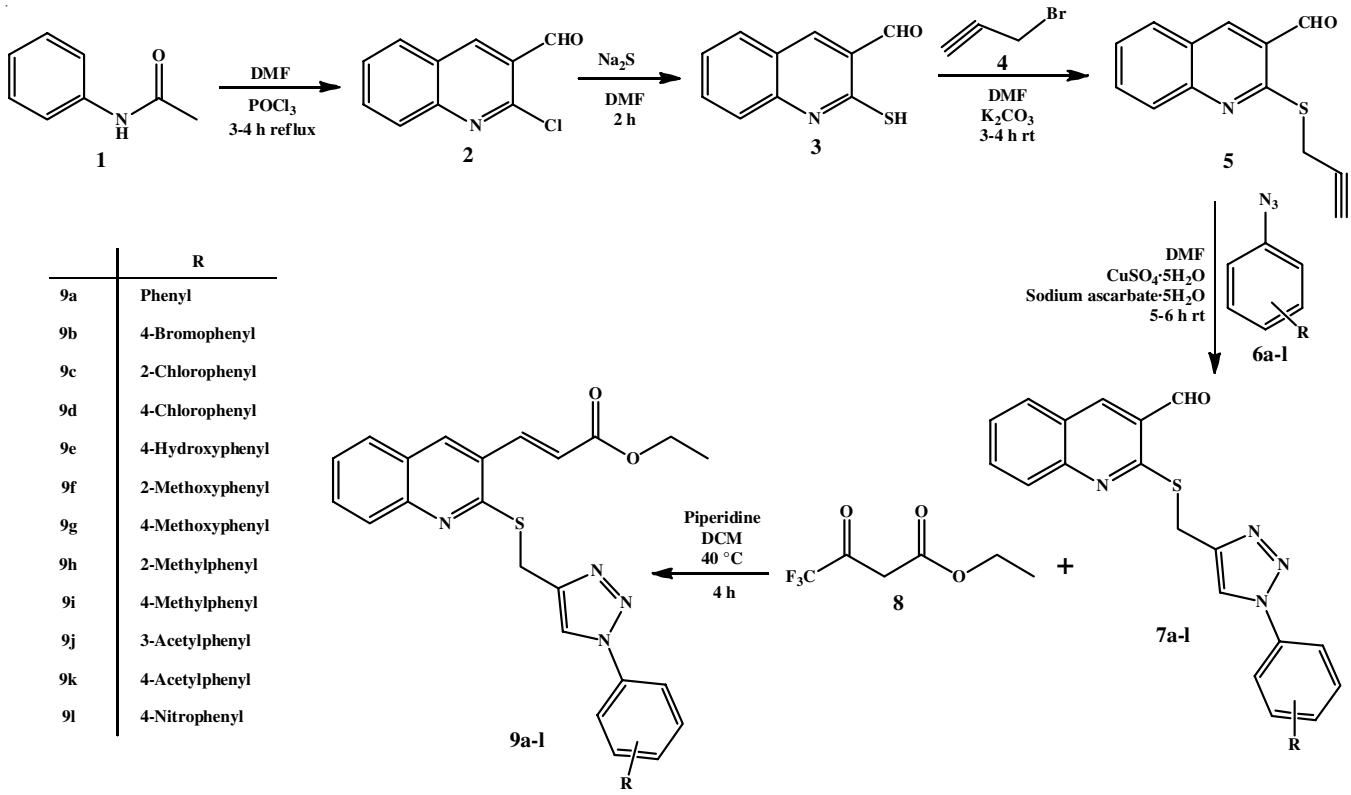
Synthesis of ethyl (*E*)-3-(2-(((substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9a-l): The title compounds, ethyl (*E*)-3-(2-(((substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (**9a-l**), were synthesized from intermediate compounds (**7a-l**, 1 mmol) by condensation with 2-((4,4,4-trifluoro-3-oxobutan-oyl)oxy)-ethan-1-ylium (**8**) (1.5 mmol) in the presence of piperdine in DCM at 40 ºC for 4 h, yielding ethyl (*E*)-3-(2-((((substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)-acrylate derivatives (**9a-l**) (**Scheme-I**).

Ethyl (*E*)-3-(2-(((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-thio)quinolin-3-yl)acrylate (9a): Yield: 61%, m.p.: 142-144 ºC; R_f = 0.32 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.995, 7.995 Hz, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.735 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.410-7.556 (m, 4H), 7.636-7.775 (m, 5H), 7.923 (s, 1H), 8.051 (d, *J* = 7.573 Hz, 1H), 8.288 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.83, 156.58, 148.17, 146.91, 142.90, 136.31, 131.77, 129.84, 129.71, 127.63, 127.59, 127.32, 127.29, 126.93, 126.62, 123.93, 120.68, 118.39, 60.50, 39.53, 22.54, 14.20. MS-ESI for $C_{23}H_{20}N_4O_2S$, *m/z*: 417 $[M+H]^+$. Calculated, %: C, 66.33; H, 4.84; N, 13.45; found, %: C, 66.30; H, 4.80; N, 13.42.

Ethyl (*E*)-3-(2-(((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9b): Yield: 67%, m.p.: 137-139 ºC; R_f = 0.40 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.997, 7.997 Hz, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.735 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.472 (td, *J* = 1.507, 7.358, 7.433 Hz, 1H), 7.688 (s, 4H), 7.636-7.776 (m, 3H), 7.910 (s, 1H), 8.051 (d, *J* = 7.229 Hz, 1H), 8.288 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.83, 156.58, 148.17, 147.01, 142.90, 135.22, 133.52, 131.77, 129.71, 127.63, 127.59, 127.29, 126.93, 126.62, 123.94, 121.19, 119.59, 118.39, 60.50, 39.53, 39.53, 22.54, 14.20. MS-ESI for $C_{23}H_{19}BrN_4O_2S$, *m/z*: 495 $[M+H]^+$. Calculated, %: C, 55.76; H, 3.87; N, 11.31; found, %: C, 55.73; H, 3.84; N, 11.29.

Ethyl(*E*)-3-(2-(((1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9c): Yield: 63%, m.p.: 144-146 ºC; R_f = 0.34 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.996, 7.996 Hz, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.741 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.189-7.287 (m, 2H), 7.371 (d, *J* = 1.980, 6.934 Hz, 1H), 7.472 (td, *J* = 1.509, 7.348, 7.463 Hz, 1H), 7.563 (d, *J* = 2.033, 6.872 Hz, 1H), 7.636-7.775 (m, 3H), 7.972 (s, 1H), 8.051 (d, *J* = 7.343 Hz, 1H), 8.288 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.83, 156.58, 148.17, 146.64, 142.90, 136.51, 131.77, 131.41, 129.71, 127.89, 127.77, 127.63, 127.59, 127.29, 127.10, 126.93, 126.62, 124.45, 120.87, 118.39, 60.50, 39.56, 22.67, 14.20. MS-ESI for $C_{23}H_{19}ClN_4O_2S$, *m/z*: 451 $[M+H]^+$. Calculated, %: C, 61.26; H, 4.25; N, 12.42; found, %: C, 61.23; H, 4.21; N, 12.39.

Ethyl (*E*)-3-(2-(((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9d): Yield: 65%, m.p.: 140-142 ºC; R_f = 0.34 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.989, 7.989 Hz, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.735 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.438-7.506 (m, 2H), 7.505 (d, *J* = 7.339 Hz, 2H), 7.636-7.720 (m, 2H), 7.747 (d, *J* = 2.404, 8.729 Hz, 2H), 7.851 (d, *J* = 7.373 Hz, 2H), 7.920 (s, 1H), 8.051 (d, *J* = 7.262 Hz, 1H), 8.288 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.83, 156.58, 148.17, 147.01, 142.90, 134.66, 134.54, 131.77, 130.24, 129.71, 127.63, 127.59, 127.29, 126.93, 126.62, 123.95, 122.08, 118.39, 60.50, 39.58, 22.54, 14.20. MS-ESI for $C_{23}H_{19}ClN_4O_2S$, *m/z*: 451 $[M+H]^+$. Calculated, %: C, 61.26; H, 4.25; N, 12.42; found, %: C, 61.23; H, 4.21; N, 12.39.



Scheme-I: Synthesis of ethyl (*E*)-3-(2-(((substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylatederivatives (**9a-l**)

Ethyl (*E*)-3-(2-(((1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9e): Yield: 60%, m.p.: 132-130 ºC; R_f = 0.30 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.991, 7.991 Hz, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.735 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 6.914 (d, *J* = 7.360 Hz, 2H), 7.474 (dd, 1H), 7.587 (d, *J* = 7.334 Hz, 2H), 7.636-7.705 (m, 2H), 7.739 (d, 2H), 7.960 (s, 1H), 8.051 (d, *J* = 7.383 Hz, 1H), 8.289 (s, 1H), 10.091 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.83, 156.58, 156.35, 148.17, 147.05, 142.90, 131.77, 129.76, 129.71, 127.63, 127.59, 127.29, 126.93, 126.62, 124.04, 121.82, 118.39, 117.17, 60.50, 39.58, 22.54, 14.20. MS-ESI for $C_{23}H_{20}N_4O_3S$, *m/z*: 433 $[M+H]^+$. Calculated, %: C, 63.87; H, 4.66; N, 12.95; found, %: C, 63.83; H, 4.62; N, 12.93.

Ethyl (*E*)-3-(2-(((1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9f): Yield: 64%, m.p.: 146-148 ºC; R_f = 0.38 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.997, 7.997 Hz, 3H), 3.873 (s, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.737 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.039 (d, *J* = 1.548, 7.468 Hz, 1H), 7.203 (dd, *J* = 1.459, 7.300, 7.388 Hz, 1H), 7.369 (dd, *J* = 1.469, 7.338, 7.447 Hz, 1H), 7.471 (td, *J* = 1.496, 7.275, 7.411 Hz, 1H), 7.636-7.776 (m, 4H), 7.950 (s, 1H), 8.051 (d, *J* = 7.076 Hz, 1H), 8.288 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.83, 156.58, 153.60, 148.17, 146.38, 142.90, 131.77, 129.71, 128.91, 127.63, 127.59, 127.29, 126.93, 126.63, 126.62, 124.66, 124.33, 119.96, 118.39, 113.54, 60.50, 55.68, 39.53, 22.63, 14.20. MS-ESI for $C_{24}H_{22}N_4O_3S$, *m/z*: 447 $[M+H]^+$. Calculated, %: C, 64.56; H, 4.97; N, 12.55; found, %: C, 64.52; H, 4.93; N, 12.53.

Ethyl (*E*)-3-(2-(((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9g): Yield: 66%, m.p.: 141-143 ºC; R_f = 0.38 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.992, 7.992 Hz, 3H), 3.790 (s, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.735 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.000 (d, *J* = 7.342 Hz, 2H), 7.474 (dd, 1H), 7.601 (d, *J* = 7.320 Hz, 2H), 7.636-7.720 (m, 2H), 7.747 (d, *J* = 2.284, 8.599 Hz, 1H), 7.960 (s, 1H), 8.051 (d, *J* = 7.385 Hz, 1H), 8.289 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.83, 159.75, 156.58, 148.17, 147.05, 142.90, 131.77, 131.12, 129.71, 127.63, 127.59, 127.29, 126.93, 126.62, 124.04, 122.13, 118.39, 115.20, 60.50, 55.34, 39.50, 22.54, 14.20. MS-ESI for $C_{24}H_{22}N_4O_3S$, *m/z*: 447 $[M+H]^+$. Calculated, %: C, 64.56; H, 4.97; N, 12.55; found, %: C, 64.52; H, 4.93; N, 12.53.

Ethyl (*E*)-3-(2-(((1-(*o*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9h): Yield: 63%, m.p.: 137-139 ºC; R_f = 0.40 (EtOAc:*n*-hexane 2:3) ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.996, 7.996 Hz, 3H), 2.050 (s, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.735 (s, 1H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.312-7.413 (m, 2H), 7.437-7.528 (m, 2H), 7.495-7.552 (m, 2H), 7.636-7.720 (m, 2H), 7.747 (d, *J* = 2.432, 8.803 Hz, 1H), 7.950 (s, 1H), 8.051 (d, *J* = 7.364 Hz, 1H), 8.288 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.83, 156.58, 148.17, 146.74, 142.90, 137.36, 132.31, 131.77, 130.72, 129.71, 128.36, 127.63, 127.59, 127.29, 126.93, 126.77, 126.62, 124.57, 120.30, 118.39, 60.50, 39.51, 22.65, 17.49, 14.20. MS-ESI for $C_{24}H_{22}N_4O_2S$, *m/z*: 431 $[M+H]^+$. Calculated, %: C, 66.96; H, 5.15; N, 13.01; found, %: C, 66.94; H, 5.12; N, 12.97.

Ethyl (*E*)-3-(2-(((1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9i): Yield: 65%, m.p.: 133-131 ºC;

R_f = 0.40 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.993, 7.993 Hz, 3H), 2.383 (s, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.735 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.338 (d, *J* = 7.228 Hz, 2H), 7.472 (dd, *J* = 1.535, 7.333, 7.428 Hz, 1H), 7.641-7.720 (m, 4H), 7.747 (d, *J* = 2.421, 8.742 Hz, 1H), 7.910 (s, 1H), 8.051 (d, *J* = 7.602 Hz, 1H), 8.288 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.83, 156.58, 148.17, 146.91, 142.90, 137.06, 134.60, 131.77, 130.26, 129.71, 127.63, 127.59, 127.29, 126.93, 126.62, 123.93, 119.97, 118.39, 60.50, 39.56, 39.56, 22.54, 21.07, 14.20. MS-ESI for $C_{24}H_{22}N_4O_2S$, *m/z*: 431 $[M+H]^+$. Calculated, %: C, 66.96; H, 5.15; N, 13.01; found, %: C, 66.94; H, 5.12; N, 12.97.

Ethyl (*E*)-3-(2-(((1-(3-acetylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9j): Yield: 67%, m.p.: 159-161 ºC; R_f = 0.40 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.993, 7.993 Hz, 3H), 2.572 (s, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.735 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.472 (td, *J* = 1.518, 7.362, 7.425 Hz, 1H), 7.636-7.788 (m, 5H), 7.848 (d, 1H), 7.910 (s, 1H), 7.991 (s, 1H), 8.026-8.080 (m, 1H), 8.288 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 197.44, 166.83, 156.58, 148.17, 147.11, 142.90, 137.67, 137.64, 131.77, 129.71, 129.53, 127.63, 127.59, 127.29, 126.93, 126.62, 126.02, 124.16, 121.86, 118.79, 118.39, 60.50, 39.57, 26.69, 22.54, 14.20. MS-ESI for $C_{25}H_{22}N_4O_3S$, *m/z*: 459 $[M+H]^+$. Calculated, %: C, 65.49; H, 4.84; N, 12.22; found, %: C, 65.45; H, 4.81; N, 12.20.

Ethyl (*E*)-3-(2-(((1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9k): Yield: 68%, m.p.: 156-154 ºC; R_f = 0.40 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.994, 7.994 Hz, 3H), 2.527 (s, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.735 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.472 (td, *J* = 1.509, 7.326, 7.412 Hz, 1H), 7.601-7.720 (m, 3H), 7.747 (d, *J* = 2.449, 8.744 Hz, 2H), 7.864 (d, *J* = 7.342 Hz, 2H), 7.920 (s, 1H), 8.051 (d, *J* = 7.273 Hz, 1H), 8.288 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 196.74, 166.83, 156.58, 148.17, 147.01, 142.90, 137.95, 135.35, 131.77, 130.34, 129.71, 127.63, 127.59, 127.29, 126.93, 126.62, 123.90, 119.93, 118.39, 60.50, 39.58, 26.40, 22.54, 14.20. MS-ESI for $C_{25}H_{22}N_4O_3S$, *m/z*: 459 $[M+H]^+$. Calculated, %: C, 65.49; H, 4.84; N, 12.22; found, %: C, 65.45; H, 4.81; N, 12.20.

Ethyl (*E*)-3-(2-(((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (9l): Yield: 70%, m.p.: 164-162 ºC; R_f = 0.8 (EtOAc:*n*-hexane 2:3); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 1.278 (t, *J* = 7.995, 7.995 Hz, 3H), 4.210 (q, *J* = 8.013, 8.013, 8.013 Hz, 2H), 4.735 (s, 2H), 6.341 (d, *J* = 15.110 Hz, 1H), 7.472 (dd, *J* = 1.515, 7.355, 7.426 Hz, 1H), 7.636-7.720 (m, 2H), 7.747 (d, *J* = 2.419, 8.724 Hz, 1H), 7.974-8.025 (m, 3H), 8.051 (d, *J* = 7.458 Hz, 1H), 8.288 (s, 1H), 8.362 (d, *J* = 7.433 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.83, 156.58, 149.44, 148.17, 147.10, 142.90, 139.66, 131.77, 129.71, 127.63, 127.59, 127.29, 126.93, 126.62, 125.98, 123.83, 120.97, 118.39, 60.50, 39.56, 22.54, 14.20. MS-ESI for $C_{23}H_{19}N_5O_4S$, *m/z*: 462 $[M+H]^+$. Calculated, %: C, 59.86; H, 4.15; N, 15.18; found, %: C, 59.83; H, 4.11; N, 15.14.

MTT assay: The cancer cells were carefully plated and nurtured (100 µL each well) in clear-bottom 96-well tissue culture plates at a concentration of 10^5 cells per well. The test solutions were introduced to the well plates at concentrations of 5, 10, 20, 40, 60, 80 and 100 µM in triplicate, following a 24 h cell seeding period, and were subsequently incubated for 72 h. The cells in the wells were washed twice with phosphate buffer solution, followed by the addition of 20 mL of MTT staining solution (5 mg/mL in phosphate buffer solution) to each well. The plate was thereafter incubated at 37 ºC. After 4 h, 100 mL of DMSO was carefully added to each well to dissolve the formazan crystals and a microplate reader was employed to measure the absorbance at 570 nm. Pad Prism Version 5.1 was utilized to calculate the IC_{50} values from the graph.

Docking experimental

Protein preparation: The three-dimensional structure of the target protein was obtained from the RCSB Protein Data Bank (PDB) [22]. Water molecules and other non-essential entities such as ions or cofactors were removed from the protein structure using Discovery Studio Visualizer [23] to ensure a clean docking environment.

Ligand preparation: The molecular structures of the compounds **9a-l**, along with the standard drug doxorubicin and the widely used enoyl reductase inhibitor tamoxifen, were drawn using ChemDraw software. These structures were saved in mol format to be used in the docking studies.

Energy minimization: Prior to docking, energy minimization of the ligand structures was performed using PyRx software [24] to optimize the geometries of compounds **9a-l** and the standard drugs. This step ensures that the ligands are in their most stable conformations for accurate docking analysis.

Molecular docking: The docking studies were conducted using PyRx, a virtual screening software. Each ligand was docked with the prepared target protein and binding affinities were calculated based on the docking scores.

Visualization of ligand-protein interactions: The interactions between the docked ligands and the target protein were visualized using PyMOL [25], Chimera Visualizer and Discovery Studio Visualizer. These tools were used to analyze and identify key interactions such as hydrogen bonds, hydrophobic interactions and π-π stacking, along with the specific amino acid residues involved.

RESULTS AND DISCUSSION

Scheme-I provides an overview of the synthesis of the title compounds ethyl (*E*)-3-(2-(((substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (**9a-l**). The synthesis of the title compounds began with a commercially available compound called acetanilide (**1**), which underwent Vilsmeier-Haack formylation to yield 2-chloroquinoline-3-carbaldehyde (**2**). Sodium sulphide and DMF were then combined and the mixture was stirred for 2 h at room temperature to yield 2-mercaptoquinoline-3-carbaldehyde (**3**). After the compound **3** was propargylated using propargyl bromide (**4**) in DMF for 3-4 h at room temperature with K_2CO_3, it produced 2-(prop-2-yn-1-ylthio)quinoline-3-carbaldehyde (**5**). This

compound then underwent a click reaction with substituted aryl azides (**6a-l**) to form 2-(((substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinoline-3-carbaldehyde (**7a-l**). After a 4 h condensation process using 2-((4,4,4-trifluoro-3-oxobutanoyl)oxy)ethan-1-ylium (**8**) in DCM at 40 ºC with piperdine present, the intermediate compounds (**7a-l**) produced derivatives of ethyl (*E*)-3-(2-(((substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (**9a-l**) in the yields of 60-70%. The spectral data confirmed the structure of final derivatives. Compound **9k** was confirmed by the characteristic two doublets of two olefinic protons, three singlets of triazole and quinoline protons flunked methylene protons and a quartet of methylene protons and triplet of methyl protons appeared at δ 6.341, 7.864, 7.920, 8.288, 4.735, 4.210 and 1.278 ppm in ^{1}H NMR spectrum. ^{13}C NMR spectrum of compound **9k** characteristic carbons of two carbonyl carbons, keto and ester carbons appeared at δ 196.74, 166.83 ppm. Olefinic, triazole, fluncked methylene, methylene and methyl carbons appeared at δ 147.01, 119.93, 39.58, 60.50 and 14.20 ppm, respectively.

Anticancer activity: The MTT assay was applied to conduct a cytotoxicity activity against two cancer cell lines, HT-1080 and A-549, utilizing the novel series of ethyl (*E*)-3-(2-(((substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)-quinolin-3-yl)acrylate derivatives (**9a-l**). Compounds **9c**, **9j** and **9d** had the strongest anticancer activity against the cancer cell lines HT-1080 and A-549 out of all those examined. It is found that compounds **9c** (*o*-chloro), **9j** (*m*-acetyl) and **9d** (*p*-chloro) demonstrated greater efficacy in comparison to the standard drug doxorubicin (Table-1). Their respective IC_{50} values against HT-1080 and A-549 cancer cell lines ranged from 10.19 ± 1.09, 12.19 ± 1.19, 11.76 ± 1.17, 16.45 ± 1.34 and 12.10 ± 1.19, 14.56 ± 1.23 and 21.09 ± 0.23, 25.06 ± 2.11 μM. Compounds **9c**, **9j** and **9d** exhibit activity that can be explained by the electron-drawing effect of the *o*-, *m*- and *p*-chloro groups, which activates the triazole ring. The activity of the other compounds that were substituted with drawing groups and electron donating groups ranged from good to poor.

Molecular docking: The standard drug doxorubicin and the commonly used drug tamoxifen were used in molecular docking investigations against the enzyme enoyl reductase (PDB ID: 1QSG) [26], which is essential for lipid biosynthesis and helps cancer cells proliferate and grow quickly. Enoyl-ACP reductase is a critical enzyme in the fatty acid synthesis pathway. Overexpression of this enzyme is linked to the poor prognosis and tumor aggressiveness in a number of malignancies, including lung, prostate and breast cancers [27]. By reducing the availability of vital fatty acids, targeting enoyl-ACP reductase with certain inhibitors can interfere with the metabolism of cancer cells, hence halting tumor growth and encouraging apoptosis [28]. Because of this, the enoyl-ACP reductase is a potential therapeutic target for the creation of innovative anticancer drugs. Tamoxifen is a selective estrogen receptor modulator (SERM) that is frequently used in both breast cancer therapy and prevention. The binding energies of compounds **9a-l** ranged from -8.6 Kcal/mol to -9.7 Kcal/mol, which is greater than the binding energies of tamoxifen (-8.4 Kcal/mol) and conventional doxorubicin (-8.5 Kcal/mol) (Table-2). Interestingly, compounds **9c** and **9j** demonstrated their greater binding affinities, scoring binding energies of -9.3 Kcal/mol and -9.7 Kcal/mol, respectively (Figs. 1 and 2). The new chemicals and the enoyl reductase can interact by traditional hydrogen bonding, carbon-hydrogen bonding, pi-sigma, pi-anion, pi-cation, pi-alkyl and van der Waals interactions.

TABLE-1
ANTICANCER ACTIVITY OF THE SYNTHESIZED COMPOUNDS (**9a-l**)

Compd.	HT-1080	A-549
9a	49.21 ± 1.23	22.04 ± 1.13
9b	23.45 ± 1.12	47.19 ± 1.04
9c	10.19 ± 1.09	12.19 ± 1.19
9d	12.10 ± 1.19	14.56 ± 1.23
9e	27.19 ± 1.11	34.65 ± 1.11
9f	27.45 ± 1.43	33.29 ± 1.15
9g	15.63 ± 1.51	21.65 ± 1.33
9h	32.10 ± 1.30	41.29 ± 1.76
9i	43.51 ± 1.19	49.34 ± 1.52
9j	11.76 ± 1.17	16.45 ± 1.34
9k	47.12 ± 1.43	54.19 ± 1.67
9l	25.23 ± 1.19	29.57 ± 1.61
Doxorubicin	10.32 ± 1.32	12.27 ± 1.53

TABLE-2
MOLECULAR DOCKING OF THE SYNTHESIZED COMPOUNDS (**9a-l**)

Compd.	Binding energy	Interacting A.A residues	
		H-Bonding	Other types of interactions
9a	-8.8	NIL	ALA 15, SER 19, ILE 20, SER 91, ILE 92, GLY 93, LEU 144, SER 145, TYR 146, MET 159, LYS 163, ALA 189, GLY 190, PRO 191, ILE 192, THR 194, ALA 196, ALA 197, ILE 200, PHE 203, MET 206.
9b	-9.0	ILE 192	GLY 13, SER 19, ILE 20, ALA 21, SER 91, GLY 93, PHE 94, ALA 95, LEU 100, LEU 144, TYR 146, TYR 156, MET 159, LYS 163, PRO 191, THR 194, ALA 196, ALA 197, GLY199,ILE 200, PHE 203, MET 206.
9c	-9.3	ALA 21, SER 91	GLY 13, ALA 15,SER 19, ILE 20, ILE 92, GLY 93, PHE 94,ALA 95, LEU 100, LEU 144, TYR 146, MET 159, LYS 163, ALA 189, GLY 190, PRO 191, ILE 192, THR 194, LEU 195, ALA 196, ALA 197, ILE 200, PHE 203.
9d	-8.6	SER 91, TYR 156	GLY 13, ALA 15, SER 19, ILE 20, ILE 92, GLY 93, LEU 100, LEU 144, TYR 146, TYR 156, MET 159, LYS 163, THR 194, ALA 196, ALA 197, ILE 200, PHE 203, MET 206.
9e	-9.1	GLY 13, SER 91, LYS 163, THR 194	ALA 14, ALA 15, SER 19, ILE 20, ALA 21, TYR 22, ILE 92, GLY 93, LEU 144, TYR 146, TYR 156,MET 159, ALA 189, GLY 190, PRO 191, ILE 192, ALA 196, ALA 197, ILE 200, PHE 203, MET 206.

9f	-9.0	TYR 156, LYS 163	GLY 13, ALA 15, SER 19, ILE 20, ALA 21,SER 91, ILE 92, GLY 93, LEU 100, LEU 144, SER 145, TYR 146, MET 159, ALA 189, GLY 190, PRO 191, ILE 192, THR 194, ALA 196, ILE 200, PHE 203, MET 206.
9g	-8.8	ILE 192	GLY 13, SER 19, ILE 20, ALA 21, SER 91, GLY 93, PHE 94, ALA 95, LEU 100, LEU 144, TYR 146, TYR 156, MET 159, LYS 163, PRO 191, THR 194, ALA 196, ALA 197, GLY 199, ILE 200, PHE 203, MET 206.
9h	-9.2	THR 194	ALA 15, SER 19, ALA 21, SER 91, ILE 92, GLY 93, PHE 94, ALA 95, LEU 100, LEU 144, SER 145, TYR 146, TYR 156, MET 159, LYS 163, ALA 189,PRO 191, ILE 192, THR 194, ALA 196, ALA 197, ILE 200, PHE 203.
9i	-9.1	THR 194	ALA 15, SER 19, ILE 20, SER 91, ILE 92, GLY 93, LEU 144, TYR 146, TYR 156, LYS 163, ALA 189, GLY 190, PRO 191, ILE 192, ALA 196, ALA 197, ILE 200, PHE 203, MET 206.
9j	-9.7	ALA 21, SER 91, ALA 95	ALA 15, SER 19, ILE 20, ILE 92, GLY 93, PHE 94, LEU 100, LEU 144, SER 145, TYR 146, TYR 156, MET 159, LYS 163, ALA 189, GLY 190, PRO 191, ILE 192, THR 194, LEU 195, ALA 196, ALA 197, ILE 200, PHE 203.
9k	-9.0	SER 91	GLY 13, ALA 15, SER 19, ILE 20, ILE 92, GLY 93, LEU144, SER 145, TYR 146, TYR 156, LYS 163, ALA 189, GLY 190, PRO 191, ILE 192, THR 194, LEU 195, ALA 196, ALA 197, ILE 200, PHE 203, MET 206.
9l	-9.2	ALA 21, SER 91	GLY 13, ALA 15, SER 19, ILE 20, ILE 92, GLY 93, LEU 144, SER 145, TYR 146, TYR 156, MET 159, LYS 163, ALA 189, GLY 190, PRO 191, ILE 192, THR 194,LEU 195, ALA 196, ALA 197, ILE 200, PHE 203, MET 206.
Tamoxifen	-8.4	NIL	SER 19, ILE 20, ALA 21, SER 91, GLY 93, PHE 94, ALA 95, LEU 100, LEU 144, TYR 146, TYR 156, MET 159, LYS 163, ALA 189, GLY 190, PRO 191, ILE 192, THR 194, ALA 196, ALA 197, GLY 199, ILE 200, PHE 203, MET 206
Doxo	-8.5	ILE 20, GLY 93, LEU 195	GLY 13, VAL 14, ALA 15, SER 16, SER 19, ALA 21, GLN 40, LEU 44, CYS 63, ASP 64, VAL 65, SER 91, ILE 92, PHE 94, ILE 119, LEU 144, LYS 163, THR 194, ALA 196

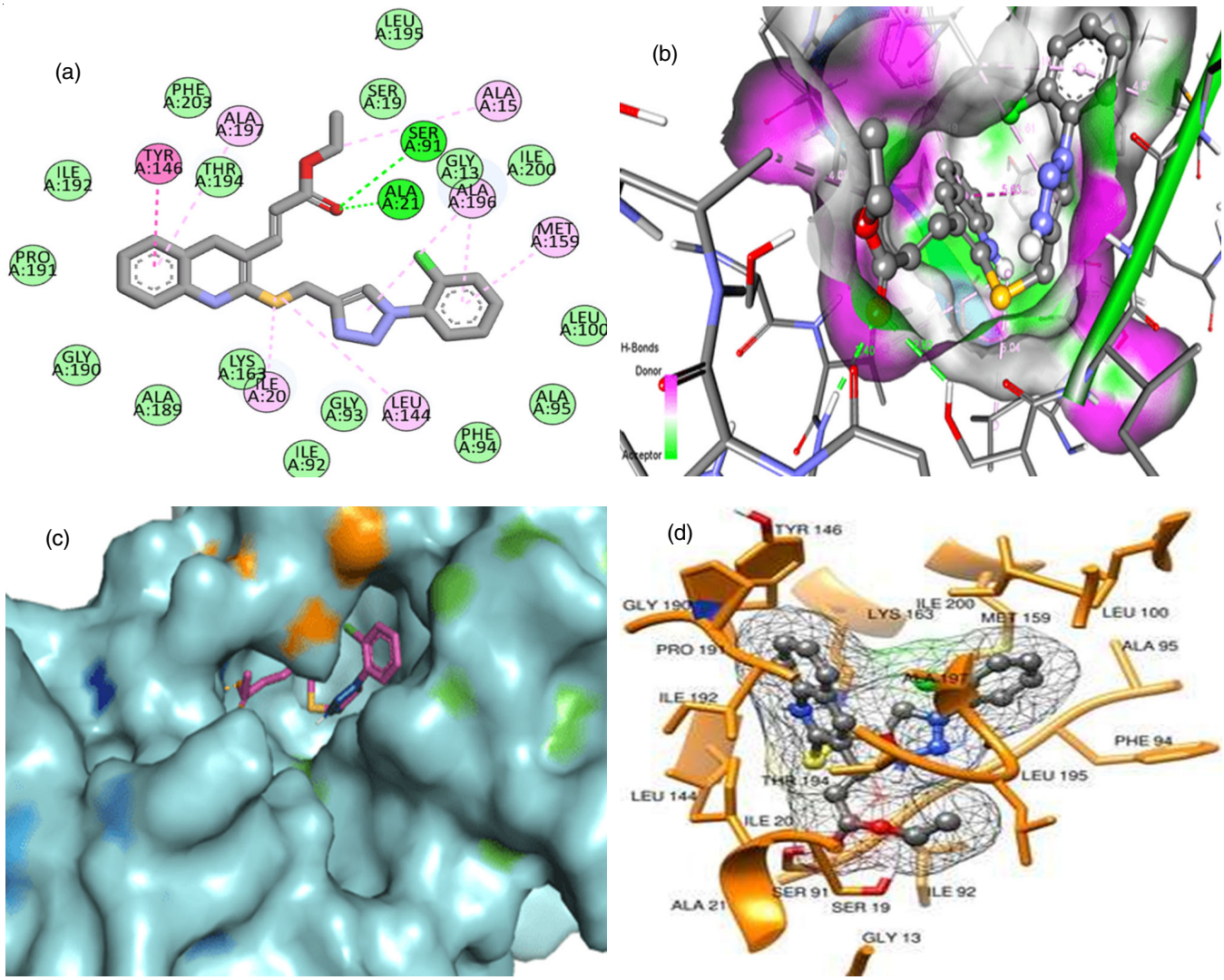


Fig. 1. The interaction images of 2D (a), 3D (b), binding pocket of compound **9c** (c) and within 4 Å (d) with enoyl reductase

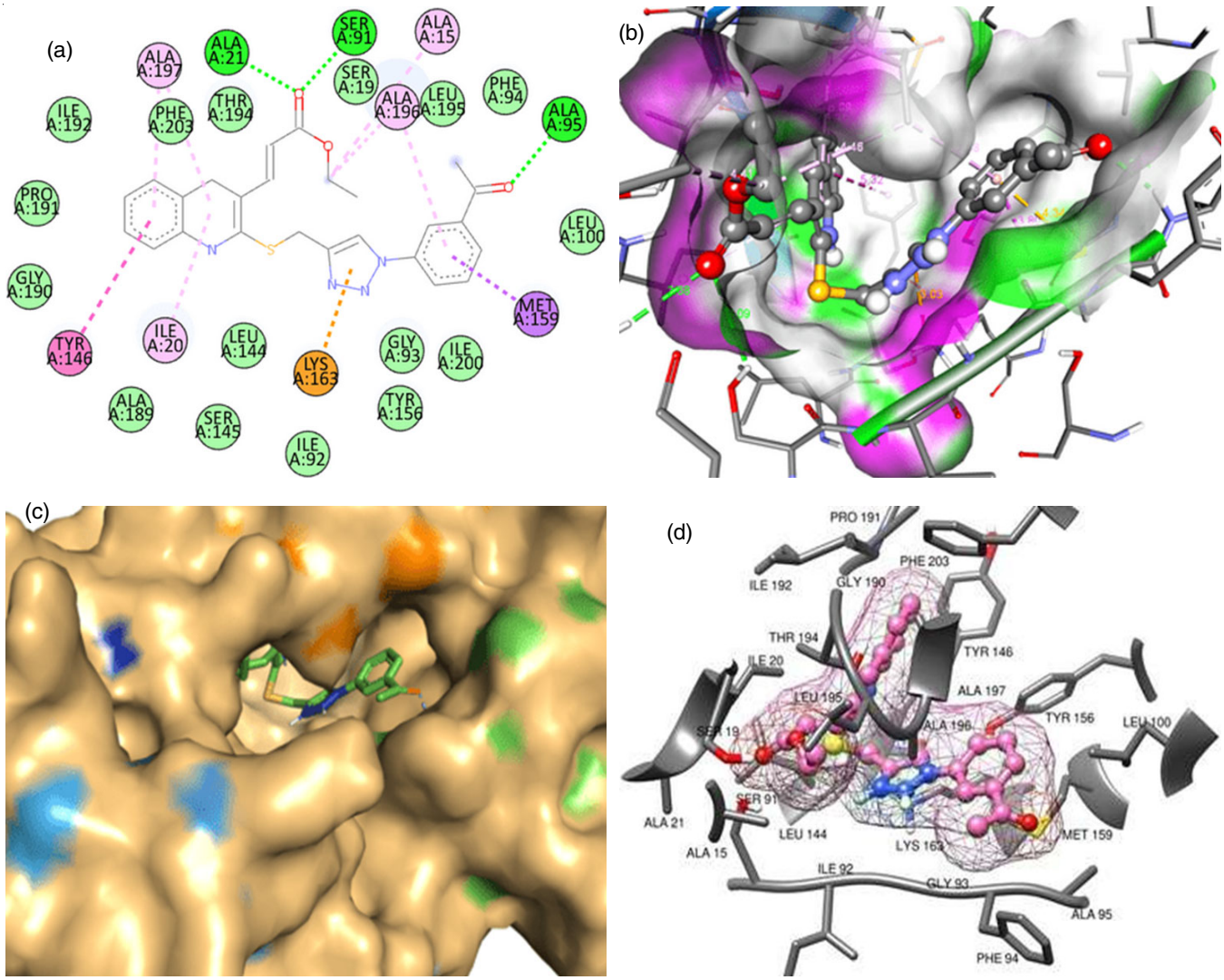


Fig. 2. The interaction images of 2D (a), 3D (b), binding pocket of compound **9j** (c) and within 4 Å (d) with enoyl reductase

Conclusion

A novel series of 1,2,3-triazole and thiadiazole molecular hybrid compounds were synthesized and investigated for their anticancer activity against HT-1080 and MCF-7 cell lines. Among the evaluated series, compounds **9c**, **9j** and **9d**, which consist of phenyl and 4-methoxy phenyl substitutents respectively, have inhibited HT-1080 and A-549 cells, with IC_{50} values comparable to those of standard drug doxorubicin. Nonetheless, the remaining compounds in the series exhibited weak to moderate efficacy against the evaluated cell lines. The hybridization technique enhanced the synthesis of compounds, demonstrating the potential to produce superior lead hybrids for novel anticancer drugs targeting enoyl reductase that support further biological research.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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