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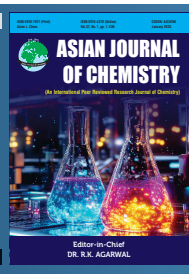

Synthesis and Characterization of Novel 1,2,3-Triazole linked Quinoline-based Thiazolidine-2,4-dione Derivatives as Potential Anticancer Agents and their Molecular Docking Studies

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Novel hybrid molecules incorporating 1,2,3-triazole linked quinoline-based thiazolidine-2,4-dione derivatives (**9a-l**) were synthesized and validated through various ^{1}H NMR, ^{13}C NMR and ESI-MS. All the synthesized hybrid compounds were assessed for their anticancer activity against two cancer cell lines, MCF-7 and HEPG2, utilizing the MTT assay with doxorubicin as the standard reference drug. In comparison to the standard, compounds **9l**, **9h**, **9k**, **9d** and **9b** exhibited superior activity against the tested cancer cell lines, MCF-7 and HEPG2. Additionally, molecular docking studies were conducted on the novel derivatives **9a-l** against dihydrofolate reductase (DHFR), revealing a correlation between the molecular docking results and the observed anticancer activity.

Keywords: 1,2,3-Triazole, Quinoline, Thiazolidine-2,4-dione, Anticancer activity, Molecular docking studies.

INTRODUCTION

Cancer encompasses a complex and multifaceted group of diseases characterized by uncontrolled cell proliferation. Cancer cells form tumours and can impair the immune system, disrupting normal bodily functions. The disease often involves invasion into surrounding tissues and metastasis to distant parts of the body [1]. It is estimated that nearly 10 million deaths globally are attributed to cancer. Despite the availability of various effective therapies, significant challenges remain, including adverse chemotherapy reactions and the development of drug resistance [2]. Consequently, cancer research is essential for the discovery of novel and improved therapeutic approaches. Ultimately, such investigation contributes to the advancement of successful, cost-effective drug development, enhancing patient's chances of recovery and their overall quality of life.

Heterocyclic compounds play a crucial role in many medicinal applications, display their importance in the development of new cancer treatments. The incorporation of such structures into drug design enhances the efficacy and safety of therapeutic interventions [3,4]. Quinoline, often referred to as benzo-pyridine or aza-naphthalene, is an aromatic nitrogen-containing heterocyclic compound composed of pyridine and benzene [5]. This scaffold exhibits a broad range of pharmacological activities, including anti-inflammatory [6], anti-HCV [7], anti-tubercular [8-10], antimalarial [11,12], anti-HIV [13,14] activities. The quinoline scaffold is particularly significant in anticancer research due to its various mechanisms of action, such as growth inhibition *via* cell cycle arrest, induction of apoptosis, inhibition of angiogenesis, disruption of cell migration and modulation of nuclear receptor responsiveness [15].

Furthermore, 1,2,3-triazole derivatives represent a prominent class of nitrogen-containing heterocycles that can establish diverse non-covalent interactions with various biological targets, including hydrophobic interactions, hydrogen bonds, van der Waals forces and dipole-dipole interactions. These compounds exhibit a wide array of pharmacological properties, including antioxidant [16], antiviral [17], antidiabetic [18], antifungal [19], anticancer [20,21] and antiobesity [22] activities. Notably, certain 1,2,3-triazole-containing compounds, such as cefatrizine and carboxyamido-triazole, have been utilized in clinical settings or are under clinical evaluation for cancer treatment, highlighting their potential as promising anticancer agents [23].

Thiazolidinedione (TZD) derivatives, particularly those that act as PPARγ agonists, play a significant role in cancer treatment by affecting gene expression related to cell death (apoptosis) and cancer growth. When thiazolidinedione derivatives bind to the PPARγ receptor, they activate various genes involved in metabolism, inflammation and cell differentiation. This activation can influence key pathways in cancer development, such as PI3K/Akt and MAPK, leading to an environment that promotes apoptosis and inhibits cancer cell growth [24,25]. Moreover, TZDs can induce cell death by blocking the VEGFR-2 pathway, which is involved in the tumour blood supply and growth [26]. In addition, the molecular docking has become an increasingly essential technique within the field of drug discovery. This computational method predicts the affinity of ligands for receptor proteins, enabling a detailed characterization of the interactions between small molecules and proteins at the atomic level. Through molecular docking, researchers can elucidate the behaviour of small compounds within target protein binding sites, as well as clarify essential biochemical processes.

Molecular hybridization represents a strategic approach in drug discovery, wherein researchers endeavour to create novel therapeutics by amalgamating components of two or more existing drugs or active compounds [27,28]. This is accomplished through the utilization of a chemical linker to facilitate their connection. One promising avenue being pursued to address various challenges is the synthesis of hybrid molecules based on triazole, which exhibit multiple mechanisms of action directed towards different targets within microbial cells. The extension of the triazole pharmacophore by incorporating an additional fragment, whether directly or *via* a linker, is a subject of considerable interest. The hybridization of triazole ring can significantly influence its activity by enhancing binding affinity to the target, improving specificity, mitigating resistance and increasing potency, thereby contributing to the advancement of more effective anticancer agents [29]. The overarching objective of this research is to develop new hybrid compounds that exhibit superior efficacy compared to the original drugs, while also enabling the targeting of diverse pathways and the formulation of innovative treatments [30].

EXPERIMENTAL

All chemicals and solvents were purchased from different commercial vendors and used only after further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO by using 500 MHz spectrometers (Bruker Avance III 500 MHz). Purification by using column chromatography was performed on silica gel (60-120 mesh) using distilled hexane and ethyl acetate solvents. The mass and infrared spectra were recorded on QSTAR XL GCMS, Shimadzu FT-IR-8400s mass spectrometer. Melting points were determined in open glass capillary tube on a DbkProg. melting point apparatus and are uncorrected.

Synthesis of 2-chloroquinoline-3-carbaldehyde (2): The synthesis of 2-chloroquinoline-3-carbaldehyde (**2**) was acheived from the commercially available acetanilide (**1**) by following Vilsmeier-Haack formylation method as described elsewhere.

Synthesis of 2-mercaptoquinoline-3-carbaldehyde (3): 2-chloroquinoline-3-carbaldehyde (**2**) (1 mmol) was reacted with Na_2S (2 mmol) in presence DMF solvent stirred for 2 h at room temperature to obtain 2-mercapto-quinoline-3-carbaldehyde (**3**).

Synthesis of 2-(prop-2-yn-1-ylthio)quinoline-3-carbaldehyde (5): Synthesis of 2-(prop-2-yn-1-ylthio)quinoline-3-carbaldehyde (**5**) from compound **3** (1 mmol) which upon propargylated by using propargyl bromide (**4**) (1.2 mmol) in the presence of K_2CO_3 in DMF solvent 3-4 h at room temperature to obtain 2-(prop-2-yn-1-ylthio)quinoline-3-carbaldehyde (**5**).

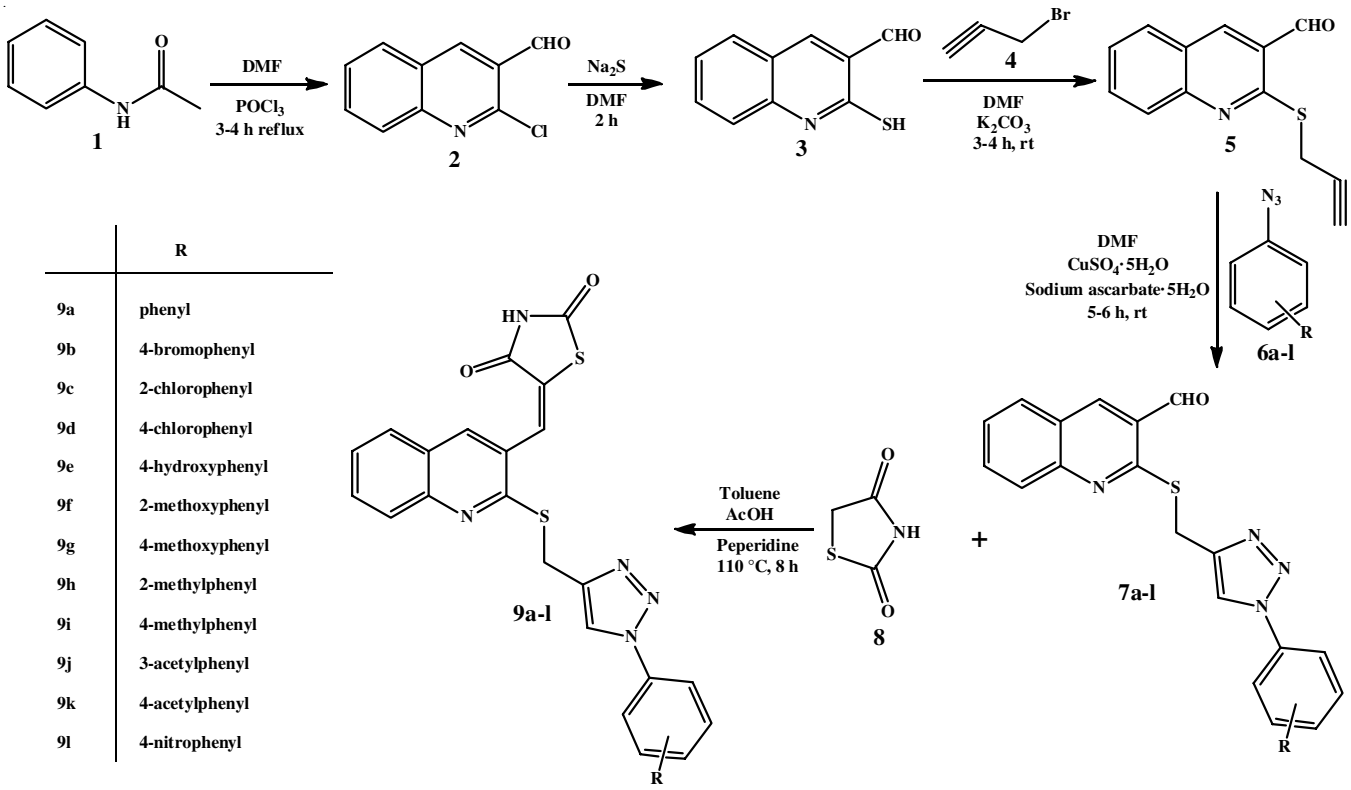
Synthesis of 2-(((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinoline-3-carbaldehyde (7a-l): Synthesis of 2-(((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinoline-3-carbaldehyde (**7a-l**) from compound **5** (1 mmol), which on further click reaction with substituted aryl azides (**6a-l**) to the formation of 2-(((substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-thio)quinoline-3-carbaldehyde (**7a-l**) [31].

Synthesis of (*E*)-5-((2-(((substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9a-l): Synthetic protocol for the synthesis of title compounds ethyl (*E*)-3-(2-(((substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)acrylate (**9a-l**) from the intermediate compounds (**7a-l**) (1 mmol) condensation with thiazolidine-2,4-dione (**8**, 1.5 mmol) in presence of piperdine and catalytical amount of acetic acid in toluene reflux at 100 ºC for 8 h to obtain (*E*)-5-((2-(((substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)methylene)-thiazolidine-2,4-dione derivatives (**9a-l**) (**Scheme-I**).

(*E*)-5-((2-(((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9a): Yield: 62%, m.p.: 147-149 ºC; R_f: 0.32 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{22}H_{15}N_5O_2$: calcd. (found) %: C, 59.31 (59.29); H, 3.39 (3.38); N, 15.72 (15.70); IR (KBr, ν_{max}, cm^{-1}): 2321, 1736, 1683, 1593,1531; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 4.741 (s, 2H), 7.410-7.556 (m, 4H), 7.636-7.725 (m, 3H), 7.749 (d, *J* = 8.166 Hz, 1H), 7.997-8.093 (m, 3H), 8.352 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.68, 164.53, 158.47, 148.41, 147.01, 136.31, 130.42, 129.90, 129.84, 129.79, 127.68, 127.32, 127.25, 126.93, 126.62, 125.71, 123.93, 122.96, 121.42, 120.68, 39.58, 22.55.

(*E*)-5-((2-(((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)thio)quinolin-3-l)methylene)thiazolidine-2,4-dione (9b): Yield: 66%, m.p.: 140-142 ºC; R_f: 0.36 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{22}H_{14}BrN_5O_2S_2$: calcd. (found) %: C, 50.39 (50.37); H, 2.69 (2.66); N, 13.35 (13.33); IR (KBr, ν_{max}, cm^{-1}): 2229, 1730, 1674, 1604, 1533; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 4.741 (s, 2H), 7.472 (td, *J* = 1.508, 7.369, 7.435 Hz, 1H), 7.663 (dd, *J* = 1.444, 7.485 Hz, 1H), 7.688 (s, 4H), 7.723-7.776 (m, 1H), 8.008 (s, 1H), 8.026-8.093 (m, 2H), 8.352 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.68, 164.53, 158.47, 148.41, 147.01, 135.22, 133.52, 130.42, 129.78, 127.68, 127.25, 126.93, 126.62, 125.71, 123.94, 122.96, 121.42, 121.19, 119.59, 39.51, 22.55.

(*E*)-5-((2-(((1-(2-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9c): Yield: 63%, m.p.: 145-147 ºC; R_f: 0.34 (EtOAc:*n*-hexane



Scheme-I

2:3); Elemental analysis of $C_{22}H_{14}ClN_5O_2S_2$: calcd. (found) %: C, 55.06 (55.03); H, 2.94 (2.93); N, 14.59 (14.56); IR (KBr, ν_{max}, cm^{-1}): 2315, 1734, 1683, 1592, 1531; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 4.735 (s, 2H), 7.238 (dd, *J* = 1.824, 7.548, Hz, 2H), 7.371 (dd, *J* = 1.978, 6.938 Hz, 1H), 7.472 (td, *J* = 1.532, 7.326, 7.457 Hz, 1H), 7.563 (dd, *J* = 1.993, 6.888 Hz, 1H), 7.670 (td, *J* = 1.496, 7.326, 7.437 Hz, 1H), 7.723-7.776 (m, 1H), 7.972 (s, 1H), 8.026-8.093 (m, 2H), 8.352 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.68, 164.53, 158.47, 148.41, 146.64, 136.51, 131.41, 130.42, 129.78, 127.89, 127.77, 127.68, 127.25, 127.10, 126.93, 126.62, 125.71, 124.45, 122.96, 121.42, 120.87, 39.56, 22.66.

(*E*)-5-((2-(((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9d): Yield: 65%, m.p.: 148-150 ºC; R_f: 0.34 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{22}H_{14}ClN_5O_2S_2$: calcd. (found) %: C, 55.06 (55.03); H, 2.94 (2.93); N, 14.59 (14.56); IR (KBr, ν_{max}, cm^{-1}): 2315, 1734, 1683, 1592, 1531; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 4.741 (s, 2H), 7.437-7.515 (m, 2H), 7.512 (s, 1H), 7.670 (td, *J* = 1.476, 7.326, 7.453 Hz, 1H), 7.749 (d, *J* = 8.139 Hz, 1H), 7.851 (d, *J* = 7.375 Hz, 2H), 8.008 (s, 1H), 8.059 (d, *J* = 15.396 Hz, 2H), 8.352 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.68, 164.53, 158.47, 148.41, 147.01, 134.66, 134.54, 130.42, 130.24, 129.78, 127.68, 127.25, 126.93, 126.62, 125.71, 123.95, 122.96, 122.08, 121.42, 39.58, 22.55.

(*E*)-5-((2-(((1-(4-Hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9e): Yield: 60%, m.p.: 144-146 ºC; R_f: 0.34 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{22}H_{15}N_5O_3S_2$: calcd. (found) %: C, 57.26 (57.23); H, 3.28 (3.24); N, 15.18 (15.16); IR (KBr, ν_{max}, cm^{-1}): 3119, 1735, 1681, 1593, 1511; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 4.741 (s, 2H), 6.914 (d, *J* = 7.358 Hz, 2H), 7.472 (td, *J* = 1.515, 7.326, 7.424 Hz, 1H), 7.587 (d, *J* = 7.347 Hz, 2H), 7.670 (td, *J* = 1.475, 7.326, 7.438 Hz, 1H), 7.723-7.776 (m, 1H), 8.005 (s, 1H), 8.059 (d, *J* = 15.411 Hz, 2H), 8.352 (s, 1H), 10.091 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.68, 164.53, 158.47, 156.35, 148.41, 147.10, 130.42, 129.78, 129.76, 127.68, 127.25, 126.93, 126.62, 125.71, 124.04, 122.96, 121.82, 121.42, 117.17, 39.53, 22.55.

(*E*)-5-((2-(((1-(2-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9f): Yield: 64%, m.p.: 139-141 ºC; R_f: 0.35 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{23}H_{17}N_5O_3S_2$: calcd. (found) %: C, 58.09 (58.07); H, 3.60 (3.57); N, 14.73 (14.70); IR (KBr, ν_{max}, cm^{-1}): 2319, 17332, 1677, 1614, 1515; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.873 (s, 3H), 4.737 (s, 2H), 7.039 (dd, *J* = 1.532, 7.469 Hz, 1H), 7.203 (td, *J* = 1.464, 7.302, 7.400 Hz, 1H), 7.369 (td, *J* = 1.469, 7.336, 7.445 Hz, 1H), 7.471 (td, *J* = 1.493, 7.272, 7.405 Hz, 1H), 7.636-7.776 (m, 3H), 8.010-8.093 (m, 3H), 8.352 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.68, 164.53, 158.47, 153.60, 148.41, 146.38, 130.42, 129.78, 128.91, 127.68, 127.25, 126.93, 126.63, 126.62, 125.71, 124.66, 124.33, 122.96, 121.42, 119.96, 113.54, 55.68, 39.58, 22.68.

(*E*)-5-((2-(((1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9g): Yield: 65%, m.p.: 143-145 ºC; R_f: 0.35 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{23}H_{17}N_5O_3S_2$: calcd. (found) %: C,

58.09 (58.07); H, 3.60 (3.57); N, 14.73 (14.70); IR (KBr, ν_{max}, cm^{-1}): 2312, 1731, 1674, 1609, 1511; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 3.790 (s, 3H), 4.741 (s, 2H), 7.000 (d, *J* = 7.339 Hz, 2H), 7.472 (td, *J* = 1.507, 7.326, 7.427 Hz, 1H), 7.601 (d, *J* = 7.297 Hz, 2H), 7.670 (td, *J* = 1.481, 7.326, 7.443 Hz, 1H), 7.723-7.776 (m, 1H), 8.005 (s, 1H), 8.026-8.093 (m, 2H), 8.352 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.68, 164.53, 159.75, 158.47, 148.41, 147.10, 131.12, 130.42, 129.78, 127.68, 127.25, 126.93, 126.62, 125.71, 124.04, 122.96, 122.13, 121.42, 115.20, 55.34, 39.56, 22.55.

(*E*)-5-((2-(((1-(*o*-Tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9h): Yield: 63%, m.p.: 134-136 ºC; R_f: 0.36 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{23}H_{17}N_5O_2S_2$: calcd. (found) %: C, 60.11 (60.08); H, 3.73 (3.71); N, 15.24 (15.22); IR (KBr, ν_{max}, cm^{-1}): 2316, 1732, 1684, 1606, 1537; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 2.050 (s, 3H), 4.741 (s, 2H), 7.312-7.413 (m, 2H), 7.438-7.506 (m, 1H), 7.477-7.550 (m, 2H), 7.636-7.705 (m, 1H), 7.749 (d, *J* = 7.907 Hz, 1H), 7.950 (s, 1H), 8.026-8.093 (m, 2H), 8.352 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.68, 164.53, 158.47, 148.41, 146.74, 137.36, 132.31, 130.72, 130.42, 129.78, 128.36, 127.68, 127.25, 126.93, 126.77, 126.62, 125.71, 124.57, 122.96, 121.42, 120.30, 39.51, 22.66, 17.49.

(*E*)-5-((2-(((1-(*p*-Tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9i): Yield: 66%, m.p.: 137-139 ºC; R_f: 0.36 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{23}H_{17}N_5O_2S_2$: calcd. (found) %: C, 60.11 (60.08); H, 3.73 (3.71); N, 15.24 (15.22); IR (KBr, ν_{max}, cm^{-1}): 2321, 1734, 1681, 1602, 1533; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 2.383 (s, 2H), 4.741 (s, 2H), 7.338 (d, *J* = 7.156 Hz, 1H), 7.438-7.506 (m, 1H), 7.672 (dd, *J* = 5.646, 7.935 Hz, 2H), 7.749 (d, *J* = 7.961 Hz, 1H), 7.997-8.093 (m, 2H), 8.352 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.68, 164.53, 158.47, 148.41, 147.01, 137.06, 134.60, 130.42, 130.26, 129.78, 127.68, 127.25, 126.93, 126.62, 125.71, 123.93, 122.96, 121.42, 119.97, 39.59, 39.58, 22.55, 21.07.

(*E*)-5-((2-(((1-(3-Acetylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9j): Yield: 67%, m.p.: 147-149 ºC; R_f: 0.38 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{24}H_{17}N_5O_3S_2$: calcd. (found) %: C, 59.12 (59.10); H, 3.51 (3.49); N, 14.36 (14.33); IR (KBr, ν_{max}, cm^{-1}): 2321, 1734, 1672, 1591, 1527; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 2.630 (s, 3H), 4.741 (s, 2H), 7.472 (td, *J* = 1.526, 7.337, 7.423 Hz, 1H), 7.636-7.719 (m, 2H), 7.723-7.788 (m, 2H), 7.846 (dd, *J* = 1.962, 7.390 Hz, 1H), 7.991 (d, *J* = 1.729 Hz, 1H), 8.057 (dd, *J* = 6.358, 9.144 Hz, 3H), 8.352 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 197.44, 167.68, 164.53, 158.47, 148.41, 147.11, 137.67, 137.64, 130.42, 129.78, 129.53, 127.68, 127.25, 126.93, 126.62, 126.02, 125.71, 124.16, 122.96, 121.86, 121.42, 118.79, 39.53, 26.69, 22.55.

(*E*)-5-((2-(((1-(4-Acetylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9k): Yield: 69%, m.p.: 153-155 ºC; R_f: 0.38 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{24}H_{17}N_5O_3S_2$: calcd. (found) %: C, 59.12 (59.10); H, 3.51 (3.49); N, 14.36 (14.33); IR (KBr, ν_{max}, cm^{-1}): 2321, 1734, 1672, 1591, 1527; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 2.510 (s, 3H), 4.741 (s, 2H), 7.472 (td, *J* = 1.508, 7.344, 7.425 Hz, 1H), 7.600-7.705 (m, 3H), 7.723-7.776 (m, 1H), 7.864 (d, *J* = 7.338 Hz, 2H), 7.997-8.093 (m, 3H), 8.352 (s, 1H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 196.74, 167.68, 164.53, 158.47, 148.41, 147.01, 137.95, 135.35, 130.42, 130.34, 129.78, 127.68, 127.25, 126.93, 126.62, 125.71, 123.90, 122.96, 121.42, 119.93, 39.58, 26.40, 22.55.

(*E*)-5-((2-(((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (9l): Yield: 70%, m.p.: 157-159 ºC; R_f: 0.36 (EtOAc:*n*-hexane 2:3); Elemental analysis of $C_{22}H_{14}N_6O_4S_2$: calcd. (found) %: C, 53.87 (53.85); H, 2.88 (2.85); N, 17.13 (17.10); IR (KBr, ν_{max}, cm^{-1}): 2327, 1732, 1680, 1597, 1529; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 4.741 (s, 2H), 7.472 (td, *J* = 1.507, 7.326, 7.410 Hz, 1H), 7.670 (td, *J* = 1.479, 7.311, 7.419 Hz, 1H), 7.723-7.776 (m, 1H), 8.000 (d, *J* = 7.819 Hz, 3H), 8.026-8.093 (m, 2H), 8.361 (d, *J* = 7.735 Hz, 3H), 11.114 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.68, 164.53, 158.47, 149.44, 148.41, 147.10, 139.66, 130.42, 129.78, 127.68, 127.25, 126.93, 126.62, 125.98, 125.71, 123.83, 122.96, 121.42, 120.97, 39.54, 22.55.

MTT assay: The cancer cells were appropriately plated and cultured (100 µL per well) in a clear bottom 96-well tissue culture plates with a concentration of 10^5 cells per well. The test samples were added to the well plates with concentrations ranging from 5 to 100 µM (5, 10, 20, 40, 60, 80 and 100 µM) in triplicate after 24 h seeding the cells were incubated for 72 h. Phosphate buffer solution was used to wash the cells in well for twice followed by adding 20 µL of MTT staining solution (5 mg/mL in phosphate buffer solution) to each well. The place was then incubated at 37 ºC. Subsequently, after 4 h, 100 µL of DMSO was carefully added to each well in order to dissolve the formazan crystals and micro plate reader was used to record the absorbance at 570 nm. Pad Prism Version 5.1. graph was employed to calculate the IC_{50} values.

Docking studies: The protein structure was obtained from RCSB PDB database [32]. Water molecules and other entities were cleaned from the protein using Discovery Studio Visualizer [33]. ChemDraw software was used to draw the molecular structures of compounds **9a-l**, the standard drug doxorubicin and widely used drug methotrexate. The docking studies were performed using PyRx, a virtual screening software [34,35]. Visualization of the interactions of the ligands with the target protein was done using Pymol [36] and Discovery Studio visualizer.

RESULTS AND DISCUSSION

The synthetic pathway of the title compounds, (*E*)-5-((2-(((substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione (**9a-l**), is illustrated in **Scheme-I**. The synthesis of the desired compounds commenced with the commercially available acetanilide (**1**), which underwent Vilsmeier-Haack formylation to yield 2-chloroquinoline-3-carbaldehyde (**2**). Subsequently, compound **2** was

reacted with sodium sulfide in the presence of DMF and stirred for 2 h at ambient temperature, resulting in the formation of 2-mercaptoquinoline-3-carbaldehyde (**3**). This compound was further advanced through a reaction with propargyl bromide (**4**) in the presence of K_2CO_3 in DMF, conducted over 3-4 h at room temperature, leading to the formation of 2-(prop-2-yn-1-ylthio)quinoline-3-carbaldehyde (**5**). Compound **5** subsequently underwent a click reaction with substituted aryl azides (**6a-l**), facilitating the formation of 2-(((substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinoline-3-carbaldehyde (**7a-l**). The intermediate compounds (**7a-l**) were then subjected to condensation with thiazolidine-2,4-dione (**8**) in the presence of piperidine and catalytic acetic acid in toluene at 110 ºC for 8 h, resulting in the synthesis of (*E*)-5-((2-(((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinolin-3-yl)methylene)thiazolidine-2,4-dione derivatives (**9a-l**). The products obtained exhibited yields ranging from 70% to 80%.

Anticancer activity: The novel series of substituted thiazolidine-2,4-dione derivatives (**9a-l**) were evaluated to carry out the cytotoxicity study against two cancer cell lines MCF-7 and HEPG-2 using MTT assay. Among all the tested compounds **9j**, **9l**, **9k**, **9h** and **9d** showed superior anticancer activity against both cancer cell lines MCF-7 and HEPG-2 cell lines. The calculated IC_{50} values of compound **9a-l** are presented in Table-1. Compound **9j** (*m*-acetyl), compound **9l** (*p*-nitro), compound **9k** (*p*-acetyl), compound **9h** (*o*-methyl) and compound **9d** (*p*-chloro) exhibited superior activity compared with standard drug doxorubicin with IC_{50} ranging from 0.598 ± 0.08, 0.923 ± 0.07, 0.563 ± 0.09, 0.893 ± 0.03, 0.698 ± 0.07, 1.254 ± 0.15, 0.643 ± 0.03, 0.957 ± 0.07 and 0.743 ± 0.03, 1.052 ± 0.02 μM against MCF-7 and HEPG-2 cancer cell lines, respectively. The anticancer activity of compounds **9j**, **9l**, **9k**, **9h** and **9d** may be attributed to electron with drawing and electron donating effect

TABLE-1
CYTOTOXICITY OF COMPOUNDS **9a-l** AGAINST MCF-7 AND HEPG2

Compound	MCF-7	HEPG2
9a	1.671 ± 0.09	1.542 ± 0.03
9b	1.015 ± 0.05	0.976 ± 0.03
9c	1.763 ± 0.03	0.987 ± 0.03
9d	0.743 ± 0.03	1.052 ± 0.02
9e	1.023 ± 0.09	1.431 ± 0.01
9f	1.053 ± 0.07	1.437 ± 0.19
9g	1.894 ± 0.04	1.983 ± 0.04
9h	0.643 ± 0.03	0.957 ± 0.07
9i	0.932 ± 0.08	0.957 ± 0.03
9j	0.598 ± 0.08	0.923 ± 0.07
9k	0.698 ± 0.07	1.254 ± 0.15
9l	0.563 ± 0.09	0.893 ± 0.03
Doxorubicin	0.534 ± 004	0.871 ± 0.13

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

Molecule	Binding energy	Interacting A.A residues	
		H-Bonding	Other types of interactions
9a	-9.3	ILE 5, TRP 22	ALA 6, ALA 7, ILE 14, GLY 15, MET 16, GLU 17, MET 20, LEU 28, PHE 31, HIS 45, THR 46, SER 49, ILE 50, LEU 54, ILE 94, GLY 96, GLY 97, TYR 100
9b	-9.6	TRP 22	ILE 5, ALA 6, ALA 7, ILE 14, GLY 15, MET 16, GLU 17, ALA 19, MET 20, LEU 28, PHE 31, HIS 45, THR 46, SER 49, ILE 50, LEU 54, ILE 94, GLY 96, TYR 100
9c	-9.6	ALA 7	ALA 6, ALA 7, ILE 14, GLY 15, MET 16, GLU 17, ASN 18, ALA 19, MET 20, TRP 22, ASN 23, LEU 24, ASP 27, LEU28, HIS 45, THR 46, SER 49, ILE 94, GLY 96, GLY 97, TYR 100
9d	-9.7	NIL	ILE 5, ALA 6, ALA 7, ILE 14, GLY 15, MET 16, GLU 17, ALA 19, MET 20, TRP 22, LEU 28, PHE 31, HIS 45, THR 46, SER 49, ILE 50, LEU 54, ILE 94, GLY 96, TYR 100
9e	-9.1	ALA 7	ALA 6, ALA 7, ILE 14, GLY 15, MET 16, GLU 17, MET 20, TRP 22, LEU 28, PHE 31, HIS 45, THR 46, SER 49, ILE 50, ARG 52, LEU 54, ILE 94, GLY 95, GLY 96, GLY 97, TYR 100
9f	-9.1	THR 46	ALA 7, GLY 15, MET 16, GLU 17, ASN 18, ALA 19, MET 20, TRP 22, ASN 23, LEU 24, ASP 27, LEU 28, PHE 31, HIS 45, SER 49, ILE 50, LEU 54, ILE 94
9g	-9.0	ALA 7	ALA 6, ALA 7, ILE 14, MET 16, GLU 17, MET 20, TRP 22, LEU 28, PHE 31, HIS 45, THR 46, SER 49, ILE 50, LEU 54, ILE 94, GLY 95, GLY 96, GLY 97, TYR 100
9h	-10.0	ILE 5, TRP 22	ALA 6, ALA 7, ILE 14, GLY 15, MET 16, GLU 17, MET 20, ASP 27, LEU 28, PHE 31, HIS 45, THR 46, SER 49, ILE 50, LEU 54, ILE 94, GLY 96, TYR 100
9i	-9.8	NIL	ILE 5, ALA 6, ALA 7, ILE 14, GLY 15, MET 16, GLU 17, ALA 19, MET 20, TRP 22, LEU 28, PHE 31, HIS 45, THR 46, SER 49, ILE 50, LEU 54, ILE 94, GLY 96, TYR 100
9j	-9.4	ALA 7, THR 46	ILE 5, ALA 6, ALA 7, ILE 14, GLY 15, MET 16, GLU 17, ALA 19, MET 20, LEU 28, PHE 31, HIS 45, SER 49, ILE 50, ARG 52, LEU 54, ILE 94, GLY 95, GLY 96, TYR 100
9k	-9.8	ILE 5	ALA 6, ALA 7, ILE 14, GLY 15, MET 16, GLU 17, MET 20, TRP 22, LEU 28, PHE 31, HIS 45, THR 46, SER 49, ILE 50, LEU 54, ILE 94, GLY 95, GLY 96, TYR 100
9l	-10.3	ASP 27, THR 46, GLY 96	ILE 5, ALA 6, ALA 7, GLY 15, MET 16, GLU 17, ASN 18, ALA 19, MET 20, LEU 28, TRP30, PHE 31, HIS 45, SER 49, ILE 50, LEU 54, GLY 97, TYR 100
Methotrexate	-9.4	ILE 5, GLY 15, ASP 27, HIS 45, THR 46, ILE 94, GLY 96, ARG 98, TYR 100, THR 123	ALA 6, ALA 7, MET 16, GLU 17, ALA 19, MET 20, TRP 22, LEU 28, TRP 30, PHE 31, GLY 43, ARG 44, SER 49, GLY 95, GLY 97, VAL 99
Doxo	-8.5	ASP 27	ILE 5, ALA 6, ALA 7, ILE 14, GLY 15, MET 20, LEU 28, TRP 30, PHE 31, HIS 45, THR 46, SER 49, ILE 50, ARG 52, LEU 54, ILE 94, GLY 96, TYR 100

of *m*-acetyl, *p*-nitro, *p*-acetyl, *o*-metyl and *p*-chloro groups are *ortho* and *para*-directing nature which activates triazole ring. The other compounds substituted with electron donating and withdrawing group indicated good to poor activity.

Molecular docking studies: Molecular docking investigations were performed on the novel derivatives **9a-l** with the standard reference drug doxorubicin and widely used drug methotrexate [37] against the dihydrofolate reductase (DHFR), (PDB ID: 4DFR) [38]. Dihydrofolate reductase (DHFR) is a critical enzyme in cellular metabolism, particularly in the synthesis of nucleotides, which are the building blocks of DNA and RNA. Rapidly dividing cells, such as cancer cells, have a high demand for nucleotides and thus require increased DHFR activity [39]. This makes DHFR a target for chemotherapy drugs. DHFR inhibitors are integral in cancer treatment regimens, particularly in hematologic malignancies and solid tumours.

Methotrexate is a commonly used chemotherapeutic agent and immune suppressant that inhibits DHFR, preventing the formation of (THF) and thereby inhibiting DNA synthesis and cell division [40]. All the synthesized compounds **9a-l** displayed binding energies ranging from -9.0 Kcal/mol to -10.3 kcal/mol, which is superior to the binding energy of standard reference drug doxorubicin (-8.5 Kcal/mol) and close to methotrexate (-9.4 Kcal/mol) (Table-2). Remarkably, compounds **9h** and **9l** scored binding energies of -10.0 and -10.3 Kcal/mol respectively, displaying their superior binding affinities. This can be attributed to the conventional hydrogen bonding interactions, carbon-hydrogen bonding, pi-sigma, pi-anion, pi-cation, pi-alkyl and van der Waals interactions between the novel compounds and the enoyl reductase (Fig. 1).

Conclusion

A novel series of 1,2,3-triazole linked quinoline based thiazolidine-2,4-dione hybrids weres ynthesized, characterized and evaluated for their anticancer activity against MCF-7 and HEPG2 cell lines. Among the tested series, compounds **9j**, **9l**, **9k**, **9h** and **9d** containing phenyl and 4-methoxy phenyl substitutions, respectively have suppressed the MCF-7 and HEPG2 cells with IC_{50} values being relatively closer to those of the standard drug doxorubicin. However, rest of the compounds in the series demonstrated mild to moderate activity against the tested cell lines. In summary, the hybridization strategy that was employed to prepare the compounds has been demonstrated to produce superior lead hybrids for the purpose of developing novel anticancer medications that could target dihydrofolate reductase (DHFR). Consequently, additional biological studies still required.

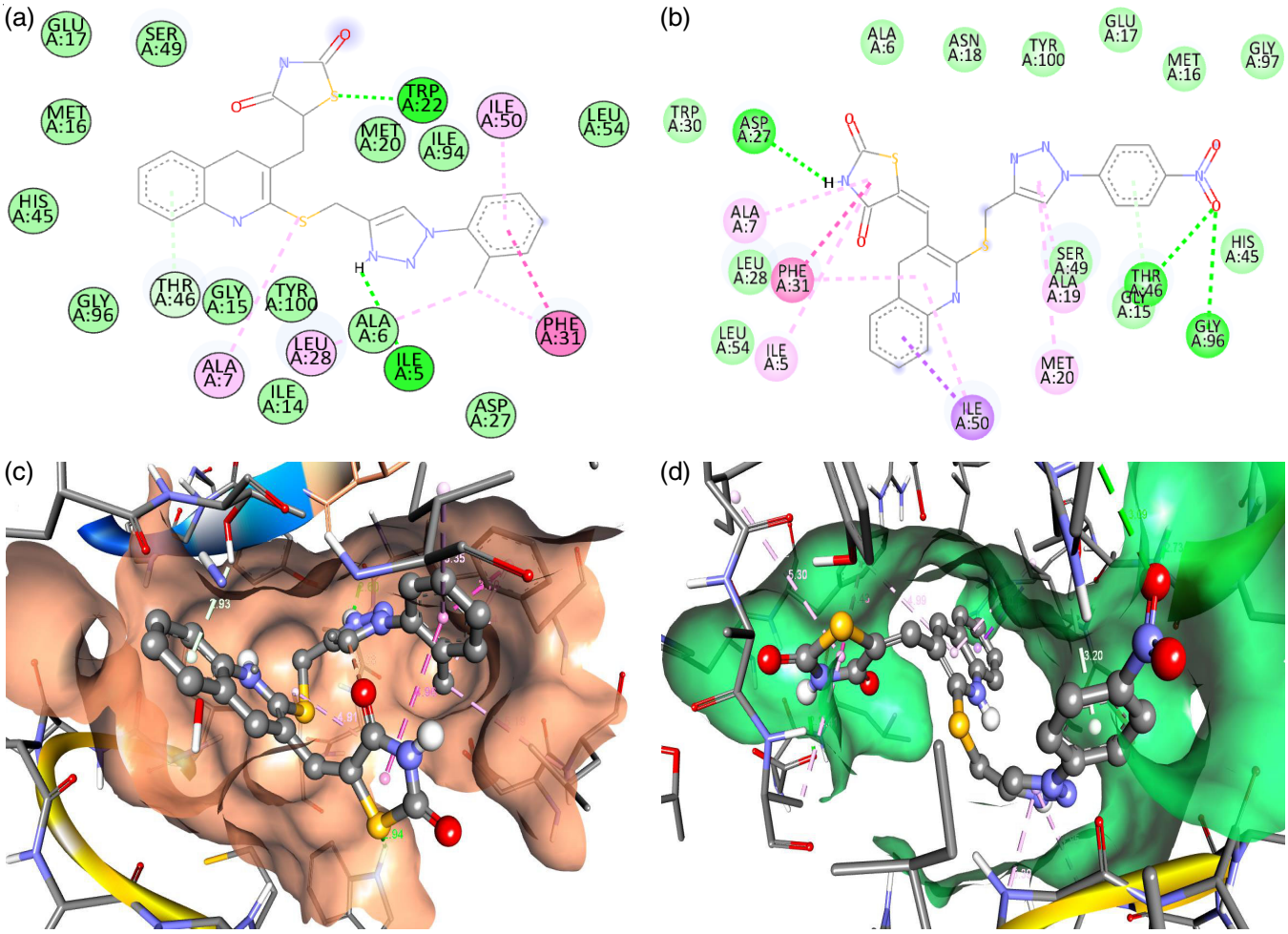


Fig. 1. 2D and 3D interaction images of compounds **9h** (a-b) and **9l** (c-d) with the dihydrofolate reductase (DHFR)

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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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