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# Synthesis of Novel Chromene/[1,2,3]triazole Hybrid Derivatives: Cytotoxicity/Molecular Docking Studies

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An easy and convenient approach has been adopted to synthesize a new series of chromene/[1,2,3]triazole hybrid derivatives involving Cu(I) catalyzed alkyne-azide 1,3-dipolar cycloaddition and a single step multicomponent reaction. The novel synthesized compounds (**8a-l**) were screened for cytotoxicity against three tumour cell lines *i.e.* MCF-7, PC-3 and HeLa using reference drug doxorubicin. Compound **8j** (*m*-acetyl) showed an outstanding activity against all the three cell lines with $IC_{50}$ values of 2.67 ± 0.03, 3.13 ± 0.03 and 3.05 ± 0.05 µM respectively. Compound **8k** (*p*-acetyl) also exhibited good activity with $IC_{50}$ values of 3.16 ± 0.05, 4.68 ± 0.03 and 3.81 ± 0.02 µM and the values are closer to doxorubicin $IC_{50}$values. The rest of the synthesized compounds have displayed good to moderate activity compared to reference drug. Molecular docking simulations of compounds **8b**, **8f** and **8j** exhibited an excellent binding interactions against the crystal structure of epidermal growth factor receptor (EGFR).

**Keywords: Click chemistry, Click cycloaddition, 1,2,3-Triazoles, Chromene, Regioselective, Cytotoxicity.**

## INTRODUCTION

One of the effective medications in inhibiting tumour growth is chemotherapy [1] with various anticancer drugs. The development of resistance to chemotherapeutic agents and their associated side effects are the barriers [2]. The discovery of diversified chemotherapeutic drugs with improved efficiency and minimal side effects is challenging and an emerging research area in anticancer drugs. 1,2,3-Triazole derivatives have favourable binding properties with macromolecular receptor sites like π-π stacking interactions and ability of forming hydrogen bonds [3-5]. Generally, triazoles are stable to hydrolysis under acidic or alkaline conditions, metabolic degradation and redox process. 1,2,3-Triazole derivatives exhibit a broad spectrum of pharmacological activities such as antibacterial [6-8], antitubercular [6], anti-inflammatory [6], antifungal [9,10], antiallergic [11] and anticancer properties [4,6,12-14]. In addition, several bioactive compounds containing chromene nuclei display a wide range of medicinal properties such as anti-HIV [15-20], anticancer [21,22], antimicrobial [23,24], antitumor [25], antiviral [26], anti-inflammatory [27] and antioxidant [28] activities.

Multicomponent reactions are highly efficient techniques for the synthesis of various fused heterocycles which form product in a single step reaction between three or more different reactants. Inspired by diverse applications of the chromenes and 1,2,3-triazole hybrids in medicinal chemistry, in this work, we have synthesized novel 1,2,3-triazole pendent chromene derivatives by involving Cu(I) catalyzed click [3+2] alkyne azide cycloaddition and multicomponent reactions and screened for their anticancer activity against human breast cancer (MCF-7), human prostate cancer (PC-3) and human cervical cancer (HeLa) cell lines. The binding efficiency of the epidermal growth factor receptor to its target macromolecule was also investigated by conducting the molecular docking experiments.

## EXPERIMENTAL

All chemicals were procured from commercial suppliers *viz.* Sigma-Aldrich, Merck, SD Fine and Avra Chemicals and

the involved chemical reactions in this work were monitored by thin layer chromatography (TLC) on silica gel plates (60 $F_{254}$), visualizing with ultraviolet light/iodine vapours, column chromatography was performed on silica gel (60-120 mesh) using distilled hexane and ethyl acetate solvents.$^1$H NMR and $^{13}$C NMR spectra were determined in $CDCl_3$ and few in DMSO by using 500 and 125 MHz spectrometers, respectively (Instrument Bruker Advance II 500MHz). Mass spectra were recorded on QSTAR XL GCMS mass spectrometer. Infrared spectra were recorded on a Shimadzu FT-IR-8400s spectrometer. Melting points were determined in open glass capillary tube on a Dbk-Prog. melting point apparatus and the values are uncorrected.

**Synthesis of 8-(prop-2-yn-1-yloxy)-1-naphthaldehyde (3):** To a solution of 2-hydroxy-naphthalene-1-carbaldehyde (1.0 eq.) dissolved in 15 mL of dry DMF was added 0.7 mL of propargyl bromide and dry $K_2CO_3$ (1.2 equiv.). The reaction mixture was stirred at room temperature for 3-4 h. After completion, the reaction mixture was poured into ice cold water and solid (2-prop-2-ynyloxy-naphthalene-1-carbaldehyde) was separated by filtration.

**Synthesis of 8-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde (5):** To a mixture of compound **3** (1.0 equiv.), $CuSO_4{\cdot}5H_2O$ (0.05 equiv.) and sodium ascorbate (0.05 equiv.) in DMF, added aryl azides **4a-l** (1.2 equiv.) individually. The reaction was stirred for 4 h and monitored by TLC. After the completion, the reaction mixture was poured on crushed ice, the solid obtained was filtered and purified by column chromatography using ethyl acetate:hexane as eluent.

**Synthesis of substituted 2-amino-7,7-dimethyl-5-oxo-4-[8-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)naphthalen-1-yl]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8a-l):** Synthesis of substituted 2-amino-7,7-dimethyl-5-oxo-4-[8-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)naphthalen-1-yl]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**8a-l**) were carried out by reaction of substituted 3-(4,5-diphenyl-1-((substituted 2-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)naphthalene-1-carbaldehyde (**5**) (0.12 mmol) was reacted with 5,5-dimethylcyclohexane-1,3-dione (**6**) (0.1mmol) and malononitrile (**7**) in presence of 4-dimethyl aminopyridine (DMAP), in EtOH at 70 ºC for 4-5 h. The progress of the reaction was monitored by TLC. Crude compounds which were purified by column chromatography using hexane/ethyl acetate (1:3 v/v) to afford substituted 2-amino-7,7-dimethyl-5-oxo-4-[8-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)naphthalen-1-yl]-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**8a-l**) gave good yields in the range of 76-85%.

**2-Amino-7,7-dimethyl-5-oxo-4-(8-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8a):** m.p. 212-214 ºC. IR (KBr, $\nu_{max}$, cm$^{-1}$): 3401 (*str.* N-H), 2080 (*str.* -CN), 1680 (*str.* C=O). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.49 (s, 1H), 7.78 (d, *J* = 7.85 Hz, 1H), 7.74 (d, *J* = 7.57 Hz, 3H), 7.37 (dd, *J* = 7.57, 7.20 Hz, 2H), 7.36 (dd, *J* = 7.85, 7.87 Hz, 1H), 7.35 (t, *J* = 7.20 Hz, 1H), 7.33 (dd, *J* = 7.85, 7.47 Hz, 1H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.96 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 5.36-5.32 (d, 2H), 4.50 (s, 1H), 2.43 (d, 2H), 2.19 (d, 2H), 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 195.7, 161.3, 158.2, 155.4, 143.4, 135.7, 132.5, 132.1, 129.1, 128.4, 127.8, 127.2, 127.1, 127.0, 126.2, 125.7, 123.8, 122.1, 119.4, 112.2, 112.1, 69.6, 58.8, 50.1, 40.2, 36.9, 33.6, 27.9; LC-MS *m/z*: 520.3 [M+H]$^+$. Elemental analysis of $C_{31}H_{29}N_5O_3$ calcd. (found) %: C, 66.52 (66.51); H, 3.31 (3.41); N, 20.56 (20.51).

**2-Amino-4-(8-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8b):** m.p. 236-238 ºC. IR (KBr, $\nu_{max}$, cm$^{-1}$): 3380 (*str.* N-H), 2084 (*str.* -CN), 1695 (*str.* C=O). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.49 (s, 1H), 7.95 (d, *J* = 8.30 Hz, 2H), 7.74 (d, *J* = 7.85 Hz, 1H), 7.73 (d, *J* = 7.85 Hz, 1H), 7.47 (d, *J* = 8.30 Hz, 2H), 7.38 (dd, *J* = 7.85, 7.81 Hz, 1H), 7.36 (dd, *J* = 7.85, 7.47 Hz, 1H) 6.99 (d, *J* = 7.85 Hz, 1H), 6.96 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 5.33-5.32 (d, 2H), 4.50 (s, 1H), 2.43-2.39 (d, 2H), 2.20-2.09 (d, 2H), 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 195.7, 159.7, 158.2, 154.2, 143.4, 135.2, 133.8, 132.8, 132.2, 128.4, 127.7, 127.2, 127.0, 125.7, 123.8, 123.4, 122.1, 121.8, 119.4, 112.2, 112.1, 69.6, 58.8, 50.1, 39.8, 36.9, 36.0, 28.0; LC-MS *m/z*: 597.4 [M+H]+ Elemental analysis, Calculated, %:$C_{31}H_{28}N_5O_3Br$: C, 66.57; H, 3.95; N, 20.83; Found %: C, 66.51; H, 3.91; N, 20.79.

**2-Amino-4-(8-((1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile(8c):** m.p. 222-224 ºC. IR (KBr, $\nu_{max}$, cm$^{-1}$): 3405 (*str.* N-H), 2068 (*str.* -CN), 1684 (*str.* C=O).$^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.45 (s, 1H), 7.74 (d, *J* = 7.85 Hz, 1H), 7.72 (d, *J* = 7.85 Hz, 1H), 7.66 (d, *J* = 7.85 Hz, 1H), 7.49 (d, *J* = 7.85 Hz, 1H), 7.36 (t, *J* = 7.85 Hz, 1H), 7.33 (t, *J* = 7.85 Hz, 1H), 7.30 (dd, *J* = 7.85, 7.44 Hz, 1H), 7.22 (dd, *J* = 7.85, 7.44 Hz, 1H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.96 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 5.36-5.32 (d, 2H), 4.50 (s, 1H), 2.43-2.39 (d, 2H), 2.20-2.08 (d, 2H), 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 195.7, 159.7, 158.2, 155.4, 143.4, 138.4, 132.8, 132.1, 129.9, 129.7, 129.0, 128.4, 127.7, 127.2, 127.0, 126.2, 125.6, 124.3, 123.6, 122.1, 119.4, 112.2, 112.1, 69.6, 58.8, 50.1, 40.2, 36.9, 36.0, 27.9; LC-MS *m/z*: 551.5 [M+H]$^+$. Elemental analysis of $C_{31}H_{28}N_5O_3Cl$ calcd. (found) %: C, 65.57 (65.51); H, 3.23 (3.31); N, 21.83 (19.79).

**2-Amino-4-(8-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8d):** m.p. 228-230 ºC. IR (KBr, $\nu_{max}$, cm$^{-1}$): 3396 (*str.* N-H), 2023 (*str.* -CN), 1662 (*str.* C=O).$^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.49 (s, 1H), 7.74 (d, *J* = 7.85 Hz, 1H), 7.72 (d, *J* = 7.85 Hz, 1H), 7.66 (d, *J* = 8.43 Hz, 2H), 7.49 (d, *J* = 8.43 Hz, 2H), 7.36 (t *J* = 7.85 Hz, 1H), 7.33 (t, *J* = 7.85 Hz, 1H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.96 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 5.36-5.32 (d, 2H), 4.50 (s, 1H), 2.43-2.39 (d, 2H), 2.20-2.08 (d, 2H) 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 195.7, 157.7, 158.2, 155.4, 143.4, 135.2, 132.8, 132.1, 131.7, 129.7, 128.4, 127.7, 127.2, 127.0, 125.6, 123.8, 123.6, 122.1, 119.4, 112.2, 112.1, 69.6, 58.8, 50.1, 40.2, 36.9, 36.0, 27.9; LC-MS *m/z*: 551.5 [M+H]$^+$. Elemental analysis of $C_{31}H_{28}N_5O_3Cl$ calcd. (found) %: C, 64.98 (65.05); H, 3.03 (3.79); N, 21.83 (20.02).

**2-Amino-4-(8-((1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8e):** m.p. 232-234 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3440 (*str.* N-H), 2089 (*str.* -CN), 1672 (*str.* C=O). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 9.44 (s, 1H), 8.50 (s, 1H), 7.74 (d, *J* = 7.85 Hz, 1H), 7.72 (d, *J* = 7.85 Hz, 1H), 7.57 (d, *J* = 8.43 Hz, 2H), 7.36 (t, *J* = 7.85 Hz, 1H), 7.33 (t, *J* = 7.85 Hz, 1H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.96 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 6.79 (d, *J* = 8.43 Hz, 2H), 5.36-5.32 (d, 2H), 4.50 (s, 1H), 2.43-2.39 (d, 2H), 2.20-2.09 (d, 2H), 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 195.7, 159.7, 158.2, 157.3, 155.4, 143.4, 135.7, 1332.8, 132.1, 128.4, 127.7, 127.2, 127.0, 125.6, 123.8, 122.1, 119.4, 119.1, 115.2, 112.2, 112.1, 69.6, 58.8, 50.1, 40.2, 36.9, 36.0, 27.9; LC-MS *m/z*: 535.2 $[M+H]^+$. Elemental analysis of $C_{31}H_{29}N_5O_4$ calcd. (found) %: C, 64.53 (65.51); H, 3.31 (3.02); N, 19.02 (19.57).

**2-Amino-4-(8-((1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8f):** m.p. 210-212 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3412 (*str.* N-H), 2078 (*str.* -CN), 1678 (*str.* C=O).$^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.45 (s, 1H), 7.74 (d, *J* = 7.85 Hz, 1H), 7.72 (d, *J* = 7.85 Hz, 1H), 7.53 (d, *J* = 7.85 Hz, 1H), 7.36 (t, *J* = 7.85 Hz, 1H), 7.34 (t, *J* = 7.85 Hz, 1H), 7.24 (dd, *J* = 7.85, 7.44 Hz, 1H), 7.16 (dd, *J* =7.85, 7.44 Hz, 1H), 7.06 (d, *J* = 7.85 Hz, 1H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.96 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 5.30-5.28 (d, 2H), 4.50 (s, 1H), 3.76 (s, 3H), 2.43-2.39 (d, 2H), 2.20-2.08 (d, 2H), 1.2 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 195.7, 159.7, 158.2, 155.4, 150.8, 143.4, 134.4, 132.8, 132.1, 128.4, 127.7, 127.3, 127.2, 127.0, 125.6, 122.4, 122.1, 120.9, 119.4, 114.2, 112.2, 112.1, 69.6, 58.8, 56.8, 50.1, 40.2, 36.9, 36.0, 27.9; LC-MS *m/z*: 549.1 $[M+H]^+$. Elemental analysis of $C_{32}H_{31}N_5O_5$ calcd. (found) %: C, 67.50 (67.08); H, 3.71 (3.82); N, 18.08 (18.91).

**2-Amino-4-(8-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8g):** m.p. 218-220 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3410 (*str.* N-H), 2101 (*str.* -CN), 1672 (*str.* C=O).$^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.50 (s, 1H), 7.74 (d, *J* = 7.85 Hz, 1H), 7.72 (d, *J* = 7.85 Hz, 1H), 7.41 (d, *J* = 8.43 Hz, 2H), 7.36 (t, *J* = 7.85 Hz, 1H), 7.34 (t, *J* = 7.85 Hz, 1H), 7.07 (d, *J* = 8.43 Hz, 2H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.96 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 5.36-5.32 (d, 2H), 4.50 (s, 1H), 3.80 (s, 3H), 2.43-2.39 (d, 2H), 2.20-2.08 (d, 2H), 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 195.7, 159.7, 158.3, 158.2, 155.4, 143.4, 135.7, 132.8, 132.1, 128.4, 127.7, 127.2, 127.0, 125.6, 123.8, 122.1, 120.9, 119.4, 114.2, 112.2, 112.1, 69.6, 58.8, 55.5, 50.1, 40.2, 36.9, 36.0, 27.9; LC-MS *m/z*: 549.3 $[M+H]^+$. Elemental analysis of $C_{32}H_{31}N_5O_2$ calcd. (found) %: C, 68.01 (67.79); H, 3.42 (3.38); N, 19.12 (19.42).

**2-Amino-7,7-dimethyl-5-oxo-4-(8-((1-(*o*-tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8h):** m.p. 212-214 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3378 (*str.* N-H), 2061 (*str.* -CN), 1681 (*str.* C=O).$^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.45 (s, 1H), 7.74 (d, *J* = 7.85 Hz, 1H), 7.72 (d, *J* = 7.85 Hz, 1H), 7.49 (d, *J* = 7.85 Hz, 1H), 7.36 (t, *J* = 7.85 Hz, 1H), 7.34 (dd, *J* = 7.85, 7.44 Hz, 1H), 7.33 (t, *J* = 7.85 Hz, 1H), 7.14 (dd, *J* = 7.85, 7.44 Hz, 1H), 7.11 (d, *J* = 7.85 Hz, 1H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.96 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 5.36-5.32 (d, 2H), 4.50 (s, 1H), 2.43-2.39 (d, 2H), 2.20-2.09 (d, 2H), 2.19 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 195.7, 159.7, 158.2, 155.4, 143.4, 139.6, 134.6, 132.8, 132.1, 129.4, 128.3, 127.8, 127.2, 127.1, 127.0, 125.6, 124.3, 122.6, 122.1, 119.4, 112.2, 112.1, 69.6, 58.8, 50.1, 40.2, 36.9, 36.0, 27.9, 17.6; LC-MS *m/z*: 533.6 $[M+H]^+$. Elemental analysis of $C_{32}H_{31}N_5O_3$ calcd. (found) %: C, 65.92 (65.61); H, 3.01 (3.23); N, 18.05 (20.56).

**2-Amino-7,7-dimethyl-5-oxo-4-(8-((1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8i):** m.p. 216-218 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3401 (*str.* N-H), 2080 (*str.* -CN), 1680 (*str.* C=O).$^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.49 (s, 1H), 7.74 (d, *J* = 7.85 Hz, 1H), 7.72 (d, *J* = 7.85 Hz, 1H), 7.49 (d, *J* = 8.60 Hz, 2H), 7.36 (t, *J* = 7.85 Hz, 1H), 7.33 (t, *J* = 7.85 Hz, 1H), 7.11 (d, *J* = 8.60 Hz, 2H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.96 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 5.36-5.32 (d, 2H), 4.50 (s, 1H), 2.43-2.39 (d, 2H), 2.35 (s, 3H), 2.20-2.09 (d, 2H), 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 195.7, 159.7, 158.2, 155.4, 143.4, 138.5, 135.2, 132.8, 132.1, 129.4, 127.8, 127.2, 127.1, 127.0, 125.6, 123.8, 122.6, 122.1, 119.4, 112.2, 112.1, 69.6, 58.8, 50.1, 40.2, 36.9, 36.0, 27.9, 21.5; LC-MS *m/z*: 533.1 $[M+H]^+$. Elemental analysis of $C_{32}H_{31}N_5O_3$ calcd. (found) %: C, 67.27 (66.98); H, 3.23 (3.02); N, 19.52 (N, 17.79).

**4-(8-((1-(3-Acetylphenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)naphthalen-1-yl)-2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8j):** m.p. 220-222 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3498 (*str.* N-H), 2065 (*str.* -CN), 1720 (*str.* C=O), 1668 (*str.* C=O). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.49 (s, 1H), 7.83 (s, 1H), 7.74 (d, *J* = 7.85 Hz, 1H), 7.72 (d, *J* = 7.85 Hz, 1H), 7.67 (d, *J* = 7.85 Hz, 1H), 7.58 (d, *J* = 7.85 Hz, 1H), 7.54 (t, *J* = 7.85 Hz, 1H), 7.36 (t, *J* = 7.85 Hz, 1H), 7.34 (t, *J* = 7.85 Hz, 1H), 7.06 (d, *J* = 7.85 Hz, 1H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 5.36-5.32 (d, 2H), 4.46 (s, 1H), 2.54 (s, 3H), 2.43-2.39 (d, 2H), 2.20-2.08 (d, 2H), 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 197.5, 195.9, 159.7, 158.2, 155.4, 143.4, 135.9, 133.2, 132.8, 132.1, 129.0, 128.4, 127.7, 127.1, 127.0, 125.6, 123.8, 123.7, 123.3, 122.1, 119.4, 115.9, 112.2, 112.1, 69.6, 58.8, 50.1, 40.2, 36.9, 36.0, 27.9, 26.5; LC-MS *m/z*: 561.4 $[M+H]^+$. Elemental analysis of $C_{33}H_{31}N_5O_4$ calcd. (found) %: C, 63.25 (64.5); H, 4.01 (3.99); N, 18.05 (19.99).

**4-(8-((1-(4-Acetylphenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)naphthalen-1-yl)-2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8k):** m.p. 224-226 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3368 (*str.* N-H), 2068 (*str.* -CN), 1721 (*str.* C=O),1667 (*str.* C=O).$^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.49 (s, 1H), 7.80 (d, *J* = 8.43 Hz, 2H), 7.74 (d, *J* =7.85 Hz, 1H), 7.72 (d, *J* = 7.85 Hz, 1H), 7.65 (d, *J* = 8.43 Hz, 2H), 7.36 (t, *J* = 7.85 Hz, 1H), 7.34 (t, *J* = 7.85 Hz, 1H), 7.06 (d, *J* = 7.85 Hz, 1H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.89

(s, 2H), 5.36-5.32 (d, 2H), 4.46 (s, 1H), 2.59 (s, 3H), 2.43-2.39 (d, 2H), 2.20-2.08 (d, 2H), 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 198.6, 195.9, 159.7, 158.2, 155.4, 143.4, 134.9, 133.4, 132.8, 132.1, 128.4, 127.7, 127.1, 127.0, 125.6, 123.8, 122.7, 122.1, 119.4, 112.2, 112.1, 69.6, 58.8, 50.1, 40.1, 36.9, 36.0, 27.9, 27.2; LC-MS *m/z*: 561.1 $[M+H]^+$. Elemental analysis of $C_{33}H_{31}N_5O_4$ calcd. (found) %: C, 68.01 (68.00); H, 3.23 (3.02); N, 18.02 (18.01).

**2-Amino-7,7-dimethyl-4-(8-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (8l):** m.p. 240-242 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3398 (*str.* N-H), 2068 (*str.* -CN), 1682 (*str.* C=O). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 8.49 (s, 1H), 8.26 (d, *J* = 9.20 Hz, 2H), 7.79 (d, *J* = 9.20 Hz, 2H), 7.74 (d, *J* = 7.85 Hz, 1H), 7.72 (d, *J* = 7.85 Hz, 1H), 7.36 (t, *J* =7.85 Hz, 1H), 7.35 (t, *J* = 7.85 Hz, 1H), 7.06 (d, *J* = 7.85 Hz, 1H), 6.99 (d, *J* = 7.85 Hz, 1H), 6.89 (s, 2H), 5.36-5.32 (d, 2H), 4.46 (s, 1H), 2.43-2.39 (d, 2H), 2.20-2.08 (d, 2H), 1.02 (s, 3H), 0.97 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm: 195.9, 159.7, 158.2, 155.4, 145.4, 143.4, 135.3, 132.8, 132.1, 128.4, 127.7, 127.1, 127.0, 126.3, 125.6, 124.1, 123.3, 122.1, 119.4, 112.2, 112.1, 69.6, 58.8, 50.1, 40.2, 36.1, 36.0, 27.2; LC-MS *m/z*: 564.6 $[M+H]^+$. Elemental analysis of $C_{33}H_{31}N_6O_5$ calcd. (found) %: $C_{33}H_{31}N_6O_5$: C, 63.23 (62.51); H, 3.38 (3.29); N, 21.83 (21.79).

**Molecular docking protocol:** Autodock Vina integrated PyRx tool was employed for docking simulations [29-33]. The crystal structure of epidermal growth factor receptor (EGFR) (PDB ID: 1M17), fibroblast growth factor receptor 2 (FGFR2) (PDB ID:4J96) and cyclin dependent kinase-2 (CDK2) (PDB ID: 6GUE) were retrieved from Protein Data Bank (www.rcsb.org). Initially, the water molecules of proteins were removed and added polar hydrogens. The ligands were sketched by using ChemDraw Professional 16.0 in MDL file format. Both target and ligand molecules were loaded into PyRx tool. The energies of ligands were minimized and converted to PDBQT file format. The protein was chosen as macromolecule. The active site pockets of target molecules were determined by CASTp online server [34]. The 3D grid box parameters were configured as presented in Table-1 in such a way to cover active site pocket of target molecule and docking simulation were performed with exhaustiveness of 8. After docking, conformations were ranked according to their binding energy and the conformation with the lowest binding energy was considered as the best docking score. The docking results were visualized using Pymol and Biovia Discovery Studio Visualizer.

**Cell culture:** MCF-7, PC-3 and HeLa were cultured in RPMI-1640 medium supplemented with 10% FBS, MCF-7 cells were maintained in MEM medium supplemented with 10% FBS. All the cell lines were cultured at humidified atmosphere containing 5% $CO_2$ at 37 ºC. The stock solutions of the synthesized derivatives were prepared in DMSO and added at desired concentrations to the cell culture. The DMSO concentration did not exceed 1:1,000 in the final culture.

**MTT assay:** The cytotoxic activities of the synthesized chromene-triazole derivatives (**8a-l**) were evaluated by MTT assay. The stock solutions of synthesized derivatives were diluted with culture medium. The cells were seeded in 96-well plates at a density $5 \times 10^4$ cells per well and incubated until confluency 90-95%, then each well was treated with 100 µL medium containing the desired concentrations of synthesized derivatives and incubated for 48 h. A 20 µL MTT working solution (5 mg/mL) was then added to each well and incubated for another 4 h. At the end of incubation, the medium was carefully removed and 200 µL DMSO was added. The optical density at 490 nm and 630 nm were then measured with a microplate reader (MODEL). The percentage of cell growth inhibition was calculated with the following equation:

$$\text{Inhibition (\%)} = \left(1 - \frac{\text{Sample group OD490} - \text{Sample group OD630}}{\text{Control group OD490} - \text{Control group OD630}}\right) \times 100$$

The $IC_{50}$ values were calculated with Graphpad prism software and standard deviations of the $IC_{50}$ values were obtained from at least three-independent experiments.

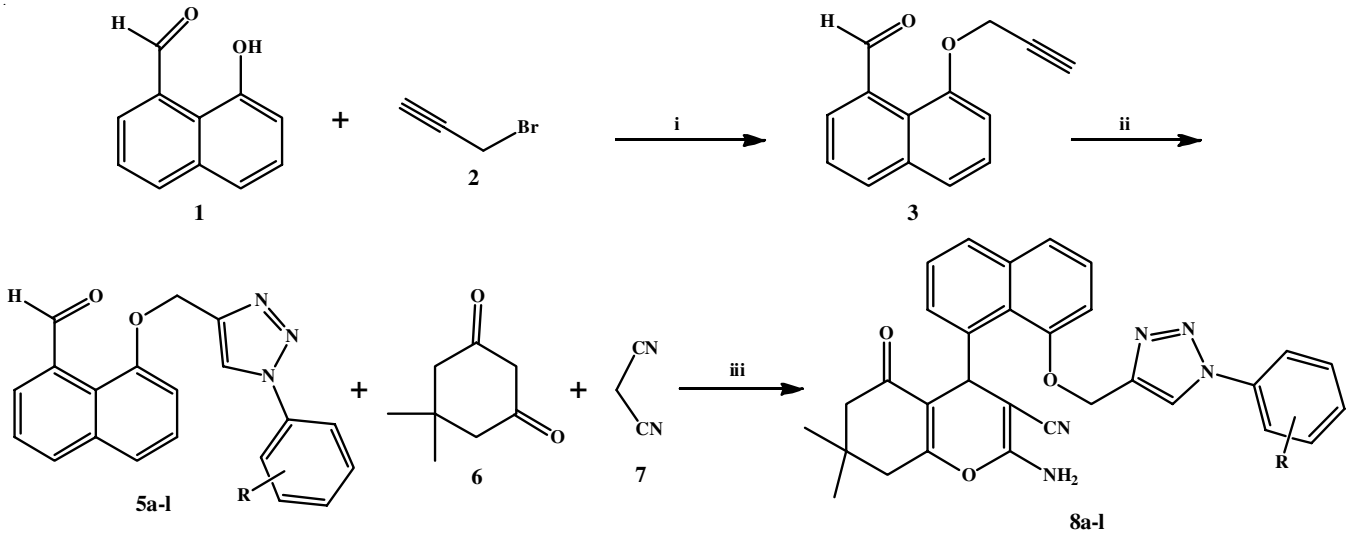
TABLE-1
3D GRID BOX PARAMETERS

| Receptor | PDB ID | Grid box dimensions |
|---|---|---|
| Epidermal growth factor receptor | 1M17 | Centerx = 22.9311722336;<br>Centery = 0.613662956852<br>Centerz = 55.4071473062<br>Sizex = 25.8124852225<br>Sizey = 16.6519406301<br>Sizez = 19.5287890709 |
| Fibroblast growth factor receptor 2 | 4J96 | Centerx = 34.8641759257<br>Centery = 5.75150970302<br>Centerz = 16.9964909359<br>Sizex = 27.3277042416<br>Sizey = 34.5031918123<br>Sizez = 41.721615661 |
| Cyclin dependent kinase 2 | 6GUE | Centerx = -7.50219595897<br>Centery = -22.1971518301<br>Centerz = 22.2006749071<br>Sizex = 21.8875746946<br>Sizey = 25.8153131151<br>Sizez = 17.6935314481 |

## RESULTS AND DISCUSSION

The synthesis of novel 2-amino-7,7-dimethyl-5-oxo-4-(8-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives is presented in **Scheme-I**. Propargylation of phenolic hydroxy group on 8-hydroxy-1-naphthaldehyde (**1**) in presence of $K_2CO_3$ in DMF yielded key intermediate 8-(prop-2-yn-1-yloxy)-1-naphthaldehyde (**3**) [35]. The Cu(I) catalyzed click [3+2] cycloaddition of terminal alkyne of precursor 3 with various aryl azides individually produced 1,4-regioisomer, 8-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehydes (**5a-l**) [36]. The multicomponent reaction between compounds **5a-l**, dimedone (**6**) and melanonitrile (**7**) by cyclocondensation gave 2-amino-7,7-dimethyl-5-oxo-4-(8-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3 carbonitrile derivatives (**8a-1**).

In IR, the peak around 1680 $cm^{-1}$ confirms the presence of C=O group in final products **8a-l**. The absorption stretching frequency near 2080 $cm^{-1}$ confirm the presence C≡N group. In $^1$H NMR of compound **8a**, the newly formed pyran




**Scheme-I:** Synthesis of 1,2,3-triazole-pendent chromene scaffolds

characteristic signals are δ 2.43 (d, $CH_2$), δ 2.19 (d, $CH_2$), δ 1.09 and 0.97 (s, 2 × $CH_3$). The -$CH_2$- protons planked between naphthalene and triazole ring appeared as singlet at δ 5.36 and the amine (-$NH_2$) proton signal appeared at δ 6.89 (bs). The signal at δ 195.7 in $^{13}C$ spectrum of **8a** confirm the presence of carbonyl carbon.

**Molecular docking:** To understand the binding interactions of synthesized compounds against biological targets, performed docking simulations against the crystal structures of epidermal growth factor receptor (EGFR) (PDB ID: 1M17) [33], fibroblast growth factor receptor 2 (FGFR2) (PDB ID: 4J96) [34] and cyclin dependent kinase-2 (CDK2) (PDB ID: 6GUE) [38]. EGFR is a driver of tumorigenesis, its over expression is observed in lung, colorectal, prostate, cervical and breast cancer, due to its inappropriate activation [37-40]. FGFR2 signalling axis is a major factor in breast, cervical and prostate cancer [39-41]. CDK2 and its regulatory subunits are deregulated in many human cancers and there is emerging evidence suggesting CDK2 inhibition elicits antitumor activity in a subset of tumours with defined genetic features [42-44]. The PDB files were selected as the basis for conducting a docking investigation, and afterwards, the obtained results were validated by comparing them with the reference drug doxorubicin. The newly synthesized chromene/1,2,3-triazole hybrid derivatives and the reference drug doxorubicin were docked into the active site pockets of all the target molecules and tabulated the binding energy values are shown in Table-2. The docking scores of all the compounds were notably good against the EGFR, FGFR2 and CDK2.

Compounds **8j**, a 3-acetyl substituted analogue was scored highest binding affinity value of -10.5 Kcal/mol against EGFR, which is better than reference drug value of -10.0 Kcal/mol. It has established key interactions with Met769, Phe771, Gly772 and Cys773(2) of EGFR, the bond distance corresponding to these interactions were 2.24 Å, 2.57 Å, 2.81 Å, 2.40 and 2.95 Å, respectively. The hydrophobic interactions also indicated by compound **8j** with Leu694, Val702, Lys704, Ala719, Lys721, Thr766, Leu768, Met769, Gly772 and Leu820 of EGFR (Fig. 1). The standard drug doxorubicin indicated the H-bond interactions with Met769, Thr830, Asp831 and hydro-phobic interactions with Leu694, Val702, Ala719, Leu738, Leu820, Asp831 of EGFR (Fig. 1). The interactions of compound **8j** are like doxorubicin at active sites Leu694, Val702, Met769, Ala719 and Leu820, which indicated the binding capacities of compounds in capacity of EGFR.

TABLE-2
DOCKING SCORES OF COMPOUNDS **8a-l**
AGAINST TARGET RECEPTORS

| Compound No. | Binding affinity (Kcal/mol) | | |
|---|---|---|---|
| | 1M17 | 4J96 | 6GUE |
| **8a** | -9.7 | -9.3 | -9.1 |
| **8b** | -10.1 | -10.2 | -10.9 |
| **8c** | -9.2 | -9.4 | -9.6 |
| **8d** | -9.7 | -9.9 | -9.4 |
| **8e** | -9.5 | -9.3 | -9.1 |
| **8f** | -10.0 | -10.6 | -9.3 |
| **8g** | -9.8 | -10.5 | -8.4 |
| **8h** | -9.8 | -9.7 | -9.7 |
| **8i** | -9.8 | -10.0 | -9.5 |
| **8j** | -10.5 | -9.7 | -9.9 |
| **8k** | -10.4 | -10.3 | -10.0 |
| **8l** | -9.7 | -10.4 | -9.0 |
| Doxorubicin | -10.0 | -9.8 | -9.8 |

The docking scores of the synthesized compounds (**8a-l**) are also interestingly ranging from -9.3 to -10.6 Kcal/mol against FGFR2 and doxorubicin scored a value of -9.6 Kcal/mol. Here, 2-methoxy substituted compound (**8f**) scored the highest binding affinity value of -10.6 Kcal/mol, which demonstrated key interactions with Ala491 (2.64 Å), Phe492 (2.08 Å), Gly493 (2.64 Å), Asp626 (1.90 Å) and Asp644 (2.43 Å) of FGFR2. The hydrophobic interactions also established by compound

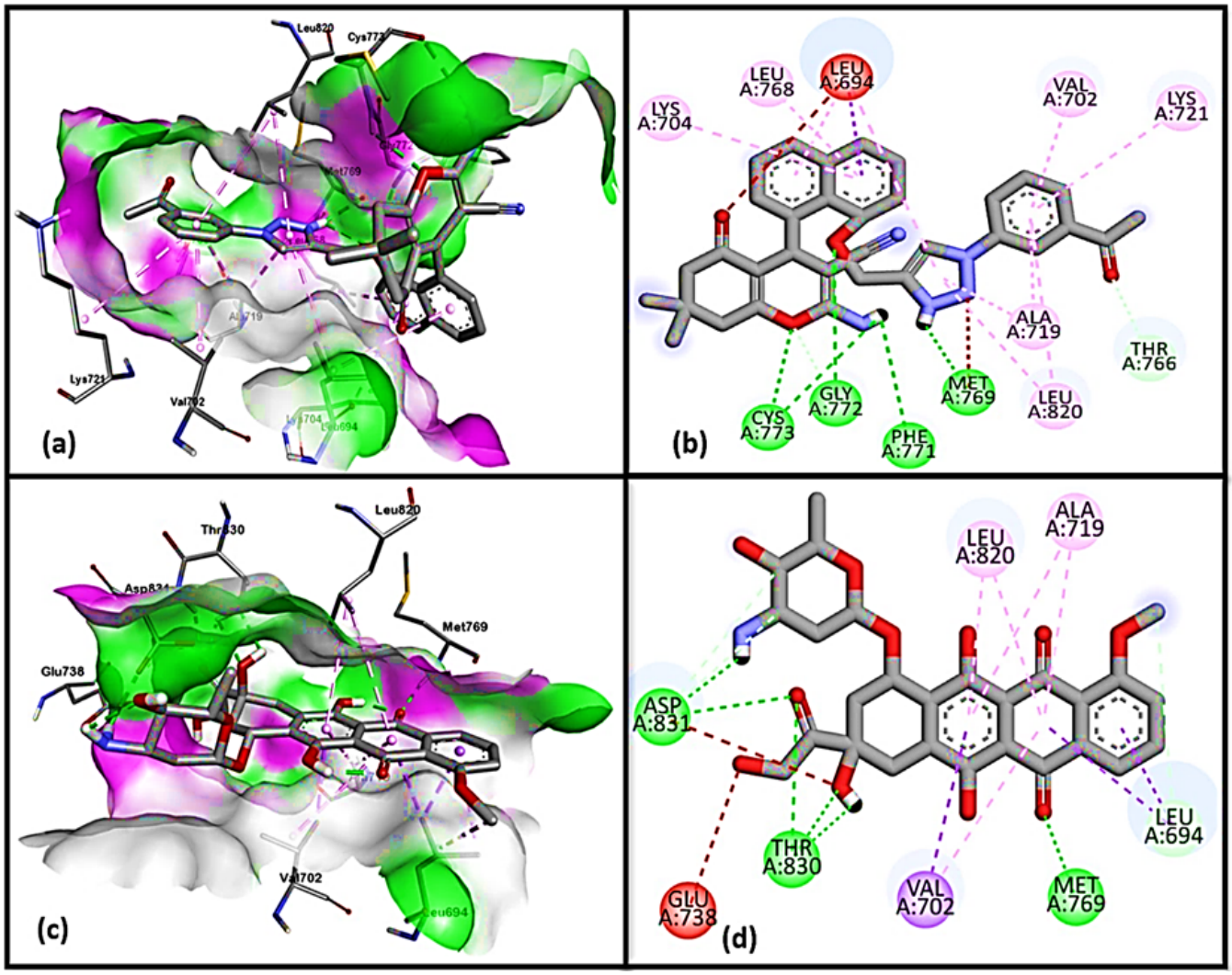



Fig. 1. (a) Docking pose of compound **8j** (b) binding interactions of compound **8j**, (c) docking pose of doxorubicin (d) binding interactions of doxorubicin in cavity of EGFR (PDB ID: 1M17)

**8f** with Gly490, Val495, Ala515, Lys517, Ile548, Val564, Leu 633, Ala643 and Asp644 of FGFR2 (Fig. 2). The doxorubicin showed the H-bond interactions with Glu534, Ala567, Asn631, Asp644 and hydrophobic interactions with Leu487, Val495, Ala515, Glu534, Asn631, Leu633, Asp644 of FGFR2 (Fig. 2). Here also the interactions of **8f** are matched with doxorubicin, at active sites Val495, Ala515 and Asp644, which indicate these compounds can bind and fit into the cavity of FGFR2.

The binding affinities of **8a-l** with CDK2 are ranging from -8.4 to -10.9 Kcal/mol and doxorubicin scored a value of -9.8 Kcal/mol. Among all, compound **8b** scored highest binding energy value of -10.9 Kcal/mol, which indicated H-bond interactions with Asp86 (2.38 Å), Gln131 (2.44 Å), Asn132 (2.84 and 3.20 Å), Asp145 (1.94 Å) and hydrophobic interactions with Ile10, Tyr15, Val18, Ala31, Phe80, Lys89, Asn132, Leu134 of CDK2 (Fig. 3). The doxorubicin established H-bond interactions with Ile10, Tyr15, Glu12, Asp127, Lys129, Asp145 and Gly11, Tyr15, Val18, Ala31, Val64, Phe80, Leu134, Ala144, Asp145 of CDK2 (Fig. 3). Now, the binding interactions of compound **8b** are matching with doxorubicin, at active sites Ile10, Tyr15, Val18, Ala31, Phe80, Leu134 and Asp145 of CDK2. It proves that these compounds also can be fit into the cavity of CDK2.

**Cytotoxicity:** The anticancer activity of all the synthesized 1,2,3-triazole-pendent chromene scaffolds (**8a-l**) were evaluated against three tumour cell lines (MCF-7, PC3 and Hela) by employing MTT assay. The *in vitro* screening for the anticancer activity of all the synthesized compounds was done in two steps. Initially, all the synthesized compounds were tested at two concentrations (5 and 10 µM) against the above three cell lines and summarized in Table-3 to sort out the best compounds based on their percentage of cancer cell growth inhibition when incubated for 48 h. The screening study revealed that 8 derivatives out of the total 12 compounds exhibited significant anticancer activity with a range of 70-85% of cancer cell growth inhibition than the rest of the compounds.

As per the above preliminary screening studies, synthesized compounds **8b**, **8c**, **8d**, **8f**, **8g**, **8j**, **8k** and **8l** were found to have inhibited the growth of cancer cells effectively when compared with the other compounds. This compounds % growth inhibition was above 70% at the tested concentrations of 5 and 10 µM. Hence, these compounds with the best % growth

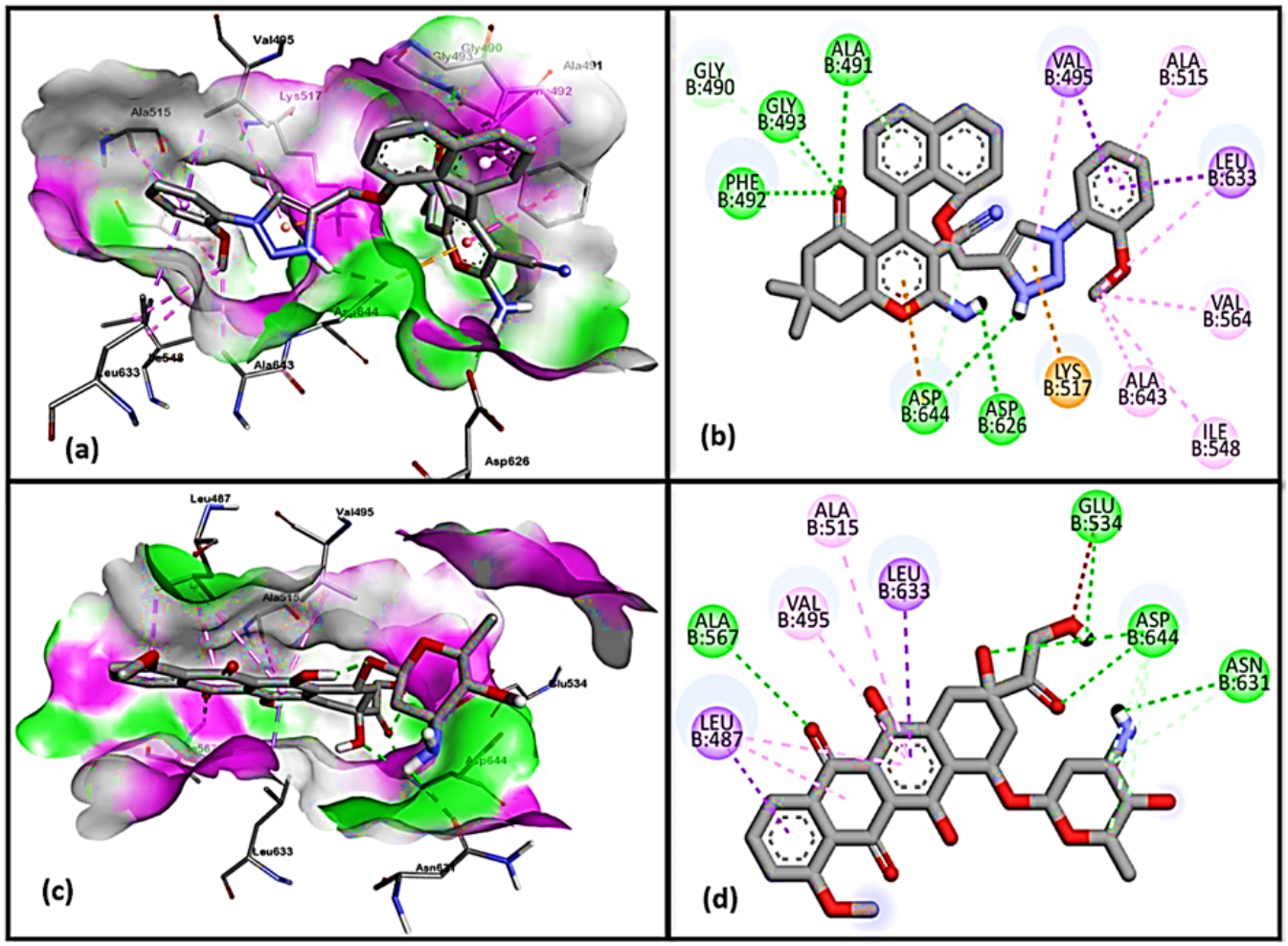



Fig. 2. (a) Docking pose of compound **8f** (b) binding interactions of compound **8f** (c) docking pose of doxorubicin (d) binding interactions of doxorubicin in cavity of FGFR2 (PDB ID: J96)

TABLE-3
% GROWTH INHIBITORY ACTIVITIES OF THE SYNTHESIZED COMPOUNDS **8a-l** AGAINST MCF-7, HeLa AND PC-3 CELL LINES [39]

| Entry code | Breast cancer cell lines (MCF-7) | | Prostate cancer cell lines (PC-3) | | Cervical cancer cell lines (HeLa) | |
|---|---|---|---|---|---|---|
| | 5 µM | 10 µM | 5 µM | 10 µM | 5 µM | 10 µM |
| **8a** | 69 | 74 | 58 | 66 | 65 | 72 |
| **8b** | 85 | 93 | 72 | 79 | 78 | 83 |
| **8c** | 74 | 81 | 61 | 68 | 70 | 74 |
| **8d** | 76 | 84 | 66 | 71 | 72 | 77 |
| **8e** | 65 | 72 | 55 | 63 | 62 | 69 |
| **8f** | 72 | 79 | 59 | 63 | 68 | 72 |
| **8g** | 74 | 82 | 60 | 66 | 68 | 73 |
| **8h** | 64 | 70 | 53 | 59 | 61 | 69 |
| **8i** | 66 | 72 | 56 | 61 | 64 | 70 |
| **8j** | 90 | 96 | 71 | 79 | 87 | 93 |
| **8k** | 88 | 93 | 78 | 85 | 80 | 89 |
| **8l** | 71 | 78 | 57 | 66 | 67 | 71 |
| Doxorubicin | 92 | 98 | 83 | 92 | 86 | 96 |
| Control | 10 | 10 | 10 | 10 | 10 | 10 |

**Note:** [a]Values are average of three determinations and deviation of data results is 10-20%; [b]All compounds were dissolved in DMSO for testing.

inhibitory activity were selected and they were further evaluated under the same conditions to determine the $IC_{50}$ value at several concentrations such as 2, 4, 8, 16 and 32 µM. The $IC_{50}$ values of the selected compounds were presented in Table-4 and found to be in the range of 2.87 ± 0.03 to 7.39 ± 0.05 µM, 4.13 ± 0.06 to 12.62 ± 0.14 µM and 3.50 ± 0.05 to 9.07 ± 0.11 µM against MCF-7, PC-3 and HeLa cancer cell lines, respectively. Whereas the $IC_{50}$ value of the standard drug,

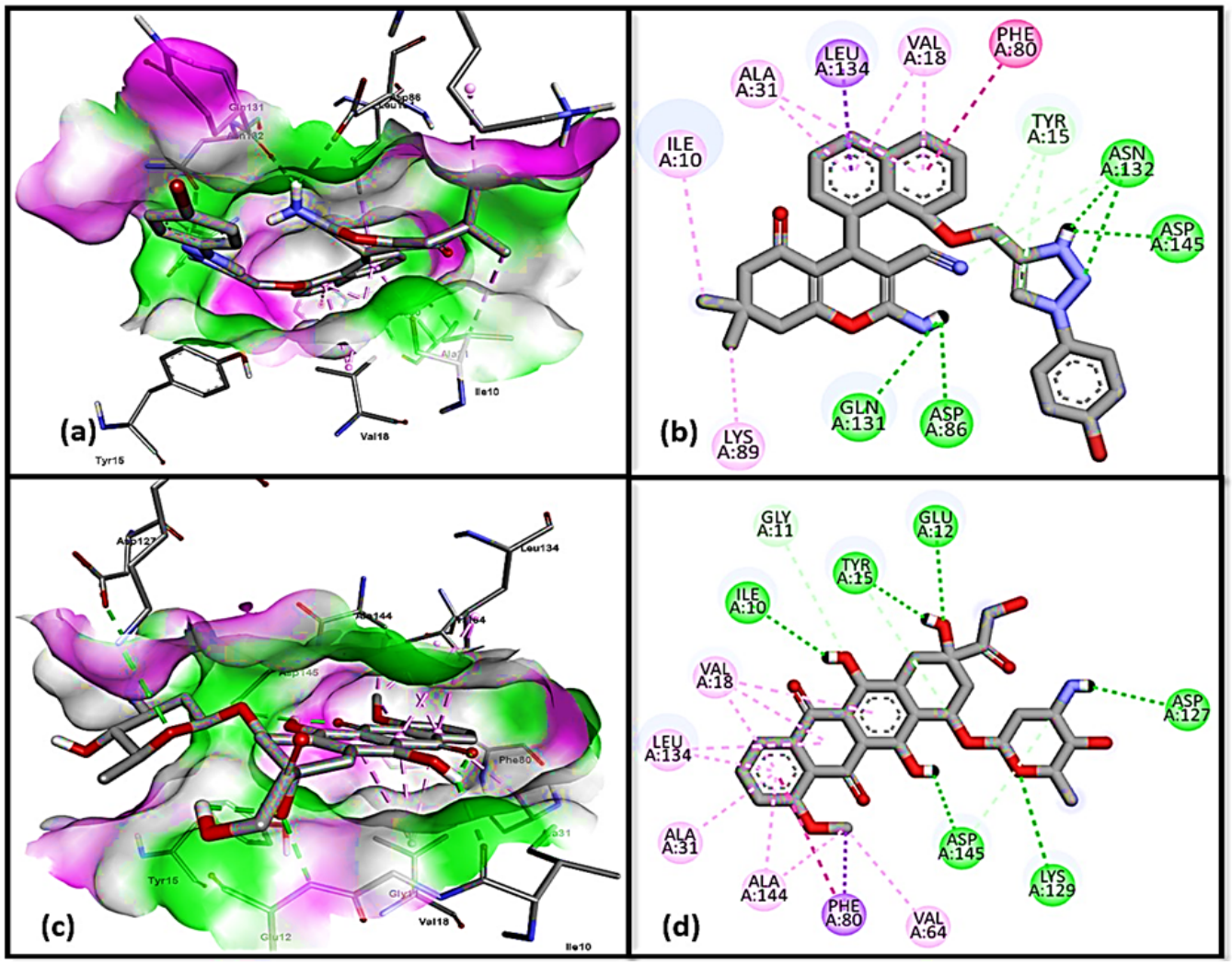



Fig. 3. (a) Docking pose of compound **8b** (b) binding interactions of compound **8b** (c) docking pose of doxorubicin (d) binding interactions of doxorubicin in cavity of CDK2 (PDB ID: 6GUE)

TABLE-4
$IC_{50}$ VALUES OF SELECTED COMPOUNDS WITH THE STANDARD DRUG DOXORUBICIN

| Compd. No. | $IC_{50}$ (μM ± SEM) | | |
|---|---|---|---|
| | MCF-7 | PC-3 | HeLa |
| **8b** | 4.62 ± 0.03 | 8.30 ± 0.09 | 7.41 ± 0.06 |
| **8c** | 6.34 ± 0.05 | 10.27 ± 0.07 | 8.24 ± 0.08 |
| **8d** | 5.92 ± 0.04 | 9.43 ± 0.06 | 8.16 ± 0.09 |
| **8f** | 7.39 ± 0.05 | 12.62 ± 0.14 | 9.07 ± 0.11 |
| **8g** | 6.73 ± 0.08 | 10.51 ± 0.12 | 8.86 ± 0.14 |
| **8j** | 2.67 ± 0.03 | 3.13 ± 0.03 | 3.05 ± 0.05 |
| **8k** | 3.16 ± 0.05 | 4.68 ± 0.03 | 3.81 ± 0.02 |
| **8l** | 6.48 ± 0.03 | 10.79 ± 0.11 | 8.60 ± 0.12 |
| Doxorubicin | 2.71 ± 0.04 | 3.82 ± 0.03 | 3.15 ± 0.08 |

doxorubicin was found to be 2.71 ± 0.04 μM (MCF-7), 3.82 ± 0.03 μM (PC-3) and 3.15 ± 0.08 μM (HeLa). These results showed that the selected compounds are more sensitive towards MCF-7 cancer cell lines than PC-3 and HeLa cancer cell lines.

## Conclusion

In this work, the synthesis and characterization of chromene/1,2,3-triazole hybrid derivatives (**8a-l**) was carreid out in good yields by adopting Cu(I) catalyzed alkyne-azide regioselective 1,3-dipolar cyclo-addition. The synthesized compounds were screened for cyto-toxic activity against three tumour cell lines *i.e.* MCF-7, PC-3 and HeLa (breast, prostate and cervical cancer, respectively). The novel compounds were exhibited excellent cytotoxicity against tested cell lines and the values are closer to reference drug doxorubicin. Compound **8j** (*m*-acetyl) showed an outstanding activity against all the three cell lines with $IC_{50}$ values of 2.67 ± 0.03, 3.13 ± 0.03 and 3.05 ± 0.05 μM, respectively. Compound **8k** (*p*-acetyl) also exhibited good activity with $IC_{50}$ values of 3.16 ± 0.05, 4.68 ± 0.03 and 3.81 ± 0.02 μM correspondingly. The other synthesized compounds have displayed good to moderate cytotoxicity compared to reference drug and the molecular docking simulations of compounds **8b**, **8f** and **8j** have exhibited excellent binding interactions against the crystal structure of epidermal growth factor receptor (EGFR).

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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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