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Synthesis and Molecular Docking Studies of Triazole Conjugated Novel 2,4-Disubstituted Thiazole Derivatives as CDK2 Inhibitors

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A series of triazole conjugated novel 2,4-disubstituted thiazole derivatives (**9a-l**) were synthesized from salicylaldehyde. These new chemical entities were characterized by their IR, ^{1}H & ^{13}C NMR, mass spectral data and their molecular docking studies were performed to identify potential inhibitors of CDK2 protein. The synthesized analogs **9a-l** were docked with CDK2 protein (PDB: 1GIJ). Among these **9h**, **9j** and **9k** showed better Glide score, Prime MM-GBSA and ADME properties as compared to seliciclib and dinaciclib cancer inhibiting drugs of CDK2 protein. The amino acid Val83 of CDK2 protein was consistently binding to new chemical entities indicating that amino acid is crucial and responsible for its inhibition. Present findings suggested that compound **9h** has 100% human oral absorption with highest Glide score -8.3kcal/mol whereas drug molecules have feebler binding capacity and less Glide score indicating that the synthesized new chemical entity as potential inhibitor for CDK2 protein.

Keywords: Substituted Triazoles, Molecular Docking, GLIDE, Prime MM-GBSA, ADME.

INTRODUCTION

Cancer is one of the major health problems worldwide. As per WHO guidelines, it is estimated that 18.1 million new cases and 9.6 million deaths will be occurring every year. It is the second leading disease causing death globally. In cancer, the normal cells are converted to abnormal cells by uncontrolled growth of the abnormal cells in the human body [1]. Therefore, there is an emergency need for the discovery of the most efficient and selective inhibitors for cancer therapy. Heteroatoms S, N and O containing five numbered heterocyclic rings play an important role as cancer inhibitors in medicinal chemistry with thiazole moiety contained drugs playing a crucial role in cancer treatment such as Dasatinib, Tiazofurin and Bleomcyin which are antineoplastic drugs [2-5]. Mubritinib contained triazole moiety which is now used extensively as drug in cancer treatment [6]. Moreover, thiazole moiety also plays an important role in antimicrobial, antiviral, anti-inflammatory and analgesic drugs [7-10]. These derivatives have high efficient pharmacophore in drug molecular design.

Herein, we report the synthesized derivatives from easily available substrates *ortho*-hydroxyl benzaldehyde, propargyl bromide, thiosemicarbazide and phenacyl bromide. Azide derivates were also synthesized and used to prepare stable and essential core moieties containing triazole conjugated 2,4-substituted thiazole derivates. These novel chemical entities were synthesized and then *in silico* docking studies were carried to identify better potential anticancer agents, having high binding affinities to the 1GIL template of CDK2 protein. Among these **9h**, **9j** and **9k** compounds showed better binding affinity, Prime MM-GBSA and their ADME properties compared to standard dinaciclib and seliciclib drugs [11-13]. The pharmacology and drug-likeness were also discussed in this study.

EXPERIMENTAL

All chemicals used were of commercially available reagent grade and utilized without purifying. Melting points were determined on Veego melting point apparatus and are uncorrected. Proton (^{1}H) nuclear magnetic resonance spectroscopy was performed using a Brucker AC-400F, 400 MHz spectrophotometer for solutions in $CHCl_3$-d_6 and deuterated DMSO and are reported in parts per million (ppm) downfield from tetramethylsilane (Me_4Si) as internal reference. Reaction progress was monitored

by precoated (silica gel 60 F_{254}) plates which were procured from E. Merck, Germany. Spots were visualized using UV-chamber (Perfit, India). Anhydrous sodium sulphate was utilized as drying agent.

Synthesis of propargylated salicylaldehyde (3): The reaction of salicylaldehyde (**1**, 1.0 equiv.) and propargyl bromide (**2**, 1.5 equiv.) in the presence of K_2CO_3 in dry DMF as solvent was stirred for 4 h under room temperature in inert condition, resulted in the formation of propargylated salicylaldehyde (**3**). The reaction was monitored by TLC. After completion of the reaction, it was poured in ice cold water and extracted with dichloromethane (3 × 40 mL). The organic layer was dried with Na_2SO_4, concentrated under *vacuo* and purified by silica gel column using 20% EtOAc in hexane as eluent to afford the pure product (**3**) [14].

General procedure of aromatic azide synthesis (4a-c): Synthesis of aromatic azide was conducted under inertness conditions. A 2N HCl solution was added in respective amines dissolved CH_2Cl_2 solvent followed by the slow addition of $NaNO_2$ solution with continuous stirring for 30 min at 0 ºC. To this solution, NaN_3 was added at 0ºC and then stirred for 2.5 h at room temperature, finally left the solution till the aqueous and organic layers separated. The organic layer was taken and washed with $NaHCO_3$ followed by brine and dried with Na_2SO_4. The solvent was evaporated *in vacuo* which resulted in in the formation of aryl azides (**4a-c**).

Synthesis of 1,2,3-triazoles (5): To a mixture of propargylated salicylaldehyde (**3**, 1.0 equiv.) and compound **4a-c** (1.5 equiv.) in dry methyl formamide (25 mL) was added to a solution of $CuSO_4.5H_2O$ (0.01 equiv.) followed by sodium ascarbate (0.01 equiv.). This mixture was stirred for 6 h at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was extracted with ethyl acetate and ice cold water (3 × 40 mL). The organic layer was washed with brine and dried with Na_2SO_4, respectively. The solvent was evaporated *in vacuo* and crude product passed through silica gel column (25% EtOAc in hexane) to get pure products **5a-c** [15].

Synthesis of thiosemicarbazide derivatives (7): A solution of thiosemicarbazide (**6**, 1.5 equiv.) in ethanol solvent was added slowly to a solution of compound (**5**, 1.0 equiv.) and refluxed for 4 h. The completion of the reaction was indicated by TLC. The reaction mixture was cooled to room temperature and transferred into ice-water, filtered and recrystallized in absolute ethanol to give product **7**.

Synthesis of thiazole derivatives (9a-l): The mixture of phenacyl bromide **8a-e** (1.0 equiv.), compound (**7**, 1.0 equiv.) in acetonitrile solvent was added in $NaHCO_3$ (1.2 equiv.) solution and then refluxed for 2 h. The reaction was monitored by TLC, after completion of the reaction. The solvent was removed under reduced pressure and absorbed over silica gel purified by column chromatography (eluent: 30% EtOAc in hexane) to get the desired pure product **9a-l**.

2-((1-(3,4-Dimethylphenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)benzaldehyde (5a): White solid, yield: 85%, m.p.: 77-79 ºC. ^{1}H NMR (400 MHz, DMSO + $CDCl_3$) δ ppm: 10.42 (s, 1H), 8.64 (s, 1H), 8.04 (s, 1H), 7.77-7.70 (m, 2H), 7.58-7.51 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.00 (t, *J* = 7.0 Hz, 1H), 5.34 (s, 2H), 2.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 189.60, 160.43, 138.54, 137.90, 136.05, 135.04, 130.76, 128.86, 125.16, 121.84, 121.43, 118.01, 113.05, 62.52, 19.91, 19.50. IR (neat, cm^{-1}): 3183, 3055, 2934, 1732, 1567, 1244, 1050. Elemental analysis calcd. (found) % for $C_{18}H_{17}N_3O_2$: C, 70.31 (70.30); H, 5.56 (5.52); N, 13.63 (13.62). ESI-MS: *m/z*: 308 (M + 1).

2-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-benzaldehyde (5b): White solid, yield: 86%, m.p.: 73-75 ºC. ^{1}H NMR (400 MHz, DMSO + $CDCl_3$) δ ppm: 10.41 (s, 1H), 8.55 (s, 1H), 7.78 (dd, *J* = 9.3, 2.4 Hz, 2H), 7.70 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.67 (d, *J* = 1.4 Hz, 1H), 7.55-7.52 (m, 1H), 7.47-7.44 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 194.24, 178.17, 165.22, 140.88, 140.20, 139.11, 134.64, 133.11, 129.77, 126.53, 126.12, 117.99, 67.06. IR (neat, cm^{-1}): 3186, 3065, 2914, 1730, 1567, 1245, 1051. Elemental analysis calcd. (found) % for $C_{16}H_{12}N_3O_2Cl$: C, 61.23 (61.23); H, 3.84 (3.82); N, 13.36 (13.33). ESI-MS: *m/z*: 314 (M + 1).

2-((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde (5c): White solid, yield: 86%, m.p.: 72-74 ºC. ^{1}H NMR (400 MHz, DMSO + $CDCl_3$) δ ppm: 10.41 (s, 1H), 8.55 (s, 1H), 7.78 (dd, *J* = 9.3, 2.4 Hz, 2H), 7.70 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.67 (d, *J* = 1.4 Hz, 1H), 7.55-7.52 (m, 1H), 7.47-7.44 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 194.24, 165.22, 140.88, 140.20, 139.11, 134.64, 133.11, 129.77, 126.74, 126.53, 126.12, 117.99, 67.06. IR (neat, cm^{-1}): 3183, 3075, 2934, 1730, 1566, 1245, 1050. Elemental analysis calcd. (found) % for $C_{16}H_{13}N_3O_2$: C, 68.79 (68.75); H, 4.66 (4.63); N, 15.01 (15.00). ESI-MS: *m/z*: 280 (M + 1).

4-Phenyl-2-(2-(2-((1-phenyl-1*H*-1,2,3-triazol-4-yl)-methoxy)benzylidene)hydrazinyl)thiazole (9a): Light brown powder, yield: 89%, m.p.: 127-129 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.16 (s, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.74-7.70 (m, 4H), 7.55-7.51 (m, 2H), 7.45 (ddd, *J* = 7.4, 3.8, 1.1 Hz, 1H), 7.37-7.27 (m, 4H), 7.22 (t, *J* = 7.1 Hz, 1H), 7.06-7.02 (m, 2H), 6.76 (s, 1H), 5.24 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.3, 156.16, 144.53, 138.55, 131.75, 131.05, 129.83, 128.97, 127.48, 121.73, 120.88, 120.60, 112.68, 103.73, 62.53. IR (neat, cm^{-1}): 3158, 3075, 2924, 1602, 1567, 144, 1245, 1050. Elemental analysis calcd. (found) % for $C_{25}H_{20}N_6OS$: C, 66.34 (66.32); H, 4.46 (4.41); N, 18.56 (18.50). ESI-MS: *m/z*: 452.95 (M + 1).

4-(4-Bromophenyl)-2-(2-(2-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)hydrazinyl)thiazole (9b): Thick brown powder, yield: 88%, m.p.: 127-129 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.19 (s, 1H), 7.95-7.91 (m, 2H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.51 (dd, *J* = 16.9, 8.3 Hz, 5H), 7.39 (t, *J* = 6.9 Hz, 3H), 7.34 (dd, *J* = 10.2, 3.4 Hz, 1H), 7.05-7.01 (m, 2H), 6.72 (s, 1H), 5.23 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.04, 156.16, 144.55, 138.59, 131.76, 131.05, 129.83, 128.97, 127.48, 126.41, 122.91, 121.73, 120.88, 120.60, 112.68, 103.75, 62.56. IR (neat, cm^{-1}): 3187, 3075, 2998, 1602, 1567, 1446, 1246, 1102, 1051. Elemental analysis calcd. (found) % for $C_{25}H_{19}N_6OSBr$: C, 56.51 (56.50); H, 3.61 (3.59); N, 15.78 (15.76). ESI-MS: *m/z*: 532.85 (M + 1).

4-(3,4-Dichlorophenyl)-2-(2-(2-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)hydrazinyl)thiazole (9c): Light brown powder, yield: 85%, m.p.: 143-145 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.24 (s, 1H), 8.02 (s, 1H), 7.95 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.77-7.72 (m, 2H), 7.58 (t, *J* = 7.0 Hz, 2H), 7.53 (dd, *J* = 10.5, 4.9 Hz, 2H), 7.49-7.42 (m, 3H), 7.38-7.33 (m, 1H), 7.06 (dd, *J* = 16.7, 8.1 Hz, 2H), 6.79 (s, 1H), 5.33 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.40, 156.10, 149.38, 144.65, 138.65, 131.74, 131.05, 129.80, 127.45, 126.29, 121.68, 120.80, 112.59, 103.65, 62.50. IR (neat, cm^{-1}): 3009, 2925, 2855, 1743, 1602, 1570, 1461, 1248, 1102, 1039. Elemental analysis calcd. (found) % for $C_{25}H_{18}N_6OSCl_2$: C, 57.57 (57.56); H, 3.49 (3.48); N, 16.13 (16.10). ESI-MS: *m/z*: 522.90 (M + 1).

4-(4-Chlorophenyl)-2-(2-(2-((1-(3,4-dimethylphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)hydrazinyl)-thiazole (9d): Brown powder, yield: 87%, m.p.: 121-123 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.16 (s, 1H), 7.95 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.91 (s, 1H), 7.68-7.65 (m, 2H), 7.51 (s, 1H), 7.43-7.40 (m, 1H), 7.36-7.32 (m, 1H), 7.31-7.28 (m, 2H), 7.27 (s, 1H), 7.25 (s, 1H), 7.08-7.04 (m, 2H), 6.79 (s, 1H), 5.28 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 168.79, 156.16, 144.25, 138.45, 138.24, 137.78, 134.78, 133.50, 130.97, 130.68, 128.77, 127.15, 126.33, 122.91, 121.71, 120.87, 117.88, 112.67, 103.74, 62.58, 19.90, 19.46. IR (neat, cm^{-1}): 3142, 3051, 2859, 1602, 1567, 1451, 1249, 1050. Elemental analysis calcd. (found) % for $C_{27}H_{23}N_6OSCl$: C, 62.96 (62.90); H, 4.51 (4.50); N, 16.30 (16.28). ESI-MS: *m/z*: 514.95 (M + 1).

4-(3,4-Dichlorophenyl)-2-(2-(2-((1-(3,4-dimethylphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-hydrazinyl)thiazole (9e): Brown powder, yield: 89%, m.p.: 137-139 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.17 (s, 1H), 7.96-7.93 (m, 2H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.42-7.39 (m, 2H), 7.37-7.32 (m, 1H), 7.23 (dd, *J* = 8.4, 2.2 Hz, 3H), 7.15 (s, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 5.32 (s, 2H), 2.33 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 168.01, 156.15, 146.03, 144.26, 138.42, 138.27, 137.74, 134.79, 133.65, 132.43, 131.79, 131.75, 130.93, 130.65, 130.12, 127.19, 126.39, 123.00, 121.74, 121.68, 120.93, 117.88, 112.69, 109.02, 62.60, 19.88, 19.45. IR (neat, cm^{-1}): 3141, 3075, 2924, 1602, 1566, 1448, 1246, 1051. Elemental analysis calcd. (found) % for $C_{27}H_{22}N_6OSCl_2$: C, 59.00 (59.01); H, 4.05 (4.03); N, 15.30 (15.29). ESI-MS: *m/z*: 548.90 (M + 1).

2-(2-(2-((1-(3,4-Dimethylphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)hydrazinyl)-4-phenylthiazole (9f): Brown powder, yield: 80%, m.p.: 151-152 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.16 (s, 1H), 7.96 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.90 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.52 (s, 1H), 7.41 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 3H), 7.27 (d, *J* = 1.9 Hz, 1H), 7.24 (d, *J* = 9.3 Hz, 2H), 7.05 (dd, *J* = 7.9, 3.3 Hz, 2H), 6.79 (s, 1H), 5.27 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.33, 156.10, 150.83, 144.44, 138.43, 138.17, 137.72, 134.81, 134.37, 130.75, 130.67, 128.63, 127.76, 126.30, 125.87, 123.14, 121.71, 121.58, 120.79, 117.88, 112.62, 103.19, 62.63, 19.90, 19.46. IR (neat, cm^{-1}): 3197, 2995, 2854, 1674, 1568, 1451, 1248, 1051. Elemental analysis calcd. (Found) % for $C_{27}H_{24}N_6OS$: C, 67.49 (67.45); H, 5.02 (5.00); N, 17.51 (17.50). ESI-MS: *m/z*: 481.00 (M + 1).

4-(4-Methoxyphenyl)-2-(2-(2-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)hydrazinyl)thiazole (9g): Light brown powder, yield: 82%, m.p.: 133-135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.13 (s, 1H), 7.97-7.94 (m, 1H), 7.89 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.53 (dd, *J* = 10.1, 4.7 Hz, 2H), 7.43 (d, *J* = 6.9 Hz, 1H), 7.35-7.30 (m, 1H), 7.05-7.01 (m, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.60 (s, 1H), 5.22 (s, 2H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: δ 169.40, 159.37, 156.06, 144.74, 138.59, 136.87, 133.45, 130.82, 129.82, 128.89, 127.22, 126.31, 123.06, 121.60, 120.82, 120.72, 120.53, 114.02, 112.50, 101.21, 62.59, 55.21. IR (neat, cm^{-1}): 2925, 2831, 1602, 1568, 1492, 1250, 1032. Elemental analysis calcd. (found) % for $C_{26}H_{22}N_6O_2S$: C, 64.70 (64.71); H, 4.63 (4.62); N, 17.41 (17.40). ESI-MS: *m/z*: 483.00 (M + 1).

4-(4-Bromophenyl)-2-(2-(2-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)hydrazinyl)-thiazole (9h): Thick brown powder, yield: 84%; m.p.: 139-141 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.19 (s, 1H), 7.98-7.94 (m, 2H), 7.71-7.67 (m, 4H), 7.51 (d, *J* = 4.0 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.11-7.06 (m, 2H), 6.82 (s, 1H), 5.42 (s, 1H), 5.32 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 168.78, 156.18, 144.25, 138.45, 138.24, 137.78, 130.97, 130.68, 128.78, 127.15, 126.33, 122.91, 121.71, 120.87, 117.88, 117.67, 1.3074, 62.55. IR (neat, cm^{-1}): 3076, 2925, 2857, 1601, 1574, 1452, 1243, 1010. Elemental analysis calcd. (found) % for $C_{25}H_{18}N_6OSBrCl$: C, 53.04 (52.71); H, 3.20 (3.19); N, 14.88 (14.85). ESI-MS: *m/z*: 516.90 (M + 1).

2-(2-(2-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)benzylidene)hydrazinyl)-4-phenylthiazole (9i): Brown powder, yield: 87%, m.p.: 133-135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.22 (s, 1H), 7.95 (dt, *J* = 7.9, 3.3 Hz, 2H), 7.72-7.67 (m, 4H), 7.54-7.46 (m, 4H), 7.32 (dd, *J* = 8.0, 6.7 Hz, 3H), 7.06-7.02 (m, 2H), 6.78 (s, 1H), 5.25 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 156.07, 144.91, 138.90, 135.29, 134.89, 134.63, 134.52, 131.02, 130.04, 130.01, 129.95, 129.09, 129.06, 128.70, 128.03, 126.36, 125.86, 122.96, 121.95, 121.79, 121.73, 121.64, 121.54, 120.67, 112.96, 112.56, 62.56. IR (neat, cm^{-1}): 3188, 3074, 2925, 1601, 1566, 1501, 1450, 1245, 1024. Elemental analysis calcd. (found) % for $C_{25}H_{19}N_6OSCl$: C, 61.64 (61.62); H, 3.94 (3.92); N, 17.28 (17.26). ESI-MS: *m/z*: 486.95 (M + 1).

4-(4-Chlorophenyl)-2-(2-(2-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)hydrazinyl)-thiazole (9j): Brown powder, yield: 85%, m.p.: 125-127 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.20 (s, 1H), 7.99-7.95 (m, 2H), 7.71-7.68 (m, 4H), 7.51 (d, *J* = 4.1 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.10-7.06 (m, 2H), 6.83 (s, 1H), 5.43 (s, 1H), 5.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.41, 156.11, 149.38, 144.61, 138.61, 138.65, 131.74, 131.05, 129.80, 128.95, 127.41, 126.29, 121.68, 120.80, 120.53, 112.59, 103.65, 62.50. IR (neat, cm^{-1}): 3184, 3019, 2915, 1601, 1566, 1453, 1243, 1096. Elemental analysis calcd. (found) % for $C_{25}H_{18}N_6OSCl_2$: C, 57.57 (57.56); H, 3.49 (3.48); N, 16.10 (16.11). ESI-MS: *m/z*: 520.90 (M + 1).

2-(2-(2-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)benzylidene)hydrazinyl)-4-(4-methoxyphenyl)-

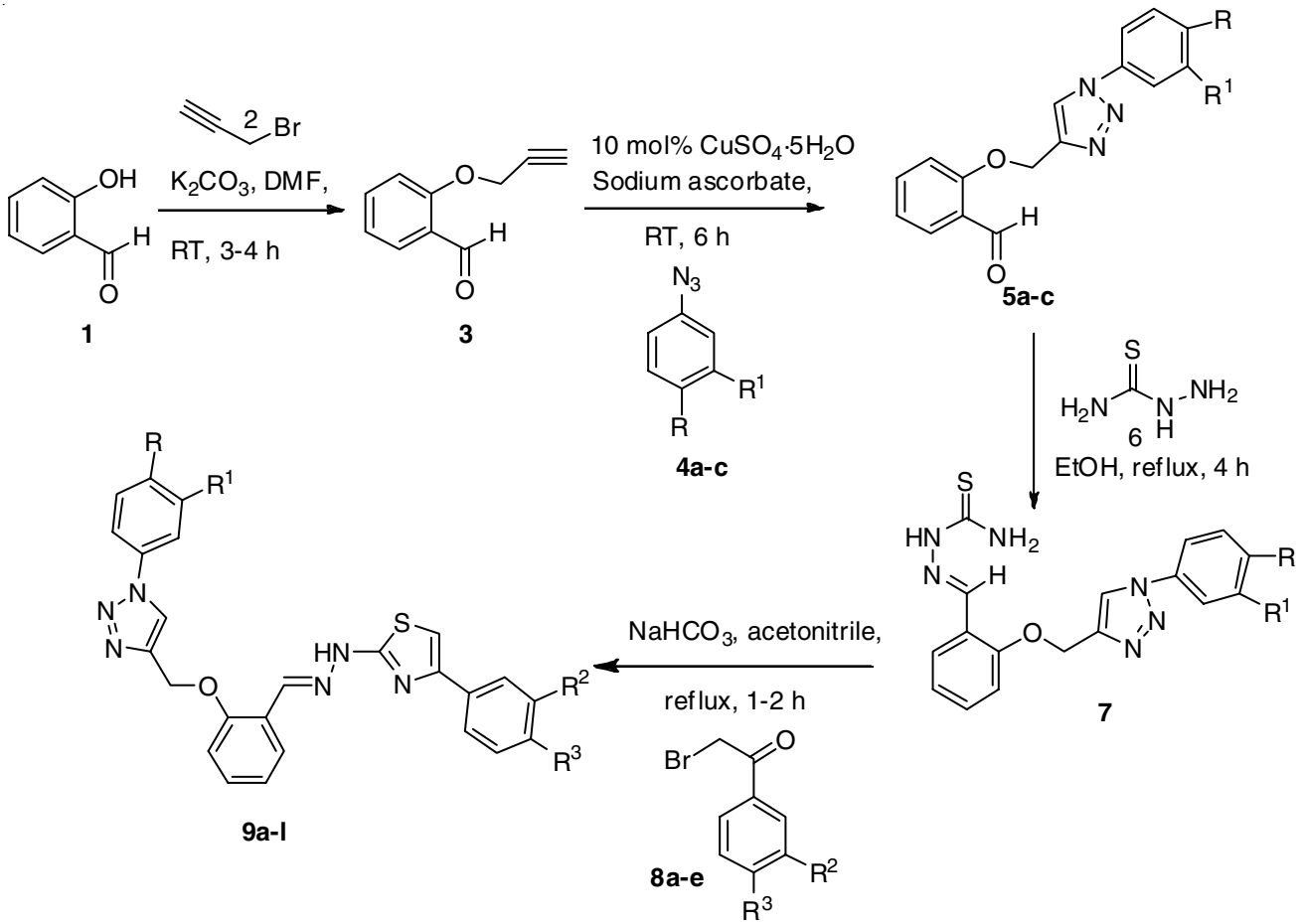
thiazole (9k): Light Brown powder, yield: 83%, m.p.: 143-145 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.14 (s, 1H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.89 (s, 1H), 7.69-7.62 (m, 5H), 7.51-7.48 (m, 2H), 7.35-7.31 (m, 1H), 7.04 (t, *J* = 7.7 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.65 (s, 1H), 5.24 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:160.18, 159.37, 155.98, 144.98, 138.40, 135.33, 134.67, 133.46, 130.84, 130.00, 129.98, 127.22, 126.32, 123.05, 122.65, 121.95, 121.71, 121.66, 120.82, 120.59, 114.74, 114.01, 112.55, 112.48, 101.28, 62.53, 55.22. IR (neat, cm^{-1}): 2924, 2832, 1603, 1566, 1498, 1250, 1030. Elemental analysis calcd. (found) % for $C_{26}H_{21}N_6O_2SCl$: C, 60.41 (60.4); H, 4.10 (4.09); N, 16.22 (16.21). ESI-MS: *m/z*: 516.90 (M + 1).

2-(2-(2-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)benzylidene)hydrazinyl)-4-(3,4-dichlorophenyl)-thiazole (9l): Thick brown powder, yield: 84%, m.p.: 155-157 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.17 (s, 1H), 7.98 (s, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.70-7.70 (m, 1H), 7.68 (s, 1H), 7.51 (s, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.38-7.33 (m, 2H), 7.23 (t, *J* = 2.8 Hz, 1H), 7.19 (s, 1H), 7.08 (s, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 5.43 (s, 1H), 5.33 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 169.42, 156.10, 149.38, 144.63, 138.67, 136.84, 133.08, 131.74, 131.00, 129.82, 128.94, 127.45, 126.29, 122.89, 121.78, 121.68, 120.80, 120.53, 112.59, 103.67, 62.55. IR (neat, cm^{-1}): 31084, 3109, 2916, 1653, 1568, 1459, 1244, 1035. Elemental analysis calcd. (found) % for $C_{25}H_{17}N_6OSCl_3$: C, 54.00; H, 3.06; N, 15.14. ESI-MS: *m/z*: 516.90 (M + 1).

RESULTS AND DISCUSSION

The synthetic route of 4-phenyl-2-(2-(2-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)hydrazinyl)thiazole (**9a-l**) derivatives is presented in **Scheme-I**. The synthesis was initiated by the propargylation of *o*-hydroxyl benzaldehyde (**1**) with propargyl bromide (**2**) in the presence of K_2CO_3, used as base and dry DMF was used as solvent. The reaction was proceeded at room temperature for 3-4 h to afford compound **3**. Triazoles (**5**) were synthesized by using copper catalyzed Huisgene 1,3-dipolar cycloaddition of alkyne **3** with aryl azides (**4a-c**) resulted in the formation of compound (**5**). Semithiocarbazide (**6**) when reacted with triazole aldehyde (**5**) in ethanol solvent and refluxed for 4 h to give Schiff base product **7**, which further reacted with substituted phenacyl bromide (**8**) in the presence of $NaHCO_3$ and CH_3CN solvent and refluxed for 1-2 h to get the desired product **9a-l** with 80-89% yield (Table-1).

All the synthesized compounds **9a-l** were confirmed by their spectral data. The infrared spectrum of compound **9a** revealed its attribute C-NH absorption band at 3100 cm^{-1}. The ^{1}H NMR spectrum of the triazole ring proton appeared as a singlet at δ 8.16 ppm and -OCH_2 protons appeared as a singlet at δ 5.24 ppm while ^{13}C NMR of -OCH_3 carbon appeared at δ 62.5 ppm.



Scheme-I: Synthesis of triazole conjugated 2,4-disubstituted novel thiazole derivatives **9(a-l)**

TABLE-1
SYNTHESIZED **9(a-l)** ALL 12 NEW MOLECULES
WITH R-R_3 DIFFERENT SUBSTITUENTS

Compound	R	R^1	R^2	R^3	Yield (%)
9a	H	H	H	H	89
9b	H	H	Br	H	88
9c	H	H	Cl	Cl	85
9d	CH_3	CH_3	H	Cl	87
9e	CH_3	CH_3	Cl	Cl	89
9f	CH_3	CH_3	H	H	80
9g	H	H	OCH_3	H	82
9h	Cl	H	Br	H	84
9i	Cl	H	H	H	87
9j	Cl	H	H	Cl	85
9k	Cl	H	OCH_3	H	83
9l	Cl	H	Cl	Cl	84

Molecular docking studies: The molecular docking studies were done by the Glide tool in Maestro Schrodinger suite [16,17]. The X-crystallographic structure of CDK2 (PDB ID: 1GIJ) protein was taken from protein data bank [18,19]. Protein preparation wizard was used for refine and energy minimization of CDK2 protein by applying the OPLS 2005 force field. Protein Grid was generated around the active site region of CDK2 protein using GLIDE tool. All the synthesized compounds **9a-l** were drawn in Maestro build panel. The drawn structures were converted into 3D and prepared using LigPrep module. Finally, low energy conformers were generated [20]. All the 12 synthesized molecules were docked into the active site of the CDK2 protein in Glide tool [21] and results the new chemical entities were prioritized based on docking score and Prime MM-GBSA [22,23] with the best ADME properties [24].

The molecular docking studies revealed that **9h**, **9j** and **9k** protein-ligand complexes showed a good Glide score, Prime MM-GBSA and maximum human oral absorption towards the active site of CDK2 protein (Table-2). These molecules were consistently binded with Val83 indicating that this amino acid is responsible for its inhibition. These results indicated that **9h** has 100% human oral absorption, best GLIDE score -8.3 kcal/mol and Prime MM-GBSA -78.67 kcal/mol also maximum bioavailability with better drug-likeness property than the existing drug molecules seliciclib and dinaciclib suggesting that this molecule is a potential inhibitor for CDK2 protein (Fig. 1).

TABLE-2
TABLE REPRESENTS THE SCORING FUNCTIONS OF SYNTHESIZED
MOLECULES AND THE EXISTING DRUGS AGAINST CDK2 PROTEIN

Compound ID	Glide score (kcal/mol)	Glide energy (kcal/mol)	%Human oral absorption	PrimeMM-GBSA (dGbind)	Interactions (protein-ligand) complex
9h	-8.38	-64.68	100	-78.67	Hbond:VAL83
9j	-7.90	-60.31	96	-71.31	Hbond:VAL83
9k	-7.81	-58.06	100	-70.18	Hbond:VAL83
Seliciclib	-6.99	-55.62	95	-67.93	Hbond:VAL83
Dinaciclib	-7.00	-53.04	100	-69.73	Hbond:Asp86

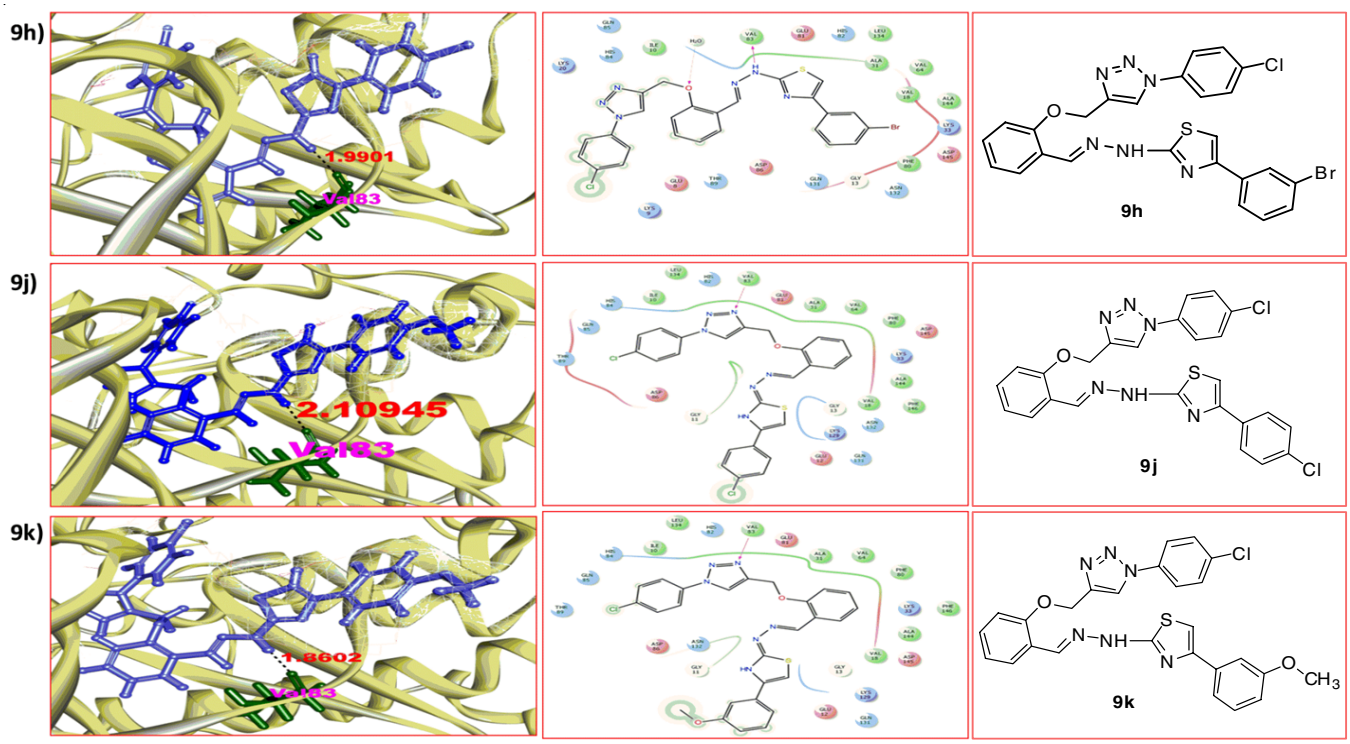


Fig. 1. Docking complex of synthesized novel lead molecules **9h**, **9j** and **9k** were docked at the binding pocket of CDK2 protein represented in three and two dimensional diagrams

Conclusion

We have successfully synthesized and characterized the conjugated 2,4-disubstituted thiazole derivatives using simple and efficient methods with good yields (80-89%). The synthesized derivatives (**9a-l**) were docked with (PDB ID: 1GIJ) template of CDK2 Protein. It has been observed that novel ligands **9h**, **9j** and **9k** are having good being Glide score, Prime MM-GBSA and maximum oral absorption than certain existing drugs such as seliciclib and dinaciclib.

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CONFLICT OF INTEREST

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

REFERENCES

1. F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre and A. Jemal, *CA Cancer J. Clin.*, **68**, 394 (2018); https://doi.org/10.3322/caac.21492
2. P. Martins, J. Jesus, S. Santos, L.R. Raposo, C. Roma-Rodrigues, P.V. Baptista and A.R. Fernandes, *Molecules*, **20**, 16852 (2015); https://doi.org/10.3390/molecules200916852
3. B.L. Abbott, *Clin. Ther.*, **34**, 272 (2012); https://doi.org/10.1016/j.clinthera.2012.01.009
4. M. Popsavin, L. Torovic, M. Svircev, V. Kojic, G. Bogdanovic and V. Popsavin, *Bioorg. Med. Chem. Lett.*, **16**, 2773 (2006); https://doi.org/10.1016/j.bmcl.2006.02.001
5. R.H. Blum, S.K. Carter and K. Agre, *Cancer*, **31**, 903 (1973); https://doi.org/10.1002/1097-0142(197304)31:4<903::AID-CNCR2820310422>3.0.CO;2-N
6. Z.A. Stephenson, R.F. Harvey, K.R. Pryde, S. Mistry, R.E. Hardy, R. Serreli, I. Chung, T.E.H. Allen, M. Stoneley, M. MacFarlane, P.M. Fischer, J. Hirst, B. Kellam and A.E. Willis, *eLife*, **9**, e55845 (2020); https://doi.org/10.7554/eLife.55845
7. M.S. Karthikeyan, *Eur. J. Med. Chem.*, **44**, 827 (2009); https://doi.org/10.1016/j.ejmech.2008.04.022
8. I.P. Singh, S. Gupta and S. Kumar, *Med. Chem.*, **16**, 4 (2020); https://doi.org/10.2174/1573406415666190614101253
9. M.H. Helal, M.A. Salem, M.S. El-Gaby and M. Aljahdali, *Eur. J. Med. Chem.*, **65**, 517 (2013); https://doi.org/10.1016/j.ejmech.2013.04.005
10. Z.A. Muhammad, G.S. Masaret, M.M. Amin, M.A. Abdallah and T.A. Farghaly, *Med. Chem.*, **13**, 226 (2017); https://doi.org/10.2174/1573406412666160920091146
11. M. Ikuta, K. Kamata, K. Fukasawa, T. Honma, T. Machida, H. Hirai, T. Suzuki-Takahashi, T. Hayama and S. Nishimura, *J. Biol. Chem.*, **276**, 27548 (2001); https://doi.org/10.1074/jbc.M102060200
12. H. Saqub, H. Proetsch-Gugerbauer, V. Bezrookove, M. Nosrati, E.M. Vaquero, D. de Semir, R.J. Ice, S. McAllister, L. Soroceanu, M. Kashani-Sabet, R. Osorio and A.A. Dar, *Sci. Rep.*, **10**, 18489 (2020); https://doi.org/10.1038/s41598-020-75578-5
13. H.S. Khalil, V. Mitev, T. Vlaykova, L. Cavicchi and N. Zhelev, *J. Biotechnol.*, **202**, 40 (2015); https://doi.org/10.1016/j.jbiotec.2015.02.032
14. P. Prabhakaran, S. Kanagasabai, G. Seshan, K. Gugan, S. Usharani and P. Rajakumar, *Chem. Data Coll.*, **28**, 100427 (2020); https://doi.org/10.1016/j.cdc.2020.100427
15. A.Naouri, A. Djemoui, M.R. Ouahrani, M.B. Lahrech, N. Lemouari, D.H.A. Rocha, H. Albuquerque, R.F. Mendes, L.A. Helguero, F.A.A. Paz, K. Bachari, O. Talhi and A.M.S. Silva, *J. Mol. Struct.*, **1217**, 128325 (2020); https://doi.org/10.1016/j.molstruc.2020.128325
16. G. Lanka, R. Bathula, M. Dasari, S. Nakkala, M. Bhargavi, G. Somadi and S.R. Potlapally, *J. Recept. Signal Transduct.*, **39**, 253 (2019); https://doi.org/10.1080/10799893.2019.1660897
17. K.K. Mustyala, V. Malkhed, V.R. Chittireddy and U. Vuruputuri, *Int. J. Mycobacteriol.*, **4**, 330 (2015); https://doi.org/10.1016/j.ijmyco.2015.05.013
18. D.S. Goodsell, C. Zardecki, L. Di Costanzo, J.M. Duarte, B.P. Hudson, I. Persikova, J. Segura, C. Shao, M. Voigt, J.D. Westbrook, J.Y. Young and S.K. Burley, *Protein Sci.*, **29**, 52 (2020); https://doi.org/10.1002/pro.3730
19. Target Protein Structure Download, www.rcsb.org/ (accessed Feb 10, 2018).
20. R.A. Friesner, J.L. Banks, R.B. Murphy, T.A. Halgren, J.J. Klicic, D.T. Mainz, M.P. Repasky, E.H. Knoll, M. Shelley, J.K. Perry, D.E. Shaw, P. Francis and P.S. Shenkin, *J. Med. Chem.*, **47**, 1739 (2004); https://doi.org/10.1021/jm0306430
21. F. Broccatelli and N. Brown, *J. Chem. Inf. Model.*, **54**, 1634 (2014); https://doi.org/10.1021/ci5001604
22. J. Du, H. Sun, L. Xi, J. Li, Y. Yang, H. Liu and X. Yao, *J. Comput. Chem.*, **32**, 2800 (2011); https://doi.org/10.1002/jcc.21859
23. M.M. Ignjatovic, O. Caldararu, G. Dong, C. Munoz-Gutierrez, F. Adasme-Carreno and U. Ryde, *J. Comput. Aided Mol. Des.*, **30**, 707 (2016); https://doi.org/10.1007/s10822-016-9942-z
24. K.M. Honorio, T.L. Moda and A.D. Andricopulo, *Med. Chem.*, **9**, 163 (2013); https://doi.org/10.2174/1573406411309020002