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Synthesis, Biological Evaluation, and Molecular Docking Studies of Novel 1,2,3-Triazole Tagged 5-[(1*H*-Indol-3-yl)methylene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione Derivatives[1]

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Abstract—Novel 5-{(1-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6-(1*H*,3*H*,5*H*)trione derivatives (**5a–5k**) were synthesized by the click reaction. All compounds **5a–5k** were characterized by ^{1}H and ^{13}C NMR, IR and Mass spectra and evaluated for their *in vitro* anticancer activity against cervical cancer cell lines. Among all, compound **5e** (IC_{50} = 6.76 μM), shown high inhibitory activity. Docking analysis of all the compounds with the Lipid kinase PI3K-α revealed that the compound **5e** fitted well in the active site pocket, showing the best docking score (LibDock) of 123.274.

Keywords: 1,2,3-triazole, indole, click reaction, cervical cancer, molecular docking

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INTRODUCTION

One of the most fruitful paradigms for discovery of new bioactive chemical entities is starting with established structural cores, known to be part of other bioactive molecules [1]. Barbiturates exhibit a broad range of biological activities, including sedative [2], anticancer [3], antibacterial [4], antioxidant [5], hypnotic [6], anti-convulsant [7], immuno-modulating [8], radio-sensitizing [9], and gelatinase inhibiting [10]. Indole derivatives constitute an important class of heterocyclic compounds with a wide range of pharmacological properties including anticancer [11], antimicrobial [12], anti-malarial [13], anti-tubercular [14], anti-inflammatory [15], antiviral [16], antioxidant [17] activities, and HIV inhibiting [18]. Following the same approach, 1,4-disubstituted 1,2,3-triazoles display a number of agrochemical and pharmaceuticals properties such as anticancer [19, 20], anti-microbial [21, 22], antiviral [23], anti-inflammatory [24], anti-tubercular [25], anti-HIV [26], and anticonvulsant [27] along with significant insecticidal [28], anti-phyto-pathogenic [29] and antidiabetic [39] activities. In view of the above observations, it was important to synthesize a new functionalized barbituric acid, indole and 1,2,3-triazole hybrid derivatives. All newly synthesized compounds were evaluated for their *in vitro* anticancer activity. Molecular docking studies were performed for those. Some of the known barbituric acid, indole and 1,2,3-triazole derivatives were reported to be pharmacologically active (Fig. 1).

RESULTS AND DISCUSSION

Synthesis. All title compounds were synthesized in three consecutive steps (Scheme 1). In the first step, reaction between 1*H*-indole-3-carbaldehyde (**1**) and propargyl-bromide in the presence of K_2CO_3 in dry DMF lasted for 1 h upon stirred at 80°C with

[1] The text was submitted by the authors in English.

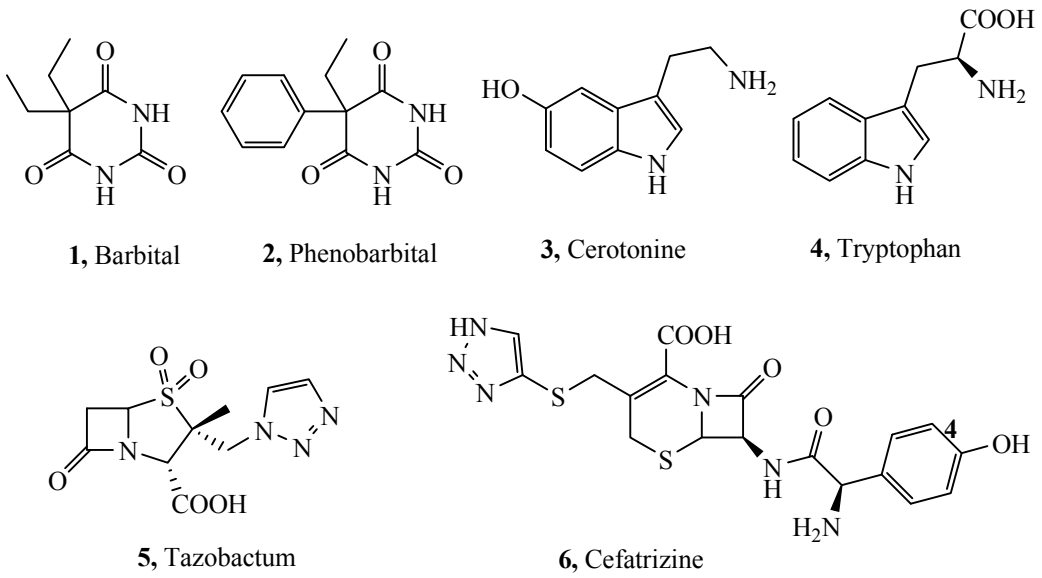


Fig. 1. Selected examples of pharmacologically important barbituric acid, indole, and 1,2,3-triazole derivatives.

formation of 1-(prop-2-yn-1-yl)-1*H*-indole-3-carbaldehyde (**2**). In the second step, inter-mediate **2** was subjected to the Knoevenagel condensation with pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione (**3**) upon refluxing in the presence of piperidine as a catalyst in ethanol for 4 h leading to 5-{[1-(prop-2-yn-1-yl)-1*H*-indol-3-yl]-methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione intermediate (**4**). In the final step intermediate **4** was introduced in cycloaddition with various substituted aromatic azides/substituted benzyl azides under the click reaction conditions in the presence of Cu(I) as a catalyst in dry THF for 12 h to give the corresponding derivatives of 5-{(1-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)-methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6-(1*H*,3*H*,5*H*)trione (**5a–5k**) in quantitative yield.

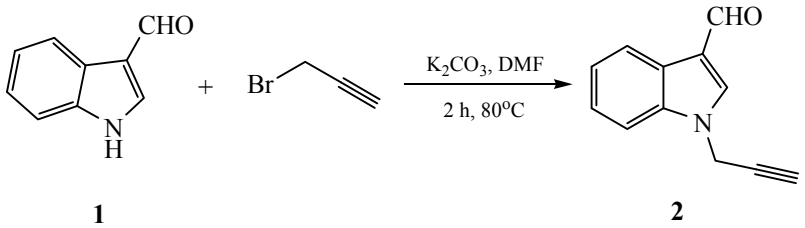
The structures of all derivatives **5a–5k** (Table 1) were confirmed by ^{1}H and ^{13}C NMR, IR, and ESI-MS spectra. ^{1}H NMR spectra of compounds **5a–5k** exposed singlets in the ranges of 5.58–5.86 ppm and 8.63–9.70 ppm that were attributed to the methylene protons attached to nitrogen atom of indole ring and proton of 1,2,3-triazole ring respectively, whereas the corresponding carbon resonances in the ^{13}C NMR spectra were observed at 41.2–42.3 and 121.9–123.2 ppm, respectively. The other protons and carbons resonated at the expected regions.

Anti-cancer activity. The *in vitro* cytotoxic activity of the synthesized compounds was evaluated using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay on the HeLa (cervical cancer cell line). The results of cytotoxic tests were expressed in terms of IC_{50} (μM), and doxorubicin was used as a positive control (Table 2). The structural diversity of the derivatives was achieved by varying substituents at the third position of the triazole ring. According to the accumulated data (Table 2), most of compounds were moderately active but some compounds **5b, 5d**, **5e, 5g** demonstrated high inhibition against HeLa (IC_{50} 27.09 μM), (IC_{50} 36.08 μM), (IC_{50} 6.76 μM), and (IC_{50} 33.46 μM) cell line respectively.

Molecular docking. Molecular interactions of the synthesized compounds were studied by means of molecular docking using Discovery Studio 2.1 software. Crystallographic data of Lipid kinase PI3K-α (PDB: 3ZIM) were retrieved from the Protein Data Bank. Retrieved crystal structure of Lipid kinase PI3K-α was cleaned and hydrogen atoms were added. All heteroatoms were removed before docking study.

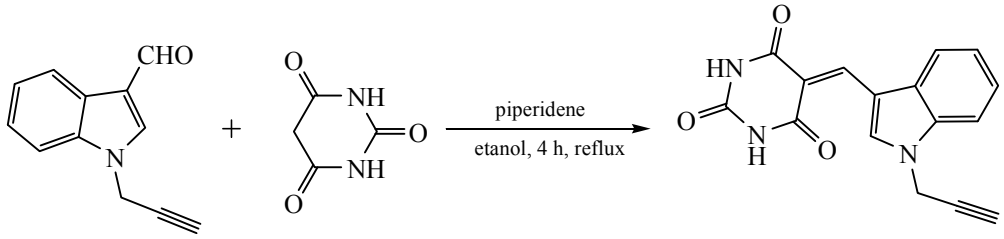
Docking study of the title derivatives **5a–5k** with lipid kinase PI3K-α revealed the high docking scores (LibDock) and binding affinities, in the range of 111.171–123.274, as compared to Doxorubicin 125.50. In the active site pocket of Lipid kinase PI3K-α target protein interacting residues were Tyr836, Glu849, Val851, Val850, Ile848, Ile800, Asp810, Asp933, Met772, Ser854, Gln859, Cys862, Met858, and Lys802. Among all compounds, the derivative **5e** fitted well in the active site pocket of Lipid kinase PI3K-α, showing the best docking score (LibDock) of 123.274 (Table 3, Fig. 2).

Scheme 1. Synthesis of 5-{(1-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione derivatives (**5a–5k**).



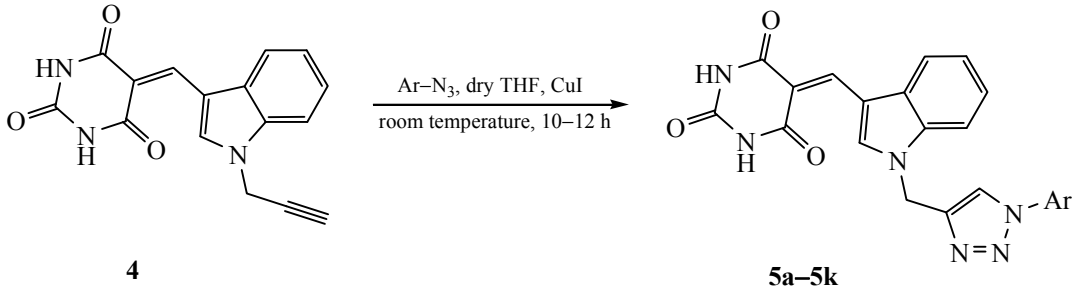
1 **2**

Step 1. Synthesis of 1-(prop-2-yn-1-yl)-1*H*-indole-3-carbaldehyde (**2**).



2 **3** **4**

Step 2. Synthesis of 5-{[1-(prop-2-yn-1-yl)-1*H*-indol-3-yl]methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione (**4**).



4 **5a–5k**

Step 3. Synthesis of 1,2,3-triazole derivatives **5a–5k**.

EXPERIMENTAL

Melting points of all compounds were determined on a Casia-Siamia (VMP-AM) melting point apparatus. IR spectra were recorded on a Perkin–Elmer FT-IR spectrophotometer for KBr discs. NMR spectra were measured for DMSO-d_6 solutions on a Bruker Avance 400 MHz using TMS as an internal standard. Electron impact (EI) and chemical ionization mass spectra were recorded on a VG Micro mass model 7070H instrument. All reactions were monitored by TLC on precoated Merck silica gel plates and spots were visualized under UV light. Column chromatography was carried out on Silica gel, 100–200 mesh (Merck).

Synthesis of 1-(prop-2-yn-1-yl)-1*H*-indole-3-carbaldehyde (2). 1*H*-Indole-3-carbaldehyde **1** (23 mmol) along with potassium carbonate (25 mmol) were dissolved in 10 mL of dry dimethyl formamide. Later, propargylbromide (23 mmol) was added slowly upon stirring. The reaction mixture was stirred at 80°C temperature for 2 h and then extracted with ethyl acetate to afford crude *N*-propargyl benzaldehyde. Purification of the crude residue by column chromatography using 15% ethyl acetate in hexane as an eluent led to isolation of pure compound **2**.

Synthesis of 5-[(1-(prop-2-yn-1-yl)-1*H*-indol-3-yl]methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione. Pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione **3** (33 mmol) was dissolved in ethanol (10 mL) and catalytic amount of piperidine was added. To this mixture 1-(prop-2-yn-1-yl)-1*H*-indole-3-carbaldehyde **2** (33 mmol) was added. The reaction mixture was refluxed for 4 h. The solvent was removed under reduced pressure and the residue was diluted by distilled water and extracted thrice with dichloromethane. The combined organic layers were

Table 1. 5-{(1-[(1-Phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione derivatives (**5a–5k**)

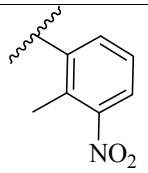
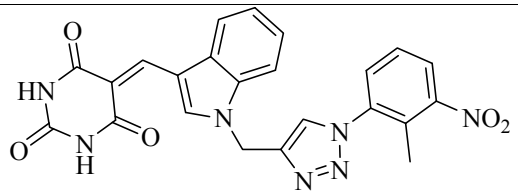
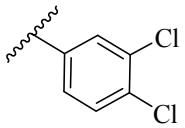
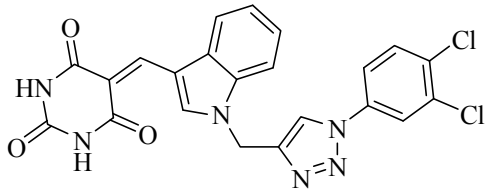
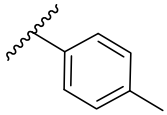
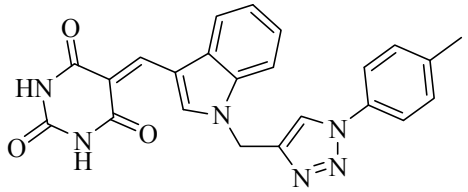
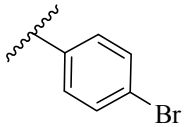
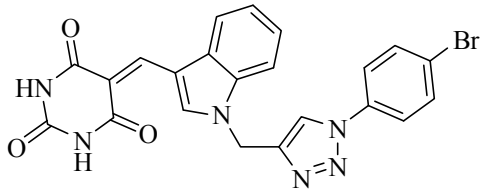
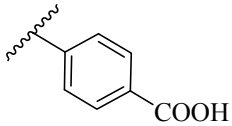
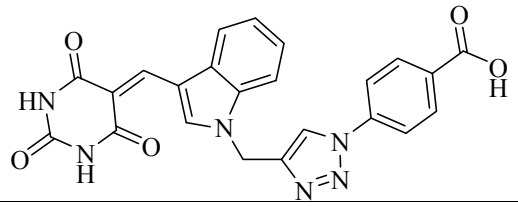
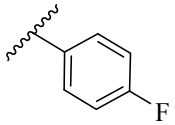
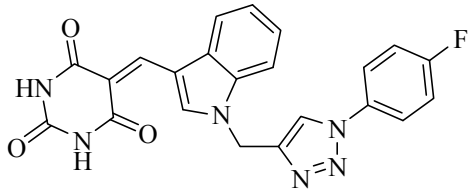
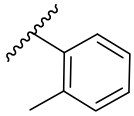
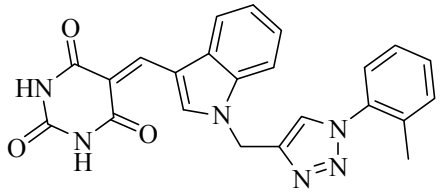
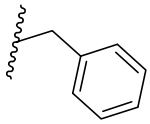
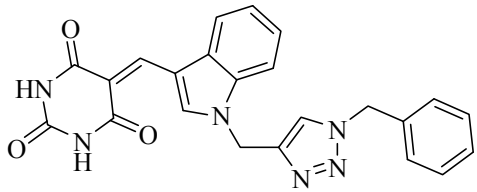
Comp. no.	Ar	Product
5a		
5b		
5c		
5d		
5e		
5f		
5g		
5h		

Table 1. (Contd.)

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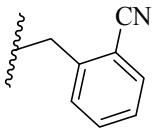
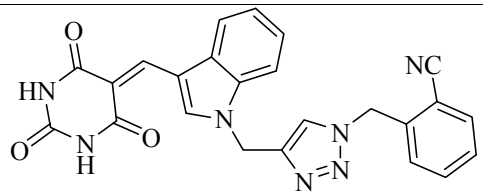
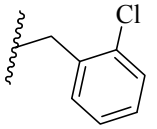
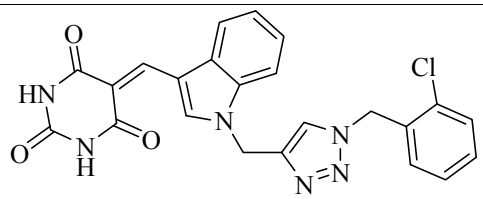
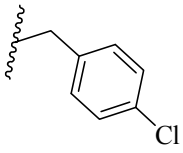
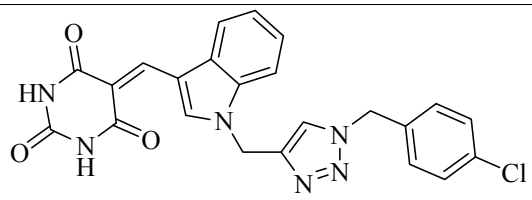
5i		
5j		
5k		

Table 2. Anticancer activity of the compounds **5a–5k**

Compound	HeLa cervical cancer cell line IC_{50}, μM	Compound	HeLa cervical cancer cell line IC_{50}, μM
5a	57.90	**5g**	33.460
5b	27.09	**5h**	54.560
5c	91.64	**5i**	62.900
5d	36.08	**5j**	66.210
5e	6.76	**5k**	70.270
5f	49.81	Doxorubicin	4.719

dried over anhydrous Na_2SO_4 and concentrated giving the product **4**, which was purified by column chromatography using ethyl acetate in hexane.

Synthesis of 5-{(1-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione derivatives (5a–5k). The intermediate, 5-{[1-(prop-2-yn-1-yl)-1*H*-indol-3-yl]methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione **4** (3.0 mmol), was dissolved in dry THF (10 mL) and catalytic amount of CuI was added. To this, substituted aromatic azide/benzyl azide (3.0 mmol) in dry THF were added slowly upon stirring at room temperature under nitrogen atmosphere. After 12 h of stirring the solvent was removed under reduced pressure, the residue was diluted by distilled water and extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give the product which was purified by column chromatography using ethyl acetate in hexane.

5-{(1-[(1-(2-Methyl-3-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione (5a). Yield 90%, mp 243–245°C. IR spectrum, ν, cm^{-1}: 3093, 2947, 1738, 1669, 1554, 1439. ^1H NMR spectrum, δ, ppm: 2.13 s (3H). 5.86 s (2H), 7.43–7.35 m (2H), 7.66 t (*J* = 8.1 Hz, 1H), 7.81–7.89 m (2H), 7.92 d.d (*J* = 6.2, 2.7 Hz, 1H), 8.16 d.d (*J* = 8.2, 1.0 Hz, 1H), 8.68 s (1H), 8.78 s (1H), 9.67 s (1H), 11.10 s (1H), 11.17 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 13.86, 41.94, 109.10, 110.73, 112.06, 117.89, 123.10, 123.79, 125.67,

Table 3. Docking score (LibDock) and ligand interaction data for the compounds **5a–5k**

Comp. no.	Electrostatic energy	LibDock score	Interacting atoms	H-Distance	Comp. no.	Electrostatic energy	LibDock score	Interacting atoms	H-Distance
5a	118.579	–44.601	A:TYR836:HH-**5a**:O^{9}	2.407000	**5g**	116.002	–53.280	A:LYS802:HZ1-**5g**:O^{11}	1.544000
			A:LYS802:HZ1-**5a**:O^{11}	1.785000				A:TYR836:HH-**5g**:O^{10}	1.867000
			5a:H37-A:ASP933:O^{D1}	2.446000				**5g**:H34-A:ASP810:O^{D1}	1.975000
			5a:H37-A:ASP933:O^{D2}	1.981000				**5g**:H34-A:ASP810:O^{D2}	2.443000
			A:GLN859:HN-**5a**:O^{34}	2.405000					
			A:GLN859:HN-**5a**:O^{35}	1.812000					
			A:MET858:HN1-**5a**:O^{35}	1.313000					
5b	119.425	–41.523	A:GLN859:HN-**5b**:O^{34}	1.756000	**5h**	112.821	–50.387	A:VAL851:HN-**5h**:N^{22}	2.494000
			A:GLN859:HN-**5b**:O^{35}	2.469000				A:VAL851:HN-**5h**:N^{23}	2.117000
			A:LYS802:HZ1-**5b**:O^{11}	1.512000				**5h**:H34-A:ASP810:O^{D1}	2.092000
			A:TYR836:HH-**5b**:O^{10}	1.848000				A:TYR836:HH-**5h**:O^{11}	1.911000
			5b:H37-A:ASP810:O^{D1}	2.026000				A:TYR836:HH-**5h**:N8	2.345000
			5b:H37-A:ASP810:O^{D2}	2.456000				A:ASP933:HN-**5h**:N8	2.477000
			A:MET858:HN1-**5b**:O^{34}	1.477000					
5c	117.203	–55.506	A:LYS802:HZ1-**5c**:N^{6}	1.466000	**5i**	111.171	–44.647	A:VAL851:HN-**5i**:N^{22}	2.494000
			A:LYS802:HZ1-**5c**:O^{10}	2.121000				A:VAL851:HN-**5i**:N^{23}	2.247000
			A:LYS802:HZ3-**5c**:N^{6}	2.277000				A:MET858:HN1-**5i**:O^{11}	1.854000
			A:VAL851:HN-**5c**:N^{22}	2.165000				A:GLN859:HN-**5i**:N^{6}	2.260000
			5c:H34-A:ASP933:O^{D1}	2.381000				A:GLN859:HN-**5i**:O^{11}	2.290000
			5c:H34-A:ASP933:O^{D2}	2.451000				**5i**:H36-A:MET858:N	1.872000
5d	116.91	–53.473	**5d**:H34-A:ASP810:O^{D1}	2.431000	**5j**	119.187	–49.887	A:VAL851:HN-**5j**:N^{22}	2.496000
			5d:H34-A:ASP810:O^{D2}	2.494000				A:VAL851:HN-**5j**:N^{23}	2.250000
			A:LYS802:HZ1-**5d**:O^{11}	1.562000				A:MET858:HN1-**5j**:O^{11}	1.858000
			A:TYR836:HH-**5d**:O^{10}	2.455000				A:GLN859:HN-**5j**:N^{6}	2.257000
			A:GLN859:HN-**5d**:Br^{32}	2.390000				A:GLN859:HN-**5j**:O^{11}	2.281000
								5j:H35-A:MET858:N	1.877000
5e	123.274	–56.057	A:LYS802:HZ1-**5e**:O^{11}	1.363000	**5k**	119.112	–54.839	A:LYS802:HZ1-**5k**:O^{10}	1.815000
			A:TYR836:HH-**5e**:O^{10}	1.620000				A:TYR836:HH-**5k**:O^{11}	1.639000
			A:GLN859:HN-**5e**:O^{33}	2.090000				A:ASP933:HN-**5k**:N8	2.417000
				2.298000				A:ASP933:HN-**5k**:O^{11}	2.297000
			A:GLN859:HN-**5e**:O^{34}	2.404000				**5k**:H35-A:TYR836:OH	2.452000
			A:ASP933:HN-**5e**:O^{10}	2.118000					
			5e:H36-A:ASP810:O^{D1}	2.420000					
			5e:H36-A:ASP810:O^{D2}	1.932000					
			A:MET858:HN1-**5e**:O^{33}						

126.54, 127.90, 128.41, 129.80, 131.07, 136.34, 137.44, 141.71, 142.10, 142.87, 150.40, 150.60, 163.10, 164.42. ESI-MS: *m/z*: 486 [*M* + 1] observed for $C_{24}H_{19}N_7O_5$.

5-{(1-([1-(2,3-Dichlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione (5b). Yield 85%, mp 220–222°C. IR spectrum, ν, cm^{-1}: 3087, 2826, 1740, 1668, 1544, 1435. ^{1}H NMR spectrum, δ, ppm: 5.85 s (2H), 7.25–7.42 m (3H), 7.85 d (*J* = 9.0 Hz, 1H), 7.89–7.94 m (2H), 8.24 s (1H), 8.68 s (1H), 9.04 s (1H), 9.70 s (1H), 11.11 s (1H), 11.18 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 41.53, 110.02, 114.57, 115.22, 115.87, 120.20, 121.93, 123.40, 125.50, 129.90, 131.15, 131.23, 131.81, 132.34, 135.90, 137.36, 143.50, 150.17, 154.73, 161.91, 163.84. ESI-MS: *m/z*: 495 [*M* + 1] observed for $C_{23}H_{16}Cl_2N_6O_3$.

5-{(1-([1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)-methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6-

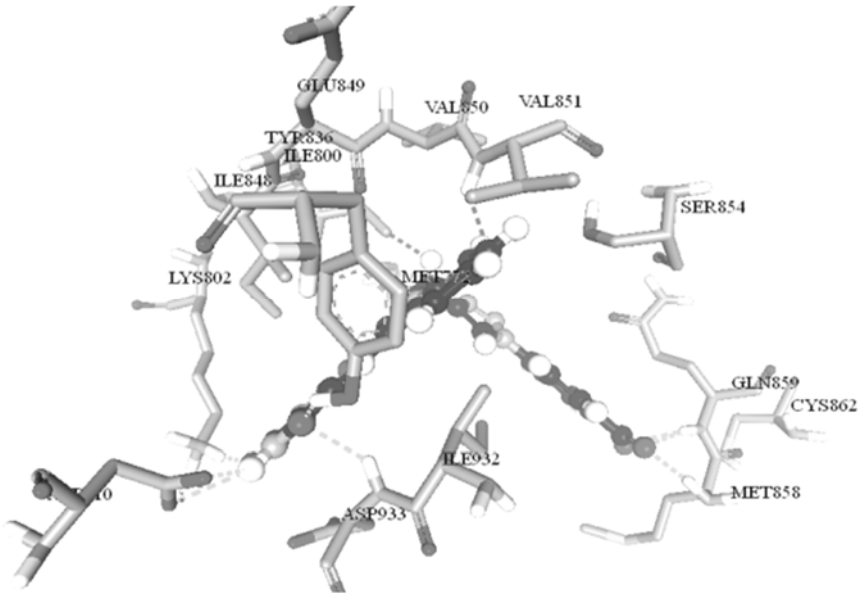


Fig. 2. Receptor-ligand hydrogen bonds and bumps of compound **5e** with the active site residues of α-lipid kinase PI3K (PDB: 3ZIM).

(1*H*,3*H*,5*H*)trione (5c). Yield 86%, mp 230–231°C. IR spectrum, ν, cm^{-1}: 3090, 2971, 1723, 1677, 1588, 1452. ^{1}H NMR spectrum, δ, ppm: 5.82 s (2H), 2.36 s (3H), 7.31–7.43 m (4H), 7.75 d (J = 8.3 Hz, 2H), 7.89 d (J = 8.9 Hz, 2H), 8.68 s (1H), 8.92 s (1H), 9.69 s (1H), 11.10 s (1H), 11.17 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 14.13, 42.30, 109.03, 112.32, 115.56, 117.01, 120.07, 123.26, 123.57, 125.68, 126.31, 127.10, 130.24, 131.23, 134.24, 138.48, 142.94, 150.14, 161.30, 163.91. ESI-MS: *m/z*: 441 [M + 1] observed for $C_{24}H_{20}N_6O_3$.

5-{(1-([1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl)-methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6-(1*H*,3*H*,5*H*)trione (5d). Yield 80%, mp 208-210°C. IR spectrum, ν, cm^{-1}: 3087, 2826, 1741, 1668, 1540, 1435. ^{1}H NMR spectrum, δ, ppm: 5.84 s (2H), 7.23–7.42 m (4H), 7.69–7.95 m (4H), 8.46 s (1H), 8.94 s (1H), 9.70 s (1H), 11.11 s (1H), 11.19 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 42.06, 109.90, 110.83, 111.03, 117.54, 121.13, 122.71, 123.65, 124.82, 130.02, 136.51, 136.82, 139.91, 140.70, 142.51, 143.51, 150.01, 153.40, 160.93, 162.06. ESI-MS: *m/z*: 505 [M + 1] observed for $C_{23}H_{17}BrN_6O_3$.

4-{(4-[(3-{(2,4,6-Trioxotetrahydropyrimidin-5(2*H*)-ylidene)methyl}-1*H*-indol-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl)methyl}benzoic acid (5e). Yield 92%, mp 251–252°C. IR spectrum, ν, cm^{-1}: 3104, 3020, 2930, 1721, 1703, 1675, 1541, 1445. ^{1}H NMR spectrum, δ, ppm: 5.86 s (2H), 7.19–7.46 m (4H), 7.61–8.04 m (4H), 8.46 s (1H), 8.68 s (1H), 9.70 s (1H), 11.10 s (1H), 11.17 s (1H), 13.27 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 41.42, 109.17, 110.70, 111.28, 117.49, 121.04, 122.30, 122.62, 123.65, 129.81, 136.26, 136.80, 140.74, 141.79, 143.70, 150.37, 163.12, 164.40, 184.78. ESI-MS: *m/z*: 471 [M + 1] observed for $C_{24}H_{18}N_6O_5$.

5-{(1-[(1-{4-Fluorobenzyl}-1*H*-1,2,3-triazol-4-yl)-methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6-(1*H*,3*H*,5*H*)trione (5f). Yield 81%, mp 218–220°C. IR spectrum, ν, cm^{-1}: 3049, 2971, 1735, 1663, 1546, 1457. ^{1}H NMR spectrum, δ, ppm: 5.84 s (2H), 7.28–7.46 m (4H), 7.73–7.92 m (4H), 8.68 s (1H), 8.95 s (1H), 9.70 s (1H), 11.11 s (1H), 11.18 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 41.83, 109.91, 112.34, 114.93, 115.59, 122.56, 122.65, 123.63, 124.56, 125.71, 130.01, 131.19, 133.06, 136.08, 136.91, 143.11, 155.23, 162.30, 162.80, 163.91. ESI-MS: *m/z*: 445 [M + 1] observed for $C_{23}H_{17}FN_6O_3$.

5-{(1-[(1-{2-Methylbenzyl}-1*H*-1,2,3-triazol-4-yl)-methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6-(1*H*,3*H*,5*H*)trione (5g). Yield 80%, mp 212–215°C. ^{1}H NMR spectrum, δ, ppm: 2.32 s (3H), 5.79 s (2H), 7.35 d.d (J = 9.5, 6.3 Hz, 4H), 7.70–7.90 m (4H), 8.68 s (1H), 8.90 s (1H), 9.68 s (1H), 11.07 s (1H), 11.12 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 13.80, 41.93, 109.15, 110.80, 112.10, 117.90, 120.93, 123.06, 123.81, 125.60, 126.50, 127.91, 128.42, 129.31, 131.01, 136.30, 137.40, 141.93, 150.31, 163.15, 164.40. ESI-MS: *m/z*: 441 [M + 1] observed for $C_{24}H_{20}N_6O_3$.

5-{(1-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5h). Yield 88%, mp 225–227°C. IR spectrum, ν, cm^{-1}: 3087, 2826, 1740, 1668, 1544, 1435. ^1H NMR spectrum, δ, ppm: 5.58 s (2H), 5.72 s (2H), 7.24–7.47 m (7H), 7.54–7.95 m (2H), 8.29 s (1H), 8.66 s (1H), 9.63 s (1H), 11.10 s (1H), 11.17 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 42.92, 52.61, 109.22, 110.64, 112.02, 117.91, 123.09, 123.80, 125.86, 127.17, 128.06, 130.77, 133.27, 136.36, 137.54, 141.89, 142.90, 150.36, 163.11, 164.37. ESI-MS: *m/z*: 427 [*M* + 1] observed for $C_{23}H_{18}N_6O_3$.

2-{(4-[(3-{(2,4,6-Trioxotetrahydropyrimidin-5(2*H*)-ylidene)methyl}-1*H*-indol-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl)methyl}benzonitrile (5i). Yield 85%, mp 231–232°C. IR spectrum, ν, cm^{-1}: 3079, 2229, 1740, 1701, 1672, 1549, 1426. ^1H NMR spectrum, δ, ppm: 5.75 s (2H), 5.81 s (2H), 7.32 d (*J* = 7.8 Hz, 1H), 7.37 m (2H), 7.55 t (*J* = 7.5 Hz, 1H), 7.68–7.74 m (1H), 7.78–7.84 m (1H), 7.91 d (*J* = 6.9 Hz, 2H), 8.36 s (1H), 8.66 s (1H), 9.63 s (1H), 11.09 s (1H), 11.17 s (1H). ESI-MS: *m/z*: 452 [*M* + 1] observed for $C_{24}H_{17}N_7O_3$.

5-{(1-[(1-{2-Chlorobenzyl}-1*H*-1,2,3-triazol-4-yl)-methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6-(1*H*,3*H*,5*H*)trione (5j). Yield 88%, mp 235–236°C. ^1H NMR spectrum, δ, ppm: 5.68 s (2H), 5.71 s (2H), 6.99–7.10 m (1H), 7.24 s (1H), 7.34–7.41 m (4H), 7.69–7.81 m (1H), 7.86–7.95 m (1H), 8.33 s (1H), 8.66 s (1H), 9.63 s (1H), 11.09 s (1H),11.18 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 43.21, 52.61, 109.22, 110.64, 112.02, 117.91, 123.09, 123.80, 125.86, 127.17, 127.96, 128.06, 129.96, 130.77, 131.06, 133.27, 136.36, 137.51, 141.89, 142.63, 150.36, 163.11, 164.37.

5-{(1-[(1-{4-Chlorobenzyl}-1*H*-1,2,3-triazol-4-yl)-methyl]-1*H*-indol-3-yl)methylene}pyrimidine-2,4,6-(1*H*,3*H*,5*H*)trione (5k). Yield 90%, mp 245–247°C. IR spectrum, ν, cm^{-1}: 3087, 2973, 1672, 1526, 1429. ^1H NMR spectrum, δ, ppm: 5.73 s (2H), 5.86 s (2H), 7.20–7.44 m (4H), 7.89 d (*J* = 9.2 Hz, 2H), 8.11 d (*J* = 9.2 Hz, 2H), 8.46 s (1H), 8.67 s (1H), 9.70 s (1H), 11.10 s (1H), 11.16 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 43.20, 52.41, 109.31, 110.70, 112.10, 118.01, 123.13, 123.79, 125.90, 127.71, 128.10, 129.91, 130.77, 133.01, 136.40, 137.51, 142.01, 143.51, 149.95, 163.31, 164.29. ESI-MS: *m/z*: 461 [*M* + 1] observed for $C_{23}H_{17}ClN_6O_3$.

CONCLUSIONS

Novel 1,2,3-triazole tagged 5-[(1*H*-indol-3-yl)methylene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione derivatives **5a–5k** have been synthesized, and their *in vitro* anticancer activity against HeLa (cervical cancer cell line) was tested. The structures of all newly synthesized derivatives were confirmed by ^1H and ^{13}C NMR, IR, and ESI-MS spectra. Among the tested compounds, the compound **5e** exhibited selective activity against cervical cancer cell line with IC_{50} value of 6.76 μM. Molecular docking of the synthesized derivatives with human Lipid kinase PI3K-α revealed the LibDock score in the range of 111.171–123.274.

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