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SYNTHESIS OF 2-BROMO-6-(4,5-DIPHENYL-1-((1-PHENYL-1*H*-1,2,3-TRIAZOL-4-YL) METHYL)-1*H*-IMIDAZOL-2-YL) PYRIDINE DERIVATIVES: EVALUATION OF ANTICANCER ACTIVITY AND MOLECULAR DOCKING STUDIES

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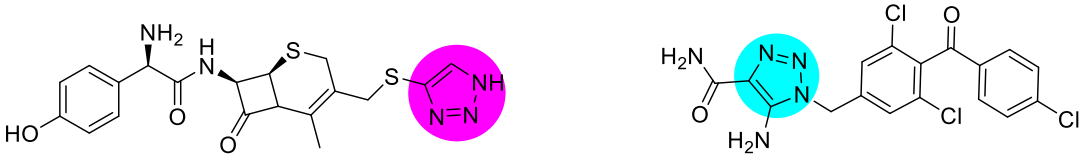
Abstract:
A series for novel 2-bromo-6-(4,5-diphenyl-1-((subtituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)pyridine (**7a-l**) were synthesized and characterized by various analytical techniques. All the synthesized compounds were evaluated for their *in vitro* anticancer activity against two human cancer cell lines such as HT-1080 (Human fibro sarcoma cells) and Caco-2(Human colorectal adenocarcinoma cells) and IC_{50}values were compared against standard anticancer drug doxorubicin. Among all the synthesized compounds **7b**, **7c** and **7f** has shown potent activity against HT-1080. Similarly compounds **7b** and **7c** shown significant activity among all the synthesized compounds against Caco-2**.** Furthermore, the results were supported by molecular docking studies.

Keywords:1,2,3- Triazole-pyridine hybrids, anticancer activity and molecular docking studies.

Introduction:

Cancer has become one of the major global health concerns Since it is the second leading cause of death after cardiovascular diseases, it remains a major health problem around the world [i]. Cancer is a collection of related diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. Since it involves the conversion of any normal cells to a cancerous cell showing tandem replication and cell divisions at much faster rate in comparison to the normal cells and thus provides a potential target for the development of chemotherapeutic agents. The all over world estimated deaths and new cancer cases in 2020 were 10.0 million and 19.3 million. The cancer burden globally is expected to be raise 47% from 2020 to 2040 with 28.4 million cases. Chemo resistance is an important phenomenon associated with the cell division. In addition, safety profile and side effects are the major concerns with anticancer drugs. Therefore, the development of novel agents with increased efficacy while reducing the side effects will encourage the researchers towards the drug design and development.

1,2,3-Triazoles, are the most important nitrogen containing heterocycles, and these derivatives possess diverse biological properties Moreover, some of 1,2,3-triazole containing anticancer agents such as Cefatrizine[a] and Carboxyamido-triazole[b] (Fig. 1) have already been under clinical evaluation for the treatment of cancer.



Cefatrizine[a] Carboxyamidotriazole[b]

Figure 1- (a), (b) The chemical structures of anticancer agents containing 1,2,3 triazole as a scaffold.

Derivatives of Pyridine are the privileged scaffolds with wide range of pharmacological properties, which plays an important role by inhibition of CDK, EGFR, PI3K, and RGGT etc in different cancers [ii, iii]. Anti-cancer agents like Masitinib and ABT-751 (E7010) containing pyridine as a core moiety have already been under clinical trials for the treatment of cancers, indicating the importance of pyridine derivatives in the discovery of anticancer agents [iv]. All 1,2,3-triazole-pyridine derivative (Fig-2) with IC_{50}: 0.1-19.5 mM, showed considerable activity against HT-29, DU-145 and A549 cancer cell lines, and most of them were not less active than ABT-751 IC50: 1.31-1.62 mM and Nocodazole with IC_{50}: 2.2-3.1 mM [v, vi].

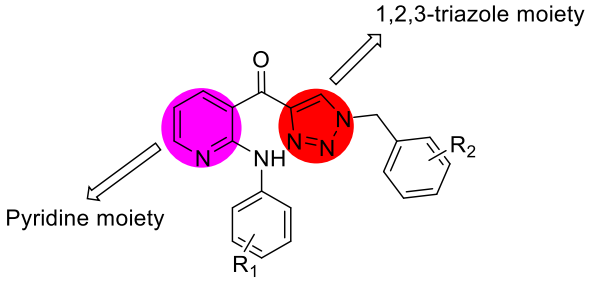


Figure 2- The chemical structures of anticancer agents containing 1,2,3 triazole pyridine hybrid scaffold.

A series of 1,2,3- triazole-pyridine hybrids Fig-3 was highly active against the two enzymes NAMPT and HDAC with IC_{50} value 18-190 nM [vii, viii].

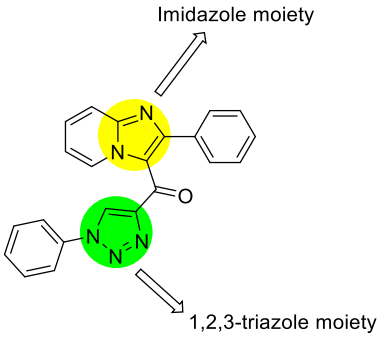


Figure 3- The chemical structures of anticancer agents containing 1,2,3 triazole pyridine hybrid scaffold.

Hybrid molecules have the potential to reduce side effects and overcome the drug resistance since hybrids with two or more different pharmacophores may also own multiple action mechanism

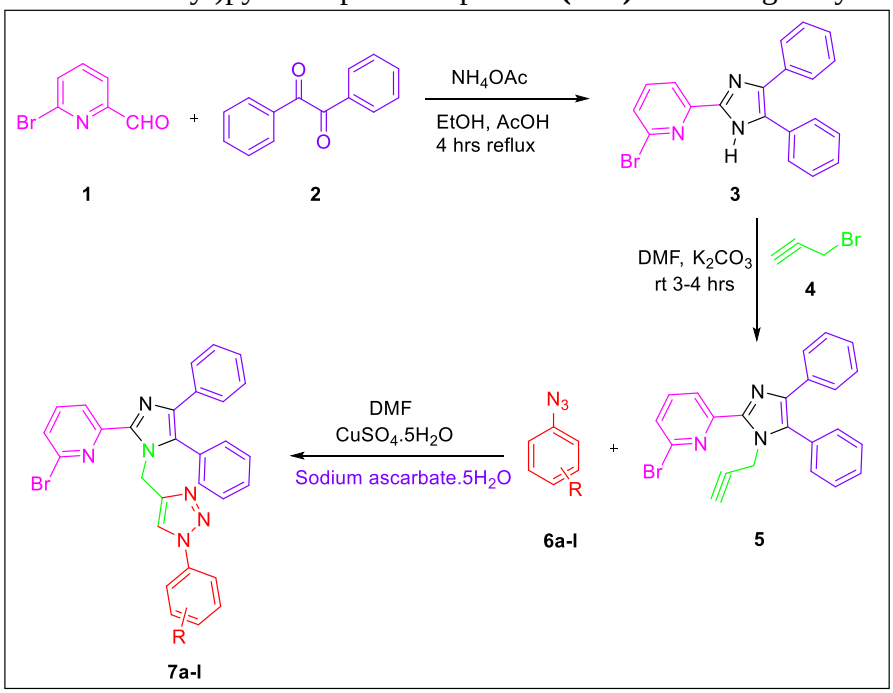
Considering the anti-cancer activity exhibited by both 1,2,3- triazole derivatives and the pyridine derivatives from literature search and that fusion of 1,2,3- triazole and pyridine could

result in molecules having greater anti-cancer activity due to synergistic effect of both 1,2,3-triazole-pyridine scaffolds. Hence, a series of 1,2,3- triazole-pyridine hybrids have been synthesized and evaluated for their *in vitro* anti-cancer activity using human cell lines with results supported by docking studies.

Results and discussion:

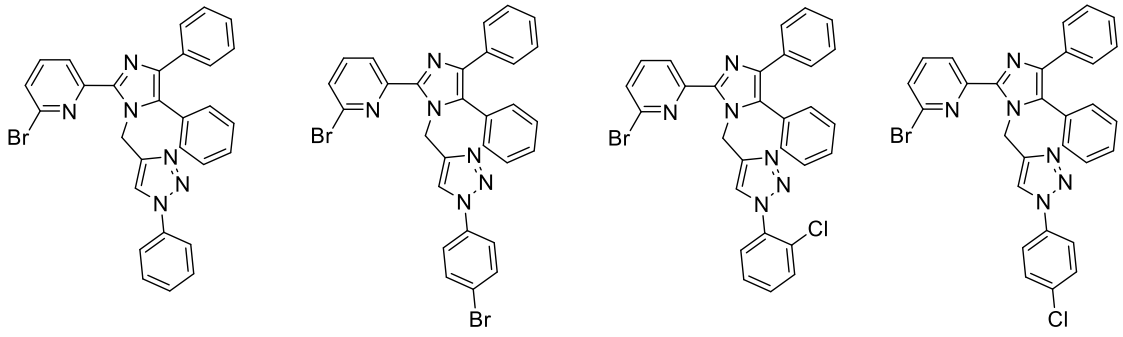
Chemistry

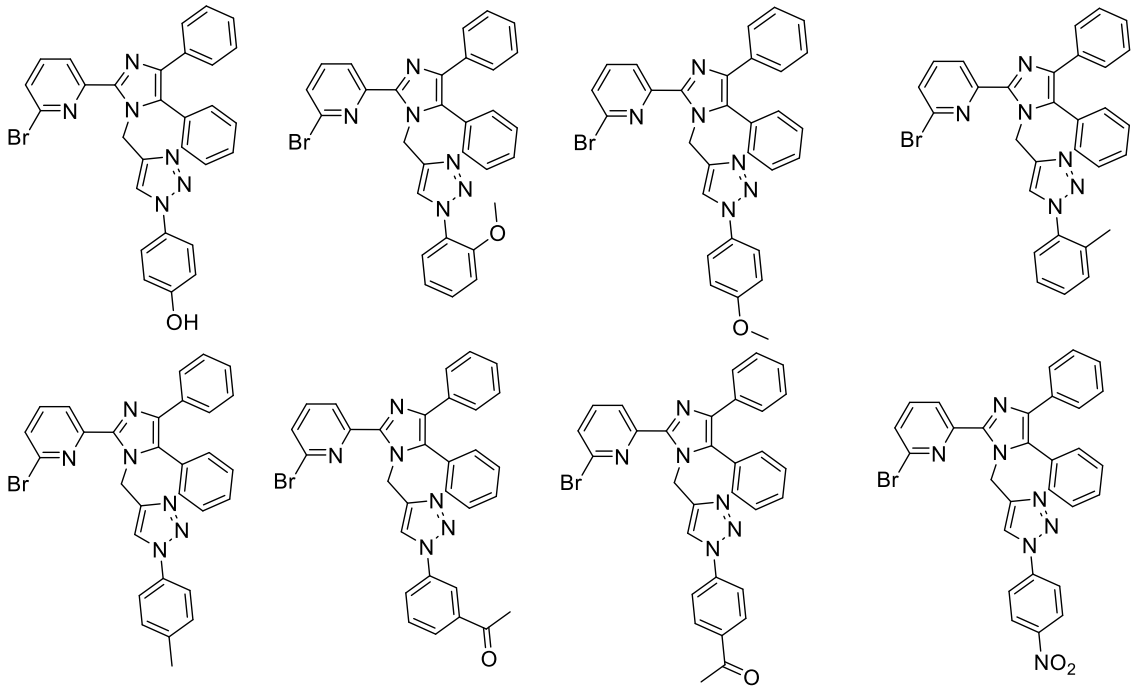
Synthetic route for 2-bromo-6-(4,5-diphenyl-1-((subtituted-phenyl-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-imidazol-2-yl) pyridine (**7a-l**) were summarized in scheme 1. The 1,2,3-triazole tethered pyridine core nucleus was constructed from commercially available starting materials. The synthesis was carried as one pot three component condensation of 6-bromopicolinaldehyde **(1)** benzil (**2**) and ammonium acetate in presence of ethanol in acetic acid at 70°C for 4hrs to afford compound**(3)**with the propargylation with propargyl bromide (**4**) dry DMF and dry K_2CO_3 rt for 3-4hrs to yield 2-bromo-6-(4,5-diphenyl-1-(prop-2-yn-1-yl)-1*H*-imidazol-2-yl)pyridine **(5)** which on further click reaction of substituted aryl azides **(6a-l)** at the terminal alkyne position to obtain 2-bromo-6-(4,5-diphenyl-1-((subtituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)pyridine pure compounds **(7a-l)** in the range of yields (70-80%).



Scheme 1

Derivatives:





Biological Evaluation and Structural Activity Relationship (SAR):

The newly synthesized compounds (**7a-l**) were screened for their *in vitro* anti-cancer activity using two human cancer cell lines such as HT-1080 (Human fibro sarcoma cells) and **Caco-2** (Human colorectal adenocarcinoma cells) by MTT assay. Doxorubicin was used as a reference anti-cancer drug and the results were expressed in terms of IC_{50} (µM) values as summarized in Table 1.

Among the synthesized compounds, **7b, and 7c shown** more potent anti-cancer activity against HT-1080 and Caco-2 cell lines, compared to control drug. It showed that compound (**7b)** with 4-bromo group on the phenyl ring exhibited more potent activity than the control doxorubicin. Similarly, substitution with strong electron withdrawing agent like chloro group at ortho position on the phenyl ring resulted compound **7c** shown slightly decrease in activity compared to **7b**. whereas replacement of 4-bromo on the phenyl ring with 4-chloro resulted compound **7d** which showed lower activity than **7b**. The unsubstituted and alkyl substitutions on the phenyl ring were not tolerated. Compound **7g** with electron donating agent, 4-methoxy substitution shown slightly decrease in activity compared to control drug. Shifting of methoxy substitution from ortho position to para position compound resulted in loss of activity.

Molecular docking studies:

The ligands were sketched in chemdraw and saved it in mol2 format. All the sketched molecules were converted to energy minimized 3D structures by using ligprep module for in-silico protein – ligand docking using Schrödinger 11.4. Each molecule was docked separately. Initially the molecule was loaded; torsions were set and saved it in PDB format. All the heteroatoms were removed from the 5FGK. PDB (CDK8-CYCC IN COMPLEX WITH 8-[3-(3-Amino-1H-indazol-6-yl)-5-chloro- pyridine-4-yl]-2,8-diaza-spiro [4.5] decan-1-one). The Mediator complex-associated cyclin-dependent kinase CDK8 has been implicated in human disease, particularly in **colorectal cancer** where it has been reported as a putative oncogene to make complex receptor free of any ligand before docking. Receptor grid generated using glide module. The best conformation was chosen with the lowest docked energy after the docking search was completed. The interactions of 5FGK protein and ligand conformations, including hydrogen bonds and the bond lengths were analyzed. Molecular docking study was performed by using maestro

Table 1: The IC_{50} values of compounds 7a-l

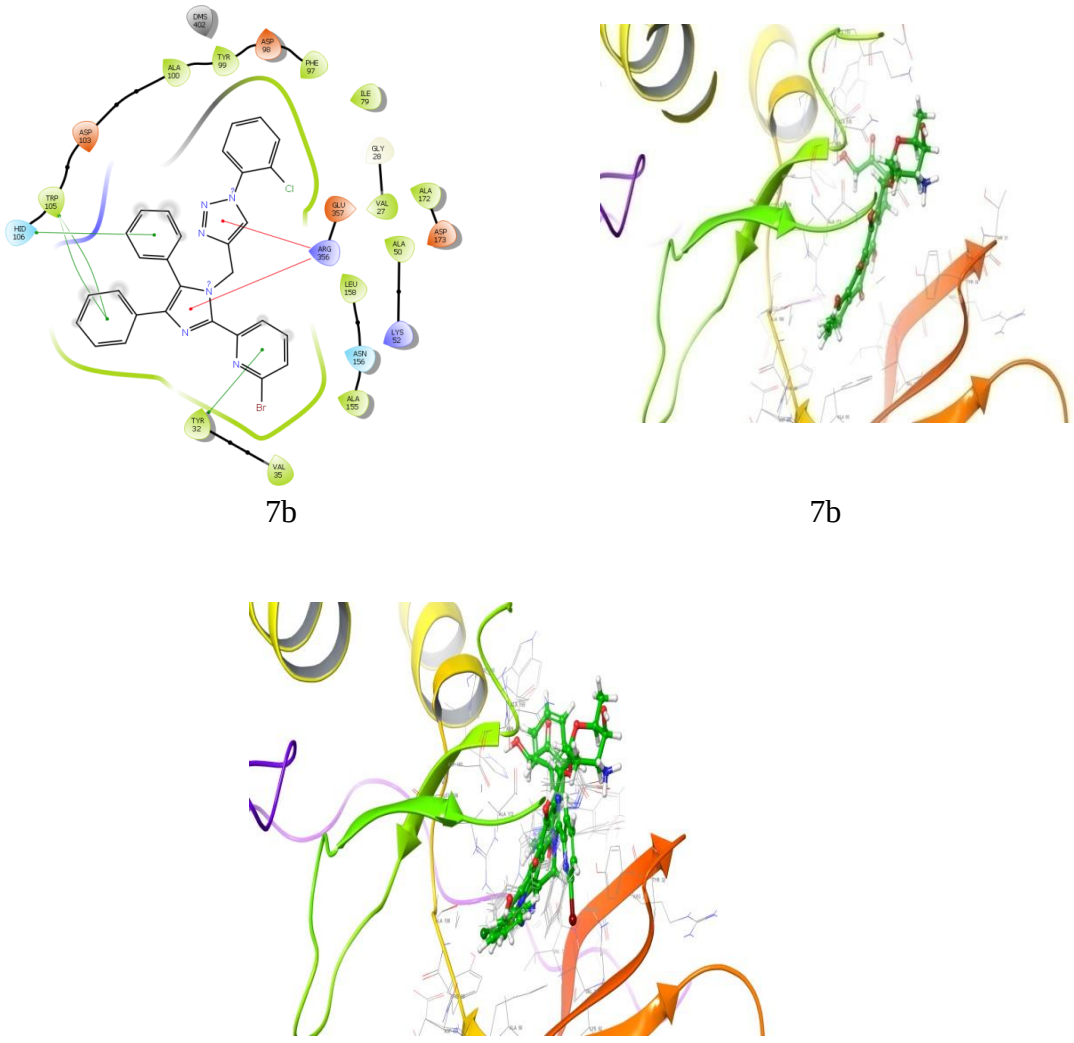
Compound Name	**IC_{50} in µM at 72 hr's**	
	HT-1080 (Human fibro sarcoma cells)	**Caco-2** (Human colorectal adenocarcinoma cells)
7a	47.5±1.28	41.62±1.06
7b	**9.5±1.64**	**12.29±1.21**
7c	**10.8±2.46**	**24.53±1.48**
7d	36.2±1.92	53.11±1.76
7e	43.4±1.47	58.12±1.21
7f	**12.4±2.29**	**32.62±1.18**
7g	42.4±1.34	47.15±1.23
7h	29.4±2.02	39.30±1.82
7i	30.8±1.69	46.31±1.01
7j	47.6±2.13	52.79±1.35
7k	43.1±1.29	49.73±1.28
7l	33.8±1.95	46.71±1.53
Doxorubicin	**11.2±1.04**	**6.17±1.88**

(Schrödinger 11.4) which was a suite of automated docking tools and was used to predict the affinity, activity, binding orientation of ligand with the target protein and to analyze best conformations, the protein with all the compounds (7a-l) were loaded individually evaluated. We observed that in the compound 7b molecule two aromatic rings showing Π-Π stacking interactions with amino acids histidine and tryptophan, Triazole & Imidazole rings showing cation pi interaction with amino acid arginine, pyridine moiety showing Π-Π stacking interactions with amino acid Tyrosine and showed best fit, potent dock score then compared with doxorubicin.

Compound name	**Docking score**
5FGK	
7a	-6.183
7b	**-6.783**
7c	-5.98
7d	-5.156

7e	-5.87
7f	**-6.185**
7g	-5.517
7h	-5.982
7i	-5.522
7J	-5.749
7k	-5.256
7l	-5.277
Doxorubicin	**-7.065**

Table 2: The Dock scores of synthesized molecules



7b 7b

Figure 4- Dock poses and ligand interaction diagrams of molecules 7b.

Conclusion

In conclusion, a series of 1,2,3-triazole linked pyridine hybrids derivatives (**7a-l**) were synthesized and characterized by ^{1}HNMR, ^{13}CNMR, and mass spectral analysis. Further, these synthesized compounds were tested for their anticancer activity against two human cancer cell

lines, HT-1080(Human fibro sarcoma cells), **Caco-2** (Human colorectal adenocarcinoma cells). Doxorubicin is used as a control. Among them, compounds **7b, 7c** and **7f** showed potent anticancer activity compared to control drug. Docking results shown that compounds exhibited potent dock score then compared with doxorubicin.

Experimental:

General experimental methods:

Were purchased all the chemical of the organic reagents and solvents from Tci, Merk, were used, further ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO by using 500 and 125 MHz spectrometers (Instrument Bruker Avance II 500MHz). Chemical shift values are displayed as ppm and spin multiplicities are indicated as singlet (s); doublet (d); doublet of doublet (dd); triplet(t); multiplets (m); and coupling constants are shown in hertz. Column chromatography was performed on silica gel (60-120 mesh) using distilled hexane and ethyl acetate solvents. 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 were uncorrected.

General procedure for the preparation of 2-bromo-6-(4,5-diphenyl-1*H*-imidazol-2-yl) pyridine (3)

The synthetic route for the 2-bromo-6-(4,5-diphenyl-1*H*-imidazol-2-yl) pyridine **(3)** was carried out by one pot three component condensation of 6-bromopicolinaldehyde **(1)**, benzil (**2**) and ammonium acetate and catalytical amount of acetic acid in ethanol at 70°C for 5 hrs to afford compound **(3)**

General procedure for the preparation of 2-bromo-6-(4,5-diphenyl-1-(prop-2-yn-1-yl)-1*H*-imidazol-2-yl) pyridine (5)

The synthetic route for the 2-bromo-6-(4,5-diphenyl-1-(prop-2-yn-1-yl)-1*H*-imidazol-2-yl) pyridine (5) was carried out by propargylation of compound (3) with propargylic bromide (4) dry DMF and dry K_2CO_3 at rt for 4 hrs propargylation at the position of free N-H group yields to -propargylated compound bromo-6-(4,5-diphenyl-1-(prop-2-yn-1-yl)-1H-imidazol-2-yl) pyridine (5)

General procedure for the preparation of 2-bromo-6-(4,5-diphenyl-1-((substituted-phenyl-1H-1,2,3-triazol-4-yl) methyl)-1*H*-imidazol-2-yl) pyridine (7a-l)

Synthesis of 2-bromo-6-(4,5-diphenyl-1-((substituted-phenyl-1H-1,2,3-triazol-4-yl) methyl)-1H-imidazol-2-yl) pyridine (7a-l) (7a-l) were carried out by click reaction of propargylated compound (5) (0.1 mmol) with different aryl azides (6a-l) (0.2mmol) using Click chemistry in $CuSO_4.5H_2O$ with sodium ascorbate and DMF at room temperature for 8 hours. The completion of the reaction was monitored by TLC. Upon completion of the reaction mass were purified by column chromatography using hexane/ ethyl acetate (2:3 v/v) to afford 2-bromo-6-(4,5-diphenyl-1-((substituted-phenyl-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-imidazol-2-yl) pyridine (7a-l) gave excellent yields 70-80%.

MTT Assay Principle:

This MTT assay is a colorimetric assay that measures the reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The MTT enters the cells and passes into the mitochondria where it gets reduced and forms insoluble dark purple formazan crystals. The crystals are then solubilized with an organic solvent DMSO and the soluble formazan product is measured by reading absorbance at 570 nm with spectrophotometer. Since reduction of MTT can only occur in metabolically active cells, the level of activity is the measure of the viability of the cells. The HT-1080 & Caco-2 cellswere seeded in 96-well plates with density of 10^5 cells per well in 100 µL of complete

medium and allowed to grow overnight for attachment. The cells are then treated with various concentrations (5, 10, 20, 40, 60, 80 and 100 µM) of test samples C8 and C10 in triplicate for 24 hr and incubated for 72 hr. After treatment, the cells were washed twice with PBS. Then 15 µL MTT reagent in PBS medium with concentration of 0.5 mg/mL was added each well and adjusted the volume then the cells were incubated for 3 hours at 37°C until intracellular purple formazan crystals are visible under microscope. Then MTT reagent was aspirated and the formazan crystals formed were dissolved by the addition of 100 µL of DMSO for 1hr at 37 °C. The quantity of formazan was measured by using a absorbance plate reader at 570 nm wavelength.

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Conflict of interest:
Authors declare no conflict of interest.

Spectral data:
2-bromo-6-(4,5-diphenyl-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)pyridine (7a) Yield 72%, mp: 139-141 ^{o}C; Rf = 0.30 (EtOAc:n-Hexane 2:3); ^{1}H NMR NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 7.97 (d, J = 7.85 Hz, 1H), 7.77 (d, J = 7.57 Hz, 2H), 7.71 (d, J = 7.85 Hz, 2H), 7.63 (t, J = 7.85 Hz, 1H), 7.57 (d, J = 7.85 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 4H), 7.41 (t, J = 7.45 Hz, 1H), 7.40 (dd, J = 7.57 , 7.20 Hz, 2H), 7.40 (d, J = 7.85 Hz, 1H), 7.35 (t, J = 7.20 Hz, 1H), 7.33 (t, J = 7.45 Hz, 1H), 5.33 (s, 2H).^{3}C NMR (125 MHz, DMSO-*d6*)δ 148.7, 145.1, 144.5, 139.2, 138.5, 135.2, 134.7, 133.6, 130.1, 129.4, 128.9, 128.4, 128.3, 128.2, 127.8, 127.6, 126.8, 125.8, 123.6, 120.7, 47.3.LC-MS m/z: 535 [M+H]+ Elemental analysis, Calculated, %:$C_{29}H_{21}BrN_6$:C, 65.30; H, 3.97; N, 15.75; Found %:C, 65.25; H, 3.89; N, 15.69;

2-bromo-6-(1-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)pyridine (7b)Yield 78%, mp: 143-145 ^{o}C; Rf = 0.42 (EtOAc:n-Hexane 2:3);^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.48 (s, 1H), 7.92 (d, J = 7.85 Hz, 1H), 7.81 (d, J = 8.30 Hz, 2H), 7.74 (d, J = 7.85 Hz, 2H), 7.64 (dd, J = 7.85, 7.48 Hz, 1H), 7.57 (d, J = 7.85 Hz, 2H), 7.53 (d, J = 8.30, 9.30 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (d, J = 7.85 Hz 1H), 7.40 (t, J = 7.45 Hz, 1H), 7.40 (dd, J = 7.85, 7.45 Hz, 2H), 7.40 (dd, J = 7.85, 7.45 Hz, 1H), 7.34 (t, J = 7.45 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.21, 142.13, 140.14, 139.72, 135.77, 133.68, 133.41, 132.14, 130.27, 128.73, 128.37, 127.83, 127.67, 127.30, 127.04, 125.07, 124.33, 124.06, 122.03, 121.02, 120.12, 119.54, 118.95, 118.82, 110.41, 109.67, 40.13, 38.12.LC-MS m/z**:** 613[M+H]+ Elemental analysis, Calculated, %: $C_{29}H_{20}Br_2N_6$:C, 56.88; H, 3.29; N, 13.72; Found %:C, 56.81; H, 3.21; N, 13.65;

2-bromo-6-(1-((1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)pyridine (7c)Yield 73%, mp: 151-153 ^{o}C; Rf = 0.38 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.55 (s, 1H), 8.10 (dd, J = 8.01, 1.03 Hz, 1H), 7.79 (dd, J = 7.51, 2.02 Hz, 1H), 7.74 (m, 2H), 7.66 (t, J = 8.01 Hz, 1H), 7.56 (m, 2H), 7.46 - 7.36 (m, 10H), 5.26 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.43, 141.87, 140.26, 139.94, 135.84, 133.96, 133.84, 132.02, 131.96, 130.27, 128.76, 128.52, 128.30, 127.98, 127.83, 127.60,

127.51, 127.49, 127.03, 125.09, 124.38, 124.17, 122.05, 121.37, 120.50, 119.38, 118.94, 110.42, 109.36, 40.36, 38.52.LC-MS m/z**:** 568[M+H]+ Elemental analysis, Calculated, %: $C_{29}H_{20}BrClN_6$: C, 61.34; H, 3.55; N, 14.80 ; Found %:C, 61.27; H, 3.48; N, 14.71;

2-bromo-6-(1-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)pyridine (7d)Yield 75%, mp: 157-159 ºC; Rf = 0.35 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 7.92 (d, J = 7.85 Hz, 1H), 7.74 (d, J = 7.85 Hz, 2H), 7.73 (d, J = 8.43 Hz, 2H), 7.63 (dd, J = 7.85, 7.44 Hz, 1H), 7.59 (d, J = 7.85 Hz, 2H), 7.48 (d, J = 8.43 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (d, J = 7.85 Hz, 1H), 7.40 (m, 3H), 7.34 (t, J = 7.45 Hz, 1H), 5.36 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.48, 142.13, 140.26, 139.75, 135.82, 133.82, 132.97, 132.53, 132.08, 130.34, 130.26, 128.74, 158.35, 127.86, 127.64, 127.49, 127.06, 125.07, 124.39, 124.18, 122.07, 121.47, 119.56, 118.94, 110.42, 109.32, 40.12, 38.17.LC-MS m/z**:** 568[M+H]+ Elemental analysis, Calculated, %: $C_{29}H_{20}BrClN_6$: C, 61.34; H, 3.55; N, 14.80 ; Found %:C, 61.27; H, 3.48; N, 14.71;

4-(4-((2-(6-bromopyridin-2-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)phenol (7e)Yield 70%, mp: 135-137 ºC; Rf = 0.28 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 9.57 (s, 1H) 8.60 (s, 1H), 7.97 (d, J = 7.85 Hz, 1H), 7.71 (d, J = 7.85 Hz, 2H), 7.62 (t, J = 7.85 Hz, 1H), 7.59 (d, J = 8.43 Hz, 2H), 7.57 (d, J = 7.85 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (dd, J = 7.85, 7.45 Hz, 2H), 7.40 (t, J = 7.45 Hz, 1H), 7.40 (d, J = 7.85 Hz, 1H), 7.33 (t, J = 7.45 Hz, 1H), 6.76 (d, J = 8.43 Hz, 2H), 5.34 (s, 2H).^{13}C NMR (125 MHz, DMSO-*d6*) δ 157.3, 148.7, 145.5, 144.5, 140.6, 139.2, 138.5, 135.2, 133.6, 130.1, 128.9, 128.4, 128.2, 127.8, 127.6, 125.8, 124.1, 120.7, 119.1, 115.2, 47.3. LC-MS m/z**:** 550[M+H]+ Elemental analysis, Calculated, %: $C_{29}H_{21}BrN_6O$: C, 63.40; H, 3.85; N, 15.30; Found %:C, 63.32; H, 3.79; N, 15.21;

2-bromo-6-(1-((1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)pyridine (7f)Yield 72%, mp: 129-131 ºC; Rf = 0.40 (EtOAc:n-Hexane 2:3); ^{1}H NMR(500 MHz, *DMSO-d6*) δ 8.48 (s, 1H) 7.90 (d, J = 7.85 Hz, 1H), 7.71 (d, J = 7.85 Hz, 2H), 7.63 (dd, J = 7.85, 7.47 Hz, 1H), 7.59 (d, J = 7.85 Hz, 2H), 7.49 (d, J = 7.85 Hz, 1H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (d, J = 7.85 Hz, 1H), 7.40 (m, J = 7.45, 7.85 Hz, 3H), 7.34 (t, J = 7.45 Hz, 1H), 7.26 (dd, J = 7.85 7.44 Hz, 1H), 7.06 (d, J = 7.85 Hz, 1H), 6.97 (dd, J = 7.85 7.44 Hz, 1H), 5.35 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.60, 145.42, 141.53, 140.39, 139.68, 135.82, 133.85, 132.06, 130.27, 128.74, 128.46, 128.37, 127.85, 127.59, 127.02, 125.06, 124.37, 124.23, 123.09, 122.04, 120.84, 118.95, 118.32, 114.72, 110.48, 109.36, 55.69, 40.32, 38.52.LC-MS m/z**:** 564[M+H]+ Elemental analysis, Calculated, %: $C_{30}H_{23}BrN_6O$: C, 63.95; H, 4.11; N, 14.92; Found %:C,63.87; H, 4.01; N, 14.84;

2-bromo-6-(1-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)pyridine(7g) Yield 74%, mp: 125-127 ºC; Rf = 0.38 (EtOAc:n-Hexane 2:3); ^{1}H NMR(500 MHz, *DMSO-d6*) δ 8.49 (s, 1H) 7.92 (d, J = 7.85 Hz, 1H), 7.73 (d, J = 7.85 Hz, 2H), 7.64 (dd, J = 7.85, 7.47 Hz, 1H), 7.61(d, J = 7.85 Hz, 2H), 7.51 (d, J = 7.85 Hz, 1H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.43 (d, J = 7.85 Hz, 1H), 7.42 (m, J = 7.45, 7.85 Hz, 3H), 7.30 (d, J = 7.85 7.44 Hz, 2H), 7.09 (d, J = 7.85 Hz, 2H), 5.33 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.82, 145.42, 142.13, 140.36, 139.72, 135.82, 133.87, 132.06, 130.28, 128.75, 128.36, 128.29, 127.84, 127.53, 127.03, 125.03, 124.35, 124.29, 122.07, 120.98, 119.53, 118.97, 118.72, 116.23, 110.72, 109.38, 55.87, 40.17, 38.12.LC-MS m/z**:** 564[M+H]+ Elemental analysis, Calculated, %: $C_{30}H_{23}BrN_6O$: C, 63.95; H, 4.11; N, 14.92; Found %:C,63.87; H, 4.01; N, 14.84;

2-bromo-6-(4,5-diphenyl-1-((1-(o-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)pyridine (7h)Yield 73%, mp: 119-121 ºC; Rf = 0.42 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.50 (s, 1H), 8.10 (dd, J = 8.02, 1.03 Hz, 1H), 7.72 (m, 2H), 7.66 (t, J = 8.01 Hz, 1H), 7.56 (m, 2H), 7.51 – 7.27 (m, 11H), 5.26 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.47, 141.56, 140.13, 139.05, 135.82, 135.34, 133.85, 132.06, 130.95, 130.24, 129.26, 128.74, 128.36, 127.98, 127.63, 127.54, 127.31, 127.25, 127.09, 125.08, 124.35, 124.26, 122.05, 120.37, 119.63, 118.95, 118.54, 110.47, 109.38, 40.32, 38.53, 17.39.LC-MS m/z: 548 [M+H]+ Elemental analysis, Calculated, %: $C_{30}H_{23}BrN_6$: C, 65.82; H, 4.23; N, 15.35; Found %:C, 65.73; H, 4.17; N, 15.28;

2-bromo-6-(4,5-diphenyl-1-((1-(p-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)pyridine(7i)Yield 77%, mp: 123-125 ºC; Rf = 0.45 (EtOAc:n-Hexane 2:3); Found %:C, 65.73; H, 4.17; N, 1528;^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.54 (s, 1H), 8.10 (dd, J = 8.02, 1.03 Hz, 1H), 7.72 (m, 2H), 7.66 (t, J = 8.01 Hz, 1H), 7.56 (m, 2H), 7.46 -7.33 (m, 11H), 5.26 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.47, 142.13, 140.18, 139.69, 137.85, 135.89, 133.84, 132.09, 131.95, 130.82, 130.25, 128.74, 128.39, 127.76, 127.63, 127.59, 127.28, 125.06, 124.36, 124.28, 122.04, 119.68, 119.35, 119.08, 118.94, 110.47, 109.38, 40.18, 38.17, 21.14.LC-MS m/z: 548 [M+H]+ Elemental analysis, Calculated, %: $C_{30}H_{23}BrN_6$: C, 65.82; H, 4.23; N, 15.35;

1-(3-(4-((2-(6-bromopyridin-2-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-one(7j)Yield 75%, mp: 143-145 ºC; Rf = 0.37 (EtOAc:n-Hexane 2:3);
^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.56 (s, 1H), 7.92 (d, J = 7.85 Hz, 1H), 7.90 (s, 1H), 7.74 (d, J = 7.85 Hz, 2H), 7.63 (d, J = 7.85 Hz, 2H), 7.59 (d, J = 7.85 Hz, 2H) 7.55 (d, J = 7.85 Hz, 1H), 7.48 (dd, J = 7.87, 7.48 Hz, 1H) 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (d, J = 7.85 Hz, 1H), 7.40 (t, J = 7.75 Hz, 3H), 7.34 (t, J = 7.45 Hz, 1H), 5.36 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.26, 145.42, 142.23, 139.96, 139.74, 136.85, 136.32, 135.84, 133.86, 131.96, 130.17, 129.34, 128.74, 128.36, 127.85, 127.65, 127.35, 127.14, 127.03, 125.02, 124.37, 123.98, 122.05, 121.45, 120.49, 119.63, 118.94, 118.02, 110.42, 109.63, 43.41, 39.38, 26.75.LC-MS m/z: 576 [M+H]+ Elemental analysis, Calculated, %: $C_{31}H_{23}BrN_6O$: C, 64.70; H, 4.03; N, 14.60; Found %:C, 64.61; H, 3.94; N,14.51;

1-(4-(4-((2-(6-bromopyridin-2-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-one(7k)Yield 78%, mp: 149-151 ºC; Rf = 0.35 (EtOAc:n-Hexane 2:3); N,14.51;^{1}H NMR (500 MHz, *DMSO-d6*)δ 8.42 (s, 1H), 7.92 (d, J = 7.85 Hz, 1H), 7.80 (d, J = 8.43 Hz, 2H), 7.74 (d, J = 8.43 Hz, 4H), 7.63 (dd, J = 7.85, 7.47 Hz, 1H), 7.59 (d, J = 7.85 Hz, 2H), 7.43 (dd, J = 7.85 7.45 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 1H), 7.41 (d, J = 7.85 Hz, 1H), 7.40 (m, J = 7.45 7.85 Hz, 3H), 7.34 (t, J = 7.45 Hz, 1H), 5.35 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 196.84, 145.47, 142.16, 139.98, 139.74, 137.85, 136.22, 135.84, 133.84, 131.96, 130.32, 130.17, 128.74, 128.36, 127.85, 127.63, 127.12, 127.03, 125.02, 124.39, 123.95, 122.07, 119.53, 118.97, 118.85, 110.47, 109.63, 43.42, 39.30, 26.40.LC-MS m/z: 576 [M+H]+ Elemental analysis, Calculated, %: $C_{31}H_{23}BrN_6O$: C, 64.70; H, 4.03; N, 14.60; Found %:C, 64.61; H, 3.94;

2-bromo-6-(1-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)pyridine(7l)Yield 80%, mp: 160-162 ºC; Rf = 0.34 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.34 (d, J = 9.20 Hz, 2H), 7.92 (d, J = 7.85 Hz, 1H), 7.79 (d, J = 9.20 Hz, 2H), 7.74 (d, J = 7.85 Hz, 2H), 7.63 (dd, J = 7.85 7.82 Hz, 1H), 7.59

(d, J = 7.85 Hz, 2H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (d, J = 7.85 Hz, 1H), 7.40 (m, 3H), 7.35 (t, J = 7.45 Hz, 1H), 5.34 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.05, 145.47, 142.17, 139.98, 139.75, 135.82, 133.86, 131.97, 130.17, 128.76, 128.36, 127.84, 127.66, 127.13, 127.04, 126.17, 125.03, 124.38, 123.98, 121.95, 120.14, 119.53, 118.92, 118.87, 110.42, 109.63, 43.48, 39.31.LC-MS m/z: 579 [M+H]+ Elemental analysis, Calculated, %:$C_{29}H_{20}BrN_7O_2$ Exact Mass: C, 60.22; H, 3.49; N, 16.95; Found %:C, C, 60.16; H, 3.39; N, 16.89;

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