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SYNTHESIS, EVALUATION, AND MOLECULAR DOCKING STUDIES OF NOVEL 1, 2, 3-TRIAZOLE TETHERED INDOLE HYBRID DERIVATIVES AS POTENT ANTI-CANCER AGENTS

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Abstract:
In an attempt to find potential anti-cancer agents, a series of new 1,2,3 triazole linked indole hybrids **(7a-I)** were synthesized in good yields from suitable reaction procedures and their chemical structures were analyzed by ^{1}H NMR, ^{13}C NMR, IR, and mass spectral analysis. The synthesized derivatives further screened for anticancer activity against two human cancer cell lines A549 (Lung Cancer) and MCF7 (Breast Cancer). Among them, compounds**7b, 7c, and 7d** exhibited good anti-proliferation activity compared with standard drug Doxorubicin. The docking results obtained are complementary to the experimental observations.

Keywords: 1, 2, 3 triazole linked indole hybrids, anti-cancer activity, and molecular docking.

Introduction

Cancer is one of the most common deadly diseases, identified by the multiplication and expansion of cells in different tissues and organs. [i]. Global cancer incidences are steadily increasing with approximately 18.1 million new cases by 2018 and almost one in six deaths globally [ii]. The remarkable treatment of cancer still remains a drawback, due to the severe side effects of chemotherapeutics. Despite existing diagnostic methods and management of cancer showing remarkable progress. So there is always a high demand to develop new and attentive anticancer agents [iii, iv].

Indole or 1H-benzo[b]pyrrole, is the most important bicyclic heterocyclic compound with fused benzene and pyrrole ring. It is considered a biologically privileged scaffold, dispersed in various natural products like plants, animals, alkaloids, and microbial hormones [v,vi]. It exhibits broad range of pharmacological properties such as antibacterial, antiviral [vii] anti-fungal [viii-xii] antioxidant [xiii-xvi] anti-inflammatory [xvii-xxii] anticholinesterase [xxiii, xxiv] antihistamine [xxv] anti-diabetic [xxvi] and anticancer [xxvii-xxxii].

A few examples of natural anticancer agents containing indole as backbones are vincristine and vinblastine isolated from *Catharanthus roseus* act as antimitotic agents and are used to treat breast cancer, Kaposi's sarcoma, Hodgkin's disease, and non-Hodgkin's lymphoma [xxiii]. The marine alkaloid eudistomin K (1) acts against the P-388 tumor cell line with an IC_{50} range of 0.01 μg/mL[xxiv]. The analog of cinnamic hydroxamic acid, Panobinostat (LBH-589) (2)a marketed drug used in the treatment of multiple myeloma.

Similarly1,2,3 Triazoles, class of nitrogen containing heterocyclic compounds. Its non-covalent interactions with various biological targets possess broad range ofpharmacological properties like antibacterial [xxxv,xxxvi] antimalarial [xxxvii,xxxviii] antifungal [xxxix,xl] antiviral [xli,xlii] antitubercular [xliii,xliv]and anticancer [xlv,xlvi] activities. Cefatrizine (3) and Carboxyamidotriazole(4)[xvvii] are anticancer agents containing 1,2,3-triazole as main skeleton.

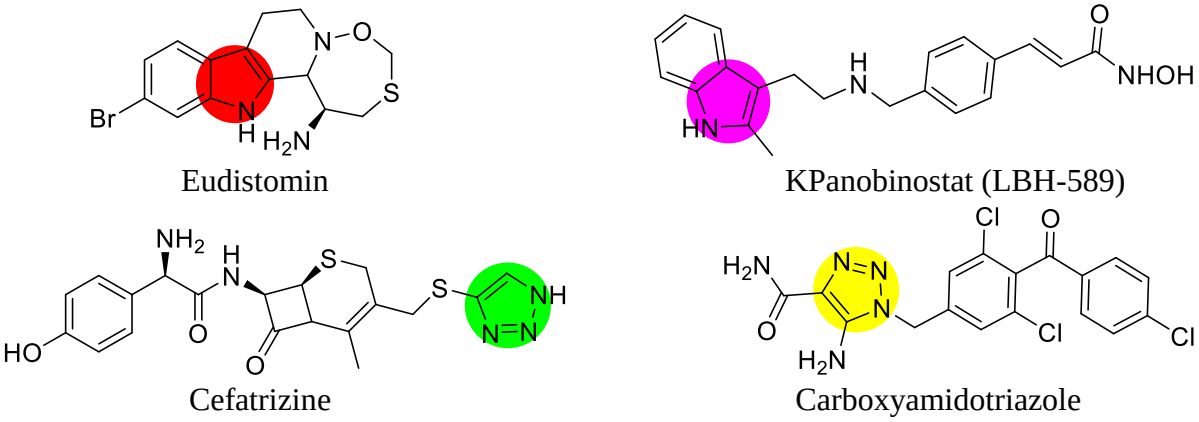


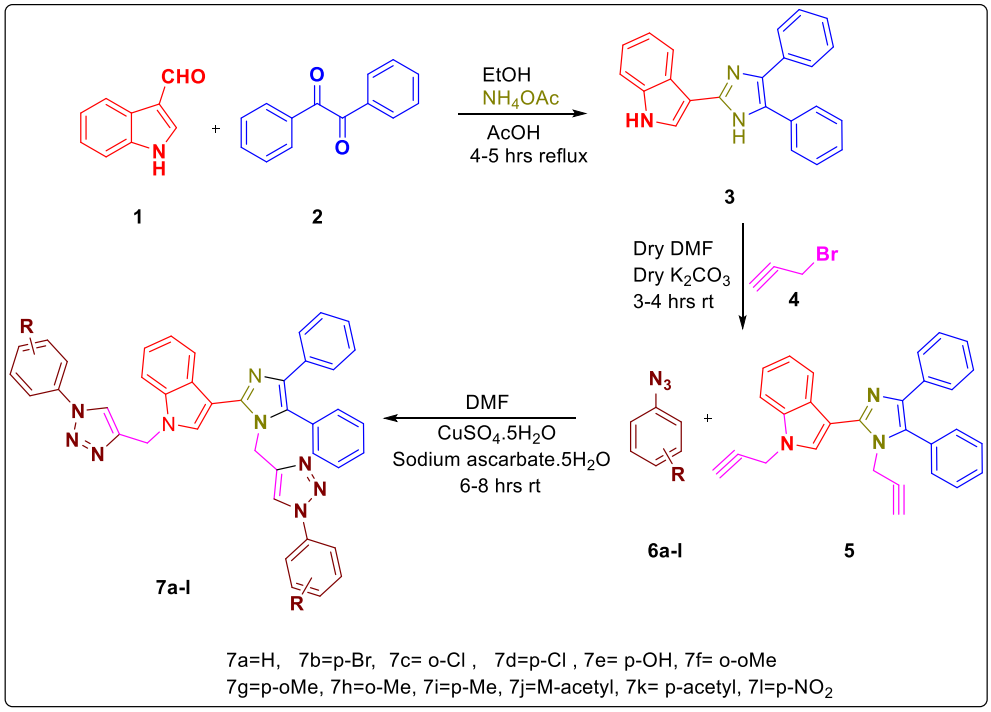
Figure 1- The chemical structures of anticancer agents containing Indole and 1,2,3 triazole as a scaffold.

Considering the anti-cancer activity exhibited by both indole derivatives and 1,2,3-Triazole derivatives from the literature search, it was hypothesized that the fusion of indole and 1,2,3 triazole could result in molecules having greater anti-cancer activity due to the synergistic effect of both indole and 1,2,3 triazole scaffolds. Hence, the synthesized hybrid derivatives were evaluated for anti-cancer activity against two human cell lines with results supported by docking studies.

2. Results and discussion:

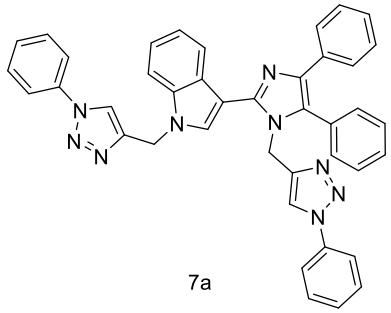
Chemistry

Synthesis of 3-(4,5-diphenyl-1-((substituted-phenyl-1*H*-1,2,3-triazole-4-yl)methyl)-1*H*-imidazole-2-yl)-1-((substituted-phenyl-1*H*-1,2,3-triazole-4-yl)methyl)-1*H*-indole.The synthetic route for the desired 1,2,3 triazole linked indole hybrids (**7a-l**) were carried out by one-pot three-component reaction. The condensation of 1*H*-indole-3-carbaldehyde **(1)**, benzil (**2**), and catalytical amount of acetic acid in ethanol at 70°C for 4-5 hrs to afford compound **(3)** followed by bis propargylation at the position of free N-H group with propargylic bromide (**4**) dry DMF and dry K_2CO_3 at rt for 3-4 hrs lead to the formation of compound **(5)**, which on further click reaction with substituted aryl azides **(6a-l)** obtained 1,2,3-triazole linked indole hybrids **(7a-l)** in yields (75-82%), shown in **Scheme1.**

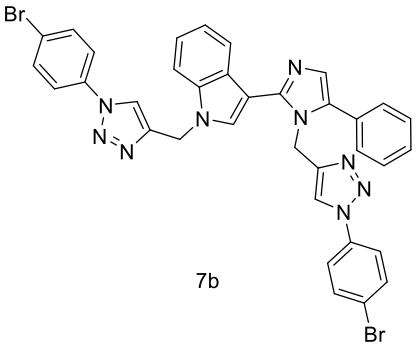


Scheme 1: The synthetic route of 1,2,3-tethered indole hybrids

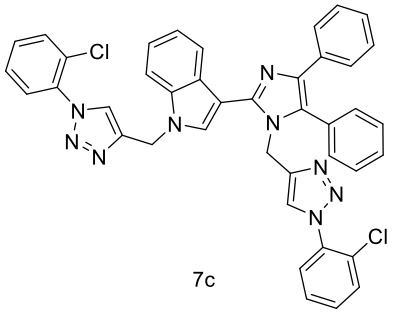
Derivatives:



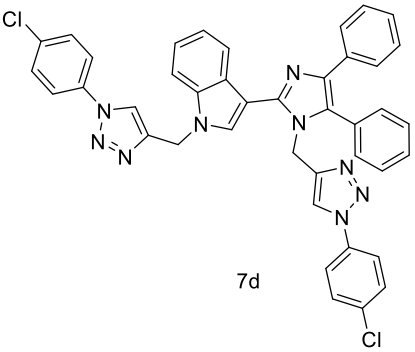
7a



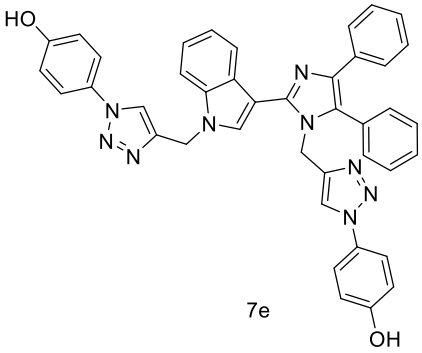
7b



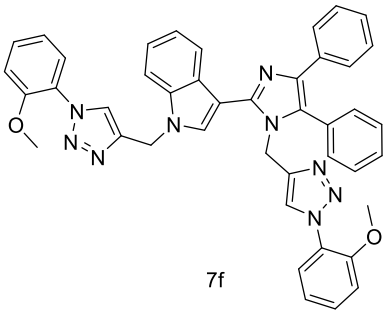
7c



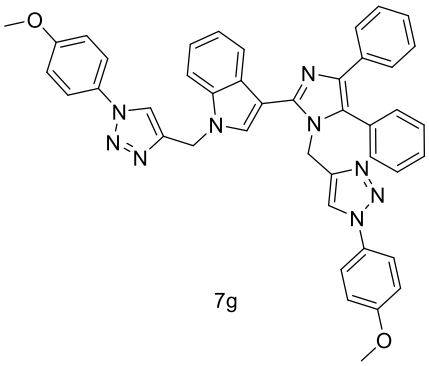
7d



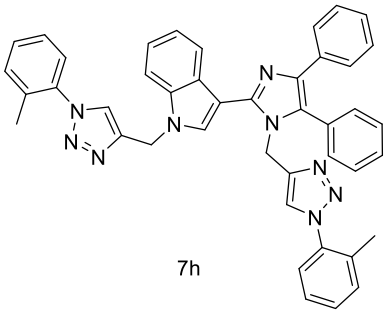
7e



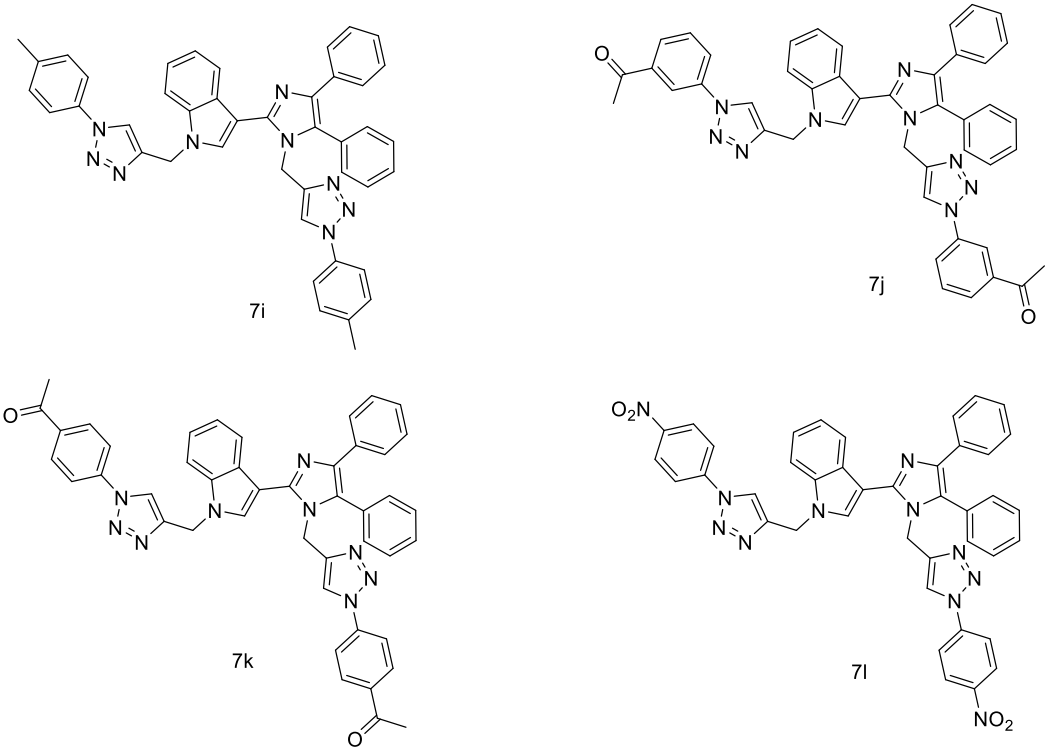
7f



7g



7h



Biological evaluation:

The synthesized compounds**(7a-l)** were screened for anti-cancer activity against two human cancer cell lines such as A549 (lung cancer), and MCF-7 (breast cancer), by MTT assay. The IC_{50} values of compounds **(7a-l)** displayed good to moderate anti-cancer activities were summarized in Table 1. Among them, compounds **7b, 7c, and 7d** exhibited good anticancer activity compared to the standard drug. Further, a structural activity relationship study was investigated for these compounds **(7a-l)**. It showed that compound **7d** with the para-chloro group on the phenyl ring exhibited more potent activity than doxorubicin. Replacement of chlorine with bromine in compound **7b** with para Bromo position on phenyl ring resulted in a decrease in activity than **7d**. Shifting of para position to ortho position on the phenyl ring, Compound **7c** with ortho-chloro substitution showed lower activity compared with **7d**. Compound 7e with para hydroxyl group showed a loss of activity. Substitution with OCH_3 group at para 7g and ortho 7h position, methyl group at para 7i position, acetyl group at meta 7j and para 7k position, and nitro at para 7l position on the phenyl ring are not tolerated, resulting in loss of activity.

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

Compound	IC_{50} in μM at 72 hrs	
	A-549	MCF-7
7a	31.21%±1.69	29.61%±4.1
7b	**18.59%±8.86**	**16.23%±1.4**
7c	**19.08%±1.04**	**18.51%±1.38**
7d	**15.13%±1.86**	**15.69%±0.076**

7e	57.21%±1.02	51.13%±2.13
7f	42.39%±1.04	53.17%±2.16
7g	52.75%±1.497	44.17%±1.275
7h	48.28%±6.29	54.60%±2.08
7i	40.16%±1.74	59.63%±4.6
7j	59.13%±4.9	65.31%±7.82
7k	50.93%±1.67	68.31%±1.275
7l	53.17%±2.16	59.72%±0.335
Doxorubicin	**21.48 ± 1.40**	**28.17%±2.84**

Molecular docking studies:

Molecular docking is a reliable, cost-effective, and time-saving technique in the process of drug discovery [xlviii]. Autodock Vina of PyRx tool is an open-source software tool [xlix] used for performing docking studies. Autodock vina uses an empirical scoring function to calculate the binding affinity of the protein-ligand complex [l].

For a better understanding of the binding interactions between ligand molecules and target cancer cells, the best active compounds **7b, 7c,** and **7d** along with doxorubicin were docked into the active site pockets of a lung cancer drug target extracellular signal-related kinase 2 (ERK2) (PDB ID: 4ZXT) [li] and a breast cancer drug target aurora-related kinase 1 (PDB ID: 1MQ4) [xlii]. The crystal structures of both targets were retrieved from Protein Data Bank (www.rcsb.org). The proteins were prepared by using the Biovia Discovery Studio software tool (https://discover.3ds.com/discovery-studio-visualizer-download). Initially, water molecules were removed and polar hydrogens were added to a macromolecule. The ligands were sketched by using the Chemsketch tool (www.acdlabs.com) and saved in MDL file format. Both target and ligand molecules were loaded into the PyRx tool. The energies of ligands were minimized and converted to PDBQT file format. The protein was chosen as a macromolecule. The active site pockets of target molecules were determined by CASTp online server [xliii]. The 3D grid box was set up in such a way to cover the active site pocket of the target molecule and docking simulations were performed.

After docking, conformations were ranked according to their binding energy, and the confirmation with the lowest binding energy was considered the best docking score. The docking results were visualized using Pymol and Biovia Discovery Studio Visualizer.

Molecular docking with extracellular signal-related kinase 2 (ERK2):

The three compounds **7b, 7c,** and **7d** scored excellent binding energy values than standard reference doxorubicin. The binding affinity values of compounds **7b, 7c,** and **7d** were -10.0 Kcal/mol, -11.8 Kcal/mol, and -11.7 Kcal/mol respectively, whereas doxorubicin was scored -9.2 Kcal/mol. (Table2). The active site pocket of ERK2 comprised of amino acids Ile31, Gly32, Glu33, Gly34, Ala35, Tyr36, Gly37, Met38, Val39, Ala52, Lys54, Lys55, Ile56, Arg67, Thr68, Glu71, Ile72, Leu75, Ile84, Ile103, Gln105, Asp106, Leu107, Met108, Glu109, Thr110, Asp111, Lys114, Asp149, Lys151, Ser153, Asn154, Leu156, Ile165, Asp167, Gly169, and Leu170. The 3D grid box was configured with dimensions of 32.38 x 26.75 x 29.71 A^0along the X, Y, and Z axis respectively to cover the cavity of 4ZXT.

Table 2: The binding energies and interactions of compounds **7b, 7c,** and **7d** with extracellular signal-related kinase 2 (PDB ID: 4ZXT)

Compound	Docking Score (Kcal/mol)	Interacting amino acid	
		H-bond	Hydrophobic
7b	-10.0	Glu33, Ser153	Ile31, Ala35, Tyr36, Val39, Ala52, Lys54, Arg67, Asp111, Lys114, Asp167
7c	-11.8	--	Ala35, Tyr36, Val39, Ala52, Tyr113, Lys151, Ser153, Leu156, Asp167
7d	-11.7	Asp111	Ile31, Ala35, Tyr36, Val39, Arg67, Asp111, Lys114, Lys151, Asn154, Leu156, Asp167, Arg191, Trp192
Doxorubicin	-9.2	Lys54, Gln105, Asp111, Lys114, Ser153	Ile31, Gly34, Ala35, Tyr36, Asp167

Compound **7b** demonstrated key interactions with Glu33, Ser153, and hydrophobic interactions with Ile31, Ala35, Val39, Lys54, and Lys114 of ERK2 (figure-2,3). Compound **7c** has defined only hydrophobic interactions with Ala35, Tyr36, Val39, Ala52, Tyr113, Lys151, Ser153, Leu156, Asp167 of ERK2 (figure-4,5), and H-bond interactions were absent. Compound **7d** was defined as an H-bond interaction with Asp111and hydrophobic interactions with Ile31, Ala35, Tyr36, Val39, Arg67, Asp111, Lys114, Lys151, Asn154, Leu156, Asp167, Arg191, Trp192 of ERK2 (figure-6,7). The standard drug doxorubicin was defined as H-bond interactions with Lys54, Gln105, Asp111, Lys114, Ser153, and hydrophobic interactions with Ile31, Gly34, Ala35, Tyr36, Asp167 of ERK2 (figure-8,9).

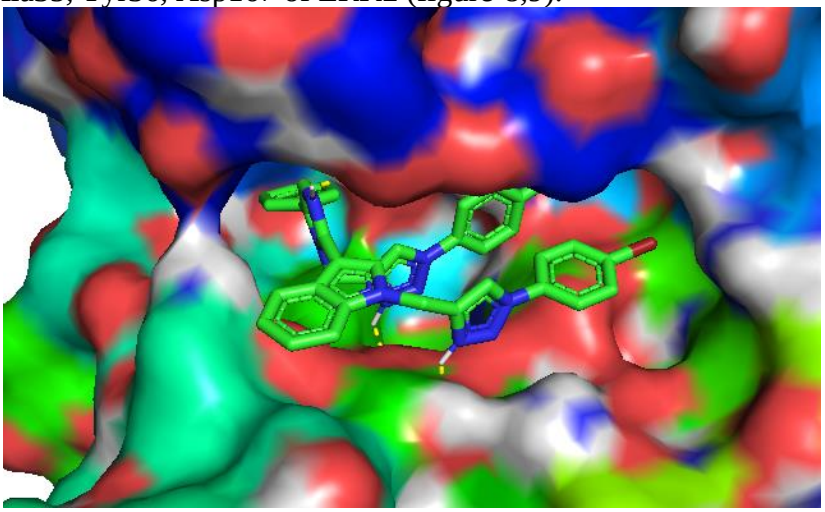


Figure-2: Docking pose of compound 7b in cavity of ERK2 (PDB ID: 4ZXT)

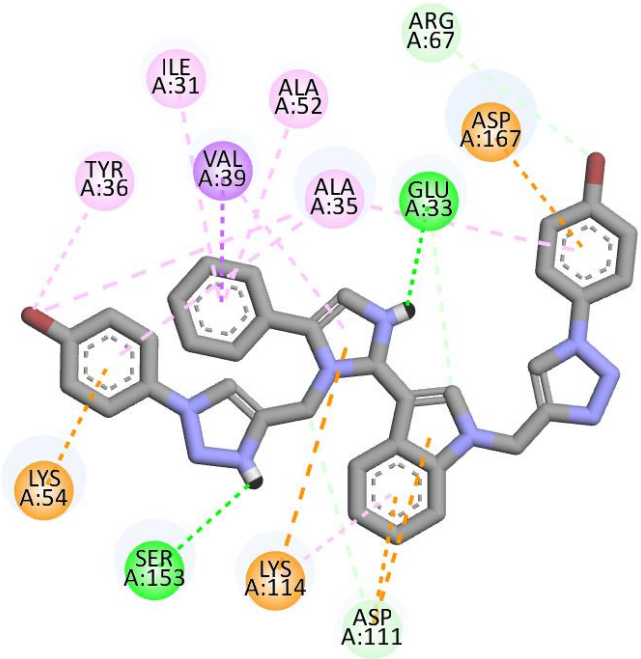


Figure-3. 2D interactions of compound 7b with ERK2 (PDB ID: 4ZXT)

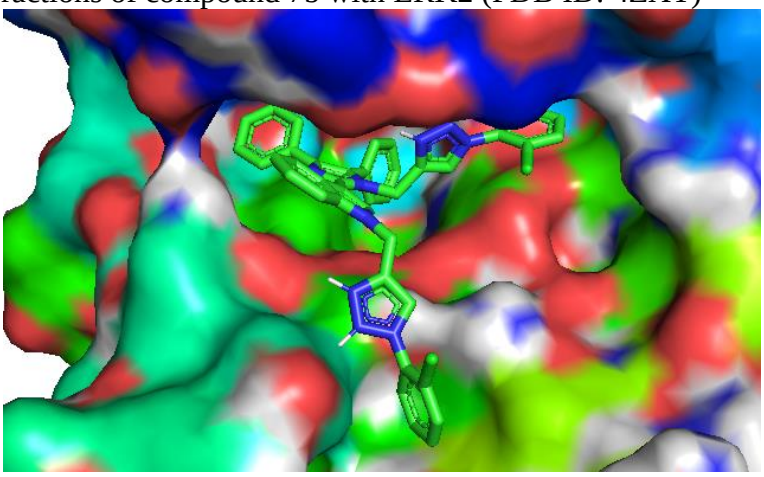


Figure-4. Docking pose of compound 7c in cavity of ERK2 (4ZXT)

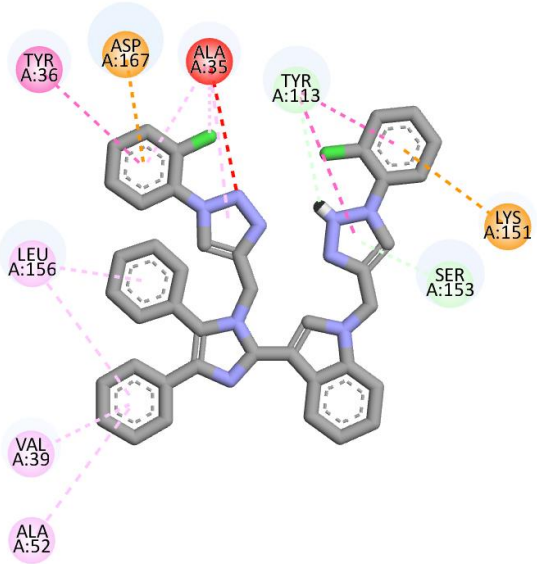


Figure-5. 2D interactions of compound 7c with ERK2 (PDB ID: 4ZXT)

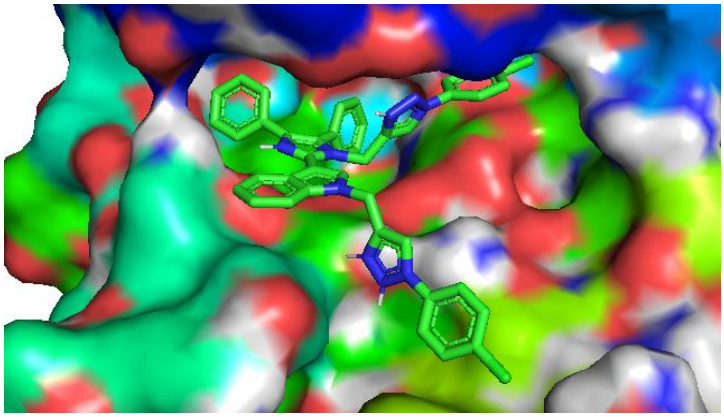


Figure-6. Docking pose of compound 7d in cavity of ERK2 (PDB ID: 4ZXT)

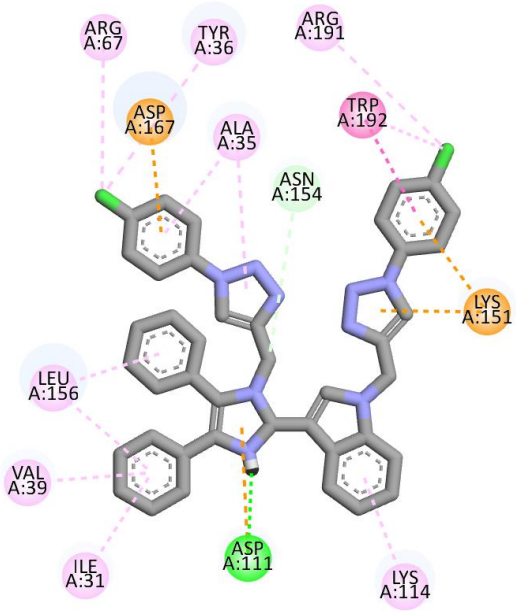


Figure-7. 2D interactions of compound 7d with ERK2 (PDB ID: 4ZXT)

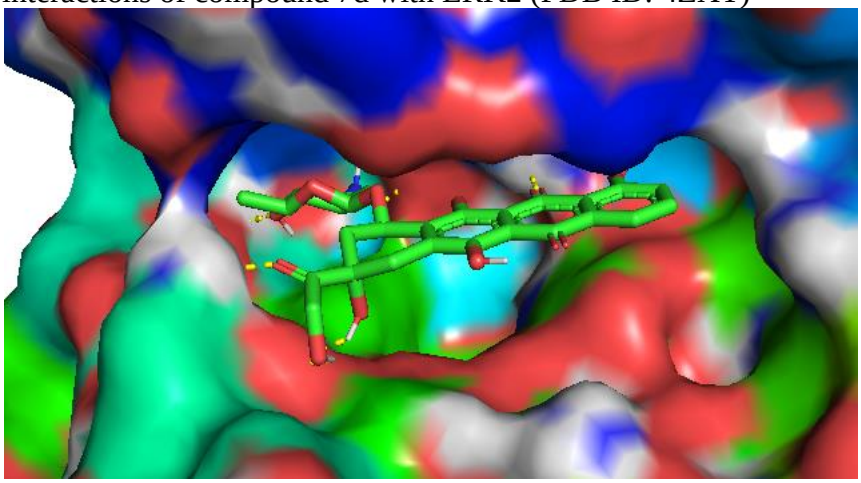


Figure-8. Docking pose of doxorubicin in cavity of ERK2 (PDB ID: 4ZXT)

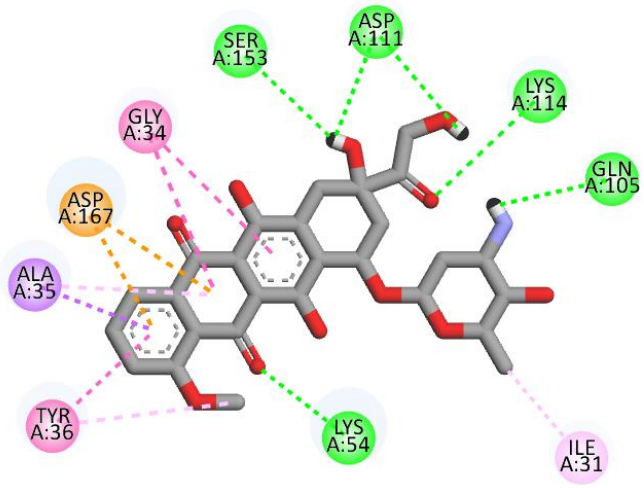


Figure-9. 2D interactions of doxorubicin with ERK2 (PDB ID: 4ZXT)

Molecular docking with aurora-related kinase 1:

The three compounds 7b, 7c and 7c scored best binding energy values compared to doxorubicin. The docking score of compounds 7b, 7c, and 7d were -11.3 Kcal/mol, -12.3 Kcal/mol, and -11.6 Kcal/mol respectively and the doxorubicin score was -9.9 Kcal/mol (Table-3). The active site pocket of Aurora kinase 1 comprised of amino acids Leu139, Gly140, Lys141, Gly142, Lys143, Val147, Ala160, Lys162, His176, Arg180, Leu194, Glu211, Ala213, Thr217, Arg255, Glu260, Asn261, Leu263, Asp274, Trp277, Ser284, Arg285, and Thr288**.** The 3D grid box was configured with dimensions of 35.88 x 27.84 x 25.54 A^0 along the X, Y, and Z-axis respectively to cover the cavity of 4ZXT.

Table 3: The binding energies and interactions of compounds **7b, 7c,** and **7d** with aurora-related kinase 1 (PDB ID: 1MQ4)

Compound	Docking Score (Kcal/mol)	Interacting amino acid	
		H-bond	Hydrophobic
7b	-11.3	Glu260	Leu139, Lys141, Lys143, Phe144, Val147, Lys162, Leu169, Val174, Leu178, Ala213, Tyr219, Arg220, Leu263, Asp274
7c	-12.3	Asp256, Asn261, Asp274	Lys143, Phe144, Val147, Ala160, Glu181, Leu263, Ala273, Asp274, Trp277
7d	-11.6	Lys141	Leu139, Gly142, Lys143, Val147, Lys162, Ala213, Tyr212, Tyr219, Arg220, Glu260, Leu263, Asp274
Doxorubicin	-9.9	Lys143, Asp256, Glu260	Leu139, Lys141, Gly142, Val147, Ala160, Ala213, Leu263, Asp274

Compound **7b** was demonstrated two key interactions with Glu260 and hydrophobic interactions with Leu139, Lys141, Lys143, Phe144, Val147, Lys162, Leu169, Val174, Leu178, Ala213, Tyr219, Arg220, Leu263, Asp274 of 1MQ4 (figure 10,11). Compound **7c** has defined H-bond interactions with Asp256, Asn261, Asp274 and hydrophobic interactions with Lys143, Phe144, Val147, Ala160, Glu181, Leu263, Ala273, Asp274, Trp277 of aurora kinase 1 (figure 12,13). Compound 7d demonstrated a key interaction with Lys141 and hydrophobic interactions with Leu139, Gly142, Lys143, Val147, Lys162, Ala213, Tyr212, Tyr219, Arg220,

Glu260, Leu263, Asp274 of kinase 1 (figure 14,15). The standard compound doxorubicin was defined as key interactions with Lys143, Asp256, Gly260 and hydrophobic interactions with Leu139, Lys141, Gly142, Val147, Ala160, Ala213, Leu263, Asp274 with aurora-related kinase 1 (figure 16,17).

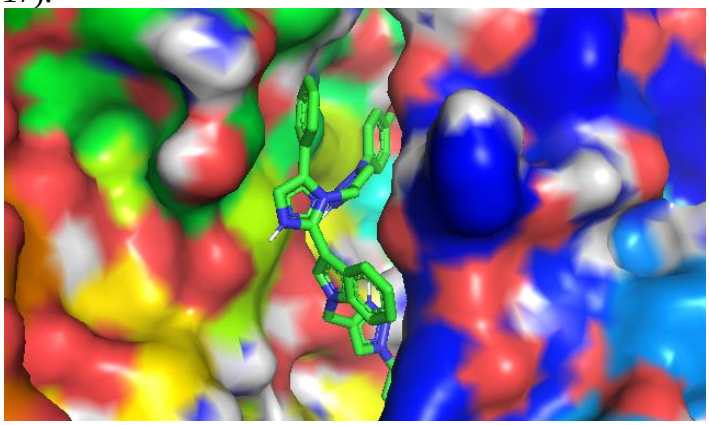


Figure-10. Docking pose of compound 7b in cavity of aurora-related kinase 1 (PDB ID: 1MQ4)

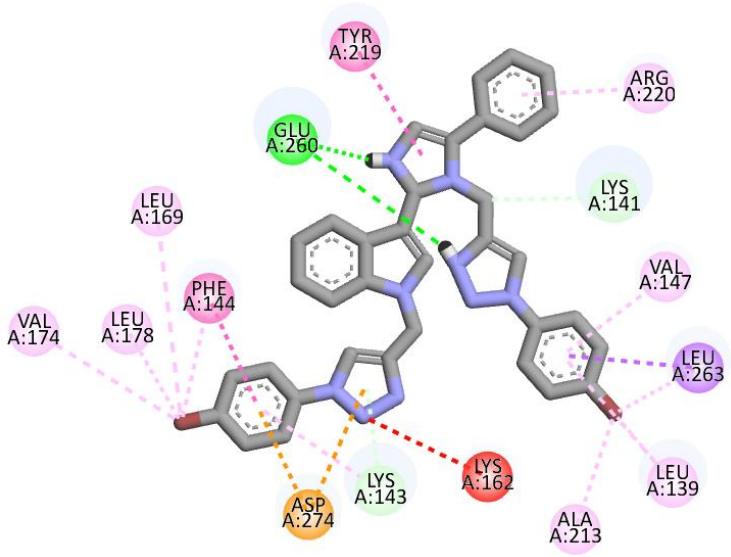


Figure-11. 2D interactions of compound 7b with aurora-related kinase 1 (PDB ID: 1MQ4)

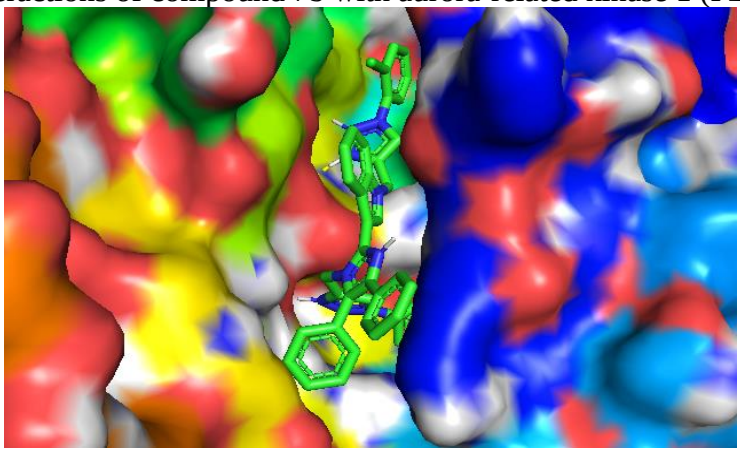


Figure-12. Docking pose of compound 7c in cavity of aurora-related kinase 1 (PDB ID: 1MQ4)

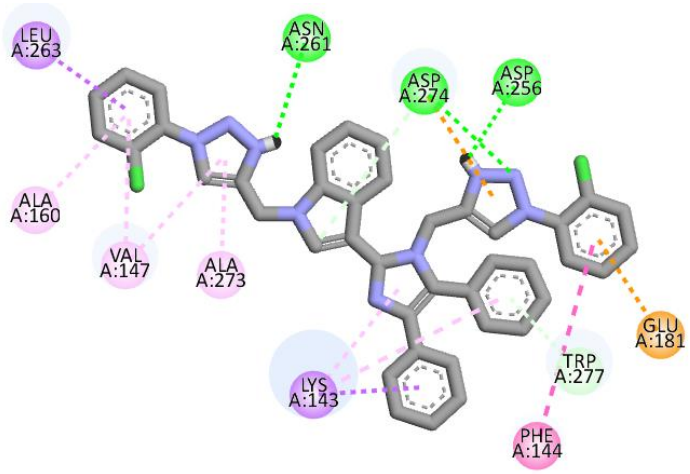


Figure-13. 2D interactions of compound 7c with aurora-related kinase 1 (PDB ID: 1MQ4)

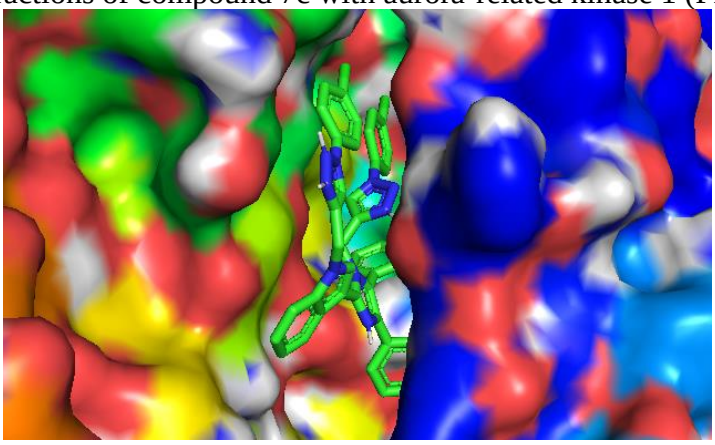


Figure14. Docking pose of compound 7d in cavity of aurora-related kinase 1 (1MQ4)

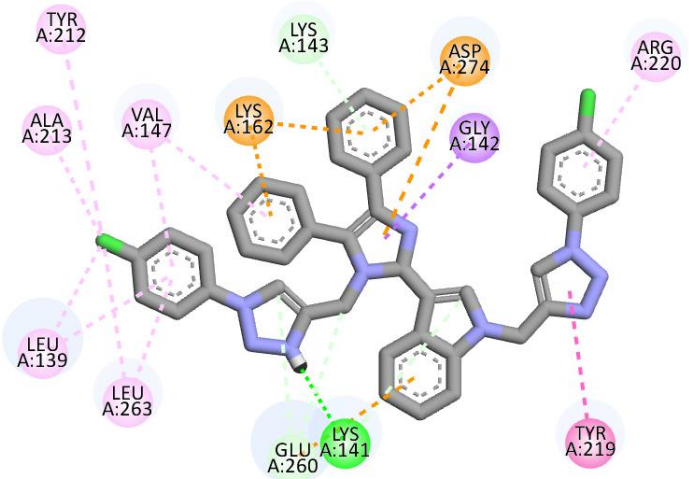


Figure-15. 2D interactions of compound 7d with aurora-related kinase 1 (PDB ID: 1MQ4)

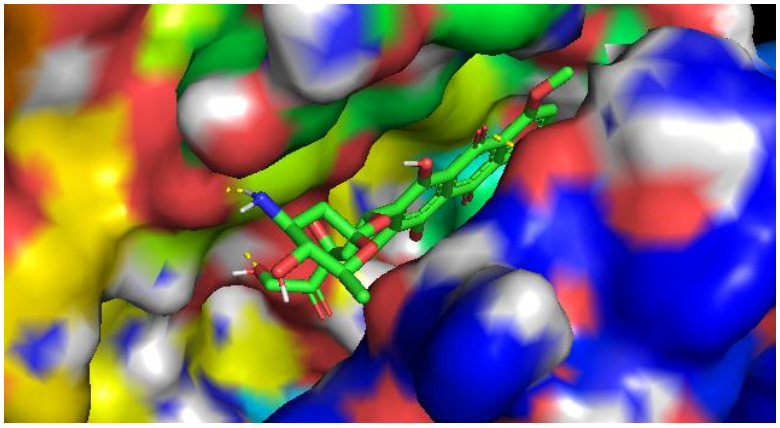


Figure-16. Docking pose of doxorubicin in cavity of aurora-related kinase 1 (PDB ID: 1MQ4)

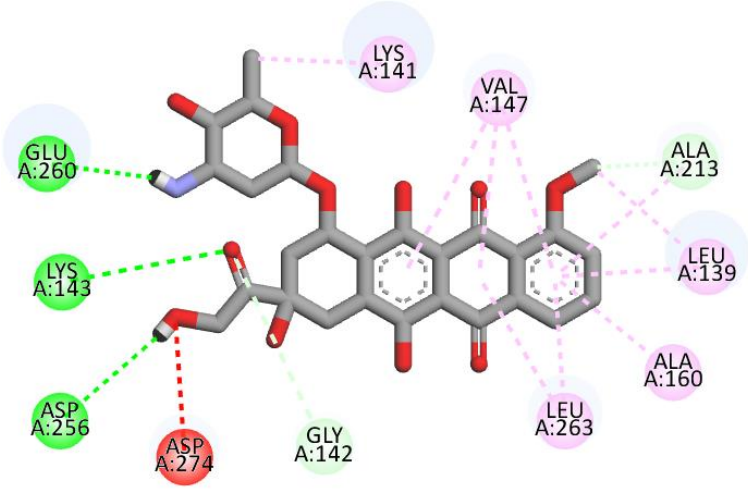


Figure-17. 2D interactions of doxorubicin with aurora-related kinase 1 (PDB ID: 1MQ4)

3. Conclusion

In summary, a series of 1,2,3-triazole tethered indole 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, A549 (Lung cancer), and MCF7 (Breast cancer). Doxorubicin is used as a control. Among them, compounds **7b, 7c,** and **7d** showed potent anticancer activity compared to control drugs. The docking study results were well in agreement with experimental screening, compounds 7b, 7c, and 7d scored the best binding affinity values compared to doxorubicin. Hence, these compounds could be the potent therapeutics to treat malignancy.

4. Experimental:

4.1 General experimental methods:

Were purchased all the chemicals of the organic reagents and solvents from Tci, and Merk was used without 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 an open glass capillary tube on a DbkProg. Melting Point apparatus and were uncorrected.

General procedure for the preparation of 3-(4,5-diphenyl-1*H*-imidazole-2-yl)-1*H*-indole (3)

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

General procedure for the preparation of 3-(4,5-diphenyl-1-(prop-2-yn-1-yl)-1*H*-imidazol-2-yl)-1-(prop-2-yn-1-yl)-1*H*-indole (5)

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

General procedure for the preparation of 3-(4,5-diphenyl-1-((substituted 1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)-1-((substituted1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole(7a-l)

Synthesis of 3-(4,5-diphenyl-1-((substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)-1-((substituted-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole (**7a-l**) were carried out by click reaction of bis-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 6-8 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 (1:3 v/v) to afford 3-(4,5-diphenyl-1-((substituted 1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)-1-((substituted1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole **(7a-l)** gave excellent yields 75-82%.

Anticancer activity:

MTT Assay:

Individual wells of a 96-well tissue culture microtitre plate have been inoculated with one hundred µL of complete medium containing 1×104 cells. The plates have been incubated at 37℃ in a humidified 5% CO_2 incubator for 18 hours before the experiment. The medium used to be as soon as eradicated and a hundred µL of smooth medium containing the test compounds and elegant at wonderful concentrations have been delivered to every desirable and incubated at 37℃ for 24 hours. Then the medium used to be discarded and 10 µL MTT dye used to be added. Plates have been incubated at 37℃ for two hours. The ensuing formazan crystals have been solubilized in a one hundred µL extraction buffer. The optical density (O.D) was once as soon as recorded at 570 nm with a microplate reader (Multi-mode Varioskan Instrument-Thermo Scientific). The share of DMSO in the medium through no skill passed 0.25%.

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Conflict of interest:

The authors declare no conflict of interest

Spectral data:

3-(4,5-diphenyl-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1*H*-indole(7a)

Yield 75%, mp: 187-189°C; Rf = 0.40 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 2H), 7.78 (d, J = 7.57 Hz, 2H), 7.76 (d, J = 7.57 Hz, 2H), 7.72 (d, J = 7.90 Hz, 1H), 7.64 (d, J = 7.85 Hz, 2H), 7.58 (s, 1H), 7.50 (dd, J = 7.90, 6.99 Hz, 1H), 7.44 (d, J = 7.85 Hz, 1H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (dd, J = 7.57, 7.20 Hz, 2H), 7.41 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (t, J = 7.45 Hz, 2H), 7.37 (t, J = 7.20 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.35 (dd, J = 7.57, 7.20 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 7.20 (dd, J = 7.85, 6.99 Hz, 1H), 5.38 (s, 2H), 5.33 (s, 2H).^{13}C NMR (125 MHz, DMSO-*d6*) δ 150.1, 144.2, 143.9, 143.3, 139.6, 137.4, 135.7, 133.2, 130.1, 129.8, 129.4, 128.6, 128.5, 128.0, 127.9, 127.8, 127.6, 125.0, 124.8, 124.4, 124.3, 123.0, 122.7, 120.7, 112.8, 110.1, 50.1, 50.0.LC-MS m/z: 740.7 [M+H]+ Elemental analysis, Calculated, %:$C_{41}H_{29}N_{11}O_4$: C, 66.57; H, 3.95; N, 20.83; Found %: C, 66.51; H, 3.91; N, 20.79.

1-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole(7b)

Yield 80%, mp: 191-193°C; Rf = 0.40 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.48 (s, 1H), 7.96 (d, J = 8.30, 9.30 Hz, 2H), 7.81 (d, J = 8.30, 9.30 Hz, 2H) 7.72 (d, J = 7.90 Hz, 1H), 7.64 (d, J = 7.85 Hz, 2H), 7.58 (s, 1H), 7.56 (d, J = 8.30, 9.30 Hz, 2H), 7.53 (d, J = 8.30, 9.30 Hz, 2H), 7.45 (dd, J = 7.85, 7.45 Hz, 2H), 7.44 (t, J = 7.45 Hz, 1H), 7.42 (dd, J = 7.90, 6.99 Hz, 1H), 7.40 (d, J = 7.85 Hz, 1H), 7.39 (t, J = 7.85 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H) 7.33 (t, J = 7.45 Hz, 1H), 7.16 (dd, J = 7.85 6.99 Hz, 1H), 5.32 (s, 2H), 5.30 (s, 2H).^{13}C NMR (125 MHz, DMSO-d_6) δ 145.21, 12.13, 140.14, 139.72, 135.77, 133.68, 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, 109.41, 40.13, 38.12. LC-MS m/z: 808 $[M+H]^+$ Elemental analysis, Calculated, %:$C_{41}H_{29}Br2N_9$: C, 60.98; H, 3.62; N, 15.61 Found %:C, 60.92; H, 3.59; Br, 19.79; N, 15.57.

1-((1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole(7c)

Yield 78%, mp: 195-197°C; Rf = 0.38 (EtOAc:n-Hexane 2:3);^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.47 (s, 1H), 8.45 (s, 1H), 8.21(s, 1H), 7.96 (dd, J = 7.51, 2.03 Hz,1H), 7.47-7.36 (m, J = 7.80, 7.49, 2.02 Hz, 14H), 7.30 (m, 7.50, 2.0 Hz, 2H), 7.21 (t, J = 7.85, 6.99 Hz, 1H), 5.23 (s, 2H), 4.97 (s, 2H).^{13}C NMR (125 MHz, DMSO-d_6) δ 145.43, 141.87, 140.26, 139.94, 125.84, 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: 718 [M+H]+ Elemental analysis, Calculated, %:$C_{41}H_{29}Cl_2N_9$: C, 68.52; H, 4.07; N, 17.54 Found %:C,68.48; H, 4.02; N, 17.49.

1-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole(7d)

Yield 80%, mp: 193-195°C; Rf = 0.38 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.48 (s, 1H), 7.92 (d, J = 8.43 Hz, 2H), 7.82 (d, J = 8.43 Hz, 2H), 7.72 (d, J = 7.90 Hz, 1H), 7.64 (d, J = 7.85 Hz, 2H), 7.58 (s, 1H), 7.44 (t, J = 7.45 Hz, 1H), 7.42 (dd, J = 7.90, 6.99 Hz, 1H), 7.41 (dd, J = 7.85 7.45 Hz, 2H), 7.40 (d, J = 7.85 Hz, 1H), 7.39 (dd, J = 7.85, 7.45 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 7.23 (d, J = 8.43 Hz, 2H), 7.22 (d, J = 8.43 Hz, 2H), 7.16 (dd, J = 7.85, 6.99 Hz, 1H), 5.32 (s, 2H), 5.30 (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, 127.06, 125.07, 124.39, 124.18, 122.07, 121.47, 119.56, 118.94, 110.42, 109.32, 40.12, 38.17.

4-(4-((2-(1-((1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)phenol(7e)

Yield 75%, mp: 189-191°C; Rf = 0.30 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 9.41 (s, 1H), 8.60 (s, 1H), 8.49 (s, 1H), 7.72 (d, J = 7.90 Hz, 1H), 7.64 (d, J = 7.85 Hz,

2H), 7.58 (s, 1H), 7.57 (d, J = 8.43 Hz, 4H), 7.47 (dd, J = 7.90, 6.99 Hz, 1H), 7.44 (d, J = 7.85 Hz, 1H), 7.41 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (dd, J = 7.85, 7.45 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 7.20 (dd, J = 7.85, 6.99 Hz, 1H), 6.84 (d, J = 8.43 Hz, 2H), 6.83 (d, J = 8.43 Hz, 2H), 5.33 (s, 2H), 5.32 (s, 2H).^{13}C NMR (125 MHz, DMSO-*d6*) δ 157.6, 150.1, 144.2, 143.9, 139.7, 139.6, 137.4, 136.0, 134.1, 130.9, 129.8, 128.6, 128.3, 128.1, 128.0, 127.8, 126.1, 125.0, 124.1, 123.2, 122.9, 120.7, 115.3, 112.8, 110.1, 50.3, 50.1.LC-MS m/z: 682 [M+H]+ Elemental analysis, Calculated, %:$C_{41}H_{31}N_9O_2$:C, 72.23; H, 4.58; N, 18.49; Found %:C,72.19; H, 4.52; N, 18.44.

1-((1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole(7f)

Yield 77%, mp: 187-189°C; Rf = 0.36 (EtOAc:n-Hexane 2:3);^{1}H NMR (500 MHz, *DMSO-d6*) δ8.44 (s, 1H), 8.41 (s, 1H), 8.19 (s, 1H), 7.86 (d, J = 7.90 Hz, 1H), 7.37 - 7.35 (m,4H), 7.21 - 7.19 (m, 5H), 7.01 (m, 2H), 5.18 (s, 2H), 5.03 (s, 2H), 3.82 (s, 6H).^{13}C NMR (125 MHz, DMSO-d_6) δ 154.6, 145.42, 141.53, 140.39, 139.68, 125.82, 133.85, 132.06, 130.27, 128.74, 128.46, 128.37, 127.85, 127.02, 125.06, 124.37, 124.23, 123.09, 122.04, 120.84, 118.95, 118.32, 114.72, 110.48, 109.36, 55.67, 40.32, 38.52.LC-MS m/z: 710 [M+H]+ Elemental analysis, Calculated, %:$C_{43}H_{35}N_9O_2$:C, 72.76; H, 4.97; N, 17.76; Found %:C, 72.71; H, 4.93; N, 17.71.

1-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole(7g)

Yield 79%, mp: 184-186°C; Rf = 0.36 (EtOAc:n-Hexane 2:3);^{1}H NMR (500 MHz, *DMSO-d6*)δ8.52 (s, 1H), 8.49 (s, 1H), 8.21 (s, 1H), 7.86 (d, J = 7.90 Hz, 1H), 7.65 (m, 2H), 7.55 – 7.54 (m, 4H), 7.48 – 7.42 (m, 6H), 7.37 – 7.35 (m, 4H), 7.19 (dd, J = 7.85, 6.98 Hz, 1H), 7.08 – 7.07 (m, 4H), 5.23 (s, 2H), 5.23 (s, 2H), 3.80 (s, 2H).^{13}C NMR (125 MHz, DMSO-d_6) δ 158.82, 145.42, 142.13, 140.36, 139.72, 135.34, 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, 110.42, 109.38, 55.87, 40.17, 38.12.LC-MS m/z: 710 [M+H]+ Elemental analysis, Calculated, %:$C_{43}H_{35}N_9O_2$:C, 72.76; H, 4.97; N, 17.76; Found %:C, 72.71; H, 4.93; N, 17.71.

3-(4,5-diphenyl-1-((1-(o-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)-1-((1-(o-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole(7h)

Yield 76%, mp: 183-185°C; Rf = 0.42 (EtOAc:n-Hexane 2:3);^{1}H NMR (500 MHz, *DMSO-d6*)δ8.43 (s, 1H), 8.42 (s, 1H), 8.21 (s, 1H), 7.86 (d, J = 7.91 Hz, 1H), 7.65 (m, J = 7.49, 2.01 Hz, 2H), 7.53 – 7.21(m, 19H), 5.24 (s, 2H), 5.10 (s, 2H), 2.28 (s, 3H), 2.26 (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, 127.25, 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: 678 [M+H]+ Elemental analysis, Calculated, %:$C_{43}H_{35}N_9$:C, 76.20; H, 5.20; N, 18.60; Found %:C, 76.16; H, 5.15; N, 18.53.

3-(4,5-diphenyl-1-((1-(p-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)-1-((1-(p-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole(7i)

Yield 77%, mp: 181-183°C; Rf = 0.42 (EtOAc:n-Hexane 2:3);^{1}H NMR (500 MHz, *DMSO-d6*)δ8.53 (s, 1H), 8.50 (s, 1H), 8.21 (s, 1H), 7.86 (d, J = 7.92 Hz, 1H), 7.65 (m, 2H), 7.49 – 7.33 (m, 18H), 7.21 (t, J = 7.85, 6.97 Hz, 1H), 5.25 (s, 2H), 5.10 (s, 2H), 2.36 (s, 6H).^{13}C NMR (125 MHz, DMSO-d_6) δ 145.47, 14213, 140.18, 139.67, 137.85, 135.89, 133.84, 132.09, 131.95, 130.82, 145.25, 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: 678 [M+H]+ Elemental analysis, Calculated, %:$C_{43}H_{35}N_9$:C, 76.20; H, 5.20; N, 18.60; Found %:C, 76.16; H, 5.15; N, 18.53.

1-(3-(4-((2-(1-((1-(3-acetylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-one(7j)

Yield 78%, mp: 189-191^{o}C; Rf = 0.38 (EtOAc:n-Hexane 2:3);^{1}H NMR (500 MHz, *DMSO-d6*)δ8.55 (s, 1H), 8.54 (s, 1H), 8.25 (d, J = 2.01 Hz, 1H), 8.23 (d, J = 2.02 Hz, 1H), 8.21 (d, J = 2.00 Hz, 1H), 7.86 (m, 3H), 7.76 – 7.73 (m, 2H), 7.65 – 7.62 (m, 4H), 7.48 – 7.35 (m, 10H), 7.19 (dd, J = 7.85, 6.97 Hz, 1H), 5.23 (s, 2H), 4.92 (s, 2H), 2.55 (s, 6H).^{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, 124.02, 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: 734.8 [M+H]+ Elemental analysis, Calculated, %:$C_{45}H_{35}N_9O_2$:C, 73.65; H, 4.81; N, 17.18; Found %:C, 73.61; H, 4.75; N, 17.13.

1-(4-(4-((2-(1-((1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-one(7k)

Yield 82%, mp: 192-194^{o}C; Rf = 0.38 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.48 (s, 1H), 7.76 (d, J = 8.43 Hz, 4H), 7.74 (d, J = 8.43 Hz, 2H), 7.72 (d, J = 7.90 Hz, 1H), 7.71 (d, J = 8.43 Hz, 2H), 7.64 (d, J = 7.85 Hz, 2H), 7.58 (s, 1H), 7.42 (t, J = 7.45 Hz, 1H), 7.41 (dd, J = 7.90, 6.99 Hz, 1H), 7.40 (d, J = 7.85 Hz, 1H), 7.39 (dd, J = 7.85, 745 Hz, 2H), 7.38 (dd, J = 7.85, 7.45 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.32 (t, J = 7.45 Hz, 1H), 7.12 (dd, J = 7.85, 6.99 Hz, 1H), 5.31 (s, 2H), 5.30 (s, 2H), 2.56 (s, 6H).^{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, 109.47, 43.42, 39.3, 26.4. LC-MS m/z: 734.8 [M+H]+ Elemental analysis, Calculated, %:$C_{45}H_{35}N_9O_2$:C, 73.65; H, 4.81; N, 17.18; Found %:C, 73.61; H, 4.75; N, 17.13.

1-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole(7l)

Yield 80%, mp: 193-195^{o}C; Rf = 0.36 (EtOAc:n-Hexane 2:3); ^{1}H NMR (500 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.41 (s, 1H), 8.36 (d, J = 9.20 Hz, 2H), 8.29 (d, J = 9.20, 10.00 Hz, 2H), 7.79 (d, J = 9.20, 10.00 Hz, 2H), 7.73 (d, J = 9.20, 10.00 Hz, 2H), 7.72 (d, J =7.90 Hz, 1H), 7.64 (d, J = 7.85 Hz, 2H), 7.58 (s, 1H), 7.42 (t, J = 7.45 Hz, 1H), 7.41 (dd, J = 7.90, 6.99 Hz, 1H), 7.40 (d, J = 7.85 Hz, 1H), 7.39 (dd, J = 7.85, 7.45 Hz, 2H), 7.38 (dd, J = 7.85, 7.45 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.32 (t, J = 7.45 Hz, 1H), 7.12 (dd, J = 7.85 6.99 Hz, 1H), 5.31 (s, 2H), 5.24 (s, 2H).^{13}C NMR (125 MHz, DMSO-d_6) δ 146.05, 145.47, 142.17, 139.98, 139.75, 135.82, 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: 740.7 [M+H]+ Elemental analysis, Calculated, %:$C_{41}H_{29}N_{11}O_4$:C, 66.57; H, 3.95; N, 20.83; Found %:C, 66.51; H, 3.91; N, 20.79.

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