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Design, Synthesis, and Molecular Docking Studies of Some New Quinoxaline Derivatives as EGFR Targeting Agents

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Abstract—The synthesis of some new quinoxaline derivatives (**IVa**–**n**) and their structure determination using ^{1}H NMR, ^{13}C NMR and mass spectral analysis was described herein. The in vitro anti-cancer activity of the these compounds (**IVa–n**) revealed that the compound1-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (**IVd**) has shown promising activity, whereas, compounds 1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (**IVa**), 1-(tetrazolo[1,5-*a*]quinoxalin-4-yl)-2-((1-(*m*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrazolidine-3,5-dione (**IVb**), 1-((1-(3,5-dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (**IVh**) and 1-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (**IVi**) exhibited good to moderate activity against four human cancer cell lines such as HeLa, MCF-7, HEK 293T, and A549 as compared to the doxorubicin. Predominantly, the compound displayed excellent activity over HeLa, MCF-7, HEK 293T, and A549 with IC_{50} values of 3.20 ± 1.32, 4.19 ± 1.87, 3.59 ± 1.34, and 5.29 ± 1.34 μM, respectively. Moreover, molecular docking studies of derivatives (**IVa**–**n**) on EGFR receptor suggested that the most potent compound strongly binds to protein EGFR (pdbid:4HJO) and the energy calculations of in silico studies were also in good agreement with the obtained IC_{50} values.

Keywords: in vitro anti-cancer activity, molecular docking studies, quinoxalines, pyrazolidine-3,5-dione, 1,2,3-triazole

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INTRODUCTION

Cancer is a life threatening disease that fall under large category of diseases. Cancer occurs in one part of organ and spread to the remaining organs of the body. Cancer is the condition where the normal cells loose the control on its growth and undergo rapid uncountable cell divisions and subsequent increase in number of cells. It takes the second place globally in death due to cancer. According to World Health Organization (WHO) it is estimated 9.6 million deaths (one in six deaths) occurred in 2018. Prostate, lung, stomach colorectal and liver cancer are the common cancer types reported men, while breast, lung, colorectal, cervical and thyroid cancer are common among women.

The quinoxaline, pyrazole, tetrazole and 1,2,3-triazole are the important class of purely nitrogen containing heterocycles that present in several natural products [1–4]. Besides, all these heterocyclic pharmacophores having keen roles in the development of potent medicines which were already available in the market [5, 6] and under clinical trials [7–10]. Because of their easy synthetic approaches, much efforts have been devoted on the synthesis of novel quinoxaline [11–14], pyrazole [15–18], tetrazole [19–22] and 1,2,3-triazole [23–26] based compounds having potent pharmacological activities till date. Interestingly, during the literature search, we found that the several compounds consisting any one [27–31] as well as two or more [32–35] of the above heterocycles were proved as anticancer agents. From Fig. 1, it has also been found that the role of all these above heterocycles was significant in the designing of the new anticancer drugs. Nevertheless, to the best of our knowledge, there was no single framework compound containing all the above heterocycles.

Based on the above observations and in view of the (**I**) demand to develop more safe, promising and selective anti-cancer compounds in the contemporary cancer drug research commune and (**II**) concept of bioavailability for the efficient drug action, in the present work, we interested to merge all these heterocyclic pharmacophores as single frameworks and further examine their in vitro anti-cancer activity. We have also interested to study the molecular docking and SAR studies which would give suitable idea about the

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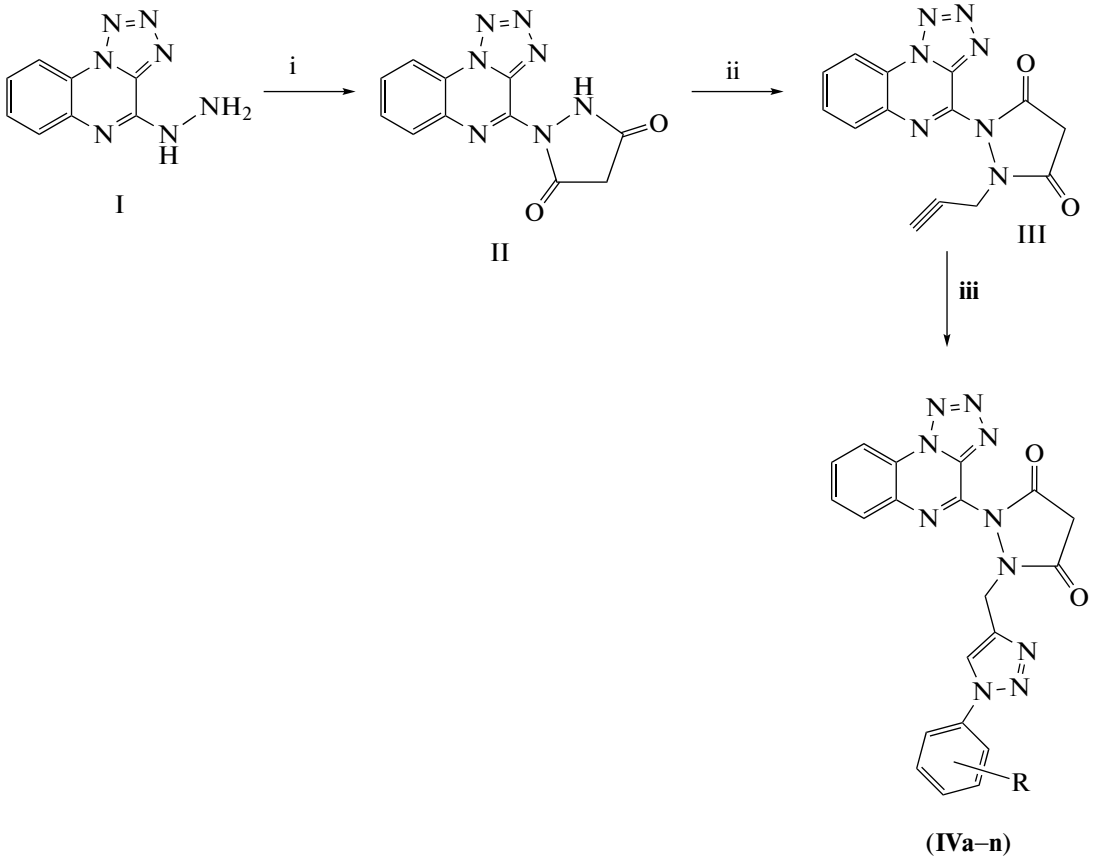
anti-cancer activity properties of our designed frameworks.

RESULTS AND DISCUSSION

The synthetic approach of targeted 2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione-1,2,3-triazoles derivatives (**IVa**–**n**) was shown in Scheme 1. The initial compound 4-hydrazinyl tetrazolo[1,5-*a*]quinoxaline was synthesized according to reported procedure [36]. Later, the compound (**I**) treated with diethyl malanoate in glacial aceticacid solvent under reflux condition for 4 h to give 1-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (**II**). Then, the treatment of compound (**II**) with propargyl bromide by meansof Cs_2CO_3 in THF at 60°C after 4 h afforded the 1-(prop-2-yn-1-yl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (**III**). Finally, the Cu(I) (obtained from the combination of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate) promoted 1,3-dipolar cyclo-addition reaction between the compound (**III**) and several aryl azides atambient temperature in (1 : 1) aq. ^{t}BuOH was provided the targeted compounds (**IVa**–**n**) in moderate to good yields.



(IVa–n)

Reagents and conditions: (i) Diethyl malonate, AcOH, reflux, 4 hours, 73%;

(ii) Propargyl bromide, Cs_2CO_3, THF, 60°C, 4 hours, 67%;

(iii) Sodium ascorbate, Ar–N_3, ^{t}BuOH (1 : 1), $CuSO_4{\cdot}5H_2O$, ambient temperature, 7 h

Scheme 1.

In Vitro Anti-Cancer Studies

The in vitro anti-cancer activities of the newly synthesized compounds (**IVa**–**n**) were studied against four different human cancer cell lines HeLa (cervical cancer), MCF-7(breast cancer), HEK 293T (embryonic kidney) and A549 (human lung cancer cell line) using doxorubicin as standard by employing MTT assay method [37]. From Table 1, it was observed that majority of the synthesized compounds were exhibited well to moderate anticancer activity against all the cell lines. These compounds were demonstrated IC_{50} values ranging from 3.48 ± 1.32 to 19.86 ± 2.69 μM, while

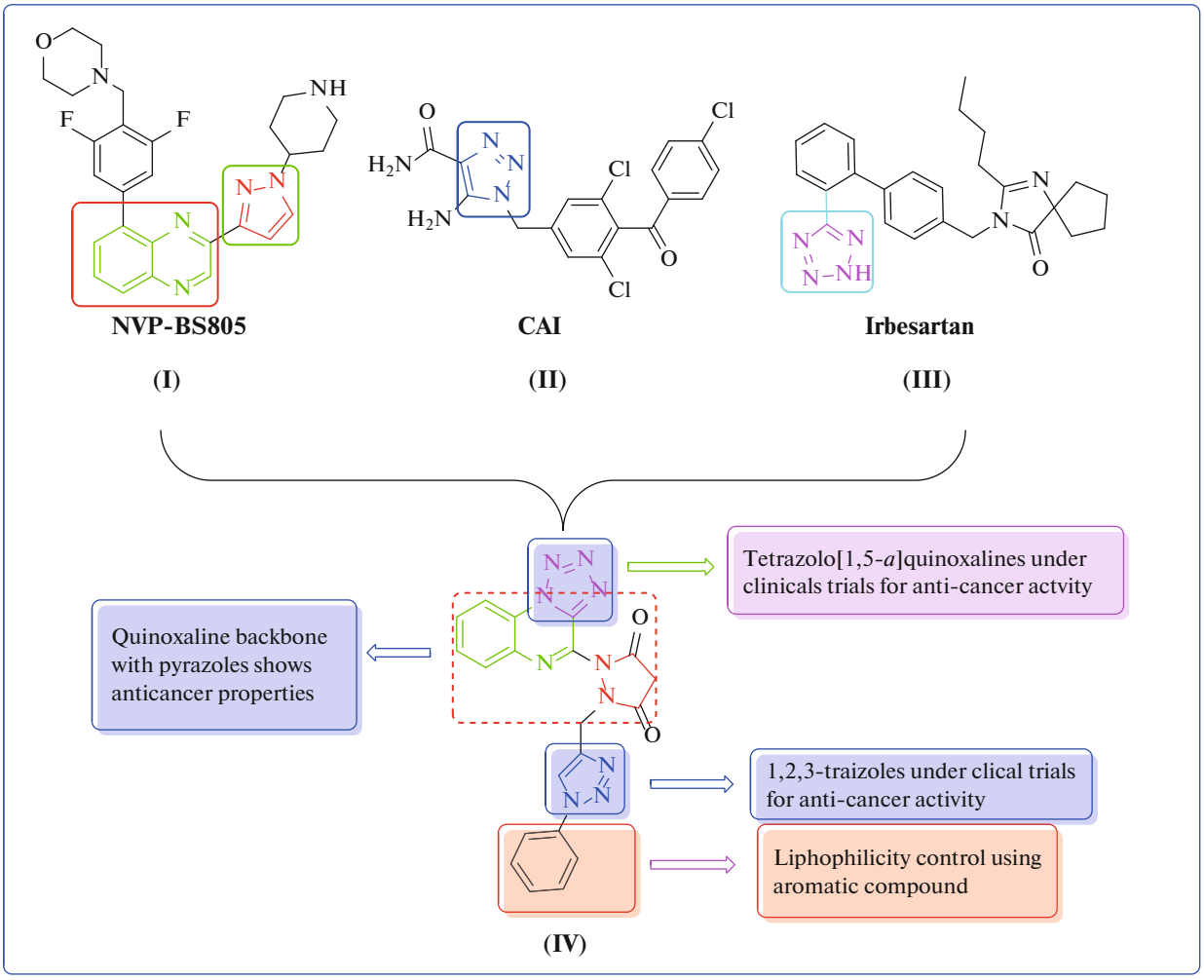


Fig. 1. (**I**) (NVP-BS805), (**II**) (CAI) and (**III**) (Irbesartan) are commercially available anticancer drugs and (**IV**) designed molecule using merging approach.

the standard drug displayed values ranging from 3.18 ± 1.02 to 5.23 ± 2.02 μM, respectively. Among all, the compound (**IVd**) (HeLa = 3.20 ± 1.32 μM; MCF-7 = 4.19 ± 1.87 μM; HEK 293T = 3.59 ± 1.34 μM and A549 = 5.29 ± 1.34 μM), (**IVb**) (HeLa = 3.40 ± 0.13 μM; MCF-7 = 4.27 ± 1.32 μM; HEK 293T = 3.72 ± 1.58 μM and A549 = 5.45 ± 1.63 μM), (**IVa**) (HeLa = 3.89 ± 0.45 μM; MCF-7 = 4.76 ± 1.23 μM; HEK 293T = 3.92 ± 0.60 μM and A549 = 5.78 ± 0.76 μM), (**IVi**) (HeLa = 5.13 ± 1.85 μM; MCF-7 = 6.34 ± 0.40 μM; HEK 293T = 5.78 ± 1.19 μM and A549 = 6.09 ± 1.21 μM), (**IVh**) (HeLa = 7.25 ± 0.95 μM; MCF-7 = 7.14 ± 0.71 μM; HEK 293T = 8.78 ± 1.72 μM and A549 = 8.34 ± 1.52 μM) have displayed promising activity, while, rest of compounds showed moderate to low activity when compared with doxorubicin.

In addition, the nature of substituent on the 1,2,3-triazole basic moiety which subsequently affected the in vitro anticancer activity was explained based on the structure-activity relationship (SARs) studies. The studies revealed that the compound (**IVd**) with electron withdrawing bromine substituent on the 4th position of phenyl ring showed more prominent activity against all the cancer cell lines used as compared to standard drug. Later, the replacement of 4-Br with 4-NO_2 group resulted compound (**IVi**) showed less activity as compared to (**IVd**). Change in the position of $-NO_2$ from *para* to *meta* resulted compound (**IVm**) was exhibited poorer activity than the compound (**IVi**). Interestingly, the compounds containing other electron withdrawing substituents like Cl, F, CN, and CF_3 i.e. compounds (**IVc**), (**IVe**), (**IVf**) and (**IVj**) on the 4th position of phenyl ring were exhibited poorer activity. Similarly, the two electron withdrawing substituent like 3,5-dichloro containing (**IVg**) compound showed very less activity when compared with the compounds (**IVd**) and (**IVi**).

In the context of electron releasing groups, the compound (**IVb**) bearing weak electron donating methyl group on the 3rd position of phenyl ring exhib-

Table 1. In vitro cytotoxicity of newly synthesized targets (**IVa–n**) with IC_{50} in μM

Comp.	Ar	IC_{50} values, μM			
		[c]HeLa	[d]MCF-7	[e]HEK 293T	[f]A549
(IVa)	C_6H_5	3.89 ± 0.45	4.76 ± 1.23	3.92 ± 0.60	5.78 ± 0.76
(IVb)	3-$CH_3C_6H_4$,	3.40 ± 0.13	4.27 ± 1.32	3.72 ± 1.58	5.45 ± 1.63
(IVc)	4-ClC_6H_4	17.76 ± 1.28	15.75 ± 1.40	18.00 ± 2.18	ND
(IVd)	4-BrC_6H_4	3.20 ± 1.32	4.19 ± 1.87	3.59 ± 1.34	5.29 ± 1.34
(IVe)	4-FC_6H_4	18.11 ± 2.10	19.86 ± 2.69	18.63 ± 1.61	16.13 ± 1.21
(IVf)	4-CNC_6H_4	18.97 ± 2.48	17.82 ± 2.86	17.47 ± 2.50	16.12 ± 1.23
(IVg)	3,5-di-ClC_6H_3	16.12 ± 1.27	16.02 ± 1.49	18.22 ± 2.26	16.22 ± 1.36
(IVh)	3,5-di-$OCH_3C_6H_3$	7.25 ± 0.95	7.14 ± 0.71	8.78 ± 1.72	8.34 ± 1.52
(IVi)	4-$NO_2C_6H_4$	5.13 ± 1.85	6.34 ± 0.40	5.78 ± 1.19	6.09 ± 1.21
(IVj)	4-$CF_3C_6H_4$	14.22 ± 2.19	16.03 ± 2.18	17.89 ± 2.38	15.19 ± 1.32
(IVk)	3-$OCH_3C_6H_4$	ND	18.28 ± 2.59	ND	17.12 ± 1.22
(IVl)	3,5-di-CH_3 C_6H_3	16.01 ± 2.56	17.10 ± 2.45	ND	15.02 ± 1.04
(IVm)	3-$NO_2C_6H_4$	17.12 ± 1.27	17.02 ± 3.49	15.30 ± 3.26	16.13 ± 1.24
(IVn)	2-$CH_3C_6H_4$	16.23 ± 2.17	18.23 ± 2.49	16.12 ± 3.26	17.45 ± 1.36
Doxorubicin		3.18 ± 1.02	4.13 ± 1.23	3.56 ± 2.17	5.23 ± 2.02

ND = Not determine; [a] Each data represents as mean ± S.D. values; [b] From three different experiments performed in triplicates; [c] HeLa: human cervical cancer cell line; [d] MCF-7: human breast cancer cell line; [e] HEK 293T: embryonic kidneycancer cell line; [f] A549; human lung cancer cell line

ited more activity against tested cancer cell lines. Nevertheless, the 1,2,3-triazole skeleton substituted by simple phenyl ring (**IVa**) showed lesser activity as compared to (**IVb**). On the other hand, the compound (**IVh**) with strong electron donating 3,5-dimethoxy substituent on phenyl ring exhibited very poor activity compared to both (**IVb**) and (**IVa**). The other compounds containing weak-electron donating methyl substituent's on phenyl ring (**IVl**) and (**IVn**) and strong electron donating methoxy substituent (**IVk**) were showed very poor activity than the doxorubicin.

Molecular Docking Studies

The epidermal growth factor receptor (EGFR) is takenas the target for in silico studies which is a cell-surface receptor for member of the epidermal growth factor family of extracellular protein ligands [38]. It is important for the ductal development of the mammary glands and when the protein over expressed it leads to a number of cancers which include epithelian tumors of the head and neck and anal cancers [39, 40]. Thus this protein is a remarkable target in the cancer disease and specific tyrosine kinase inhibitors [41]. The EGFR is downloaded in pdb format (pdb id-4HJO) from protein data bank [42]. Accordingly, we thought to study the in silico study of our synthesized compounds (**IVa–n**) which would give the further understanding about the obtained in vitro anticancer activity results and the particulars were presented in Table 2. The prepared 1,2,3-triazole derivatives on molecular docking study with target protein shown significant binding connection shaving binding energies in the range −9.57 to −12.03 kcal/mol and having inhibition constant in nanomolar concentration from 97.04 to 1.53. Among the fourteen hybrids that are tested the compounds (**IVa**), (**IVb**), (**IVd**), (**IVh**) and (**IVI**) are shown more interaction with target with binding energies −11.18, −11.82, −12.03, −11.04, −11.02 and −11.11 kcal/mol respectively. The compounds (**IVd**) which is having bromine substituent shown strong affinity towards the target protein with inhibition constant 1.53 in nanomolar concentration and formed two hydrogen bonds with LYS721, MET 769 having bond lengths 1.88, 2.50 Å respectively. It is also formed π-cation with LYS721 residue. The compounds (**IVa**) and (**IVb**) formed two hydrogen bonds each with LYS721, MET 769 residues (Fig. 2), and (**IVi**) formed five hydrogen bonds with ALA698, LYS721, ARG817 and ASN818 residues. Similarly the compound (**IVh**) formed three hydrogen bonds with-ARG817 and LYS851 residues. Nevertheless, the triazole ring and tetrazole ring of the desired compounds was crucially forming the H-bond towards LYS721and MET769 of the target protein. The docking study was done by using AUTODOCK 4.2 version and the images are be rendered using Schrodinger's maestro v9.5 visualizer interface.

Table 2. Molecular docking results of compounds (**IVa–n**)

Comp.	Binding energy, kcal/mol	Inhibition constant, nanomolar	No. of hydrogen bonds	Residues involved in hydrogen bonding (bond length in Å)	π–π Stacking
(IVa)	−11.18	6.39	2	LYS721 (2.00), MET769 (2.34)	LYS721 π cation
(IVb)	−11.82	2.18	2	LYS721 (2.00), MET769 (2.36)	LYS721 π cation
(IVc)	−10.71	32.40	3	LYS721 (1.98), ARG817 (2.23), ASN818 (2.57)	PHE699, ARG817 and ARG817 π cation
(IVd)	−12.03	1.53	2	MET769 (2.50)	LYS721 π cation
(IVe)	−10.99	8.76	–	–	–
(IVf)	−11.04	8.05	1	LYS721 (2.22)	–
(IVg)	−10.96	14.15	1	LYS721 (2.17)	PHE699, ARG817
(IVh)	−11.02	8.01	3	ARG817 (1.72), ARG817 (2.79), LYS851 (2.32)	TRP856, LYS721 π cation
(IVi)	−11.11	7.24	5	ALA698 (2.10), LYS721 (2.06), ARG817 (1.91), ARG817 (2.64), ASN818 (2.07)	PHE699, ARG817 and LYS 852 formed salt bridge
(IVj)	−10.79	12.26	1	LYS721 (2.30)	–
(IVk)	−9.57	97.04	–	–	TRP856, ARG817 π cation and LYS851 π cation
(IVl)	−10.95	9.39	1	LYS721 (1.64)	–
(IVm)	−10.95	9.43	2	LYS721 (2.23), PHE832 (2.15)	LYS721 π cation
(IVn)	−10.17	35.22	–	–	–

EXPERIMENTAL

All the reactants were purchased from the Aldrich chemical company. All the reagents and solvents were purchased from SD Fine chemicals limited and used without further purification. Thin-layer chromatography (TLC) was performed using Merck silica gel 60F254 pre-coated plates (0.25 mm), and silica gel (particle size 60–120 mesh) was used for column chromatography. ^{1}H NMR spectra were recorded on a 400 MHz instrument. ^{1}H NMR spectra were reported relative to Me_4Si and residual DMSO. Mass spectra were recorded on a Jeol JMC-300 spectrometer (ESI, 70 eV). Elemental analyses were performed on Carlo Erba 106 and PerkinElmer model 240 analyzers. Melting points were determined using a Cintex apparatus and are uncorrected.

Synthesis of 1-(tetrazolo[1,5-*a*]quinoxalin-4-yl) pyrazolidine-3,5-dione (II). To a solution of 4-hydrazinyl tetrazolo[1,5-*a*]quinoxaline (**I**) (0.01 mol) in glacial acetic acid (10 mL), diethyl malanoate (0.01 mol) was added slowly and refluxed for 4–5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled, poured into ice cold water and extracted with chloroform (3 × 10 mL). The organic layers were collected, washed with brine solution (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under *vaccum* to get corresponding compounds, than purified by recrystallization with ethanol (73%).

Synthesis of 1-(prop-2-yn-1-yl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (III). To a round bottom flask containing 1-(tetrazolo[1,5-*a*]quinoxalin-4-yl) pyrazolidine-3,5-dione (**II**) (10 mmol) in dry THF (10 mL), Cs_2CO_3 (28 mmol) was added portion wise 10–15 min and then propagyl bromide (16 mmol) was added and the resulting mixture was stirred at room temperature for 4 h. After completion of reaction as monitored by TLC, the reaction mixture

was extracted twice with 10 ml of ethyl acetate and water respectively. The combined organic layers were dried over anhydrous Na_2SO_4 and the excess of organic layer was reduced under *vaccum* to give crude product which then further purified by column chromatography (60–120 silica gel) by using 3:7 ethyl acetate and hexane (67%).

General procedure for the synthesis of tetrazolo quinoxaline pyrazolidine-3,5-dione-1,2,3-triazole hybrids (IVa–n). In a clean, dry reaction vial equipped with a stirring bar were placed the alkyne (**III**) (15 mmol) and aryl azide (20 mmol) in THF-H_2O (10 mL), to this solution, a catalytic volume of TEA, $CuSO_4{\cdot}5H_2O$ (10 mmol %), and sodium ascorbate (10 mmol %). The reaction mixture was stirred for 2 h at room temperature and then heated at 60°C for 6 to 8 h. After completing the reaction by TLC, the reaction mixture was carefully poured into ice water (50 mL). The resulting solid was filtered, washed with excess water, and dried under *vaccum* for 1 h, and the crude product obtained was purified by column chromatography (ethyl acetate/hexane gradient in 4 : 6) to afford the pure desired2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione-triazole hybrids (**IVa–n**) derivatives in good yields.

All the ^{1}H NMR and ^{13}C NMR spectral, docking figures present in the supporting material.

Synthesis of 1-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (II). White solid (73%); mp 234–236°C; ^{1}HNMR(400 MHz, DMSO-d_6, δ in ppm): 3.09 (s, 2H, $-CH_2-$), 7.96–8.12 (m, 4H), 10.12 (bs, 1H, –NH);^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): δ 47.7, 125.6, 126.1, 128.3, 132.1, 137.1, 139.2, 145.1, 162.3, 165.4, 172.2; MS: *m/z* 270; Anal. Calcd. for $C_{11}H_7N_7O_2$: C, 49.07; H, 2.62; N, 36.42. Found: C, 49.02; H, 2.60; N, 36.41%.

Synthesis of 1-(prop-2-yn-1-yl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (III). Brown solid (67%); mp 252–254°C; ^{1}H NMR(400 MHz, DMSO-d_6, δ in ppm): 2.71 (s, 1H, ≡CH), 3.18 (s, 2H, $-CH_2-$), 4.32 (s, 2H, $-CH_2-$), 7.64 (t, 1H, *J* = 5.6 Hz, Qui-H), 7.71 (t, 1H, *J* = 5.6 Hz, Qui-H), 7.75 (d, 1H, *J* = 6.3Hz, Qui-H), 7.81(d, 1H, *J* = 6.4 Hz, Qui-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 38.4,41.5, 73.6, 91.5, 117.2, 129.3, 130.3, 131.6, 132.2, 133.3, 136.5, 145.3, 172.5, 176.8; MS: *m/z* 308 $(M + H)^+$; Anal. Calcd. for $C_{14}H_9N_7O_2$: C, 54.72; H, 2.95; N, 31.91. Found: C, 54.70; H, 2.94; N, 31.90%.

1-((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (IVa). Light white solid(68%); mp 286–288°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 3.45 (s, 2H, $-CH_2-$), 4.65 (s, 2H, $-CH_2-$), 7.36 (t, 1H, *J* = 4.4 Hz, Qui-H), 7.43 (t, 1H, *J* = 4.8 Hz, Qui-H), 7.55 (t, 1H, *J* = 4.8 Hz, Ar–H), 7.63 (d, 2H, *J* = 5.6 Hz, Ar–H), 7.67 (d, 2H, *J* = 5.7 Hz, Ar–H), 7.72 (d, 1H, *J* = 6.2 Hz, Qui-H), 7.80 (d, 1H, *J* = 6.2 Hz, Qui-H), 8.10 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 37.2, 42.2, 115.3, 117.4, 118.4, 118.7, 119.5, 122.6, 129.6, 132.1, 132.4, 135.5, 136.3, 140.2, 145.2, 147.2, 172.6, 178.1; MS: *m/z* 427 $(M + H)^+$; Anal. Calcd. for $C_{20}H_{14}N_{10}O_2$: C, 56.34; H, 3.31; N, 32.85. Found: C, 56.32; H, 3.29; N, 32.85%.

1-(Tetrazolo[1,5-*a*]quinoxalin-4-yl)-2-((1-(*m*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl) pyrazolidine-3,5-dione (IVb). White solid (73%); mp 310–312°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 2.40 (s, 3H, $-CH_3$), 3.38 (s, 2H, $-CH_2-$), 4.70 (s, 2H, $-CH_2-$), 7.30 (s, 1H, Ar–H), 7.42–7.48 (m, 3H, Ar–H), 7.62 (t, 1H, *J* = 4.9 Hz, Qui-H), 7.70 (t, 1H, *J* = 4.9 Hz, Qui-H), 7.77 (d, 1H, *J* = 5.7 Hz, Qui-H), 7.83 (d, 1H, *J* = 5.7 Hz, Qui-H), 8.06 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 22.4, 37.5, 41.1, 117.2, 119.2, 120.4, 124.5, 126.5, 127.4, 128.4, 129.2, 130.6, 134.3, 135.6, 137.7, 139.7, 141.4, 145.3, 146.5, 168.2, 169.8; MS: *m/z* 441 $(M + H)^+$. Anal. Calcd. for $C_{21}H_{16}N_{10}O_2$: C, 57.27; H, 3.36; N, 31.80. Found: C, 57.26; H, 3.35; N, 31.79%.

1-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (IVc). White solid (78%); mp 316–318°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 3.52 (s, 2H, $-CH_2-$), 4.80 (s, 2H, $-CH_2-$),7.62 (t, 1H, *J* = 4.7 Hz, Qui-H), 7.67 (t, 1H, *J* = 4.7 Hz, Qui-H), 7.82 (d, 1H, *J* = 5.2 Hz, Qui-H), 7.86 (d, 2H, *J* = 5.2 Hz, Ar–H), 7.89 (d, 2H, *J* = 5.6 Hz, Ar–H), 8.04 (d, 1H, *J* = 5.6 Hz, Qui-H 8.12 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 38.4, 41.9, 120.2, 124.5, 124.9, 126.4, 127.6, 129.2, 130.0, 131.6, 133.6, 134.4, 136.6, 137.4, 145.3, 147.3, 175.5, 176.4; MS: *m/z* 461 $(M + H)^+$, 463 $(M + 2)^+$; Anal. Calcd. for $C_{21}H_{13}ClN_{10}O_2$: C, 52.13; H, 2.84; N, 30.39. Found: C, 52.12; H, 2.83; N, 30.38%.

1-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (IVd). Light brown solid (81%); mp 320–322°C; ^{1}H NMR (400 MHz DMSO-d_6, δ in ppm): 3.48 (s, 2H, $-CH_2-$), 4.72 (s, 2H, $-CH_2-$), 7.67 (t, 1H, *J* = 5.5 Qui-H), 7.72 (t, 1H, *J* = 5.5 Qui-H), 7.78 (d, 1H, *J* = 6.2 Hz, Qui-H), 7.82 (d, 1H, *J* = 6.2 Hz, Qui-H), 7.90 (d, 2H, *J* = 6.7 Hz, Ar–H), 8.00 (d, 2H, *J* = 6.7 Hz, Ar–H), 8.15 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 38.1, 43.4, 116.5, 117.7, 119.3, 120.8, 129.3, 130.3, 131.2, 132.4, 133.4, 134.3, 140.3, 141.3, 147.5, 148.5, 175.4, 176.7; MS: *m/z* 505 $(M + H)^+$, 507 $(M + 2)^+$; Anal. Calcd. for $C_{20}H_{13}BrN_{10}O_2$: C, 52.13; H, 2.84; N, 38.1. Found: C, 52.12; H, 2.83; N, 30.38%.

1-((1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl) pyrazolidine-3,5-dione (IVe). Light brown solid (86%); mp 308–310°C;^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm):

3.54 (s, 2H, $-CH_2-$), 4.78 (s, 2H, $-CH_2-$), 7.70 (t, 1H, J = 5.3 Hz, Qui-H), 7.76 (t, 1H, J = 5.3 Hz, Qui-H), 7.89 (d, 2H, J = 5.1 Hz, Ar–H), 7.94 (d, 2H, J = 5.1 Hz, Ar–H), 7.99 (d, 1H, J = 6.9 Hz, Qui-H), 8.12 (d, 1H, J = 7.0 Hz, Qui-H), 8.20 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 38.7, 41.9, 117.9, 118.4, 120.9, 123.8, 128.2, 130.7, 131.2, 132.6, 133.7, 134.2, 138.6, 145.3, 147.4, 162.5, 175.3, 176.3; MS: m/z 445 $(M + H)^+$; Anal. Calcd. for $C_{20}H_{13}FN_{10}O_2$: C, 54.06; H, 2.95; N, 31.52. Found: C, 54.05; H, 2.92; N, 31.50%.

4-(4-((3,5-Dioxo-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl) benzonitrile (IVf). White solid (64%); mp 334–336°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 3.51 (s, 2H, $-CH_2-$), 4.74 (s, 2H, $-CH_2-$), 7.66 (t, 1H, J = 6.2 Hz, Qui-H), 7.72 (t, 1H, J = 6.2 Hz, Qui-H), 7.92 (d, 2H, J = 6.6 Hz, Ar–H),7.96 (d, 2H, J = 6.6 Hz, Ar–H), 8.04 (d, 1H, J = 6.9 Hz, Qui-H), 8.10 (d, 1H, J = 6.9 Hz, Qui-H), 8.16 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 38.4, 39.5, 116.4, 117.5, 118.2, 121.9, 123.8, 125.9, 128.2, 130.7, 132.4, 133.6, 134.2, 137.6, 140.3, 145.4, 147.1, 175.4, 176.5; MS: m/z 452 $(M + H)^+$; Anal. Calcd. for $C_{21}H_{13}N_{11}O_2$: C, 55.88; H, 2.90; N, 34.13. Found: C, 55.87; H, 2.89; N, 34.12%.

1-((1-(3,5-Dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl) pyrazolidine-3,5-dione (IVg). White solid (78%); mp 342–344°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 3.57 (s, 2H, $-CH_2-$), 4.82 (s, 2H, $-CH_2-$), 7.72 (t, 1H, J = 6.9 Hz, Qui-H), 7.78 (t, 1H, J = 6.9 Hz, Qui-H), 7.94 (d, 1H, J = 7.3 Hz, Qui-H), 8.02 (d, 1H, J = 7.3 Hz, Qui-H), 8.06 (s, 1H, Ar–H), 8.10 (s, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.24 (s, 1H, triazol-H);^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 38.9, 41.6, 116.1, 118.6, 126.3, 127.3, 128.5, 130.2, 130.7, 131.2, 133.2, 136.2, 137.3, 138.3, 145.6, 147.6, 175.3, 175.8; MS: m/z 495 $(M + H)^+$, 497 $(M + 2)$; Anal. Calcd. for $C_{20}H_{12}Cl_2N_{10}O_2$: C, 48.50; H, 2.44; N, 28.28. Found: C, 48.49; H, 2.44; N, 28.27%.

1-((1-(3,5-Dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (IVh). Light yellow solid (61%); mp 356–358°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 3.52 (s, 2H, $-CH_2-$), 3.95 (s, 6H, $-OCH_3$), 4.72 (s, 2H, $-CH_2-$), 6.76 (s, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 7.24 (s, 1H, Ar–H), 7.54 (t, 1H, J = 6.4 Hz, Qui-H), 7.64 (t, 1H, J = 6.4Hz, Qui-H), 7.85 (d, 1H, J = 7.4 Hz, Qui-H), 7.92 (d, 1H, J = 7.4 Hz, Qui-H), 8.04 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 38.6, 41.4, 56.6, 98.5, 100.5, 118.7, 122.5, 128.6, 130.8, 131.4, 132.6, 133.6, 137.7, 142.2, 145.3, 147.2, 160.8, 175.3, 175.7; MS: m/z 486 $(M + H)^+$; Anal. Calcd. for $C_{22}H_{18}N_{10}O_4$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.31; H, 3.72; N, 28.79%.

1-((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl) pyrazolidine-3,5-dione (IVi). Light yellow solid (74%); mp 329–331°C;^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 3.58 (s, 2H, $-CH_2-$), 4.76 (s, 2H, $-CH_2-$), 7.96 (t, 1H, J = 5.9 Hz, Qui-H), 8.10 (t, 1H, J = 5.9 Hz, Qui-H), 8.15 (d, 1H, J = 6.8 Hz, Qui-H), 8.19 (d, 1H, J = 6.8 Hz, Qui-H), 8.30 (d, 2H, J = 7.2 Hz, Ar–H), 8.36 (d, 2H, J = 7.2 Hz, Ar–H), 8.54 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 38.6, 41.8, 117.3, 118.5, 125.5, 127.3, 129.8, 131.7, 133.3, 135.6, 136.2, 138.8, 142.0, 143.5, 146.9, 147.6, 174.3, 174.9; MS: m/z 472 $(M + H)^+$; Anal. Calcd. for $C_{20}H_{13}N_{11}O_4$: C, 50.96; H, 2.78; N, 32.69. Found: C, 50.95; H, 2.77; N, 32.69%.

1-(Tetrazolo[1,5-*a*]quinoxalin-4-yl)-2-((1-(4-trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methyl) pyrazolidine-3,5-dione (IVj). White solid (67%); mp 317–319°C; ^{1}H NMR (400 MHz DMSO-d_6, δ in ppm): 3.58 (s, 2H, $-CH_2-$), 4.78 (s, 2H, $-CH_2-$), 7.68 (t, 1H, J = 5.5 Hz, Qui-H), 7.73 (t, 1H, J = 5.6 Hz, Qui-H), 7.89 (d, 1H, J = 6.2 Hz, Ar–H), 7.93 (d, 1H, J = 6.2Hz, Ar–H), 7.96 (d, 1H, J = 5.6 Hz, Ar–H), 8.02 (d, 1H, J = 5.7 Hz, Qui-H), 8.06 (d, 1H, J = 7.4 Hz, Qui-H), 8.10 (d, 1H, J = 7.4 Hz, Ar–H), 8.28 (s, 1H, triazol-H);^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 40.8, 43.5, 118.7, 121.0, 121.4, 122.7, 123.9, 124.4, 125.7, 127.8, 129.2, 131.0, 132.4, 133.6, 135.2, 138.7, 144.6, 146.4, 148.5, 178.3, 178.5; MS: m/z 495 $(M + H)^+$; Anal. Calcd. for $C_{21}H_{13}F_3N_{10}O_2$: C, 51.02; H, 2.65; N, 28.33. Found: C, 51.00; H, 2.64; N, 28.33%.

1-((1-(3-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (IVk). White solid (62%); mp 347–349°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 3.49 (s, 2H, $-CH_2-$), 3.75 (s, 2H, $-CH_2-$), 4.92 (s, 3H, $-OCH_3$), 7.42–7.48 (m, 3H, Ar–H), 7.51 (s, 1H, Ar–H), 7.73 (t, 1H, J = 5.2 Hz, Qui-H), 7.77 (t, 1H, J = 5.2 Hz, Qui-H), 7.82 (d, 1H, J = 6.1 Hz, Qui-H), 7.87 (d, 1H, J = 6.2 Hz, Qui-H), 8.20 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 38.2, 41.7, 58.4, 108.3, 115.4, 116.4, 119.7, 124.9, 129.2, 131.7, 132.2, 132.8, 134.2, 134.9, 139.7, 142.3, 145.4, 147.5, 164.2, 176.0, 176.6; MS: m/z 456 $(M + H)^+$; Anal. Calcd. for $C_{21}H_{16}N_{10}O_3$: C, 55.26; H, 3.53; N, 30.69. Found: C, 55.25; H, 3.53; N, 30.69%.

1-((1-(3,5-Dimethylphenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (IVl). Brown solid (66%); mp 322–324°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 2.40 (s, 6H, $-CH_3$), 3.36 (s, 2H, $-CH_2-$); 4.58 (s, 2H, $-CH_2-$), 7.06 (s, 1H, Ar–H), 7.46 (s, 1H, Ar–H), 7.62 (s, 1H, Ar–H), 7.83–7.68 (m, 3H, Qui-H), 7.90 (d, 1H, J = 6.5 Hz, Qui-H), 8.06 (s, 1H, triazol-

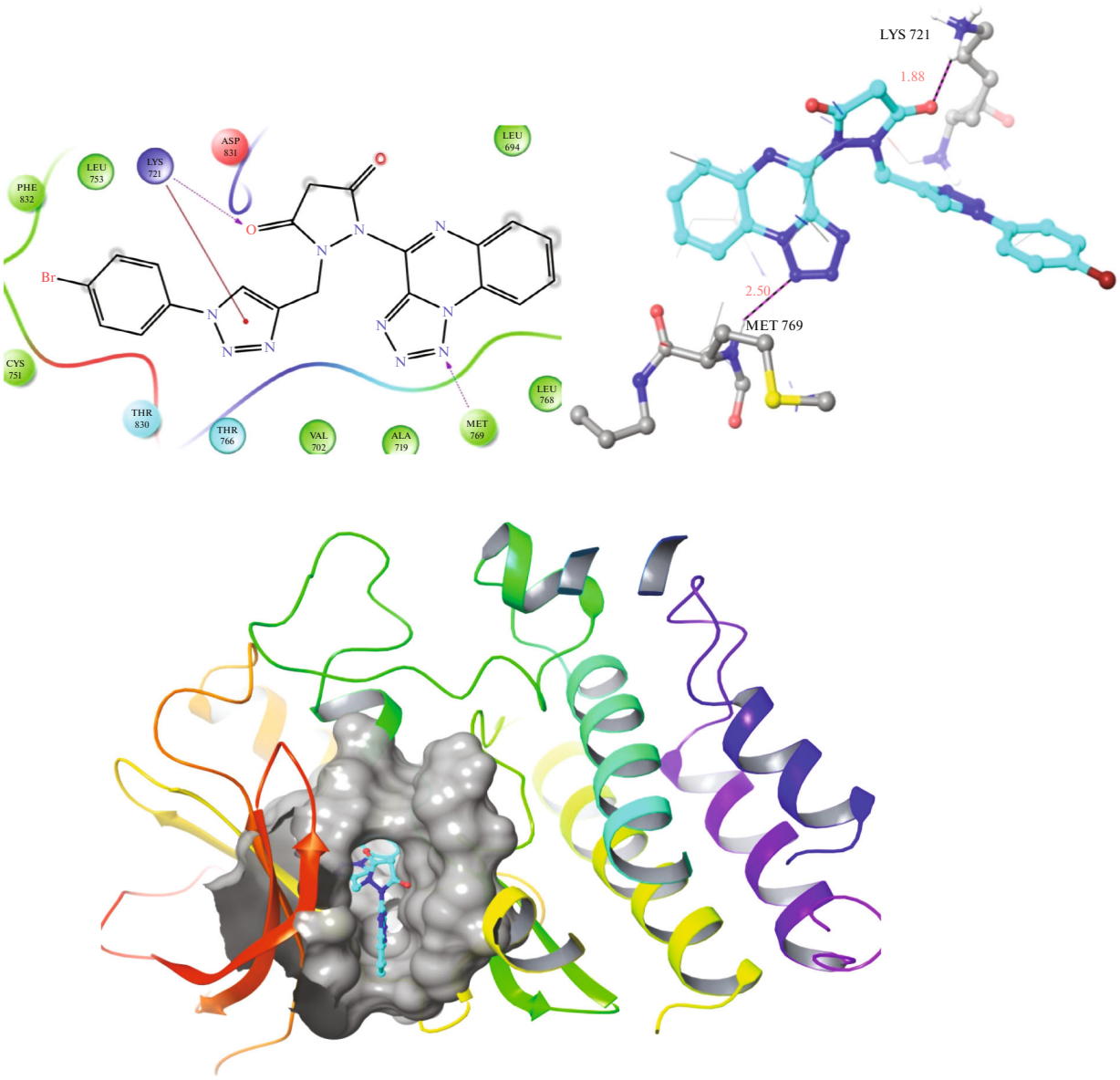


Fig. 2. 2D, 3D, and 3D Surface interaction of compound (**IVd**) with EGFR.

H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 23.1, 38.1, 41.6, 118.9, 125.8, 126.5, 128.3, 130.3, 131.0, 133.5, 134.1, 137.3, 138.7, 140.0, 142.5, 146.5, 147.7, 174.2, 174.9; MS: *m/z* 455 $(M + H)^+$. Anal. Calcd. for $C_{22}H_{18}N_{10}O_2$: C, 58.14; H, 3.99; N, 30.82. Found: C, 58.13; H, 3.99; N, 30.80%.

1-((1-(3-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)pyrazolidine-3,5-dione (IVm). Brown solid (73%); mp 335–337°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 3.52 (s, 2H, $-CH_2-$), 4.73 (s, 2H, $-CH_2-$), 7.55 (t, 1H, *J* = 6.7 Hz, Ar–H), 7.63 (t, 1H, *J* = 6.7 Hz, Qui-H), 7.72 (t, 1H, *J* = 6.7 Hz, Qui-H), 7.78 (d, 1H, *J* = 6.7 Hz, Qui-H), 7.84 (d, 1H, *J* = 6.7 Hz, Qui-H), 7.92 (d, 1H, *J* = 6.7 Hz, Ar–H), 8.05 (d, 1H, *J* = 6.8 Hz, Ar–H), 8.16 (s, 1H, Ar–H), 8.48 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 41.4, 43.1, 118.9, 120.8, 122.9, 124.5, 127.6, 129.3, 130.1, 130.8, 132.9, 133.1, 134.3, 136.8, 138.9, 145.6, 146.6, 148.5, 176.1, 176.8; MS: *m/z* 472 $(M + H)^+$. Anal. Calcd. for $C_{20}H_{13}N_{11}O_4$: C, 50.96; H, 2.78; N, 32.69. Found: C, 50.95; H, 2.77; N, 32.68%.

1-(Tetrazolo[1,5-*a*]quinoxalin-4-yl)-2-((1-(*o*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrazolidine-3,5-dione (IVn). White solid (65%); mp 315–317°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 2.42 (s, 3H, $-CH_3$), 3.43 (s, 2H, $-CH_2-$), 4.64 (s, 2H, $-CH_2-$), 7.20 (d, 1H, *J* = 6.3 Hz, Ar–H), 7.32 (t, 1H, *J* = 5.7 Hz, Ar–

H), 7.38 (t, 1H, J = 5.7 Hz, Ar–H), 7.56 (t, 1H, J = 5.8 Hz, Qui-H), 7.63 (t, 1H, J = 5.8 Hz, Qui-H), 7.74 (d, 1H, J = 6.4 Hz, Qui-H), 7.80 (d, 1H, J = 6.4 Hz, Ar–H), 7.85 (d, 1H, J = 6.5 Hz, Qui-H), 8.06 (s, 1H, triazol-H); ^{13}C NMR (125 MHz, DMSO-d_6, δ in ppm): 18.8, 38.8, 41.5, 116.7, 120.9, 122.4, 125.8, 126.1, 129.8, 130.2, 130.9, 131.2, 132.4, 132.6, 133.1, 136.4, 135.7, 145.5, 147.6, 173.1, 173.5; MS: m/z 441 $(M + H)^+$. Anal. Calcd. for $C_{21}H_{16}N_{10}O_2$: C, 57.27; H, 3.66; N, 31.80. Found: C, 57.27; H, 3.631.79N, 31.79%.

MTT Assay

In vitro anticancer activity of the synthesized compounds (**IVa–n**) was tested using MTT colorimetric assay as per ATCC protocol. Cell lines that were used for testing in vitro cytotoxicity included HeLa, MCF-7, HEK 293T and A549 Cell lines were maintained at 37°C in a humidified 5% CO_2 incubator using suitable media prescribed in NCCS Protocol. Decontaminated flasks were incubated for subculture. Cells were passed by 12 numbers. After getting 70% confluence; from culture flasks take 100 μL cell suspension and make a cell count using haemocytometer and found 5000–6000 per well in a 96-well plate. Cell suspension was mixed thoroughly by pip petting several times to get a uniform single cell suspension. Different dilutions of drugs solutions 3, 10, 30, 100 μM were made in media with final 0.5% DMSO. 100 μL of cell suspension was transferred aseptically to each well of a 96 well plate and to it 100 μL of drug solution in (quadruplicate) in media was added. The plate was then incubated at 37°C for 72 h in CO_2 incubator. After 48 h of incubation, 20 μL of MTT was added to each well. The plate was again incubated for 2 h, 80 μL of analysis buffer was added to each well the plate was wrapped in aluminium foil to prevent the oxidation of the dye and the plate was placed on a shaker for 30 min. The absorbance were recorded on the ELISA reader (Biotech EL × 800) at 570 nm wavelength. We will calculate % inhibition by following formula.

% inhibition = Control ODs – Test ODs + Control ODs × 100 and finally IC_{50} Values to asses anti-cancer activity. Doxorubicin was used as the standard drug in the assay.

CONCLUSIONS

The synthesis of some new highly polar quinoxaline derivatives **(IVa–n)** was described using merging of four types of heterocyclic pharmacophores. The in vitro anticancer activity of the these compounds (**IVa–n**) over three human cancer cell lines namely HeLa (cervical cancer), MCF-7 (breast cancer), HEK 293T (embryonic kidney) and A549 (human lung cancer) using doxorubicin as standard suggested that the five compounds named by (**IVa)**, (**IVb**), **(IVd**), **(IVh**) and (**IVI**) have shown promising activity against all the cell lines used when compared with the positive control. The compound (**IVd**) was displayed excellent activity against HeLa, MCF-7 and HEK 293T and A549 with IC_{50} values of 3.20 ± 1.32, 4.19 ± 1.87, 3.59 ± 1.34 and 5.29 ± 1.34 μM, respectively. Besides, the molecular docking studies of derivatives (**IVa–n**) on EGFR receptor revealed the potent compound (**IVd**) was strongly binds to the protein EGFR (pdbid: 4HJO). Further structural modifications on the quinaxoline ring in order to study the in vitro anti-cancer activity results are under progress.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving human participants performed by any of the authors and does not contain any studies involving animals performed by any of the author.

Conflict of Interests

The authors declare that they have no conflicts of interest.

SUPPLEMENTARY INFORMATION

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