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FULL PAPER

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Design, synthesis, and docking study of new quinoline derivatives as antitumor agents

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Abstract

New quinolines substituted with various heterocycles and chalcone moieties were synthesized and evaluated as antitumor agents. All the synthesized compounds were in vitro screened against 60 human cancer cell lines. Compound **13** showed the highest cytotoxicity toward 58 cell lines, exhibiting distinct growth inhibition values (GI_{50}) against the majority of them, including SR, HL-60 (TB) strains (leukemia), and MDA-MB-435 strains (melanoma), with GI_{50} values of 0.232, 0.260, and 0.300 μM, respectively. It exhibited great selectivity toward cancer cell lines, with less toxic effect against normal cells represented by skin fibroblast (BJ) and breast epithelial cell lines (MCF-10F). The enzyme inhibitory activity of compound **13** was evaluated against topoisomerase 1 (Topo 1), epidermal growth factor receptor and vascular endothelial growth factor receptor 2, where it displayed worthy Topo 1 inhibition activity with an IC_{50} value of 0.278 μM compared with camptothecin as a reference drug (IC_{50} 0.224 μM). Docking studies were performed to investigate the recognition profile of compound **13** with the Topo 1 enzyme binding site.

KEYWORDS
antitumor activity, chalcones, docking, EGFR, quinolone, Topo 1, VEGFR2

1 | INTRODUCTION

Quinoline is an important ring system, found in many natural and synthetic products that have diversity of applications.[1–3] Many derivatives have various pharmacological activities, the majority of which having antimalarial,[4] antibacterial,[5] antifungal,[6] anti-inflammatory,[7] and anticancer activities.[8]

The quinoline scaffold has a significant contribution in anticancer drug development; since many derivatives had shown magnificent results throughout different mechanisms of action varying between inhibition of angiogenesis, apoptosis, disruption of cell migration, growth inhibition (GI) by cell cycle arrest, or modulation of nuclear receptor responsiveness.[8,9]

Literature surveys have revealed the importance of quinoline derivatives as potent anticancer agents, either from natural source like camptothecin (**A**) (MCF7: IC_{50} = 0.23 μM),[10] or synthetic compounds as bosutinib (**B**) (MDA-MB-231: IC_{50} = 0.25 μM),[11] lenvatinib,[12,13] cabozantinib,[14] topotecan,[15] and irinotecan.[16]

In addition, many heterocycle-containing compounds proved to have considerable anticancer activity. They may contain tetrazoloquinoline (**C**) (HL-60: 70% inhibition at 100 μM),[17] tetrazole (**D**) (Hep-G2: IC_{50} = 2.07 μM) and (**E**) (Hep-G2: IC_{50} = 1.65 μM),[18] pyrazoloquinoline (**F**) (HCT-116: IC_{50} = 2.3 μM),[19] or naphthopyran nucleus in their structure (**G**) (PC-3: IC_{50} = 43.6 μM)[20] and (**H**) (BT-20: 34% inhibition at 50 μM).[21] Besides, several chalcone derivatives were well established to show antiproliferative activities (**I**) (MDA-MB-468: IC_{50} = 0.12 μM)[22] (Figure 1).

Guided by these findings, and in a trial to develop new anticancer therapeutic agents, we were encouraged to incorporate quinoline moiety as a main scaffold with various heterocycles and chalcone moieties to form new hybrid molecules.

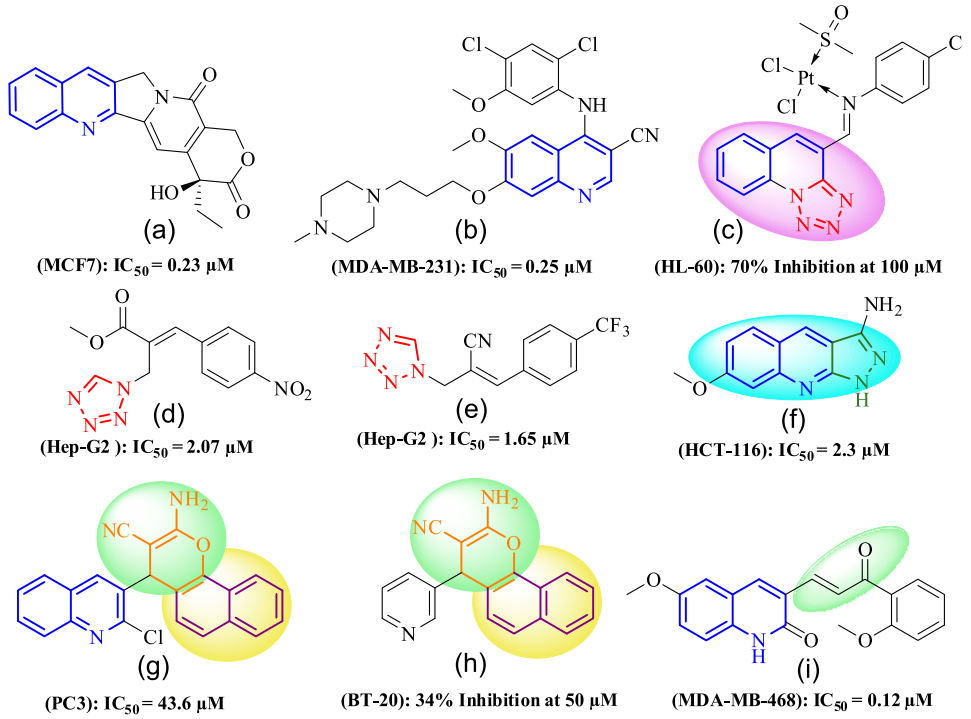


FIGURE 1 Quinoline (**a**,**b**), tetrazoloquinolines (**c**), tetrazole (**d**,**e**), pyrazoloquinoline (**f**), naphthopyrane (**g**,**h**), and chalcone (**i**) containing compounds with reported anticancer activity

1.1 | Rationale of the molecular design

Our rationale depended mainly on molecular hybridization approach that involved the combination of two or more pharmacophoric moieties with relevant biological properties to obtain a new hybrid compound with enhanced potency, efficacy, and safety.[23] This approach allowed us to construct new quinoline-hybrids which could serve as effective anticancer agents, since quinoline nucleus was hybridized with four heterocyclic moieties in addition to a chalcone moiety. Embodying tetrazole moiety at N_1 and C_2 of quinoline ring gave rise to the fused tetrazolo[1,5-*a*]quinoline scaffold which in turn was hybridized with pyrane, naphthopyrane, and chalcone moieties at C_3 of quinoline ring to afford the target hybrids. Furthermore, quinoline nucleus at C_2 and C_3 was hybridized with pyrazole ring to afford fused 1*H*-pyrazolo[3,4-*b*]quinoline nucleus substituted with amino group which is easily converted into cyclic imides (Figure 2).

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

Our target compounds were obtained throughout three Schemes 1 to 3. Scheme 1 illustrates the synthetic pathways embraced for the

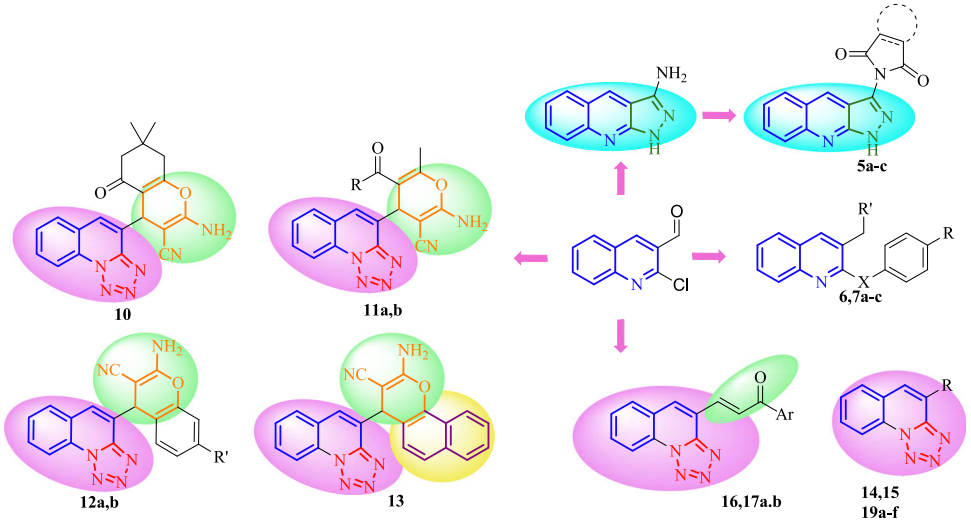
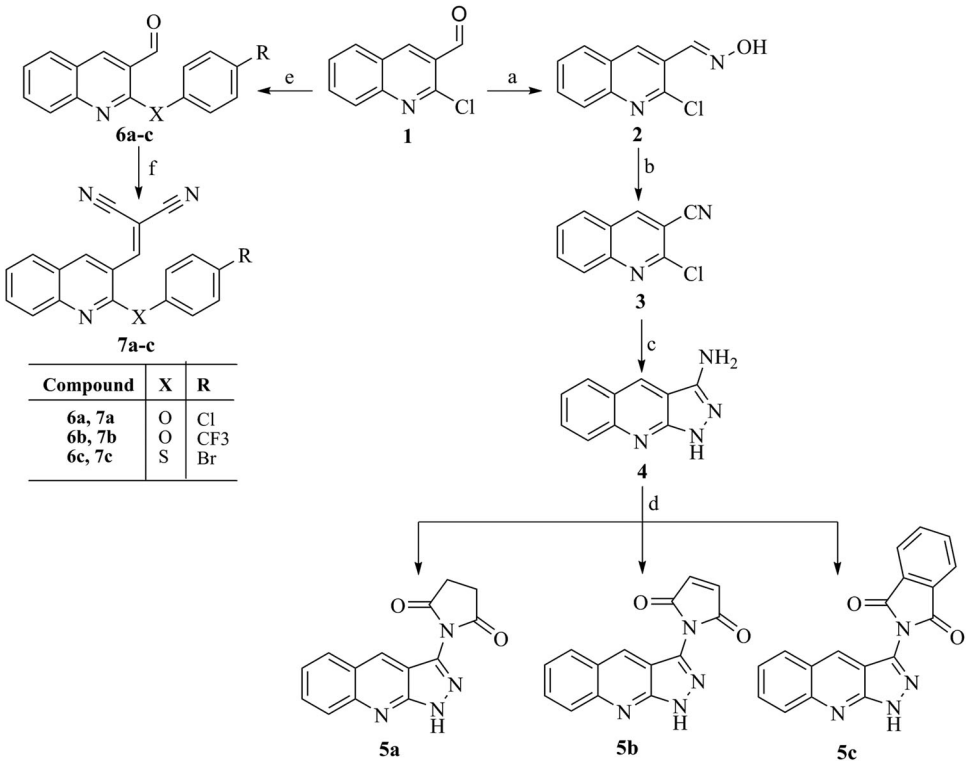
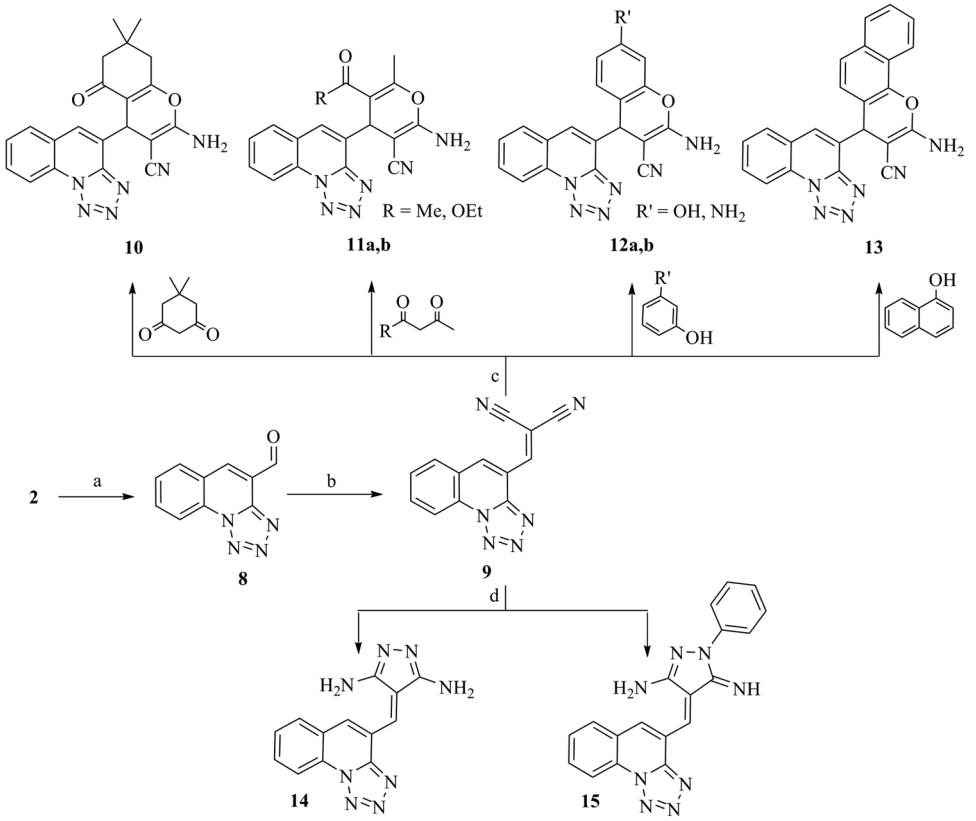


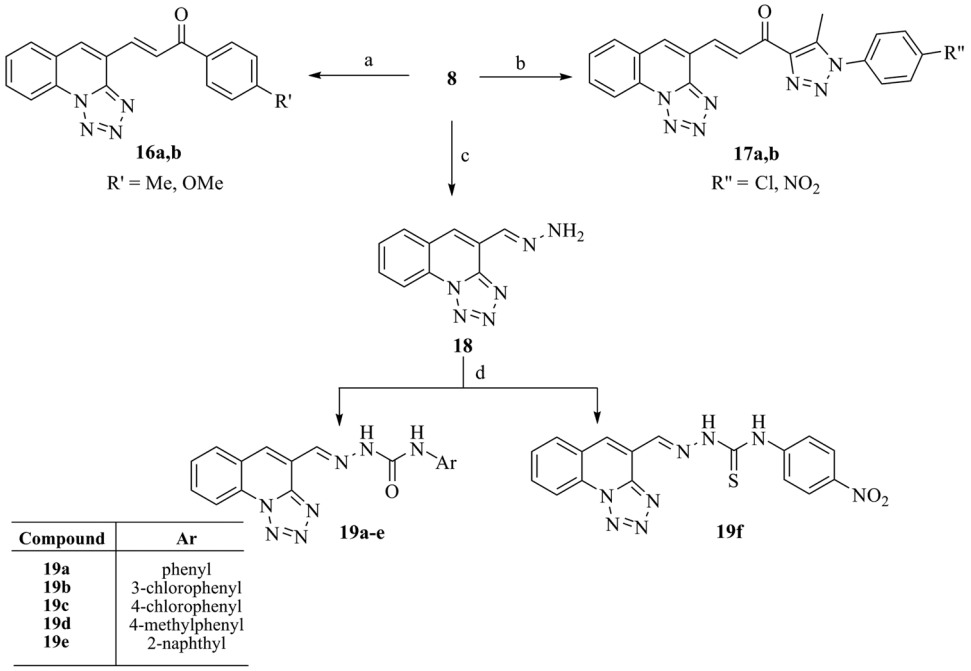
FIGURE 2 Rationale of molecular design of the target compounds



SCHEME 1 Reagents and conditions: (a) CH_3COONa, NH_2OH, $EtOH/H_2O$, stirring, rt, 2 hr, then reflux, 3 hr; (b) $SOCl_2$, DMF, stirring, rt, 24 hr; (c) $N_2H_4.H_2O$, abs. EtOH, reflux, 24 hr; (d) appropriate acid anhydride, glacial acetic acid, reflux, 3 hr; (e) appropriate phenol or thiophenol, DMF, K_2CO_3, 85°C, 24 hr; (f) malononitrile, abs. EtOH, reflux 20 hr. DMF: dimethylformamide; rt: room temperature



SCHEME 2 Reagents and conditions: (a) NaN_3, H_2O, acetic acid, dimethyl sulfoxide, 40°C, 3 hr; (b) malononitrile, abs. EtOH, reflux, 12 hr; (c) TBAB, abs. EtOH, reflux 12 hr; (d) $N_2H_4.H_2O$ or $PhNHNH_2$, abs. EtOH, reflux, 20 hr. TBAB: tetrabutylammonium bromide



Compound	Ar
19a	phenyl
19b	3-chlorophenyl
19c	4-chlorophenyl
19d	4-methylphenyl
19e	2-naphthyl

SCHEME 3 Reagents and conditions: (a,b) Appropriate aromatic ketone, DMF, alcoholic KOH 2%, stirring, rt, 24 hr; (c) $N_2H_4.H_2O$, abs. EtOH, reflux, 5 hr; (d) appropriate iso(thio)cyanate, THF, stirring, rt, 24 hr. DMF: dimethylformamide; rt: room temperature; THF: tetrahydrofuran

preparation of compounds **5a–c, 6a–c** and **7a–c**. The starting compound **1** was obtained using the method described by Meth-Cohn[24,25] via the treatment of acetanilide with the Vilsmeier–Haack reagent. Condensation of **1** with hydroxylamine hydrochloride gave rise to oxime **2**.[2] Dehydration of **2** using thionyl chloride in the presence of dimethylformamide (DMF) yielded nitrile **3** which was refluxed with hydrazine hydrate in ethanol to give **4**.[26] The reaction of amino group in compound **4** with different acids anhydride (succinic anhydride, maleic anhydride, and phthalic anhydride, respectively) in the presence of glacial acetic acid yielded the cyclic imide derivatives **5a–c.** The reaction of **1** with appropriate phenol or thiophenol in the presence of potassium carbonate and DMF yielded **6a–c** which were refluxed with malononitrile in ethanol to give **7a–c** (Scheme 1).

Compound **8** was prepared through the reaction of **1** with sodium azide according to the reported method.[27] Under Knoevenagel condensation reaction compound **8** was reacted with malononitrile to yield 2-(tetrazolo[1,5-*a*]quinolin-4-ylmethylene)malononitrile (**9**) which was reacted via Michael cycloaddition reaction with the appropriate β-diketone (dimedone and acetylacetone), β-ketoester (ethyl acetoacetate) or the appropriate phenol in the presence of tetrabutylammonium bromide (TBAB) as phase transfer catalyst to give **10**, **11a**,**b**, **12a**,**b**, and **13**, respectively. The reaction of **9** with hydrazine or phenylhydrazine afforded **14** and **15**, respectively (Scheme 2).

α,β-Unsaturated carbonyl derivatives **16a**,**b** and **17a**,**b** were synthesized via condensation of **8** with the appropriate aryl or heteroaryl ketone. Hydrazone **18** was prepared by the reported method[28] from **8**. It was then reacted with the appropriate iso(thio)-cyanate to yield **19a–f**, respectively (Scheme 3).

2.2 | Biological evaluation

2.2.1 | In vitro one-dose anticancer screening

Out of the 27 synthesized compounds, 25 compounds were selected by the National Cancer Institute (NCI) under the Developmental Therapeutic Program (DTP) for evaluation of their anticancer activity against 60 human tumor cell lines at a single dose of 10 μM. The 60-cell panel is derived from nine different cancer types: leukemia, lung, colon, melanoma, central nervous system, ovary, renal, breast, and prostate cancers. The yield from single dose screening was reported as a mean graph that was analyzed by the COMPARE program.[29] Results for the most cytotoxic compounds **6b, 7a–c, 13** and **19f** are listed in Table 1, expressed as GI% of cancer cells.

Analysis of data resulted from the primary assay proved that compounds **13** and **19f** displayed considerable antiproliferative activity. Compounds **6b** and **7a–c** showed moderate to good activity against leukemia cancer cell lines. Compound **13** exhibited high selectivity and potency against CCRF-CEM, HL-60(TB) and RPMI-8226 (leukemia cancer cell lines), HCT-116 (colon cancer cell line), SF-539 (CNS cancer cell line), MDA-MB-435 (melanoma cancer cell line), OVCAR-3 (ovarian cancer cell line), A498 (renal cancer cell line), MDA-MB-468 (breast cancer cell line) that impressively reached to 100% inhibition of tumor cell growth. It showed excellent activity against other leukemia cell lines (K-562, MOLT-4, and SR) with GI% values of 95.87, 89.37, and 96.12, respectively. Moreover, compound **13** exhibited GI% of lung cancer cell lines with values ranging from 46.36% to 88.68% with the best activity showed against the NCI-H460 cell line. It also showed good activity against prostate cancer cell lines, in addition to the rest of cancer cell lines. The rest of our synthesized compounds gave average % GI <12%.

TABLE 1 Single dose screening expressed as GI% of cancer cells by compounds (**6b**, **7a–c**, **13**, and **19f**)

	GI %					
Panel/cell line	**6b**	**7a**	**7b**	**7c**	**13**	**19f**
Leukemia						
CCRF-CEM	93.02	89.88	99.71	71.95	100	88.7
HL-60(TB)	7.96	32.17	21.6	33	100	72.65
K-562	40.95	50.79	35.49	35.8	95.87	87.52
MOLT-4	39.45	70.64	45.22	35.19	89.37	79.6
RPMI-8226	67.03	38.94	96.34	37.52	100	52.33
SR 23.64	76.36	86.25	69.21	71.45	96.12	95.67
Non-small cell lung cancer						
A549/ATCC	1.59	0	0.46	0	66.59	44.44
EKVX	17.56	6.67	15.86	11.16	47.92	63.43
HOP-62	19.12	1.19	6.31	0.86	75.41	50.71
HOP-92	47.24	46.72	51.33	32.94	50.84	100
NCI-H226	23.05	11.02	22.88	12.32	46.36	28.04
NCI-H23	14.68	8.64	18.2	16.28	63.38	69.92
NCI-H322M	5.15	5.08	0.83	6.29	65.98	48.11
NCI-H460	1.23	3.73	2.65	4.77	88.68	67.75
NCI-H522	14.58	14.4	8.24	14.95	87.72	64.59
Colon cancer						
COLO 205	16.38	3.33	0	0	51.63	3.11
HCC-2998	0	0	0	0	53.07	46.03
HCT-116	0	5.44	10.22	48.55	100	38.69
HCT-15	19.25	10.55	14.91	18.75	88.24	72.67
HT29	5.9	0	0	0	91.27	0.19
KM12	7.62	8.11	11.5	6.36	81.88	33.12
SW-620	32.97	15.58	25.49	38.31	90.42	75.63
CNS cancer						
SF-268	16.58	11.49	15.63	12.53	73.72	61.74
SF-295	17.13	0	7.83	5.26	89.29	81.1
SF-539	2.16	4.76	3.14	0.83	100	90.1
SNB-19	9.34	17.59	6.81	9.33	73.76	70.23
SNB-75	16.81	11.51	15.77	16.17	91.18	41.83
U251	18.42	8.79	8.79	11.72	81.28	69.79
Melanoma						
LOX IMVI	25.71	17.3	23.6	31.39	75.47	60.83
MALME-3M	4.04	0.77	1.24	11.53	46.57	28.12
M14 99.79	0.21	4.98	7.17	11.37	87.34	24.53
MDA-MB-435	0	0	2.96	2.41	100	17.62
SK-MEL-2	0	0	0	0.71	87.99	50.73
SK-MEL-28	0	0	0	0	60.67	21.02
SK-MEL-5	5.52	1.75	5.29	6.89	92.03	28.96
UACC-257	0	0	0	0	52.61	9.78
UACC-62	27.51	24.32	21.65	33.47	74.64	34.57

(Continues)

TABLE 1 (Continued)

	GI %					
Panel/cell line	**6b**	**7a**	**7b**	**7c**	**13**	**19f**
Ovarian cancer						
IGROV1	31.71	20.46	20.68	28.39	66.69	45.53
OVCAR-3	3.34	0	0	0	100	85.66
OVCAR-4	1.41	0	0.34	0	34.96	36.23
OVCAR-5	0.84	0	0	0	60.55	20.4
OVCAR-8	8.96	6.09	7.51	8.49	73.4	28.84
NCI/ADR-RES	7.06	3.59	7.46	10.93	99.07	48.27
SK-OV-3	18.48	4	11.35	7.32	87.51	26.31
Renal cancer						
786-0	0	0	1.17	0	86.6	38.44
A498	–	–	–	100	–	
ACHN	12.29	4.32	11.31	4.41	77.28	70.12
CAKI-1	36.55	22.76	32.32	22.5	68.42	74.57
RXF 393	8.12	5.04	7.65	9.16	88.59	69.86
SN12C	29.51	21.66	8.09	25.35	72.72	41.46
TK-10	1.96	0	0	0	62.66	43.17
UO-31	64.92	48.51	56.19	46.23	74.08	100
Prostate cancer						
PC-3	32.2	34.55	48.54	23.79	89.9	65.47
DU-145	1.61	0	0.85	0	80.53	35.95
Breast cancer						
MCF7	51.89	30.58	43.08	48.57	90.19	86.22
MDA-MB-231/ATCC	24.27	14.31	15.53	38.91	67.13	38.78
HS 578T	10.31	6.19	3.14	8.95	82.27	33.04
BT-549	0.3	3.66	3.81	3.87	83.83	19.6
T-47D	16.3	0	9.4	11.37	75.02	53.48
MDA-MB-468	9.26	7.18	13.86	14.12	100	38.3

Note. GI: growth inhibition.

TABLE 2 Five dose screening results of compound **13**

Panel/cell line	GI_{50} (μM)	TGI (μM)	LC_{50} (μM)
Leukemia			
CCRF-CEM	0.739	>100	>100
HL-60(TB)	0.260	16.7	>100
K-562	0.365	>100	>100
MOLT-4	0.557	>100	>100
RPMI-8226	0.927	>100	>100
SR	0.232	>100	>100
Non-small cell lung cancer			
A549/ATCC	3.02	>100	>100
EKVX	5.80	>100	>100
HOP-62	0.812	>100	>100
HOP-92	0.490	>100	>100
NCI-H226	3.08	>100	>100
NCI-H23	3.45	>100	>100
NCI-H322M	2.15	>100	>100
NCI-H460	0.496	>100	>100
NCI-H522	0.407	2.90	>100
Colon cancer			
COLO 205	2.69	7.32	>100
HCC-2998	2.36	>1.00	>1.00
HCT-116	0. 685	>100	>100
HCT-15	0.524	>100	>100
HT29	3.00	>100	>100
KM12	0.628	>100	>100
SW-620	0.467	>100	>100
CNS cancer			
SF-268	3.23	>100	>100
SF-295	0.832	>100	>100
SF-539	0.483	2.48	
SNB-19	0.702	>100	>100
U251	0.748	>100	>100
Melanoma			
LOX	0.966	>100	>100
MALME-3M	0.852	>100	>100
M14	0.948	>100	>100
MDA-MB-435	0.300	1.01	7.83
SK-MEL-2	0.616	6.84	>100
SK-MEL-28	4.04	>100	>100
SK-MEL-5	0.610	>100	>100
UACC-257	9.09	>100	>100
UACC-62	0.451	>100	>100
Ovarian cancer			
IGROV1	0.820	>100	>100
OVCAR-3	0.440	3.36	>100
OVCAR-4	18.7	>100	>100
OVCAR-5	2.76	>100	>100
OVCAR-8	2.85	>100	>100
NCI/ADR-RES	0.534	46.6	>100
SK-OV-3	2.05	>100	>100
Renal cancer			
786-0	1.28	>100	>100
A498	0.783	>100	>100
ACHN	1.71	>100	>100
CAKI-1	5.74	>100	>100
RXF 393	1.40	6.59	>1.00
SN12C	0.990	>100	>100
TK-10	4.80	>100	>100
UO-31	0.725	>100	>100
Prostate cancer			
PC-3	0.545	>100	>100
DU-145	2.77	>100	>100
Breast cancer			
MCF7	0.471	>100	>100
MDA-MB-231/ATCC	0.976	>100	>100
HS 578T	1.51	49.3	>100
BT-549	1.61	>100	>100
T-47D	1.83	>100	>100
MDA-MB-468	0.466		>100

Note. GI_{50}: molar concentration of the compound that inhibits 50% net cell growth; LC_{50}: molar concentration of the compound leading to 50% net cell death; TGI: molar concentration of the compound resulting in total growth inhibition.

2.2.2 | In vitro five-dose anticancer screening

Based on the promising results obtained from single dose testing, compound **13** was selected for further assay against the full 60-cell panel at five different concentrations (100, 10, 1.0, 0.1, and 0.001 μM). The anticancer activity was expressed according to three dose-response parameters namely, GI_{50}, TGI, and LC_{50}. Furthermore, a mean graph midpoint (MG_MID) was calculated for each of the aforementioned parameters, giving an averaged activity parameter over all cell lines. The five-dose assay results are shown in Table 2, and graphically represented in Figure 1, as dose-response curves against nine different cancer panels.

Compound **13** showed significant anticancer activity against most of the tested cancer cell lines with GI_{50} values in the range of 0.232–18.7 μM. It was found to be highly sensitive against the leukemia SR cell line (GI_{50} = 0.232 μM), HL-60(TB) (GI_{50} = 0.260 μM), K-562 (GI_{50} = 0.365 μM), non-small cell lung cancer NCI-H522 cell line (GI_{50} = 0.407 μM), colon cancer SW-620 cell line (GI_{50} = 0.467 μM), CNS cancer SF-539 cell line (GI_{50} = 0.483 μM), melanoma MDA-MB-435 cell line (GI_{50} = 0.300 μM), ovarian cancer OVCAR-3 cell line (GI_{50} = 0.440 μM), prostate cancer PC-3 cell line (GI_{50} = 0.545 μM) and breast cancer MDA-MB-468 cell line (GI_{50} = 0.466 μM). Furthermore, it showed very good activity against other human cancer cell lines.

2.2.3 | In vitro cytotoxicity against human normal cells

Cytotoxic selectivity of compound **13** toward cancer cell lines was evaluated throughout screening against human normal cell lines, represented by skin fibroblast cell line (BJ) and breast epithelial cell line (MCF 10F), using staurosporine as a standard drug. The compound showed increased IC_{50} in both cell lines, compared to the reference drug, indicating higher selectivity toward cancer cell lines over normal cells (Table 3).

2.2.4 | Epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor 2 (VEGFR2), and topoisomerase 1 (Topo 1) enzyme inhibition assay

EGFR, VEGFR2, and Topo 1 were selected as specific targets to examine the in vitro inhibitory activity of compound **13** against them; to inspect the possible mechanism of action by which this compound may exert its

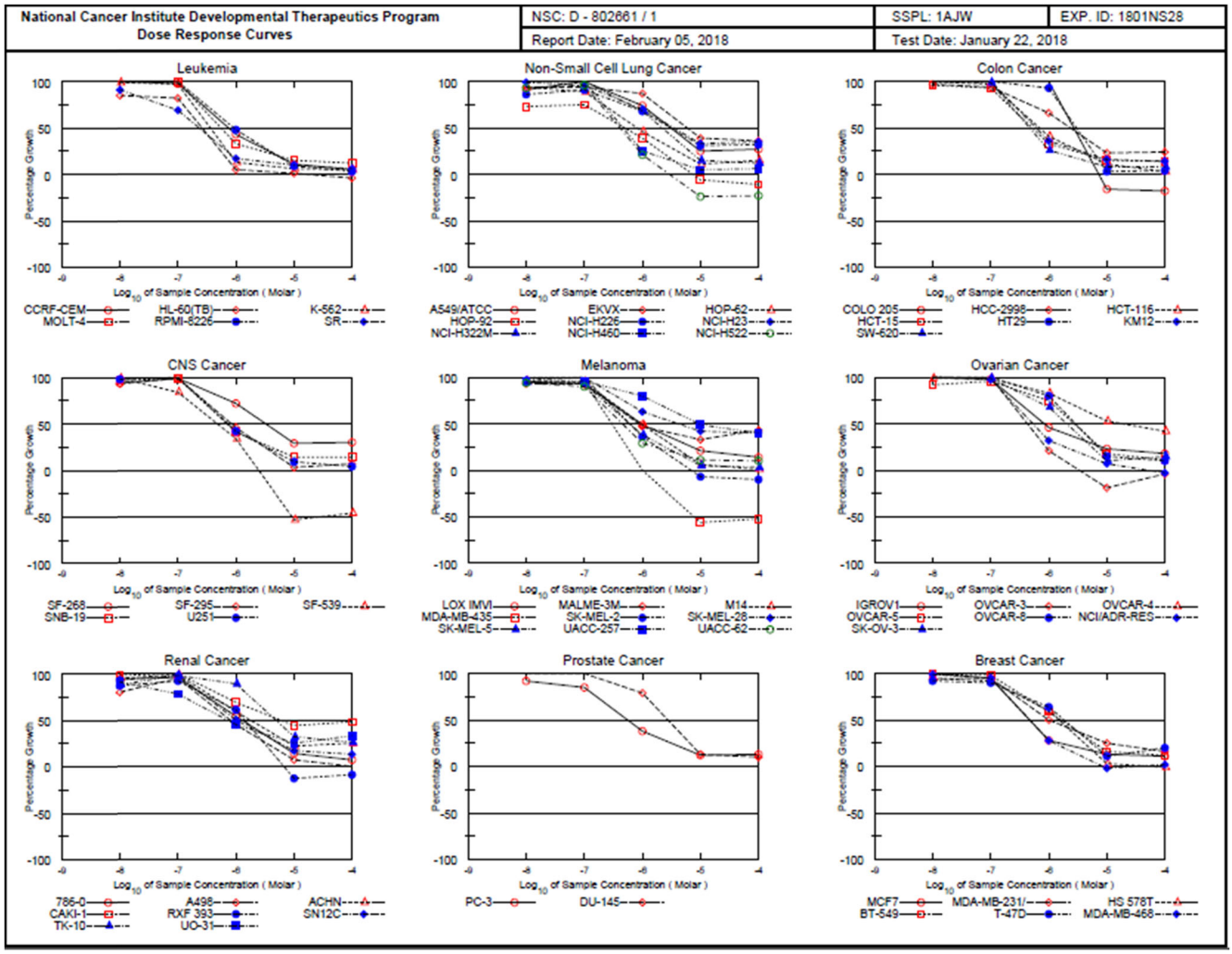


FIGURE 3 Five dose assay graph of compound **13** against the nine panel cancer cell lines at NCI

antitumor activity. Selection of such targets was based on the reported inhibitory activity of many quinoline-derived anticancer agents toward one or more of these enzymes, such as camptothecin,[30] topotecan[15] and irinotecan,[16] which exert their anticancer activity throughout inhibition of Topo I. Besides, lenvatinib,[12,13] tivozanib[31] and cabozantinib[14] are quinoline derivatives that proved to have considerable inhibitory activity against VEGFR. Furthermore, many other quinoline-based derivatives[32] and quinoline isosteres[33] are well known to exhibit anticancer activity via inhibition of EGFR. The tested compound showed significant inhibition against Topo 1 with IC_{50} value of 0.278 µg/ml which is comparable to that of the reference drug camptothecin (IC_{50} 0.224 µg/ml). On the other hand it displayed merely 60% of sorafenib activity against VEGFR2 and about 30% of erlotinib activity against EGFR (Table 4). The results supported that Topo 1 could be a possible target for compound **13** rather than VEGFR2 or EGFR kinases.

TABLE 3 Cytotoxic activity (IC_{50}) of compound **13** against human normal cell lines

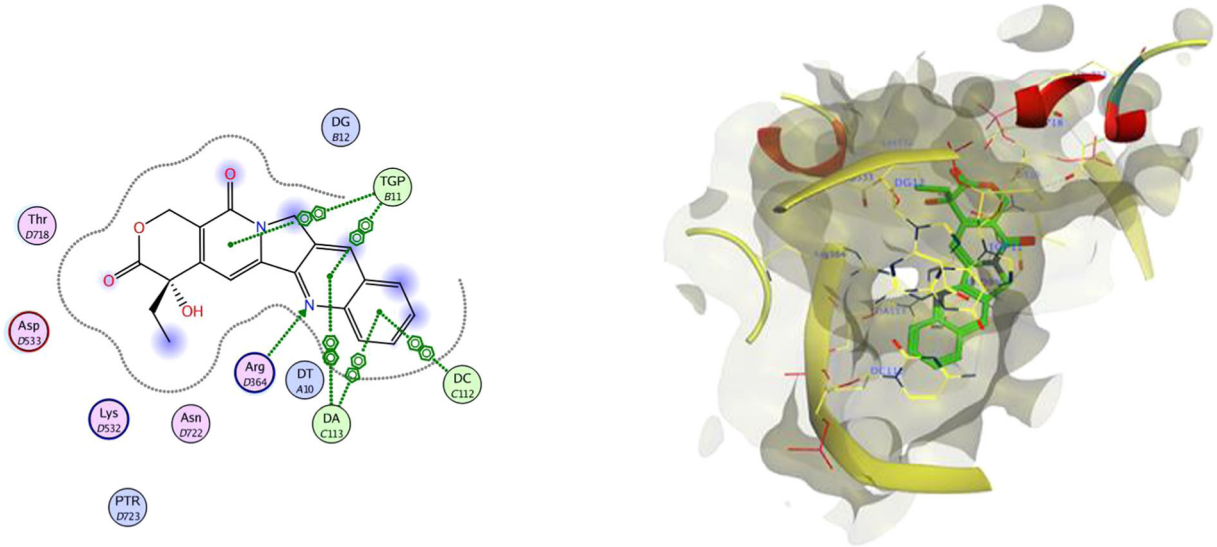
	In vitro cytotoxicity IC_{50} (µg/ml)	
Compounds	**BJ**	**MCF-10F**
13	79.91 ± 2.14	32.92 ± 0.73
Staurosporine	25.88 ± 0.61	27.95 ± 0.75

2.3 | Docking study

Molecular docking study of compound **13** was performed to rationalize the promising Topo 1 inhibitory activity through inspection of the potential binding affinity and binding mode with the active site. The crystalline structure needed for determination of absolute configuration of chiral C_4 of pyran ring by X-ray crystallography was not satisfying.

TABLE 4 In vitro enzyme inhibition of compound **13**

Compounds	EGFR IC_{50} (µg/ml)	VEGFR2 IC_{50} (µg/ml)	Topo 1 IC_{50} (µg/ml)
13	0.721	0.412	0.278
Erlotinib	0.218	–	–
Sorafenib	–	0.243	–
Camptothecin	–	–	0.224



(a) 2D binding of camptothecin with Topo 1 active site

(b) 3D docked conformation of camptothecin inside the pocket of Topo 1 active site

FIGURE 4 Binding of camptothecin with Topo 1 active site (PDB code 1T8I). Topo 1: topoisomerase 1

Therefore, we proposed both *R* and *S* enantiomers to perform docking study.

Docking was carried out using the X-ray crystal structure of Topo 1 with camptothecin, PDB entry 1T8I.[34] Binding of camptothecin to the target pocket involved both the hydrogen bond formed between the quinoline-N atom with the conserved amino acid Arg364, and the arene–arene interaction between quinoline ring with TGP, DC, and deoxy adenine (DA; Figure 2). Docking of (*R*)-enantiomer of compound **13** demonstrated interesting binding modes similar to that of camptothecin; with dockig score value of −5.9 kcal/mol; through a hydrogen bond interaction that occurred between the nitrogen atom of ligand-CN group and the amino group hydrogen of Arg364. Besides, a π–π stacking interaction was found to be formed between the tetrazole ring and DA. Furthermore, an additional interaction occurred with Lys425 residue in the enzyme pocket, hence maintaining an improved binding pattern, comparable to that of camptothecin. (*S*)-Enantiomer of compound **13** shows weaker binding affinity with Topo 1 active site in comparison to (*R*)-enantiomer, with dockig score value of −3.9 kcal/mol (Figure 3).

3 | CONCLUSION

Molecular hybrids of quinoline were designed, synthesized and biologically evaluated for their anticancer activity via NCI protocol. Compound **13** was proved to have the most potent anticancer activity; with growth inhibition (GI_{50}) values <1.0 μM, exhibiting the highest selectivity toward leukemia, breast cancer, and CNS cancer cell lines, while proved to be less toxic against human normal cell lines. Furthermore, it showed significant Topo 1 enzyme inhibitory activity, comparable to the standard drug camptothecin. Docking study supported that Topo 1 could be a possible target for the designed compound for its antitumor activity owing to its unique binding pattern to the active site.

4 | EXPERIMENTAL

4.1 | Chemistry

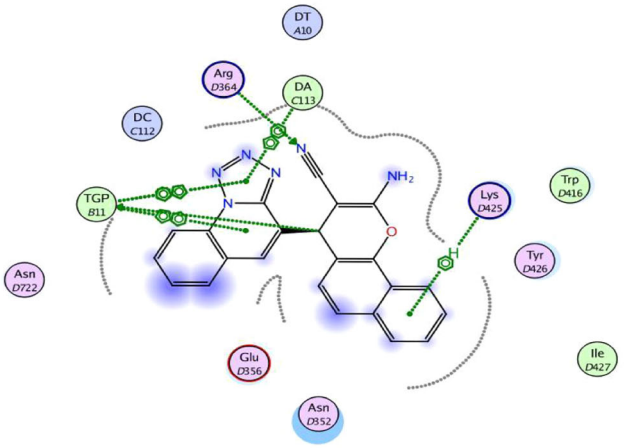
4.1.1 | General

Melting points (°C) are uncorrected and were recorded using Fisher–John melting point apparatus. Microanalyses were performed at the microanalytical unit, Cairo University. IR spectra were recorded on a Mattson 5000 FT-IR spectrometer (υ in cm^{-1}) in KBr disks at the Faculty of Pharmacy, Mansoura University. The ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra were recorded on Jeol ECA-500 II NMR spectrometer in dimethyl sulfoxide (DMSO)-*d6* at the Faculty of Science, Mansoura University. Chemical shifts in ppm are expressed in δ units using tetramethylsilane (TMS) as internal standard. TLC technique was used for determination of reaction times using silica gel plates 60 F245E (Merck Merck KGaA, Darmstadt, Germany), the spots were visualized by UV (366 nm). All reagents were purchased from the Sigma-Aldrich Co. (St. Louis, MO). Compounds **1**–**4** were synthesized in accordance with method described in the literature.[24–26]

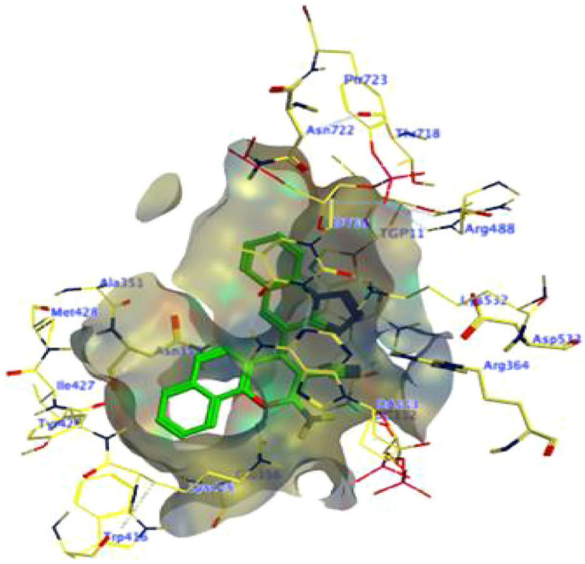
The InChI codes of the investigated compounds are provided as Supporting Information.

4.1.2 | General procedure for synthesis of compounds 5a–c

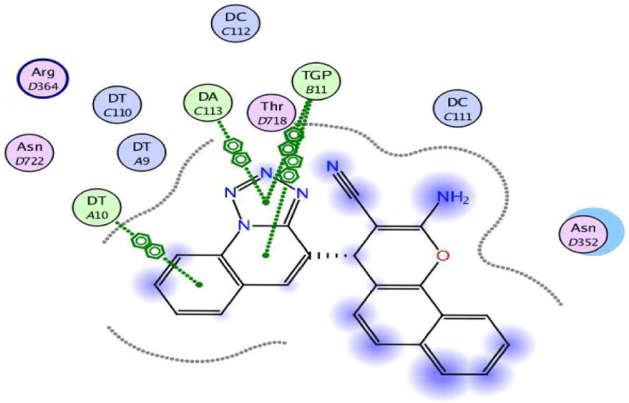
Mixture of 1*H*-pyrazolo[3,4-*b*]quinolin-3-amine (**4**) (1.84 g, 0.01 mol) and the appropriate acid anhydride (0.01 mol) in glacial acetic acid



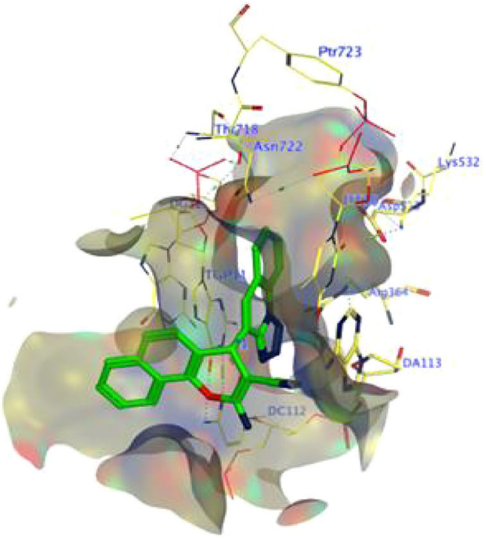
(a) 2D binding of compound **13** (*R*)-enantiomer with Topo 1 active site



(b) 3D docked conformation of compound **13** (*R*)-enantiomer inside the pocket of Topo 1 active site



(c) 2D binding of compound **13** (*S*)-enantiomer with Topo 1 active site



(d) 3D docked conformation of compound **13** (*S*)-enantiomer inside the pocket of Topo 1 active site

FIGURE 5 Binding mode of (*R*)- and (*S*)-enantiomers of compound **13** in Topo 1 active site (PDB code 1T8I)

(30 ml) was refluxed for 3 hr. The reaction mixture was cooled to 0°C and the solid product was filtered, washed with water, dried, and crystallized from ethanol.

1-(1*H*-Pyrazolo[3,4-*b*]quinolin-3-yl)pyrrolidine-2,5-dione (5a)

Compound **5a** was prepared by using succinic anhydride, yield (39%); mp > 300°C; IR (cm^{-1}): 3427 (NH), 1707 (C=O); ^1H NMR: δ 2.61 (t, *J* = 6.0 Hz, 2H, CH_2 pyrrolidine), 2.71 (t, *J* = 6.2 Hz, 2H, CH_2 pyrrolidine), 7.45 (dd, *J* = 7.3, 7.4 Hz, 1H, Ar–H), 7.77 (dd, *J* = 7.2, 7.7 Hz, 1H, Ar–H), 7.94 (d, *J* = 8.6 Hz, 1H, Ar–H), 8.12 (d, *J* = 8.2 Hz, 1H, Ar–H), 9.05 (s, 1H, Ar–H), 10.92 (s, 1H, NH); Anal. calcd. for $C_{14}H_{10}N_4O_2$ (266): C, 63.15; H, 3.79; N, 21.04%. Found: C, 63.25; H, 3.67; N, 21.23%.

1-(1*H*-Pyrazolo[3,4-*b*]quinolin-3-yl)−1*H*-pyrrole-2,5-dione (5b)

Compound **5b** was prepared by using maleic anhydride, yield (45%); mp > 300°C; IR (cm^{-1}): 3422 (NH), 1702 (C=O); ^1H NMR: δ 6.42 (d, *J* = 12.0 Hz, 1H, CH pyrrole), 6.62 (d, *J* = 12.0 Hz, 1H, CH pyrrole), 7.47 (dd, *J* = 7.3, 7.4 Hz, 1H, Ar–H), 7.79 (dd, *J* = 8.1, 8.4 Hz, 1H, Ar–H),

7.96 (d, *J* = 8.7 Hz, 1H, Ar–H), 8.11 (d, *J* = 8.1 Hz, 1H, Ar–H), 9.09 (s, 1H, Ar–H); Anal. calcd. for $C_{14}H_8N_4O_2$ (264): C, 63.64; H, 3.05; N, 21.20%. Found: C, 63.48; H, 3.11; N, 21.13%.

2-(1*H*-Pyrazolo[3,4-*b*]quinolin-3-yl)isoindoline-1,3-dione (5c)

Compound **5c** was prepared by using phthalic anhydride, yield (33%); mp > 300°C; IR (cm^{-1}): 3425 (NH), 1722 (C=O); ^1H NMR: δ 7.53 (dd, *J* = 7.3, 7.4 Hz, 1H, Ar–H), 7.85 (dd, *J* = 7.3, 7.7 Hz, 1H, Ar–H), 7.95–8.14 (m, 6H, Ar–H), 9.02 (s, 1H, Ar–H); ^{13}C NMR: 111.68, 123.89, 124.11, 127.87, 129.58, 130.84, 131.12, 131.60, 132.84, 135.13, 148.11, 151.37, 151.55, 166.47; Anal. calcd. for $C_{18}H_{10}N_4O_2$ (314): C, 68.79; H, 3.21; N, 17.83%. Found: C, 68.66; H, 3.12; N, 17.95%.

4.1.3 | General procedure for synthesis of compounds 6a–c

2-Chloroquinoline-3-carbaldehyde (**1)** (1.91 g, 0.01 mol) was dissolved in DMF (25 ml), to which 4-substituted phenol or thiophenol (0.01 mol) and potassium carbonate (2.76 g, 0.02 mol) were added. The reaction mixture was heated at 75°C overnight, then allowed to cool, and poured on iced water. The precipitated solid was filtered and washed with water, dried and recrystallized from methanol.

2-(4-Chlorophenoxy)quinoline-3-carbaldehyde (6a)

Yield (58%); mp 141–142°C; IR (cm^{-1}): 2860, 2730 (C–H, aldehyde), 1691 (C=O), 1590 (C=N); ^1H NMR: δ 7.40 (d, *J* = 8.9 Hz, 2H, Ar–H), 7.53–7.60 (m, 3H, Ar–H), 7.66 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.80 (dd, *J* = 8.4, 8.5 Hz, 1H, Ar–H), 8.18 (d, *J* = 8.1 Hz, 1H, Ar–H), 8.95 (s, 1H, Ar–H), 10.49 (s, 1H, CHO); ^{13}C NMR: 120.07, 124.02, 124.98, 125.98, 126.90, 129.27, 129.56, 130.13, 133.17, 141.50, 147.41, 151.74, 159.90, 188.85; Anal. calcd. for $C_{16}H_{10}ClNO_2$ (283.71): C, 67.74; H, 3.55; N, 4.94%. Found: C, 67.66; H, 3.75; N, 4.74%.

2-(4-(Trifluoromethyl)phenoxy)quinoline-3-carbaldehyde (6b)

Yield (53%); mp 124–125°C; IR (cm^{-1}): 2853, 2728 (C–H, aldehyde), 1695 (C=O), 1595 (C=N); ^1H NMR: δ 7.58–7.63 (m, 3H, Ar–H), 7.69 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.82 (dd, *J* = 7.4, 7.9 Hz, 1H, Ar–H), 7.89 (d, *J* = 8.5 Hz, 2H, Ar–H), 8.21 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.99 (s, 1H, Ar–H), 10.50 (s, 1H, CHO); ^{13}C NMR: 120.64, 120.64, 123.26, 125.62, 125.97, 126.03, 126.29, 126.66, 127.43, 127.51, 127.55, 130.62, 133.74, 142.23, 147.79, 156.59, 159.99, 189.25; Anal. calcd. for $C_{17}H_{10}F_3NO_2$ (317): C, 64.36; H, 3.18; N, 4.41%. Found: C, 64.24; H, 3.29; N, 4.74%.

2-((4-Bromophenyl)thio)quinoline-3-carbaldehyde (6c)[35]

Yield (43%), mp 84–85°C as recorded, 83.4–84.3°C as reported.

4.1.4 | General procedure for the synthesis of compounds 7a–c

To a mixture of compound **6a–c** (0.01 mol) in absolute ethanol (30 ml), malononitrile (2.64 g, 0.04 mol) was added. The reaction mixture was refluxed for 20 hr, and then allowed to cool. The precipitated solid was filtered, dried and recrystallized from ethanol.

2-((2-(4-Chlorophenoxy)quinolin-3-yl)methylene)malononitrile (7a)

Yield (44%); mp 219–220°C; IR (cm^{-1}): 2227 (CN), 1618 (C=C), 1579 (C=N); ^1H NMR: δ 7.39 (d, *J* = 8.9 Hz, 2H, Ar–H, phenyl), 7.57 (d, *J* = 8.7 Hz, 2H, Ar–H, phenyl), 7.60 (dd, *J* = 7.9, 7.9 Hz, 1H, Ar–H), 7.67 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.82 (dd, *J* = 8.2, 8.5 Hz, 1H, Ar–H), 8.11 (d, *J* = 8.2 Hz, 1H, Ar–H), 8.87 (s, 1 H, CH=C$(CN)_2$), 9.06 (s, 1H, Ar–H); ^{13}C NMR: 85.80, 112.71, 113.72, 116.69, 124.07, 124.53, 126.35, 127.00, 129.43, 129.56, 133.39, 141.31, 146.96, 151.38, 155.87, 157.66; Anal. calcd. for $C_{19}H_{10}ClN_3O$ (331.7): C, 68.79; H, 3.04; N, 12.67%. Found: C, 68.66; H, 3.26; N, 12.54%.

2-((2-(4-(Trifluoromethyl)phenoxy)quinolin-3-yl)methylene)-malononitrile (7b)

Yield (56%); mp 194–195°C; IR (cm^{-1}): 2228 (CN), 1617 (C=C), 1585 (C=N); ^1H NMR: δ 7.53–7.65 (m, 3H, Ar–H), 7.68 (d, *J* = 8.3 Hz, 1H, Ar–H), 7.83 (dd, *J* = 7.3, 7.5 Hz, 1H, Ar–H), 7.89 (d, *J* = 8.1 Hz, 2H, Ar–H, phenyl), 8.12 (d, *J* = 7.9 Hz, 1H, Ar–H), 8.88 (s, 1H, CH=C$(CN)_2$), 9.09 (s, 1H, Ar–H); ^{13}C NMR: 86.34, 113.16, 114.17, 117.21, 123.39, 125.13, 125.99, 126.20, 126.52, 127.00, 127.49, 127.51, 129.92, 133.92, 141.90, 147.31, 156.13, 157.78; Anal. calcd. for $C_{20}H_{10}F_3N_3O$ (365): C, 65.76; H, 2.76; N, 11.50%. Found: C, 65.55; H, 2.89; N, 11.62%.

2-((2-((4-Bromophenyl)thio)quinolin-3-yl)methylene)-malononitrile (7c)

Yield (66%); mp 190–191°C; IR (cm^{-1}): 2230 (CN), 1615 (C=C), 1572 (C=N); ^1H NMR: δ 7.55 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.66 (dd, *J* = 7.8, 7.9 Hz, 1H, Ar–H), 7.70 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.76 (d, *J* = 8.3 Hz, 1H, Ar–H), 7.85 (dd, *J* = 8.2, 8.3 Hz, 1H, Ar–H), 8.08 (d, *J* = 7.8 Hz, 1H, Ar–H), 8.84 (s, 1H, CH=C$(CN)_2$), 8.85 (s, 1H, Ar–H); ^{13}C NMR: 87.64, 112.17, 113.11, 122.88, 124.80, 125.13, 127.59, 127.85, 129.04, 129.15, 132.45, 133.07, 136.18, 138.31, 148.12, 157.55; Anal. calcd. for $C_{19}H_{10}BrN_3S$ (392): C, 58.17; H, 2.57; N, 10.71%. Found: C, 58.34; H, 2.41; N, 10.64%.

2-(Tetrazolo[1,5-*a*]quinolin-4-ylmethylene)malononitrile (9)

To a mixture of compound **8** (1.98 g, 0.01 mol) in absolute ethanol (30 ml) malononitrile (2.64 g, 0.04 mol) was added. The reaction mixture was refluxed for 20 h, allowed to cool. The precipitated solid was filtered, washed with ethanol and dried to obtain the titled compound as light green solid. Yield (80%); mp 200–201°C; IR (cm^{-1}): 2236 (CN); ^1H NMR: δ 7.84 (dd, *J* = 7.5, 7.7 Hz, 1H, Ar–H), 8.07 (dd, *J* = 7.6, 7.8 Hz, 1H, Ar–H), 8.18 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.69 (s, 1H, CH=CC$(CN)_2$), 8.74 (d, *J* = 8.4 Hz, 1H, Ar–H), 9.03 (s, 1H, Ar–H); ^{13}C NMR: 87.15, 112.38, 113.40, 116.53, 117.20, 122.97, 128.93, 131.12, 131.31, 134.44, 136.07, 145.70, 153.12; Anal. calcd. for $C_{13}H_6N_6$ (246): C, 63.41; H, 2.46; N, 34.13%. Found: C, 63.38; H, 2.49; N, 34.11%.

4.1.5 | General procedure for the synthesis of compounds 10, 11a,b, 12a,b and 13

A mixture of compound **9** (2.46 g, 0.01 mol) with either dimedone, the appropriate 2,4-dicarbonyl compound, the appropriate

3-substituted phenol or α-naphthol (0.01 mol) and TBAB (0.8 g, 0.0025 mol) in absolute ethanol (30 ml) was heated under reflux for 12 hr. The reaction mixture was allowed to cool to room temperature where the precipitated solid was filtered, dried and crystallized from ethanol to give the target compounds.

2-Amino-7,7-dimethyl-5-oxo-4-(tetrazolo[1,5-*a*]quinolin-4-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (10)

Yield (75%); mp 265–266°C; IR (cm^{-1}): 3414, 3327 (NH_2), 2189 (CN), 1666 (C=O); ^1H NMR: δ 0.83 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.00 (d, *J* = 16.1 Hz, 1H, CH_2 cyclohex-2-enone), 2.28 (d, *J* = 16.2 Hz, 1H, CH_2 cyclohex-2-enone), 2.48 (d, *J* = 15.1 Hz, 1H, CH_2 cyclohex-2-enone), 2.63 (d, *J* = 17.7 Hz, 1H, CH_2 cyclohex-2-enone), 4.79 (s, 1H, CH pyran), 7.24 (s, 2H, NH_2), 7.81 (dd, *J* = 7.2, 7.6 Hz, 1H, Ar–H), 7.94 (dd, *J* = 8.0, 8.3 Hz, 1H, Ar–H), 8.22 (s, 1H, Ar–H), 8.27 (d, *J* = 7.8 Hz, 1H, Ar–H), 8.58 (d, *J* = 8.3 Hz, 1H, Ar–H); ^{13}C NMR: 26.49, 28.67, 31.81, 33.97, 49.92, 54.57, 109.59, 116.20, 119.53, 123.72, 127.88, 128.50, 129.24, 129.42, 130.89, 131.16, 146.17, 159.63, 164.27, 196.11; Anal. calcd. for $C_{21}H_{18}N_6O_2$ (386): C, 65.27; H, 4.70; N, 21.75%. Found: C, 65.44; H, 4.59; N, 21.37%.

5-Acetyl-2-amino-6-methyl-4-(tetrazolo[1,5-*a*]quinolin-4-yl)-4*H*-pyran-3-carbonitrile (11a)

Compound **11a** was prepared by using acetylacetone, yield (65%); mp 240–241°C; IR (cm^{-1}): 3414, 3327 (NH_2), 2189 (CN), 1669 (C=O); ^1H NMR: δ 2.19 (s, 3H, CH_3), 2.33 (s, 3H, $COCH_3$), 5.08 (s, 1H, CH pyran), 7.09 (s, 2H, NH_2), 7.81 (dd, *J* = 7.6, 7.9 Hz, 1H, Ar–H), 7.95 (dd, *J* = 8.1, 8.3 Hz, 1H, Ar–H), 8.15 (s, 1H, Ar–H), 8.25 (d, *J* = 7.7 Hz, 1H, Ar–H), 8.59 (d, *J* = 8.3 Hz, 1H, Ar–H); ^{13}C NMR: 19.18, 30.30, 36.32, 54.35, 112.57, 116.14, 119.54, 123.78, 128.31, 128.54, 129.36, 129.45, 130.57, 131.15, 146.38, 157.31, 159.57, 197.69; Anal. calcd. for $C_{18}H_{14}N_6O_2$ (346): C, 62.42; H, 4.07; N, 24.27%. Found: C, 62.29; H, 4.13; N, 24.47%.

Ethyl 6-amino-5-cyano-2-methyl-4-(tetrazolo[1,5-*a*]quinolin-4-yl)-4*H*-pyran-3-carboxylate (11b)

Compound **11b** was prepared by using ethylacetoacetate, yield (73%); mp 222–223°C; IR (cm^{-1}): 3417, 3325 (NH_2), 2187 (CN), 1663 (C=O); ^1H NMR: δ 0.90 (t, *J* = 7.1 Hz, 3H, CH_3CH_2COO), 2.38 (s, 3H, CH_3), 3.89 (m, 2H, CH_2COO), 4.95 (s, 1H, CH pyran), 7.14 (s, 2H, NH_2), 7.81 (dd, *J* = 7.6, 7.8 Hz, 1H, Ar–H), 7.94 (dd, *J* = 7.9, 8.3 Hz, 1H, Ar–H), 8.15 (s, 1H, Ar–H), 8.26 (d, *J* = 7.9 Hz, 1H, Ar–H), 8.59 (d, *J* = 8.3 Hz, 1H, Ar–H); ^{13}C NMR: 13.60, 18.55, 36.35, 53.96, 60.16, 103.78, 116.15, 119.49, 123.75, 128.38, 128.87, 129.24, 129.37, 130.88, 131.12, 146.42, 159.10, 159.49, 165.16; Anal. calcd. for $C_{19}H_{16}N_6O_3$ (376): C, 60.63; H, 4.28; N, 22.33%. Found: C, 60.44; H, 4.35; N, 22.57%.

2-Amino-7-hydroxy-4-(tetrazolo[1,5-*a*]quinolin-4-yl)-4*H*-chromene-3-carbonitrile (12a)

Compound **12a** was prepared by using resorcinol, yield (60%); mp 285–286°C; IR (cm^{-1}): 3522 (OH), 3461, 3339 (NH_2), 2186 (CN); ^1H NMR: δ 5.26 (s, 1H, CH pyran), 6.40 (dd, *J* = 2.3, 8.5 Hz, 1H, Ar–H), 6.46 (d, *J* = 2.3 Hz, 1H, Ar–H), 6.96 (d, *J* = 8.5 Hz, 1H, Ar–H), 7.08 (s, 2H, NH_2), 7.82 (dd, *J* = 7.1, 7.5 Hz, 1H, Ar–H), 7.95 (dd, *J* = 8.4, 8.5 Hz, 1H, Ar–H), 8.23 (s, 1H, Ar–H), 8.27 (d, *J* = 7.7 Hz, 1H, Ar–H), 8.59 (d, *J* = 8.2 Hz, 1H, Ar–H), 9.76 (s, 1H, OH); ^{13}C NMR: 37.61, 52.78, 102.44, 110.66, 112.13, 116.22, 120.55, 123.75, 128.48, 129.42, 129.52, 129.57, 130.16, 131.18, 146.39, 149.44, 157.66, 161.23; Anal. calcd. for $C_{19}H_{12}N_6O_2$ (356.34): C, 64.04; H, 3.39; N, 23.58%. Found: C, 64.23; H, 3.78; N, 23.34%.

2,7-Diamino-4-(tetrazolo[1,5-*a*]quinolin-4-yl)−4*H*-chromene-3-carbonitrile (12b)

Compound **12b** was prepared by using 3-aminophenol, yield (69%); mp 262–263°C; IR (cm^{-1}): 3403, 3353 (NH_2), 2182 (CN); ^1H NMR: δ 5.17 (s, 1H, CH pyran), 5.29 (s, 2H, NH_2), 6.18 (dd, *J* = 2.1, 8.3 Hz, 1H, Ar–H), 6.25 (d, *J* = 2.1 Hz, 1H, Ar–H), 6.78 (d, *J* = 8.3 Hz, 1H, Ar–H), 7.00 (s, 2H, NH_2), 7.81 (dd, *J* = 7.5, 7.9 Hz, 1H, Ar–H), 7.94 (dd, *J* = 7.9, 8.3 Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.25 (d, *J* = 7.8 Hz, 1H, Ar–H), 8.59 (d, *J* = 8.3 Hz, 1H, Ar–H); ^{13}C NMR: 37.58, 52.86, 100.13, 106.90, 110.74, 116.16, 120.74, 123.78, 128.40, 128.92, 129.32, 129.41, 129.82, 130.08, 131.03, 146.46, 149.37, 149.41, 161.42; Anal. calcd. for $C_{19}H_{13}N_7O$ (355): C, 64.22; H, 3.69; N, 27.59%. Found: C, 64.12; H, 3.88; N, 27.45%.

2-Amino-4-(tetrazolo[1,5-*a*]quinolin-4-yl)−4*H*-benzo[h]-chromene-3-carbonitrile (13)

Compound **13** was prepared by using α-naphthol, yield (57%); mp 288–289°C; IR (cm^{-1}): 3475, 3377 (NH_2), 2187 (CN); ^1H NMR: δ 5.56 (s, 1H, CH pyran), 7.26 (d, *J* = 8.6 Hz, 1H, Ar–H), 7.36 (s, 2H, NH_2), 7.55 (d, *J* = 8.6 Hz, 1H, Ar–H), 7.58 (dd, *J* = 7.3, 7.5 Hz, 1H, Ar–H), 7.67 (dd, *J* = 7.2, 7.6 Hz, 1H, Ar–H), 7.83 (dd, *J* = 7.7, 7.8 Hz, 1H, Ar–H), 7.87 (d, *J* = 8.1 Hz, 1H, Ar–H), 7.96 (dd, *J* = 7.6, 8.4 Hz, 1H, Ar–H), 8.29 (d, *J* = 7.9 Hz, 1H, Ar–H), 8.33 (d, *J* = 8.4 Hz, 1H, Ar–H), 8.36 (s, 1H, Ar–H), 8.59 (d, *J* = 8.3 Hz, 1H, Ar–H); ^{13}C NMR: 38.51, 52.94, 114.79, 116.20, 120.34, 120.90, 122.73, 123.70, 123.75, 125.61, 126.67, 126.95, 127.67, 128.45, 128.83, 129.50, 129.59, 130.92, 131.29, 133.08, 143.52, 146.42, 161.07; Anal. calcd. for $C_{23}H_{14}N_6O$ (390): C, 70.76; H, 3.61; N, 21.53%. Found: C, 70.56; H, 3.45; N, 21.33%.

4-(Tetrazolo[1,5-*a*]quinolin-4-ylmethylene)−4*H*-pyrazole-3,5-diamine (14)

A mixture of compound **9** (2.46 g, 0.01 mol) and hydrazine hydrate (99%, 1 g, 0.02 mol) in absolute ethanol (30 ml) was heated under reflux for 20 hr. The reaction mixture was cooled to room temperature. The titled compound precipitated as green crystalline solid which was filtered and washed with ethanol. Yield (43%); mp 271–272°C; IR (cm^{-1}): 3307, 3385 (NH_2), 1566 (C=N); ^1H NMR: δ 7.49 (dd, *J* = 7.7, 7.9 Hz, 1H, Ar–H), 7.78 (dd, *J* = 8.2, 8.3 Hz, 1H, Ar–H), 7.99 (d, *J* = 8.7 Hz, 1H, Ar–H), 8.14 (d, *J* = 8.2 Hz, 1H, Ar–H), 8.44 (s, 1H, CH=C), 8.95 (s, 1H, Ar–H); ^{13}C NMR: 116.06, 121.72, 123.79, 123.83, 124.43, 128.17, 128.67, 128.74, 128.87, 129.34, 130.21, 146.26; Anal. calcd. for $C_{13}H_{10}N_8$ (278): C, 56.11; H, 3.62; N, 40.27%. Found: C, 56.23; H, 3.44; N, 40.12%.

(*E*)-5-Imino-1-phenyl-4-(tetrazolo[1,5-*a*]quinolin-4-ylmethylene)-4,5-dihydro-1*H*-pyrazol-3-amine (15)

To a mixture of compound **9** (2.46 g, 0.01 mol) in absolute ethanol (30 ml), phenylhydrazine (1.47 g, 0.015 mol) was added and the mixture was heated under reflux for 20 hr. The formed precipitate was filtered and dried to give the titled compound as a yellow solid. Yield (66%); mp 210–211°C; IR (cm^{-1}): 3260 (NH), 1556 (C=N); ^{1}H NMR: δ 6.86 (dd, *J* = 7.1, 7.3 Hz, 1H, Ar–H), 7.24 (d, *J* = 7.5 Hz, 2H, Ar–H), 7.3 (dd, *J* = 7.3, 8.4 Hz, 2H, Ar–H), 7.80 (dd, *J* = 8.1, 8.2 Hz, 1H, Ar–H), 7.91 (dd, *J* = 8.4, 8.5 Hz, 1H, Ar–H), 8.30 (d, *J* = 7.6 Hz, 1H, Ar–H), 8.41 (s, 1H, Ar–H), 8.57 (s, 1H, CH=C), 8.59 (d, *J* = 8.3 Hz, 1H), 11.10 (s, 1H, NH); ^{13}C NMR: 112.60, 116.15, 119.99, 121.10, 124.42, 125.28, 128.32, 128.58, 129.11, 129.27, 129.53, 130.58, 144.43, 146.25; Anal. calcd. for $C_{19}H_{14}N_8$ (354): C, 64.40; H, 3.98; N, 31.62%. Found: C, 64.69; H, 3.87; N, 31.33%.

4.1.6 | General procedure for synthesis of compounds 16a,b and 17a,b

A solution of tetrazolo[1,5-a]quinoline-4-carbaldehyde **(8)** (1.98 g, 0.01 mol) in DMF (10 ml) was added gradually to a solution of 4-substituted acetophenone or 1-(1-(4-substituted phenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (0.01 mol) in alcoholic KOH (2%, 25 ml). The mixture was stirred for 24 hr, then filtered, dried and crystallized from DMF.

3-(Tetrazolo[1,5-*a*]quinolin-4-yl)−1-(*p*-tolyl)prop-2-en-1-one (16a)

Yield (23%); mp > 300°C; IR (cm^{-1}): 1656 (C=O), 1586 (C=N); ^{1}H NMR: δ 2.41 (s, 3H, CH_3), 7.44 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.85 (dd, *J* = 7.6, 7.6 Hz, 1H, Ar–H), 8.01–8.04 (m, 4H), 8.22 (d, *J* = 7.9 Hz, 1H, Ar–H), 8.65 (d, *J* = 8.3 Hz, 1H, Ar–H), 8.78 (d, *J* = 16.5 Hz, 1H, CH=CH), 8.8 (s, 1H, Ar–H); Anal. calcd. for $C_{19}H_{14}N_4O$ (314): C, 72.60; H, 4.49; N, 17.82%. Found: C, 72.55; H, 4.57; N, 17.63%.

1-(4-Methoxyphenyl)−3-(tetrazolo[1,5-*a*]quinolin-4-yl)prop-2-en-1-one (16b)

Yield (19%); mp > 300°C; IR (cm^{-1}): 1659 (C=O), 1583 (C=N); ^{1}H NMR: δ 3.90 (s, 3H, OCH_3), 7.19 (d, *J* = 8.8 Hz, 2H, Ar–H), 7.87 (dd, *J* = 7.4, 7.9 Hz, 1H, Ar–H), 8.01–8.07 (m, 2H), 8.14 (d, *J* = 8.8 Hz, 2H, Ar–H), 8.25 (d, *J* = 7.8 Hz, 1H, Ar–H), 8.67 (d, *J* = 8.3 Hz, 1H, Ar–H), 8.81 (s, 1H, Ar–H), 8.82 (d, *J* = 15.5 Hz, 1H, CH=CH); ^{13}C NMR: 55.67, 114.44, 116.39, 120.76, 123.87, 127.42, 128.64, 130.03, 130.07, 130.14, 130.80, 132.57, 136.30, 136.42, 146.26, 163.57, 187.20; Anal. calcd. for $C_{19}H_{14}N_4O_2$ (330): C, 69.08; H, 4.27; N, 16.96%. Found: C, 69.23; H, 4.15; N, 16.88%.

(*E*)-1-(1-(4-Chlorophenyl)−5-methyl-1*H*−1,2,3-triazol-4-yl)-3-(tetrazolo[1,5-*a*]quinolin-4-yl)prop-2-en-1-one (17a)

Yield (25%); mp 290–291°C; IR (cm^{-1}): 1661 (C=O), 1593 (C=N); ^{1}H NMR: δ 2.65 (s, 3H, CH_3), 7.77 (s, 4H, Ar–H), 7.87 (dd, *J* = 7.6, 7.7 Hz, 1H, Ar–H), 8.05 (dd, *J* = 7.6, 7.9 Hz, 1H, Ar–H), 8.11 (d, *J* = 15.9 Hz, 1H, CH=CH), 8.27 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.67 (d, *J* = 8.3 Hz, 1H, Ar–H), 8.82 (s, 1H, Ar–H), 9.10 (d, *J* = 15.9 Hz, 1H, CH=CH); Anal. calcd. for $C_{21}H_{14}ClN_7O$ (415.8): C, 60.65; H, 3.39; N, 23.58%. Found: C, 60.48; H, 3.55; N, 23.42%.

(*E*)-1-(5-Methyl-1-(4-nitrophenyl)-1*H*−1,2,3-triazol-4-yl)-3-(tetrazolo[1,5-*a*]quinolin-4-yl)prop-2-en-1-one (17b)

Yield (20%); mp > 300°C; IR (cm^{-1}): 1663 (C=O), 1592 (C=N); ^{1}H NMR: δ 2.75 (s, 3H, CH_3), 7.91 (dd, *J* = 7.1, 7.6 Hz, 1H, Ar–H), 8.05–8.11 (m, 3H, Ar–H), 8.17 (d, *J* = 15.9 Hz, 1H, CH=CH), 8.31 (d, *J* = 7.5 Hz, 1H, Ar–H), 8.55 (d, *J* = 9.0 Hz, 2H, Ar–H), 8.71 (d, *J* = 8.3 Hz, 1H, Ar–H), 8.87 (s, 1H, Ar–H), 9.16 (d, *J* = 15.9 Hz, 1H, CH=CH); Anal. calcd. for $C_{21}H_{14}N_8O_3$ (426): C, 59.15; H, 3.31; N, 26.28%. Found: C, 59.25; H, 3.41; N, 26.35%.

4.1.7 | General procedure for synthesis of compounds 19a–f

To a solution of compound **18**[28] (2.12 g, 0.01 mol) in tetrahydrofuran (THF) (50 ml), the appropriate iso(thio)cyanate (0.012 mol) was added. The mixture was allowed to stir overnight. The formed precipitate was filtered and washed with THF, dried and crystallized from ethanol.

***N*-Phenyl-2-(tetrazolo[1,5-*a*]quinolin-4-ylmethylene)hydrazinecarboxamide (19a)**

Yield (40%); mp 246–247°C; IR (cm^{-1}): 3370 (NH), 1691 (C=O), 1570 (C=N); ^{1}H NMR: δ 7.07 (dd, *J* = 7.3, 7.3 Hz, 1H, Ar–H), 7.37 (dd, *J* = 7.6, 7.9 Hz, 2H, Ar–H), 7.70 (d, *J* = 7.7 Hz, 2H, Ar–H), 7.86 (dd, *J* = 7.4, 7.5 Hz, 1H, Ar–H), 8.00 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar–H), 8.25 (d, *J* = 7.8 Hz, 1H, Ar–H), 8.51 (s, 1H, CH=N), 8.66 (d, *J* = 8.2 Hz, 1H, Ar–H), 8.92 (s, 1H, Ar–H), 9.27 (s, 1H, NH), 11.38 (s, 1H, NH); ^{13}C NMR: 116.38, 119.60, 120.07, 122.81, 123.98, 128.55, 128.64, 129.31, 129.78, 131.65, 133.04, 138.79, 146.16, 152.76; Anal. calcd. for $C_{17}H_{13}N_7O$ (331): C, 61.62; H, 3.95; N, 29.59%. Found: C, 61.53; H, 3.88; N, 29.78%.

***N*-(3-Chlorophenyl)−2-(tetrazolo[1,5-*a*]quinolin-4-ylmethylene)-hydrazinecarboxamide (19b)**

Yield (45%); mp 252–253°C; IR (cm^{-1}): 3271 (NH), 1709 (C=O), 1587 (C=N); ^{1}H NMR: δ 7.12 (d, *J* = 9.1 Hz, 1H, Ar–H), 7.39 (dd, *J* = 8.1, 8.1 Hz, 1H, Ar–H), 7.66 (d, *J* = 8.1 Hz, 1H, Ar–H), 7.86 (dd, *J* = 7.4, 7.5 Hz, 1H, Ar–H), 7.90 (s, 1H), 8.00 (dd, *J* = 8.0, 8.1 Hz, 1H, Ar–H), 8.25 (d, *J* = 7.9 Hz, 1H, Ar–H), 8.52 (s, 1H, CH=N), 8.65 (d, *J* = 8.3 Hz, 1H, Ar–H), 8.94 (s, 1H, Ar–H), 9.41 (s, 1H, NH), 11.48 (s, 1H, NH); ^{13}C NMR: 116.37, 117.91, 118.84, 119.85, 122.37, 123.93, 128.56, 129.13, 129.82, 130.34, 131.69, 133.05, 133.39, 140.44, 146.22, 152.65; Anal. calcd. for $C_{17}H_{12}ClN_7O$ (365.7): C, 55.82; H, 3.31; N, 26.81%. Found: C, 55.77; H, 3.54; N, 26.92%.

***N*-(4-Chlorophenyl)−2-(tetrazolo[1,5-*a*]quinolin-4-ylmethylene)-hydrazinecarboxamide (19c)**

Yield (33%); mp 268–269°C; IR (cm^{-1}): 3298 (NH), 1704 (C=O), 1591 (C=N); ^{1}H NMR: δ 7.38 (d, *J* = 9.0 Hz, 2H, Ar–H), 7.71 (d, *J* = 8.9 Hz,

2H, Ar–H), 7.82 (dd, *J* = 7.8, 8.0 Hz, 1H, Ar–H), 7.96 (dd, *J* = 8.4, 8.5 Hz, 1H, Ar–H), 8.21 (d, *J* = 7.5 Hz, 1H, Ar–H), 8.48 (s, 1H, CH=N), 8.62 (d, *J* = 8.2 Hz, 1H, Ar–H), 8.89 (s, 1H, Ar–H), 9.33 (s, 1H, NH), 11.40 (s, 1H, NH); ^{13}C NMR: 116.46, 119.95, 121.22, 124.01, 126.49, 128.51, 128.65, 129.22, 129.34, 129.87, 131.80, 133.43, 137.91, 146.26, 152.81; Anal. calcd. for $C_{17}H_{12}ClN_7O$ (365.7): C, 55.82; H, 3.31; N, 26.81%. Found: C, 55.74; H, 3.54; N, 26.77%.

2-(Tetrazolo[1,5-*a*]quinolin-4-ylmethylene)-*N*-(*p*-tolyl)hydrazinecarboxamide (19d)

Yield (55%); mp 252–253°C; IR (cm^{-1}): 3264 (NH), 1689 (C=O), 1578 (C=N); ^{1}H NMR: δ 2.28 (s, 3H, CH3), 7.16 (d, *J* = 8.2 Hz, 2H, Ar–H), 7.57 (d, *J* = 8.3 Hz, 2H, Ar–H), 7.85 (dd, *J* = 7.2, 7.6 Hz, 1H, Ar–H), 7.99 (dd, *J* = 8.1, 8.2 Hz, 1H, Ar–H), 8.24 (d, *J* = 7.8 Hz, 1H, Ar–H), 8.49 (s, 1H, CH=N), 8.64 (d, *J* = 8.3 Hz, 1H, Ar–H), 8.91 (s, 1H, Ar–H), 9.16 (s, 1H, NH), 11.32 (s, 1H, NH); ^{13}C NMR: 20.40, 116.35, 119.65, 120.07, 123.97, 128.52, 129.09, 129.19, 129.74, 131.60, 131.68, 132.83, 136.23, 146.14, 152.77; Anal. calcd. for $C_{18}H_{15}N_7O$ (345): C, 62.60; H, 4.38; N, 28.39%. Found: C, 62.51; H, 4.44; N, 28.24%.

***N*-(Naphthalen-2-yl)-2-(tetrazolo[1,5-*a*]quinolin-4-ylmethylene)hydrazinecarboxamide (19e)**

Yield (40%); mp 271–272°C; IR (cm^{-1}): 3301 (NH), 1691 (C=O), 1,573 (C=N); 1H NMR: δ 7.46–7.61 (m, 2H, Ar–H), 7.71 (dd, J = 7.7, 7.9 Hz, 1H, Ar–H), 7.76 (d, J = 8.2 Hz, 1H, Ar–H), 7.85 (dd, J = 7.7, 7.8 Hz, 1H, Ar–H), 7.95–8.10 (m, 3H, Ar–H), 8.22 (d, J = 7.8 Hz, 1H, Ar–H), 8.48 (s, 1H, Ar–H), 8.61 (d, J = 8.5 Hz, 1H, Ar–H), 8.67 (d, J = 8.3 Hz, 1H, Ar–H), 8.81 (s, 1H, CH=N), 9.70 (s, 1H, Ar–H), 11.53 (s, 1H, NH);^{13C} NMR: 116.38, 117.42, 118.60, 120.39, 121.94, 123.94, 124.10, 125.74, 125.92, 126.13, 126.25, 128.33, 128.52, 129.70, 131.22, 131.76, 133.58, 133.71, 134.11, 145.66, 153.31; Anal. calcd. for $C_{21}H_{15}N_7O$ (381): C, 66.13; H, 3.96; N, 25.71%. Found: C, 66.27; H, 3.87; N, 25.54%.

***N*-(4-Nitrophenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-ylmethylene)-hydrazinecarbothioamide (19f)**

Yield (44%); mp 269–260°C; IR (cm^{-1}): 3238 (NH), 1599 (C=C), 1556 (C=N); ^{1}H NMR: δ 7.85 (dd, *J* = 7.6, 7.8 Hz, 1H, Ar–H), 8.00 (dd, *J* = 7.6, 7.8 Hz, 1H, Ar–H), 8.17 (d, *J* = 9.1 Hz, 2H, Ar–H), 8.23 (d, *J* = 7.9 Hz, 1H, Ar–H), 8.31 (d, *J* = 9.1 Hz, 2H, Ar–H), 8.64 (d, *J* = 8.3 Hz, 1H, Ar–H), 8.71 (s, 1H, CH=N), 8.98 (s, 1H, Ar–H), 10.78 (s, 1H, NH); ^{13}C NMR: 116.45, 119.53, 123.80, 124.13, 128.66, 129.99, 130.07, 130.63, 132.14, 135.96, 143.66, 145.04, 146.20, 175.61; Anal. calcd. for $C_{17}H_{12}N_8O_2S$ (392): C, 52.03; H, 3.08; N, 28.56%. Found: C, 52.20; H, 3.19; N, 28.47%.

4.2 | Biology

4.2.1 | Preliminary in vitro cytotoxic screening

The human tumor cell lines of the cancer screening panel were grown in supplemented RPMI 1640 medium which contains 2 mM L-glutamine and 5% fetal bovine serum. For a typical screening test, cells were inoculated into 96-well microtiter plates in 100 µl. The plating densities ranging from 5000 to 40,000 cells/well depending on the replication time of individual cell lines. After cell inoculation, the microtiter plates were incubated at 37°C, 95% air, 5% CO_2, and 100% relative humidity for 24 hr before addition of experimental compound. Two plates of each cell line were fixed in situ with trichloroacetic acid, to signify a measurement of the cell population for each cell line at the time of compound addition (Tz).

The experimental compounds were dissolved in DMSO at 400-fold the desired final maximum test concentration and put away frozen before utilization. At the time of compound addition, an aliquot of frozen concentrate was defrosted and diluted to double the wanted final maximum test concentration with total medium containing 50 mg/ml gentamicin extra four, 10-fold, or 1/2log serial dilutions were made to afford a total of five drug concentrations in addition to control. Aliquots of 100 µl of these distinctive compound dilutions were added to the proper microtiter wells already containing 100 µl of medium, bringing about the required final drug concentrations. More details of this evaluation technique and the integral data which is encoded by the activity pattern for all cell lines were reported elsewhere.[36]

4.2.2 | In vitro cytotoxic screening against normal cell lines (MTT [3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide] assay)[37]

Cell lines and reagents: The skin fibroblast cell line (BJ) and the breast epithelial cell line (MCF-10F) were obtained from The American Type Culture Collection. RPMI-1640 medium, staurosporine, MTT, and DMSO (Sigma-Aldrich, St. Louis, MO), fetal bovine serum (Gibco, UK).

The assay depends on the ability of mitochondrial dehydrogenases in viable cell to cleave the tetrazolium ring of MTT (yellow color) yielding purple formazan crystals which are dissolved in acidified isopropanol where the resulting purple solution is spectrophotometrically measured. An increase or decrease in cell number results in a simultaneous change in the amount of formazan created, demonstrating the degree of cytotoxicity caused by the test compound. Cells were cultured in fresh growth medium and incubated at 37°C for 24 hr. After that, cells were treated with (0.39, 1.56, 6.25, 25, and 100 µg/ml) concentrations of the tested compound and incubated for 24 hr. MTT solution was then added in an amount equivalent to 10% of the culture medium volume and incubated for further 4 hr; after which the resulting formazan crystals were dissolved by adding an amount of acidified isopropanol equal to the original culture medium volume. The absorbance was measured spectrophotometrically at a wavelength of 570 nm using ROBONIK TM P2000 Eliza plate reader, Robonik India Pvt. Ltd, Maharashtra.

4.2.3 | Enzyme inhibition assay

Topo 1 in vitro enzyme assay

The inhibitory activities of compounds **13** and camptothecin toward Topo 1 enzyme were evaluated using enzyme-linked immunosorbent assay (ELISA) technique with purified human DNA Topo 1 ELISA kit.

TABLE 5 In silico physicochemical properties of compound **13** in comparison to camptothecin

Compounds	Log *P*	MW	n-HBA	n-HBD	n-RB	TPSA	Log S	Lipiniski's violation
13	3.65	390.41	7	1	1	170.15	−3.79	0
Camptothecin	2.08	348.36	6	1	1	148.23	−3.01	0

Note. Log *P*: Compound's hydrophobicity; MW: molecular weight; n-HBA: number of hydrogen bond acceptors; n-HBD: number of hydrogen bond donors; n-RB: number of rotatable bonds; TPSA: topological polar surface area; Log S: solubility parameter.

Ninety-six-well plates were precoated by antibody specific to Topo 1 enzyme. One hundred microliter of standards or test sample were added to the appropriate wells and incubated for 2 hr at 37°C. One hundred microlite of biotin-conjugated antibody was added to each well and incubated for 1 hr at 37°C. Avidin conjugated to horseradish peroxidase (HRP-avidin) (100 μl) was added and the wells were incubated for 1 hr at 37°C. 3,3′,5,5′-Tetramethylbenzidine (TMB) substrate solution (90 μl) was added to the wells and they were incubated for 15−30 minutes at 37°C. Enzyme-substrate reaction was terminated by addition of stop solution (50 μl) to each well and the color change was measured by the determination the optical density of each well using a microplate reader set to wavelength 450 nm. The concentration of Topo 1 was then determined by using standard curve.

EGFR-TK and VEGFR2 in vitro enzyme assay

Ninety-six-well plates were precoated with substrate peptide (poly (Glu:Tyr 4:1) solution in case of EGFR-TK inhibition assay and biotin-gastrin precursor (Tyr87) peptide for VEGFR2 inhibition assay). The enzyme was transferred from −80°C and allowed to thaw on ice. The enzyme reaction was conducted in kinase assay buffer (240 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid pH 7.5, 20 mM $MgCl_2$, 20 mM $MnCl_2$, 12 μM Na_3VO_4). The prediluted test sample (10 μl) and diluted solution of purified enzyme (20 μl) were added to each reaction well. Adenosine-5′-triphosphate disodium salt solution (50 μl, 5 mmol/l) was added to initiate the reaction, incubated at 37°C for 1 hr, and then the plates were washed with phosphate-buffered saline (PBS) three times. Prediluted monoclonal phosphotyrosine antibody in PBS (100 μl) were added to each well. After incubation for another 1 hr at 37°C, the wells were washed with PBS three times. The reaction was visualized by the addition of TMB. After incubation at room temperature for 15 minutes, the reaction was terminated by adding the stop solution and read spectrophotometrically at 450 nm. The enzyme concentration was then determined by using standard curve.

4.3 | Docking study

Molecular docking study of compound **13** was performed using the docking suite of MOE (Molecular Operating Environment, version 2014.09, Chemical Computing Group Inc., St. W. Montreal, Canada). Compound **13** was docked into the crystallographic structure of Topo 1 in complex with camptothecin obtained from the Protein Data Bank (PDB ID: 1T8I).[34] The new compound **13** was built and optimized at the ChemDraw professional 2016 then docked and analyzed by MOE software to identify ligand–receptor interactions and to predict its binding affinity and binding mode with the active site.

4.4 | In silico prediction of physicochemical properties

Theoretical prediction of physicochemical properties for both compound **13** and the reference drug camptothecin was performed, using pkCSM online software.[38] Results in Table 5 revealed that compound **13** complies with Lipinski's rule of five with no violations, suggesting that it has drug-likeness compared with camptothecin, and hence it would be a promising candidate as a lead structure for future design of new anticancer agents.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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