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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

One-pot synthesis and cytotoxic evaluation of amide-linked 1,4-disubstituted 1,2,3-bistriazoles

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Abstract A series of amide-linked 1,4-disubstituted 1,2,3-bistriazoles have been synthesized employing copper(I)-catalyzed azide–alkyne cycloaddition reaction. All the newly synthesized compounds were screened for in vitro cytotoxicity against a panel of five human cancer cell lines; Fibrosarcoma (HT-1080), Colon (colo205, HCT-116), and Lung (A549, NCIH322). Some of the bistriazoles exhibited moderate to good activity. Compounds **3n** and **3o** were found to be the more active and displayed broad spectrum activity against all the cancer cell lines under investigation. Further, to study the binding modes for the two more potent compounds **3n** and **3o** against Human topoisomerase II, docking simulations have been carried out.

Keywords 1,2,3-Bistriazoles · Click chemistry · Cytotoxic activity · Docking simulation

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Introduction

1,2,3-Triazoles have received considerable attention in recent years because of their numerous applications in pharmaceutical, chemical, biological (Thirumurugan *et al.*, 2013), and material sciences (Nandivada *et al.*, 2007; Lutz, 2007). The 1,2,3-triazole derivatives have been reported to possess promising biological activities including antiprotozoal (Bakunov *et al.*, 2010), anti-HIV (Velazquez *et al.*, 1998; Whiting *et al.*, 2006), antimicrobial (Genin *et al.*, 2000; Abdel-Wahab *et al.*, 2012), antiallergic (Buckle *et al.*, 1986), and antitubercular activity (Gupte *et al.*, 2008; Shanmugavelan *et al.*, 2011). Moreover, some of the 1,4-disubstituted 1,2,3-triazoles have also shown significant anticancer activity against a variety of human cancer cell lines (Vantikommu *et al.*, 2010; Singh *et al.*, 2012). Recently, the copper(I)-catalyzed azide–alkyne cycloaddition has become an efficient tool for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles in excellent yields (Tornoe *et al.*, 2002; Rostovtsev *et al.*, 2002). This metal-catalyzed reaction discovered independently by Meldal and Sharpless led to substantial improvement of Huisgen thermal 1,3-dipolar cycloaddition, which affords a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazoles (Huisgen, 1984). Exclusive regioselectivity, wide substrate scope, mild reaction conditions, and high efficiency have made it as one of the most powerful click reactions (Kolb *et al.*, 2001). However, to improve the utility and user-friendliness of this methodology multicomponent one-pot variant have also been developed (Odlo *et al.*, 2007; Kumar *et al.*, 2011). Therefore, on the basis of these observations and in continuation of our interest toward synthesis of biologically important 1,2,3-triazoles (Lal et al., 2012), we report herein, one-pot synthesis of a series of amide-linked 1,4-disubstituted 1,2,3-bistriazoles through click chemistry

and their cytotoxic evaluation against five human cancer cell lines.

Results and discussion

Chemistry

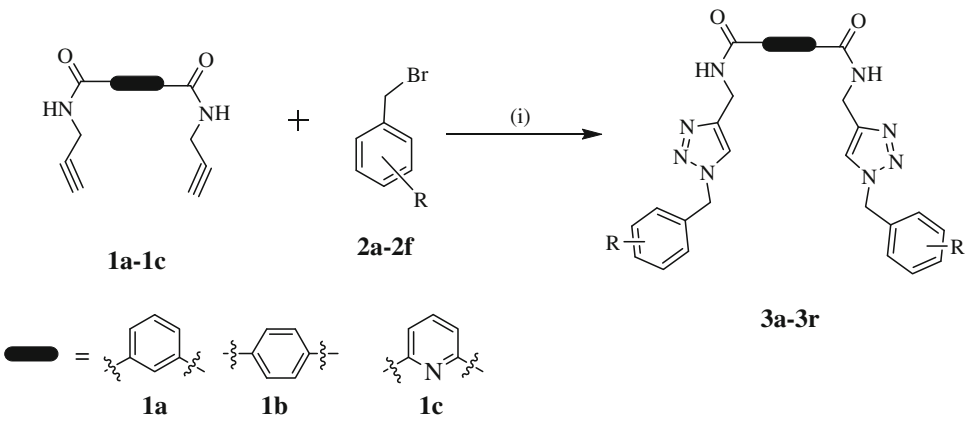
Bisalkynes (**1a–1c**) and benzyl bromides (**2a–2f**) were selected as the required building blocks for synthesis. Isophthaloyl chloride, terphthaloyl chloride, and pyridine-2,6-dicarbonyl dichloride were treated with propargyl amine to prepare the desired bisalkynes (**1a–1c**) using reported procedure (Haridas *et al.*, 2011). The title compounds (**3a–3r**) were synthesized regioselectively via three component reaction of bisalkynes, benzyl bromides, sodium azide in presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in DMF: water mixture at ambient temperature (Scheme 1). The reactions involve in situ formation of organic azides from corresponding benzyl bromides and avoid isolation of potentially unstable organic azides.

All the synthesized triazoles were well characterized by analytical and spectral techniques. The IR spectra of all the compounds displayed a characteristic absorption band about 3138–3129 cm^{-1} due to =C–H stretching of triazole ring. The ^1H NMR spectra exhibited a characteristic singlet due to two triazolyl protons at about δ 8.0 ppm. Two singlets each corresponding to four methylene protons in the aliphatic region were also observed in ^1H NMR spectra of all the compounds. In ^{13}C NMR spectra, signals in the region at δ 163.5–166.5 ppm and δ 122.2–124.1 ppm were observed, which can easily be assigned to the carbonyl carbon atom and C-5 of the triazole moiety, respectively. The HRMS spectral data of all the compounds were found to be in good agreement with their molecular formula.

Biological activity

All the newly synthesized compounds were evaluated for in vitro cytotoxicity against a panel of five human cancer cell lines viz. Fibrosarcoma (HT-1080), Colon (colo205, HCT-116), and Lung (A549, NCIH322). The percentage inhibition of cell proliferation of the synthesized compounds was tested at three different concentrations, i.e., 20, 30, and 50 μM using SRB method (Houghton *et al.*, 2007) and presented in Table 1. Paclitaxel and 5-fluorouracil were used as standard.

As evident from the anticancer activity results that most of the compounds exhibited moderate activity. The results clearly indicate concentration dependent cytotoxicity, as there is increase in growth inhibition with increase in concentration of tested compounds from 20 to 50 μM (Table 1). In case of analogues derived from isophthaloyl bisalkyne, **3a–3c** with methyl substituent on benzene rings showed better cytotoxicity compared to their nitro counterparts (**3d–3f**). Compound **3a** having 2-methyl on benzene rings inhibited the cell proliferation of colo-205 and HCT-116 by 65 and 58 %, respectively, at 50 μM



Scheme 1 Synthesis of 1,4-disubstituted 1,2,3-bistriazoles. (i) NaN_3, sodium ascorbate, $CuSO_4{\cdot}5H_2O$, DMF/H_2O (9:1), 6–12 h

	—	R		—	R		—	R
3a	1,3-C_6H_4	2-CH_3	**3g**	1,4-C_6H_4	2-CH_3	**3m**	2,6-C_5H_3N	2-CH_3
3b	1,3-C_6H_4	3-CH_3	**3h**	1,4-C_6H_4	3-CH_3	**3n**	2,6-C_5H_3N	3-CH_3
3c	1,3-C_6H_4	4-CH_3	**3i**	1,4-C_6H_4	4-CH_3	**3o**	2,6-C_5H_3N	4-CH_3
3d	1,3-C_6H_4	2-NO_2	**3j**	1,4-C_6H_4	2-NO_2	**3p**	2,6-C_5H_3N	2-NO_2
3e	1,3-C_6H_4	3-NO_2	**3k**	1,4-C_6H_4	3-NO_2	**3q**	2,6-C_5H_3N	3-NO_2
3f	1,3-C_6H_4	4-NO_2	**3l**	1,4-C_6H_4	4-NO_2	**3r**	2,6-C_5H_3N	4-NO_2

Table 1 In vitro cytotoxic evaluation of 1,4-disubstituted 1,2,3-bistriazoles (**3a–3r**)

Tissue type			Fibrosarcoma	Colon		Lung	
Cell type			HT-1080	Colo-205	HCT-116	A549	NCIH322
Entry	Compounds	Conc (μM)	% Age growth inhibition				
1	**3a**	20	21	11	16	8	12
		30	32	52	35	17	14
		50	40	65	58	27	26
2	**3b**	20	4	10	15	6	1
		30	10	32	33	21	3
		50	11	47	48	33	12
3	**3c**	20	2	3	17	11	1
		30	17	11	23	13	3
		50	22	20	40	22	5
4	**3d**	20	2	12	1	10	10
		30	5	39	3	22	15
		50	10	42	13	27	25
5	**3e**	20	13	10	1	23	5
		30	22	12	1	20	8
		50	30	14	4	27	9
6	**3f**	20	9	8	31	3	3
		30	11	14	37	6	4
		50	21	16	40	10	7
7	**3g**	20	2	3	10	5	9
		30	17	3	15	10	10
		50	23	8	25	16	14
8	**3h**	20	2	3	7	11	1
		30	7	1	13	13	13
		50	12	10	20	22	25
9	**3i**	20	2	2	1	1	4
		30	15	9	3	2	15
		50	20	22	3	7	25
10	**3j**	20	12	3	1	1	1
		30	27	6	3	3	13
		50	32	20	10	22	15
11	**3k**	20	6	6	20	16	8
		30	17	20	34	32	11
		50	24	75	40	58	20
12	**3l**	20	4	9	4	1	11
		30	6	10	21	3	15
		50	10	29	22	8	30
13	**3m**	20	10	10	4	5	9
		30	22	12	11	10	10
		50	35	19	43	12	15
14	**3n**	20	20	28	30	30	38
		30	34	56	65	40	62
		50	62	68	82	55	80
15	**3o**	20	34	22	37	23	16
		30	58	50	64	40	25
		50	65	68	78	62	70

Table 1 continued

Tissue type			Fibrosarcoma	Colon		Lung	
Cell type			HT-1080	Colo-205	HCT-116	A549	NCIH322
Entry	Compounds	Conc (μM)	% Age growth inhibition				
16	**3p**	20	3	11	12	3	21
		30	5	26	14	21	25
		50	7	38	20	35	31
17	**3q**	20	2	10	1	5	9
		30	2	12	1	10	10
		50	5	39	3	22	15
18	**3r**	20	20	10	5	5	9
		30	22	12	11	10	10
		50	25	39	13	22	15
19	5-Fluorouracil	20	–	70	58	90	72
20	Paclitaxil	1	–	92	73	84	56

Table 2 IC_{50} value of hit 1,4-disubstituted 1,2,3-bistriazoles

Tissue type		Fibrosarcoma	Colon		Lung	
Cell type		HT-1080	Colo-205	HCT-116	A549	NCIH322
Entry	Compounds	IC_{50} value (μM)				
1	**3a**	>50	28	42	>50	>50
2	**3k**	>50	41	>50	44	>50
3	**3n**	42	26	24	42	24
4	**3o**	26	30	24	38	42

concentration. Moreover, it was also found to be active against colo-205 at 30 μM concentration.

While in case of terphthaloyl-derived bistriazoles, nitro-containing analogues (**3j–3l**) are more effective than methyl substituted (**3g–3i**) against most of the cell lines under study at 50 μM concentration. Compound **3k** with 3-nitro substitution, inhibited the cell proliferation of colo-205 and A-549 by 75 and 58 %, respectively, at 50 μM concentration. Among the pyridyl-derived bistriazoles, **3n** and **3o** displayed good activity against all the five cell lines. Compound **3n** inhibited the cell proliferation of colon (HCT-116) and lung (NCIH322) cell lines by 82 and 80 %, respectively, at 50 μM concentrations. It was also found to be active against colon cell lines and NCIH-322 even at 30 μM concentration. Likewise, **3o** showed 78 % inhibition of cell proliferation against HCT-116 and was active against both the colon cell lines and HT-1080 at 30 μM concentration.

It can be inferred from the cytotoxic evaluation data that out of the eighteen tested compounds **3a**, **3k**, **3n**, and **3o** exhibited comparatively good activity. Based on these observations, the IC_{50} values (Table 2) for the hit compounds (**3a**, **3k**, **3n**, and **3o**) exhibiting more than 50 % inhibition of cell proliferation have been determined. Further, compounds **3n** and **3o** derived from pyridyl bisalkyne with 3- and 4-methyl substituent, exhibited highest and broad spectrum activity against all the cell lines under study with IC_{50} values ranging from 24 to 42 μM.

Docking studies

In an effort to investigate the plausible mode of action for cytotoxic activity and to predict orientation of the molecules at the active site, docking simulations were performed using AutoDock Vina program (Trott and Olson 2010). Two more active compounds **3n** and **3o** were docked into the crystal structure of Human Type IIA DNA Topoisomerase complexed with the ligand Phosphoaminophosphonic acid-adenylate ester (1ZXM). Human Type IIA DNA Topoisomerase was chosen for docking because it is a good target for cytotoxic activities of many heterocyclic compounds (Walker and Nitiss 2002). The docked conformations of compounds **3n**, and **3o** into the active sites of 1ZXM are illustrated in Figs. 1, 2, 3, and 4.

It can be clearly seen from docking snapshots, that both molecules show hydrogen bonding interactions with Asn 150. Beside this, compounds **3n** and **3o** are also engaged in hydrogen bonding with Lys 157, Ser 148, Ser 149, and Arg 98. In compound **3n**, one phenyl ring is involved in σ-cation interactions with Pro 126, Asn 95, and Lys 157, while other phenyl ring exhibits σ–π interactions with Ser 149 residue. All the above discussed residues are involved in hydrogen bonding interactions with co-crystallized ligand also. Therefore, it can be said that the compounds under study inhibits human DNA topoisomerase successfully.

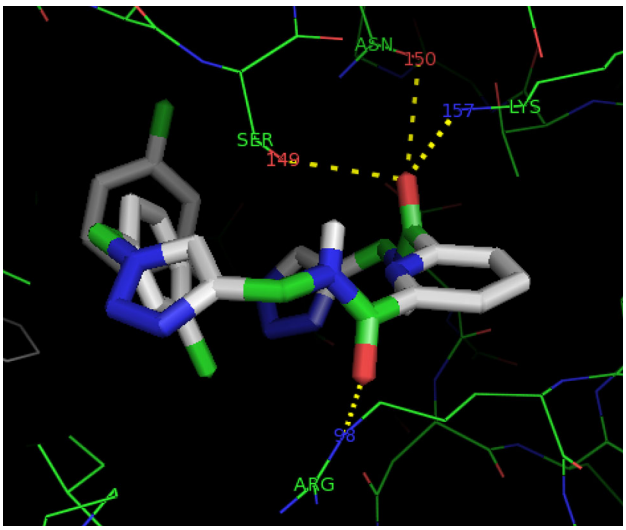


Fig. 1 Docked pose of compound **3n** showing H-bonding interactions with human topoisomerase II

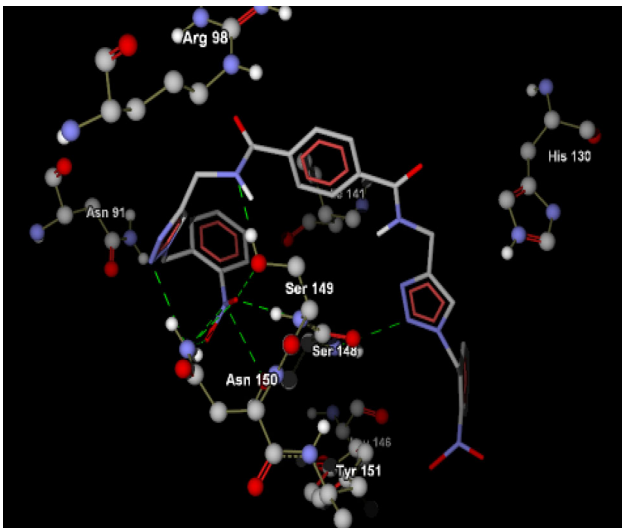


Fig. 3 Docked pose of compound **3o** showing H-bonding interactions with human topoisomerase II

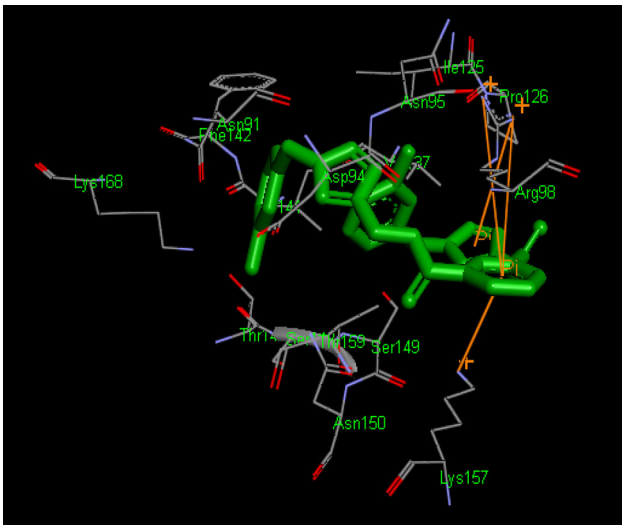


Fig. 2 Docked pose showing Sigma-pi and pi-cation interaction of compound **3n** with human topoisomerase II

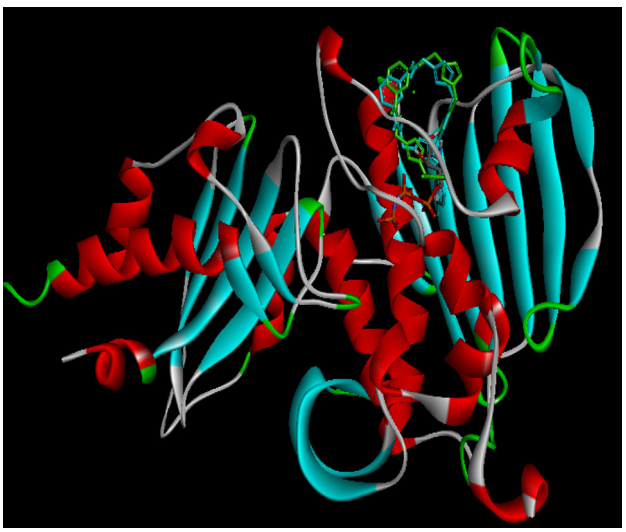


Fig. 4 Secondary structure view of docked molecules (**3n** and **3o**) along with co-crystallized ligand

Conclusion

In conclusion, a new series of amide-linked 1,4-disubstituted 1,2,3-bistriazoles have been synthesized in good yields utilizing one-pot click reaction and evaluated for cytotoxic activity. Compounds **3n** and **3o** were found to be more active and showed good activity against all the five cancer cell lines under study. Further, docking studies showed that compounds **3n** and **3o** inhibit Human Type IIA DNA Topoisomerase through hydrogen bonding and pi-cation interactions. The studied bistriazoles can be exploited toward designing of novel molecules for better cytotoxic activity.

Experimental

Chemistry

All melting points (°C) were recorded in open capillaries and are uncorrected. The IR spectra were recorded on SHIMAZDU IR AFFINITY-I FTIR spectrophotometer using potassium bromide (KBr) and values are presented in cm^{-1}. The ^{1}H NMR spectra were observed on Bruker Avance II 400/Bruker 300 MHz spectrophotometer and ^{13}C NMR at 100 and 75 MHz, in deuterated DMSO (DMSO-d_6) using tetramethysilane (TMS) as an internal standard (chemical shift in δ, ppm). Coupling constant

(*J*) values are given in Hertz (Hz). High-resolution mass spectra (HRMS) were observed on LCMS-QTOF Module No. G6540 A (UHD) instrument. The completion of all the reactions was examined by thin-layer chromatography (TLC) using readymade silica gel plates (SIL G/UV254, ALUGRAM) and visualized under Ultraviolet lamp. Starting materials were purchased from Aldrich and were used as such without further purification.

*General method for the preparation of 1,2,3-triazoles (**3a–3r**)*

To a stirred solution of substituted benzyl bromide (1 mmol), sodium azide (2.5 mmol), and bisalkynes (0.5 mmol) in DMF/water (9:1) was added copper sulfate (5 mol%) and sodium ascorbate (10 mol%). The reaction mixture was stirred at ambient temperature for 6–12 h and the progress was monitored by TLC. Upon completion of the reaction ice–cold water (30 ml) was added to the reaction mixture, precipitates were collected by filtration and washed with aqueous ammonia solution followed by water. To remove traces of reactant, precipitates were further washed with ethyl acetate and dried under vacuum to afford pure product.

*N^1,N^3-bis((1-(2-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)isophthalamide (**3a**)*

Yield: 77 %; White solid; mp: 162–164 °C. IR (KBr): 3314 (N–H str), 3134 (=C–H str triazole), 3067, 2957, 1653, 1576, 1545, 1287, 1051, cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.20 (s, 6H, CH_3), 4.52 (s, 4H, $NHCH_2$), 5.52 (s, 4H, NCH_2), 7.14–7.25 (m, 8H, Ar–H), 7.56 (brs, 1H, Ar–H), 7.98–8.02 (m, 4H, Ar–H + triazole), 8.35 (s, 1H, Ar–H), 9.11 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.1 (CH_3), 35.0 ($NHCH_2$), 52.9 (NCH_2), 123.2 (C-5 triazole), 125.3 (C-2), 126.6 (C-4′), 128.6 (C-5′), 128.7 (C-6′), 128.8 (C-5), 128.9 (C-3′), 130.1 (C-4, C-6), 134.4 (C-1, C-3), 136.1 (C-2′), 138.1(C-1′), 145.3 (C-4 triazole), 165.9 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{30}H_{30}N_8O_2$: 534.2492, found: 535.2562 $(M+H)^+$.

*N^1,N^3-bis((1-(3-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)isophthalamide (**3b**)*

Yield: 74 %; White solid; mp: 126–128 °C; IR (KBr): 3310 (N–H str), 3143 (=C–H str triazole), 3061, 2949, 1657, 1530, 1462, 1273, 1049 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.37 (s, 6H, CH_3), 4.58 (s, 4H, $NHCH_2$), 5.52 (s, 4H, NCH_2), 7.04–7.34 (m, 8H, Ar–H), 7.56 (s, 1H), 7.99–8.05 (m, 4H, Ar–H + triazole), 8.35 (s, 1H, Ar–H), 9.06 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.3 (CH_3), 35.4 ($NHCH_2$), 53.1 (NCH_2), 123.3 (C-5 triazole), 125.4 (C-6′), 126.8 (C-2), 128.9 (C-4′), 129.0 (C-5, C-2′, C-5′), 130.3 (C-4, C-6), 134.6 (C-1, C-3), 136.3 (C-1′), 138.2 (C-3′), 145.6 (C-4 triazole), 166.1 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{30}H_{30}N_8O_2$: 534.2492, found: 535.2567 $(M+H)^+$.

*N^1,N^3-bis((1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)isophthalamide (**3c**)*

White solid; Yield: 72 %; mp: 168–170 °C; IR (KBr): 3315 (N–H str), 3130 (=C–H str triazole), 3074, 1655, 1539, 1290, 1053 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 6H, CH_3), 4.09 (s, 4H, $NHCH_2$), 4.65 (s, 4H, NCH_2), 7.11–7.24 (m, 8H, Ar–H), 7.58 (brs, 1H, Ar–H), 7.95–8.00 (m, 4H, Ar–H + triazole), 8.37 (s, 1H, Ar–H), 9.11 (d, 2H, $J = 6.0$ Hz, NH, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.2 (CH_3), 35.5 ($NHCH_2$), 53.2 (NCH_2), 123.5 (C-5 triazole), 125.5 (C-2), 126.7 (C-2′, C-6′), 128.8 (C-3′, C-5′), 129.2 (C-5), 130.5 (C-4, C-6), 134.7 (C-1, C-3), 136.2 (C-1′), 138.4 (C-4′), 145.7 (C-4 triazole), 166.3 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{30}H_{30}N_8O_2$: 534.2492, found: 535.2577 $(M+H)^+$.

*N^1,N^3-bis((1-(2-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)isophthalamide (**3d**)*

Yield = 84 %; Yield = 84 %; Yellowish solid; mp: 178–180 °C; IR (KBr): 3320 (N–H str), 3130 (=C–H str triazole), 3075, 1647, 1516, 1348, 1265, 1057 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 4.56 (s, 4H, $NHCH_2$), 5.94 (s, 4H, NCH_2), 7.03 (d, 2H, $J = 7.5$ Hz, Ar–H), 7.54–7.65 (m, 3H, Ar–H), 7.73 (t, 2H, $J = 7.2$ Hz, Ar–H), 7.99 (d, 2H, $J = 7.5$ Hz, Ar–H), 8.07 (s, 2H, triazole), 8.13 (d, 2H, $J = 8.1$ Hz, Ar–H), 8.36 (s, 1H, Ar–H), 9.15 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.2 ($NHCH_2$), 52.3 (NCH_2), 124.1 (C-5 triazole), 124.5 (C-3′), 126.9 (C-2), 128.7 (C-4′, C-5), 130.5 (C-4, C-6, C-1′), 134.8 (C-1, C-3, C-6′), 143.9 (C-4 triazole), 145.6 (C-5′), 147.4 (C-2′), 166.5 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{28}H_{24}N_{10}O_6$: 596.1880, found: 597.1964 $(M+H)^+$.

*N^1,N^3-bis((1-(3-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)isophthalamide (**3e**)*

Yield : 84 %; Pale yellowish solid; mp: 160–161 °C; IR (KBr): 3335 (N–H str), 3132 (=C–H str triazole), 3070, 1665, 1520, 1340, 1285, 1051 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 4.54 (s, 4H, $NHCH_2$), 5.75 (s, 4H, NCH_2), 7.55 (t, 1H, $J = 7.8$ Hz, Ar–H), 7.65–7.78 (m, 4H, Ar–H), 7.98 (d, 2H, $J = 7.2$ Hz, Ar–H), 8.08 (s, 2H, triazole), 8.15–8.23 (m, 4H, Ar–H), 8.36 (s, 1H, Ar–H), 9.13 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (75 MHz,

DMSO-d_6): δ 35.3 ($NHCH_2$), 52.4 (NCH_2), 124.0 (C-5 triazole), 124.6 (C-4′), 127.2 (C-2), 128.8 (C-2′), 129.6 (C-5, C-5′), 130.3 (C-4, C-6), 134.9 (C-1, C-3, C-6′), 144.2 (C-4 triazole), 145.8 (C-1′), 147.6 (C-3′), 166.3 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{28}H_{24}N_{10}O_6$: 596.1880, found: 597.1972 $(M+H)^+$.

*N^1,N^3-bis((1-(4-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)isophthalamide (**3f**)*

Yield: 90 %; Pale yellowish solid; mp: 208–211 °C; IR (KBr): 3334 (N–H str), 3132 (=C–H str triazole), 3075, 1665, 1520, 1346, 1285, 1051 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 4.54 (s, 4H, $NHCH_2$), 5.76 (s, 4H, NCH_2), 7.52–7.58 (m, 5H, Ar–H), 7.99 (d, 2H, $J = 7.5$ Hz, Ar–H), 8.13 (s, 2H, triazole), 8.22 (d, 4H, $J = 8.1$ Hz, Ar–H), 8.36 (s, 1H, Ar–H), 9.14 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.4 ($NHCH_2$), 52.3 (NCH_2), 124.1 (C-5 triazole), 124.6 (C-3′, C-5′), 127.0 (C-2), 128.9 (C-2′, C-6′), 129.5 (C-5), 130.4 (C-4, C-6), 134.7 (C-1, C-3), 144.0 (C-4 triazole), 145.9 (C-1′), 147.7 (C-4′), 166.2 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{28}H_{24}N_{10}O_6$: 596.1880, found: 597.1959 $(M+H)^+$.

*N^1,N^4-bis((1-(2-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)terephthalamide (**3g**)*

White solid; Yield: 77 %; mp: 231–233 °C; IR (KBr): 3321 (N–H str), 3132 (=C–H str triazole), 3068, 2943, 1639, 1545, 1049 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 6H, CH_3), 4.50 (s, 4H, $NHCH_2$), 5.51 (s, 4H, NCH_2), 7.09–7.13 (m, 6H, Ar–H), 7.22–7.26 (m, 2H, Ar–H), 7.94 (brs, 4H, Ar–H), 8.0 (s, 2H, triazole), 9.23 (d, 2H, $J = 5.2$ Hz, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.9 (CH_3), 35.0 ($NHCH_2$), 53.3 (NCH_2), 122.4 (C-5 triazole), 124.7 (C-4′), 127.0 (C-2, C-3, C-5, C-6), 128.4 (C-5′), 128.7 (C-6′), 134.7 (C-3′), 136.3 (C-2′), 138.0 (C-1, C-4, C-1′), 145.1 (C-4 triazole), 165.9 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{30}H_{30}N_8O_2$: 534.2492, found: 535.2557 $(M+H)^+$.

*N^1,N^4-bis((1-(3-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)terephthalamide (**3h**)*

Yield: 80 %; White solid; mp: 189–190 °C; IR (KBr): 3332 (N–H str), 3138 (=C–H str triazole), 3066, 2941, 1641, 1541, 1292, 1049 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 6H, CH_3), 4.65 (s, 4H, $NHCH_2$), 5.47 (s, 4H, NCH_2), 7.07–7.14 (m, 4H, Ar–H), 7.21–7.25 (m, 2H, Ar–H), 7.75–7.82 (m, 2H, Ar–H), 7.93–7.94 (m, 6H, Ar–H + triazole), 8.91 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.6 (CH_3), 35.2 ($NHCH_2$), 53.4 (NCH_2), 122.5 (C-5 triazole), 124.4 (C-6′), 127.2 (C-2, C-3, C-5, C-6), 128.5 (C-4′), 128.3 (C-5′), 128.8 (C-2′), 136.5 (C-1, C-4, C-1′), 138.2 (C-3′), 145.2 (C-4 triazole), 166.1 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{30}H_{30}N_8O_2$: 534.2492, found: 535.2563 $(M+H)^+$.

*N^1,N^4-bis((1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)terephthalamide (**3i**)*

Yield: 78 %; White solid; mp: 240–242 °C; IR (KBr): 3352 (N–H str), 3134 (=C–H str triazole), 3066, 1636, 1543, 1288, 1053 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 6H, CH_3), 4.62 (s, 4H, $NHCH_2$), 5.47 (s, 4H, NCH_2), 7.07–7.14 (m, 4H, Ar–H), 7.21–7.25 (m, 4H, Ar–H), 7.75–8.02 (m, 6H, Ar–H + triazole), 9.12 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.8 (CH_3), 35.3 ($NHCH_2$), 53.3 (NCH_2), 122.4 (C-5 triazole), 127.3 (C-2, C-3, C-5, C-6), 128.7 (C-2′, C-6′), 130.2 (C-3′, C-5′), 134.5 (C-1′), 136.6 (C-4′), 138.5 (C-1, C-4), 145.3 (C-4 triazole), 166.3 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{30}H_{30}N_8O_2$: 534.2492, found: 535.2551 $(M+H)^+$.

*N^1,N^4-bis((1-(2-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)terephthalamide (**3j**)*

Yield: 87 %; Pale yellowish solid; mp: 153–155 °C; IR (KBr): 3336 (N–H str), 3147 (=C–H str triazole), 3074, 1636, 1533, 1346, 1294, 1051 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 4.49 (s, 4H, $NHCH_2$), 5.51 (s, 4H, NCH_2), 7.59–7.63 (m, 4H, Ar–H), 7.71–8.72 (m, 2H, Ar–H), 7.96 (s, 4H, Ar–H) 8.02 (s, 2H, triazole), 8.18–8.26 (m, 2H, Ar–H), 9.03 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.4 ($NHCH_2$), 52.3 (NCH_2), 124.1 (C-5 triazole), 124.4 (C-3′), 127.0 (C-4′), 128.9 (C-2, C-3, C-5, C-6, C-6′), 129.5 (C-1′), 130.4 (C-5′), 134.7 (C-1, C-4), 144.0 (C-4 triazole), 147.7 (C-2′), 166.2 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{28}H_{24}N_{10}O_6$: 596.1880, found: 597.1961 $(M+H)^+$.

*N^1,N^4-bis((1-(3-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)terephthalamide (**3k**)*

Yield: 85 %; Pale yellowish solid; mp: 242–244 °C; IR (KBr): 3343 (N–H str), 3134 (=C–H str triazole), 3066, 1639, 1539, 1333, 1242, 1049 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 4.59 (s, 4H, $NHCH_2$), 5.71 (s, 4H, NCH_2), 7.59–7.63 (m, 2H, Ar–H), 7.73–7.75 (m, 2H, Ar–H), 7.94 (m, 4H, Ar–H), 8.0 (s, 2H, triazole), 8.16–8.22 (m, 4H, Ar–H), 9.01 (d, 2H, $J = 5.7$ Hz, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.2 ($NHCH_2$), 52.1 (NCH_2), 124.0 (C-5 triazole), 125.1 (C-4′), 127.1 (C-2′), 128.6 (C-2, C-3, C-5, C-6), 129.3 (C-5′), 130.1 (C-1′), 134.5 (C-1, C-4), 144.1 (C-4 triazole), 147.5 (C-3′), 166.1

(C=O). HRMS: *m/z* (M^+) Cacld. for $C_{28}H_{24}N_{10}O_6$: 596.1880, found: 597.1970 $(M+H)^+$.

*N^1,N^4-bis((1-(4-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)terephthalamide (**3l**)*

Yield: 86 %; Pale yellowish solid; mp: >250 °C (decom); IR (KBr): 3338 (N–H str), 3137 (=C–H str triazole), 3074, 3129, 1647, 1533, 1346, 1051 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 4.60 (s, 4H, $NHCH_2$), 5.72 (s, 4H, NCH_2), 7.52 (d, 4H, J = 8.2 Hz, Ar–H), 7.95–7.99 (m, 6H, Ar–H + triazole), 8.19 (d, 4H, J = 8.4 Hz, Ar–H), 9.03 (d, 2H, J = 5.4 Hz, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.9 ($NHCH_2$), 52.0 (NCH_2), 123.5 (C-5 triazole), 125.6 (C-3′, C-5′), 127.1 (C-2′, C-6′), 128.7 (C-2, C-3, C-5, C-6), 136.0, 136.3 (C-1, C-4), 142.7 (C-4 triazole), 144.5 (C-1′), 147.2 (C-4′), 165.7 (C=O). HRMS: *m/z m/z* (M^+) Cacld. for $C_{28}H_{24}N_{10}O_6$: 596.1880, found: 597.1966 $(M+H)^+$.

*N^2,N^6-bis((1-(2-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)pyridine-2,6-dicarboxamide (**3m**)*

Yield: 70 %; White solid; mp: 99–100 °C; IR (KBr): 3381 (N–H str), 3080, 3130 (=C–H str triazole), 1672, 1533, 1221, 1051 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 6H, CH_3), 4.68 (s, 4H, $NHCH_2$), 5.45 (s, 4H, NCH_2), 7.01–7.18 (m, 6H, Ar–H), 7.20–7.24 (m, 2H, Ar–H), 7.83 (s, 2H, triazole), 8.03 (t, 1H, J = 7.7 Hz, Pyridyl-H), 8.23-8.25 (m, 2H, Pyridyl-H) 9.86 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.5 (CH_3), 34.6 ($NHCH_2$), 53.4 (NCH_2), 122.5 (C-5 triazole), 124.2 (C-3, C-5), 124.4 (C-4′), 128.5 (C-5′, C-6′), 128.6 (C-3′), 128.9 (C-2′), 134.4 (C-1′), 138.3 (C-4), 143.1 (C-4 triazole), 148.5 (C-2, C-6), 163.8 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{29}H_{29}N_9O_2$: 535.2444, found:536.2534 $(M+H)^+$.

*N^2,N^6-bis((1-(3-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)pyridine-2,6-dicarboxamide (**3n**)*

Yield = 73 %; White solid; mp: 178–181 °C; IR (KBr): 3383 (N–H str), 3117 (=C–H str triazole), 3072, 1682, 1528, 1248, 1051 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 6H, CH_3), 4.68 (s, 4H, $NHCH_2$), 5.45 (s, 4H, NCH_2), 7.06–7.13 (m, 6H, Ar–H), 7.22 (t, 2H, J = 7.4 Hz, Ar–H), 7.71 (s, 2H, triazole), 8.01(t, 1H, J = 7.7 Hz, Pyridyl-H), 8.24 (d, 2H, J = 7.7 Hz, Pyridyl-H), 9.86 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.8 (CH_3), 34.4 ($NHCH_2$), 53.4 (NCH_2), 122.3 (C-5 triazole), 124.7 (C-3, C-5, C-6′), 128.3 (C-5′), 128.4 (C-4′),128.8 (C-2′), 134.5 (C-1′), 138.1 (C-3′), 138.2 (C-4), 142.2 (C-4 triazole), 148.3 (C-2, C-6), 163.5 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{29}H_{29}N_9O_2$: 535.2444, found: 536.2539 $(M+H)^+$.

*N^2,N^6-bis((1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)pyridine-2,6-dicarboxamide (**3o**)*

Yield: 73 %; White solid; mp: 118–121 °C; IR (KBr): 3379 (N–H str), 3130 (=C–H str triazole), 3082, 1670, 1530, 1227, 1049 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 6H, CH_3), 4.67 (brs, 4H, $NHCH_2$), 5.43 (s, 4H, NCH_2), 7.13–7.19 (m, 8H, Ar–H), 7.66 (s, 2H, triazole), 8.01 (t, 1H, J = 7.8 Hz, Pyridyl-H), 8.24 (d, 2H, J = 7.7 Hz, Pyridyl-H), 9.83 (t, 2H, J = 5.9 Hz, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.6 (CH_3), 34.4 ($NHCH_2$), 53.2 (NCH_2), 122.2 (C-5 triazole), 124.1 (C-3, C-5), 127.7 (C-2′, C-6′), 129.1 (C-3′, C-5′), 131.4 (C-1′), 137.9 (C-4′), 138.2 (C-4), 145.2 (C-4 triazole), 148.3 (C-2, C-6), 163.5 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{29}H_{29}N_9O_2$: 535.2444, found: 536.2530 $(M+H)^+$.

*N^2,N^6-bis((1-(2-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)pyridine-2,6-dicarboxamide (**3p**)*

Yield: 91 %; Pale yellow solid; mp: 150–152 °C; IR (KBr): 3318 (N–H str), 3132 (=C–H str triazole), 3082, 1667, 1531, 1346, 1238, 1059 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 4.65 (s, 4H, $NHCH_2$), 5.93 (s, 4H, NCH_2), 7.06 (brs, 2H, Ar–H), 7.62–7.72 (m, 4H, Ar–H), 7.96 (brs, 1H, Pyridyl-H), 8.08-8.21 (m, 6H, Ar–H + Pyridyl-H + triazole), 9.90 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.6 ($NHCH_2$), 52.0 (NCH_2), 123.1 (C-5 triazole), 124.5 (C-3, C-5, C-3′), 127.2 (C-4′, C-6′), 130.7 (C-1′), 135.0 (C-5′), 138.5 (C-4), 140.2 (C-4 triazole), 148.4 (C-2′), 148.6 (C-2, C-6), 163.6 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{27}H_{23}N_{11}O_6$: 597.1833, found: 598.1911 $(M+H)^+$, 620.2.

*N^2,N^6-bis((1-(3-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)pyridine-2,6-dicarboxamide (**3q**)*

Pale Yield: 89 %; yellowish solid; mp: 138–140 °C; IR (KBr): 3339 (N–H str), 3132 (=C–H str triazole), 3088, 1672, 1530, 1352, 1051 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 4.64 (s, 4H, $NHCH_2$), 5.75 (s, 4H, NCH_2), 7.69–7.78 (m, 4H, Ar–H), 8.22 (m, 9H, Ar–H + Pyridyl-H + triazole), 9.95 (brs, 2H, NH, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.9 ($NHCH_2$), 52.2 (NCH_2), 123.3 (C-5 triazole), 124.9 (C-3, C-5, C-4′), 130.8 (C-2′, C-5′), 135.3 (C-6′), 138.6 (C-4, C-1′), 140.0 (C-4 triazole), 148.3 (C-2, C-6, C-3′), 163.7 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{27}H_{23}N_{11}O_6$: 597.1833, found:598.1914 $(M+H)^+$.

*N^2,N^6-bis((1-(4-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)pyridine-2,6-dicarboxamide (**3r**)*

Yield: 92 %; Pale yellowish solid; mp: 228–230 °C; IR (KBr): 3360 (N–H str), 3129 (=C–H str triazole), 3082, 1688, 1526, 1342, 1231, 1058 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 4.63 (s, 4H, $NHCH_2$), 5.74 (s, 4H, NCH_2), 7.53 (d, 4H, $J = 8.7$ Hz, Ar–H), 8.15 (s, 2H, triazole), 8.18-8.24 (m, 7H, Ar–H + Pyridyl-H + triazole), 9.94 (t, 2H, $J = 6.1$ Hz, NH, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.4, 53.2, 122.2 (C-5 triazole), 124.3 (C-3, C-5), 127.7 (C-3′, C-5′), 129.1 (C-2′, C-6′), 137.9 (C-4), 138.2 (C-1′), 145.2 (C-4 triazole), 148.3 (C-2, C-6, C-4′), 163.5 (C=O). HRMS: *m/z* (M^+) Cacld. for $C_{27}H_{23}N_{11}O_6$: 597.1833, found: 598.1917 $(M+H)^+$.

Cytotoxic activity

All the synthesized compounds were evaluated for their in vitro cytotoxicity against a panel of five human cancer cell lines. Human cancer cell line Fibrosarcoma (HT-1080), Colon (colo205, HCT-116), Lung (A549, NCIH322) were procured from European Collection of cell culture (ECACC), UK. Cells were grown in RPMI-1640 medium supplemented with 10 % FCS and 1 % penicillin dissolved in PBS and sterilized by filtering through 0.2 μm filter in laminar air flow hood. Cells were cultured in CO_2 incubator (New Brunswick, Galaxy 170R, Eppendorf) with an internal atmosphere of 95 % air and 5 % CO_2 gas and the cell lines were maintained at 37 °C. The media were stored at low temperature (2–8 °C). The medium for cryopreservation contained 20 % FCS and 10 % DMSO in growth medium.

SRB assay was performed in which cell suspension of optimum cell density was seeded and exposed to 20, 30, and 50 μM concentration of the synthesized bistriazoles (**3a**–**3r**) in the culture medium. Cells were incubated with the different concentrations of samples for 48 h. The cells were fixed with ice cold TCA for 1 h at 40 °C. The plates were washed five times with distilled water and allowed to dry in air. Then, 0.4 % sulphorhodamine (SRB) solution was added to each well of the dry 96-well plates and allowed staining at room temperature for 30 min. The plates were washed quickly with 1 % v/v acetic acid to remove unbound SRB dye. The bound SRB dye was solubilised by adding 10 mM unbuffered Tris base (pH 10.5) to each 96-well plate on a shaker platform and the absorbance was read at 540 nm (Houghton *et al.*, 2007).

Computational detail

The crystal structure of Topoisomerase II was obtained from the Brookhaven Protein Data Bank http://www.rcsb.org/pdb (PDB entry: 1ZXM). To carry out docking studies, the 2D structures of various ligands were drawn, and these were converted to 3D, and their energy was minimized (Marvin Sketch 5.0.3). Ligand files were prepared in pdb format with explicit hydrogen addition. Co-crystallized ligand was removed from pdb files, and protein molecule was prepared by deleting solvent molecules and non-complex ions using Chimera (UCSF Chimera 1.5.3. Incomplete side chains were replaced using Dun Brack Rotamer library (Dunbrack, 2002). Hydrogens were added and gasteiger charges were calculated using Antechamber (Wang *et al.*, 2006). The prepared file was saved as pdb format and is used for further studies. All pdb files were transformed into pdbqt format. Docking studies were carried out by using Auto Dock Vina 1.1.2. Grid center was placed on the active site. The centers and sizes of grid box were as follows: center_$x = 36.6051885359$, center_$y = -0.119306499332$, and center_$z = 36.9217846187$, size_$x = 25.0$, and size_$y = 25.0$, size_$z = 25.0$. Exhaustiveness of the global search algorithm was set to be 8. Then, finally docking results were viewed using pdb and pdbqt files (Discovery Studio Visualizer 2.5.5.9350; PyMol, 2008).

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