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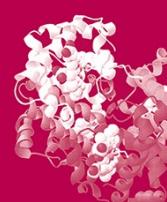
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Synthesis, docking study, and DNA photocleavage activity of some pyrimidinyl hydrazones and 3-(quinolin-3-yl)-5,7-dimethyl-1,2,4-triazolo[4,3-*a*]pyrimidine derivatives

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Abstract In the present study, synthesis of a series of some novel 3-(Quinolin-3-yl)-5,7-dimethyl-1,2,4-triazolo[4,3-*a*]pyrimidine derivatives (**4a–e**) has been achieved by oxidative cyclization of new pyrimidinyl hydrazone intermediates (**3a–e**) using hypervalent iodine reagent(III) under mild conditions. The structures of all synthesized compounds were established on the basis of IR, NMR (^1H and ^{13}C), mass spectral data, and elemental analysis. All compounds were evaluated for their DNA photocleavage activity. Compounds **4a**, **4b**, **4d** and **3a–e** were found to possess good activity at 40 $\mu\text{g}/\text{ml}$ concentration and were mainly responsible for the conversion of supercoiled form of DNA into open circular form. Further, docking study was carried out using Molegro Virtual Docker version 2010.4.2.0 using PDB (1AB4) in support of the results obtained.

Keywords Quinoline · Triazolopyrimidine · Hydrazone · (Diacetoxyiodo)benzene · DNA photocleavage activity · Docking study

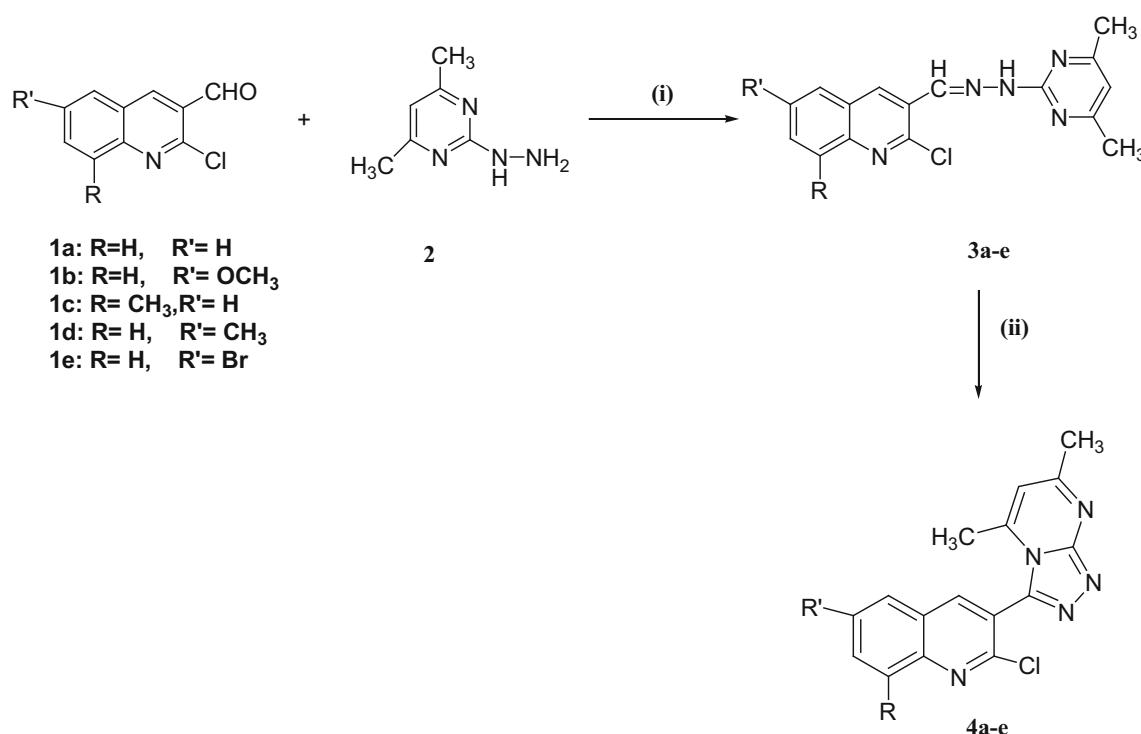
Introduction

Compounds possessing triazole, quinoline, and pyrimidine ring systems are well recognized by synthetic chemists, as well as biologists due to their wide applications in global pharmaceutical world. Quinoline and its derivatives act as an important class of pharmacologically active compounds due to a broad spectrum of biological activities (Abdel-Wahab *et al.*, 2012; Marella *et al.*, 2013) such as anti-bacterial (Bekhit *et al.*, 2004; Kaminsky and Meltzer, 1968), anti-malarial (Xiao *et al.*, 2001), anti-cancer (Nakamura *et al.*, 1999), anti-inflammatory (Bekhit *et al.*, 2004; Chia *et al.*, 2008), DNA binding capability (Atwell *et al.*, 1989), anti-tumor (Kuo *et al.*, 1993; Xia *et al.*, 1998), DNA intercalating carrier (Chen *et al.*, 2000), anti-HIV (Strekowski *et al.*, 1991), anti-depressant (Oshiro *et al.*, 2000), and anti-allergic (Cairns *et al.*, 1985). Pyrimidine and its fused products are another important class of bioactive compounds (Dinakaran *et al.*, 2012; Jain *et al.*, 2006; Selvam *et al.*, 2012) that showed numerous pharmacological activities. In case of fused pyrimidines, it has also been found that triazolopyrimidines have a wide range of biological actions such as anti-tumor, cytotoxicity, selective ATP site-directed inhibition of the EGF-receptor protein tyrosine kinase, cardiovascular activities, and DNA-intercalations (Dandia *et al.*, 2006; El Ashry and Rashed, 1999; Shaban and Morgan, 1999). Moreover, some biological reports have already been demonstrated that DNA is the primary receptor of most of the anti-cancer/anti-tumor and antibiotic drugs (Daniels and Gates, 1996; Pelaprat *et al.*, 1980a, b; Ozturk *et al.*, 2012). The DNA can be damaged as a result of interaction with small molecules which inhibit DNA transcription and replication. Also, it is of a great chemical and biological interest to study DNA cleavage under UV-irradiation without any additives such as metal and reducing agents. The reported methods for the syntheses of triazolopyrimidines via oxidative transformation of hydrazone

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Scheme 1 (i) EtOH, H₂SO₄/40–45 min, reflux; (ii) DCM, IBD/1 h, stir, rt

derivatives by copper(II) chloride (Aggarwal *et al.*, 2011), bromine (Gibson, 1963; Pollak and Tisler, 1966), and lead tetraacetate (Allen *et al.*, 1960) are not eco-friendly and provide lesser yields. However, there are several reports which have already disclosed the use of hypervalent iodine(III) compounds as mild and eco-friendly reagents in various oxidative rearrangements selectively to yield the products (Vorvoglis, 1997; Zhdankin, 2009).

In view of importance of these fused heterocycles and in continuation of our work related to synthesis of bioactive compounds (Kumar *et al.*, 2013; Saini *et al.*, 2014), it was planned to synthesize and evaluate DNA cleavage activity of some novel quinoline-based triazolopyrimidines and their hydrazone intermediates. In addition, docking study was also conducted to predict the interactions of compounds with binding sites of protein DNA gyrase with an objective to find the potential of synthesized compounds, as well as to support the results obtained from DNA photocleavage activity.

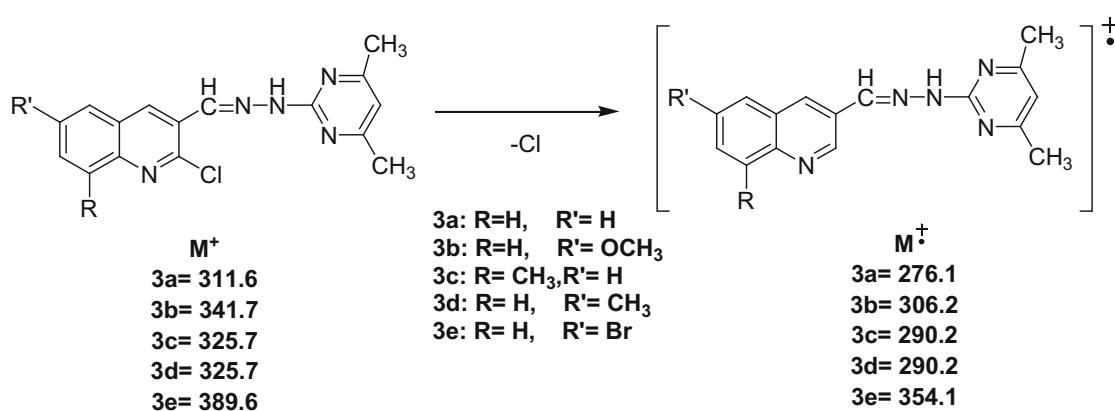
Results and discussion

Chemistry

In this study, synthesis of some new pyrimidinyl hydrazone derivatives **3a–e** was carried out by reacting 2-hydrazino-4,6-dimethylpyrimidine **2** with substituted 2-chloroquinoline-3-

carbaldehydes (**1a–e**) in presence of sulfuric acid under refluxing ethanol. Further, the compounds **3a–e** were subjected to treat with iodobenzene diacetate (IBD)-mediated oxidative cyclization in dichloromethane at room temperature to obtain triazolopyrimidine derivatives **4a–e** (Scheme 1). The syntheses of various substituted 2-chloroquinoline-3-carbaldehydes (**1a–e**) and **2** were carried out according to literature procedures. The synthesis of **1a–e** was accomplished by the acetylation of aromatic amines with acetyl chloride in chloroform under basic conditions (Furniss *et al.*, 1989) followed by the reaction of intermediates with vilsmeier haack reagent (DMF/POCl₃) (Meth-Cohn *et al.*, 1981). The synthesis of substrate **2** was carried out in three steps namely; (i) reaction of acetyl acetone with urea in acidic conditions, (ii) chlorination with POCl₃, and (iii) reaction of chloropyrimidine with hydrazine (Aggarwal *et al.*, 2006; Kumar *et al.*, 2005). The structures of all synthesized pyrimidinyl hydrazones and triazolopyrimidines were established on the basis of their spectral data and elemental analysis results.

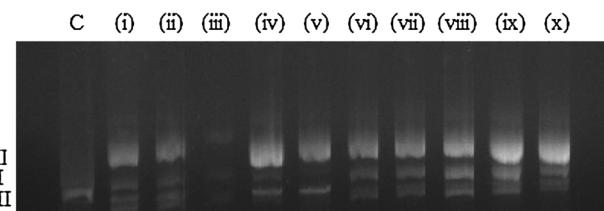
The FTIR spectra of **3a–e** showed the characteristics bands in the range of 3,380–3,220 cm⁻¹ due to –NH str. which indicates the presence of –NH group in the hydrazones. The bands appeared in the range 3,120–2,910 cm⁻¹ were due to aromatic C–H str., 1,600–1,400 cm⁻¹ for aromatic C=C str., and at 830–600 cm⁻¹ for C–Cl str. The appearance of bands near 1,520–690 cm⁻¹ is due to C=N str. which further supports the presence of C=N functionality in quinoline,

**Fig. 1** Mass fragmentation of compounds (**3a–e**)

hydrazone, and pyrimidine ring. However, for **4a–e** disappearance of –NH str. bands in a range of 3,380–3,220 indicates the successful oxidative cyclization of **3a–e** into triazolopyrimidine system. These results are in good agreement with the information obtained from ¹H NMR spectra. The characteristics singlet at δ 8.20–8.79 due to N=CH group's proton and at δ 11.1–11.4 due to NH proton was observed in ¹H NMR spectra of compounds **3a–e** which were further disappeared after cyclization. In addition to this, six protons of two different methyl groups of pyrimidine ring in **3a–e** resonated at the same value, i.e., at 2.3 ppm due to magnetically equivalent environment but after cyclization, the environment of these protons gets changed, as a result two signals at 2.2 and 2.6 ppm were obtained for both methyl groups in the ¹H NMR spectra of **4a–e**. The ¹³C spectral data also support the above results, the chemical shifts at δ 135–136 due to HC=N group's carbon of compounds **3a–e** (a characteristic signal for hydrazones) were found to be disappeared after cyclization. The two methyl carbon atoms of **3a–e** were appeared at 23.4 ppm due to magnetically equivalent environment, but after cyclization two signals at 18 and 24.5 ppm were observed due to the change in environment in ¹³C NMR spectra of final products **4a–e**. Finally, the formation of **4a–e** from **3a–e** compounds was confirmed on the basis of their mass spectral data and elemental analysis. In mass spectra, no fragmented ion peak was observed in case of **4a–e**. However, in case of **3a–e**, a fragmented ion peak in each case has been observed by the loss of chloride ion (Fig. 1).

DNA photocleavage activity

The molecules possessing quinoline and triazole rings with in the same motif were found to exhibit DNA photocleavage activity due to complex formation with DNA (Aravinda *et al.*, 2009). The aromatic heterocycles containing conjugated C=N bond system have more tendency to

**Fig. 2** Gel electrophoretogram of compounds: *C* DNA (control); *Lane-i* DNA + **4a**; *Lane-ii* DNA + **4b**; *Lane-iii* DNA + **4c**; *Lane-iv* DNA + **4d**; *Lane-v* DNA + **4e**; *Lane-vi* DNA + **3a**; *Lane-vii* DNA + **3b**; *Lane-viii* DNA + **3c**; *Lane-ix* DNA + **3d**; *Lane-x* DNA + **3e**

cleave DNA photochemically due to the generation of photoexcited (n–π*) state which would have radical character (Toshima *et al.*, 1999; Yao and Qian, 2001). In a recent communication, compounds having quinoline pharmacophore have been reported to exhibit DNA cleavage photochemically (Bindu *et al.*, 2012). In the present investigation, the ability of the titled compounds (**3a–e** and **4a–e**) to interact with plasmid DNA was examined by Agarose Gel Electrophoresis method and the results are presented in Fig. 2. The agarose gel electrophoresis worked on the principle that super coiled DNA (III) migrates faster than open circular form (II) (when one strand gets nicked), a linear form (I) (both strands cleavage) migrates in between form (II) and (III). Compounds **4a**, **4b** and **4d** showed good DNA photocleavage activity compared to other and interacted significantly as shown in Fig. 2. As a result of interaction, form (II) of DNA was appeared and visualized clearly due to the conversion of form (III) in form (II). However, in the case of hydrazones **3a–e**, all the three forms of DNA were well visualized and thus suggested that DNA molecule is nicked by these compounds into open coil (II) and linear (I) as well.

Fig. 3 Molecular interaction of compound (**3a**) with binding site of PDB: 1AB4

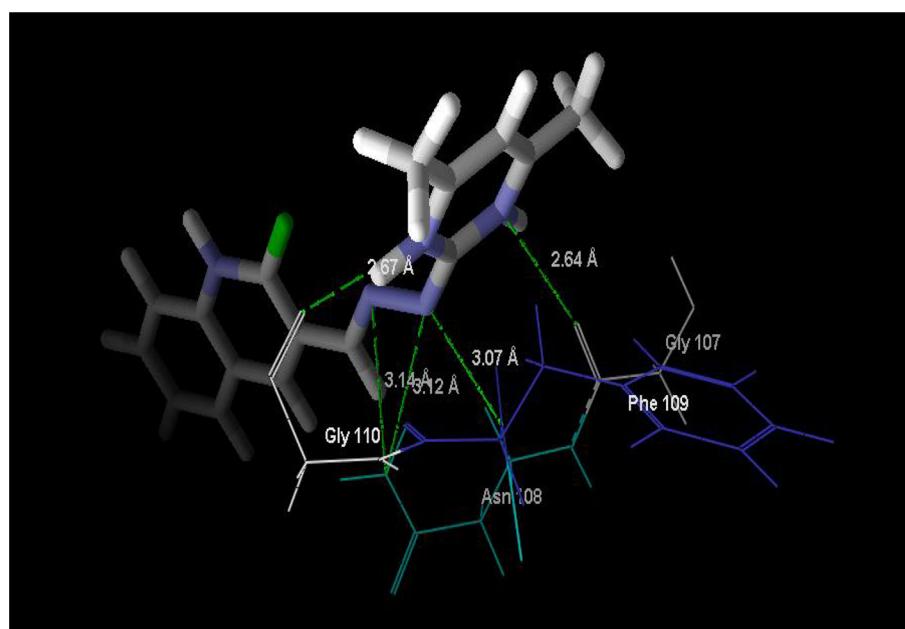
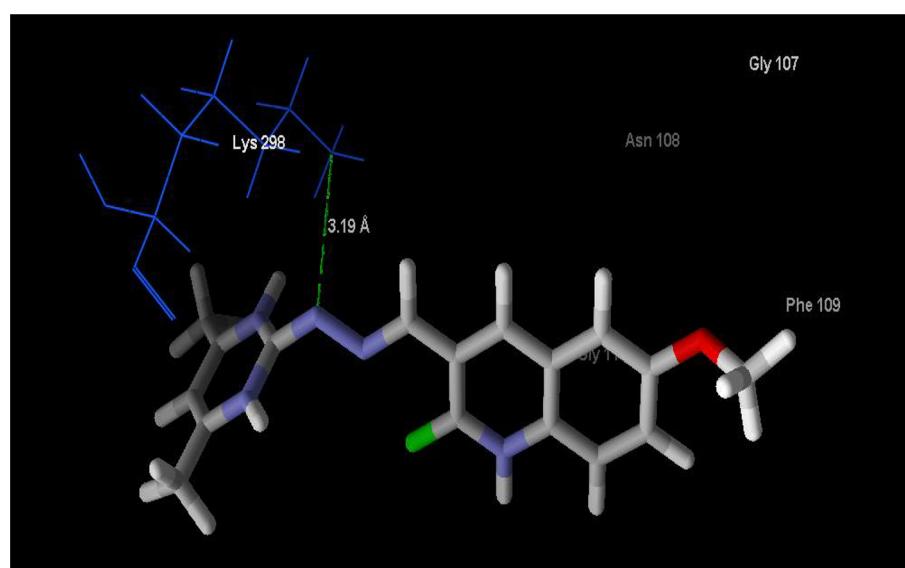


Fig. 4 Molecular interaction of compound (**3b**) with binding site of PDB: 1AB4



Docking study

Molecular docking is an in silico method that predicts how does a ligand interact with a receptor (e.g., proteins involved in several biological processes) and has been successfully applied in several therapeutic programs at the lead discovery stage (Ghosh *et al.*, 2006). The results of docking study have inferred that compound **3a** was found to possess five hydrogen bonds as shown with binding sites of protein by green dotted lines in Fig. 3. It has been observed that two of

hydrogen bonds were formed between N-1 of pyrimidine and N-3 of pyrimidine with Gly110 and Gly107 of distances 2.67 and 2.64 Å, respectively. Moreover, in case of **3b** only one hydrogen bond with binding site of protein was found (Fig. 4) with higher moldock score (-82.76) compared to compound **3a** (-67.69) (Table 1). However, the compound **3c** showed five hydrogen bonds (Fig. 5) out of which, one hydrogen bond between N-1 of pyrimidine with Gly110 of distance 2.63 Å was most preferred. But in case of compound **3d**, only one hydrogen bond with binding site of

Table 1 Results of docking analysis

	Compounds	Moldock score	Amino acids involved	Distance (Å)	Structural features
3a	—67.69	Gly110	2.67	N-1 of pyrimidine	
		Asn108	3.14	N-1 of hydrazine	
		Asn108	3.12	N-2 of hydrazine	
		Phe109	3.07	N-2 of hydrazine	
		Gly107	2.64	N-3 of pyrimidine	
3b	—82.76	Lys298	3.19	N-2 of hydrazine	
3c	—69.34	Asn108	3.17	N-1 of hydrazine	
		Asn108	3.14	N-2 of hydrazine	
		Gly107	2.64	N-3 of pyrimidine	
		Phe109	3.11	N-2 of hydrazine	
		Gly110	2.63	N-1 of pyrimidine	
3d	—80.32	Gly110	2.75	N of quinoline	
3e	—74.54	Ile264	3.23	N of quinoline	
		His262	2.86	N-1 of pyrimidine	
4a	—73.75	Asp115	3.36	N-8 of triazolopyrimidine	
		Gly114	2.46	N-2 of triazole	
		Gly114	3.18	N-1 of triazole	
		Asn269	3.19	N-2 of triazole	
		Asn269	2.98	N-1 of triazole	
4b	—81.05	Val268	3.55	N of quinoline	
		Pro265	3.01	N-8 of triazolopyrimidine	
		Thr219	2.54	N-8 of triazolopyrimidine	
		Thr219	3.02	N-2 of triazole	
		Gln267	3.33	N-4 of triazole	
4c	—57.80	Gln267	2.90	N-1 of triazole	
		Gln267	2.51	N-2 of triazole	
		Pro265	3.05	N-8 of triazolopyrimidine	
		Ile264	3.04	N-8 of triazolopyrimidine	
		Ile264	2.86	N-2 of triazole	
4d	—85.87	Ile264	3.25	N-1 of triazole	
		Thr219	3.05	N-1 of triazole	
		Thr219	2.61	N-8 of triazolopyrimidine	
		Pro265	3.14	N-8 of triazolopyrimidine	
		Gln267	2.34	N-1 of triazole	
4e	—74.85	Gln267	2.75	N-2 of triazole	
		Val268	3.37	N of quinoline	
		Asn269	2.99	N-1 of triazole	
		Asn269	3.24	N-2 of triazole	
		Gly114	3.09	N-1 of triazole	
		Gly114	2.42	N-2 of triazole	
		ASP115	3.41	N-8 of triazolopyrimidine	

Bold values indicate the strong bonding of the compounds

protein was found between N of quinoline with Gly110 of distance 2.75 Å with good moldock score (−80.32) as shown in Fig. 6 and Table 1. However, the compound **3e** showed two hydrogen bonds between N atom of quinoline and N-1 of pyrimidine with Ile264 and His262 of distances 3.23, and 2.86 Å, respectively as shown in Fig. 7. On the

other hand, compound **4a** possessed six hydrogen bonds (Fig. 8), where two bonds were formed between N-2 of triazole and N-1 of triazole with Gly114 and Asn269 of distances 2.46 and 2.98 Å, respectively. Six hydrogen bonds with binding sites of protein were also found in **4b** (Fig. 9) out of which three hydrogen bonds were between N-8 of

Fig. 5 Molecular interaction of compound (**3c**) with binding site of PDB: 1AB4

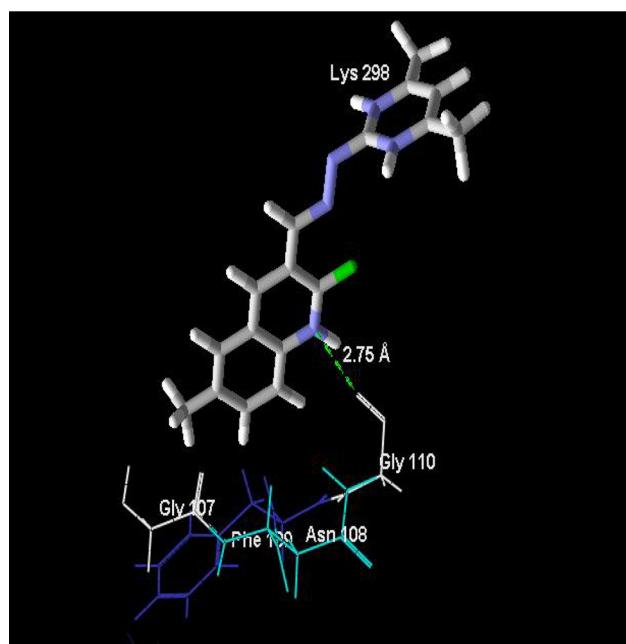
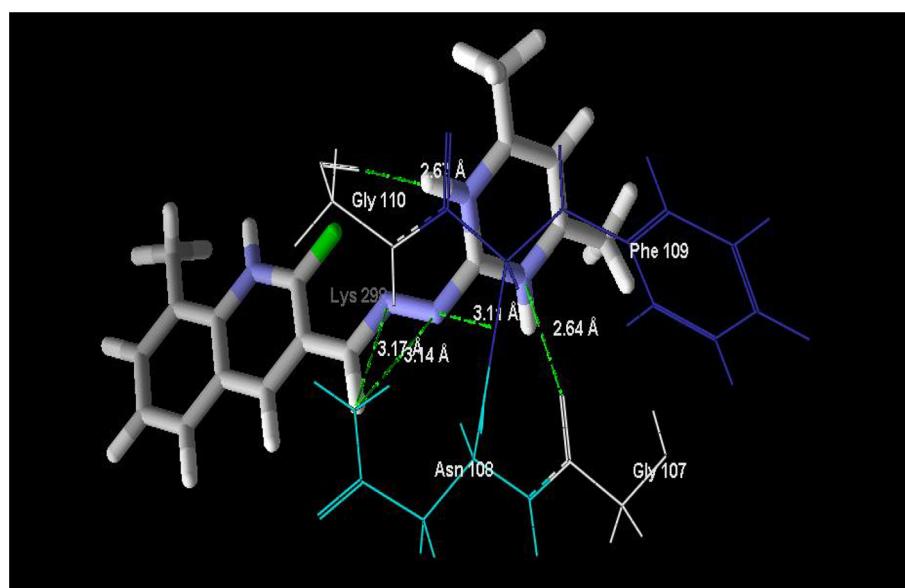


Fig. 6 Molecular interaction of compound (**3d**) with binding site of PDB: 1AB4

Triazolopyrimidine, N-1 and N-2 of Triazole with Thr219, Gln267, and Gln267 of distances 2.54, 2.90, and 2.51 Å, respectively. In case of compound **4d**, five hydrogen bonds with binding sites of protein have been observed as shown in Fig. 10 in which three hydrogen bonds were between N-8 of Triazolopyrimidine, N-1 and N-2 of Triazole with Thr219, Gln267, and Gln267 as in the case of **4b** but having distances 2.61, 2.34, and 2.75 Å, respectively. The compounds

4b and **4d** showed moldock scores (−81.05) and (−85.87), respectively, which are good compared to **4a**, i.e., (−74.54). Outcome of this study provides an indication that an electron releasing group strategically positioned in the molecule was also an important requirement for activity. However, nitrogen atoms of quinoline, pyrimidine, triazolopyrimidine, and triazole are other essential structural features required for the retention of biological activity. All the values are summarized in Table 1.

Conclusions

In conclusion, some novel quinoline-based triazolopyrimidine derivatives (**4a–e**) were prepared by oxidative cyclization of newly synthesized pyrimidinyl hydrazones (**3a–e**) using iodobenzene diacetate (a hypervalent iodine(III) reagent) under mild reaction conditions. All the synthesized compounds (**3a–e** and **4a–e**) were evaluated for their DNA photocleavage activity using plasmid DNA and further allowed to conduct docking study to explore the compared interactive ability of hydrazones and triazolopyrimidines with protein DNA enzyme. It has been found that compounds **4a**, **4b**, **4d**, and **3a–e** show excellent photocleavage activity at 40 µg/µl. It is very clear from Table 1, the reason of strong protein interaction with hydrazones (**3a–e**) is due to the involvement of pyrimidine nitrogen atom as evident by shorter hydrogen bond. However, in case of **4a–e**, strong interactions were found mainly due to the involvement of triazole's nitrogen atoms instead of pyrimidine nitrogen. From the docking study, it is concluded that triazolopyrimidines in general have more

Fig. 7 Molecular interaction of compound (**3e**) with binding site of PDB: 1AB4

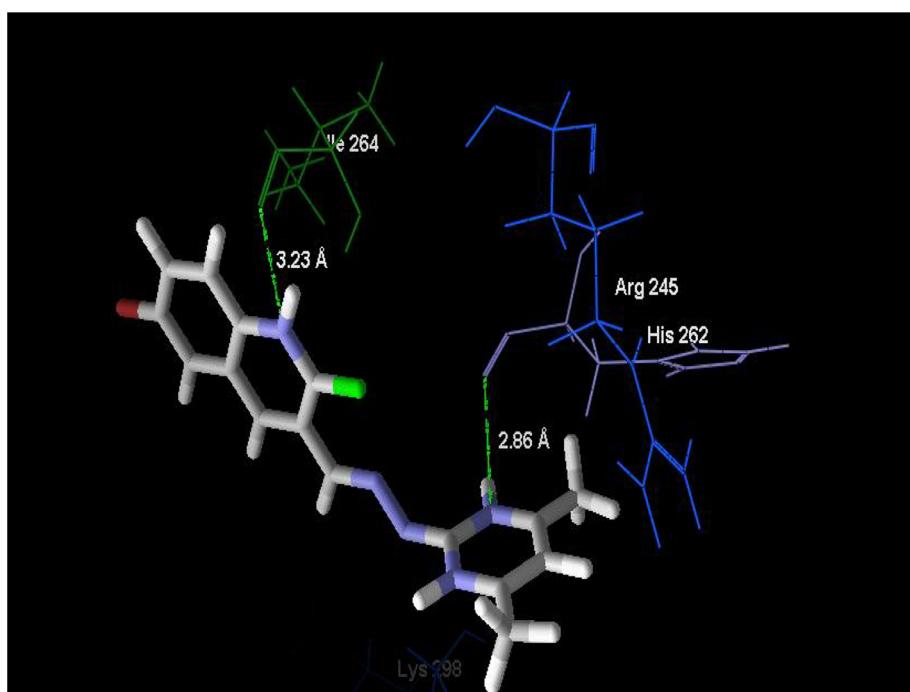
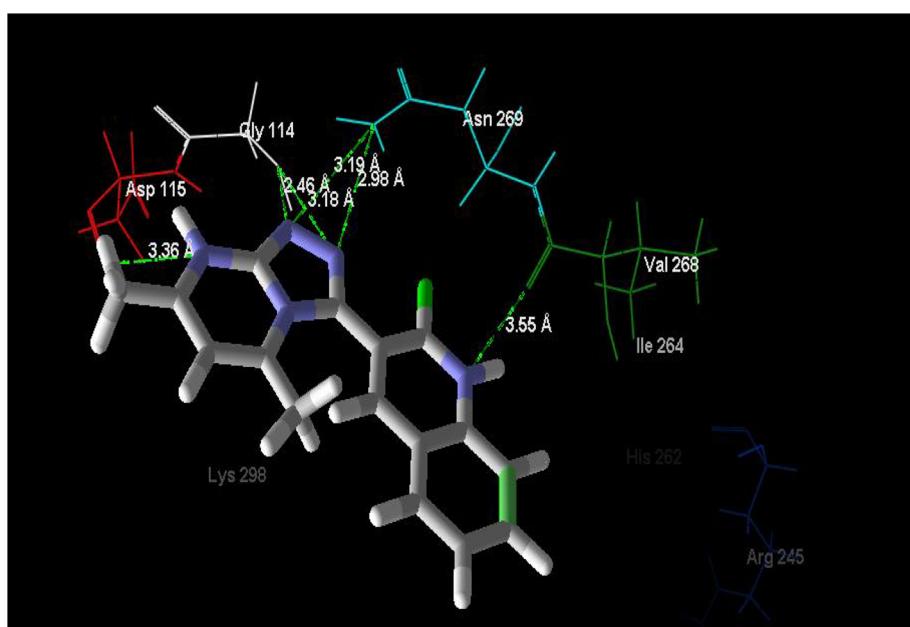


Fig. 8 Molecular interaction of compound (**4a**) with binding site of PDB: 1AB4



ability to interact strongly with active binding site of DNA enzyme compared to hydrazones (**3a–e**) due to the presence of triazole nucleus. Overall, it is concluded here that compounds **4a**, **4b**, and **4d** as such or with some structural modifications can serve the basis of some potent biological active agents in future.

Experimental

Materials and methods

All the chemicals were purchased from common commercial supplier (Hi-media, Loba, S.D. Fine chemicals and

Fig. 9 Molecular interaction of compound (**4b**) with binding site of PDB: 1AB4

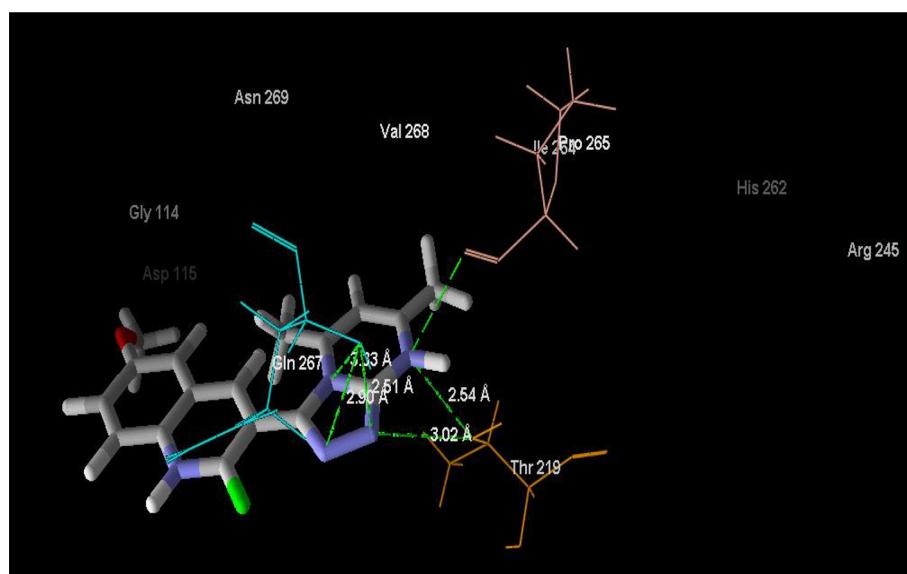
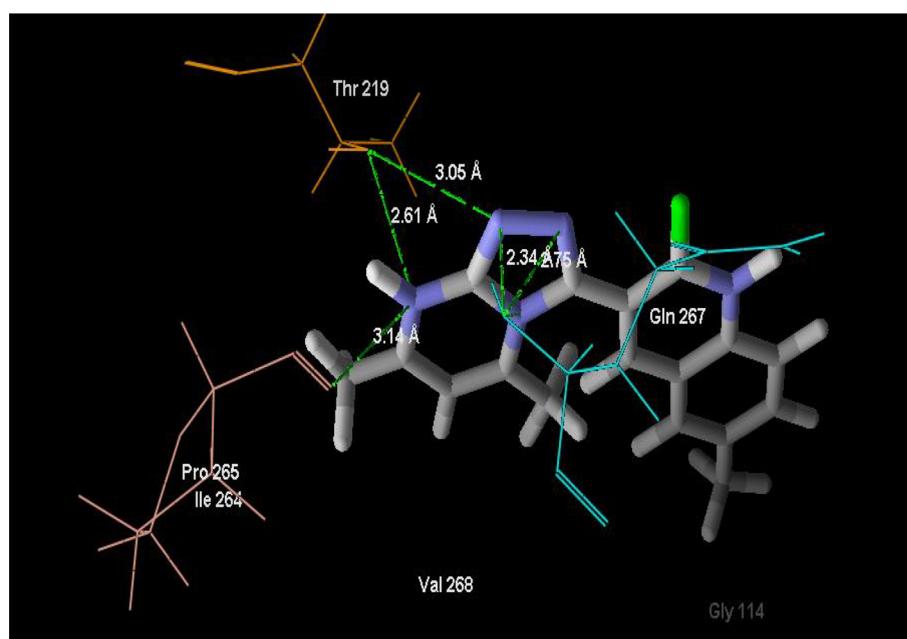


Fig. 10 Molecular interaction of compound (**4d**) with binding site of PDB: 1AB4



Rankem) including solvents were of LR grade and used as supplied. Double distilled water was used in the present investigation. Melting points were determined using Digital melting point apparatus (Paraffin bath) and are uncorrected. Thin-layer chromatography was performed on silica gel G for TLC (Rankem) and spots were visualized by iodine vapors or by irradiation with UV light (254 nm). Infra red spectra were recorded using KBr disk on Perkin

Elmer RZX FTIR spectrophotometer. ^1H -NMR and ^{13}C -NMR spectra were recorded at 400 and 100 MHz, respectively, on Bruker spectrophotometer instrument, using TMS as internal reference standard in $\text{DMSO}-d_6$ and coupling constants (J) are given in Hz. Carbon, nitrogen, and hydrogen contents were analyzed using LECO 9320 analyzer. The mass spectra were recorded on Q-ToF Micro Waters LC-MS spectrometer on TOF MS ES $^+$ mode.

*General procedure for synthesis of quinoline pyrimidinylhydrazones (**3a–e**)*

2-Hydrazino-4,6-dimethylpyrimidine **2** (0.01 mol) was dissolved in ethanol and added 2-chloro-3-formylquinoline **1a–e** (0.01 mol) and one drop of conc. sulfuric acid. The mixture was allowed to reflux on water bath and progress of reaction was monitored by TLC till completion of reaction (40–45 min). The excess of solvent was evaporated and then cooled to room temperature and poured the reaction mass into cold water. The obtained product was filtered on buchner funnel, washed with dilute ethanol, and recrystallized from ethanol (Fig. 11).

*1-[(2-Chloroquinolin-3-yl) methylene]-2-(4,6-dimethylpyrimidin-2-yl)hydrazine (**3a**)* Orange red; Yield: 89 %; M.p.: 212–214 °C; IR (KBr) cm^{-1} : 3229 (N–H str.), 3064 (Ar. C–H str.), 1596, 1557 (C=N str.), 1488, 1458 (Ar. C=C str.), 752 (C–Cl str.); ^1H NMR (DMSO- d_6) δ_H : 2.36 (s, 6H, CH_3), 6.64 (s, 1H, 5''-H), 7.61–7.65 (m, 1H, 6'-H), 7.76–7.80 (m, 1H, 7'-H), 7.92 (d, 1H, 5'-H, J = 8.44 Hz), 8.08 (d, 1H, 8'-H, J = 7.76 Hz), 8.58 (s, 1H, N=CH), 8.86 (s, 1H, 4'-H), 11.60 (s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ_C : 23.4 (CH_3), 112.2 (C-5''), 126.8 (C-6'), 127.06 (C-5'), 127.3 (C-4a'), 127.5 (C-7'), 128.2 (C-8'), 130.6 (C-4'), 134.3 (C-3'), 135.9 (C-methylene), 146.5 (C-8a'), 148.2 (C-2'), 159.3 (C-4'', 6''), 167.3 (C-2''); MS (ES $^+$) m/z observed [M+1] $^+$: 312.1, calcd.: 311.6; Anal. Calcd. For $\text{C}_{16}\text{H}_{14}\text{ClN}_5$: C 61.64, H 4.53, N 22.46. Found: C 61.61, H 4.51, N 22.43.

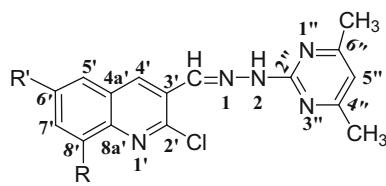
*1-[(2-Chloro-6-methoxyquinolin-3-yl) methylene]-2-(4,6-dimethylpyrimidin-2-yl)hydrazine (**3b**)* Light yellow; Yield: 90 %; M.p.: 230–232 °C; IR (KBr) cm^{-1} : 3303 (N–H str.), 3035 (Ar. C–H str.), 1597, 1562 (C=N str.), 1498, 1457 (Ar. C=C str.) 716 (C–Cl str.); ^1H NMR (DMSO- d_6) δ_H : 2.33 (s, 6H, CH_3), 3.90 (s, 3H, OCH_3), 6.69 (s, 1H, 5''-H), 7.43 (d, 1H, 7'-H, J = 9.08 Hz), 7.61 (s, 1H, 5'-H), 7.83 (d, 1H, 8'-H, J = 9.12 Hz), 8.53 (s, 1H, N=CH), 8.75 (s, 1H, 4'-H), 11.59 (s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ_C : 23.4 (CH_3), 55.5 (6'- OCH_3), 105.8 (C-5'), 112.2 (C-5''), 123.3 (C-7'), 127.09 (C-4a'), 128.1 (C-8'), 128.8 (C-4'), 133.04 (C-3'), 136.09 (C-methylene), 142.6 (C-8a'), 145.5 (C-2'), 157.8 (C-6'), 159.3 (C-4'', 6''), 167.3 (C-2''); MS (ES $^+$) m/z

observed [M+1] $^+$: 342.1, calcd.: 341.7; Anal. Calcd. For $\text{C}_{17}\text{H}_{16}\text{ClN}_5\text{O}$: C 59.74, H 4.72, N 20.49. Found: C 59.72, H 4.70, N 20.46.

*1-[(2-Chloro-8-methylquinolin-3-yl) methylene]-2-(4,6-dimethylpyrimidin-2-yl)hydrazine (**3c**)* Pale yellow; Yield: 82 %; M.p.: 214–216 °C; IR (KBr) cm^{-1} : 3315 (N–H str.), 3045 (Ar. C–H str.), 1575, 1558 (C=N str.), 1494, 1456 (Ar. C=C str.), 719 (C–Cl str.); ^1H NMR (DMSO- d_6) δ_H : 2.36 (s, 6H, CH_3), 2.68 (s, 3H, 8'- CH_3), 6.65 (s, 1H, 5''-H), 7.50–7.54 (m, 1H, 6'-H), 7.63 (d, 1H, 7'-H, J = 6.96 Hz), 7.92 (d, 1H, 5'-H, J = 7.96 Hz), 8.58 (s, 1H, N=CH), 8.82 (s, 1H, 4'-H), 11.59 (s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ_C : 17.3 (8'- CH_3), 23.4 (CH_3), 112.1 (C-5''), 126.06 (C-5'), 126.7 (C-4a'), 126.8 (C-6'), 127.04 (C-7'), 130.5 (C-4'), 134.5 (C-3'), 135.4 (C-8'), 136.1 (C-methylene), 145.7 (C-8a'), 147.2 (C-2'), 159.3 (C-4'', 6''), 167.3 (C-2''); MS (ES $^+$) m/z observed [M+1] $^+$: 326.1, calcd.: 325.7; Anal. Calcd. For $\text{C}_{17}\text{H}_{16}\text{ClN}_5$: C 62.67, H 4.95, N 21.50. Found: C 62.65, H 4.92, N 21.49.

*1-[(2-Chloro-6-methylquinolin-3-yl) methylene]-2-(4,6-dimethylpyrimidin-2-yl)hydrazine (**3d**)* Orange red; Yield: 80 %; M.p.: 216–218 °C; IR (KBr) cm^{-1} : 3320 (N–H str.), 3048 (Ar. C–H str.), 1573, 1554 (C=N str.), 1490, 1448 (Ar. C=C str.) 718 (C–Cl str.); ^1H NMR (DMSO- d_6) δ_H : 2.37 (s, 6H, CH_3), 2.52 (s, 3H, 6'- CH_3), 6.65 (s, 1H, 5''-H), 7.61 (d, 1H, 7'-H, J = 9.52), 7.81 (s, 1H, 5'-H), 7.82 (d, 1H, 8'-H, J = 9.20), 8.56 (s, 1H, N=CH), 8.75 (s, 1H, 4'-H), 11.58 (s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ_C : 21.1 (6'- CH_3), 23.4 (CH_3), 112.2 (C-5''), 126.3 (C-5'), 126.8 (C-4a'), 126.9 (C-8'), 129.8 (C-7'), 130.5 (C-4'), 134.6 (C-3'), 135.7 (C-6'), 136.2 (C-methylene), 144.7 (C-8a'), 148.2 (C-2'), 159.4 (C-4'', 6''), 167.5 (C-2''); MS (ES $^+$) m/z observed [M+1] $^+$: 326.1, calcd.: 325.7; Anal. Calcd. For $\text{C}_{17}\text{H}_{16}\text{ClN}_5$: C 62.67, H 4.95, N 21.50. Found: C 62.64, H 4.93, N 21.48.

*1-[(6-Bromo-2-chloroquinolin-3-yl) methylene]-2-(4,6-dimethylpyrimidin-2-yl)hydrazine (**3e**)* Fire brick red; Yield: 81 %; M.p.: 221–223 °C; IR (KBr) cm^{-1} : 3272 (N–H str.), 3054 (Ar. C–H str.), 1569, 1525 (C=N str.), 1476, 1442 (Ar. C=C str.) 722 (C–Cl str.); ^1H NMR (DMSO- d_6) δ_H : 2.36 (s, 6H, CH_3), 6.66 (s, 1H, 5''-H), 7.86 (s, 1H, 5'-H), 7.86 (d, 2H, 8'-H, J = 1.28), 8.56 (s, 1H, N=CH), 8.83 (s, 1H, 4'-H), 11.63 (s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ_C : 23.4 (CH_3), 112.4 (C-5''), 120.5 (C-7'), 128.1 (C-5'), 128.2 (C-8'), 129.6 (C-4a'), 130.2 (C-4'), 133.3 (C-3'), 133.6 (C-methylene), 135.5 (C-6'), 145.08 (C-8a'), 148.7 (C-2'), 159.3 (C-4'', 6''), 167.3 (C-2''); MS (ES $^+$) m/z observed [M+1] $^+$: 390.0, calcd.: 389.6; Anal. Calcd. For $\text{C}_{16}\text{H}_{13}\text{BrClN}_5$: C 49.19, H 3.35, N 17.93. Found: C 49.17, H 3.31, N 17.91.



General procedure of synthesis of 3-(quinolin-3-yl)-5,7-dimethyl-1,2,4-triazolo[4,3-a]pyrimidines (4a–e**)**

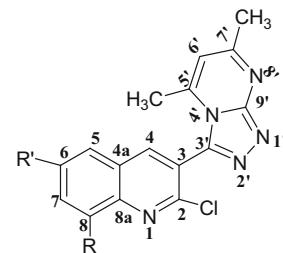
To the suspension or solution of **3a–e** (0.01 mol) in dichloromethane, iodobenzene diacetate (IBD, 0.011 mol) was added in a portion-wise manner under stirring. The reaction mass stirred for 1.0 h and progress of reaction was checked by TLC. On completion, the solvent was evaporated. The residue was titrated with petroleum ether 2–3 times. The obtained precipitates were recrystallized from ethanol (Fig. 12).

3-(2-Chloroquinolin-3-yl)-5,7-dimethyl-[1,2,4]triazolo[4,3-a]pyrimidine (4a**)** Peru brown; Yield: 80 %; M.p.: 222–224 °C; IR (KBr) cm^{-1} : 3063 (Ar. C–H str.), 1626 (C=N str.), 1493, 1442 (Ar. C=C str.) 748 (C–Cl str.); ^1H NMR (DMSO- d_6) δ_H : 2.22¹ (s, 3H, 7'-CH₃), 2.60* (s, 3H, 5'-CH₃), 6.95 (d, 1H, 6'-H, J = 0.8 Hz), 7.77–7.81 (m, 1H, 6-H), 7.96–8.00 (m, 1H, 7-H), 8.10 (d, 1H, 5-H, J = 8.52 Hz), 8.16 (d, 1H, 8-H, J = 7.52 Hz), 8.88 (s, 1H, 4-H); ^{13}C NMR (DMSO- d_6) δ_C : 18.2* (5'-CH₃), 24.5* (7'-CH₃), 111.8 (C-6'), 122.6 (C-6), 125.6 (C-5), 127.9 (C-4a), 128.2 (C-7), 128.7 (C-8), 132.4 (C-4), 141.04 (C-8a), 143.1 (C-3), 143.5 (C-2), 147.5 (C-3'), 148.9* (C-7'), 154.5* (C-5'), 164.9 (C-9'); MS (ES⁺) m/z observed [M+1]⁺: 324.1, calcd.: 323.7; Anal. Calcd. For C₁₇H₁₄ClN₅: C 63.06, H 4.36, N 21.63. Found: C 63.03, H 4.34, N 21.61.

3-(2-Chloro-6-methoxyquinolin-3-yl)-5,7-dimethyl-[1,2,4]triazolo[4,3-a]pyrimidine (4b**)** Moccasin red; Yield: 82 %; M.p.: 238–240 °C; IR (KBr) cm^{-1} : 3064 (Ar. C–H str.), 1623 (C=N str.), 1497, 1447 (Ar. C=C str.) 749 (C–Cl str.); ^1H NMR (DMSO- d_6) δ_H : 2.23* (s, 3H, 7'-CH₃), 2.60* (s, 3H, 5'-CH₃), 3.95 (s, 3H, OCH₃), 6.92 (d, 1H, 6'-H, J = 0.48 Hz), 7.49 (d, 1H, 5-H, J = 2.76), 7.56–7.59 (m, 1H, 7-H), 7.99 (d, 1H, 8-H, J = 9.2 Hz), 8.70 (s, 1H, 4-H); ^{13}C NMR (DMSO- d_6) δ_C : 18.2* (5'-CH₃), 24.5* (7'-CH₃), 55.6 (6-OCH₃), 106.22 (C-5), 111.78 (C-6'), 122.7 (C-7), 124.8 (C-4a), 127.07 (C-8), 129.3 (C-4), 141.1 (C-3), 141.5 (C-8a), 143.4 (C-2), 143.5 (C-3'), 146.1* (C-7'), 154.5* (C-5'), 158.4 (C-6), 164.8 (C-9'); MS (ES⁺) m/z observed [M+1]⁺: 340.1, calcd.: 339.7; Anal. Calcd. For C₁₇H₁₄ClN₅O: C 60.09, H 4.15, N 20.16. Found: C 60.06, H 4.12, N 20.13.

3-(2-Chloro-8-methylquinolin-3-yl)-5,7-dimethyl-[1,2,4]triazolo[4,3-a]pyrimidine (4c**)** Yellow; Yield: 79 %; M.p.: 245–247 °C; IR (KBr) cm^{-1} : 3064 (Ar. C–H str.), 1624 (C=N str.), 1493, 1449 (Ar. C=C str.), 751 (C–Cl str.). ^1H NMR (DMSO- d_6) δ_H : 2.22* (s, 3H, 7'-CH₃), 2.60* (s, 3H, 5-CH₃), 2.75 (s, 3H, 8-CH₃), 6.95 (d, 1H, 6'-H, J =

Fig. 12 Numbered chemical structure of **4a–e**



0.96 Hz), 7.65–7.69 (m, 1H, 6-H), 7.82 (d, 1H, 7-H, J = 7 Hz), 7.97 (d, 1H, 5-H, J = 7.92 Hz), 8.84 (s, 1H, 4-H). ^{13}C NMR (DMSO- d_6) δ_C : 17.3 (8-CH₃), 18.2* (5'-CH₃), 24.5* (7'-CH₃), 111.7 (C-6'), 122.4 (C-5), 125.7 (C-4a), 126.5 (C-6), 128.01 (C-7), 132.4 (C-4), 135.8 (C-8), 141.1 (C-3), 143.4 (C-8a), 143.5 (C-2), 146.6 (C-3'), 148.0* (C-7'), 154.5* (C-5'), 164.9 (C-9'); MS (ES⁺) m/z observed [M+1]⁺: 324.1, calcd.: 323.7; Anal. Calcd. For C₁₇H₁₄ClN₅: C 63.06, H 4.36, N 21.63. Found: C 63.03, H 4.34, N 21.61.

3-(2-Chloro-6-methylquinolin-3-yl)-5,7-dimethyl-[1,2,4]triazolo[4,3-a]pyrimidine (4d**)** Golkenrod brown; Yield: 80 %; M.p.: 230–232 °C; IR (KBr) cm^{-1} : 3064 (Ar. C–H str.), 1628 (C=N str.), 1482, 1447 (Ar. C=C str.) 740 (C–Cl str.); ^1H NMR (DMSO- d_6) δ_H : 2.22* (s, 3H, 7'-CH₃), 2.58* (s, 3H, 5'-CH₃), 2.61 (s, 3H, 6-CH₃), 6.90 (d, 1H, 6'-H, J = 0.52 Hz), 7.77–7.80 (m, 1H, 7-H), 7.88 (s, 1H, 5-H), 7.97–8.02 (m, 1H, 8-H), 8.72 (s, 1H, 4-H); ^{13}C NMR (DMSO- d_6) δ_C : 18.2* (5'-CH₃), 21.1 (6-CH₃), 24.5* (7'-CH₃), 111.7 (C-6'), 122.4 (C-5), 125.6 (C-4a), 127.2 (C-8), 127.6 (C-7), 128.7 (C-4), 134.4 (C-6), 138.07 (C-3), 141.1 (C-8a), 142.2 (C-2), 143.4 (C-3'), 146.1 (C-7'), 154.5 (C-5'), 164.8 (C-9'); MS (ES⁺) m/z observed [M+1]⁺: 324.1, calcd.: 323.7; Anal. Calcd. For C₁₇H₁₄ClN₅: C 63.06, H 4.36, N 21.63. Found: C 63.04, H 4.32, N 21.61.

3-(6-Bromo-2-chloroquinolin-3-yl)-5,7-dimethyl-[1,2,4]triazolo[4,3-a]pyrimidine (4e**)** Sandy brown; Yield: 81 %; M.p.: 248–250 °C; IR (KBr) cm^{-1} : 3065 (Ar. C–H str.), 1632 (C=N str.), 1478, 1449 (Ar. C=C str.), 771 (C–Cl str.); ^1H NMR (DMSO- d_6) δ_H : 2.24* (s, 3H, 7'-CH₃), 2.62* (s, 3H, 5'-CH₃), 6.90 (d, 1H, 6'-H, J = 0.96 Hz), 8.01–8.06 (m, 2H, 7,8-H), 8.40 (s, 1H, 5-H), 8.81 (s, 1H, 4-H); ^{13}C NMR (DMSO- d_6) δ_C : 18.3* (5'-CH₃), 24.5* (7'-CH₃), 111.8 (C-6'), 121.3 (C-6), 123.5 (C-4a), 126.3 (C-5), 126.9 (C-8), 129.9 (C-7), 130.5 (C-4), 135.3 (C-3), 142.08 (C-8a), 143.3 (C-2), 146.2 (C-3'), 149.4* (C-7'), 154.7* (C-5'), 164.9 (C-9'); MS (ES⁺) m/z [M+1]⁺: 388.0, calcd.: 387.6; Anal. Calcd. For C₁₆H₁₁BrClN₅: C 49.45, H 2.85, N 18.02. Found: C 49.43, H 2.82, N 18.00.

¹ inter-convertible between 5' and 7'.

DNA photocleavage activity

The photocleavage of plasmid DNA was determined by agarose gel electrophoresis (Guidi *et al.*, 1998; Reddy and Raju, 2012). The experiments were performed in a volume of 10 µl containing the plasmid DNA in TE (*Tris* 10 mM, EDTA 0.01 mM, pH 8.0) buffer in the presence of 40 µg of synthesized compounds. The samples were taken in polyethylene microcentrifuge tubes which were then irradiated for 30 min at room temperature in trans-illuminator (8000 mW/cm) at 360 nm. Further, the samples were incubated at 37 °C for 1 h. The 6X loading dye containing 0.25 % bromophenol blue and 30 % glycerol (8 µl) was mixed with irradiated sample. The analysis of samples was carried out on a 0.8 % agarose horizontal slab gel in Tris-Acetate EDTA buffer (40 mM *Tris*, 20 mM acetic acid, 1 mM EDTA, pH 8.0). Untreated plasmid DNA was maintained as a control in each run of gel electrophoresis which was carried out at 5 V/cm for 2.0 h. Gel was stained with ethidium bromide (1 µg/ml) and photographed under UV light.

Computational methodology

Ligand preparation

The molecules were built using Chem Sketch 12.0.1 and converted into 3D structures from the 2D structures and further 3D structures were energetically minimized and saved as sybyl mol2 file.

Enzyme setup and docking procedure

Docking can be performed by Molegro Virtual Docker 4.2.0 program (Thomsen and Christensen, 2006). The crystal structure of target protein DNA gyrase subunit A *Escherichia coli* (1AB4) was retrieved from the Protein Data Bank (<http://www.rcsb.org/pdb/explore.do>). All bound water ligands and cofactors were removed from the protein, since they are not taken into account during the scoring.

The three-dimensional (3D) chemical structures were drawn by ACD Chem-Sketch 8.0, ACD Labs, Toronto. Docking studies were carried out by Molegro Virtual Docker 4.2.0. The ligand structure was constructed using Chem-Sketch software (ACD Labs) and saved in MOL format. The protein structure of DNA gyrase subunit A *E. coli* (PDB Code: 1AB4) was imported in MVD, and missing bond orders, hybridization states, and angles were then assigned. A maximum of five cavities was detected using parameters such as molecular surface (expanded van der Waals), maximum number of cavities ($n = 5$), minimum cavity volume (10), probe size (1.20), maximum

number of ray checks ($n = 16$), minimum number of ray hits ($n = 12$), and grid resolution (0.80). Out of them, cavity number 1 (volume = 125.44, surface = 385; co-ordinates $x = 78.72$, $y = 81.80$, $z = 27.15$) has been used in the current protocol by default. The setup for side chain flexibility by selection of the add-visible option, the setting for the selected flexible side chain during the docking option, and other parameters all were kept in default. All docking calculations were carried out using the grid-based MolDock score (GRID) function with a grid resolution of 0.30 Å. The MolDock optimization search algorithm with a maximum of 50 runs was used through the calculations by keeping all other parameters as defaults. All the five poses were examined manually and the best pose was retained.

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