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Synthesis, biological evaluation and computational studies of fused acridine containing 1,2,4-triazole derivatives as anticancer agents

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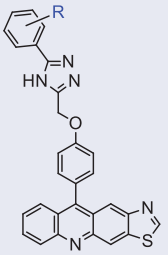
ABSTRACT

A novel series of fused acridine containing 1,2,4-triazole derivatives **(13a-j)** have been synthesized and their structures were confirmed by ^{1}HNMR, 13CNMR and mass spectral data. Further, all these derivatives were tested for their anticancer activity against four human cancer cell lines A549 (Lung), MCF7 (Breast), A375 (Melanoma) and HT-29 (Colon). The IC_{50} values range of target compounds shown 0.11 ± 0.02 to 13.8 ± 0.99 μM as compared with standard drug range 0.11 ± 0.02 to 0.93 ± 0.056 μM. Among them, compounds **13d, 13f, 13g, 13h, 13i,** and **13j** were exhibited more potent activity. Docking simulation was performed as a trial to study the mechanisms and binding modes of these compounds towards the DNA target. The results showed these compounds have intercalated placement in the active sites and stable interactions similar to the co-crystallized reference ligand. Further, these compounds (**13a-j**) were investigated for Drug-likeness, ADME properties and Toxicity risk assessment.

GRAPHICAL ABSTRACT

Four cancer cell lines: lung (A-549), colon (HT-29), breast (MCF-7) and melanoma (A-375)



R; 13d = 3,4,5-trimethoxy	IC_{50} = 1.90 ± 0.96, 0.23 ± 0.02, 1.23 ± 0.11 and 0.11 ± 0.03 μM
R; 13f = 4-chloro	IC_{50} = 0.28 ± 0.03, 1.20 ± 0.13, 0.39 ± 0.02 and 1.10 ± 0.09 μM
R; 13h = 4-trifluoromethyl	IC_{50} = 1.45 ± 0.18, 0.17 ± 0.01, 1.67 ± 0.12 and 2.54 ± 0.19 μM

ARTICLE HISTORY

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KEYWORDS

Acridine; docking and anticancer activity; 1,2,4-triazole

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Introduction

Cancer, which is mostly caused by a mutation of normal cell, has become the disease mostly urgent to be solved because of its high mortality. Novel effective anticancer drugs with a fewer side effects are urgently needed to be developed. As a large percentage of chemotherapeutic drugs currently used in cancer therapeutics are DNA-binding and/or DNA-modifying agents, such as cisplatin, topotecan, adriamycin, et al.[1] As cancer cells express high level of topoisomerase activity and show remarkable sensitivity to DNA-targeted drugs, a large number of anticancer drugs targeted DNA and topoisomerases have been designed and synthesized in these years.[2] In spite of the side effects caused by DNA-targeted compounds and topoisomerase inhibitors, it is still recognized as the main choice to prolong the patents' life. Therefore, the search for novel DNA-binding agents and topoisomerase inhibitors remain a major role in the fight against cancer.

The synthesis of acridine and analogs has attracted considerable attention from organic and medicinal chemists for many years. Further literature survey revealed that various N-substituted containing acridine is a fused polycyclic heteroaromatic compound and has a main scaffold in natural acridine alkaloids,[3] which was possessed a wide range of biological activities such as antitumor,[4,5] DNA Topoisomerase-I/II,[6,7] antimicrobial,[8] fungicidal,[9,10] antiparasitic,[11] antiviral,[12] anti-alzheimer.[13] Furthermore, the pyrido-thiazolo-acridine series with potent anticancer properties[14,15] of natural alkaloids have suggested that thiazolo-acridine derivatives could be of great interest. The FDA approved anticancer drug Amsacrine (**1a,** Fig. 1), was a known acridine derivative and was used for treatment of acute leukemia.

On the other hand, the chemistry involving triazoles has a significant role due to their medicinal and industrial properties as drugs and intermediates respectively in various areas. In that way of aspect, 1,2,4-triazoles are evident for possessing various applications like agricultural, industrial and biological activities.[16] Triazoles are known as

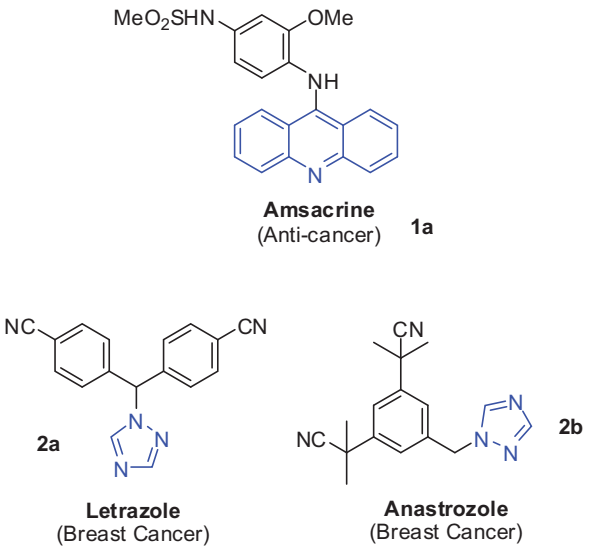


Figure 1. Biologically active acridine and 1,2,4-triazole anticancer drugs.

antimicrobial, antidepressant,[17] anticancer,[18,19] anti-inflammatory,[20,21] antimalarial[22] agents. Examples of anticancer drugs with different medicinal important containing 1,2,4-triazoles are shown in Figure 1.

Based on the above literature survey, we designed newly synthesized fused acridine containing 1,2,4-triazole derivatives and explored for their *in vitro* anticancer profile against a panel of the selected human cancer cell in lines and also correlated with docking studies. In addition, structure-activity relationship (SAR) studies, ADME and risk of toxicity screening properties were evaluated.

Results and discussion

Chemistry

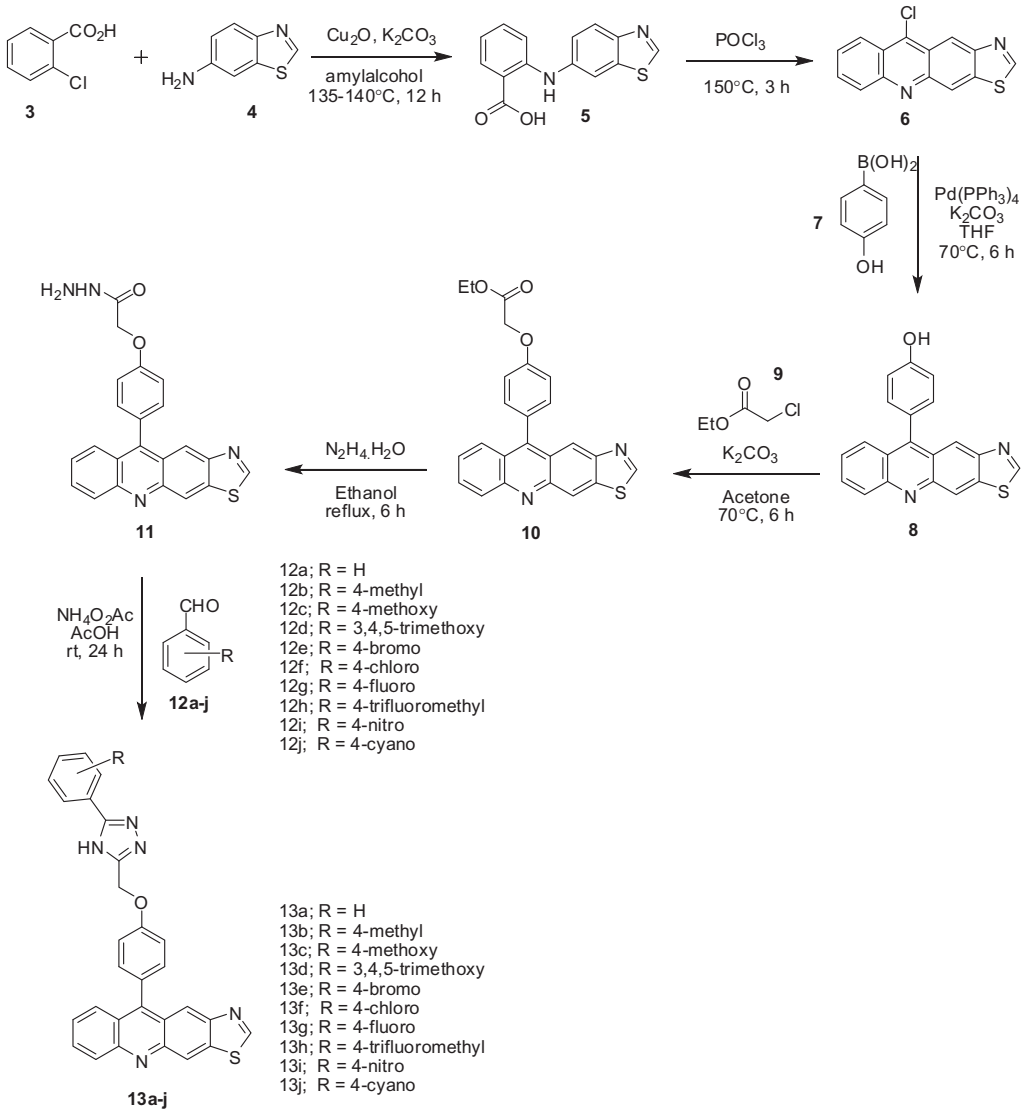
The synthesis of fused acridine containing 1,2,4-triazole derivatives (**13a-j**) was shown in (Scheme 1). Accordingly, Compound **3** was coupled with benzo[d]thiazol-6-amine **4** in the presence of Cu_2O and K_2CO_3 by using amyl alcohol at 135–140 °C for 12 hours to give compound **5** in 77% yield. Then the resulting compound **5** was subjected to cyclization using $POCl_3$ at 150 °C for 3 hours to obtain 10-chlorothiazolo[4,5-b]acridine **6** in 81% yield, which was then subjected to Suzuki coupling reaction with 4-hydroxyphenyl boronic acid **7** in the presence of $Pd(PPh_3)_4$, K_2CO_3 in dry THF at 70 °C for 6 hours to afford 4-(thiazolo[4,5-b]acridin-10-yl)phenol **8** in 80% yield. Later, The compound **8** was treated with ethyl 2-chloroacetate **9** in the presence of K_2CO_3 in dry acetone at 60 °C for 6 hours to afford ester compound **10** in 86% yield. The resulting ester intermediate **10** was then converted to acid hydrazide **11** using hydrazine hydrate in ethanol under reflux conditions for 6 hours to produce acid hydrazide compound **11** in 86% yield.

Finally, compound **11** was cyclized with various substituted aromatic aldehydes (**12a-j**) by using ammonium acetate and acetic acid at room temperature for 24 hours to afford compounds (**13a-j**) in 56–85% yields.

Biological evaluation

Anticancer activity

The anticancer activity of the target compounds (**13a-j**) were evaluated against four different human cancer cell lines such as A549 (Lung), MCF7 (Breast), A375 (Melanoma) and HT-29 (Colon) were assessed utilizing an MTT assay. Here combretastatin-A4 used as reference anticancer drug and the results were expressed in terms of IC_{50} values summarized in Table 1. Most of the compounds showed moderate to excellent activity against all the tested cancer cell lines as compared with the standard. Among them, compounds **13d, 13f, 13 g, 13h, 13i,** and **13j** were exhibited more potent anticancer activity. In general, the highest activity showed by compounds **13f, 13d,** and **13h** were the most active and effective against four cell lines, in which compounds **13f** (IC_{50} = 0.28 ± 0.03, 1.20 ± 0.13, 0.39 ± 0.02 and 1.10 ± 0.09 μM), **13d** (IC_{50} = 1.90 ± 0.96, 0.23 ± 0.02, 1.23 ± 0.11 and 0.11 ± 0.03 μM) and **13h** (IC_{50} = 1.45 ± 0.18, 0.17 ± 0.01, 1.67 ± 0.12, and 2.54 ± 0.19 μM) for A549 (Lung), MCF7 (Breast), A375 (Melanoma) and



Scheme 1. Synthesis of fused acridine containing 1,2,4-triazole derivatives.

HT-29 (Colon) respectively. The next better activity showed by compounds **13i, 13g** and **13j** against three cancer cell lines, in which compounds **13i** (IC_{50} = 0.19 ± 0.02, 0.98 ± 0.08, and 2.34 ± 0.21 μM), **13g** (IC_{50} = 1.36 ± 0.24, 0.52 ± 0.04, and 2.66 ± 0.23 μM) for A549 (Lung), MCF7 (Breast), HT-29 (Colon) and **13j** (IC_{50} = 0.87 ± 0.06, 1.44 ± 0.12, and 1.78 ± 0.14 μM) for A549 (Lung), MCF7 (Breast), and A375 (Melanoma) respectively. Interestingly the highest activity compounds **13f, 13d** and **13h** as compared with reference drug by cell wise showing top highest activity compounds such as lung for **13i** (IC_{50} = 0.19 ± 0.02 μM), breast for **13h** (IC_{50} = 0.17 ± 0.01 μM) and melanoma for **13f** and **13d** (IC_{50} = 1.10 ± 0.09 and 0.11 ± 0.03 μM), respectively.

Table 1. *In vitro* anticancer activities of compounds (**13a-j**) against various cancer cell lines.

Compound	R	A549	MCF-7	A375	HT-29
13a	H	3.78 ± 0.25	2.88 ± 0.21	–	7.45 ± 0.76
13b	4-methyl	12.3 ± 0.98	6.39 ± 0.54	–	–
13c	4-methoxy	13.8 ± 0.99	2.13 ± 0.26	4.89 ± 0.39	10.4 ± 0.94
13d	3,4,5-trimethoxy	1.90 ± 0.96	0.23 ± 0.02	1.23 ± 0.11	0.11 ± 0.03
13e	4-bromo	2.88 ± 0.15	3.54 ± 0.33	–	2.10 ± 0.19
13f	4-chloro	0.28 ± 0.03	1.20 ± 0.13	0.39 ± 0.02	1.10 ± 0.09
13g	4-fluro	1.36 ± 0.24	0.52 ± 0.04	9.78 ± 0.74	2.66 ± 0.23
13h	4-trifluoromethyl	1.45 ± 0.18	0.17 ± 0.01	1.67 ± 0.12	2.54 ± 0.19
13i	4-nitro	0.19 ± 0.02	0.98 ± 0.08	–	2.34 ± 0.21
13j	4-cyano	0.87 ± 0.06	1.44 ± 0.12	1.78 ± 0.14	5.78 ± 0.46
Combretastatin-A4		0.11 ± 0.02	0.18 ± 0.01	0.21 ± 0.02	0.93 ± 0.05

The anticancer activities of the compounds determined by using the MTT assay. The results were expressed as the (IC_{50} μM). "–"= Not active.
Values are mean ± SEM.

Based on the results of anticancer activity of the tested compounds, the structure-activity relationship (SAR) can be summarized which indicate that the change of substituent affects anticancer activity. Introduction of electron-donating groups such as 3,4,5-trimethoxy **13d** in di-meta and para positions of the phenyl ring results in a significant increased anticancer activity against four cell lines. Next, decreases these methoxy groups at phenyl ring and to the only para position 4-methoxy **13c** results shown decreased anticancer activity as compared with compound **13d**. Additional, the introduction of the methyl group at para-position of the phenyl ring **13b** resulted in a decrease of the anticancer activity as compared with **13c** and **13d** respectively. Furthermore, a dramatic increase in activity was observed by compounds 1**3e-j,** in which para position is introduced by electron withdrawing groups at the phenyl ring compound of **13a**. In the halogen withdrawing series **13e-g**, results show that 4-chloro **13f** at the para position of phenyl ring displayed most potent anticancer activity against four cell lines and as compared with 4-fluoro **13g** lost one cell line and 4-bromo **13e** lost three cell lines. After that, compounds **13h-j** introduced strong electron withdrawing groups, it is an interesting point to note that all three compounds shown good activity, in which phenyl group at para position 4-trifluoromethyl **13h** shown highest activity against four cell lines. Compounds with 4-cyano **13j** and 4-nitro **13i** also shown good promising activity as compared with compound **13h**. In particular, compounds with strong donating **13d** and strong with-drawing substitutions **13f-j** at the phenyl were found to be the most active compound of the series. In summary, the information of SAR provided us a guideline to improve the anticancer activity in the future structural modification.

Computational analysis

Molecular docking studies

Docking studies were performed using Autodock Vina to investigate the synthesized compounds for binding affinity with DNA. The DNA was downloaded from protein data bank using PDB ID: **1DSC** octamer duplex complexed with Actinomycin D. Ten different ligands **13a-j** was used for the docking studies for DNA intercalation. Energy minimization for all compounds were carried out using UCSF Chimera. The initial

Table 2. Binding energy (kcal/mole) of acridine-1,2,4-triazole and their interactions with DNA.

S.No	Ligand	Binding energy (kcal/mole)	Interactions (DNA-ligand)	No of hydrogen bonds	Bond-length
1	**13a**	−6.3	DA3, DG4, DC5, DT14, DC13	01	2.00
2	**13b**	−7	DA11, DC13,	01	3.05
3	**13c**	−6.8	DC5, DC13, DA11	02	2.44, 3.03
4	**13d**	−6.7	DA3, DA11, DG12, DT15	02	2.66, 3.23
5	**13e**	−7.1	DA3, DT6, DA11, DG12, DC13, DT15,	–	–
6	**13f**	−7.1	DT6, DA3, DT15, DA11, DG12, DT15	01	3.05
7	**13g**	−7.1	DA3, DC5, DC13, DT6, DA11, DG12, DT15,	02	2.78, 3.05
8	**13h**	−7.4	DA3, DG4, DC5, DT6, DG12, DC13, DT14	01	1.80
9	**13i**	−7.2	DA3, DC5, DT6, DA11, DC13, DT15	02	2.14, 2.73
10	**13j**	−7.4	DA3, DG4, DC5, DA11, DG12, DC13, DT14, DT15	01	2.89
11	Actinomycin D	−3.6	DT6, DT7, DC8, DA11, DG12	03	1.80, 2.60, 2.66

DNA duplex selected for docking was octodecamer 5'-D(*GP*AP *AP*GP*CP*TP*TP*C)-3' (PDB ID: 1DSC). Docking results are presented in Table 2.

Detailed view of the acridine part of compound **13j** and **13h** in docked conformation is shown in Figure 2.

The crystal ligand was removed and sequence of DNA was used for the docking experiments. The model was selected which show the best fit with least RMSD value. The interaction energies between DNA fragment and different compounds were estimated by using the docking experiment. The binding energy values in kcal/mol of the docked structure were reported in Table 2. The calculated binding free energy values of all the ligands were ranges from –6.3 to –7.4 kcal/mol and are comparable with the crystal ligand Actinomycin D –3.6 kcal/mol. From the results, it has been observed that **13j** and **13h** have shown effective binding energy than the other ligands. The binding energy for the **13j** and **13h** was found to be –7.4 kcal/mol and **13i** is –7.2 kcal/mol. The **13j** exhibited the best value and from the (Fig. 3) indicated that acridine moiety could influence the interaction with DNA and have shown interaction with nucleotides DA3, DG4, DC5, DA11, DG12, DC13, DT14, DT15 and these could have played a key role in the binding site of DNA. Moreover, the derivatives **13a**, **13b**, **13c** and **13d** formed hydrogen bonds with the 1,2,4-triazole ring. The compounds **13f-j** have shown the best value of binding energy by forming the interaction of acridine with DNA than the compounds have weak binding energy by the interaction of 1,2,4-triazole with DNA.

Drug-likeness and ADME properties

Bioavailability of acridine containing 1,2,4-triazole derivatives (**13a-j**) was accessed through ADME (Adsorption, Distribution, Metabolism, and Excretion) using

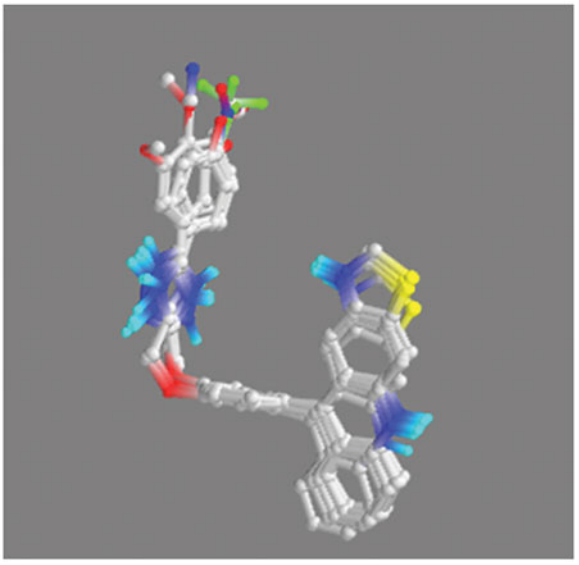


Figure 2. Clusters of all best ligand conformations.

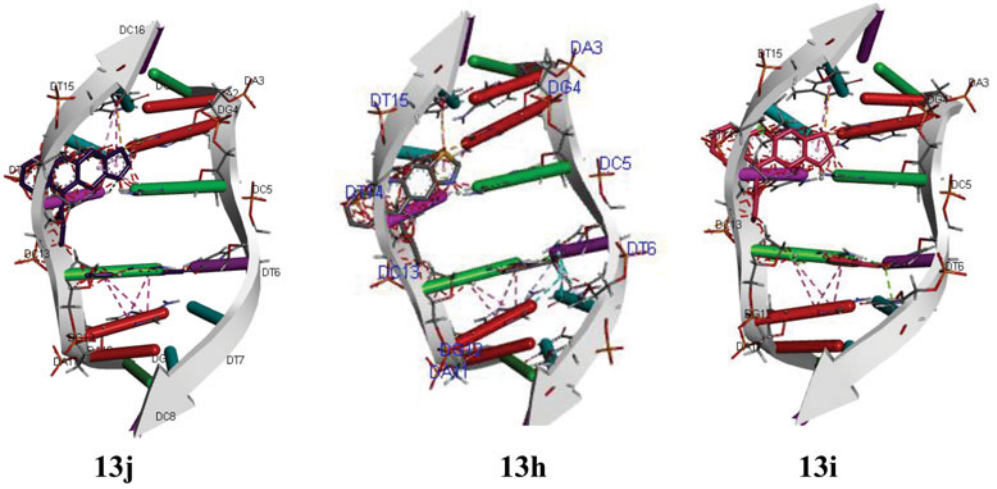


Figure 3. Docking Interactions of **13j**, **13h** and **13i** with DNA (1DSC).

molinspiration. In order to explore drug-like properties of compounds (**13a-l**), the lipophilicity, expressed as the octanol/water partition coefficient and here it is called logP(o/w), as well as other theoretical calculations such as molecular size, the number of hydrogen bond acceptors and donors, TPSA and % ABS: Percentage of absorption as shown in Table 3.

The violation of more than one of these rules may indicate problems in the bioavailability of the potential drugs. The results showed that most of the compounds complied with Lipinski's rule (Table 3), with exception slightly higher values were observed in TPSA ad also a spectra wereslightly molecular size more than 500. Finally summarizing

Table 3. ADME properties.

Compound rule	logP(o/w) <5	MW <500	TPSA <140	HBA <10	HBD <5	nRotB <10	Volume
13a	7.21	485	104	6	1	5	415.1
13b	7.35	499	104.8	6	1	5	431.66
13c	7.26	515	114	7	1	6	440.65
13d	6.84	575	132.5	9	1	8	491.74
13e	8.02	563	104.8	6	1	5	432.18
13f	7.88	519	104.8	6	1	5	428.64
13g	7.37	503	104.8	6	1	5	420.03
13h	8.1	553	104.8	6	1	6	446.05
13i	7.17	530	150.6	9	1	6	438.44
13j	6.96	510	128.6	7	1	5	431.96

Table 4. Toxicity risk assessment of compounds (**13a-j**).

Compound	cLogP	Solubility	Drug likeness	Drugscore	Mutagenic	Tumorigenic	Irritant	Reproductive effect
13a	5.56	−7.86	2.83	0.17	Medium	Medium	No	No
13b	5.9	−8.2	0.93	0.14	Medium	Medium	No	No
13c	5.49	−7.87	2.39	0.16	Medium	Medium	No	No
13d	5.35	−7.91	5.83	0.15	Medium	Medium	No	No
13e	6.28	−8.69	0.4	0.11	Medium	Medium	No	No
13f	6.16	−8.59	3.21	0.14	Medium	Medium	No	No
13g	5.66	−8.17	1.48	0.15	Medium	Medium	No	No
13h	6.4	−8.63	−5.03	0.07	Medium	Medium	No	No
13i	4.63	−8.32	−7.89	0.09	Medium	Medium	No	No
13j	5.39	−8.63	−6.16	0.08	Medium	Medium	No	No

the physicochemical properties of acridine analogs (**13a-j)**, we could conclude that almost they obey the rule-of-five and meet the criteria.

Toxicity risk assessment screening

The toxic properties such as mutagenic, tumorigenic, irritant and reproductive effects were screened for the acridine analogs (**13a-j**) using Molinsperation server. The server is inbuilt with list of about 5300 distinct substructure fragments created by 15,000 commercially available fragments with reported drug score and drug likeness. Drug score associate with clogP, drug likeness and toxicity risks as a total value may be used to judge the overall potential to qualify it as a drug. The toxicity screening of all compounds (**13a-j)** showed that no risk of mutagenic, tumorigenic, irritant and reproductive toxicity (Table 4).

Experimental

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60F-254, and visualization on TLC was achieved by UV light or iodine indicator. ^{1}H and 13C NMR spectra were recorded on Gemini Varian-VXR-unity (300 MHz) instrument. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI + software with capillary voltage 3.98 kV and ESI mode positive

ion trap detector. Melting points were determined with an electrothermal melting point apparatus, and are uncorrected.

General procedure for the synthesis of compounds *(13a-j).* All the reactions (**13a-j)** were performed by 500 mg scale. Compound (**11**) (1.25 mmol) in acetic acid (20 mL), a pinch of ammonium acetate (1.25 mmol) was added followed by the addition of different substituted benzaldehydes (**12a-j**) (1.25 mmol). The mixture was stirred at room temperature for 24 hours. After completion of the reaction as monitored by TLC, the reaction mixture was neutralization with aqueous $NaHCO_3$ solution to gave solid, which was filtered and/or recrystallized from ethanol to afford pure compounds (**13a-j).**

10-(4-((5-Phenyl-4H-1,2,4-triazol-3-yl)methoxy)phenyl)thiazolo[4,5-b]acridine *(13a).* The general procedure 13**a-j** was followed for the synthesis of **13a**, 326.4 mg with 56% yield. Mp: 358–360 °C; IR (KBr): 3266, 3039, 3022, 1514, 1435, 1262, 1033; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.12 (s, 2H), 6.93 (d, 2 H, J = 8.16 Hz), 7.57–7.68 (m, 6H), 7.71 (t, 1H, J = 7.5 Hz), 8.23–8.34 (m, 3H), 8.39 (s, 1H), 8.42 (d, 1H, J = 8.20 Hz), 8.49 (d, 2H, J = 8.09 Hz), 8.54 (s, 1H); 13C NMR (75 MHz, DMSO-d_6): δ 67.4, 117.5, 120.6, 126.4, 127.3, 127.6, 128.3, 128.9, 130.4, 130.7, 132.4, 132.8, 133.5, 135.2, 139.5, 140.4, 142.3, 143.7, 146.4, 149.6, 149.7, 151.3, 157.5, 159.6, 162.8; HRMS (ESI): *m/z* calculated for $C_{29}H_{19}N_5ONaS$ $[M + Na]^+$ 508.1208, found 508.1213.

Biological evaluation

MTT assay

The cytotoxic activity of the compounds was determined using MTT assay, 1×10^4 cells/well were seeded in 200 mL DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 hours at 37 °C in a CO_2 incubator. Compounds, diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 hours of incubation, 10 mL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (5 mg/mL) was added to each well and the plates were further incubated for 4 hours. Then the supernatant from each well was carefully removed, formazon crystals were dissolved in 100 mL of DMSO and absorbance at 540 nm wavelength was recorded.

Molecular docking

2D Structure of molecules were built on chemdraw and saved as mol2 format and these were converted into 3 D structures with open babel in .pdb. The structures were optimized with MM2 force field and refined using Chimera. The ligands were geometry optimized and Gasteiger partial atomic charges were added. Molecular docking was carried out for ligands into DNA using Autodock (v 4.2). DNA (1DSC) obtained from PDB data bank [www.rcsb.org], the crude structure of DNA was cleaned by using Discover studio visualizer and removed water molecules, other ligands are refined by competing the incomplete residues, then add hydrogen's and optimized up to the RMS gradient 0.01. The optimized protein was saved as pdb file, which is further used for

molecular docking studies. The grid box was set in dimensions of 60 × 60 × 60 and spacing of 0.375 A^{o}. Docking runs were carried out using LGA with population set to 150. Each experiment was set to following parameters viz as energy evaluations 2.5 × 10^6, mutation 0.02, and other are set to default. Ten docking runs were performed. At the end of the docking process, minimum energy of interaction between the ligand and DNA was obtained.[22] The results of the docking scores for each ligand are shown in Table 2 (refer in the supplementary material).

Conclusions

In conclusion, a series of fused acridine containing 1,2,4-triazole derivatives **13a–j** were synthesized and evaluated for their *in vitro* anticancer activity. Among the series, compound **13d, 13f** and **13h** with 3,4,5-trimethoxy, 4-chloro, and 4-trifluoromethyl group at the para position of the phenyl ring exhibited the most potent anticancer activity against four cancer cell lines. The mechanism of such derivatives in inhibition of cancer activity was investigated through the docking studies revealed with selectivity tendency for the compounds **13h** and **13j** have shown highest binding energy and in addition the reaming activity compounds have shown good binding energy scores. Overall, the current studies demonstrate that the acridine linked triazole hybrids have the potential to be developed as lead and their further structural modifications may generate promising new anticancer agents in cancer therapy.

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Supporting information

Full experimental details, spectral data of the products, ^{1}H NMR and 13C NMR of all the new compounds can be found via the Supplementary Content section of this article's Web page.

References

[1] Gurova, K. New Hopes from Old Drugs: Revisiting DNA-Binding Small Molecules as Anticancer Agents. *Future Oncol.* **2009**, *5*, 1685. DOI: 10.2217/fon.09.127.

[2] Kathiravan, M. K.; Khilare, M. M.; Nikoomanesh, K.; Chothe, A. S.; Jain, K. S. Topoisomerase as Target for Antibacterial and Anticancer Drug discovery. *J. Enzyme Inhib. Med. Chem.* **2013**, *28*, 419. DOI: 10.3109/14756366.2012.658785.

[3] Wainwright, M. Acridine-a Neglected Antibacterial chromophore. *J. Antimicrob. Chemother.* **2001**, *47*, 1. DOI: 10.1093/jac/47.1.1.

[4] Sugaya, T.; Mimura, Y.; Shida, Y.; Osawa, Y.; Matsukuma, I.; Ikeda, S.; Akinaga, S.; Morimoto, M.; Ashizawa, T.; Okabe, M. 6H-Pyrazolo[4,5,1-de]acridin-6-ones as a Novel Class of Antitumor Agents. Synthesis and Biological Activity. *J. Med. Chem.* **1994**, *37*, 1028. DOI: 10.1021/jm00033a020.

[5] Kimura, M.; Okabayash, i. I.; Kato, A. Acridine Derivatives. V. Synthesis and P388 Antitumor Activity of the Novel 9-Anilino-2,3-Ethylenedioxyacridines. *J. Heterocycl. Chem*. **1993**, *30*, 1101. DOI: 10.1002/jhet.5570300446.
[6] Zhang, B.; Li, X.; Li, B.; Gao, C. M.; Jiang, Y. Y. Acridine and Its Derivatives: A Patent Review (2009–2013)). *Expert Opin. Ther. Pat*. **2014**, *24*, 647. DOI: 10.1517/13543776.2014.902052.
[7] Gensicka-Kowalewska, M.; Cholewiński, G.; Dzierzbicka, K. Recent Developments in the Synthesis and Biological Activity of Acridine/Acridone Analogues. *RSC Adv*. **2017**, *7*, 15776. DOI: 10.1039/C7RA01026E.
[8] Gaĭdukevich, A. N.; Bashura, G. S.; Pertsev, I. M.; Piminov, A. F.; Piatikop, A. I. Determination of the Antimicrobial Activity of Some Acridine derivatives. *Farm. Zh*. **1973**, *28*, 50.
[9] Srivastava, A.; Pathak, R.; Bahel, S. Synthesis of antifungal N-acridin-5-yl, N′-α-aryloxybutanoylhydrazines. *J. Indian Chem. Soc*. **1985**, *62*, 486
[10] Srivastava, A.; Pathak, R. B.; Bahel, S. C. *J. Indian Chem. Soc*. **1985**, *62*, 486.
[11] Ngadi, L.; Bsiri, N. G.; Mahamoud, A.; Galy, A. M.; Galy, J. P.; Soyfer, J. C.; Barbe, J.; Placidi, M.; Rodriguez-Santiago, J. I.; Mesa-Valle, C. Synthesis and Antiparasitic Activity of New 1-nitro, 1-amino and 1-acetamido 9-acridinones. *Arzneimittelforschung*. **1993**, *43*, 480.
[12] Csuk, R.; Barthel, A.; Brezesinski, T.; Raschke, C. Synthesis of Dimeric Acridine Derived Antivirals. *Med Chem Lett*. **2004**, *14*, 4983. DOI: 10.1016/j.bmcl.2004.07.015.
[13] Fang, L.; Appenroth, D.; Decker, M.; Kiehntopf, M.; Roegler, C.; Deufel, T.; Fleck, C.; Peng, S.; Zhang, Y.; Lehmann, J. Synthesis and Biological Evaluation of NO-Donor-Tacrine Hybrids as Hepatoprotective anti-Alzheimer Drug Candidates. *J. Med. Chem*. **2008**, *51*, 713. DOI: 10.1021/jm701491k.
[14] Burres, N. S.; Sazesh, S.; Gunawardana, G. P.; Clement, J. J. Antitumor Activity and Nucleic Acid Binding Properties of Dercitin, a New Acridine Alkaloid Isolated from a Marine Dercitus Species Sponge. *Cancer Res*. **1989**, *49*, 5267.
[15] Taraporewala, I. B.; Cessac, J. W.; Chanh, T. C.; Delgado, A. V.; Schinazi, R. F. HIV-1 Neutralization and Tumor Cell Proliferation Inhibition *in vitro* by Simplified Analogues of pyrido[4,3,2-mn]thiazolo[5,4-b]acridine marine alkaloids. *J. Med. Chem*. **1992**, *35*, 2744. DOI: 10.1021/jm00093a005.
[16] Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-triazoles by Regiospecific Copper(i)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem*. **2002**, *67*, 3057. DOI: 10.1021/jo011148j.
[17] Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. Identification of 4-Substituted 1,2,3-Triazoles as Novel Oxazolidinone Antibacterial Agents with Reduced Activity Against Monoamine Oxidase A. *J. Med. Chem*. **2005**, *48*, 499. DOI: 10.1021/jm0400810.
[18] Li, W. T.; Wu, W. H.; Tang, C. H.; Tai, R.; Chen, S. T. One-Pot Tandem Copper-Catalyzed Library Synthesis of 1-thiazolyl-1,2,3-triazoles as Anticancer Agents. *ACS Comb. Sci*. **2011**, *13*, 72. DOI: 10.1021/co1000234.
[19] El-Sherief, H.; Youssif, B.; Bukhari, S.; Abdel-Aziz, M.; Abdel-Rahman, H. M. Novel 1,2,4-Triazole Derivatives as Potential Anticancer Agents: Design, Synthesis, Molecular Docking and Mechanistic Studies. *Bioorg. Chem*. **2018**, *76*, 314. DOI: 10.1016/j.bioorg.2017.12.013.
[20] Sarigol, D.; Uzgoren-Baran, A.; Tel, B. C.; Somuncuoglu, E. I.; Kazkayasi, I.; Ozadali-Sari, K.; Unsal-Tan, O.; Okay, G.; Ertan, M.; Tozkoparan, B. Novel Thiazolo[3,2-b]-1,2,4-triazoles Derived from Naproxen with Analgesic/Anti-Inflammatory Properties: Synthesis, Biological Evaluation and Molecular Modeling Studies. *Bioorg. Med. Chem*. **2015**, *23*, 2518. DOI: 10.1016/j.bmc.2015.03.049.
[21] Narsimha, S.; Kumar, N. S.; Swamy, B. K.; Reddy, N. V.; Hussain, S. A.; Rao, M. S. Indole-2-Carboxylic Acid Derived Mono and Bis 1,4-disubstituted 1,2,3-triazoles: Synthesis, Characterization and Evaluation of Anticancer, Antibacterial, and DNA-

Cleavage Activities. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1639. DOI: 10.1016/j.bmcl.2016.01.055.

[22] Manohar, S.; Khan, S. I.; Rawat, D. S. Synthesis of 4-aminoquinoline-1,2,3-triazole and 4-aminoquinoline-1,2,3-triazole-1,3,5-triazine Hybrids as Potential Antimalarial Agents. *Chem. Biol. Drug Des.* **2011**, *78*, 124. DOI: 10.1111/j.1747-0285.2011.01115.x.

[23] Gehlhaar, D. K.; Verkhivker, G. M.; Rejto, P. A.; Sherman, C. J.; Fogel, D. R.; Fogel, L. J.; Freer, S. T. Molecular Recognition of the Inhibitor AG-1343 by HIV-1 Protease: Conformationally Flexible Docking by Evolutionary Programming. *Chem. Biol.* **1995**, *2*, 317. DOI: 10.1016/1074-5521(95)90050-0.