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Molecular Docking Studies and Insilico ADMET Screening of Some Novel Chalcone Substituted 9-Anilinoacridines as Topoisomerase II Inhibitors

Kalirajan R*, Pandiselvi M, Sankar S and Gowramma B

Department of Pharmaceutical Chemistry, JSS College of Pharmacy, A Constituent college of Jagadguru Sri Shivarathreeshwara University, Mysuru, India

Abstract

9-anilinoacridine derivatives are inhibiting DNA topoisomerase II (topoII) due to the ability of acridine nucleus to intercalate into DNA base pair. In this study, the identification of potential ligands from chalcone substituted 9-anilinoacridines targeted against topoisomerase-II (1ZXM) by molecular modelling and docking studies using Schrodinger suit-2013 Maestro 9.3 version. *Insilco* ADMET screening also performed by qikprop module of Schrodinger suit. The binding affinity of the designed molecules towards topoisomerase-II (1ZXM) was determined based on the GLIDE score due to various interactions with aminoacids. Many of the designed compounds showed strong hydrogen bonding interactions, hydrophobic interactions and other parameters could also explain their potency to inhibit topoisomerase-II (1ZXM). The chalcone substituted 9-anilino acridine derivatives 1a- 1x have significant binding affinity with Glide score in the range of -5.88 to -7.50 when compared with the standard ledacrine (-5.24). The *insilico* ADMET screening of these compounds also performed and the values of all the properties are within the recommended values. So this work is useful to further synthesis of all the compounds for their cytotoxic activities against topoisomerase II.

Keywords: Topoisomerase-II; Acridine; Chalcone; Cytotoxic; Docking studies; *Insilico* ADMET screening

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Correspondence:
Kalirajan R, Department of Pharmaceutical Chemistry, JSS College of Pharmacy, A Constituent college of Jagadguru Sri Shivarathreeshwara University, Mysuru, India.
Tel: *+91-423-2443393*
Fax: *+91-4232442937*
E-mail: *rkalirajan@ymail.com*
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Introduction

The 9-anilinoacridinesare mainly inhibiting DNA topoisomerase II (topoII), for their ability to intercalate into DNA base pair, stabilizing the DNA–topoII and forming ‘ternary complex’ which involve DNA, intercalated compound and topoII. The inhibition of topoII activity by the double-strand breaks in DNA, leading to cell cycle arrest and apoptosis. The intercalative property was due to the planar aromatic system of the acridine moiety.

In the same context, acridine derivatives have various pharmacological activities like antimicrobial [1], antioxidant [2], anticancer [3-5], antimalarial [6], analgesic [7], antileishmanial [8], antinociceptive [9], acetyl cholinesterase inhibitors [10] and antiherpes [11] etc. The known 9-anilinoacridines seriesAmsacrine was the first DNA-intercalating agents to be considered as a Topoisomerase II inhibitor. The cytotoxicity of DNA-intercalating agents involves the inhibition of DNA- topoisomerase I or II. The detailed SAR studies of acridine-based DNA-intercalating agents suggest that the mode of binding to intercalate with the DNA base pairs. The introductions of various substitutions to 9-aminoacridines were allowed expansion of research on the SAR to afford new insight into molecular interactions at the receptor level [12]. Similarly chalcone derivatives also have various biological activities [13,14] like antimicrobial, anticancer etc. In continuous of our previous research work [15-18], on searching new potent cytotoxic agents, we have designed 9-anilinoacridine analogues bearing the chalcone residue on the anilino rings for topoisomerase II inhibition by molecular docking studies by using by using Schrodinger suit-2013 Maestro 9.3 version. The results revealed that the newly designed 9-anilinoacridine analogues derivatives exhibited significant inhibition with topo II. Generally the topo II inhibitors exhibit cytotoxic activity.

Materials and Methods

Protein preparation [16]

The crystal structure of protein Human *Topoisomerase IIa* (PDB ID: 1ZXM) at 1.87A° was

Table 1: Docking studies for compounds 1a-x with topoisomerase II (1ZXM).

Compound	GScore	Lipophilic EvdW	HBond	Electro	LowMW	RotPenal
1n	**-7.5**	-5.36	-1.66	-0.47	-0.01	0
1s	**-7.5**	-5.75	-1.24	-0.35	-0.16	0
1t	**-7.47**	-4.92	-1.03	-1.36	-0.16	0
1k	**-7.23**	-5.57	-1.24	-0.42	0	0
1o	**-7.11**	-6.4	-0.37	-0.26	-0.08	0
1l	**-7.05**	-5.58	-1.09	-0.38	0	0
1m	**-6.95**	-5.97	-0.68	-0.28	-0.02	0
1x	**-6.93**	-5.1	-0.35	-1.2	-0.29	0
1w	**-6.92**	-5.1	-0.34	-1.2	-0.28	0
1f	**-6.89**	-5.3	-1.02	-0.46	-0.11	0
1j	**-6.87**	-5.66	-0.83	-0.32	-0.07	0
1h	**-6.85**	-5.92	-0.67	-0.24	-0.02	0
1a	**-6.85**	-5.68	-0.7	-0.3	-0.17	0
1g	**-6.82**	-5.66	-0.68	-0.36	-0.11	0
1r	**-6.73**	-5.09	-1.04	-0.44	-0.16	0
1p	**-6.71**	-5.63	-0.65	-0.23	-0.2	0
1e	**-6.58**	-5.2	-0.23	-1.14	0	0
1q	**-6.55**	-5.52	-0.68	-0.21	-0.15	0
1b	**-6.54**	-5.67	-0.61	-0.21	-0.05	0
1c	**-6.46**	-5.8	-0.45	-0.17	-0.05	0
1u	**-6.38**	-5.54	-0.29	-0.18	-0.37	0
1v	**-6.1**	-4.99	-0.54	-0.23	-0.33	0
1d	**-5.88**	-5.19	-0.53	-0.11	-0.05	0
1i	**-5.88**	-5.38	-0.4	-0.08	-0.02	0
Ledacrine (std)	-5.24	-2.94	-0.22	-1.66	-0.42	0

obtained from the Protein Data Bank (PDB) and was used in this study. In general, the protein structures are refined for their bond orders, formal charges and missing hydrogen atoms, topologies, incomplete and terminal amide groups.

The water molecules beyond 5A° were removed. The possible ionization states were generated in the protein structure and the most stable state was chosen. The hydrogen bonds were assigned and orientations of the retained water molecules were corrected. Finally, a minimization of the protein structure was carried out using OPLS2005 force field to reorient side-chain hydroxyl groups and potential steric clashes. The minimization is restrained to the input protein coordinates by a predefined Root Mean Square Deviation (RMSD) tolerance of 0.3A°.

Ligand preparation

The ligands structures were generated in the CDX format using Chem Drawultra version 8.0. These ligands were then converted to the mol2 format and the ligands were prepared by LigPrep module of Maestro in the Schrodinger suite 2013. They were converted from 2D to 3D structures by including stereo chemical, ionization, tautomeric variations, as well as energy minimization and optimized for their geometry, desalted and corrected for their chiralities and missing hydrogen atoms. The bonds orders of these ligands were fixed and the charged groups were neutralized. The ionization and tautomeric states were generated between pH of 6.8 to 7.2 using Epik module. In the LigPrep module, the compounds were minimized by Optimized Potentials for Liquid Simulations-2005 (OPLS-2005) force field in Impact package of Schrodinger until a RMSD of 1.8A° was achieved. A single low energy ring confirmation per ligand was generated and the optimized ligands were used for docking analysis.

Receptor grid generation

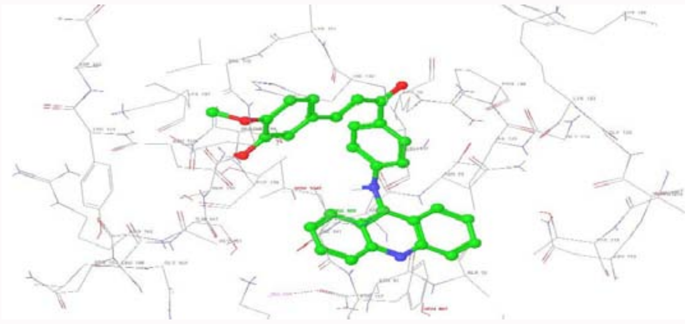
The ligand ANP (phosphoamino phosphonic acid adenylate ester) was retained in the crystal structure of the prepared protein which was used for the receptor grid construction. The binding box dimensions (within which the centroid of a docked pose is confined) of the protein was set to 14A° x 14A° x 14A°.

Validation of the docking programme

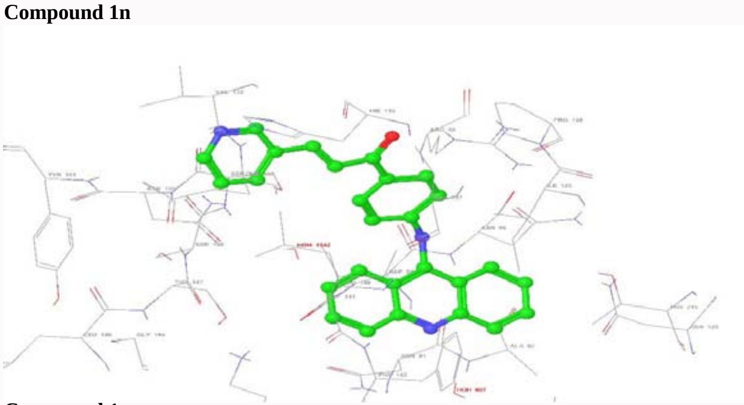
The accuracy of the docking studies are determined by finding how closely the lowest energy pose of the co-crystallized ligand predicted by the object scoring function, Glide score (G Score), resembles an experimental binding mode as determined by X-ray crystallography. The Glide docking procedure was validated by removing the co-crystallized ligand from the binding site of the protein and redocking the ligand with its binding site. The hydrogen bonding interactions and the RMSD between the predicted conformation and the observed X-ray crystallographic conformation were used for analyzing the results.

Glide ligand docking

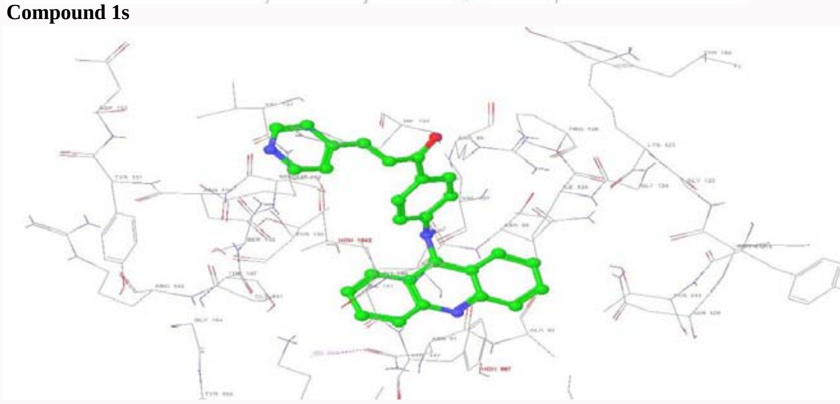
The glide docking of the designed molecules was carried out using the receptor grid and the ligand molecules. The favourable interactions



Compound 1n



Compound 1s



Compound 1t

Figure 1: Best affinity mode of docked compounds 1g & 1f with topo II (1ZXM).

between ligand molecules and the receptor were scored using Glide module of ligand docking program. All the docking calculations were performed using extra precision (XP) mode. The docking process was run in a flexible docking mode which automatically generates conformations for each input ligand. The ligand poses generated were passed through a series of hierarchal filters that evaluate the ligand's interaction with the receptor. The spatial fit of the ligand to the defined active site, and examines the complementarity of the ligand-receptor interactions using grid-based method by the empirical ChemScore function. This algorithm recognizes favourable hydrogen bonding, hydrophobic, metal-ligation interactions, and penalizes steric clashes. Poses that pass these initial screens enter the final stage of the algorithm, which involves evaluation and minimization of grid approximation OPLS non bonded ligand-receptor interaction energy. Finally, the minimized poses were re-scored using Glide Score scoring function.

The XP-Glide score of active compounds were summarized and the fitness scores for each ligand in topoisomerase II are compared. When compared with the G-score of standard compound containing acridine derivative led acrine which is used as anti tumour agent, as well as potent topoisomerase, most of the proposed compounds have good Glide scores [19].

The *in-silico* ADME properties of the proposed compounds were determined by qikprop of Schrodinger software maestro 9.3 version.

Results and Discussion

The molecular docking studies of the designed ligands with protein active sites were performed by an advanced molecular docking program Schrodinger Maestro-9.3 version to determine the various binding affinities of the compounds. The designed compounds are docked towards the topoisomerase-II (1ZXM) in order to ascertain their topo II inhibition activity. The compounds 1a-x (Figure 2) showed good affinity to the receptor when compared with standard ledacrine. The compounds 1n,1s, 1t, 1k, 1o and 1l have more Glide scores (above -7) when compared with standard drug. This is due to more lipophilic evidence and hydrogen bonding. The results are summarized in the Table 1. The best affinity modes of the top three docked compounds (1n, 1s, 1t) with Topoisomerase-II having good

Table 2: *In silico* ADME screening for Compounds 1a-x.

Compound	dipole	Donor HB	Accpt HB	logP o/w	# metab	QPlog Khsa	Rule of Five	% Human Oral Absorption
1a	1.906	1	3.5	6.354	1	1.253	1	100
1b	3.831	1	3.5	6.79	1	1.359	1	100
1c	4.122	1	3.5	6.852	1	1.375	1	100
1d	2.723	1	3.5	6.853	1	1.375	1	100
1e	3.82	1	3.5	7.297	1	1.482	1	100
1f	2.701	2	4.25	5.608	2	1.023	1	100
1g	4.61	2	4.25	5.455	2	1.021	1	95.639
1h	8.748	1	4.5	5.643	2	1.199	1	90.498
1i	7.819	1	4.5	5.645	2	1.2	1	90.495
1j	3.104	1	4.25	6.445	2	1.26	1	100
1k	2.822	1	5	6.589	3	1.283	1	100
1l	3.964	1	5	6.615	3	1.289	1	100
1m	3.473	1	4.5	6.784	2	1.415	1	100
1n	4.479	2	5	5.665	3	1.051	1	100
1o	1.77	1	3.5	7.057	1	1.457	1	100
1p	1.594	1	4	5.707	2	0.982	1	100
1q	1.226	1	3.5	6.255	2	1.171	1	100
1r	4.185	1	4.5	5.675	2	1.01	1	100
1s	4.072	1	5	5.393	3	0.903	1	100
1t	3.287	1	5	5.391	3	0.903	1	100
1u	1.83	1	3.5	4.996	2	0.853	0	100
1v	1.81	1	3.5	5.38	2	0.978	1	100
1w	1.837	1	3.5	5.765	2	1.102	1	100
1x	1.699	1	3.5	5.692	2	1.053	1	100
Recommended values	1- 12.5	0– 6	20-Feb	-8.5	1 – 8	–1.5 – 1.5	max 4	>80% is high <25% is poor

Dipole- Computed dipole moment of the molecule,
donorHB - Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution,
accptHB- Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution,
QPlogPo/w - Predicted octanol/water partition coefficient,
#metab- Number of likely metabolic reactions,
QPlogKhsa- Prediction of binding to human serum albumin,
RuleOfFive Number of violations of Lipinski's rule of five,
%Human- oral absorption- Predicted human oral absorption on 0 to 100% scale.The prediction is based on a quantitative multiple linear regression model.

Glide score are shown in Figure 1.

From the Figure 1, the ligand 4n with the Glide score -7.5, shows the binding affinity with the amino acid residues THR 151, ASN 150, SER 149, LYS 157, HIE 130, ARG 98, VAL 137, ASP 94 and ILU141. The above residues are acting as a binding pocket for the ligand.

The ADMET properties for the synthesized compounds can be determined *in-silico* by using qikprop module of Schrödinger suite 2013. The computed dipole moment of the molecule are in the range of 1,2 -8.7. Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution of the compounds is in the range of 1-2. Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution of the compounds is in the range of 3.5-5. Predicted octanol/water partition coefficient values of the compounds are in the range of 4.9-7.2. The compounds have highest QPlogP value. Numbers of likely metabolic reactions of the compounds are in the range of 1-3. Predictions of binding to human serum albumin for the compounds are in the range of 0.8-1.2. Number of violations of Lipinski's rule of five is 0-1. Many of the compounds have % Human Oral Absorption in the range of 90.4-100%. So almost all the properties of the compounds are within the recommended values. The details of the ADMET properties for the compounds 1a-x are shown in the Table 2.

Conclusion

Acridine derivatives have reported for various biological activities. Similarly chalcone derivatives are also reported for wide range of biological activities. In the present study, the *insilico* report reveals that the chalcone substituted 9-anilino acridine derivatives are significantly active as topoisomerase II inhibitors.

The docking study revealed that the chalcone substituted 9-anilino acridine derivatives showed better alignment at active site by interacting with all crucial amino acid residues. Thus, the *in silico* method adopted in the present study helped to identify the lead compounds and also may explain their beneficial effect in *in vitro* and *in vivo* study. On this basis, authors recently demonstrated that diverse compounds of the chalcone substituted 9-anilinoacridine

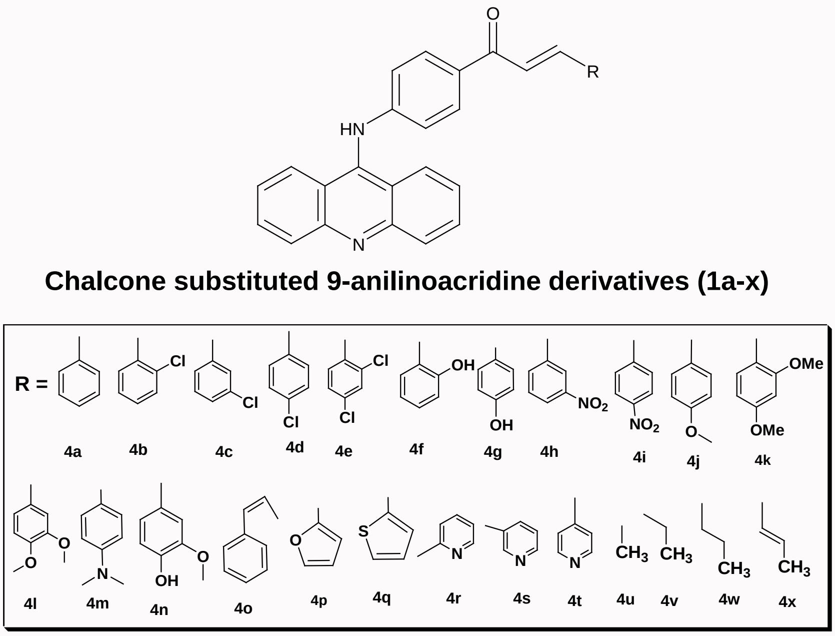


Figure 2: Structure of designed compounds (1a-x).

series exerted topoisomerase II inhibitor activity. Results observed in the present study clearly demonstrated that some derivatives of the chalcone substituted 9-anilinoacridine family may exert interesting cytotoxic activity. The compounds 1n,1s, 1t, 1k, 1o and 1l have significant cytotoxic activity with therapeutic potentials and are likely to be useful as drugs after further refinement.

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Conflicts of Interest

The authors have no conflicts of interest.

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