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RESEARCH ARTICLE

Admet Prediction and Molecular Docking Study of Acridine-Based Analogues as Potential Anti-Cancer Agents

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Abstract: 9-anilinoacridine compounds are known to stop DNA topoisomerase II (Topo II). The acridine nucleus can move between DNA base pairs. Using in silico molecular docking and ADMET prediction via Schrödinger, a number of chalcone-substituted 9-anilinoacridine analogues were created and assessed for their possible Topo II inhibitory action (PDB ID: 1ZXM). Several developed compounds had substantial binding affinity to Topo II, creating hydrophobic interactions and hydrogen bonding with important amino acid residues, according to docking data. The synthetic counterparts' Glide scores, which varied from –5.88 to –7.50, were noticeably higher than those of the common reference drug, ledacrine (–5.24). All of the anticipated pharmacokinetic parameters were found to be within the suggested ranges using in silico ADMET analysis. The chalcone-substituted 9-anilinoacridines need to be synthesized and tested in vitro more. This is especially true for compounds 1n, 1o, 1s, 1l, 1k, and 1t, which showed promising Topo II blocking and cytotoxic potential.

Keywords: Acridine, Topoisomerase II, Cancer, Cytotoxicity, Molecular Docking.

INTRODUCTION

9-Anilinoacridines are well-known DNA intercalating agents that stabilize the DNA Topo II drug ternary complex, thereby inhibiting DNA topoisomerase II (Topo II) [1]. Double-strand breaks, cell cycle arrest, and death result from this stabilization, which stops DNA religation [2]. This intercalative behavior is mainly caused by the planar aromatic acridine system. Numerous biological actions, such as antibacterial, antioxidant, anticancer, antimalarial, analgesic, antileishmanial, antinociceptive, acetylcholinesterase inhibition, and antiherpes effects, are displayed by acridine derivatives [3-5]. Amsacrine was among the first acridine-based Topo II inhibitors to be utilized in clinical settings. Studies using the structure activity relationship (SAR) have shown that DNA binding and enzyme inhibition are greatly impacted by substitution at the 9-anilino site [6, 7]. Chalcone derivatives have also been found to have a variety of pharmacological characteristics, such as antibacterial and anticancer effects [8]. Building on our earlier studies of strong cytotoxic drugs, we created analogues of 9-anilinoacridine with chalcone moieties on the anilino ring and used Schrödinger Suite 2013 for molecular docking to assess their potential to inhibit Topo II [9]. To relieve supercoiling and untangle DNA during transcription and replication, topoisomerase II (topo II), a crucial nuclear enzyme, introduces brief double-strand breaks to control DNA topology. Topo II mutations or aberrant expression in cancer lead to chromosomal translocations, genomic instability, and unchecked cell division [10, 11]. A helpful biomarker for tumor aggressiveness and response to treatment, overexpression of the Topo IIα isoform is frequently seen in quickly proliferating tumor cells and is linked to a bad prognosis. Numerous anticancer medications, including anthracyclines (doxorubicin) and epipodophyllotoxins (etoposide), which stabilize the enzyme DNA cleavage complex and cause an accumulation of DNA breaks and the death of cancer cells, also target Topo II. However, long-term use of these medications might cause chromosomal translocations, particularly affecting the MLL gene, which can lead to therapy-related leukemias. Therefore, Topo II has two roles in cancer: its dysregulation encourages the growth of tumors, and its suppression serves as the foundation for a number of successful chemotherapeutic approaches [12, 13].

MATERIALS AND METHODS

Preparation of Protein

The crystal structure of human Topoisomerase IIα (PDB ID: 1ZXM, 1.87 Å resolution) was found in the Protein Data Bank. Bond orders, formal charges, and missing

hydrogens were added to improve the structure. The OPLS-2005 force field was used to decrease the structure's energy and exclude water molecules that were more than 5 Å from the binding site [14, 15].

Ligand Preparation

ChemDraw Ultra 8.0 was used to create the ligand structures, which were then translated to MOL2 format and processed in Schrödinger's LigPrep. An RMSD of 1.8 Å was attained by minimizing the ligands under the OPLS-2005 force field and optimizing them for shape, tautomeric, and ionization states [16].

Receptor Grid Generation

To specify the binding location, the co-crystallized ligand ANP was kept. The ANP binding location served as the core of a 14 × 14 × 14 Å receptor grid box [17].

Docking Validation

Redocking the co-crystallized ligand into the active site allowed for the validation of docking accuracy. The docking protocol's dependability was validated by the resultant RMSD between docked and crystallographic positions [18].

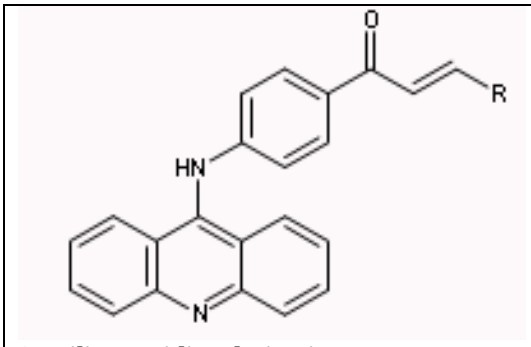
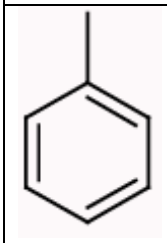
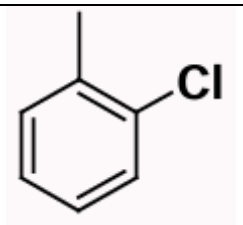
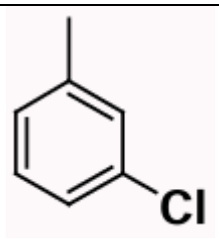
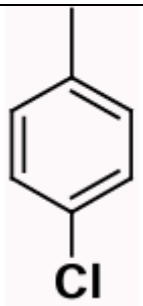
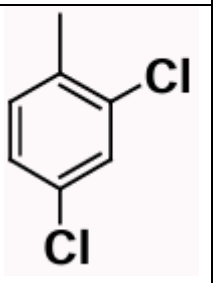
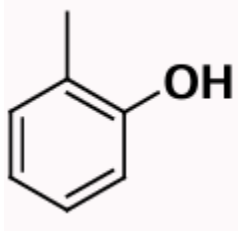
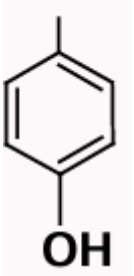
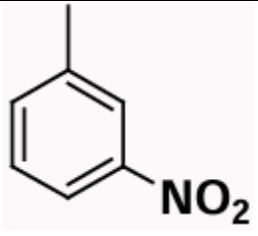
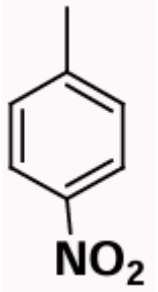
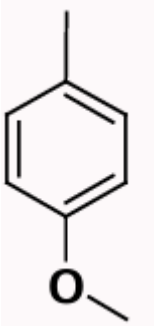
Glide Docking

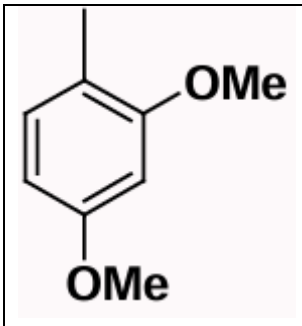
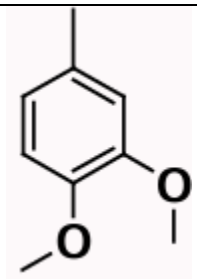
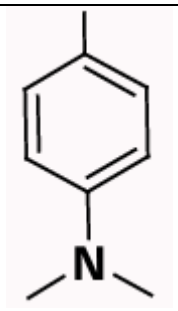
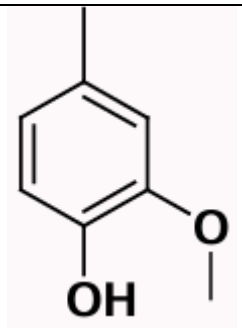
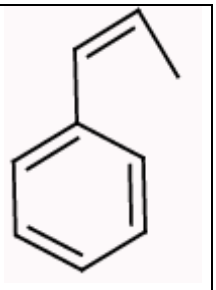
Glide with flexible docking was used to dock all of the produced ligands. Hydrogen bonds, hydrophobic contacts, electrostatic interactions, and steric complementarity were examined in ligand receptor interactions. The reference chemical, ledacrine, was used to compare glide scores [19].

ADMET Prediction

Key characteristics such as dipole moment, H-bond donors/acceptors, logP, metabolic processes, serum albumin binding (QPlogKhsa), Lipinski's rule of five, and projected human oral absorption were evaluated while analyzing in silico pharmacokinetic parameters using QikProp [20-23].

Table 1: Design 9-anilino acridine derivatives

 **9-anilino acridine derivatives**				
				
1a	**1b**	**1c**	**1d**	**1e**
				
1f	**1g**	**1h**	**1i**	**1j**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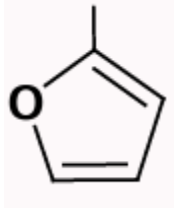
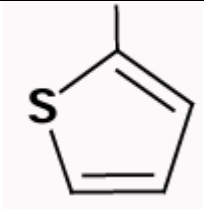
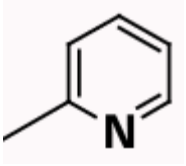
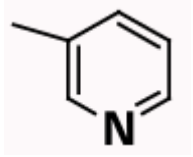
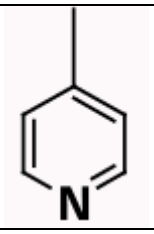
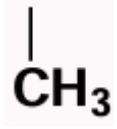
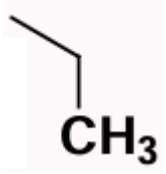
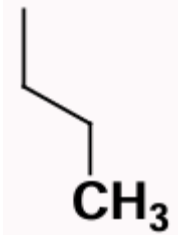
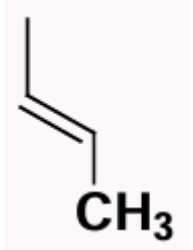
				
1p	**1q**	**1r**	**1s**	**1t**
				
1u	**1v**	**1w**	**1x**	

RESULTS AND DISCUSSION

Molecular Docking Analysis

The Topo II active site was successfully docked with all of the planned compounds (1a–1x). Compounds 1n, 1s, and 1t had the highest binding affinities (≈ –7.5), outperforming ledacrine (–5.24), with Glide scores ranging from –5.88 to –7.50 (Table 1). Key hydrogen bonding and hydrophobic interactions with residues THR151, ASN150, SER149, LYS157, HIS130, ARG98, VAL137, ASP94, and ILE141 were demonstrated by these high-scoring ligands, indicating their critical function in ligand stability inside the Topo II binding pocket. Table 2 Summary of docking results for compounds 1a–x with Topoisomerase II (PDB ID: 1ZXM).

Table 2: Molecular Docking of design compounds against topoisomerase II (PDB ID: 1ZXM).

Design Compound	Glide Score	Lipophilic EvdW	H Bond	Electro	Low MW	RotPenal
1a	-7.5	-5.36	-1.66	-0.47	-0.01	0
1b	-7.5	-5.75	-1.24	-0.35	-0.16	0
1c	-7.47	-4.92	-1.03	-1.36	-0.16	0
1d	-7.23	-5.57	-1.24	-0.42	0	0
1e	-7.11	-6.4	-0.37	-0.26	-0.08	0
1f	-7.05	-5.58	-1.09	-0.38	0	0
1g	-6.95	-5.97	-0.68	-0.28	-0.02	0
1h	-6.93	-5.1	-0.35	-1.2	-0.29	0
1i	-6.92	-5.1	-0.34	-1.2	-0.28	0
1j	-6.89	-5.3	-1.02	-0.46	-0.11	0
1k	-6.87	-5.66	-0.83	-0.32	-0.07	0
1l	-6.85	-5.92	-0.67	-0.24	-0.02	0
1m	-6.85	-5.68	-0.7	-0.3	-0.17	0

1n	-6.82	-5.66	-0.68	-0.36	-0.11	0
1o	-6.46	-5.8	-0.45	-0.17	-0.05	0
1p	-6.38	-5.54	-0.29	-0.18	-0.37	0
1q	-6.1	-4.99	-0.54	-0.23	-0.33	0
1r	-5.88	-5.19	-0.53	-0.11	-0.05	0
1s	-5.88	-5.38	-0.4	-0.08	-0.02	0
1t	-6.73	-5.09	-1.04	-0.44	-0.16	0
1u	-6.71	-5.63	-0.65	-0.23	-0.2	0
1v	-6.58	-5.2	-0.23	-1.14	0	0
1w	-6.55	-5.52	-0.68	-0.21	-0.15	0
1x	-6.54	-5.67	-0.61	-0.21	-0.05	0
Ledacrine	-5.24	-2.94	-0.22	-1.66	-0.42	0

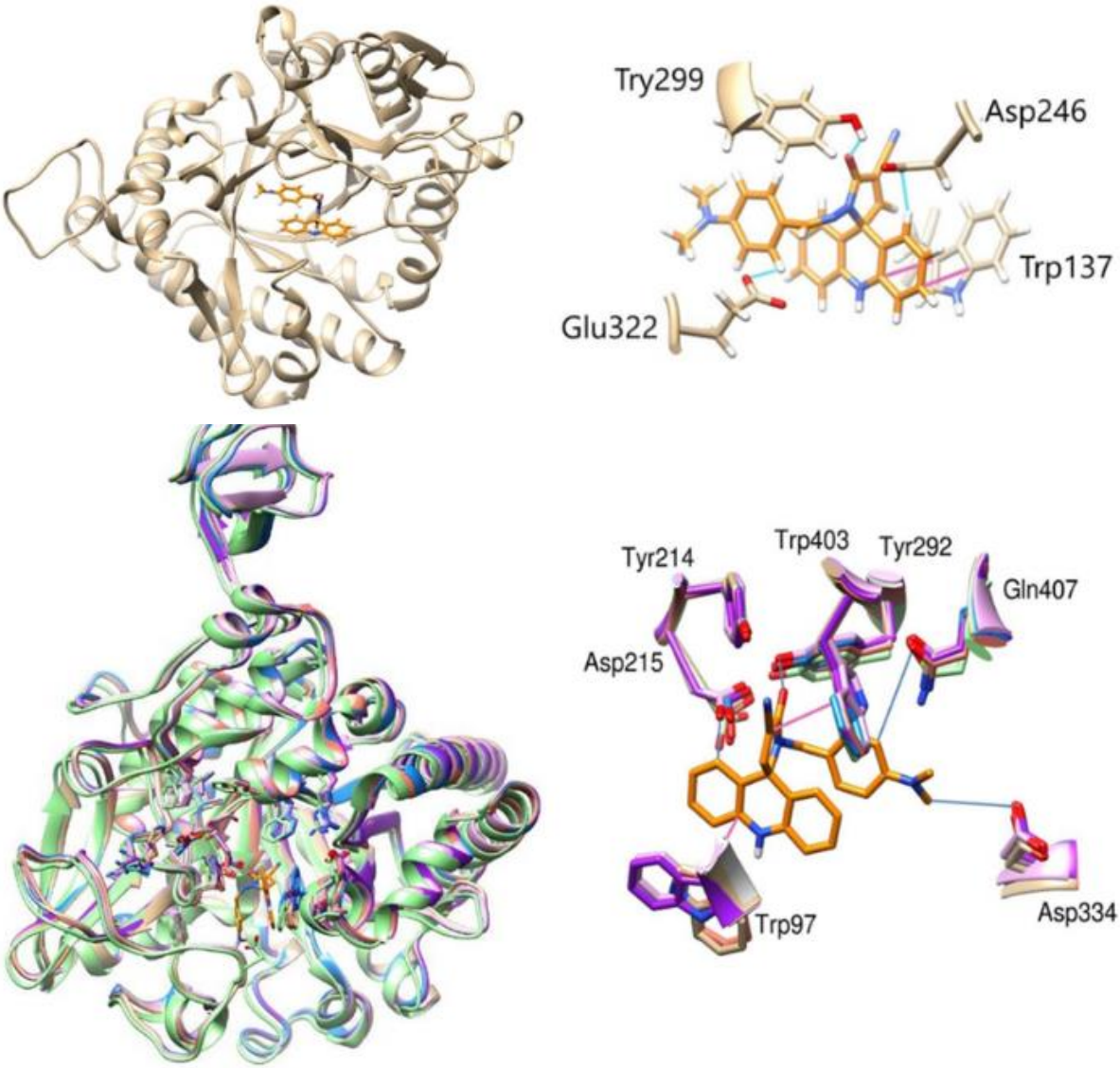


Figure 1: Best affinity molecules of 9-anilino acridine derivatives in molecular docking

ADMET Screening

According to Table 3 QikProp-based ADMET analysis, every molecule complied with Lipinski's rule of five (0–1 infractions). Important parameters that fell within acceptable bounds included logP (4.9–7.2), H-bond donors (1–2), H-bond acceptors (3.5–5), and QPlogKhsa (0.8–1.4). The predicted oral absorption for humans was 90–100%, indicating a high potential for bioavailability.

Table 3: *In silico* ADME screening for design compounds

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

CONCLUSION

Long-term use of these drugs, on the other hand, may cause chromosomal translocations, especially affecting the MLL gene, which can lead to leukemias linked to therapy. Therefore, Topo II has two roles in cancer: blocking it is the basis of many successful chemotherapy treatments, and having it out of whack helps tumors grow. Because they can stop Topo II and connect DNA, acridine derivatives, especially 9-anilinoacridines, are still important building blocks in the search for cancer drugs. A chalcone moiety was added to make these traits even better. According to the in silico study, chalcone-substituted 9-anilinoacridines have a strong binding affinity for Topo II. They also have good pharmacokinetic and toxicological profiles. The compounds 1n, 1s, 1t, 1k, 1o, and 1l showed promise as possible leads for further synthetic optimization and biological assessment, as shown by their high docking scores and ideal ADMET values.

DECLARATIONS:

Consent for publication:

All the authors approved the manuscript for publication.

Competing interests:

All authors declare no competing interests.

Funding:

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