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In Silico ADMET Optimization Studies of Potential Inhibitors of Topoisomerase II

Cosmas O. Okoro*, Aaliyah Flake

Department of Chemistry, Tennessee State University, Nashville, USA
Email: *cokoro@tnstate.edu

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Abstract

About 10 million die annually from cancer, making it one of the major health issues faced in our time. The aim of this research was to find small organic molecules that could act as catalytic inhibitors of topoisomerase IIα (topo IIα), causing cell death thereby acting as anticancer drugs. The methods used include utilization of a template compound (ARN-21934), ADMET, and molecular docking. 117 compounds were found to have structural similarity to ARN-21934 using 0.90 Tanimoto threshold. Only compounds with a molecular weight of 350 g/mol or less and a LogP of less than or equal to 3 were considered. In addition, patented compounds were removed. Sixteen out of the eighteen compounds were found to have no ADMET or Lipinski violations. Molecular docking results of the filtered compounds showed that one compound **(18)** had higher binding affinity for topoisomerase IIα than ARN-21934. The binding affinity of **18** is −10.3 kcal/mol compared to −9.5 kcal/mol observed for ARN-21934. Overall, the results of this study suggest that compound **18** could selectively inhibit topo IIα as effectively as ARN-21934. With no Lipinski violations and pharmacokinetic issues, **18** can be optimized as a viable lead compound for anticancer drug discovery research.

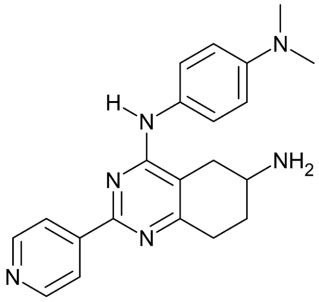
Keywords

Cancer, Topoisomerase II, Docking, Catalytic Inhibitor, Swissadme, Pharmacokinetic, Binding Affinity, LogP

1. Introduction

Cancer is a leading cause of death, claiming a staggering 9.6 million lives yearly and by 2025, 420 million new cancer cases are expected to be diagnosed [1]. In the biochemistry of the human body, topoisomerases are enzymes that are essential to the DNA replication and transcription processes. The focus of our research is the inhibition of type II topoisomerases, responsible for the breaking of the

nucleic acids double helical shape [2]. Topoisomerase II can be further classified as *α* and *β*. Topoisomerase II-*α* is primarily responsible for releasing the DNA topology by manipulating chromosomes within a cell [3]. Thus, the inhibition of this enzyme could cease DNA replication, initiating cell death [4]. A template compound ARN-21934 [5] with selective topoisomerase II-*α* inhibition was used as a starting point for this search. Compared to experimental determination of chemical ADMET properties. In silico methods have shown greater advantages, such as fast, cheap, green and accurate [6]. Moreover, ADMET filters can be used in early drug discovery, such as the selection of screening libraries. Using virtual screening, small organic molecules with similar structure to ARN-21934 (shown in **Figure 1** below) will be examined for their lead-likeness (Lipinski's Rule of 5 [7]-[9], ADMET, and binding affinity).



ARN-21934

Docking score: −9.5 kcal/mol.

Figure 1. Template molecule.

2. Results and Discussion

2.1. Similar Structures to ARN-21934

After manual visual inspection of 117 compounds, only 18 compounds were found to be unpatented and compliant with molecular weights under 350 g/mol and LogP less than 3 when one significant figure is considered. PubChem database [10] was used for compound retrieval and for confirmation that the 18 compounds have not been patented. These 18 compounds were selected for ADMET studies and molecular docking. The International Union of Pure and Applied Chemistry (IUPAC) names and the chemical structures of the 18 compounds are shown in **Table 1** and **Figure 2**, respectively.

Table 1. IUPAC names of compounds 1 - 18.

Compound number	IUPAC Name
1	4-N-(2-pyridin-3-ylmethyl)quinazoline-4,6-diamine
2	4-N-(2-piperidin-1-ylmethyl)quinazoline-4,6-diamine
3	7-N-methyl-4-N-(3-methylphenyl)pyrido[4,3-d]pyrimidine-4,7-diamine
4	4-N-(pyridin-4-ylmethyl)-5,6,7,8-tetrahydroquinoline-2,4-diamine
5	4-N-phenyl-2-pyridin-4-yl-5,6,7,8-tetrahydroquinoline-4,6-diamine

Continued

6	N',N'-dimethyl-N-(2-pyridin-3-yl quinazolin-4-yl)propane-1,3-diamine
7	(5S)-2-phenyl-N-(pyridin-4-ylmethyl)-5,6,7,8-tetrahydroquinoline-5-amine
8	(5S)-2-N,2-N-dimethyl-5-N-(pyridin-3-ylmethyl)-5,6,7,8-tetrahydroquinoline-2,5-diamine
9	(5R)-2-N,2-N-dimethyl-5-N-(pyridin-3-ylmethyl)-5,6,7,8-tetrahydroquinoline-2,5-diamine
10	2-N,2-N-dimethyl-5-N-(pyridin-3-ylmethyl)-5,6,7,8-tetrahydroquinoline-2,5-diamine
11	2-N,2-N-dimethyl-5-N-(pyridin-4-ylmethyl)-5,6,7,8-tetrahydroquinoline-2,5-diamine
12	N-(3-methylbut-2-enyl)-2-pyridin-3-yl-5,6,7,8-tetrahydroquinoline-5-amine
13	2-phenyl-N-(pyridin-4-ylmethyl)-5,6,7,8-tetrahydroquinoline-5-amine
14	2-phenyl-N-(pyridin-3-ylmethyl)-5,6,7,8-tetrahydroquinoline-5-amine
15	2-(2-aminoethyl)-N-[1-(6-methylpyridin-3-yl)ethyl]quinazolin-4-amine
16	2-N,2-N-dimethyl-4-N-(1-pyridin-3-ylmethyl)-5,6,7,8-tetrahydroquinoline-2,4-diamine
17	N-ethyl-2-(pyridin-2-ylmethyl)-5,6,7,8-tetrahydro quinazolin-4-amine
18	2-methyl-N-[(2-methyl-5,6,7,8-tetrahydroquinoline-4-yl)methyl]-5,6,7,8-tetrahydroquinoline-6-amine

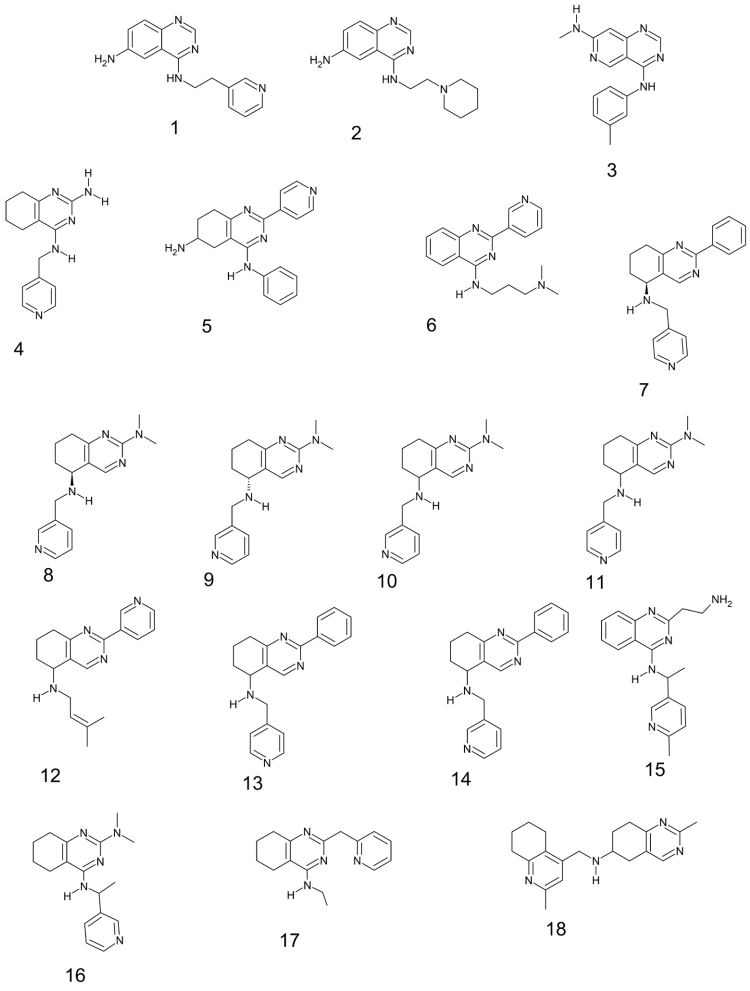


Figure 2. Structures of compounds 1 - 18.

2.2. *In Silico* ADMET

All compounds were shown to have %ABS greater than or equal to 82.53% and

high gastrointestinal absorption, making them suitable for oral ingestion and blood circulation. The bioavailability of the compounds was found to be moderate with a value of 0.55, which will impact dosage. The predicted ADMET profile of all 18 compounds is shown in **Table 2**. The molar refractivity (MR) of the compounds ranges from 73.76 to 96.72, ($cm^3 \cdot mol^{-1}$) with compound **18** having the highest value, suggesting that they have higher probability of being non-toxic in vivo, which is desirable for drug-likeness [6]. Consensus Log P values produced using *SwissADME* for each compound was less than or equal to 3. The predicted toxicity data in **Table 3** showed compounds **3** and **4** to be active (≤0.55). The remaining 16 compounds were predicted to be inactive in hepatotoxicity, cytotoxicity, Androgen receptor and ATPASE AAA domain containing protein (**Table 3**). However, as evident in etoposide, anticancer agents do not necessarily require cytotoxicity [11]. Androgen receptors have been a long-time target for anticancer agents, but studies have shown that the development of resistance to androgen receptor-targeted therapies, such as enzalutamide and abiraterone, in advanced prostate cancer require new treatment approaches [12]. In addition, ATPase domain containing protein, which is responsible for various cellular processes that are dysregulated in cancer, such as autophagy and the proteasome pathway [13], the selected compounds showed moderate toxicity. Due to the unexpectedly low toxicity of the selected compounds, molecular docking data was needed to determine each compound's binding affinity to topoisomerase II*α*.

Table 2. ADME profile of compounds 1 - 18.

Compound	MW	H bond donor	H bond accept	%ABS	rotatable bonds	Cons logP	molar refractivity	gi absorption	bioavailability	lead likeness
1	265.31	2	5	82.53	3	1.63	75.53	High	0.55	Yes
2	271.36	2	5	85.86	4	1.92	86.79	High	0.55	Yes
3	265.31	2	5	87.36	3	2.52	81.15	High	0.55	Yes
4	255.32	2	5	82.53	3	1.77	75.46	High	0.55	Yes
5	317.4	2	5	82.53	3	2.6	94.95	High	0.55	Yes
6	307.4	1	5	90.39	6	2.78	94.2	High	0.55	Yes
7	316.4	1	4	91.51	4	2.95	94.79	High	0.55	Yes
8	283.37	1	5	82.53	3	1.14	73.76	High	0.55	Yes
9	283.37	1	5	82.53	3	1.19	73.76	High	0.55	Yes
10	283.37	1	5	90.39	4	1.72	83.56	High	0.55	Yes
11	283.37	1	5	90.39	4	1.72	83.56	High	0.55	Yes
12	294.4	1	4	91.51	4	2.9	89.06	High	0.55	Yes
13	316.4	1	4	91.51	4	2.95	94.79	High	0.55	Yes
14	316.4	1	4	91.51	4	2.96	94.79	High	0.55	Yes
15	307.4	2	5	82.53	5	2.56	93.38	High	0.55	Yes
16	297.4	1	5	90.39	4	2.62	90.07	High	0.55	Yes
17	268.36	1	4	91.51	4	2.8	80.82	High	0.55	Yes
18	322.4	1	4	91.51	3	3.23	96.72	High	0.55	Yes

Table 3. Toxicity data of selected compounds and the template molecule.

Compound	Hepatotoxicity	Cytotoxicity	Androgen receptor	ATPASE AAA domain containing protein
1	inactive 0.73	inactive 0.65	inactive 0.93	inactive 0.88
2	inactive 0.84	inactive 0.79	inactive 0.98	inactive 0.87
3	active 0.55	inactive 0.85	inactive 0.98	inactive 0.62
4	active 0.55	inactive 0.85	inactive 0.98	inactive 0.62
5	inactive 0.64	inactive 0.71	inactive 0.98	inactive 0.93
6	inactive 0.64	inactive 0.71	inactive 0.98	inactive 0.93
7	inactive 0.71	inactive 0.64	inactive 0.97	inactive 0.91
8	inactive 0.68	inactive 0.54	inactive 0.96	inactive 0.91
9	inactive 0.68	inactive 0.54	inactive 0.96	inactive 0.91
10	inactive 0.68	inactive 0.54	inactive 0.96	inactive 0.91
11	inactive 0.68	inactive 0.54	inactive 0.96	inactive 0.91
12	inactive 0.68	inactive 0.64	inactive 0.96	inactive 0.92
13	inactive 0.71	inactive 0.64	inactive 0.97	inactive 0.91
14	inactive 0.71	inactive 0.64	inactive 0.97	inactive 0.91
15	inactive 0.77	inactive 0.61	inactive 0.94	inactive 0.88
16	inactive 0.63	inactive 0.62	inactive 0.95	inactive 0.88
17	inactive 0.79	inactive 0.58	inactive 0.97	inactive 0.94
18	inactive 0.74	inactive 0.63	inactive 0.98	inactive 0.95
ARN-21934	inactive 0.64	inactive 0.65	inactive 0.96	inactive 0.89

2.3. Molecular Docking

The binding affinity for topo IIα of the template compound ARN-21934 −9.5 kcal/mol versus −10.3 kcal/mol for **18**. Of the 18 docked compounds, compound **18** had the highest binding affinity for topo IIα, as shown in Table 4. Compounds **5**, **7**, **13**, and **14** were not far behind the template compound, having a range of −0.5 to −0.1 kcal/mol difference. The superior binding affinity of **18** confirmed it to be a viable lead compound for optimization. Compounds **14** and **18** are commercially available and have been purchased for *in vitro* testing and validation. The result will be published in a future article.

Compound **18** exhibited the highest molecular docking binding affinity to topo IIα (PDB 1ZXM). The 2D interaction diagram of the complex generated with Biovia Discovery Studio 2025 is shown in Figure 3 below.

Table 4. Binding affinities of compounds 1 - 18.

Compound	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Binding affinity (kcal/mol)	−8.9	−8.3	−8.2	−8.7	−9.0	−8.1	−9.3	−8.6	−8.8	n/a	−8.6	−8.7	−9.3	−9.4	−8.9	−8.0	−8.0	−10.3

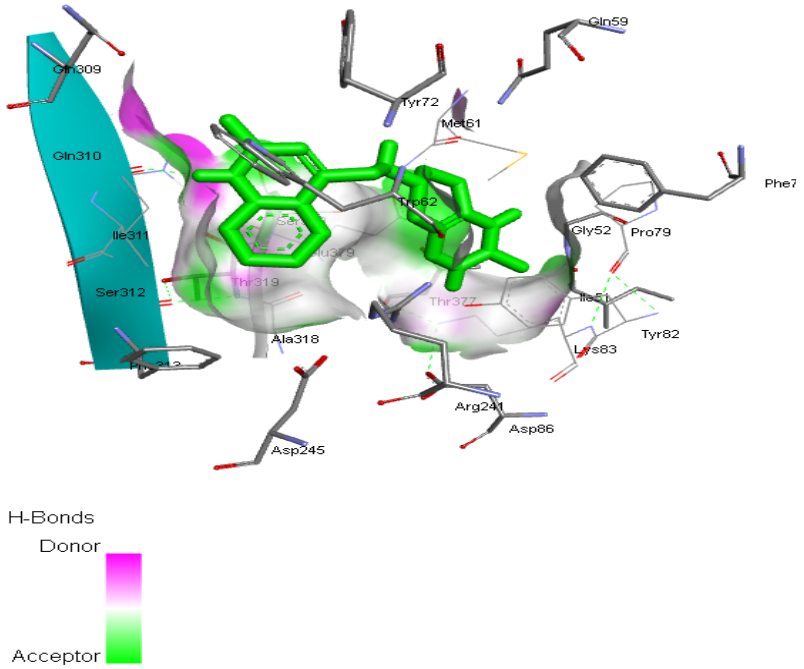


Figure 3. 2D interaction diagram of compound 3 in the active site of Topo II*α*.

3. Experimental Procedure

3.1. Similarity Search for Analogs of ARN-21934

The template compound was searched in *PubChem* database [10] using its common name, ARN-21934. Using the "Similar Structures Search", the settings were adjusted to 90% Tanimoto threshold. The filters were then adjusted from the defaults to only include compounds with molecular weights under 350 g/mol and LogP less than 3. If the entire database is searched, this search will yield over 1200 compounds, so for this round of screening, only the first 117 compounds, sorted by relevance, were used.

3.2. *In Silico* ADMET Data Collection

To obtain the ADME data for each compound, they were entered into *SwissADME* [14]. To use this electronic resource, the compounds must be in SMILES format. Using the sketching tool in *SwissADME*, each compound was drawn individually to be converted to SMILES format. After SMILES were generated for each compound, a complete data summary was generated. %ABS was derived from TPSA (obtained from *SwissADME*) using the formula $\%ABS = 109 - 0.345TPSA$ [15]. For toxicity data, the SMILES structures of the 18 compounds were entered into *ProTox II* [16] and filtered to display hepatotoxicity, cytotoxicity, androgen receptor, and ATPase AAA domain containing protein.

3.3. Molecular Docking

Computer-based molecular docking can expedite the early stages of drug

discovery via a systematic prescreening of small molecule ligands for shape and energetic compatibility with a receptor before experimental evaluation [17]-[19]. In addition, docking studies provide insight into the binding mode of potential drugs at atomic level [17]-[19]. We, therefore, commenced on the molecular docking of the 18 compounds as delineated below.

Virtual Screening: 18 compounds were screened virtually using PyRx 0.98 [20]. PyRx is an open-source program that combines the functionalities of Auto Dock, Vina, Auto Dock 4.2, and Open Babel [21].

1) ***Protein preparation***: The crystal structure of human topo II*α* ATPase/ADP was retrieved from the RCSB protein data bank (PDB ID: 1zxm) and was used as target for the screening of all 18 compounds. 1ZXM is a well-established target for catalytic inhibitors of topoisomerase. The above target was chosen because the template molecule was found to be a selective catalytic inhibitor of topoisomerase II. All water molecules were removed. PyRx automates many intermediate steps including addition of hydrogens steps, energy minimization, removal of bound ligands and heteroatoms, including setting of auto-grid dimensions. The target was initially prepared and saved in pdb file formats but was later converted to a pdbqt file format prior to docking simulation.
2) ***Ligand preparation***: For the construction of ligand files from chemical structures, all eighteen compounds were drawn using ChemSketch, an open source program available as a free download from the developers (ACD Labs) [22]. Once the structure is drawn it is saved as a mol file and then imported into OpenBabel. OpenBabel is a versatile program that converts structural files between a volume of different formats. The ligand file is saved as a pdb file before importing into PyRx, which converts the pdb file into pdbqt file format for docking simulation.

4. Conclusion

In this study, ARN-21934 was used as a template compound to find similarly structured compounds that could selectively inhibit topo II*α*. A total of **18** compounds were selected for ADMET analysis and molecular docking using computational predictions. Of the 18 compounds, **18** showed the highest affinity for topo II*α* and will proceed as our lead compound. Compounds **3** and **4** will be excluded from future studies due to predicted hepatotoxicity and low binding affinities. Compounds **5**, **7**, **13**, and **14** had slightly less binding affinities than the template compound but will be archived for future studies. The hit compound (**18**) is commercially available and will either be purchased or synthesized and then evaluated in vitro using biochemical assay for possible inhibition of topo II*α*.

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Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this article.

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