Medicinal Chemistry & Drug Discovery

In–Vitro Anticancer and Antibacterial Activities of Brominated Indeno[1,2-b]qinoline Amines Supported with Molecular Docking and MCDM**

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The present study describes mono substituted indeno[1,2-b]quinolines (**3a–c** and **5**) have much more antiproliferative potentials than positive controls against A549, HeLa, MCF7 and Hep3B cell lines (IC_{50} values 1.1–29.6 μg/mL) and show similar cytotoxicity (14.3% to 19.8%) to cells such as controls. Moreover, the mono substituted indeno[1,2-b]quinoline amines (**3a–c** and **5**) exhibit significant antimicrobial activity with MIC values between 15.62 μg/mL and 250 μg/mL. The compounds can also bind to DNA in the groove binding mode with a binding constant range of 1.1×10^{3}–$1.1\times10^{5}\,M^{-1}$. The anticancer and antibacterial properties of compounds were confirmed with the molecular docking simulation for their pharmacokinetic. As a result, the preliminary experimental data and a multi-criteria decision-making methodology (MCDM) indicated that the mono substituted indeno[1,2-b]quinoline amine derivatives, especially **3a** and **5**, exhibit effective pharmacological properties. parameters and their interaction with related cells at the molecular level.

1. Introduction

Cancer still has a very devastating effect worldwide. Approximately 18,000,000 new cancer cases were diagnosed in 2018 and 9,500,000 people died from these diseases,[1] due to the resistance to cancer drugs used in primary therapy, clinicians have to turn to secondary therapy using different drugs. This situation prolongs the treatment process and reduces the patient's resistance. Therefore, often bacterial opportunistic infections cause fatal complications in cancer patients.[2–4] However, recent excessive use of antibiotics has led to an increased prevalence of antibiotic-resistant bacteria. Several super-resistant bacteria, especially in hospital intensive care units, have become the only cause of death. Interestingly, it is stated that many tumor developments are based on inflammatory conditions.[5] In this case, people who have severe infections may be at risk of developing cancer. All these developments are challenging scientific studies for the development of new and effective anticancer and antimicrobial agents.

Indeno[1,2-b]quinolines structurally consisting of a fused indene and quinoline rings are natural tetra aromatic heterocyclic compounds having medicinally importance.[6] The Friedlander reaction, well-known method for preparing quinolines, is considered one of the most useful methods for preparing bicyclic azaaromatic compounds.[6–8] Synthetic organic chemistry also presents a new opportunity to develop functionalization and synthesis of quinoline and indole derivatives.[9–10] The pharmaceutically useful indeno[1,2-b]quinolines scaffolds are common heterocyclic structure in natural products and possess a range of significant therapeutic potential such as anti-malarial, anti-inflammatory, anti-plasmodial, antibacterial, anticancer, antiviral, antifungal, antiprotozoal, anticonvulsant and enzyme inhibitory activities.[7,11–15] The natural alkaloid camptothecin and its semi-synthetic analogue topotecan are two examples of cytotoxic quinoline-indene fused compounds with antitumor property through inhibition of DNA enzyme topoisomerase I.[16–17] Topotecan is currently used as an anticancer drug, bearing the tetracyclic indenoquinoline pharmacophore, through inhibition of topoisomerases I and II enzymes.[18–20] Today, there have been many significant findings

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between some biological samples such as DNA/BSA and the structure activity relationships of indeno[1,2-b]quinolines.[21] Moreover, the antiproliferative activities of tetracyclic indenoquinolines against breast (MCF7), lung epithelial (A549) and cervical (HeLa) adenocarcinoma cells were reported. The cytotoxicities of several of these tetracycles are comparable to or better than that of camptothecin.[22] Therefore, the indeno [1,2-b]quinolines are considered important pharmacophore scaffolds for the development of new therapeutic agents and DNA/BSA binding ligands.[23–24]

The inhibition mechanism of DNA topoisomerase I and II by indeno[1,2-b]quinolines has not been fully elucidated. However, recent studies show that these molecules exhibit anticancer activity by interacting with a G-quadruplex in DNA telomeres.[25–26] Synthetic chemists are heavily using studies involving bioorganic and bioorganometallic processes to improve the medical use of quinolines.

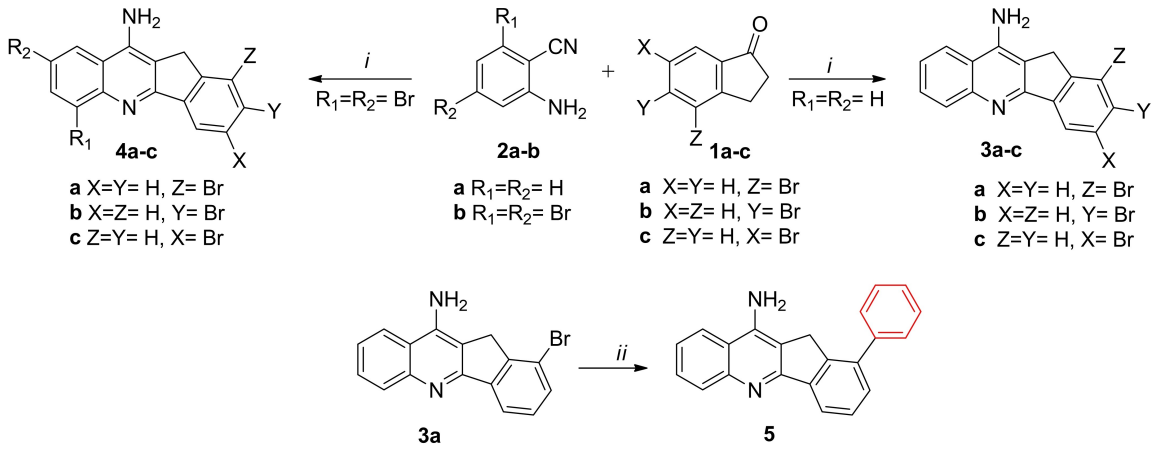
The tests of preclinical studies are long-term and costly processes. During the current COVID 19 pandemics, the importance of the pace of drug development studies has been understood more clearly. In this context, it can be said that the problem of determining the most effective compound among anticancer agents, which is one of the main objectives of this study, is critical in terms of cost and speed. In this framework, the ability to make a correct and fast decision can be considered within the scope of multi-criteria decision problems in the literature.[27–28] Therefore, it would be appropriate to use the multi-criteria decision making (MCDM) methodology for the solution of the relevant problem. MCDM methodology includes methods that aim to reach the best / most appropriate solution among the alternatives under the influence of the determined evaluation criteria. This possibility offered by MCDM algorithms is the main reason why they are frequently used in the literature for decision-making problems involving multiple criteria to select / rank the alternatives.

Recently, the preparation and enzyme inhibitory activities of bromo indeno[1,2-b]quinoline amine derivatives.[7] The significant inhibitory activities of bromo indeno[1,2-b]quinoline amine derivatives against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), cytosolic carbonic anhydrase enzymes (hCA I and hCA II) encourage us to investigate determination of anticancer effects against different cancer cell lines, and antibacterial activities against some Gram (+) and Gram (−) microorganisms. In addition, the activity of the bromo indeno [1,2-b]quinoline amines was supported by molecular docking studies and multi criteria decision making (MCDM) method.

2. Results and Discussion

2.1. Chemistry

Due to that heterocyclic aromatics, particularly *N* function aromatics, are precursors of a large amount of pharmacological compounds, the functional brominated indeno[1,2-b]quinoline amine derivatives were prepared according to our recent papers.[6–8] Mono and tribromo indeno[1,2-b]quinolines were prepared via Friedländer reactions between 2-aminobenzonitrile (**2a**) or corresponding brominated 2-aminobenzonitriles (**2b**) and bromoindan-1-ones (**1a–c**), instead of direct bromination of indeno[1,2-b]quinoline nucleus.[6,7] First, the cyclodehydration reaction under toluene reflux was evaluated with several bromo indan-1-ones **1a–c** and 2-aminobenzonitrile (**2a**) in the presence of $InCl_2$, Lewis acid as catalyze. Then, bromo indan-1-ones (**1a–c**) were treated with 2-amino-3,5-dibromobenzonitrile (**2b**) according to our previous procedure.[6,7] These reactions were furnished mono bromo (**3a–c**) and tribromo indeno[1,2-b]quinoline amines (**4a–c**) in moderate yields of products (44–50%) (Scheme 1). Next, we reinvestigated Suzuki Miyaura cross coupling reactions of compound **3a**. This coupling reaction of monobromo **3a** with one equivalent of phenylboronic acid afforded 1-phenyl **5**, indeno[1,2-b]quinoline amines in high yield (96%) (Scheme 1).[7] Furthermore, the metabolic enzyme inhibition activity of these compounds **3a–c, 4a–c** and **5** against several metabolic enzymes (AChE, BChE, hCA I and hCA II) was determined by the Ellman's method and esterase assay, respectively. The results showed that all



Scheme 1. Preparation of monobromo (**3a–c**) tribromo (**4a–c**) and phenyl substituted (**5**) indeno[1,2-b]quinoline amines. Reagents and conditions; (*i*) Toluene, $InCl_3$ (1.1 equiv), reflux, 24 h, then, NaOH (2 M), reflux, 24 h. (*ii*) $PhB(OH)_2$ (1.3 equiv), $Pd(PPh_3)_4$ (0.05 equiv), K_2CO_3 (3 M), dioxane, reflux, 4 h.

Table 1. GI_{50}, TGI, LC_{50} and IC_{50} of test compounds against A549, Hep3B, HeLa and MCF cell lines*.

Comp. #	A549				Hep3B			
	GI_{50}	TGI	LC_{50}	IC_{50}	GI_{50}	TGI	LC_{50}	IC_{50}
3a	2.2±0.2	4.9±0.3	27.5±1.9	4.4±0.2	1.0±0.1	1.1±0.1	8.8±0.5	1.1±0.1
3b	1.7±0.1	3.9±0.2	40.3±2.7	5.2±0.3	1.1±0.1	1.8±0.1	15.4±1.1	1.8±0.1
3c	2.8±0.2	7.1±0.3	36.8±2.1	6.5±0.3	1.6±0.1	3.3±0.2	26.7±1.7	3.3±0.1
4a	3.1±0.2	301.2±18.7	>1000	>1000	3.2±0.2	>1000	>1000	984.8±75.4
4b	10.7±0.7	>1000	>1000	>1000	5.4±0.4	>1000	>1000	>1000
4c	85.5±6.8	>1000	>1000	>1000	5.8±0.3	>1000	>1000	>1000
5	2.1±0.1	4.3±0.2	19.6±1.3	3.8±0.2	1.0±0.1	1.1±0.1	2.1±0.2	1.1±0.1
Cisplatin				60.49±5.1				48.69±5.2
5-FU				69.79±4.8				62.89±5.5
Comp. #	HeLa				MCF7			
	GI_{50}	TGI	LC_{50}	IC_{50}	GI_{50}	TGI	LC_{50}	IC_{50}
3a	1.2±0.1	2.1±0.1	11.5±0.9	1.9±0.1	1.4±0.1	2.8±0.1	28.1±2.3	2.7±0.1
3b	2.8±0.2	12.7±1.1	842.3±64.1	11.5±0.9	1.1±0.1	1.7±0.1	7.6±0.5	1.7±0.1
3c	1.8±0.1	3.7±0.1	18.8±1.5	3.7±0.1	1.9±0.1	4.6±0.2	31.1±2.7	4.5±0.2
4a	4.9±0.3	227.6±19.3	>1000	198.3±14.0	2.3±0.1	>1000	>1000	>1000
4b	7.1±0.5	>1000	>1000	>1000	1.7±0.1	>1000	>1000	>1000
4c	415.7±37.6	>1000	>1000	>1000	1.8±0.1	>1000	>1000	>1000
5	1.6±0.1	2.8±0.1	12.5±0.9	2.9±0.1	1.8±0.1	3.9±0.1	22.3±1.9	3.8±0.1
Cisplatin				50.29±5.2				63.79±5.6
5-FU				61.59±5.0				74.19±5.5

*Values are given as the mean±SD of three experiments and $r^2 = 0.88$ to 0.99. Significant at $P < 0.05$.

compounds inhibited cytosolic carbonic anhydrase isoenzymes, hCA I and hCA II, as compared to AZA in nM concentration scale.[7] Also, 1-phenylindeno[1,2-b]quinoline **5** amine showed high inhibition potential against AChE and BChE, as compared to tacrine in nM concentration scale.[7] These results have encouraged us to reveal their anticancer potentials. Because heterocycles, notably quinolines, have broad biological activities, i.e. chloroquine, an antimalarial agent[29–30] and a treatment agent for COVID-19.[31]

2.2. Biochemical works

2.2.1. Inhibition of cellular proliferation

The anticancer effects of tetra cyclic tacrine (indeno[1,2-b] quinoline amine) derivatives were reported in many works. In our recent study,[32] the significant antiproliferative activities of tacrine derivatives against A549, HeLa, MCF7 and Hep3B cell lines using MTT assay were reported. In this work, brominated indeno[1,2-b]quinoline amines were recently synthesized by our research group and the anticancer effects of a total of seven compounds were evaluated according to the MTT protocol. Growth inhibition (GI_{50}), total growth inhibition (TGI) and lethal concentration (LC_{50}) parameters of the compounds were evaluated according to NCI screening method and half-maximal inhibitory concentration (IC_{50}) of these compounds were calculated using Four-Parameter Logistic Function, as well.

When TGI and IC_{50} values of the compounds are examined, we found that 10-amine-1-bromo-11H-indeno[1,2-b]quinoline (**3a**) (IC_{50} values between 1.1 and 4.4 μg/mL; TGI values between 1.1 and 4.9 μg/mL) among all the above compounds showed anticancer effect against all tested cell lines (Table 1 and 2). Moreover, the other mono bromides, 2-bromo **3b** (IC_{50} values between 1.7 and 11.5 μg/mL; TGI values between 1.7 and 12.7 μg/mL) and 3-bromo **3c** (IC_{50} values between 2.8 and 6.5 μg/mL; TGI values between 3.2 and 7.1 μg/mL) cause a very strong antitumor property against all tested cell lines compared with the positive controls, cisplatin and 5-florouracyl (5-FU) (Table 1). On the other hand, 1-phenyl substituted indeno[1,2-b]quinoline amine **5** has significant antiproliferative activity against all tested cancer cell lines (IC_{50} values between 1.1 and 3.8 μg/mL; TGI values between 1.1 and 4.3 μg/mL). Furthermore, the IC_{50} and TGI values of tribromides (**4a–c**) displayed that these compounds do not have any inhibition effect of proliferation of cancer cell lines. These results showed that in terms of having high anticancer activity, the substitution of indeno[1,2-b]quinoline amine at C-1 position is important due to significant antitumor activities of both **3a** and **5** against all cancer cell lines, but three bromine atom bounded at C-1/2/3, C-6 and C-8 led to significantly decrease the antiproliferative activity. In addition, the active compounds can be used in advanced pharmacological studies when low GI_{50} values (~1–2 μg/mL) and high LC_{50} values (~40–400 μg/mL) are considered (Table 1 and 4). Overall, the GI_{50}, TGI and LC_{50} parameters

Table 2. The binding constants (K_b) of these compounds.

Compounds #	K_b (M^{-1})	Hyperchromacity	Hypochromicity
3a	1.1×10^5		✓
3b	2.9×10^3		✓
3c	1.1×10^3		✓
4a	5.2×10^4	✓	
4b	2.4×10^4	✓	
4c	2.3×10^4	✓	
5	1.5×10^3		✓

Table 3. Minimum-inhibitory concentrations (MIC, in μg/mL) of these compounds.

Compounds μg/mL	E. faecalis ATCC19433	E. faecalis ATCC29212	S. aureus ATCC25923	S. aureus ATCC29213	S. aureus ATCC46300	E. coli ATCC25922	E. coli ATCC35218	P. aeruginosa ATCC27853
3a	31.25	31.25	31.25	31.25	31.25	125	125	125
3b	62.50	125	62.50	62.50	62.50	500	1000	1000
3c	125	250	62.5	250	62.5	1000	250	500
4a	31.25	31.25	31.25	62.5	31.25	250	250	250
4b	500	1000	500	1000	1000	1000	1000	1000
4c	62.50	250	250	250	500	1000	>1000	>1000
5	31.25	31.25	125	15.62	31.25	1000	1000	1000
SCF	250	62.50	250	62.50	250	15.62	31.25	250

SCF: Sulbactam (30 μg) + cefoperazone (75 μg), as a positive control

Table 4. The estimated free energies of binding (kcal/mol) between the investigated compounds and related target proteins of cancer cell lines.

Comp. #	3VHE (A549)	5VND (Hep3B)	6İ2İ (HeLa)	1M17 (MCF7)
	The estimated binding free energies (kcal/mol)			
3a	−7.83	−7.33	−7.97	−7.99
3b	−7.76	−7.15	−7.18	−8.85
3c	−6.08	−6.83	−7.69	−6.89
4a	−3.85	−3.05	−4.18	−3.61
4b	−3.23	−3.66	−4.13	−3.53
4c	−4.13	−2.43	−4.15	−3.27
5	−9.25	−8.13	−7.75	−7.38

of the respective compounds are at the desired level and meet the NCI criteria.

2.2.2. Cytotoxic activity of the compounds

For a substance to be important, the toxicity against normal cells should be minimal. Due to that, antitumor and cytotoxicity of these compounds should be compared in order to find the forward pharmacological capacity of each. The cytotoxic activities of the compounds in cells were tested by the LDH cytotoxicity assay, another important test indirectly demonstrating membrane damage. When cytoplasmic LDH activity measurement results are evaluated for indeno[1,2-b]quinoline amine derivatives, it has been found that the compounds **4a–c** and **5**, for A549 cell lines, **4a–c** for Hep3B cell lines, **4a** and **4c** for MCF7 cell lines, **3b** and **4b** for HeLa cell lines led to approximately 14.3% to 19.8% membrane damage at their IC_{50} concentration (Figure 2) compared to controls (5-FU and Cisplatin). On the other hand, the other compounds, especially showed high anticancer activity, **3a**, **3c** and **5** have slightly cytotoxicity (20.5–32.2%) against tested cancer cell lines. These results indicated that these compounds **3a–c** and **5** cause little membrane damage at their IC_{50} concentrations.

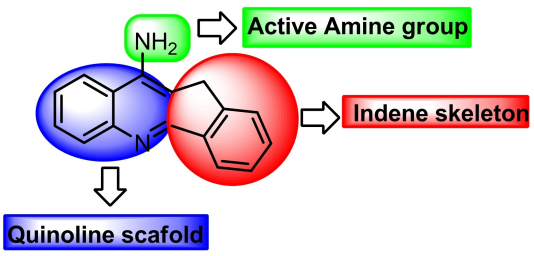


Figure 1. General Structure of Indeno[1,2-b]quinoline amine.

2.2.3. Spectral analysis of the compounds-DNA interactions

DNA binding properties of the compounds were determined using UV-Vis spectrophotometer. Binding type and binding constants of the compounds were tried to be explained below. These compounds have no clear red shifts or blue shifts at their maximum absorption peak. When the addition of CT-DNA was increased amount of the reaction mixture, the reduction in the absorption intensity of **3a–c** and **5** resulted in hypochromic effect and the increase in the absorption intensity of **4a–c** caused hyperchromic appearance (Table 2, Figure 3). The binding constants (K_b), showing the affinity of the complex to DNA, of the compounds with the aid of the following Wolf Shimner Equation equality: $[DNA]/(\varepsilon a-\varepsilon f) = [DNA]/(\varepsilon b-\varepsilon f) + 1/K_b(\varepsilon b-\varepsilon f)$ were determined, the [DNA] symbol in this equation is the DNA concentration in the base pairs and the εa, εf and εb symbols are the molar absorption coefficients of the $A_{observed}$/[compound], free compound and compound-DNA solutions, respectively. K_b, the binding constant related to affinity between the compound and DNA, can be calculated algebraically from the slope of the line drawn between [DNA]/(εa-εf) and [DNA]. The calculations of binding constants showed that the K_b values of the compounds were in ranges between 1.1×10^3 and 1.1×10^5 M^{-1} (Table 2). The binding constants of the molecules in this group are ordered from large to small as follows: **3a** > **4a** > **4b** > **4c** > **3b** > **5** > **3c**. When the data in Table 2 are examined, it is understood that **3a**, **4a** and **4b** bind DNA much more strongly than others.

2.2.4. Cell morphology

The phase-contrast microscopy was used to evaluate morphological changes of treated cancer cell lines. When the treatment of A549, Hep3B and MCF7 cell lines with **5** at 5 μg/mL concentration pronounced superficial and significant changes were observed and visualized in the cell lines. As shown in

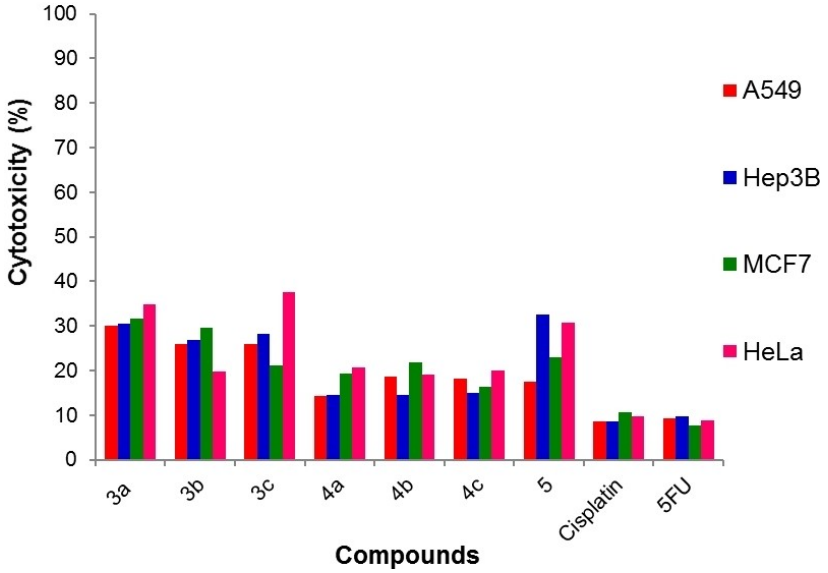


Figure 2. % Cytotoxicity of these compounds (**3a–c**, **4a–c** and **5**) against A549, Hep3B, MCF7 and HeLa at IC_{50} concentration.

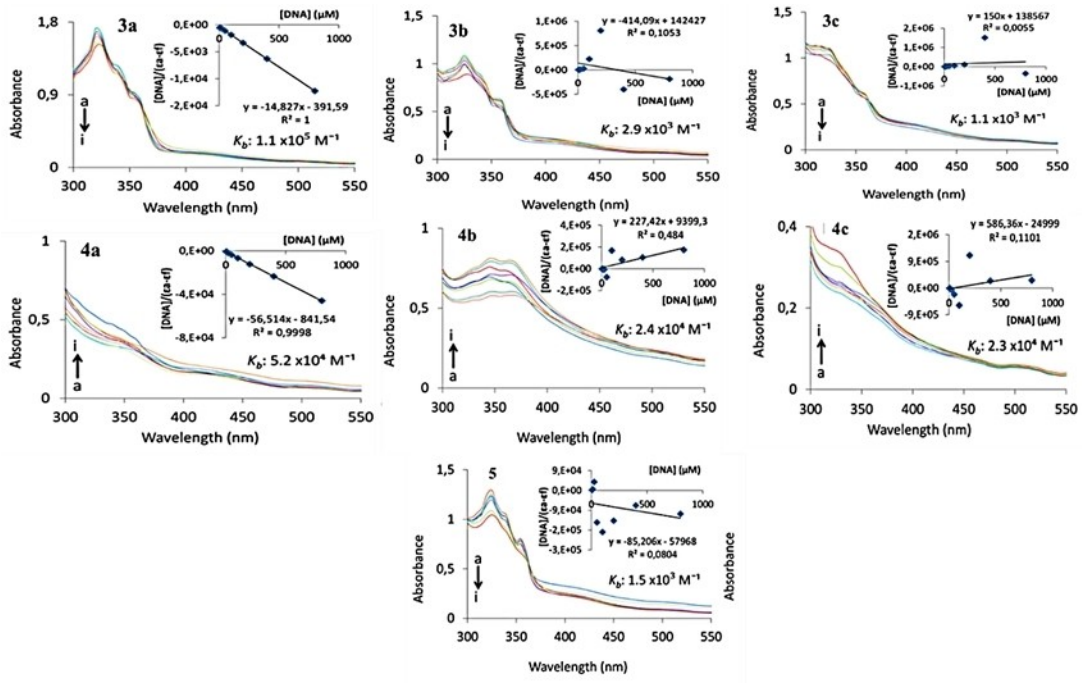


Figure 3. UV-Visible absorption spectra of 25 μM these compounds in the absence (a) and presence of 6.25 μM (b), 12.5 μM (c), 25 μM (d) 50 μM (e), 100 μM (f), 200 μM (g), 400 μM (h) and 800 μM (i) DNA. Note: The direction of arrow demonstrates increasing concentrations of DNA. Inside graph is the plot of [DNA] versus [DNA]/εa-εf to find the binding constant of complex-DNA adduct.

Figure 4, each cell line exposed to **5** exhibited low cell confluence, floating cells, blebbing, cellular and cytoplasmic shrinkage and disintegration of cell clumps. The morphological changes more likely indicate cytotoxic effect and apoptotic process.

2.2.5. Antibacterial Evaluation of the compounds

On some pathogenic bacteria causing disease in the human body, the antimicrobial activities of the compounds **3a–c**, **4a–c** and **5** have been determined using the Minimum Inhibition Concentration (MIC) method.[33] We considered the compounds **3a–c**, **4a–c** and **5** to have antibacterial effect at 250 μg/mL and below the MIC values. This evaluation made according to the

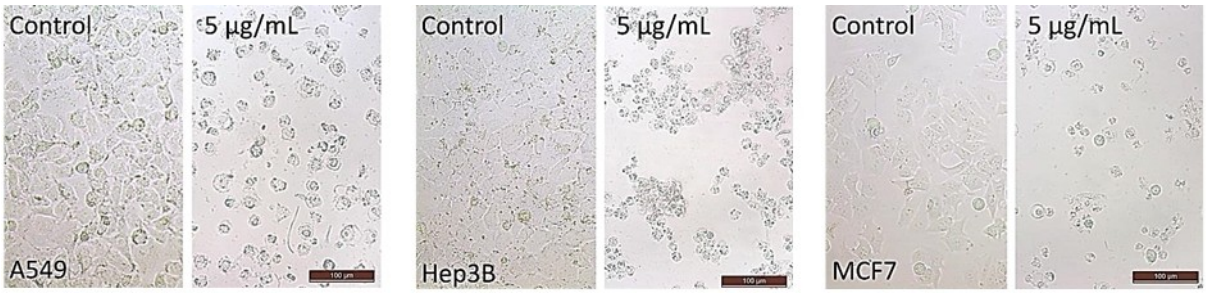


Figure 4. The effects of **5** on the morphologies of A549, Hep3B and MCF7 cell lines. Exponentially growing cells were incubated overnight with 5 µg/mL of **5** at 37 °C. Control cells were treated with only DMSO. All measurements were 100 µm.

MIC values of antibiotic [SCF = sulbactam (30 µg) + cefoperazone (75 µg)] used as positive controls. When the MIC values of compounds displayed on Gram (+) bacteria are examined, it found that all mono bromides **3a–c**, 1,6,8-tribromide **4a** and 1-phenyl indeno[1,2-b]quinoline amine **5** derivatives have effectively inhibited the proliferation of all of Gram (+) bacteria (MIC values ranging from 15.62–250 µg/mL) compared with positive control, SCF antibiotic (MIC values ranging from 62.50–250 µg/mL) (Table 3). On the other hand, 3,6,8-tribromoindeno[1,2-b]quinoline-10-amine **4c** moderately showed antibacterial effect against tested Gram (+) bacteria (62.50–500 µg/mL) while 2,6,8-tribromide **4b** did not have any inhibition activity (500–1000 µg/mL) (Table 3). According to the MIC values exhibited by recently synthesized molecules on Gram (−) bacteria, the moderate antibacterial effect of compounds **3a** and **4a** against the *E. coli* ATCC 25922, *E. coli* ATCC 35218 and *P. aeruginosa* ATCC27853 (125–250 µg/mL) strains and compound **3c** against only *E. coli* ATCC 35218 (250 µg/mL), were observed (Table 3).

As a result, it is clear that compounds **3a**, **4a** and **5** have promising antibacterial activity for future studies. Especially, substituted indeno[1,2-b]quinoline amines **3a**, **4a** and **5** at C-1 were more active against microorganisms than substituted derivatives (**3b–c**, **4b–c**) at C-2 or C-3 positions.

2.3. Molecular docking

Molecular docking studies were performed between the compounds **3a–c**, **4a–c** and **5** and PDB ID: 3VHE,[34] 5VND,[35] 1M17[36] and 6İ2İ[37] target protein representing, respectively, the A549, Hep3B, MCF7 and HeLa cell lines for anticancer activities. In addition, the investigated compounds were docked with target proteins PDB ID: 5Y63,[38] 4KNK,[39] 1D7A[40] and 4NX9[41] representing *E. faecalis*, *S. aureus*, *E. coli*, *P. aeruginosa* pathogenic bacteria, respectively, for antibacterial activities. According to the docking results obtained, the binding energy data in terms of anticancer activities and antibacterial are listed in Table 1 and 3, respectively. The binding modes of the studied compounds with the respective target proteins are shown in Figure S1–S8 presented as Supplementary Material.

The calculated docking studies for anticancer activities were generally found to be quite compatible with experimental results. When the docking results were examined as a whole, a significant decrease was observed in the calculated binding energy values of compounds with high IC_{50} values. In addition, the order of the calculated estimated free energy of binding by the experimental half maximum inhibitory concentration values of the examined compounds is quite consistent.

When the docking results of the studied compounds with the target protein, PDB ID: 3VHE, representing the A549 cell line, are examined, compound **5** with the highest experimental inhibition efficiency show the highest anticancer activity as a result of the simulation. This may be caused by the nitrogen atoms in **5** forming two hydrogen bonds with the GLU885 and the ASP1046 amino acid residue (Table 5). The binding modes and interaction types between the PDB ID: 3VHE (A549 cancer cell line) target protein and the studied compounds are given in Figure S1 in Supplementary Material. It is thought that the hydrogen bonding energy, which has the highest energy among secondary chemical interactions, increases the binding energy of the investigated compound and the related target protein. According to the experimental IC_{50} values, there is a similar situation for **3a** which exhibits anticancer activity in the second rank. Likewise, it has occurred two hydrogen bonds with the GLU885 and ASP1046 amino acid residues in **3a**. In addition, the compound **5** has polar and hydrophobic

Table 5. The molecular interactions between the most effective compounds and related target proteins of cancer cell line.

		Molecular Interactions between target protein and the most effective compound				
Compd. #	Target Protein	Hydrogen Bond	Halogen Bond	Hydrophobic	Polar	π-π
5	3VHE (A549)	GLU885, ASP1046		VAL899, CYS1045, ILE888, LEU889, ILE892, ILE104	LYS868	ASP814
5	5VND (Hep3B)	ASP641		ILE545, LEU484, VAL492, MET535, ALA512, VAL561		PHE642
3a	6İ2İ (HeLa)	THR73, GLU71	THR145, ASP98	VAL74	GLN11, ASP69	
3b	1M17 (MCF7)	ASP831	THR766, ALA719, LEU764	VAL702, LEU820, CYC772, ALA719		

interactions such as. However, the compound **5** exhibits π-π interaction with HIS1026, unlike **3a**. Due to this extra interaction, the binding energy for **5** may have been obtained slightly higher. Finally, experimental IC_{50} values for **4a–c** were recorded above 1000 μg/mL. Similarly, the calculated binding energy values were also low and if we look at the Supplementary Material in Figure S1, the interaction types are also very low.

Molecular docking was performed for studied compounds with PDB ID: 6İ2İ target protein, representing the HeLa cancer cell line. The compound **3a** with the binding energy of −7.97 kcal/mol are performed hydrogen bond with THR73, GLU71 amino acids and hydrogen bond with THR145, ASP98 (Table 5). In addition, **3a** exhibits hydrophobic and polar interactions with the related target protein. The binding modes and interaction types of all compounds with the 6İ2İ target protein are given in Figure S2.

Docking calculations between the compounds with the target protein PDB ID:5VND representing the Hep3B cancer cell line were performed. The binding energy values calculated for **3a** and **5**, whose IC_{50} values were the same experimentally, were obtained differently. The compound **5** interacted with more amino acid residues in the target protein. Therefore, different binding energies were obtained as a result of the calculation. It is placed in Figure S3 to present the difference between the binding modes of **3a** and **5** with 5VND and the types of interaction. Nitrogen atoms in **3a** and **5** formed hydrogen bonds with the ASP61 amino acid residues (Table 5). In addition, the compound **3a** had a hydrophobic interaction with the GLU531 amino acid, as well as hydrogen bonding, halogen bond and π-π interactions. The binding modes and interaction types of all compounds with the related target protein are given in Figure S3.

Finally, when the simulation data of the compounds examined with the PDB ID: 1M17 target protein, the crystal structure of the epidermal growth factor receptor (EGFRK),[42] representing the MCF7 cell line in Figure S4, the docking results of all compounds were similar to the experimental results. The binding modes and interaction types are given in Figure S5 in the Supplementary Material. The compound **3a** formed single hydrogen bond with amino acid residue ASP831 and single halogen bond with amino acid residue GLU738. In **3a**, there are polar interactions in addition to hydrophobic interactions. The compound **5** formed a single hydrogen bond with the ASP831 amino acid residue. In addition, the compound **5** had a hydrophobic interaction with LEU820, ALA719, LEU764. However, **4a–c** have binding energies at close values and as in experimental results, their anticancer activities are quite low in theory.

Antibacterial activities of the compounds were examined with in silico studies. The docking results obtained for compounds and target proteins are listed in Table 6. The binding energies of the compounds examined with the target protein PDB ID: 5Y63 representing *E. faecalis* are quite similar to MIC values of compounds against Gram (+) and Gram (−) bacteria. However, unlike experimental data, docking results give the details of interactions at the molecular level. When the docking results of compounds **3a** and **4a** with the same MIC values are compared, it is seen that the binding energy of the **4a** compound is higher. This may be due to the much halogen bonds between the compound **4a** and the 5Y63 target protein (Figure S5). The binding energies between the PDB ID: 4KNK target protein representing *S. aureus* and the compounds gave values with similar affinity (except of **4b** and **4c**) to experimental results (Figure S6). Compounds **3a** and **4a** with the same MIC values were found to have different binding energies as a result of docking calculations. The compound **4a** has the most antibacterial activity. The binding modes and interaction types for **3a** and **4a** are presented in Figure S6. On the other hand, antibacterial effect of **5** cannot be ignored due to its similarity to compounds **4a** and **3a**. As a result, even though **5** has low binding energy, it has close binding energy with compounds **4a** and **3a** which it is structurally similar. Similar results were obtained between the investigated compounds with PDB ID:1D7A and PDB ID:4NX9 target proteins representing Gram (−) bacteria, *E. coli* and *P. aeruginosa*, respectively (Table 5). The binding modes and interaction types of these docking results were showed in Figure S7 and S8 in the Supplementary Material.

Table 6. The estimated free energies of binding (kcal/mol) between the investigated compounds and related target proteins of bacteria.

Comp.#	5Y63 (E. faecalis)	4KNK (*S. aureus*)	1D7A (*E. coli*)	4NX9 (*P. aeruginosa*)
	The estimated binding free energies (kcal/mol)			
3a	−4.85	−6.87	−2.87	−5.25
3b	−4.05	−6.76	−3.05	−5.08
3c	−3.99	−6.69	−3.46	−5.05
4a	−5.02	−6.94	−4.32	−5.15
4b	−3.58	−6.11	−4.01	−5.03
4c	−4.00	−6.26	−4.27	−5.13
5	−4.21	−6.66	−4.15	−5.06

2.4. Evaluation of the priorities of compounds in terms of anticancer potentials by MCDM

In our recent study, the AHP-TOPSIS combination has been used for identifying the most promising anticancer agents against HeLa, HT29 and C6 cell lines with an accurate prediction approach for the first time of the literature.[28] In this study, the effects of seven promising anticancer quinoline compounds on three different types of cancer cell lines were evaluated according to four criteria (IC_{50} value, LDH cytotoxicity, DNA laddering feature for apoptosis and topoisomerase I enzyme inhibition) by MCDM. In that study, MCDM results were both consistent with experimental results and suggested that two brominated quinolines can be promising anticancer agent against HeLa, HT29 and C6 cell lines and used in further anticancer preclinic studies.[28] The consistent and effective results obtained in this study[28] motivated us to apply combined MCDM approach for the brominated indeno[1,2-b] quinoline amines in terms of some evaluation criteria. Five parameters of bioactive brominated indeno[1,2-b]quinoline

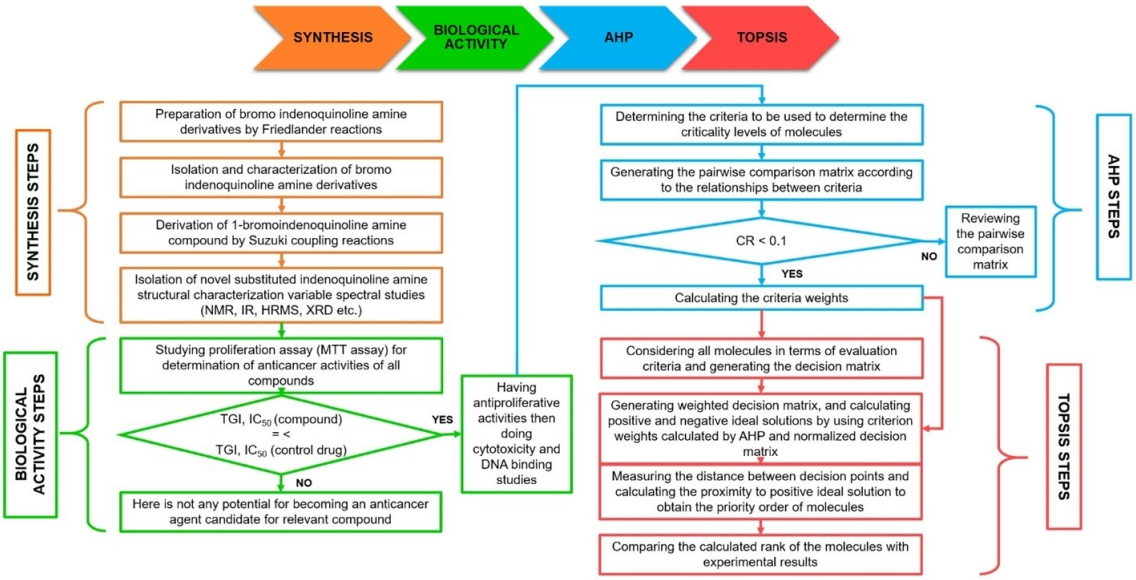


Figure 5. Conceptual framework of the study and application steps.

amines, LDH percentage, GI_{50} values, TGI values, IC_{50} values and LD_{50} values, described in Table 6, were determined by a decision maker as the key criteria for determining promising anticancer agents against the A549, HeLa, Hep3B and MCF7 cancer cell lines. The outline of conceptual framework and the implementation steps are in Figure 5.

The criteria determining the effects of the compounds determined by experimental analysis on five types of cancer were determined. Accordingly, LDH, GI_{50}, TGI, IC_{50} and LC_{50} were accepted as evaluation criteria. To determine the criterion weights, a paired comparison matrix of the criteria was created, and this matrix was presented in Supplementary Table S3. When the AHP method steps were followed, the calculated *CR* was found to be 0.0561. Accordingly, comparisons were consistent analysis. Calculated criteria weights were given in Table 7.

The weight values given in Table 7 are the percentage effect of each evaluation criterion on the compounds covered by the problem. For instance, LDH affects this decision problem at a rate of 31.98%, while the LC_{50} criterion has a 9.61% effect on the ranking of seven compounds on five cancer types.

Table 7. Evaluation criteria, their description and criteria weights.

Criteria	Scale	Description	Weight Value
LDH concentration percentage	%	Percentage of LDH release	0.3198
GI_{50} values	µg/mL	The concentration causing 50% cell growth inhibition	0.2465
TGI values	µg/mL	Total cell growth inhibition	0.1544
IC_{50} values	µg/mL	Inhibition concentration of proliferation of 50% of cancer cell lines	0.1832
LC_{50} values	µg/mL	The concentration causing 50% cell death	0.0961

The TOPSIS method was used to analyze the effect of compounds on different types of cancer by weight of significance. For this purpose, the decision matrices given in Supplementary Table S4 were constructed from the data in Table 1 and Figure 1 containing the experimental results of seven compounds under the evaluation criteria for cancer types A549, Hep3B, HeLa and MCF7.

From the data given in Table 1 and Figure 1, the rates of 100 or 1000 of the data have been calculated for ease of calculation and interpretation. Since there are >1000 values in some tables, 1000 level calculations have been made to be able to be compared with the values in the relevant column. In this calculation, the minimum values among the values in the LDH, GI_{50}, TGI and IC_{50} columns have been accepted as 100 or 1000. For the LC_{50} column, since the maximum value is the best value, the highest value has been given 100 or 1000. After giving 100 or 1000 in relevant values, other values in the same column have been calculated by dividing the minimum value by the relevant value and multiplying by the ratio value. In this context, the compound priorities with their importance level (C_i^*) obtained by running the TOPSIS algorithm with the decision matrices generated for each cancer type have been presented in Table 8.

The decision regarding the most bioactive compound among the seven brominated indeno[1,2-b]quinoline amines tested having significant antiproliferative and low cytotoxicity against A549, Hep3B, MCF7 and HeLa cell lines indicated that compounds **3a** and **5**, 1-bromoindeno[1,2-b]quinoline-10-amine and 1-phenylindeno[1,2-b]quinoline-10-amine respectively, ranked high (priority values between 0.7449 and 0.4994, Table 7). On the other hand, **3b** has significant piority value against A549, Hep3B and MCF7 cancer cell lines (priority values

Table 8. Priority ranking of the selected compounds.

Comp. #	A549	Hep3B	HeLa	MCF7
3a	0.5971	0.6533	0.7449	0.4994
3b	0.6612	0.6449	0.3833	0.6848
3c	0.4886	0.4087	0.5216	0.3605
4a	0.4447	0.3696	0.2911	0.2801
4b	0.2809	0.2792	0.2901	0.2678
4c	0.2677	0.3134	0.2550	0.3375
5	0.7342	0.6474	0.6324	0.3965
Ranking	5 > 3b > 3a > 3c > 4a > 4b > 4c	3a > 5 > 3b > 3c > 4a > 4c > 4b	3a > 5 > 3c > 3b > 4a > 4b > 4c	3b > 3a > 5 > 3c > 4c > 4a > 4b

between 0.6612 and 0.6848, Table 8) while **3c** has high activity priority against HeLa in the ranking value of 0.5216 (Table 8). These results indicated that the mono substitution of six membered ring in indene part of indeno[1,2-b]quinoline amine was improtant in terms of the displaying of anticancer activity. Moreover the position of C-1 in indeno[1,2-b]quinoline has important role of anticancer activity due to having high ranking values of **3a** and **5** (Table 8). These priority values were consisted with experimental results (Table 1 and Figure 2).

In the ranking order of anticancer activity, tribromides **4a–c** have lower activity priority against all tested cell lines, compared mono brominated indeno[1,2-b]quinoline amines **3a–c**. According to these results, it can be concluded that the presence of bromine groups at the C-6 and C-8 positions of the indeno[1,2-b]quinoline ring reduced anticancer activity against A549, Hep3B, HeLa and MCF7 cell lines due to their high IC_{50} and TGI values compared to control compounds, cisplatin and 5-FU (Table 1 and Figure 2).

3. Conclusions

Indeno quinolines are attributed promising drug candidates diplaying significant biological activity in a wide range.[43] Camptothecin, a derivative of indenoquinoline, is a well-known anticancer agent through inhibition of TOPO I enzyme.[44] The important results have been obtained in researches on the anticancer activities of indenoquinolines that piperazine and methoxy substituted indenoquinoline derivative was identified as significant inhibitory potent against the growth of HeLa, SKHep, AGS, and A549 cells with in range of GI_{50} values of 0.52–6.76 μM.[45] Similarly, this research has been reported signifaicant antiproliferative activities of the recent prepared indeno [1,2-b]quinoline amine derivatives against A549, HeLa, Hep3B and MCF7 cancer cell lines in lower concentrations. The indeno [1,2-b]quinoline amine derivatives, especially C-1 substituted indeno[1,2-b]quinoline amines **3a** and **5**, significantly exhibited promising anticancer (IC_{50} values; 1.1–29.6 μg/mL) and antimicrobial activities (MIC values; 15.62 μg/mL–250 μg/mL). The indeno[1,2-b]quinoline amine derivatives **3a** and **5** possessed modarete and close cytotoxic activity (percentage LDH relase, 14.3% to 19.8%) compared the positive control against cancer cells (percentage LDH, 7.7% to 11.2%). The interaction of indeno[1,2-b]quinoline amine derivatives with CT-DNA and BSA was shown with respect to the spectral changes in their absorbance (1.1×10^3–$1.1\times10^5\,M^{-1}$). In future studies, we will try to improve the amount and functionality of our indeno[1,2-b]quinoline amine derivatives using selective method improvement. Overall, the docking results were consistent with the experimental data. Anti-cancer activities of **3a–c** and **5** were higher than **4a–c**. Although the presence of electronegative bromine atoms in this series is considered an advantage, it could not form hydrogen bonds with the amino acid residues of the proteins due to their steric effects. Moreover, MCDM approach were consistent with experimental and in silico studies. Since the *in vitro* pharmacological features of these indeno[1,2-b]quinoline amine derivatives can be used mainly against some cancer cells and some microbial strains, *in vivo* viability-activity studies are very significant to reveal the mechanism of action of these molecules. As a result, our experimental, in silico and MCDM studies results depict that indeno[1,2-b]quinoline amine derivatives **3a** and **5** are potentially valuable drug candidates and should be evaluated for further pharmacological testing.

Supplementary Information Summary

Experimental details, molecular docking figures and decision matrixes can be found in the Supporting Information.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Antibacterial agents · Antitumor agents · Biological activity · Molecular docking · Multi criteria decision making · Indeno[1,2-b]quinoline amine

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