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Investigation of the cytotoxic and antimicrobial properties of new quinoline peptide conjugates

Yeni kinolin peptit konjugatlarının sitotoksik ve antimikrobiyal özelliklerinin araştırılması

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ABSTRACT

Background: Cancer is one of the most important health problems causing deaths in Turkey and the world. Nowadays, many treatment methods such as radiotherapy and chemotherapy are applied in cancer patients. Quinoline and its derivatives, which belong to heterocyclic compounds, have many biological activities for drug development. Quinoline compounds play a crucial role in the development of antitumor drugs due to their anticancer activity.
Materials and Methods: In this study, the cytotoxic effects of synthesized seven different quinoline derivatives on lung cancer (A549) and healthy lung epithelial cell (BEAS2B), liver cancer (Hep 3B), and endothelial cell (HUVEC) were determined. Different concentrations were applied and IC_{50} values were calculated at different time courses. The antimicrobial activites of the compounds were also determined.
Results: The IC_{50} values of compound 2 on the A549 cell line were determined to be 10.48 µg/mL, 9.738 µg/mL, and 10.14 µg/mL. IC_{50} values of compound 6 on the same cell line were determined to be 7.307 µg/mL, 9.888 µg/mL, 10.63 µg/mL.
Conclusions: Compounds 2 and 6 had a cytotoxic effect on the BEAS2B cell line. The antimicrobial activity of the compounds was determined by the minimum inhibition concentration method on different strains of bacteria and yeast. The compounds showed no antimicrobial activity on bacteria and yeast.
Keywords: Antimicrobial, quinoline-peptide conjugates, cytotoxic

ÖZET

Amaç: Kanser, Türkiye'de ve dünyada ölüme neden olan önemli sağlık sorunlarından biridir. Günümüzde radyoterapi ve kemoterapi gibi birçok tedavi yöntemi kanser hastalarında uygulanmaktadır. Heterosiklik bileşikler arasında olan kinolin ve türevleri ilaçların geliştirilmesi açısından birçok biyolojik aktivite bulundurmaktadır. Kinolin bileşikleri, antikanser aktivite gösterdikleri için antikanser ilaç gelişiminde önemli bir rolü vardır.
Materyal ve Metot: Bu çalışmada, sentezlenmiş yedi farklı kinolin türevinin akciğer kanseri (A549) ve sağlıklı akciğer epitel (BEAS2B), karaciğer kanseri (Hep 3B) ve endotelial hücreler (HUVEC) üzerine sitotoksik etkileri belirlenmiştir. Farklı konsantrasyonlar uygulanmış ve farklı zaman aralıklarında IC_{50} değerleri hesaplanmıştır. Aynı zamanda bileşiklerin antimikrobiyal aktiviteleri de belirlenmiştir.
Bulgular: A549 hücre hattı üzerine bileşik 2'nin IC_{50} değerleri 10.48 µg/mL, 9.738 µg/mL, 10.14 µg/mL olarak tespit edilmiştir. Bileşik 6'nın aynı hücre hattı üzerine IC_{50} değerleri 7.307 µg/mL, 9.888 µg/mL, 10.63 µg/mL olarak belirlenmiştir.
Sonuç: Bileşik 2 ve 6'nın BEAS2B hücre hattı üzerine sitotoksik etkisi görülmüştür. Bileşiklerin antimikrobiyal etkileri çeşitli bakteri ve maya suşları üzerine minimum inhibisyon konsantrasyonu yöntemi ile belirlenmiştir. Bileşikler bakteriler ve maya üzerine antimikrobiyal etki göstermemiştir.
Anahtar Kelimeler: Antimikrobiyal, Kinolin- peptidkonjugatı, sitotoksisite

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INTRODUCTION

Cancer is the result of a series of mechanisms that Cancer is the result of a series of mechanisms that result from the disruption of the cell's homeostasis, affecting its ability to respond to extracellular signals and intercellular communication, and causing uncontrolled cell division by triggering certain intracellular events (Gakhar et al., 2008). Cancer, one of the most significant diseases, has been awaiting research and conclusion for years. Every year, the number of deaths from cancer increases significantly. Currently, cancer is the second leading cause of death in Poland and the USA (Lewandowska et al., 2021; Siegel et al., 2021). Looking at the data from Turkey, while lung and prostate cancer are the most common cancers in men, breast cancer is the most common cancer in women. According to the Turkish Statistical Institute (TUIK), 15.2% of reported deaths in Turkey are due to cancer. Despite today's biomedical developments, cancer is still associated with death and suffering (Güleç and Büyükkınacı, 2011).

Quinoline is a heterocyclic aromatic organic compound containing a benzene ring with the formula C_9H_7N. It has eight positions with nitrogen and has an anticancer effect due tı thşs porperty. Quinoline, which is soluble in alcohol, ether, and many other organic solvents, is slightly soluble in water (Ferlin et al., 2005). In the production and development of anticancer drugs, quinoline, which has the potential to prevent cancer, has been given priority in research (Dorababu, 2020; Jain et al., 2019; Yernale, 2021). The cytotoxic activities of quinoline synthesized in mono-di-, tri-, tetra- and heterocyclic structures have been investigated. Various studies have been conducted on their effects on different mechanisms of action, such as cell cycle arrest, apoptosis, inhibition of angiogenesis, disruption of cell migration, and growth inhibition through modulation (Gasparotto et al., 2006; Jain et al., 2019). The aim of this study is to investigate the cytotoxic effects of some quinolines and their derivatives on various cell lines using the MTT method. The study also tested, the antimicrobial activity of these compounds against the gram-negative bacteria *Escherichia coli*, the gram-positive bacteria *Staphylococcus aureus*, and the yeast *Candida albicans*.

MATERIALS AND METHODS

The new quinoline peptide conjugates used in the study were synthesized by Küçükbay in the Department of Chemistry at the Inonu University Faculty of Science.

Cell Lines

Lung cancer (A549), liver cancer (Hep 3B), endothelial cell (HUVEC) and healthy lung epithelial (BEAS2B) cell lines were used in this study. All cell lines were obtained from Prof. Dr. Fahrettin Sahin (Yeditepe University, Department of Genetics and Bioengineering, İstanbul/Turkey). Cells were propagated and maintained by incubation in RPMI or DMEM (Dulbecco's Modified Eagle's Medium) containing 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin in a humidified atmosphere containing 5% CO_2 at 37ºC (Jeyaraj et al., 2013; Altuner et al., 2021).

MTT Test

For MTT analysis, an appropriate number of cells were plated in 96-well plates and treated with quinoline derivatives at concentrations of 5, 10, 30, 50 and 100 µg/mL for 24, 48 and 72 h. At the end of the 24 h, 20 µL thiazole was added to each well in the dark and incubated in a CO_2 incubator at 37ºC for 2-4 h. The thiazole in the plates removed from the incubator was discarded and 100 µL DMSO was added to each well and shaken for 5 min at 150 rpm in the dark at room temperature. After homogenization of the formazon compounds in the plates, the absorbance values were calculated on a spectrophotometer at a wavelength of 570 nm. The read absorbance values were converted into percentage values and logarithmic slope graphs were generated in the Microsoft Office Excel software program. The IC_{50} (half-maximal inhibitory concentration) values at the 24, 48 and 72 h were calculated at the point where the viability fell below 50% (Apohan et al., 2017; Ökçesiz and Bucurgat, 2017).

Antimicrobial Activity Test

Escherichia coli, a gram-negative bacterium, and *Staphylococcus aureus*, a gram-positive bacterial species, were used to determine the antibacterial activity of the quinoline-derived compounds used in our study. The bacteria were incubated in nutrient agar medium at 37°C for 18-24 h. The yeast species *Candida albicans* was incubated in Sabouraud dextrose agar medium for 24-48 h to test the antifungal activity of the compounds (Kumar et al., 2022; Diaconu et al., 2020; Apohan et al., 2017). In order to determine the antimicrobial activities of the compounds in the study, the minimum inhibitory concentration (MIC) was calculated using the microdilution method (Apohan et al., 2017).

RESULTS

In this study, the cytotoxic effects of seven different synthesized quinoline derivatives on lung cancer (A549) and healthy lung epithelial cells (BEAS2B), liver cancer (Hep3B) and endothelial cells (HUVEC) were evaluated. The exact names and formulas of seven different quinolines and their derivatives are shown below in Figures 1-7.

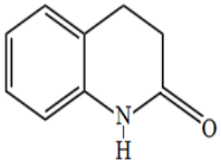

Figure 1. Quinoline (Compound 1)

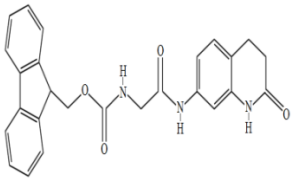

Figure 2. Fmoc-Gly-Quinoline (Compound 2)

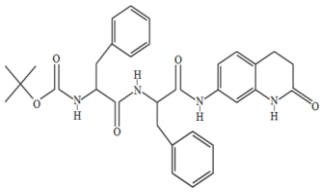

Figure 3. Boc-Phe-Phe-Quinoline (Compound 3)

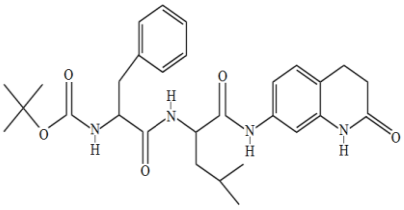

Figure 4. Boc-Phe-Leu-Quinoline (Compound 4)

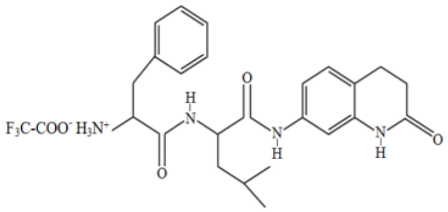

Figure 5. H-Phe-Leu-Quinoline (Compound 5)

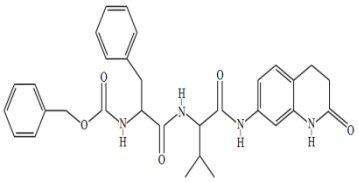

Figure 6. Z-Phe-Val-Quinoline (Compound 6)

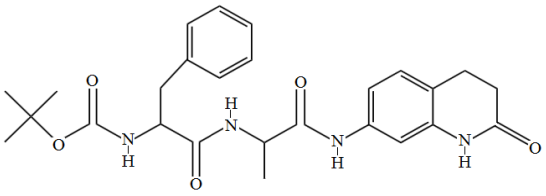

Figure 7. Boc-Phe-Ala-Quinoline (Compound 7)

Various concentrations (5-100 µg/mL) of quinoline and its derivatives were applied to A549, BEAS2B, Hep3B and HUVEC cells and IC50 values were calculated and presented in Table 1.

Table 1. Time-dependent IC_{50} values (µg/mL) of compounds 2 and 6 on cell lines.

Compound 2 cell lines	24 h	48 h	72 h	Compound 6 cell lines	24 h	48 h	72 h
A549	10.48	9.738	10.14	A549	7.307	9.888	10.63
BEAS2B	24.31	20.23	17.25	BEAS2B	7.792	16.54	19.24
HUVEC	1.795	1.532	95.94	HUVEC	8.430	29.04	37.58
HEP 3B	>100	38.35	48.90	HEP 3B	25.78	30.03	23.04

As shown in Table 1, the IC_{50} values of Compound 2 on the A549 cell line at the 24, 48 and 72 h were calculated to be 10.48 µg/mL, 9.738 µg/mL and 10.14 µg/mL, respectively. The IC_{50} values of Compound 6 were determined to be 7.307 µg/mL, 9.888 µg/mL and 10.63 µg/mL, respectively. These two compounds were cytotoxic to the BEAS2B cell line. The IC_{50} values of Compound 6 for the HUVEC cell line were determined to be 8.430 µg/mL, 29.04 µg/mL and 37.58 µg/mL, respectively. The IC_{50} values of Compound 6 for Hep 3B at 24, 48 and 72 h were found to be 25.78 µg/mL, 30.03 µg/mL and 23.04 µg/mL, respectively. Compound 6 was found to be highly cytotoxic to all cell lines. In the study, Compound 2 and Compound 6, two of the quinoline derivatives, were fount to have potent cytotoxic effects on the cancer cells used (Figures 8-11).

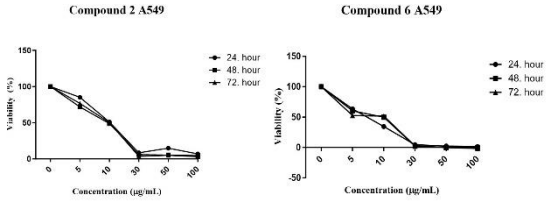

Figure 8. Cytotoxic effect of compounds 2 and 6 on A549 cells (µg/mL)

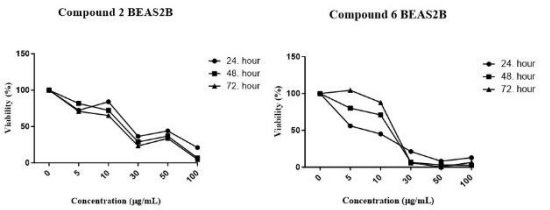

Figure 9. Cytotoxic effect of compounds 2 and 6 on BEAS2B cells (µg/mL)

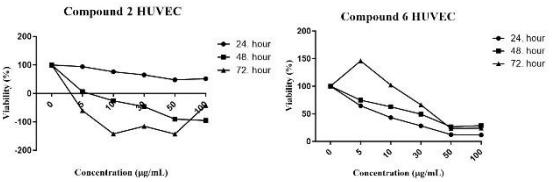

Figure 10. Cytotoxic effect of Compounds 2 and 6 on HUVEC cells (µg/mL)

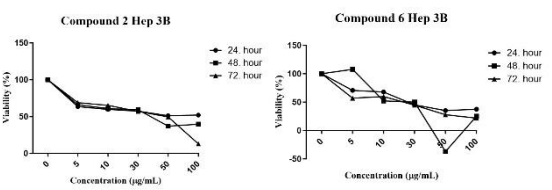

Figure 11. Cytotoxic effect of Compounds 2 and 6 on Hep 3B cells (µg/mL)

The antimicrobial activities of the synthesized quinoline and its compounds were determined based on the calculation of MIC values by microdilution method using 96-well plates.

It was found that the quinoline-derived compounds used in the study had insufficient antimicrobial activity against on *E. coli*, *S. aureus* and *C. albicans* was not sufficient. MIC values for *E. coli*, *S. aureus* bacteria and *C. albicans* yeast were determined to be >3200 µg/mL.

DISCUSSION

When the results of the quinoline derivative compounds were evaluated, it was observed that they exhibited cytotoxic activity on the A549 cell line. The cytotoxic effect of the compounds used in the study on healthy cells was investigated (Table 1). The IC_{50} value of Compound 2 at 72 h is 10.14 µg/mL for A549 and 17.25 µg/mL for BEAS2B. All compounds were found to be highly cytotoxic. Compound 2 and Compound 6 were also found to be cytotoxic to the BEAS2B cell. In the study by Alonso et al., new quinoline-derived compounds were synthesized and the cytotoxic effects of these compounds on different cell lines such as human lung adenocarcinoma (A549), ovarian carcinoma (SKOV03) and embryonic kidney (HEK293) were investigated. While 1,2,3,4-tetrahydroquinolinylphosphine oxide showed cytotoxic activity with an IC_{50} value of 0.25±0.03 mM on the A549 cell line, 1,2,3,4-tetrahydroquinolinylphosphine 9c showed cytotoxic activity with an IC_{50} value of 0.08±0.01 mM on the same cell line. It was determined that the cytotoxic activity of 0.03 ± 0.04 m MIC50 value of 2,3,4 tetrahydroquinoline phosphine sulfur derivative 10f was more effective (Alonso et al., 2018). In this study, it was determined that the cytotoxic effect of new quinoline-derived compounds, Compound 2, applied to A549 cells was found to be potent. In another study, the cytotoxic activity of newly synthesized quinoline derivatives on A549 cells was evaluated. It was determined that compound 1 showed cytotoxic effect on A549 cells with an IC_{50} value of 29.3 µg/mL (Wang et al., 2011). Similarly, this study observed that Compound 2 exhibited a cytotoxic effect on A549 cells.

Küçükbay et al. synthesized six new monopeptides, seven new dipeptides, and two deprotected monopeptide-dihydroquinoline conjugates using the benzothiazole-mediated method. The cytotoxic effects of the four synthesized compounds against A549 and BEAS2B cell lines were investigated. Among the compounds investigated, the IC_{50} values of compound 7 for 48 and 72 h in A549 cells were determined to be 26.87 and 9.979 µg/ml,

respectively, indicating strong cytotoxic activity. In BEAS2B cells (healthy cells), the IC_{50} values were >100 µg/ml, indicating a lower cytotoxic effect (Küçükbay et al., 2021). This study concluded that Compounds 2 and 6, which are quinoline derivative have potent cytotoxic effects on A549 cells and other cell lines.

The cytotoxic activity of quinoline-derived compounds synthesized by Haiba et al. was evaluated on liver cancer cells (HepG-2) and breast cancer cells (MCF-7). As a result, Compounds 4 and 11 were fount to have cytotoxic activity against HepG-2 liver cancer cells. It was found that all compounds tested had significant cytotoxic activity against MCF-7 cells (Haiba et al., 2019). In another study, a new quinoline-azetidinone hybrid was synthesized to determine its cytotoxic activities against cell lines such as Hep G2 and Hep 3B. Compound 6f (IC50 = 0.04 ± 0.01 mM) and Compound 6j (IC50 = 0.66 ± 0.01 mM) showed anti-proliferative effects against the Hep G2 cell line (Alegaon et al., 2017). In this study, Compound 6, a quinoline-derived compound, was fount to have a potent cytotoxic activity against Hep 3B cells.

In the study by Thakare et al., new 4-{1-phenyl-4-[(4-phenyl-1,2,3-triazol-1-yl)methyl] pyrazol-3-yl}quinoline (7a-l) derivatives were synthesized and the antimicrobial activities of these compounds were evaluated against gram-negative bacteria, *E.coli* (NCIM 2574) and *P.mirabilis* (NCIM 2388), gram-positive bacteria, *B.subtilis* (NCIM 2063) and *S.albus* (NCIM 2178), and yeast *C. albicans* (NCIM 3100) and the mould *A. niger* (ATCC 504). It was concluded that the antifungal activities of five different 1,2,3-triazolyl-pyrazolyl-quinoline derivatives (7d, 7g, 7h, 7k and 7l) were effective against *A. niger* with a MIC value of 62.5 µg/mL (Thakare et al., 2020). In this study, it was observed that quinoline-derived compounds applied to gram-negative bacteria, gram-positive bacteria and yeasts were found to have no antimicrobial activity.

Various studies have tested the antimicrobial activities of quinoline derived compounds against different bacteria (*B. subtilis*, *C. tetani*, *S. pneumoniae*, *S. typhi*, *V. cholerae*, *E. coli*) and fungi (*A. fumigatus* and *C. albicans*) using the broth microdilution method. Most of the compounds were found to have high antimicrobial activity (Thumar and Patel, 2011). In our study, it was concluded that the quinoline-derived compounds used did not have a strong antimicrobial effect on the microorganisms used in this research.

In another study, the antimicrobial and cytotoxic activities of triazole/quinoline hybrid products and (prop-2-yn-1-yloxy) methyl) benzene interlayers were evaluated. They were found to have no cytotoxic activities on MDA-MB-231 and Hep-G2 cell lines. Compounds with the best antifungal activity were reported to have MIC values against *S. cerevisiae* in the range of 0.35-0.63 µM (Jamshidi et al., 2022).

CONCLUSION

Other studies on the biological activity of heterocyclic quinoline derivatives indicate that they have the potential to lead the way in the production and development of anti-cancer drugs. Since two of the quinoline derivative compounds used in the study showed cytotoxic effects on all cell lines used, it is necessary to plan studies to understand the mechanism of cytotoxic action of these compounds. Cancer, one of the major health problems of our time, is on the rise. The significant cytotoxic effect of quinoline and its derivatives on cancer cell lines makes it important for researchers to work with these newly synthesized compounds.

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Conflict of Interest: The authors declare that they have no personal or financial conflicts of interest related to the study.

Author Contributions

Idea/Concept: Elif APOHAN Design: Emine ADIYAMAN Supervision/Consulting: Özgür KATRANCIOĞLU, Hasan KÜÇÜKBAY Data Collection and/or Processing: Elif APOHAN Analysis and/or Interpretation: Emine ADIYAMAN, Hasan KÜÇÜKBAY Literature Review: Özgür KATRANCIOĞLU Writing of the Article: Emine ADIYAMAN Critical Review: Özgür KATRANCIOĞLU, Hasan KÜÇÜKBAY Resources and Funding: Elif APOHAN

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