The Effect of 2-Thioxo Imidazolidin-4-Ones (2- Thiohydantion) on Anticancer Activity: An in Vitro Study

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Abstract

Background and Purpose: Cancer is one of the most common factors of death in society today. Despite much research into cancer and its treatment, it is still one of the greatest health problems. The biggest obstacle to cancer treatment is that they are inherently resistant to chemotherapy or become drug resistant during treatment. For this reason, researchers around the world have made great efforts to identify new natural or synthetic compounds with anticancer properties. So the aim of this study is to find out the effect of 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) on anticancer activity.

Materials and Methods: Imidazoles are compounds that have antibacterial, antifungal and antitumor properties in many studies. Through the results of this study, we discovered effectiveness of the new compound of 2-Thioxo imidazolidin-4-ones (2 Thiohydantion) as an anticancer agent against a cell line that is a cancer model system. To determine the IC_{50} of this compound, we treated the cancer cells by different concentrations (10, 20, 30, 40, 80 and 160 µg / ml) and then the cells were evaluated by MTT assay after 24 and 48 hour intervals.

Results: After preparing the required compound, MTT assay showed that the IC_{50} of 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) compound on MCF7 cells, 135 and 40 µg / ml, respectively, after 24 and 48 h, respectively. In addition, the toxicity of these compounds on normal cells was evaluated, which is very different from their toxicity for cancer cells, and this is a very important feature. 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) has the ability to stimulate cell death in cancer cells, and these results provide new insights into the use of these compounds in cancer treatment.

Conclusion: So 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) at different concentrations significantly reduced the growth of cancer cells compared to the control group (50% inhibition of cell growth). Future studies will need to investigate the mechanism of this cytotoxicity as well as the possible anticancer effectiveness of this compound in vitro and in vivo.

***Keywords**: 2-Thioxo imidazolidin-4-ones (2-Thiohydantion), cytotoxicity, cancer cells*

Introduction

Cancer is the second leading cause of death worldwide.[1-4] Cancer is a disease caused by proliferation and growth without cell control.[5-7] Cancer cells create a tumor that in some cases can invade and metastasize to other parts of the body.[8] Methods of treatment for this disease are often ineffective and, despite the available therapeutic methods, there is still a need for research to discover new and targeted ways to treat the disease.[9] Most types of tumors can be treated with surgery, chemotherapy or radiation, but most metastatic cancers, such as breast cancer, cannot be treated with chemotherapy or other methods. The biggest obstacle to treating these cancers is that they are inherently

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resistant to chemotherapy or become drug resistant during treatment.[10] For this reason, researchers around the world have made great efforts to identify new natural or synthetic compounds with anti-cancer properties. Among the compounds considered for the treatment of malignancies are heterocyclic organic compounds due to their presence in the reaction groups and their cytotoxic properties.[11]

The thiohydantoin heterocycles are appear in a broad field of biologically active compounds consisting therapeutic drugs for the treatment of anti-tumor compounds. Thiohydantoins have also been applied as anti-cancer agents. However, the principal current interest comes from the application of thiohydantoins for the treatment of cancers. Structural characterization of thiohydantoin is important to comprehend their effect mechanisms because of their considerable biological effects.[12]

Studies have shown that heterocyclic, in addition to its antioxidant and anti-inflammatory effects, also has anti-cancer effects and cancer-preventing properties.[13] It is used in the treatment of various diseases , including diabetes, rheumatoid arthritis, Alzheimer's and cancer. Imidazoles are among the heterocyclic compounds.[14-17] The most important therapeutic feature of imidazoles is in relation to the drugs used to synthesize chemotherapy drugs.[18] Imidazoles are an important class of heterocycles that contain nitrogen and are currently under great attention due to their wide range of pharmacological effects.[19] Given the importance of imidazoles and their derivatives and their use in the medical and pharmaceutical industry, there are always many efforts to centrally design new imidazole derivatives or provide improved methods for the synthesis of these important heterocyclic compounds with minimal disadvantages.[20]

Imidazole, a five-membered heterocyclic ring containing two nitrogen and three carbon atoms at positions 1 and 2, is found in many natural compounds and biologically active compounds.[21]

Imidazole is found in the structure of many important biological constituents of the body such as histidine, histamine, as well as a number of pharmacologically active compounds.[22]

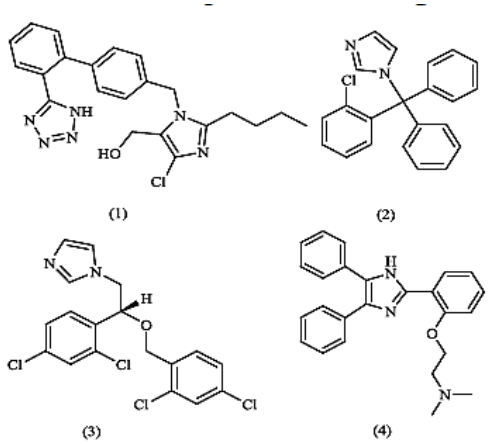

Figure 1. Structure of a number of imidazole drugs.[23]

In current study, we investigated the effect of 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) on MCF cancer cells activity.

Materials and Methods

The combination of 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) was synthesized from the reaction of orthophenylene diamine with 4-methoxybenzaldehyde in the presence of ferric hydrogen sulfate (FHS) catalyst at room temperature. This reaction was performed in a mixture of water and ethanol solvents. The reaction scheme is as follows:

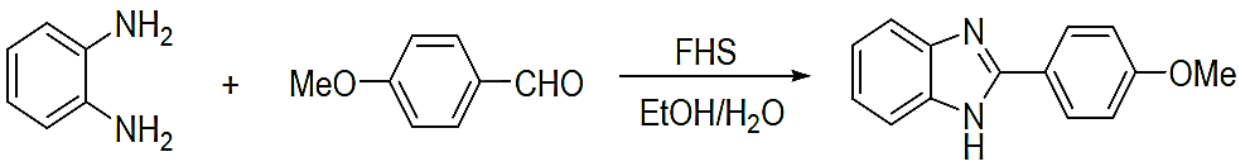

Figure 2. Reaction scheme of study

To investigate the cytotoxicity of the above compound, 8000 MCF 7 cells were cultured in each 96-well flask in DMEM cell culture medium have 10% serum of bovine then incubated in 37 ° C and CO_2 (10%) for 48 hours. To determine the concentration of 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) that causes half of the cells to die (IC_{50}) MCF7 cells with different concentrations of 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) (10 , 20, 30, 40, 80 and 160 µg/ml) and were treated with the same amount of DMSO used to dissolve the desired compound. Cell viability was evaluated by MTT assay at 24 and 48 h intervals.

For the MTT assay, the tetrazolium solution was prepared in a concentration of 5 mg/ml and after filtration in each well, a 20-ml volume of 96-well flask was added and kept for 4 hours in the dark at 37 °C. After the passage of time, during which the metabolism of tetrazolium was formed in the living cells of formazan purple crystals, the contents of each house were replaced with 150 µl of DMSO and colored violet solutions of varying color intensities were created. The amount of light absorbed by each cell, which is a measure of cell viability, was recorded by an ELISA reader at 545 nm.

Results and Discussion

In this study, we investigated the potential of the new compound of 2-Thioxo imidazolidin-4-ones (2 Thiohydantion) as an anticancer agent against a cell line that is a cancer model system. To determine the IC_{50} of this compound, cancer cells were treated with different concentrations (10, 20, 30, 40, 80 and 160 µg / ml) and then the cells were evaluated by MTT assay at 24 and 48 hour intervals.

After synthesis of the desired compound, MTT assay showed that the IC_{50} of 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) compound on MCF7 cells, 135 and 40 µg / ml, respectively, after 24 and 48 h, respectively. In addition, the toxicity of these compounds on normal cells was evaluated, which is very different from their toxicity for cancer cells, and this is a very important feature. The 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) compound has the potential to induce cell death on cancer cells, and the results revealed new insights into the use of these compounds in the treatment of cancerous tumors.

Morphological observations have also shown that it is able to exert its toxic effects in the form of cytoplasmic granules, especially after 48 h. According to the results, 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) can be considered as a substance that has the potential to kill cancer cells and given that it retains its effect for a long time, further studies could potentially be used as an anticancer compound (Figure 3).

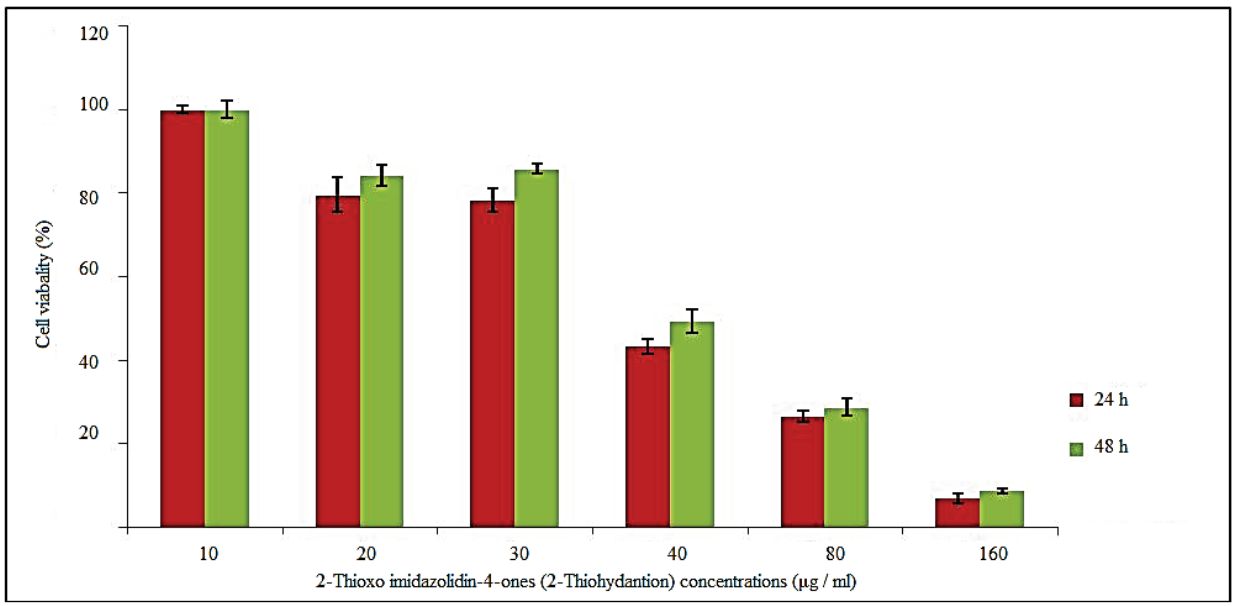

Figure 3. cells viability percent in different concentrations of 2-Thioxo imidazolidin-4-ones

(2-Thiohydantion) at time 24 and 48 hours.

Figure 3 shows that viability rates for 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) were dependent on concentration and time by analogy with the control group, the effect of this compound on the cells increased with increasing concentration and time, thus decreasing viability rate.

Repeated measurement statistical test showed that the effect of concentration increase on viability was statistically significant ($p < 0.05$). In addition, the same test to examine the effect of time showed that increasing time also had a significant effect on decreasing survival rate ($p < 0.05$). The 50 IC for 24 hours was 135 µg/ ml and for 48 hours was 40 µg/ ml.

Considering the IC_{50} of 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) for various cancer cells is different and also due to the high prevalence of breast cancer in Iran, the present study was conducted. In current study, we assessed the toxicity of this compound on the cancer cell by MTT method and determined the IC_{50} level for it. The results also showed that the viability rate for the compound 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) decreased significantly with increasing time, so that the viability rate at 24 was greater than 48.

Therefore, this substance has been considered as an effective compound for the treatment of cancer. Some studies confirm significant association between benzimidazole derivatives and reduction in cardiovascular disease and cancer and they are used to make antibacterial, antiviral, antifungal and anti-tumor drugs. This derivative of benzimidazole has anticancer properties.

Several studies have been conducted to determine the therapeutic dose and also to determine their IC_{50} on a variety of cancer cells.[24]

In this study, we determined viability rates and IC_{50} on cancer cells. The results of these study showed that the viability rate of the cells in the control group was highest, which is 100%. But after 24 and 48 hours exposure to 2-Thioxo imidazolidin-4-ones (2-Thiohydantion), at two time points, it was shown that the decrease in viability was dependent on both concentration and time and with both factors increased. The survival rate of the cells was significantly decreased. MTT assay showed that the IC_{50} of 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) compound on MCF7 cells, 135 and 40 µg / ml, respectively, after 24 and 48 h, respectively. However, the principal current interest comes from the application of thiohydantoins for the treatment of prostate cancers.[25-26] The anti-cancer effects of all synthesized compounds have been evaluated in compared with two cell lines HepG-2 cells (human hepatocellular cancer cell line), and MCF-7 (breast carcinoma cell line).[27-28]

Conclusion

The final results showed that cell viability depended on the concentration of 2-Thioxo Imidazolidin-4-Ones (2-Thiohydantion) and the incubation time. As the concentration of the solution increased, the toxicity increased and the cell viability decreased 48 hours compared to 24 hours.

So 2-Thioxo imidazolidin-4-ones (2-Thiohydantion) at different concentrations significantly inhibition the growth of cancer cells compared to the control group (50% reduce of cell growth). Future studies will need to investigate the mechanism of this cytotoxicity as well as the possible anticancer effects of this compound in vitro and in vivo.

Conflict of Interest: Nil/The authors declare no conflicts of interest.

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Ethical Clearance: Obtained from the Institutional Ethics Committee of Wasit University of Iraq.

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