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Some Heterocyclic Hydrazone Compounds: Synthesis, Spectral Characterization and Anticancer Activity Study

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ABSTRACT

Cancer is currently ongoing to be a significant health problem threatening human health. Hydrazone compounds constitute a popular class of organic compounds used in novel drug discovery studies in therapy of cancer. In the current study, the preparation and structural characterization of some heterocyclic hydrazone compounds (7-12) and their anticancer capacities against HeLa cervical cancer and MCF-7 breast cancer cell lines were reported. The target compounds were characterized by some spectroscopic techniques (^{1}H NMR, ^{13}C NMR and FT-IR). The *in vitro* cytotoxic potentials of the target molecules were assessed by using MTT assay against two cancer cell lines. L929 mouse fibroblast cell lines were employed as normal cell. The results displayed that some of the tested molecules had varying anticancer activities. Among the tested compounds, compound 8 indicated anticancer activity against HeLa cells with IC_{50} value of 34.38 µM. On the other hand, of these tested compounds, compound 11 (IC_{50} = 26.84 µM) displayed anticancer activity against MCF-7 cells.

Keywords: Hydrazone derivatives, Anticancer activity, Breast cancer, Cervical cancer.

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Introduction

Cancer is a disease that occurs as a result of uncontrolled proliferation and growth of cells in the human body [1]. Cancer cells can affect a single tissue as well as spread to other tissues and show their effects [2-4]. Today, different approaches and treatments specific to each cancer type are applied in clinical practice to combat this disease. In recent years, treatment methods based on different principles such as chemotherapy, radiotherapy, surgery, stem cell therapy, immunotherapy, hormone therapy and gene therapy have been utilized in the therapy of different types of cancer. These methods are applied either alone or in combination. There is currently no ideal treatment method for each of the existing cancer types, since the treatment methods applied have advantages and disadvantages in the treatment process of each cancer patient and the treatments may differ from patient to patient [5-6]. This disease is accepted as one of the biggest health problems facing humanity. Many scientists are still carrying out researches on the treatment of this disease. Depending on the scientific developments in this subject, important developments have occurred in the discovery of novel and effective drugs to be used in the therapy of cancer, with the detection of new intracellular pathways, target enzymes and proteins, and drug-effect mechanisms associated with cancer [7,8]. Chemotherapy is one of the most commonly used treatment methods in clinical practice for cancer patients to eradicate of cancer cells using chemotherapeutic agents. In cancer chemotherapy, the main purpose is to prevent the growth and spread of the existing tumor to other parts of the body with the chemotherapeutic agents used, and to create a cytotoxic effect that will ensure the complete eradication of the tumor as much as possible. However, the vast majority of cancer types cannot be fully treated with the chemotherapeutic agents and their combinations still used today, and the available drugs in this regard are insufficient [8-13].

Cervical cancer and breast cancer are among the cancer types with high incidence and mortality rates compared to other types of cancer. According to the report prepared with data obtained from 185 countries by the International Agency for Research on Cancer, cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated more than 600,000 novel cases and nearly 350,000 deaths worldwide in 2020. On the other hand, breast cancer is the type of cancer that surpasses lung cancer as the leading cause of global cancer incidence, with an estimated 2.3 million new cases representing 11.7% of all cancer cases according to the same report [14]. As with other types of cancer, suitable chemotherapeutic agents with the desired cytotoxic effect for these cancer types have still not been

discovered today [15]. Therefore, we have decided to investigate the cytotoxic effects of the synthesized molecules on cervical cancer and breast cancer cell lines in this research.

Heterocycles are the cyclic organic compounds, which contain at least one heteroatom. These compounds constitute the largest and most important family of organic compounds. Heterocyclic compounds are obtained synthetically or from plant extracts. There are many known heterocyclic compounds today. The number of these compounds increasing day by day. In studies conducted to examine the biological importance of these compounds, it was determined that most of them were bioactive molecules. These compounds have attracted great interest of many researchers recently due to their biological activities. It is known that most of them indicate antifungal, antibacterial, antidiabetic, enzyme inhibitory, antioxidant and anticancer activities [16].

Hydrazone derivatives, obtained by coupling hydrazide compounds with aldehydes and ketones, represent an important class of bioactive compounds that have attracted the attention of medicinal chemists due to their broad biological activities. Therefore, this class of organic compounds in medicinal chemistry is being used to discover the needed drugs in order to combat some diseases including various types of cancer [17-19]. Recently, it has been reported in many studies that hydrazone derivatives are molecules with anticancer activity [20-25]. On the other hand, it has been reported in some studies that organic molecules with nitro and methoxy functional groups as substituents show various biological activities [26, 27]. Therefore, we have preferred to use the starting molecules that have with nitro and methoxy functional groups as substituents in the synthesis of new heterocyclic hydrazone molecules with anticancer activity in this study.

The target of this study is to perform the synthesis and characterization of some heterocyclic hydrazone derivatives (7-12) and investigate for their anticancer properties against HeLa and MCF-7 cancer cell lines. To determine anticancer behavior of the synthesized compounds (1-12) on normal (non-cancer) cells, L929 mouse fibroblast cell lines were employed in this study. The target molecules were characterized by spectroscopic methods.

Materials and Methods

Chemistry

All chemicals required for the preparation of anticancer agents (1-12) and the determination studies of their anticancer activity were procured from Merck and Sigma Aldrich companies. These chemicals were of analytical grade, and employed without further purification. The reaction processes of the compounds were monitored by thin layer chromatography. FT-IR spectra was recorded using a Cary 630 FTIR spectrometer with the diamond ATR module at a scan range of 4000-400 cm^{-1}. ^{1}H- and ^{13}C NMR spectra were taken on a Bruker AVANCE III 400 MHz spectrometer using tetramethylsilane as the internal reference at 400 and 100 MHz. Dimethyl sulfoxide (DMSO) was used as a solvent in NMR analysis. Melting points were determined on a Barnstead IA9100 electrothermal digital melting points apparatus.

General procedure for the synthesis of hydrazone derivatives

In this research, hydrazone compounds (7-12) were prepared by the condensation reaction of nicotinic acid hydrazide with benzaldehyde ester derivatives derived from two benzaldehyde derivatives as starting compounds [17, 18, 28, 29]. The esters (1-6) derived from benzaldehyde derivatives were synthesized and characterized in our previous studies [28, 29].

N'-(4-((3-Nitrobenzoyl)oxy)benzylidene)nicotinohydrazide (7)

White solid. Yield: 69%. M.p. 232-233 °C. FT-IR υ_{max} (cm^{-1}): 3263 (N-H str.), 3094, 3068 (aromatic C-H, str.), 1738 (C=O str.), 1652 (C=O str.), 1605 (C=N str.), 1530 (asymmetric, NO_2 str.), 1347 (symmetric, NO_2 str.). ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm: 12.11 (s, 1H, CONH), 9.09 (d, J = 2.1 Hz, 1H, Pyr-H), 8.85 – 8.73 (m, 2H, Pyr-H and Ar-H), 8.64 – 8.54 (m, 2H, Pyr-H), 8.51 (s, 1H, CH=N), 8.28 (d, J = 7.9 Hz, 1H, Ar-H), 7.96 – 7.87 (m, 3H, Pyr-H and Ar-H), 7.58 (dd, J = 7.8, 4.9 Hz, 1H, Ar-H), 7.48 (d, J = 8.5 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 163.27 (C=O), 162.21 (C=O), 152.80 (CH=N), 152.15, 149.08, 148.45, 147.86, 136.36, 135.95, 132.80, 131.42, 130.96, 129.60, 128.96, 128.93, 124.71, 124.09, 122.92 (Pyr-C and Ar-C).

N'-(4-((3-Nitrobenzoyl)oxy)-3-ethoxybenzylidene)nicotinohydrazide (8)

White solid. Yield: 73%. Mp. 223-224 °C. FT-IR υ_{max} (cm^{-1}): 3243 (N-H str.), 3101, 3061 (aromatic C-H, str.), 2938, 2871 (aromatic C-H, str.), 1744 (C=O str.), 1649 (C=O str.), 1591 (C=N str.), 1535 (asymmetric, NO_2 str.), 1346 (symmetric, NO_2 str.). 1H NMR (300 MHz, DMSO-d_6) δ/ppm: 12.12 (s, 1H, CONH), 9.14 – 9.04 (m, 1H, Pyr-H), 8.83 – 8.74 (m, 2H, Pyr-H and Ar-H), 8.69 – 8.51 (m, 3H, Pyr-H and Ar-H), 8.50 (s, 1H, CH=N), 7.94 (t, J = 8.0 Hz, 1H, Ar-H), 7.62 – 7.55 (m, 2H, Pyr-H and Ar-H), 7.46 – 7.40 (m, 2H, Ar-H), 3.87 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 162.71 (C=O), 162.26 (C=O), 152.82 (CH=N), 151.57, 149.08, 148.55, 148.13, 141.03, 136.33, 135.97, 134.10, 131.56, 130.41, 129.63, 129.08, 124.69, 124.10, 123.87, 121.19, 110.57 (Pyr-C and Ar-C), 56.49 (-OCH_3).

N'-(4-((4-Nitrobenzoyl)oxy)benzylidene)nicotinohydrazide (9)

White solid. Yield: 78%. Mp. 252-253 °C. FT-IR υ_{max} (cm^{-1}): 3242 (N-H str.), 3109, 3071 (aromatic C-H, str.), 1728 (C=O str.), 1656 (C=O str.), 1601 (C=N str.), 1514 (asymmetric, NO_2 str.), 1343 (symmetric, NO_2 str.). ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm: 12.10 (s, 1H, CONH), 9.11 – 9.07 (m, 1H, Pyr-H), 8.78 (d, J = 4.9 Hz,1H, Pyr-H),

8.51 (s, 1H, CH=N), 8.45 – 8.37 (m, 4H, Ar-H), 8.28 (d, J = 8.0 Hz, 1H, Pyr-H), 7.89 (d, J = 8.5 Hz, 2H, Ar-H), 7.60 – 7.56 (m, 1H, Pyr-H), 7.48 (d, J = 8.6 Hz, 2H, Ar-H). 13C NMR (75 MHz, DMSO-d_6) δ/ppm: 163.49 (C=O), 162.21 (C=O), 152.81 (CH=N), 152.18, 151.10, 149.08, 147.86, 135.95, 134.80, 132.79, 131.83, 129.61, 128.96, 124.50, 124.10, 122.90 (Pyr-C and Ar-C).

N'-(4-((4-Nitrobenzoyl)oxy)-3- methoxybenzylidene)nicotinohydrazide (10)

White solid. Yield: 71%. Mp. 226-227 °C. FT-IR υ_{max} (cm^{-1}): 3184 (N-H str.), 3049, 3006 (aromatic C-H, str.), 2919, 2850 (aromatic C-H, str.), 1743 (C=O str.), 1646 (C=O str.), 1594 (C=N str.), 1523 (asymmetric, NO_2 str.), 1345 (symmetric, NO_2 str.). 1H NMR (300 MHz, DMSO-d_6) δ/ppm: 12.11 (s, 1H, CONH), 9.09 (d, J = 1.6 Hz, 1H, Pyr-H), 8.79 (dd, J = 4.9, 1.4 Hz, 1H, Pyr-H), 8.49 (s, 1H, CH=N), 8.45 – 8.37 (m, 4H, Pyr-H and Ar-H), 8.28 (d, J = 8.0 Hz, 1H, Ar-H), 7.63 – 7.56 (m, 2H, Pyr-H and Ar-H), 7.44 (d, J = 8.4 Hz, 2H, Ar-H), 3.87 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 162.96 (C=O), 162.26 (C=O), 152.82 (CH=N), 151.55, 151.19, 149.08, 148.13, 141.07, 135.96, 134.28, 134.09, 131.85, 129.64, 124.63, 124.11, 123.85, 121.18, 110.58 (Pyr-C and Ar-C), 56.50 (-OCH_3).

N'-(4-((3,5-Bisnitrobenzoyl)oxy)benzylidene)nicotinohydrazide (11)

White solid. Yield: 65%. Mp. 250-251 °C. FT-IR υ_{max} (cm^{-1}): 3237 (N-H str.), 3107, 3025 (aromatic C-H, str.), 1746 (C=O str.), 1650 (C=O str.), 1591 (C=N str.), 1537 (asymmetric, NO_2 str.), 1344 (symmetric, NO_2 str.). ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm: 12.10 (s, 1H, CONH), 9.14 – 9.11 (m, 4H, Pyr-H and Ar-H), 8.79 (d, J = 4.7 Hz, 1H, Pyr-H), 8.51 (s, 1H, CH=N), 8.29 (d, J = 8.0 Hz, 1H, Pyr-H), 7.91 (d, J = 8.4 Hz, 2H, Ar-H), 7.60 – 7.51 (m, 3H, Pyr-H and Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 162.22 (C=O), 161.89 (C=O), 152.82 (CH=N), 151.95, 149.06, 148.89, 147.79, 135.95, 133.01, 132.57, 129.91, 129.61, 129.00, 124.13, 123.59, 122.83 (Pyr-C and Ar-C).

N'-(4-((3,5-Bisnitrobenzoyl)oxy)-3-methoxybenzylidene)nicotinohydrazide (12)

White solid. Yield: 68%. Mp. 247-248 °C. FT-IR υ_{max} (cm^{-1}): 3232 (N-H str.), 3089, 3071 (aromatic C-H, str.), 2994, 2881 (aromatic C-H, str.), 1750 (C=O str.), 1653 (C=O str.), 1594 (C=N str.), 1537 (asymmetric, NO_2 str.), 1347 (symmetric, NO_2 str.). 1H NMR (300 MHz, DMSO-d_6) δ/ppm: 12.12 (s, 1H, CONH), 9.14 – 9.08 (m, 4H, Pyr-H and Ar-H), 8.79 (d, J = 4.3, 1.4 Hz, 1H, Pyr-H), 8.50 (s, 1H, CH=N), 8.28 (d, J = 7.9 Hz, 1H, Pyr-H), 7.60 (d, J = 7.7 Hz, 2H, Ar-H), 7.51 – 7.41 (m, 2H, Pyr-H and Ar-H), 3.88 (s, 3H, -OCH_3).^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm: 162.27 (C=O), 161.26 (C=O), 152.83 (CH=N), 151.43, 149.07, 148.03, 140.72, 135.99, 134.36, 131.72, 129.88, 129.63, 124.12, 123.79, 121.17, 110.69 (Pyr-C and Ar-C), 56.55 (-OCH_3).

Anticancer Assay

The cytotoxic activities of the target molecules (7-12) were evaluated by using MTT assay against two cancer cell lines (HeLa and MCF-7). In this study, L929 mouse normal fibroblast cell lines were employed as control cells [28-30]. The percentage of cell viability was measured at 570 nm by using ELISA reader (Epoch, Biotek, USA). MTT assay was performed triplicate. Also, the effects on the cells of each compound were assessed by inverted microscope (Zeiss Axiovert). Moreover, the IC_{50} values of the tested molecules on these cell lines were calculated by utilizing AATbio IC_{50} calculator.

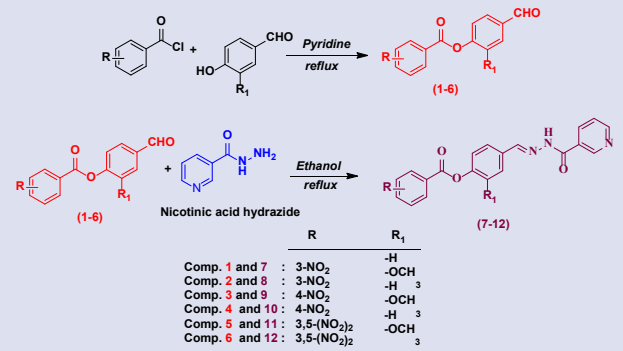
Statistical Analysis

In this research, data were gathered from three different biological replicates, and the findings were plotted as mean ± SD. One-way ANOVA was employed as statistical analysis by GraphPad Prism 7. P-value <0.05 was considered statistically important.

Results and Discussion

Chemistry

In this study, the target compounds were synthesized with high yield in two steps according to our previous studies. In the first step, six benzaldehyde ester derivatives were obtained by the reaction of two benzaldehyde derivatives (4-hydroxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde) with substituted benzoyl chloride derivatives (3-nitrobenzoyl chloride, 4-nitrobenzoyl chloride and 3,5-dinitrobenzoyl chloride) in a pyridine medium, respectively [21,22]. In the second step, hydrazone derivatives were readily acquired via condensation reaction of nicotinic acid hydrazide with benzaldehyde ester derivatives in ethanol medium (Scheme 1). Three of the target compounds (8, 11 and 12) are new, and the others are known compounds (7, 9 and 10). All synthesis reactions were monitored by thin layer chromatography.



Scheme 1. The synthetic pathway for the preparation of the target compounds

In this research, the target compounds (7-12) were characterized by FT-IR, ^{1}H- and ^{13}C NMR. Their characterization data were found to be compatible with their molecule structures. In FT-IR spectra of compounds (7–12), the band representing carbonyl group (C=O) of the ester, C=O of hydrazide and imino (–C=N), appeared at 1750 – 1728 cm^{-1}, 1656 – 1646 cm^{-1}, and 1605 – 1591 cm^{-1}, respectively. In addition, asymmetric and symmetric bands of the nitro (NO_2) group in these compounds were

detected as 1537 – 1514 cm^{-1} and 1343 – 1347 cm^{-1}. In ^{1}H NMR spectra of (7-12), the signal due to the azomethine proton (–CH=N) appeared in the region 8.49 – 8.51 ppm. Signals of the CONH proton were determined in the range of approximately 12 ppm. Pyridine ring and aromatic rings protons were observed at 9.14 – 7.40 ppm. Also, methoxy ($–OCH_3$) protons found in the structures of compounds 8, 10, and 12 were observed at 3.87 – 3.88 ppm. In their ^{13}C NMR spectra, the signal due to –CH=N carbon was observed at 152.80 – 152.83 ppm. The signal originating from the C=O carbon of the hydrazide was observed in the region of 161.89 – 162.26 ppm, while the signal originating from the C=O carbon of the ester was determined in the region 162.22 – 163.49 ppm. Furthermore, the signal due to the $–OCH_3$ carbon was detected at 56.49 – 56.55 ppm. Other carbons belonging to pyridine and aromatic rings were observed in the expected regions. On the other hand, these results were found to be compatible with the literature [31-34].

Anticancer Activity Results

In this research, the anticancer activities of synthesized hydrazone derivatives were assessed on HeLa, MCF-7 and L929 (mouse fibroblast) cell lines using MTT assay. Cisplatin was used as the standard compound. IC_{50} values of tested molecules and cisplatin are presented in Table 1.

Table 1. IC_{50} values of the synthesized hydrazone derivatives (7-12)

Compounds	HeLa (µM)	MCF-7 (µM)	L929 (µM)
7	67.78±3.98	569.12±55.10	598.60±56.72
8	34.38±2.99	107.71±10.28	204.90±20.33
9	128.5±13.65	635.41±53.45	453.02±41.08
10	240.26±21.71	246.22±21.76	59.55±6.03
11	89.1±9.45	26.84±4.35	10.76±2.78
12	364.73±30.57	215.41±25.49	324.65±34.49
Cisplatin	28.33±4.20	10.06±2.15	240.65±5.85

In this research, a total of six hydrazone compounds were synthesized for anticancer assay. When the cytotoxic activity results in Table 1 were examined, it was determined that all synthesized compounds displayed the cytotoxic activities with IC_{50} values ranging from 34.38 to 364.73 µM against HeLa cervical cancer cell lines. Amongst the tested compounds, the most ideal chemotherapeutic candidate is the 8-coded compound whose IC_{50} values were calculated as 34.38 µM and 204.90 µM in HeLa and L929 cell lines, respectively (Table 1). On the other hand, these molecules displayed anticancer activities at concentrations between 26.84 and 635.41 µM against MCF-7 breast cancer cell lines. Amongst these compounds, we found that compound **11** exhibited high cytotoxic activity on MCF-7 breast cancer cells with the IC_{50} value of 26.84. However, this compound had also cytotoxic effect on mouse fibroblast L929 cells with IC_{50}=10.76 µM. Therefore, compound **11** was not evaluated as a drug candidate because it had a toxic effect on healthy cells.

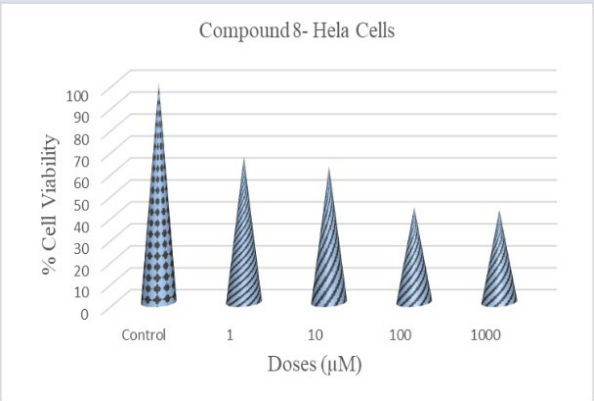


Figure 1: Cell viability percentages of HeLa cervical cancer cells by compound 8 at various doses

Conclusion

This study is conducted to discover novel anticancer drug candidates that are effective and have no side effects. For this purpose, we successfully synthesized six hydrazone derivatives, and then their characterization processes were performed by three spectroscopic techniques. The anticancer activities of the synthesized hydrazone derivatives on HeLa cervical and MCF-7 breast cancer cells were determined. It was determined that these molecules (7-12) displayed anticancer activities with IC_{50} values ranging from 26.84 to 635.41 µM. However, we determined that these molecules showed lower anticancer activities than the reference molecule. The results showed that two of the tested compounds (8 and 11) may be promising scaffolds for the discovery studies of new anticancer agents.

Conflicts of interest

The authors declare that they have no conflict of interest

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