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Synthesis, Antiproliferative Activity and *In Silico* Studies of Chalcones Derived From 4-(Imidazole-1-yl)Acetophenone

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Abstract: In this study, the synthesis of chalcone compounds (**1**-**11**) derived from 4-(imidazol-1-yl)acetophenone and the structure determination of these compounds by various spectroscopic methods were carried out. The anticancer activities of compounds **1**-**11** were examined against HeLa and PC-3 cancer cells at four different concentrations (100, 50, 25, and 5 µM) using the BrdU ELISA assay. It was determined that all molecules except compounds **1** and **6** in HeLa cancer cells and compounds **2** and **8** against PC-3 cancer cells were more active against HeLa and PC-3 than the standard drug 5-fluorouracil (**5-FU**). The best activity against PC-3 cancer cells was compound **4** (IC_{50}: 1.39±0.00 µM). In addition, compound **11** (IC_{50}: 1.58±0.01 µM) was found to have the highest activity against HeLa cancer cells. Compound **4** against PC-3 cancer cell and compound **11** against HeLa cancer cell displayed cell selective activity. The ADME properties and drug similarities of the molecules **1**-**11** using the SwissADME software were investigated. According to these properties, compounds **1-11** were found to obey Lipinski rules.

Keywords: ADME, Antiproliferative activity, HeLa cell line, *In silico*, PC-3 cell line.

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1. INTRODUCTION

The imidazole ring which is a member of the azole family, is a five-membered compound with two nitrogen atoms and acts as both a proton acceptor and a proton donor. It biologically is very important because it can bind to proteins with weak interactions and is widely found in nature. The imidazole ring can be found in many natural molecule's structures such as histidine, histamine and adenine and also in many drugs with various biological activities Figure 1 (1).

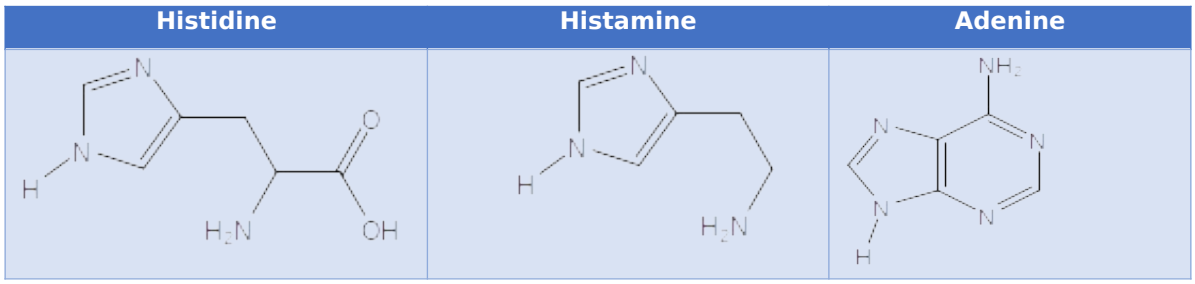


Figure 1: The structure of histidine, histamine, and adenine.

Chalcones are an open-chain intermediates used in the synthesis of flavones and aurons (1,3-diphenyl-2-*E*-propen-1-one), which are found in many conjugated forms in nature (2-3). It contains a benzylideneacetophenone scaffold in which two aromatic nuclei are joined by a three-carbon α, β unsaturated carbonyl bridge (4). Chalcones and their derivatives can be synthesized classically by the Claisen-Schmidt reaction, as well as by different catalysts and methods (5-7). Intensive research on drug discovery has led to the formation of a large number of molecules with different pharmacological activities.

Developing, designing, and bringing to market new drug candidates using only conventional procedures is a time-consuming process. Therefore, recently it has come in handy to use computational processes, also known as *in silico* techniques, to screen a large group of molecules and select the most reliable molecule among them. Thus, by evaluating with computational methods, the synthesis and biological activity evaluations of the designed molecules take less time. In addition, it is necessary to examine the ADME (Absorption, Distribution, Metabolism, and Excretion) properties of molecules and other drug similarity properties before they can be used as pharmaceutical drugs. ADME studies in the early stages of drug discovery can help reduce the likelihood of molecules pharmacokinetic failure during clinical phase trials.

Various techniques have been developed to obtain information about the ADME properties of developing molecules. Many of the compounds that were reported to be effective in the past could not be used clinically due to poor pharmacokinetic properties (8). Meanwhile, the use of computer models as an alternative to experimental approaches to predict ADME has gained importance, especially in the early stages of drug discovery (9). SwissAD-ME, developed by the molecular modeling group of the Swiss Bioinformatics Institute, is one of website-based software and plays an important role in the period of computer-aided drug design techniques for the evaluation of ADME studies.

In our previous studies, we determined that chalcones carrying F, CF_3 and OCF_3 groups have high anticancer activity. Therefore, we designed new molecules combining the imidazole ring with aldehydes with fluorine atoms in different positions in this study. Then, the anticancer activities of these compounds against HeLa (Human Uterine Cancer Cell) and PC-3 (human Prostate Cancer Cell) cells were examined, and finally, the ADME properties and other drug similarities of the synthesized molecules were examined using the SwissADME software.

2. EXPERIMENTAL

2.1. Materials and Methods

The used chemicals were provided by Sigma-Aldrich and Merck (USA). Melting points of the compounds were determined with Stuart's melting point SMP30 apparatus. FT-IR spectral analysis was performed on the Perkin Elmer Frontier spectrometer with attenuated total reflection (ATR) apparatus (Waltham, Massachusetts, USA). ^{1}H NMR and ^{13}C NMR spectral analyses were performed in DMSO-d6 with a Brucker Avance-600 MHz spectrometer (Billerica, MA, USA). Elemental analyses (CHNS) were performed on a VarioMICRO elemental analyzer.

2.2. Procedure for Synthesis of Chalcone Compounds with Imidazole Ring (1-11).

4′-Imidazolacetophenone (0.01 mol) was dissolved in methanol (25 mL). Then, the substituted aromatic aldehyde (0.01 mol) and NaOH (0.01 mol) were added to the 4′-imidazolacetophenone solution. The mixture was stirred at room temperature on a magnetic stirrer for one day. After the reaction was finished, the extraction was done with a mixture of dichloromethane and water (1:1). The solvent was evaporated and the crude material was recrystallized from ethanol to obtain a pure substance (10,11).

(*E*)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(2-fluorophenyl)prop-2-en-1-one (1)

Orange solid; yield: 40%, m.p. 135-136°C. FTIR ν_{max} (cm^{-1}): 2987,2971 (Ar-CH); 1681 (C=O); 1600, 1542, 1459, 1452 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.04 (t, 1H, j_1=7.20 Hz, j_2=6.60 Hz), 7.13 (d, 1H, j=8.40 Hz), 7.35-7.32 (m, 1H), 7.47 (t, 1H, j_1=7.80 Hz, j_2=7.80 Hz), 7.89 (d, 1H, j=13.20 Hz, $H_α$), 7,93 (s, 1H), 8.03 (d, 2H, j=6,6 Hz), 8.11 (d, 1H, j=16.80 Hz, $H_β$), 8.37 (d, 2H, j=11.40 Hz), 8.42 (s, 1H), 9.83 (s, 1H). Anal. Calcd for $C_{18}H_{13}FN_2O$ (292.31 g/mol). C, 73.96; H, 4.48; N, 9.58. Found: C, 73.97; H, 4.52; N, 9.61 (12).

(*E*)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(3-fluorophenyl)prop-2-en-1-one (2)

White solid; yield: 45%, m.p. 147-149°C. FTIR ν_{max} (cm^{-1}): 2853 (Ar-CH); 1681 (C=O); 1614, 1599, 1489, 1447 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.31 (t, 1H, j_1=9.00 Hz, j_2=6.00 Hz), 7.50 (dd, 1H, j_1=8.40 Hz, j_2=8.40 Hz), 7.73 (d, 1H, j=7.80 Hz), 7.79 (d, 1H, j=14.4Hz, $H_α$), 7.91 (d, 2H, j=13.80 Hz, $H_β$), 8.05 (d, 2H, j=9.00 Hz), 8.11 (d, 1H, j=13.20 Hz), 8.42 (d, 3H, j=8.40 Hz), 9.81 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 188.27 (C=O); 115.32, 118.07, 120.76, 122.23, 123.55, 126.36, 128.30, 130.90, 130.96, 131.35, 131.40, 135.51, 137.55, 137.81, 143.71. Anal. Calcd for $C_{18}H_{13}FN_2O$ (292.31 g/mol). C, 73.96; H, 4.48; N, 9.58. Found: C, 73.98; H, 4.51; N, 9.63 (12).

(*E*)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one (3)

White solid; yield: 36%, m.p. 141-142°C. FTIR ν_{max} (cm^{-1}): 2990, 2920 (Ar-CH); 1668 (C=O); 1597, 1509, 1348 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.32 (t, 2H, j_1=9.00 Hz, j_2=8.40 Hz), 7.80 (d, 1H, j_1=15.60 Hz, $H_α$), 7.91 (s, 1H), 7.99 (m, 5H, $H_β$, H_{AR}), 8.39 (s, 1H), 8.40 (d, 2H, j=9.00 Hz), 9.79 (s, 1H, H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 188.27 (C=O); 116.39, 116.53, 120.85, 122.00, 122.28, 130.87, 132.01, 135.52, 138.08, 138.77, 144.03, 163.20, 164.86. Anal. Calcd for $C_{18}H_{13}FN_2O$ (292.31 g/mol). C, 73.96; H, 4.48; N, 9.58. Found: C, 73.94; H, 4.53; N, 9.62 (12).

(*E*)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(2-(trifluoromethyl)phenyl)prop-2-en-1-one (4)

White solid; yield: 38%, m.p. 245-247 °C. FTIR ν_{max} (cm^{-1}): 3096, 2987 (Ar-CH); 1660 (C=O);

1602, 1573, 1543, 1486 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.68 (t, 1H, j_1=7.80 Hz, j_2=7.20 Hz), 7.81 (t, 1H, j_1=7.80 Hz, j_2=7.20 Hz), 7.85 (d, 1H, j=7.80 Hz), 7.90 (s, 1H), 8.01 (d, 1H, j=15.60 Hz, H_α), 8.05 (d, 2H, j=7.80 Hz), 8.13 (d, 1H, j=15.00 Hz, H_β), 8.39 (d, 1H, j=7.80 Hz), 8.42 (d, 2H, j=6.00 Hz), 8.44 (s, 1H), 9.80 (s, 1H). ^{13}C NMR (150 MHz, DMSO d6): δ 188.14 (C=O); 120.83, 122.32, 125.53, 126.26, 126.71, 127.95, 129.42, 131.09, 131.28, 133.02, 133.48, 135.56, 137.57, 138.85, 139.03, 163.30. Anal. Calcd for: $C_{19}H_{13}F_3N_2O$ (342.32 g/mol), C, 66.67; H, 3.83; N, 8.18. Found: C, 66.70; H, 3.85; N, 8.20 (13).

(*E*)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)prop-2-en-1-one (5)
White solid; yield: 34%, m.p. 105-106 °C. FTIR ν_{max} (cm^{-1}): 2971, 2901 (Ar-CH); 1601 (C=O); 1542, 1326 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.71 (s, 1H), 7.81 (d, 1H, j=7.80 Hz), 7.86 (d, 1H, j=6.60 Hz), 7.90 (d, 2H, j=12.00 Hz, H_α), 7.98 (t, 1H, j_1=7.80 Hz, j_2=12.00 Hz), 8.05 (d, 2H, j=7.80 Hz), 8.21 (d, 1H, j=16.20 Hz, H_β), 8.37-8.45 (m, 3H), 9.81 (s, 1H). Anal. Calcd for: $C_{19}H_{13}F_3N_2O$ (342.32 g/mol), C, 66.67; H, 3.83; N, 8.18. Found: C, 66.71; H, 3.87; N, 8.22.

(*E*)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(2-(fluoro-3-(trifluoromethyl)phenyl)prop-2-en-1-one (6)
Yellow solid; yield: 40%, m.p. 208-209 °C. FTIR ν_{max} (cm^{-1}): 3093, 2974 (Ar-CH); 1664 (C=O); 1603, 1544, 1469, 1427 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.46 (t, 1H, $j1$=6.00 Hz, $j2$=10.20 Hz), 7.80(d, 1H, j=7.80 Hz), 7.91 (s, 1H), 7.92 (d, 1H, j=16.20 Hz, H_α), 8.05 (d, 2H, j=8.40 Hz), 8.14 (d, 1H, j=15.60 Hz, H_β), 8.41 (s, 1H), 8.42 (d, 2H, j=9.00 Hz), 8.46 (d, 1H, j=7.80 Hz), 9.80 (s, 1H). ^{13}C NMR (150 MHz, DMSO d6): δ 188.40 (C=O); 120.78, 122.19, 124.42,124.89, 125.35, 129.32, 130.25, 130.75, 130.99, 133.58, 135.62, 137.00, 137.72, 139.00,157.45, 162.57. Anal. Calcd for: $C_{19}H_{12}F_4N_2O$ (360.31 g/mol), C, 63.34; H, 3.36; N, 7.77. Found: C, 63.36; H, 3.39; N, 7.81.

***E*-1-(4-(1H-imidazol-1-yl)phenyl)-3-(2-(fluoro-6-(trifluoromethyl)phenyl)prop-2-en-1-one (7)**
White solid; yield: 43%, m.p. 140-141 °C. FTIR ν_{max} (cm^{-1}): 3096, 3057 (Ar-CH); 1660 (C=O); 1602, 1543, 1458 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.66-7.71 (m, 1H), 7.72 (d, 1H, j=15.00 Hz, H_α), 7.88 (d, 1H, j=11.40 Hz, H_β), 7.92 (s, 1H), 8.04 (d, 2H, j=7.20 Hz), 8.25 (d, 2H, j=8.40 Hz), 8.30 (d, 2H, j=7.80 Hz), 8.38 (s, 1H), 9.74 (s, 1H) Anal. Calcd for: $C_{19}H_{12}F_4N_2O$ (360.31 g/mol), C, 63.34; H, 3.36; N, 7.77. Found: C, 63.37; H, 3.40; N, 7.82.

***E*-1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-fluoro-2-(trifluoromethyl)phenyl)prop-2-en-1-one (8)**
Yellow solid; yield: 45%, m.p. 149-150 °C. FTIR ν_{max} (cm^{-1}): 3364, 2987 (Ar-CH); 1693 (C=O); 1607, 1544, 1506, 1422 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.36 (d, 1H, j=8.40 Hz), 7.83 (d, 1H, j=15.60 Hz, H_α), 7.87 (s, 1H), 8.00 (d, 2H, j=9.00 Hz), 8.03 (d, 1H, j=15.60 Hz, H_β), 8.21 (d, 1H, j=9.00 Hz), 8.23 (s, 1H), 8.37 (s, 1H), 8.41 (d, 2H, j=8.40 Hz), 9.70 (s, 1H). ^{13}C NMR (150 MHz, DMSO d6): δ 188.19 (C=O); 113.84, 120.73, 121.36, 122.16, 122.90, 127.43, 128.01, 128.77, 128.82, 130.91, 134.41, 135.59, 135.80, 138.05, 138.85, 143.78. Anal. Calcd for: $C_{19}H_{12}F_4N_2O$ (360.31 g/mol), C, 63.34; H, 3.36; N, 7.77. Found: C, 63.35; H, 3.39; N, 7.81.

***E*-1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-fluoro-3-(trifluoromethyl)phenyl)prop-2-en-1-one (9)**
White solid; yield: 50%, m.p. 215-217 °C. FTIR ν_{max} (cm^{-1}): 2987, 2973 (Ar-CH); 1663 (C=O); 1607, 1507, 1423 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.37 (d, 1H, j=8.40 Hz), 7.83 (d, 1H, j=15.60 Hz, H_α), 7.88 (s, 1H), 8.02 (d, 2H, j=8.40 Hz), 8.05 (s, 1H), 8.40 (d, 1H, j=15.60 Hz, H_β), 8.41 (s, 2H), 9.74 (s, 1H), 8.21 (d, 1H, j=9.00 Hz), 8.23 (d, 1H, j=8.40 Hz). ^{13}C NMR (150 MHz, DMSO d6): δ 188.17 (C=O); 113.83, 120.65, 121.36, 122.09, 123.26, 124.85, 127.44, 128.05, 130.82, 130.91, 135.59, 135.80, 137.97, 138.91, 143.76, 159.19. Anal. Calcd for: $C_{19}H_{12}F_4N_2O$ (360.31 g/mol), C, 63.34; H, 3.36; N, 7.77. Found: C, 63.40; H, 3.38; N, 7.79.

***E*-1-(4-(1H-imidazol-1-yl)phenyl)-3-(2-(trifluoromethoxy)phenyl)prop-2-en-1-one (10)**
White solid; yield: 80%, m.p. 208-209 °C. FTIR ν_{max} (cm^{-1}): 2970, 2926 (Ar-CH); 1660 (C=O); 1602, 1562, 1543, 1485 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.48 (d, 1H, j=8.4Hz), 7.52 (t, 1H, j1=7.20 Hz, j2=7.80 Hz), 7.61 (d, 1H, j=7.80 Hz), 7.90 (d, 2H, j=15.6Hz, H_α, H_{AR}), 8.07 (d, 2H, j=6.6Hz), 8.16 (d, 1H, j=13.80, H_β), 8.37 (d, 1H, j=9.6Hz), 8.40 (s, 1H), 8.42 (d, 2H, j=6.6Hz), 9.84 (s, 1H). ^{13}C NMR (150 MHz, DMSO d6): δ 188.09 (C=O); 122.31, 124.98, 127.76, 128.05, 128.54, 129.25, 129.87, 130.71, 130.99, 133.09, 134.39, 136.14, 137.67, 138.96, 147.51, 191.66. Anal. Calcd for: $C_{19}H_{13}F_3N_2O_2$ (358.32 g/mol), C, 63.69; H, 3.66; N, 7.82. Found: C, 63.71; H, 3.69; N, 7.85.

***E*-1-(4-(1H-imidazol-1-yl)phenyl)-3-(3-(trifluoromethoxy)phenyl)prop-2-en-1-one (11)**
White solid; yield: 76%, m.p. 129-130 °C. FTIR ν_{max} (cm^{-1}): 3103, 3065 (Ar-CH); 1659 (C=O); 1603, 1591, 1541, 1485 (C=C). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.47 (d, 1H, j=7.80 Hz), 7.60 (t, 1H, j_1=7.80 Hz, j_2=7.80 Hz), 7.82 (d, 1H, j=15.60 Hz, H_α), 7.90 (s, 1H), 7.94 (d, 1H, j=7.80 Hz), 8.03 (d, 2H, j=8.40 Hz), 8.04 (s, 1H), 8.14 (d, 1H, j=15.60 Hz, H_β), 8.40 (s, 1H), 8.43 (d, 2H, j=8.40 Hz), 9.76 (s, 1H). ^{13}C NMR (150 MHz, DMSO d6): δ 188.27 (C=O); 120.81, 121.59, 122.27, 123.44, 123.93, 128.80, 129.01, 131.00, 131.36, 135.57, 137.51, 137.81, 138.94, 143.33, 149.31. Anal. Calcd for: $C_{19}H_{13}F_3N_2O_2$ (358.32 g/mol), C, 63.69; H, 3.66; N, 7.82. Found: C, 63.72; H, 3.68; N, 7.86.

2.3. Anticancer Activity Studies

2.3.1 Cell culture

HeLa and PC-3 cancer cells were incubated in DMEM medium (37 °C - 5% CO_2) for four to five days. Trypan blue solution was used for cell counting. Thoma was taken on a slide and counted under the microscope (14,15).

2.3.2 Microplate experiment design

The cells were seeded into sterile microplates. All procedures were performed in triplicate. 5-Fluorouracil was used as the standard substance and tested at the same concentrations (100, 50, 25,

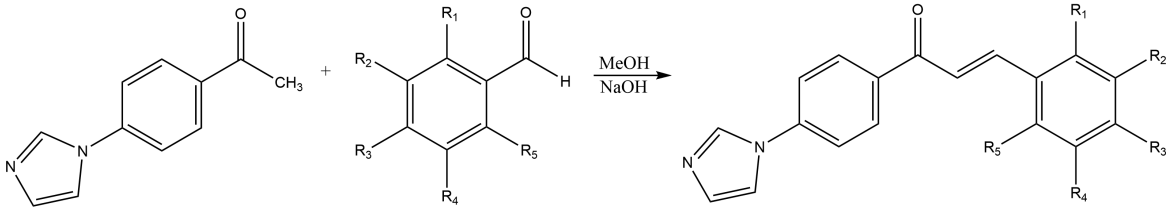
and 5 µM) as the samples. All wells were completed with the medium and kept in the incubator for 24 hours.

2.3.3. BrdU Cell ELISA cell proliferation assay
The activities of the synthesized compounds were performed using the BrdU Cell Proliferation ELISA Kit (Roche 11 647 229 001, Germany) (14,15).

2.3.4. Determination of IC50 concentration
The IC50 values of the samples were determined with the ED50V10.XLS program.

3. RESULTS AND DISCUSSION

3.1. General Chemistry
Chalcones (**1**-**11)** with imidazole rings were synthesized by Claisen-Schmidt condensation (Scheme 1). All molecules were scanned in the SciFinder search engine and molecules (**5**-**11)** were original; molecules (**1**-**4)** have been synthesized before (**Scheme 1**)(12, 13).



Scheme 1: Synthetic pathway of chalcone compounds with imidazole ring (**1**-**11**).

Table 1: Functional groups of synthesized (**1**-**11**) imidazole chalcone compounds.

Compd.	R_1	R_2	R_3	R_4	R_5
1	F	H	H	H	H
2	H	F	H	H	H
3	H	H	F	H	H
4	CF_3	H	H	H	H
5	H	CF_3	H	H	H
6	F	CF_3	H	H	H
7	F	H	H	H	CF_3
8	CF_3	H	F	H	H
9	H	CF_3	F	H	H
10	OCF_3	H	H	H	H
11	H	OCF_3	H	H	H

When the FTIR spectra were examined, aromatic C-H, C=O and C=C stretching bands were detected at 3364-2853 cm^{-1}, 1693-1601 $cm^{-1}$and 1614-1326 cm^{-1} respectively. The C-F stretching bands was found in the range of 1127-1242 cm^{-1}. When the ^1H and ^{13}C NMR spectra of the synthesized molecules were examined, the chemical shift values of protons and carbons were determined in ppm ranges in accordance with the literature (10,11,16). The biggest proof that chalcone compounds were synthesized, was that they had an olefin structure. AB spin system was observed in the ^1H NMR spectra as it had an olefin structure. The configuration of the molecule was determined by measuring the interaction constant. If the structure was in *cis* configuration, the value of j_{cis} was 7.00-10.00 Hz, if the structure was in *trans* configuration, the value of j_{trans} was 12.00-18.00 Hz (17). AB spin system was observed in all molecules (**1-11**). Determining the *j* values of the molecules between 11.40-16.20 Hz was showed that the synthesized molecules were in the *trans* configuration. Protons at α and β carbon atoms in the chalcone structure were found to resonate in the range of 7.82-8.21 ppm and 7.88-8.40, respectively.

3.2. Anticancer Activity
Anticancer activities of compounds **1**-**11** against HeLa and PC-3 cancer cells were examined at four different concentrations (100, 50, 25 and 5 µM). The IC_{50} values of compounds **1**-**11** against HeLa and PC-3 cells were given in Table 2. All compounds except compounds **1** and **6** were observed to have higher activity against HeLa cell than the standard drug **5-FU**. Compounds **10** and **11** were observed to exhibit considerably higher activity against HeLa cells compared to the standard compound. In particular, it was determined that the compounds containing the $–OCF_3$ group showed high activity. All compounds except compounds **2** and **8** were found to be more active than **5-FU** against PC-3 cancer cells. In particular, compounds **4** and **6** were found to be the most effective compounds against PC-3 cancer cells. It was observed that these two compounds contain -the CF_3 group. Many studies are showing the structure-anticancer activity analysis and showing that the fluoro group has a higher anticancer effect than other substituents. The incorporation of an electron-withdrawing group, such as a fluorine group, into a molecule leads to a marked improvement in anticancer activity (18,19).

Table 2: IC_{50} values of compounds **1**-**11** and **5-FU**.

Compd.	IC_{50}	
	HeLa	PC-3
1	93.67± 0.50	13.29± 0.05
2	26.44± 0.21	>100
3	17.56± 0.11	22.96± 0.06
4	>100	1.39± 0.00
5	21.02± 0.10	15.60±0.06
6	52.13± 0.31	2.65±0.00
7	24.11± 0.25	20.69±0.05
8	19.97± 0.05	>100
9	25.01± 0.04	41.31±0.24
10	4.27± 0.01	28.60±0.27
11	1.58± 0.01	35.40±0.15
5-FU	40.39± 0.23	50.00±0.22

3.3. SAR Study

When the anticancer activity of the compounds against Hela cell lines were examined, the activities were as follows: **11**>**10**>**3**>**8**>**5**>**7**>**9**>**2**>**6**>**1**>**4**. It was determined that compounds **10** and **11** carrying the OCF_3 group were the most active molecules and that the oxygen atom had a positive effect on the activity. It has been determined that the F atom had the best effect when it was in the 4-position (compound **3**), and its activity decreases when the 2- and 3- positions are changed.

When the anticancer activity of the compounds against PC-3 cell lines were examined, the activities were as follows: **4**>**6**>**1**>**5**>**7**>**3**>**10**>**11**>**9**>**5**-**FU**>**2**, **8**. It was determined that the activity was higher in molecules with the F atom in the 2nd position of the phenyl ring. The activity decreased when the fluorine atom was in the 3rd and 4th positions of the phenyl ring. When the compounds carrying CF_3 (compound **5,6** and **7**) and OCF_3 groups (compound **10** and **11**) were compared, it was determined that the derivatives carrying the CF_3 group were more active, while the incorporation of the oxygen atom into the structure had a negative effect on the activity.

3.4. *In silico* ADME Evaluation

In silico studies are web-based according to Lipinski and Weber rules. It was carried out with the SwissADME program (20). The drug similarity properties of compounds **1**-**11** were examined. Molecular weight (MW)<500, mLogP<5; HBA<10; and must comply with rules such as HBD<5. According to these rules, an orally active drug should not have more than one violation. The calculated logP must be less than 5. In the analysis performed, the log P values of compounds **1**-**11** were determined to be less than 5. The molecular weights of the compounds range from 292.31 to 360.31 g/mol. It was determined that compounds **1**-**5** and **10**-**11** could cross the Blood-Brain Barrier (BBB). The synthetic accessibility score of the compounds ranges from 1 (very easy) to 10 (very difficult). The synthetic accessibility of all compounds is in the range of 2.42 to 2.78. The topological polar surface area (TPSA) should be <70 Å2. The topological polar surface area value of all compounds (**1**-**11**) is less than 70 $Å^2$ (Table 3). Compounds **1**-**11** were found to have drug properties within Lipinski rules. All compounds were found to exhibit high gastrointestinal absorption (GI) (21).

Table 3: *In silico* results of compounds **1**-**11.**

Compd.	Formula	Molecular weight (g/mol)	M LOG P	BBB	GI absorption	TPSA $Å^2$	Synthetic accessibility	Lipinski
1	$C_{18}H_{13}FN_2O$	292.31	2.76	Yes	High	34.89	2.45	Yes
2	$C_{18}H_{13}FN_2O$	292.31	2.79	Yes	High	34.89	2.44	Yes
3	$C_{18}H_{13}FN_2O$	292.31	2.76	Yes	High	34.89	2.42	Yes
4	$C_{19}H_{13}F_3N_2O$	342.31	2.79	Yes	High	34.89	2.70	Yes
5	$C_{19}H_{13}F_3N_2O$	342.31	2.89	Yes	High	34.89	2.59	Yes
6	$C_{19}H_{12}F_4N_2O$	360.30	2.87	No	High	34.89	2.65	Yes
7	$C_{19}H_{12}F_4N_2O$	360.30	2.89	No	High	34.89	2.78	Yes
8	$C_{19}H_{12}F_4N_2O$	360.30	2.90	No	High	34.89	2.76	Yes
9	$C_{19}H_{12}F_4N_2O$	360.30	2.88	No	High	34.89	2.64	Yes
10	$C_{19}H_{13}F_3N_2O_2$	358.31	3.03	Yes	High	44.12	2.71	Yes
11	$C_{19}H_{13}F_3N_2O_2$	358.31	3.13	Yes	High	44.12	2.59	Yes

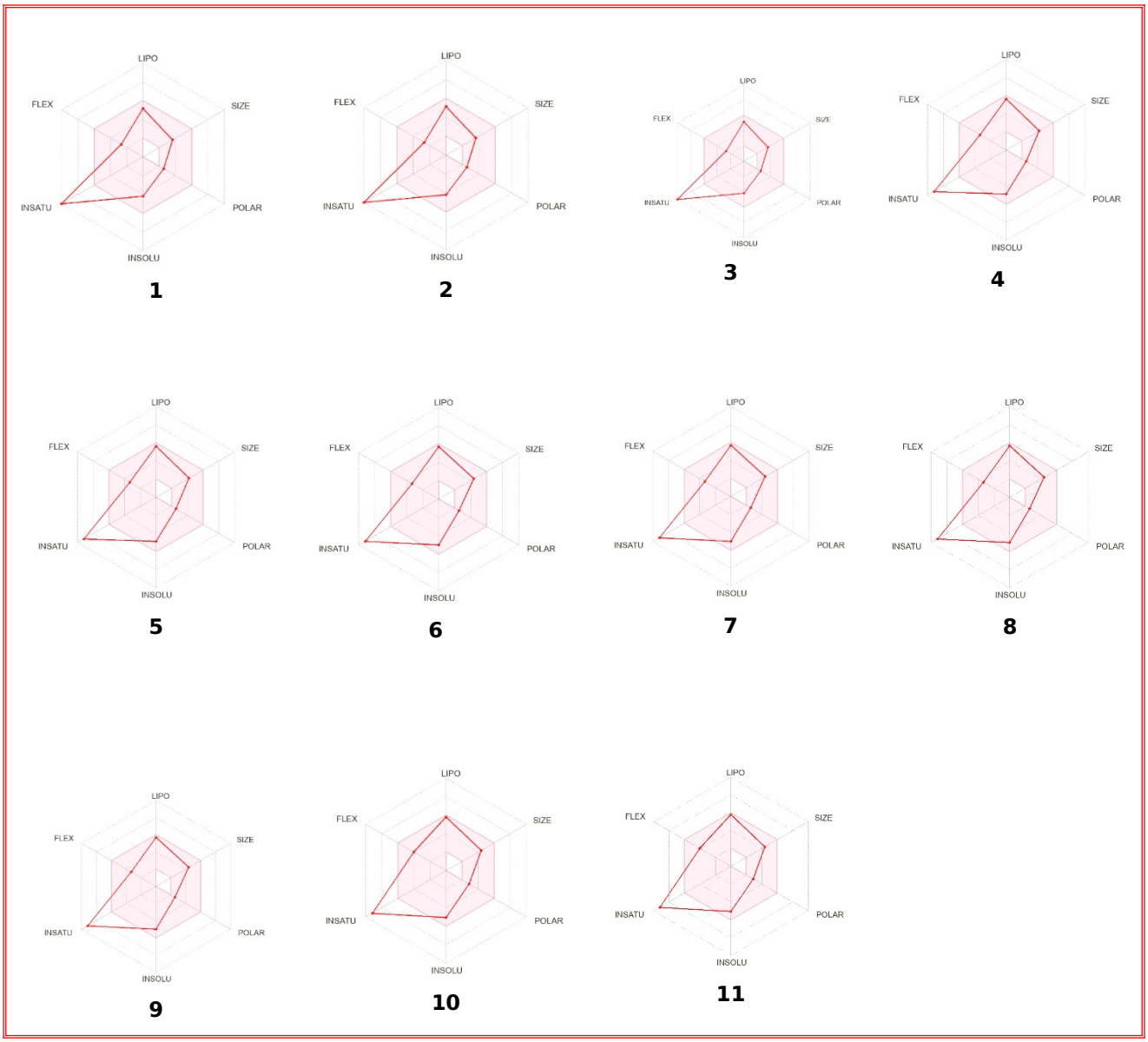


Figure 2 : Bioavailability radar of the **1**-**11**. The pink area represents the optimal range for each property (LIPO: Lipophilicity, SIZE: Molecular weight, POLAR: Total Polar Surface Area, INSOLU: Insolubility, INSATU: Instauration, FLEX: Flexibility). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

4. CONCLUSION

A series of chalcones were synthesized and their anticancer activities against Hela and PC3 cell lines were evaluated. In the Hela cell line, the compound **11** is the most active molecule; the most active molecule in the PC-3 cell line is compound **4**. Anticancer activity and *in silico* studies will make important contributions to the development of new active compounds for anticancer and to the pharmaceutical industry in the future.

5. CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

6. ACKNOWLEDGMENTS

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Bedriye Seda Kurşun Aktar: Conceptualization, Methodology, Synthesis, Biological analyses, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. Abdulraheem Mustafa Ibrahim AL-KARABASH: synthesis. Emine Elçin Oruç-Emre: Conceptualization, Methodology, Validation, Investigation, Writing - original draft, Writing - review & editing, Funding acquisition. Ayse Şahin Yağlıoğlu: Project administration, Biological

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