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NEW CHALCONE DERIVATIVES AS ANTICANCER AND ANTIOXIDANT AGENTS: SYNTHESIS, MOLECULAR DOCKING STUDY AND BIOLOGICAL EVALUATION

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Abstract: *In this approach, a series of new chalcone derivatives bearing baclofen drug were synthesized via Claisen-Schmidt condensation and evaluated in vitro as anticancer and antioxidant agents. The newly synthesized compounds were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR spectra, and elemental analysis. All products were screened in vitro against both cell lines HdFn and MCF-7. The cytotoxicity assay results revealed that derivatives **5a** and **5d** exhibited good inhibition for cell lines MCF-7 with IC_{50} values 32.5 and 37.6 µM, respectively while **5a** and **5c** exhibited acceptable inhibition for HdFn with IC_{50} values 76.7 and 78.6 µM, respectively, compared to the Tamoxifen drug. Molecular docking study of the target compounds confirmed the results of the cytotoxicity test. In addition, results of the DPPH investigation revealed good antioxidant activity for derivatives **5a**, **5c** and **5d** with inhibition percentages 86.62, 81.38, and 76.42%, respectively, compared to ascorbic acid.*
Keyword*: Chalcone, Anticancer, Antioxidant, Molecular Docking, Cytotoxicity*

Introduction

Cancer is a deadly disease that still threatens human lives despite scientific progress and continuous attempts to develop a mechanism to control and prevent the disease. Therefore, many researches and recent studies have sought to find an effective strategic treatment that meets the ambitions of the world [1]. Many synthesized chemical compounds have shown various biological activities [2-9]. Among those compounds, chalcones and their derivatives have received increasing attention from researchers because of their various activities, such as anti-bacterial [10-12], anti-fungal [13, 14], anti-cancer [15-17], anti-Alzheimer [18, 19], anti-inflammatory [20, 21], and antioxidant [22-24], in addition to their importance in the industrial field [25-27].

In this work, we created a number of chalcones combined with the baclofen drug and studied their anti-cancer and antioxidant activity, as well as studying their molecular docking.

Experimental part

General information

All the chemicals and solvents were obtained from commercial suppliers and were used as received without further purification. Melting points remained uncorrected and were determined on the Symmetric Multiprocessing (SMP) device (Gallenkamp). Fourier-transform infrared (FT-IR) spectra were recorded with FT-IR spectrophotometer (Bruker). Nuclear magnetic resonance (NMR) measurements (^{1}H NMR, ^{13}C NMR) were measured on Bruker AMX 400 and 100 instruments using tetramethylsilane (TMS) as a reference and DMSO-d_6 as a solvent. Analytical thin-layer chromatography (TLC) was carried out on Merck plates 60 F254 (0.2 mm thick). Microelements (C.H.N.) were analysed using a VEA3000 device (Shimadzu, Japan).

Synthesis

Synthesis of the 3-(4'-acetyl-[1,1'-biphenyl]-4-yl)-4-aminobutanoic acid 2 [28]

A mixture of 4-amino-3-(4-chlorophenyl) butanoic acid **1** (1 mmol), (4-acetylphenyl) boronic acid **2** (1 mmol), Pd(0)(pph3) (40 mg), sodium carbonate (5 ml) in propanol (15 ml) was refluxed for 12h, and the reaction was monitored by TLC. After the reaction completion, the reaction mixture was cooled to room temperature and poured over crushed ice with stirring. The result precipitate was collected by filtration, washed with cold water, dried and recrystallized from appropriate solvents to give target compounds good yields. The solid obtained was purified with flash chromatography using methanol–dichloromethane (8:2). Physical state **3**: Orange crystals; yield is 88%; m.p. 178-180°C. FT-IR (KBr, cm^{-1}): *ν* 3354 (OH), 3212 (N-H), 1732, 1685 (C=O), 1572 (C=C). ^{1}H-NMR (DMSO-*d6*,ppm): δ 12.41 (s,1H, OH), 8.05-7.11 (d,8H,H-arom.), 3.54 (d,2H,CH_2CO), 3.28 (s,1H, NH_2), 2.64 (d,2H,CH_2N), 2.11 (s,3H,Me), 1.78-170 (m,1H, $CH_{tertiary}$). ^{13}C-NMR (DMSO-*d6*, ppm): δ 197.3 (COOH), 177.1 (C=O), 137.6-121.3 (C-arom.), 42.1 (CH_2-N), 36.2 (CH_2-CO), 34.1 (C-$_{tertiary}$), 26.2 (Me). Analytical calculated for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.11; H, 5.74; N, 4.01.

General procedure for the synthesis of the chalcone derivatives 5a-d [15]

Aldehydes **4a-d** (2 mmol) were individually dissolved with the derivative **3** (2 mmol) in 30 mL of ethanol and reflexed for 6-8h in the presence of piperidine as a catalyst. After the reaction completion (TLC check), the reaction mixture was cooled to room temperature, washed with brine solution, and then extracted with chloroform three times. The organic extract obtained was dried and concentrated into a solid under a vacuum. The products obtained were purified with flash chromatography using methanol–dichloromethane (8:2).

4-Amino-3-(4'-(3-(4-hydroxyphenyl)acryloyl)-[1,1'-biphenyl]-4-yl)butanoic acid 5a: light red crystals, yield 78%, m.p 190-192°C. FT-IR (KBr, cm^{-1}): *ν* 3368 (OH), 3185 (N-H), 1737, 1674 (C=O), 1615 (C=C). ^{1}H-NMR (DMSO-*d6*,ppm): δ 12.03(s,1H, OH), 8.25-7.24 (d,12H,H-arom.), 3.36 (d,2H,CH_2CO), 3.22 (s,1H, NH_2), 2.52 (d,2H,CH_2N) 1.94-184 (m,1H, $CH_{tertiary}$). ^{13}C-NMR (DMSO-*d6*, ppm): δ 177.2(C=O), 135.1-123.4 (C-arom.), 39.6 (CH_2-N), 36.5 (CH_2-CO), 31.2 (C-$_{tertiary}$). Analytical calculated for $C_{25}H_{23}NO_4$: C, 74.80; H, 5.77; N, 3.49. Found: C, 74.2; H, 5.17; N, 2.89.

4-Amino-3-(4'-(dimethylamino)phenyl)acryloyl)-[1,1'-biphenyl]-4-yl)butanoic acid 5b: Dark yellow crystals, yield 64%, m.p 203-205°C. FT-IR (KBr, cm^{-1}): ν 3375(OH), 3194 (N-H), 1729, 1678 (C=O), 1608 (C=C). ^{1}H-NMR(DMSO-*d6*,ppm): δ 12.35 (s,1H, OH), 8.24-7.31 (d,12H,H-arom.), 3.28 (d,2H,CH_2CO), 3.14 (s,1H, NH_2), 2.41 (d,2H,CH_2N) 1.82-175 (m,1H, $CH_{tertiary}$). ^{13}C-NMR (DMSO-*d6*, ppm): δ 175.8(C=O), 133.6-118.7 (C-arom.), 41.8(CH_2-N), 37.7 (CH_2-CO), 32.8 (C-$_{tertiary}$). Analytical calculated for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 75.08; H, 5.99; N, 5.94.

4-Amino-3-(4'-(3-(4-nitrophenyl)acryloyl)-[1,1'-biphenyl]-4-yl)butanoic acid 5c: brown crystals, yield 68%, m.p 225-227°C. FT-IR (KBr, cm^{-1}): ν 3386 (OH), 3176 (N-H), 1732, 1675 (C=O), 1624 (C=C). ^{1}H-NMR (DMSO-*d6*,ppm): δ 12.42 (s,1H, OH), 8.19-7.26 (d,12H,H-arom.), 3.16 (d,2H,CH_2CO), 3.02 (s,1H, NH_2), 2.35 (d,2H,CH_2N) 1.94-186 (m,1H, $CH_{tertiary}$). ^{13}C-NMR (DMSO-*d6*, ppm): δ 177.3(C=O), 138.2-120.6(C-arom.), 43.5(CH_2-N), 38.1(CH_2-CO), 33.5(C-$_{tertiary}$). Analytical calculated for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.51. Found: C, 69.16; H, 4.55; N, 5.91.

4-Amino-3-(4'-(3-(4-hydrxy-3-methoxyphenyl)acryloyl)-[1,1'-biphenyl]-4-yl)butanoic acid 5d: Dark red crystals, yield 79%, m.p 212-215°C. FT-IR (KBr,cm^{-1}): ν 3423 (OH), 3183 (N-H), 1734, 1670 (C=O), 1611 (C=C). ^{1}H-NMR (DMSO-*d6*,ppm): δ 12.63, 9.65 (s,1H, OH), 8.15-7.34 (d,4H,H-arom.), 3.84 (s,3H,OCH_3), 3.23 (d,2H,CH_2CO), 3.05 (s,1H, NH_2), 2.18 (d,2H,CH_2N) 1.88-178 (m,1H, $CH_{tertiary}$). ^{13}C-NMR (DMSO-*d6*, ppm): δ 192.3(C=O), 176.4(COOH), 153.5(C-O), 132.5-122.6(C-arom.), 56.12(C-O), 44.8(CH_2-N), 37.4(CH_2-CO), 32.7(C-$_{tertiary}$). Analytical calculated for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25. Found: C, 71.77; H, 5.24; N, 2.65.

The cytotoxicity assay [29]

The cytotoxic activities of derivatives **5a–d** were investigated *in vitro* against two human cancer cell lines (HdFn, MCF-7) using the MTT test. The cell cultures, 100 µL of 2×10^4 cells/mL in DMEM (Dulbecco's Modified Eagle's medium) containing 10% FBS (fetal bovine serum), were seeded in polystyrene microplates (96-well flat-bottom) and incubated at 37°C for 24h in 5% CO_2 humidified atmosphere. Next, different concentrations of derivatives **5a–d** (10, 20, 40, 60, and 80 µM) were added to the plate and then incubated for 48 h. After that, the old medium was replaced and a solution of MTT (50 µL of 0.5 mg/mL in DMEM) was added to each well in the plate and then incubated for another 4 h. The formazan crystals obtained were solubilized by adding 100 µL of DMSO to each well. The solution absorbance obtained was determined at 570 nm on an ELISA microplate reader. The mean percentage of cell viability was calculated from the data obtained. A triplicate of experiments was performed for each test.

Antioxidant assay [30]

The antioxidant effect of compounds **5a–d** was evaluated *in vitro* using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay. Practically, a solution of DPPH (60 µM) in 2ml of ethanol was individually added to different concentrations of derivatives **5a–d** (12.5, 25, 50, 100, 250, and 500µM), and then the homogenized mixture was incubated in the dark for 30 min. After that, the absorbance of the solution was determined at wavelength 515 nm on a UV/Vis spectrophotometer Amersham Biospectro. The results obtained were compared with ascorbic acid and used to calculate the percentage of reduction of the DPPH. The percentage of inhibition was calculated using the following formula:

% of antioxidant activity= $[(A_C - A_S) \div A_C] \times 100$

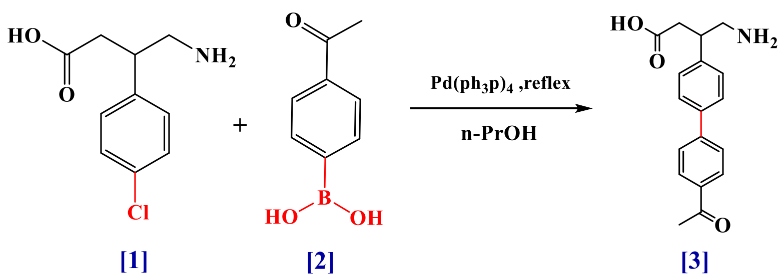
Where: A_C is absorbance of the control; A_S is absorbance of the sample.

Docking study analysis [31]

Four of the synthesized compounds underwent molecular docking studies and the target is to identify the potential binding with the estrogen receptor alpha (ERα) with ID 3ERT obtained from PDB page https://www.rcsb.org/. The selected derivatives were sketched in 2D and converted into 3D using molecular mechanics and then used as ligands. Autodock 4.2.6 program was used in calculating the result of the docking analysis as binding energy. Discovery Studio software was employed to set the receptor and shown the binding modes as 2D interaction poses.

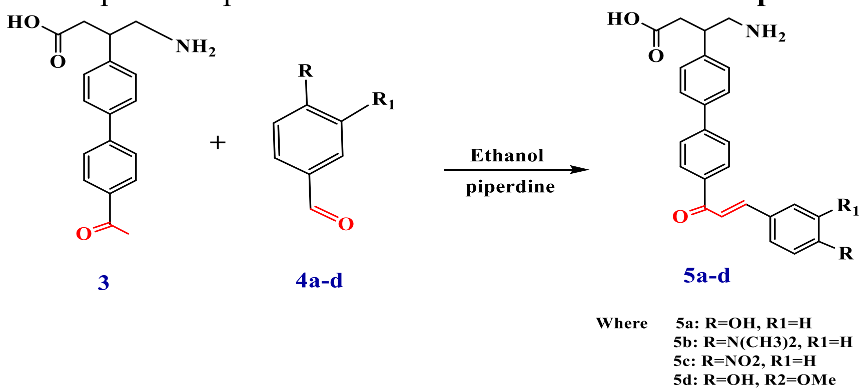
Results and Discussion

According to the Suzuki-Mayura coupling reaction, 3-(4'-acetyl-[1,1'-biphenyl]-4-yl)-4-aminobutanoic acid was synthesized from reaction 4-amino-3-(4-chlorophenyl)butanoic acid **1** (Baclofen) with (4-acetylphenyl)boronic acid **2** using a palladium catalyst and a base as sodium carbonate, as shown in **Scheme 1**.



Scheme 1. Synthesis of compound 3 by Suzuki-Mayura coupling reaction

In the next step, the derivative 3 was reacted with some aromatic aldehydes **4a-d** in the presence of piperidine as a catalyst to synthesize chalcone derivatives 5a–d according to the Claisen-Schmidt condensation mechanism, as shown in **Scheme 2**. The structures of all synthesized compounds were spectroscopically characterized by (IR, ^{1}H NMR, ^{13}C NMR) as well as micro-elements analysis. The spectroscopic data obtained were included in the **Experimental part**.



Scheme 2. The experimental steps for synthesis of compounds 5a-d

Biological activity

Cytotoxicity of synthesized compounds

The four derivatives **5a–d** were screened *in vitro* for evaluation of their antitumor activities against two cancer cell lines HdFn and MCF-7 by the standard MTT method and using Tamoxifen drug as a positive control. The percentages of cell viability of the compounds 5a and 5d are shown in **Fig.1**.

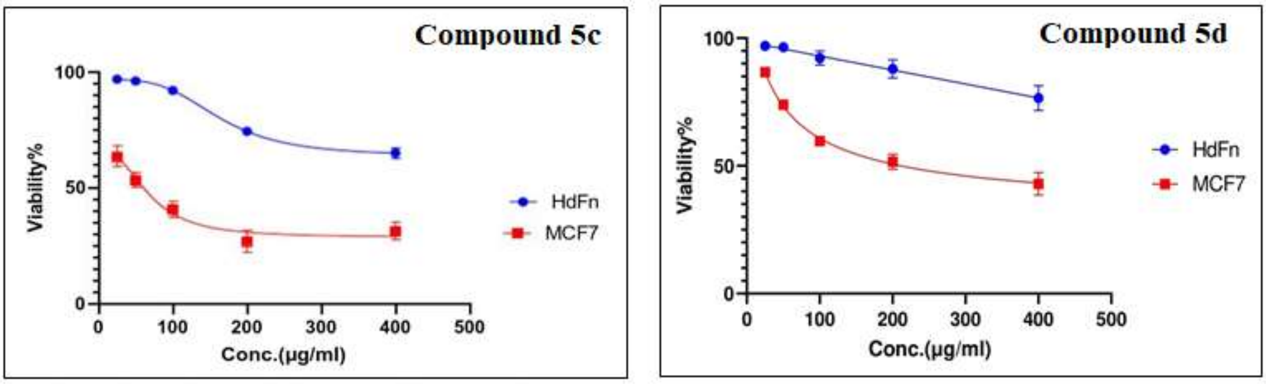


Fig. 1. Cell viability percentage of compounds 5c and 5d against two cancer cell lines HdFn and MCF-7.

The cytotoxicity results of derivatives **5a–d** against HdFn and MCF-7 were compared with the activity of Tamoxifen and presented as IC_{50} in **Table 1**. According to the results, found that some of the tested derivatives exhibited good inhibitory activity. Among those derivatives, **5a** and **5d** showed anti-proliferative effects against MCF-7 cells with an IC_{50} value of 32.5 and 37.6μM, respectively. For of HdFn cells, derivatives **5a** and **5c** showed acceptable cytotoxicity in comparison with the activity of Tamoxifen, while the other derivatives exhibited poor cytotoxic activity. Generally, the results of this test are preliminary evidence that calls on researchers to conduct many tests to use these derivatives as therapeutic agents in the future.

Table 1. The cytotoxicity results for synthesized compounds 5a-d against HdFn and MCF-7 cancer cell lines in comparison to the Tamoxifen drug.

Compounds	IC_{50}μM±SD	
	HdFn	MCF-7
5a	76.7 ± 3.24	32.5 ± 1.25

5b	> 200	86.4±4.11
5c	78.6 ± 3.95	> 200
5d	88.6 ± 4.16	37.6 ± 1.31
Tamoxifen	36 ± 1.14	30 ± 1.02

Antioxidant activity study

The antioxidant activity of new compounds **5a-d** was tested using a DPPH assay. The ascorbic acid is used as a reference for comparison. The test mechanism depends on using hydrogen donor antioxidants for the reduction of the DPPH radical solution and formation of the DPPH-H. Generally, the tested compounds showed potent activity as antioxidants according to the results obtained in **Table 2**. At a concentration of 500 µM, found that the % inhibition of **5a**, **5c** and **5d** potency of 86.62, 81.38, and 76.42%, respectively. These results revealed that compounds **5a**, **5c** and **5d** have the most potent levels of activity compared to that of standard ascorbic acid and this may be due to their structural properties that help in capturing free radicals.

Table 2. Results of DPPH assay of derivatives 5a-d at wavelength 515 nm and concentration 500 µM.

Compounds	Absorbance of Sample	% Inhibition
5a	**0.063**	**86.62±4.81**
5b	**0.214**	**32.64±1.39**
5c	**0.071**	**81.38±4.21**
5d	**0.104**	**76.42±4.05**
Ascorbic-acid	**0.065**	**86.24±4.76**

Molecular Docking study

A molecular docking of derivatives 5a-d was studied *in silico* and the aim is to justify their biological activity. A derivatives **5a-d** were docked as ligands with the receptor ERα (PDB: 3ERT). According to the docking results, the binding energy of derivatives **5a–d** were -9.26, -7.34, -3.7 and -8.81 [kcal/mol], respectively. The results obtained revealed that the derivatives 5a, 5c, and 5d bound with the active site of the protein selectively by various interactions such as hydrophobic, electrostatic interactions and hydrogen bonds. The binding pose of **5a**, **5c** and **5d** with the active pocket in the protein was shown as 2D representations in **Fig.2**. The binding energies and types of interactions are shown in **Table 3**.

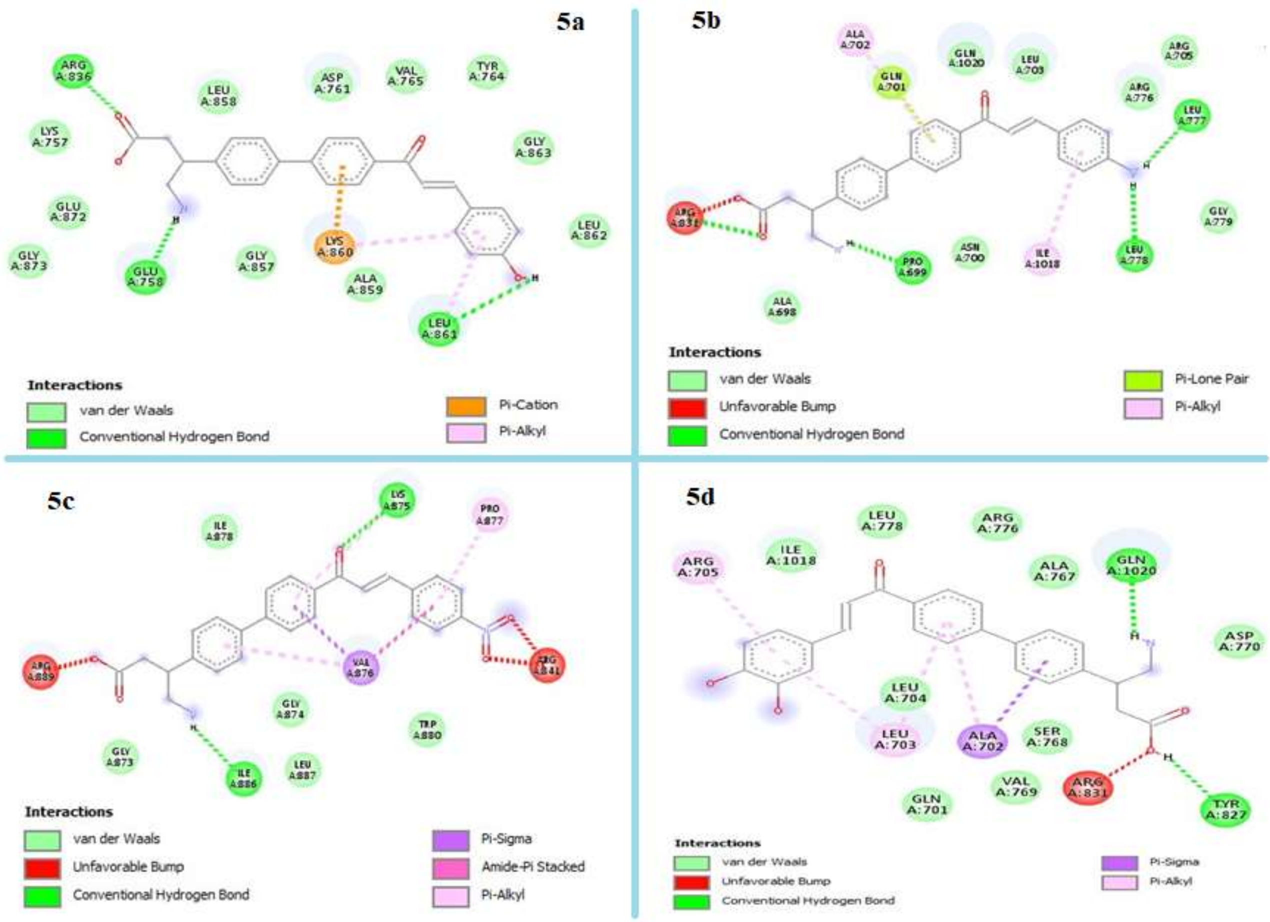


Fig. 2. 2D conformations for simulation of 5a-d with the active site of the target protein

Table 3. Docking results, the binding energy and types of interactions of derivatives 5a-d with the catalytic site of the target protein.

Compound	Ligand moiety	Site(A.A)	Interaction	E (kcal/mol)
5a	NH_2	GLU 758 (A)	H- Bond	-9.26
	OH	LEU 861(A)	H- Bond	
	6-ring	LEU 861(A)	Pi-Alkyl	
		LYS 860(A)	Pi-Alkyl	
	C=O	ARG 836(A)	H-Bond	
		Other	Electrostatic	
5b	NH_2	PRO 699(A)	H- Bond	-7.34
	N-(Me)2	LEU 777(A)	H- Bond	
	6-ring	ALA 702(A)	Pi-Alkyl	
		ILE 1018(A)	Pi-Alkyl	
	C=O	ARG 831(A)	H-Bond	
		Other	Electrostatic	
5c	NH_2	ALI 886(A)	H- Bond	-3.7
	C=O	LYS 875(A)	H- Bond	
	6-ring	PRO 877(A)	Pi-Alkyl	
		VAL 876(A)	Pi-Alkyl	
		VAL 876(A)	Pi-Sigma	
		Other	Electrostatic	
5d	OH	TYR 827(A)	H- Bond	-8.81
	NH_2	GLN 1020 (A)	H-Bond	
	6-ring	ALA 702(A)	Pi-Sigma	
		LEU 703(A)	Pi-Alkyl	
		ARG 705(A)	Pi-Alkyl	
		Other	Electrostatic	

Conclusions

A series of chalcone derivatives bearing baclofen drug were synthesized via Claisen-Schmidt condensation and biologically evaluated in vitro as anticancer and antioxidant agents. The results of the cytotoxicity assay indicated the possibility of using the compounds 4-Amino-3-(4'-(3-(4-hydroxyphenyl)acryloyl)-[1,1'-biphenyl]-4-yl)butanoic acid **5a** and 4-Amino-3-(4'-(3-(4-hydrxy-3-methoxyphenyl)acryloyl)-[1,1'-biphenyl]-4-yl)butanoic acid **5d** as antiproliferative agents of cell lines MCF-7. In the DPPH test, results obtained revealed good antioxidant activity of some new chalcone derivatives.

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НОВЫЕ ПРОИЗВОДНЫЕ ХАЛКОНА КАК ПРОТИВОРАКОВЫЕ И АНТИОКСИДАНТНЫЕ АГЕНТЫ: СИНТЕЗ, ИССЛЕДОВАНИЕ МОЛЕКУЛЯРНОГО ДОКИНГА И БИОЛОГИЧЕСКАЯ ОЦЕНКА

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Аннотация: В работе посредством конденсации Клайзена-Шмидта были синтезированы новые производные халкона, содержащие препарат баклофен, и оценены *in vitro* как противораковые и антиоксидантные средства. Синтезированные соединения были охарактеризованы спектрами ИК-Фурье, ^{1}H-ЯМР, ^{13}С-ЯМР и элементным анализом. Все продукты были проверены *in vitro* на клеточные линии HdFn и MCF-7. Результаты анализа цитотоксичности показали, что производные 5а и 5d продемонстрировали хорошее ингибирование клеточных линий MCF-7 со значениями IC50: 32,5 и 37,6 мкМ соответственно, тогда как 5а и 5с продемонстрировали приемлемое ингибирование HdFn со значениями IC50 - 76,7 и 78,6 мкМ, соответственно, по сравнению с Препарат Тамоксифен. Исследование молекулярного докинга целевых соединений подтвердило результаты теста на цитотоксичность. Кроме того, результаты ДФПГ-исследования выявили хорошую антиоксидантную активность производных 5а, 5в и 5d с процентами ингибирования 86.62, 81.38 и 76.42%, соответственно, по сравнению с аскорбиновой кислотой.
Ключевые слова: халкон, противораковое средство, антиоксидант, молекулярный докинг, цитотоксичность.

XALKONUN YENİ TÖRƏMƏLƏRİ XƏRÇƏNGƏQARŞI VƏ ANTİOKSİDANT AGENTLƏR KİMİ: SİNTEZ, MOLEKULYAR DOKİNQ TƏDQİQATI VƏ BİOLOJİ QİYMƏTLƏNDİRİLMƏ

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Xülasə: İşdə, tərkibində baklofen preparatı olan bir sıra yeni xalkon törəmələri Claisen-Schmidt kondensasiyası ilə sintez edilmiş, xərçəng əleyhinə və antioksidant agentlər kimi *in vitro* qiymətləndirilmişdir. Yeni sintez edilmiş birləşmələr FT-İK, ^{1}H-NMR, ^{13}C-NMR spektrləri ilə xarakterizə edilmişdir və həmçinin element analizi aparılmışdır. Bütün alınan maddələr həm HdFn,

həm də MCF-7 hüceyrələrə qarşı *in vitro* olaraq yoxlanılmışdır. Sitotoksik analizinin nəticələri göstərdi ki, IC50 dəyərləri müvafiq olaraq 32,5 və 37,6 µM olan 5a və 5d törəmələri MCF-7 hüceyrə sırasına qarşı yaxşı inhibisıya göstərirlər, 5a və 5c birləşmələri isə IC50 üzrə 76,7 və 778 µM qiymətlərinə malik olub Tamoksifen preparatı ilə müqayisədə HdFn hüceyrə sırasına qarşı qənaətbəxş inhibitorluq nümayiş etdirirlər. Alınmış birləşmələrin molekulyar dokinq tədqiqi onların sitotoksiklik testinin nəticələrini təsdiqlədi. Bundan əlavə, DPPH tədqiqatlarının nəticələri əsasında müəyyən edildi ki, 5a, 5c və 5d törəmələri müvafiq olaraq 86.62, 81.38 və 76.42 % inhibitorluq faizlərinə malikdirlər və askorbin turşusu ilə müqayisədə yaxşı antioksidant aktivliyi göstərirlər.
Açar sözləri: Xalkon, xərçəngə qarşı, Antioksidant, Molekulyar Dokinq, Sitotoksik