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НОВЫЕ БИАРИЛЬНЫЕ ПРОИЗВОДНЫЕ ПРЕПАРАТА ДИКЛОФЕНАКА: СИНТЕЗ, МОЛЕКУЛЯРНЫЙ ДОКИНГ И ИЗУЧЕНИЕ ИХ БИОЛОГИЧЕСКОЙ АКТИВНОСТИ КАК ПРОТИВОРАКОВЫХ И АНТИОКСИДАНТНЫХ СРЕДСТВ

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В этой работе ряд производных диклофенака были синтезированы с помощью реакции Сузуки-Мияуры и оценены in vitro как противораковые и антиоксидантные агенты. Структуры синтезированных соединений были охарактеризованы с помощью спектров FT-IR, ^{1}H ЯМР, ^{13}C ЯМР и элементного анализа. Продукты были проверены in vitro на их противораковую активность против обеих линий клеток HdFn и MCF-7, а также исследованы на их антиоксидантную активность. Результаты анализа цитотоксичности показали, что производные 3a и 3d продемонстрировали хорошее ингибирование для линий клеток MCF-7 со значениями IC50 33,1 и 38,2 мкМ соответственно, в то время как 3a и 3c продемонстрировали приемлемое ингибирование для HdFn со значениями IC50 68,7 и 72,6 мкМ соответственно по сравнению с препаратом тамоксифин. Исследование молекулярного докинга целевых соединений подтвердило результаты теста цитотоксичности. Кроме того, результаты исследования DPPH выявили хорошую антиоксидантную активность производных 3a, 3c и 3d с процентами ингибирования 83,14, 82,42 и 78,16% соответственно по сравнению с аскорбиновой кислотой.

Ключевые слова: диклофенак, реакция Сузуки-Мияуры, молекулярный докинг, противораковый, антиоксидант

NEW BIARYL DERIVATIVES OF DICLOFENAC DRUG: SYNTHESIS, MOLECULAR DOCKING AND THEIR BIOLOGICAL ACTIVITY STUDY AS ANTICANCER AND ANTIOXIDANT AGENTS

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In this work, a series of diclofenac derivatives were synthesized via the Suzuki-Miyaura reaction and evaluated in vitro as anticancer and antioxidant agents. Structures of synthesized compounds were characterized by FT- IR, ^{1}H NMR, ^{13}C NMR spectra, and elemental analysis. The products have been screened in vitro for their anticancer activity against both cell lines HdFn and MCF-7 as well as they were investigated for their antioxidant activity. The cytotoxicity assay results revealed that derivatives 3a and 3d exhibited good inhibition for cell lines MCF-7 with IC50 values 33.1 and 38.2 μM, respectively while 3a and 3c exhibited acceptable inhibition for HdFn with IC50 values 68.7 and 72.6μM, respectively compared to the Tamoxifine 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 3a, 3c and 3d with inhibition percentages of 83.14, 82.42, and 78.16%, respectively compared to ascorbic acid.

Keywords: diclofenac, Suzuki-Miyaura reaction, molecular docking, anticancer, antioxidant

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INTRODUCTION

Cancer is one of the diseases that affect humans and damages important organs in their body, thus causing their death [1-6]. Extensive studies have focused on this disease to limit and control the mechanism of its spread in various ways, including the use of chemotherapy [7-9]. Many chemical compounds have shown various biological activities [10-15], including anti-cancer activity [16-18]. Diclofenac and its derivatives are considered biologically active and medically important compounds. This type of compound has very great pharmaceutical importance, as diclofenac is used as a non-steroidal anti-inflammatory drug that was approved in the United States in 1988 to treat patients suffering from osteoporosis [19]. Where nonsteroidal anti-inflammatory drugs are compounds that produce anti-inflammatory effects reduce pain, fever, and inflammation such as rheumatoid arthritis, post-surgical pain, migraine or fever [20, 21]. Based on the above, in this work we synthesized some new diclofenac derivatives and evaluated their anti-cancer and antioxidant activity.

EXPERIMENTAL

General information

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

Synthesis

General Procedure for the Preparation of compounds [3a-e] [22, 23]

A mixture of 2-(2-((2,6-dichlorophenyl)amino)phenyl)acetic acid **1** (1 mmol), aromatic boronic acids **2a-e** (1 mmol) were individually dissolved in 1-propanol (15 ml) and reflexed for 5-9 h in the presence of tetrakis (triphenylphosphine)palladium (40 mg), potassium carbonate (5 ml). After the reaction completion (monitored by TLC), 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 in good yields. The solid obtained were purified with flash chromatography using methanol – dichloromethane (8:2).

2-(2-((3-Chloro-4'-(methoxycarbonyl)-[1,1'-biphenyl]-2-yl)amino)phenyl)acetic acid 3a: Orange crystals, yield: 88%, m.p. 178-180 °C. FT-IR (KBr, cm^{-1}): ν 1558 (C=C), 1708 (C=O), 3258 (NH), 3389 (OH). ^{1}H-NMR (DMSO-*d6*, ppm): δ 12.35 (s,OH), 9.68 (s, NH), 8.32-6.85 (d,H-$_{aromatic}$), 3.45 (s,2H,CH_2), 3.02 (s,3H,Me).^{13}C NMR (DMSO-*d6*, ppm): δ 177.3 (C=O $_{carboxylic}$), 165.3 (C=O $_{ester}$), 138.2-120.4 (C-$_{aromatic}$), 46.0 (CH_3), 27.5 (CH_2). Anal. calc. for $C_{22}H_{18}ClNO_4$ C = 66.75, H = 4.58, N = 3.54; Found: C = 66.05, H = 3.88, N = 2.94.

2-(2-((4'-(bromomethyl)-3-chloro-[1,1'-biphenyl]-2-yl)amino)phenyl)acetic 3b: Red crystals, yeild 78%, m.p 190-192 °C. FT-IR (KBr, cm^{-1}): ν 3078 (NH), 3390 (OH). ^{1}H-NMR (DMSO-*d6*,ppm): δ 12.32(s,OH), 9.71(s, NH), 7.98-6.85 (d,H-$_{aromatic}$), 3.41 (s,2H,CH_2), 1.43 (s,2H,CH_2Br).^{13}C NMR (DMSO-*d6*,ppm): δ 176.5 (C=O $_{carboxylic}$), 137.2-118.3 (C-$_{aromatic}$), 27.0 (C-CH_2). Anal. calc. for $C_{21}H_{17}BrClN_2$: C = 58.56, H = 3.98, N = 3.25; Found: C = 57.96, H = 3.29, N = 2.75.

2-(2-((3-chloro-3'-(methoxycarbonyl)-[1,1'-biphenyl]-2-yl)amino)phenyl)acetic acid 3c: Brown crystals, yeild 68%, m.p 225-227 °C. FT-IR (KBr, cm^{-1}): ν 1577 (C=C), 1713 (C=O), 3065 (NH), 3390 (OH). ^{1}H-NMR (DMSO-*d6*, ppm): δ 12.31 (s, OH), 9.64 (s, NH), 7.85-6.88 (d,H-aromatic), 3.51 (s,2H,CH_2), 1.77 (s,3H,Me). ^{13}C NMR (DMSO-*d6*, ppm): δ 175.9 (C=O $_{carboxylic}$), 164.7 (C=O $_{ester}$), 51.3 (OCH_3), 142.2-115.3 (C-aromatic). Anal. calc. for $C_{22}H_{18}ClNO_4$ C = 66.75, H = 4.58, N = 3.54; Found: C = 66.15, H = 3.98, N = 2.94.

2-(2-((3-chloro-3'-cyano-[1,1'-biphenyl]-2-yl)amino)phenyl)acetic acid 3d: Dark red crystals, yeild 59%, m.p 212-215 °C. FT-IR (KBr, cm^{-1}): ν 3423 (OH), 3183 (N-H), 2112 (C≡N), 1728 (C=O), 1611 (C=C). ^{1}H-NMR (DMSO-*d6*, ppm): δ 12.31 (s,OH), 9.58 (s, NH), 8.12-7.15 (d,H-$_{aromatic}$), 3.45 (s,2H,CH_2).^{13}C NMR (DMSO-*d6*, ppm): δ 176.2 (C=O $_{carboxylic}$), 167.6 (C=O), 138.2-115.3 (C-$_{aromatic}$), 122,6 (C≡N). Anal. calc. for $C_{21}H_{15}ClN_2O_2$ C = 69.52, H = 4.17, N = 7.72; Found: C = 69.02, H = 3.67, N = 7.12.

2-(2-((4'-acetyl-3-chloro-[1,1'-biphenyl]-2-yl)amino)phenyl)acetic acid 3e: White crystals, yeild 66%, m.p 243-245 °C. FT-IR (KBr, cm^{-1}): ν 3462 (OH), 3211 (N-H), 1728, 1685 (C=O), 1624 (C=C). ^{1}H-NMR (DMSO-*d6*, ppm): δ 12.33 (s,OH), 9.65 (s, NH), 8.24-7.32 (d,H-$_{aromatic}$), 3.41 (s,2H,CH_2), 1.78 (s,3H,Me).^{13}C NMR (DMSO-*d6*, ppm): δ 183.1 (C=O $_{ketone}$), 174.6 (C=O $_{carboxylic}$), 134.3-119.4 (C-$_{aromatic}$). Anal. calc. for $C_{22}H_{18}ClNO_3$ C = 69.57, H = 4.78, N = 3.69; Found: C = 69.07, H = 4.18 , N = 3.19.

The cytotoxicity assay [24]

The cytotoxic activities of derivatives **3a–e** was 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 **3a–e** (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 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 solutions 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 [25]

The antioxidant effect of compounds **3a–e** was evaluated *in vitro* using the DPPH radical scavenging assay. Practically, a solution of DPPH (60 μM) in 2ml of ethanol was individually added to different concentrations of derivatives **3a–e** (12.5, 25, 50, 100, 250, and 500 μM), and then the homogenized mixture was incubated in the dark for 30 min. After that, the absorbance of 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.

Docking study analysis [26]

Four of synthesized compounds underwent molecular docking studies and 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 reaction, new biaryl derivatives **3a-e** was synthesized from reaction 4-amino-3-(4-chlorophenyl)butanoic acid **1** (Diclofenac) with aromatic boronic acids **2a-e** using a palladium catalyst and potassium carbonate, as shown in Scheme. The structures of all synthesized compounds were spectroscopically characterized by (IR, ^{1}H NMR, ^{13}C NMR) as well as micro-elements analysis.

In the ^{1}H NMR spectra of compounds **3a–e**, protons of the diclofenac moiety showed almost similar patterns. The proton of the OH group resonated as a singlet at δ 12.35-12.31 ppm, while signals in the region δ 8.32-6.85 ppm were assigned to the aromatic protons. As for NH protons resonated as asinglet at δ 9.71-9.58 ppm. Besides, other substituents protons were comprehensively analyzed (c.f. Experimental Section).

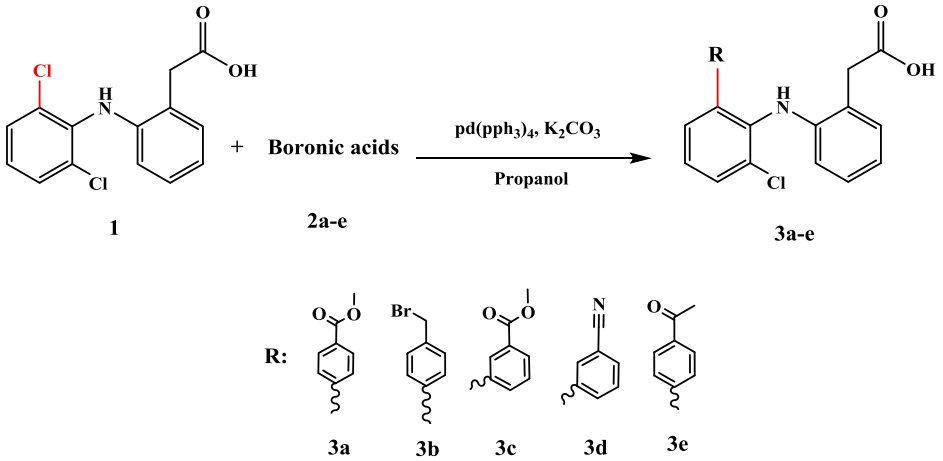
In the ^{13}C NMR spectrum, the carbon atom of the carbonyl group of diclofenac moiety resonated within the range δ = 177.3-174.6 ppm. In contrast, resonances at the regions δ = 165.3 ester, 167.6 ester and 199.1ketone ppm were attributed to the carbonyl group in 3a, 3c and 3e, respectively. While the carbon atom of the C≡N group in compound 3d resonated at δ = 112.8 ppm. Other aromatic atoms and substituents were comprehensively analyzed (c.f. Experimental Section).

Biological activity

Cell viability and cytotoxicity assay

The diclofenac derivatives **3a–e** were screened *in vitro* for evaluation against two cancer cell lines HdFn and MCF-7 by the standard MTT method and using Tamoxifine drag as a positive control. The cytotoxicity results of derivatives **3a–e** against HdFn and MCF-7 were compared with the activity of Tamoxifine 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,

3c and **3d** showed anti-proliferative effects against MCF-7 cells with an IC_{50} value of 33.1 and 38.2μM, respectively. For of HdFn cells, derivatives **3a** and **3c** showed acceptable cytotoxicity in comparison with the activity of Tamoxifine, 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.



Scheme. The experimental for preparation of compounds 3a-e
Схема. Экспериментальная часть по получению соединений 3a-e

Table1

The cytotoxicity results of synthesized compounds 3a-e against HdFn and MCF-7 cancer cell lines

Таблица 1. **Результаты цитотоксичности синтезированных соединений 3a-e против линий раковых клеток HdFn и MCF-7**

Compounds	IC_{50}μM±SD	
	HdFn	MCF-7
3a	68.7 ± 2.63	33.1 ± 1.31
3b	> 100	85.8±4.09
3c	72.6 ± 3.15	> 100
3d	87.5 ± 4.12	38.2 ± 1.36
3e	> 100	95.5 ± 4.53
Tamoxifine	35 ± 1.11	30 ± 1.02

Antioxidant activity study

The antioxidant activity of new compounds **3a-e** 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 500 μM, found that the % inhibition of **3a**, **3c** and **3d** potency of 83.14, 82.42 and 78.16%, respectively. These results revealed that compounds **3a**, **3c** and **3d** 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.

Table2

Results of DPPH assay of derivatives 3a-e at wavelength 515 nm and concentration 500 μM

Таблица 2. **Результаты анализа DPPH производных 3a-e при длине волны 515 нм и концентрации 500 мкМ**

Compounds	Absorbance of Sample	% Inhibition
3a	0.062	83.14 ± 4.25
3b	0.214	33.15 ± 1.43
3c	0.072	82.42 ± 4.21
3d	0.124	78.16 ± 4.02
3e	0.253	23.55 ± 1.08
Ascorbic-acid	0.065	86.24 ± 4.76

Molecular Docking study

A molecular docking of derivatives **3a-d** was performed *in silico* and the aim is to justify their biological activity. A derivatives **3a-d** were docked as ligands with the receptor ERα (PDB: 3ERT). According to the docking results, the binding energies of derivatives **3a–d** were -4. 6, -3.8, -1.4 and -2.5 [kcal/mol], respectively. The results obtained revealed that the derivatives **3a**, **3c**, and **3d** bound with the active site of the protein selectively by various interactions such as hydrophobic, electrostatic interactions and hydrogen bonds. The binding pose of **3a**, **3c** and **3d** with the active pocket in the protein was shown as 2D representations in Figure. The results of molecular docking are shown in Table 3.

Table 3 shows the results of molecular docking between some compounds and the protein responsible for breast cancer 3ERT.

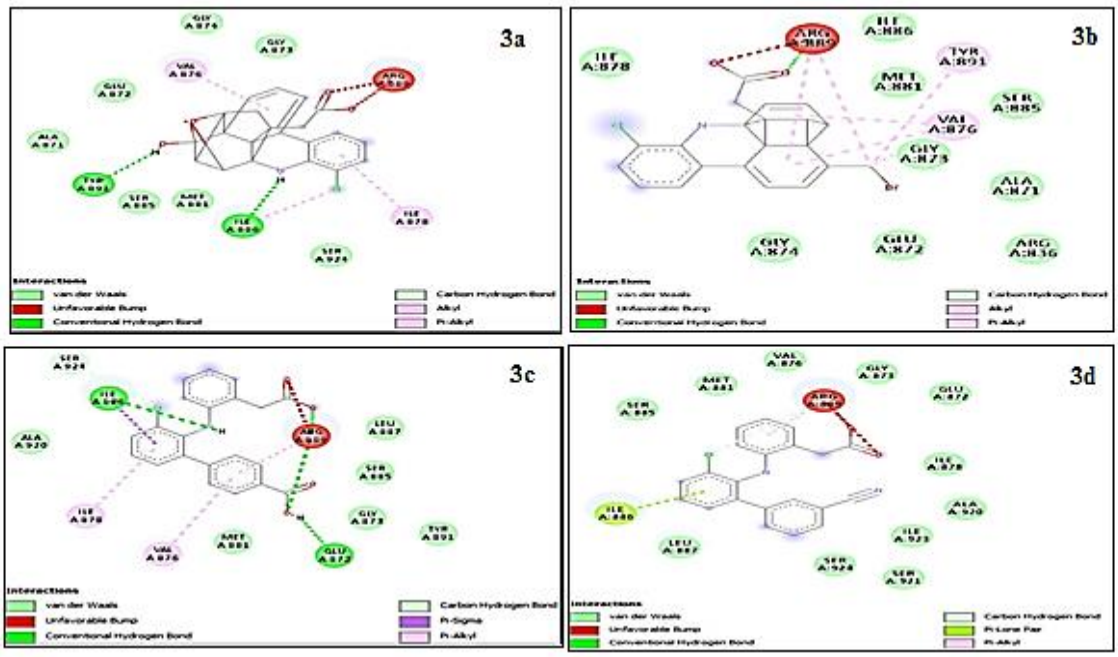


Fig. The hydrogen bonds of compounds with protein responsible for breast cancer
Рис. Водородные связи соединений с белком, ответственным за рак молочной железы

Table 3

The results of molecular docking between some compounds and the protein responsible for breast cancer 3ERT
Таблица 3. **Результаты молекулярного докинга между некоторыми соединениями и белком, ответственным за рак молочной железы 3ERT**

Compound	Ligand moiety	Site(A.A)	Interaction	E (kcal/mol)
3a	NH OH 6-ring C=O	GLU 758 (A) LEU 861(A) LEU 861(A) ARG 836(A) Other	H- Bond H- Bond Pi-Alkyl H-Bond Electrostatic	-4.6
3b	NH 6-ring C=O	PRO 699(A) ALA 702(A) ARG 831(A) Other	H- Bond Pi-Alkyl H-Bond Electrostatic	-3.8
3c	NH C=O 6-ring	ALI 886(A) LYS 875(A) PRO 877(A) Other	H- Bond H- Bond Pi-Alkyl Electrostatic	-1.4
3d	OH NH 6-ring	TYR 827(A) GLN 1020 (A) ALA 702(A) ARG 705(A) Other	H- Bond H-Bond Pi-Sigma Pi-Alkyl Electrostatic	-2.5

CONCLUSION

In conclusion, a new series of synthesized derivatives bearing diclofenac drag were synthesized via Suzuki-Miyaura cross-coupling reaction. These derivatives were biologically evaluated in vitro as anticancer and antioxidant agents. The results of tests indicated the possibility of using the compounds 2-(2-((3-Chloro-4'-(methoxycarbonyl)-[1,1'-biphenyl]-2-yl)amino)phenyl)acetic acid **3a** and 2-(2-((3-chloro-3'-cyano-[1,1'-biphenyl]-2-yl)amino)phenyl) acetic acid as antiproliferative agents of human cancer cell lines (HdFn, MCF-7), while the compound 2-(2-((4'-acetyl-3-chloro-[1,1'-biphenyl]-2-yl)amino)phenyl)acetic acid exhibited poor cytotoxic activity against both cancer cell lines HdFn and MCF-7. In addition, the DPPH test results obtained revealed that compounds 2-(2-((3-Chloro-

4'-(methoxycarbonyl)-[1,1'-biphenyl]-2-yl)amino)phenyl)acetic acid **3a** and 2-(2-((3-chloro-3'-(methoxycarbonyl)-[1,1'-biphenyl]-2-yl)amino)phenyl)acetic acid **3c** exhibited a potent level of activity compared to that of standard ascorbic acid and this may be due to their structural properties that help in capturing free radicals.

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CONFLICT OF INTEREST

The authors declare the absence a conflict of interest warranting disclosure in this article.

Авторы заявляют об отсутствии конфликта интересов, требующего раскрытия в данной статье.

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