NEW FENOFIBRATE DERIVATIVES AS ANTICANCER AND ANTIOXIDANT AGENTS: SYNTHESIS, IN SILICO STUDY AND BIOLOGICAL EVALUATION

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Abstract: *Fenofibrate is a medication derived from fibric acid that is used to treat severe cases of high triglyceride levels and a combination of abnormal lipid levels in individuals who have not shown improvement with nonpharmacological treatments. As part of this research, novel classes of Fenofibrate derivatives were synthesized and evaluated in vitro as anticancer and antioxidant agents. Spectroscopic techniques, including infrared, NMR and elemental analysis, were used to validate their structures conclusively. all products were screened in vitro against cell lines MDA-MB-231. The cytotoxicity assay results revealed that derivatives* ***5b*** *and* ***5c*** *exhibited good inhibition for MDA-MB-231. The* IC_{50} *values for derivatives* ***5b*** *and* ***5c*** *were 79.09 and 128.10 µg/m, respectively. A molecular docking study of the synthetic compounds confirmed the cytotoxicity test results. In addition, the DPPH investigation revealed good antioxidant activity for derivatives* ***5c*** *and* ***5e*** *with inhibition percentages of 93.85 and 92.31%, respectively, compared to ascorbic acid.*
Keywords: *Fenofibrate, Amide; Antioxidant; Anticancer; Molecular Docking.*
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Introduction

Fenofibrate, also known as fenoglide or lipofen, is a chlorobenzophenone that is is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid. It has received increasing attention in recent years because of its various activities as an antilipemic drug, an environmental contaminant, a xenobiotic and a geroprotector [1]. In addition to being a useful gout supplement, it helps lower blood uric acid levels [2]. Furthermore, it has pleiotropic actions such as anti-inflammatory [3], against diabetes [4], anti-atherogenic [5], and inhibits the development of liver diseases [6]. On the other hand, Amides also play a key role in medicinal chemistry due to their wide-ranging applications in the pharmaceutical industry. The amide functional group is present in numerous bioactive compounds or drugs, and modifying amides is a crucial method for optimizing new chemical entities in medicinal chemistry [7]. Studies have shown that amide bonds are very prevalent and intriguing forms of links in both organic synthesis and nature [8-12]. Some of them exhibit a variety of biological activities, such as Antibacterial [13-15], antiviral [16-18], anti-inflammatory [19-21], anticancer [22, 23], antioxidant [24] and anti-Alzheimer activity [25,26], in addition to their importance in the industrial field [27,28]. In this study, we have developed novel prodrugs based on fenofibrate derivatives. Some prodrugs were evaluated for their potential as anti-breast cancer agents, while all were assessed for their antioxidant activity. These actions were examined both theoretically via molecular docking and in vitro experiments.

Experimental part

General information

All chemicals come from Merck and Al-Drich, and the Fourier Transform Varian Spectrometer, which runs at 300 MHz, is used to get the ^{1}H-, ^{13}C- and 2D-NMR spectra. A reference standard in DMSO-d6 solvent is used

to record the spectra. FT-IR spectra were obtained using a Japanese FTIR 8400S Shimadzu Spectrophotometer covering a 400 to 4000 cm^{-1} range. The elemental analyses (C.H.N.) were determined using the EA 300 C.H.N Element Analyzer's micro-analytical unit. Gallenkamp MFB-600 Melting Point the Stuart apparatus was used to Get the melting points.

Synthesis

Preparation method of fenofibric acid [29]

A solution of Fenofibrate **1** (5.0g, 13.85mmol) in ethanol (30ml) was treated with sodium hydroxide (0.6 g, 0.01485mmol) dissolved in water (2ml). Afterward, the combination of chemicals was heated to its boiling point at 84℃ and continued at that temperature for 3 hours. The progress of the reaction was tracked by using (TLC) with a solvent mix of hexane and ethyl acetate in a volumetric ratio of 7:3. After cooling to 25^0C, the reaction mixture was subjected to vacuum distillation to get a residue. Subsequently, the remaining substance was combined with 50 cc of ice-cold water and made acidic by adding dilute hydrochloric acid. The resulting solid product **2** was isolated using filtering and then desiccated with air to get a solid white color. The material yields 92% and a melting point of 180 °C.

Preparation method of acid chloride [30]

A 100mL round-bottom flask was used in a fume hood to combine an excessive amount of thionyl chloride with 4 grams of fenofibric acid **2**. The mixture was heated to 60°C for one or two hours. Thionyl chloride was gaseous evaporated at reduced pressure.

General procedure for synthesis of the Fenofibrate derivatives 5a-e [31]

The amine **4** (1equivalent) was dissolved in 15ml of anhydrous DCM. In addition, two moles of triethylamine were added as catalyst. After cooling the mixture to 0°C, a progressive addition of the acid chloride **3** (1equivalent) solution in dichloromethane (DCM) at 0 °C was added gradually. The ice bath was later removed after the addition. The reaction mixture was agitated for 2-5 hours, after which it was washed with a 15 ml hydrochloric acid with a concentration of 0.5 N and subsequently with water. Subsequently, the resultant mixture was desiccated using anhydrous $MgSO_4$. Subsequently, the solvent was evaporated using decreased pressure, leading to the formation of a solid. The intended product **5a-e** was obtained by recrystallizing the crude product from ethanol.

2-(4-(4-chlorobenzoyl) phenoxy)-2-methyl-N-(thiazol-2-yl)propenamidev 5a: Light brown crystals, m.p 96-98°C, yield 75%. FT-IR (cm^{-1}) ν: 3379 (N-H_{amid}), 3078(C-H_{Ar}), 1681 (C=O).^{1}H NMR (DMSO-d6, 400 MHz) δ 11.80 – 6.94 (m, 9H), 1.67 (s, 6H). ^{13}C NMR (DMSO-*d6*, ppm): δ 193.71, 174.91, 172.55, 159.43, 137.98, 137.55, 136.60, 132.28, 131.64, 130.43, 129.05, 118.45, 117.52, 114.55, 80.75, 40.58, 40.37, 40.16, 39.95, 39.74, 39.53, 39.32, 25.09. Elemental Analysis for $C_{20}H_{17}ClN_2O_3S$: C, 60.54; H, 5.11; Cl, 7.89; N, 6.03; O, 12.56; S, 9.14.

2-(4-(4-chlorobenzoyl)phenoxy)-2-methyl-N-(5-phenyl-1,3,4-thiadiazol-2-yl)propenamide 5b:

Yellow brown crystals, m.p 152-154°C, yield 89%. FT-IR (cm^{-1}) ν: 3309 (N-H_{amid}), 2970 (C-H_{Ar}), 1651 (C=O).^{1}H NMR (DMSO-d*6*, ppm): δ 8.55 (s, 1H), 7.65–7.54 (m,7H), 6.92 (dd, *J* = 29.0, 8.9 Hz, 5H), 1.55 (s,7H). ^{13}C NMR (DMSO-*d6*, ppm): δ 193.69, 174.94, 160.02, 159.28, 132.33, 131.65, 131.17, 129.84, 129.71, 129.04, 127.42, 127.05, 118.55, 117.45, 79.37, 40.55, 40.34, 40.13, 39.71, 39.50, 39.29, 25.56. Elemental Analysis for $C_{25}H_{20}ClN_3O_3S$: C, 63.48; H, 5.31; Cl, 8.11; N, 9.20; O, 9.79; S, 7.18.

2-(4-(4-chlorobenzoyl) phenoxy)-N-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)-2-methylpropanamide 5c:

Yellow crystals, m.p 118-120°C, yield 85%. FT-IR (cm^{-1}) ν: 3545 (N-H_{amid}), 3190 (C-H_{Ar}), 1651 (C=O).^{1}H NMR (DMSO-d*6*, ppm): δ 8.56 (s, 1H), 7.82–7.67 (m, 8H), 6.96–6.84 (m, 5H). ^{13}C NMR (DMSO-*d6*, ppm): δ 193.68, 175.00, 160.16, 159.32, 158.84, 137.47, 136.76, 135.69, 132.28, 130.52, 129.87, 129.60, 129.03, 128.65, 118.56, 117.47, 79.55, 40.58, 40.37, 40.16, 39.95, 39.74, 39.54, 39.33, 25.63. Elemental Analysis for $C_{25}H_{19}Cl_2N_3O_3S$: C, 57.42; H, 4.23; Cl, 12.78; N, 9.33; O, 19.05; S, 7.13.

2-(4-(4-chlorobenzoyl)phenoxy)-2-methyl-N-(thiazol-4-yl)propenamide 5d: dark brown crystals, m.p 104-106°C, yield 90%. FT-IR (cm^{-1}) ν: 3379 (N-H_{amid}), 3151 (C-H_{Ar}), 1680 (C=O). ^{1}H NMR (DMOS-d*6*, ppm) δ 10.37 (s, 1H), 7.90–7.61 (m, 8H), 7.03 (d, *J* = 8.9 Hz, 3H), 1.64 (s, 6H). ^{13}C NMR (DMSO-d*6*, ppm) δ 193.70, 172.91, 159.42, 143.33, 137.57, 136.56, 132.68, 132.35, 131.65, 130.58, 129.63, 129.05,

120.12, 118.68, 81.57, 40.58, 40.37, 40.16, 39.96, 39.75, 39.54, 39.33, 25.18. Elemental Analysis for $C_{20}H_{17}ClN_2O_3S$: C, 58.76; H, 5.06; Cl, 9.49; N, 7.72; O, 12.22; S, 7.83.

2-(4-(4-chlorobenzoyl) phenoxy)-2-methyl-N-(1H-1,2,4-triazol-3-yl)propenamide5e:

Yellow crystals, m.p 145-147°C, yield 78%. FT-IR (cm^{-1}) ν: 3387 (N-H_{amid}), 3055 (C-H_{Ar}), 1647 (C=O).^{1}H NMR (DMSO-d*6*, ppm): δ 8.42 (s, 1H), 7.56 (d, *J* = 8.6 Hz, 11H), 1.72 (s, 6H). ^{13}C NMR (DMSO-d_6, ppm) δ 193.73, 173.24, 162.77, 159.99, 159.24, 137.59, 136.73, 136.57, 132.30, 131.66, 130.62, 129.77, 129.08, 120.69, 118.71, 117.49, 80.86, 40.57, 40.37, 40.16, 39.95, 39.74, 39.53, 39.32, 24.99, 9.01. Elemental Analysis for $C_{19}H_{17}ClN_4O_3$: C, 60.42; H, 5.41; Cl, 8.87; N, 15.33; O, 11.26

Antioxidant assay [32]

Antioxidants were identified in a sample using the Blois method. For the control, we dissolved DPPH in methanol, and for the standard, we used ascorbic acid. After making compound solutions of varying concentrations, 2 mL of DPPH solution was added to every sample. After two hours of incubation in a dark chamber, a UV-VIS Shimadzu spectrophotometer was used to analyze the sample's absorbance at 517 nm. An inhibition percentage was used to measure the free radical scavenging activity.

$$\textbf{Inhibition \%} = (control) - A(sample) \,/\, A(control) \times 100$$

A (control): Absorption of DPPH + solvent (MeOH)

A (sample): Absorption of DPPH + sample (sample test/standard)

The cytotoxicity assay [33]:

Cell lines and culture: A human breast cancer cell line MDA-MB-231 was grown in RPMI 1640 media with antibiotics and 10% fetal bovine serum. The Iranian National Cell Bank donated this cell line. In a controlled environment with humidity and a concentration of 5% CO_2, the cells were kept at 37 °C.

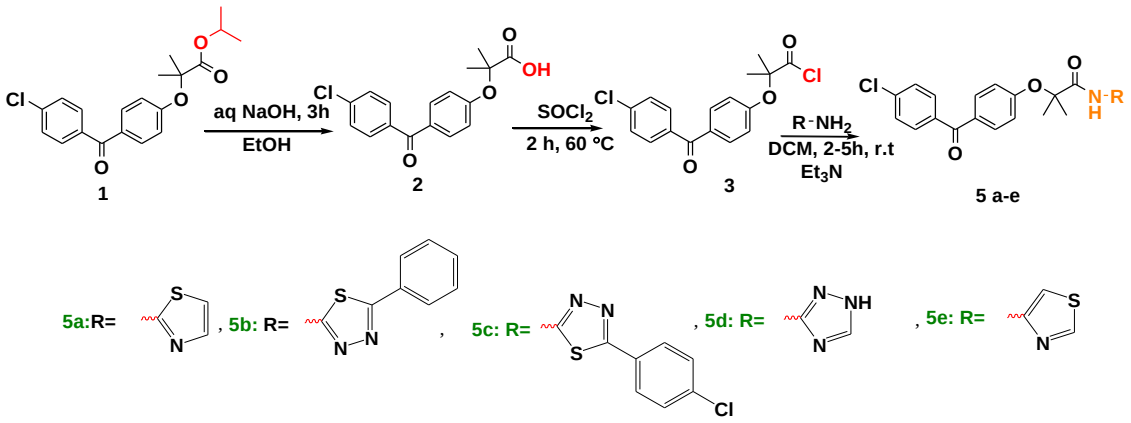
MTT cell viability assay: Cell proliferation and viability were assessed using the MTT test in this research. After being harvested, the cells were prepared to have a density of 1.4×10^1 cells/well and then placed onto 96-well plates. Following a day, the cells were exposed to compounds at concentrations ranging from 600 to 7.4 µg/ml for another day at 37°C with 5% CO2. Each well was supplemented with 100 µl of MTT solution after 24 hours, and the plate was left to incubate at 37°C for a further 4 hours. After that, the cells were shaken in an incubator set at 37°C until all of the crystals had dissolved. The ELISA reader was used to test cell viability, and the dose-response curves were utilized to estimate the concentration of compounds that induced 50% cell death.

Docking study analysis [34]

Molecular docking studies were performed on five synthetic compounds to identify potential binding interactions with placental aromatase cytochrome P450. The PDB database, accessible at https://www.rcsb.org/, was used to get the ID 3EQM. The selected derivatives were first shown in two dimensions before being converted to three dimensions by molecular mechanics. The ligands were subsequently constructed from these three-dimensional structures. The docking study findings, including the binding energy and the receptor configuration in 2D interaction poses, were computed using the MOE 2015.10 program.

Results and discussion

A series of amide derivatives were synthesized by reacting the amine derivatives with acid chloride 3 according to the addition-elimination mechanism using CH_2Cl_2 as solvent and triethylamine as catalyst to neutralize the HCl that develops after the amide formation. The reaction steps and conditions were seen in Scheme 1. The structures of all synthesized compounds were spectroscopically characterized by (IR, ^{1}H-NMR, ^{13}C-NMR) and micro-elements analysis. The spectroscopic data obtained were included in the experimental section.



Scheme 1: The experimental steps for synthesis of compounds 5a-e

Biological activity

In order to determine whether chemicals may bind to a certain protein (PDB: 3eqm) and hence prevent breast cancer, the software MOE 2015 was used. We chose the top compounds (highlighted in yellow) from **Table 1** for in vitro testing because they show strong activity against the examined protein. Protein binding to these produced compounds is seen in Fig. 1 below:

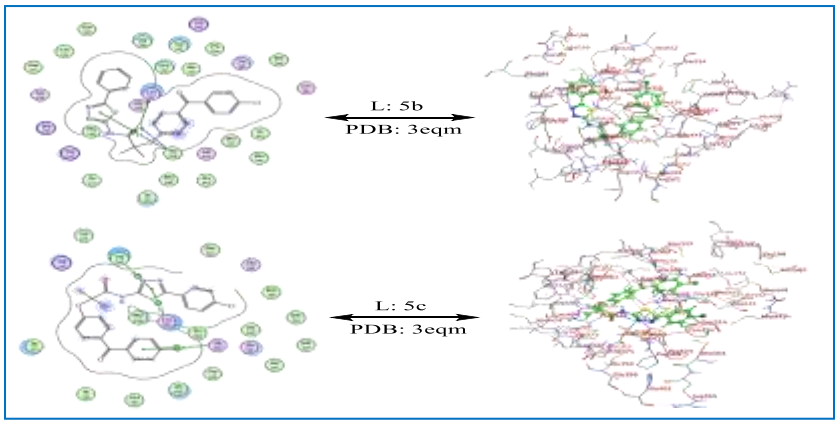


Fig. 1. The interaction mode of compounds (5b, 5c) with active site amino acids of the protein (PDB 3EQM)

Table 1. Molecular docking results for prepared derivatives 5a-e as anti-cancer agents.

Compound (Ligands)	Target protein: Oxidoreductase (3EQM)						
	E Binding Kcal/mol	RMSD	Position of interaction		Interaction	Distance (Å)	E (Kcal/mol)
			Ligand	Receptor			
5a	-8.5739	1.9765	6-ring	CA (CYS 437)	pi-H	3.83	-0.9
5b	-10.1417	1.9389	O (40)	SG (CYS 437)	H-donor	3.45	-0.9
			O (40)	N (ALA 438)	H-acceptor	3.01	-0.9
			5-ring	CB (ALA 438)	pi-H	4.21	-0.9
5c	-10.3244	1.3256	5-ring	CG2 (VAL 370)	pi-H	4.11	-0.7
			5-ring	CB (CYS 437)	pi-H	4.01	-0.6
			6-ring	CA (GLY 439)	pi-H	4.18	-0.7
5d	-9.2826	1.9454	S (27)	O (PRO 429)	H-donor	3.60	-0.9
5e	-8.3276	1.3102	N (26)	SD (MET 374)	H-donor	3.82	-1.1
			6-ring	CG1 (ILE 133)	pi-H	4.07	-0.8
			6-ring	N (ALA 438)	pi-H	4.85	-0.7

Cytotoxicity of synthesized compounds

The anticancer effects of the derivatives **5b** and **5c** were evaluated against the cancer cell line MDA-MB-231 in vitro using the conventional MTT technique. The figures in **Fig. 1** represent the cell viability percentages of compounds **5b** and **5c**.

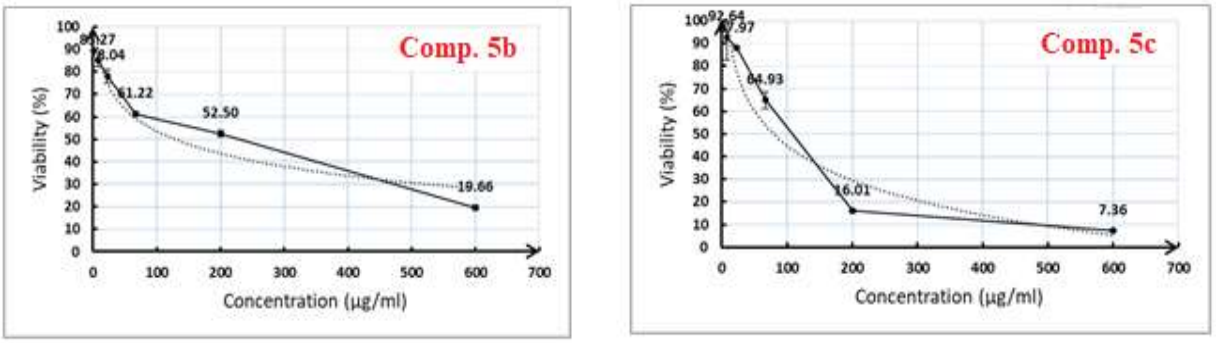


Fig. 2. Cell viability percentage of compounds (5b, 5c) against cancer cell line MDA-MB-231.

Table 2. The cytotoxicity results for compounds (5b, 5c) against the MDA-MB-231 cancer cell line.

5b: IC_{50}= 79.09 µg/mL										
Concentration (µg/mL)	7.4		22.22		66.66		200		600	
Absorption at 57 nm	0.633	0.738	0.651	0.651	0.462	0.633	0.738	0.651	0.651	0.462
Viability (%)	85.54	99.73	87.97	87.97	62.43	85.54	99.73	87.97	87.97	62.43
Average Viability (%)	92.64		87.97		64.93		16.01		7.36	
Standard Deviation (±)	10.03		0.00		3.54		0.67		0.48	
5c: IC_{50}= 128.10 µg/mL										
Concentration (µg/mL)	7.4		22.22		66.66		200		600	
Absorption at 57 nm	0.615	0.647	0.594	0.561	0.458	0.615	0.647	0.594	0.561	0.458
Viability (%)	83.11	87.43	80.27	75.81	61.89	83.11	87.43	80.27	75.81	61.89
Average Viability (%)	85.27		78.04		61.22		52.50		19.66	
Standard Deviation (±)	3.06		3.15		0.96		1.43		1.05	

Table 3. DPPH Radical Scavenging Activity of the Synthesized Compound 5a-e

Compounds	**% RSA (radical scavenging activity) at seven different concentrations (µg/ml)**						
	1000	**800**	**750**	**400**	**200**	**50**	**12.4**
5a	75.54	68.63	62.99	55.20	51.46	46.12	39.34
5b	69.35	62.43	52.30	49.87	32.22	29.19	20.33
5c	93.85	90.74	86.77	64.98	51.90	32.32	25.96
5d	79.10	74.22	68.64	57.31	48.34	37.56	30.45
5e	92.31	90.50	86.83	81.86	74.92	66.28	58.11
Ascorbic acid	99.77	98.72	97.33	95.14	93.67	92.35	91.12

Antioxidant Activity

The antioxidant activity of the produced compounds was evaluated using the DPPH assay, which is a well-used approach. The test determines how well the materials donate hydrogen to neutralize DPPH radicals. An increase in radical scavenging activity is shown by a change in color, which occurs when

antioxidant drugs convert DPPH into a stable diamagnetic molecule. The antioxidant activity of all the produced compounds was much higher than that of the conventional ascorbic acid, as shown in **Table 3**.

Conclusions

In summary, amide derivatives were produced from compounds that included fenofibrate and sulfa drugs. These compounds were purified, their structures were characterized, and their biological activity was assessed in vitro as an antioxidant and anticancer agent. The results of the cytotoxicity test point to the possibility of using compounds 2-(4-(4-chlorobenzoyl)phenoxy)-2-methyl-N-(5-phenyl-1,3,4-thiadiazol-2-yl)propenamide5b, and 2-(4-(4-chlorobenzoyl) phenoxy)-N-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)-2-methyl propanamide 5c as antiproliferative agents of MDA-MB-231cell lines. At the same time, the DPPH test results showed that some new amide derivatives have strong antioxidant activity.

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