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Research Article

Synthesis and biological activities of new hybrid chalcones with benzoic acid ring

Bedriye Seda KURŞUN AKTAR[1,*], Yusuf SICAK[2], Emine Elçin ORUÇ-EMRE[3]

[1]*Department of Hair Care and Beauty Services, Yeşilyurt Vocational School, Malatya Turgut Özal University, Malatya, Turkey*

[2]*Department of Herbal and Animal Production, Köyceğiz Vocational School, Muğla Sıtkı Koçman University, Muğla, Turkey*

[3]*Department of Chemistry, Faculty of Arts and Sciences, Gaziantep University, Gaziantep, Turkey*

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*Corresponding author e-mail: bseda.kursunaktar@ozal.edu.tr

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ABSTRACT

A series of *E*-4-(3-oxo-3-(substituted)prop-1-en-1-yl)benzoic acid derivatives (**1**-**5**) were synthesized by the Claisen-Schmidt condensation of various ketones with 4-formylbenzoic acid. The anticholinesterase (AChE and BChE), tyrosinase, and urease inhibition activities of the synthesized compounds (**1**-**5**) were examined. It was found that the most active compound against AChE enzyme in anticholinesterase inhibition activity was compound **1**. Compound **4** was the most active compound in tyrosinase inhibition activity, while compound **3** was the most active compound in urease psychological activity.

Keywords: Chalcone, anticholinesterase activity, tyrosinase inhibition activity, urease inhibition activity.

Benzoik asit halkalı yeni hibrit kalkonların sentezi ve biyolojik aktiviteleri

ÖZ

4-formilbenzoik asit ile çeşitli ketonların Claisen–Schmidt kondensasyonuyla bir dizi E-4-(3-okso-3-(sübstitüe)prop-1-en-1-il)benzoik asit türevleri (1-5) sentezlenmiştir. Sentezlenen bileşiklerin (**1**-**5**), antikolinesteraz (AChE ve BChE), tirosinaz ve üreaz inhibisyon aktiviteleri incelendi. Antikolinesteraz inhibisyon aktivitesinde AChE enzimine karşı en aktif bileşiğin, bileşik **1** olduğu tespit edilmiştir. Bileşik **4**, tirosinaz inhibisyon aktivitesinde en aktif bileşik iken bileşik **3**, üreaz inhibisyon aktivitesinde en aktif bileşiktir.

Anahtar Kelimeler: Kalkon, antikolinesteraz aktivite, tirosinaz inhibisyon aktivite, üreaz inhibisyon aktivite.

1. INTRODUCTION

There are two types of cholinesterase enzymes in our body, AChE (Acetylcholinesterase) and BChE (Butyrylcholinesterase). AChE is abundant in the healthy adult brain and is called true cholinesterase. BChE, on the other hand, is present in limited amounts and is referred to as "serum cholinesterase, pseudocholinesterase or nonspecific cholinesterase" .[1] AChE is widely distributed in all excitable tissues such as the lungs, spleen, brain, muscles, erythrocyte membranes, and nerve endings. BChE, on the other hand, is synthesized in the liver and released into plasma at high levels and is found only in the central and peripheral nervous systems.[2,3]

Tyrosinase is an enzyme that specifically affects the concentration of melanin pigment which is one of the factors that influence human skin and hair color [4,5]. Melanin plays a protective role in the development of skin cancer, absorbs ultraviolet (UV) rays, protects the skin from UV damage and reactive oxygen species (ROS), and purifies the organism from toxic substances and drug residues.[6] The increase in melanin pigmentation causes undesirable symptoms in people. These undesirable symptoms, which are visible on the skin, often affect the psychological state of the person.

Helicobacter pylori bacteria colonize and secrete urease. This enzyme acts on urea as a substrate, and as a result of its hydrolysis, CO_2 and NH_3 are formed. This protects the bacteria from the low pH of gastric juice. However, NH_3 is toxic to the epithelial cells of the stomach and also increases the effect of cytotoxins secreted by the agent by reducing intercellular adhesion.[7] Although this formation

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causes diseases such as gastritis, peptic ulcers, and gastric cancer, it has the risk of leading to some new diseases triggered by these disorders. Proton generating inhibitors are used in the treatment of *H. pylori* infection.[8] To prevent this bacterial infection, many researchers have focused their studies on new proton-generating agents.

The term "chalcone" was first used by Kostanecki, who made synthesis studies of some natural chromophoric products. It forms a benzylidene acetophenone scaffold in which two aromatic structures are linked by a three-carbon α,β unsaturated carbonyl bridge.[9] It and its derivatives can be classically synthesized by the Claisen-Schmidt reaction[10], as well as by the solid phase Claisen-Schmidt reaction[11], can also be synthesized by various methods such as the solvent-free Claisen-Schmidt reaction[12], the Suzuki Miyaura reaction[13], the coupling reaction[14], the carbonylative Heck coupling reaction[15], the one-pot reaction of chalcones[16], microwave method[17], solid acid catalyst[18], the Sonogashira isomerization connection[19], Friedel Crafts reaction[20], Juliae Kocienski Olefination.[21] Chalcones have various pharmacological activities such as anti-platelet[22], antidiabetic[23], antineoplastic[24], antiangiogenic[25], antiretroviral[26], antiinflammatory[27], antigout[28], antihistaminic[29], antioxidant[30], antiobesity[31], hypolipidemic[32], antitubercular[33], antifilarial[34], antiinvasive[35], antimalarial[36], antiprotozoal[37], antibacterial[38], antifungal[39], antiulcer[40], antisteroidal[41], immunosuppressant[42], hypnotic[43], anxiolytic[44], antispasmodic[45], antinociceptive[46], and osteogenic.[47]

Our aim in this study was to synthesize new chalcones hybridized with 4-formylbenzoic acid and to investigate the anticholinesterase (AChE and BChE), tyrosinase, and urease inhibition activities. Because the number of Alzheimer's patients is increasing day by day. And when the drugs on the market are used for a long time, the body shows resistance and the drug does not show its effect. Therefore, new drugs are needed. In addition to these activities, ADME study was also conducted, and other parameters were used to investigate whether the synthesized molecule could be a drug candidate.

2. MATERIALS AND METHODS

2.1. General

Chemicals and solvents were in analytical grade and were purchased from Merck and Sigma-Aldrich. All chemical reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates. Melting points were determined using the 18 Stuart SMP20 automatic melting point apparatus and were uncorrected. FTIR spectra were determined with a Perkin Elmer 1620 model FTIR spectrophotometer. Elemental analyses (CHNS) were performed using a VarioMICRO elemental analyzer. ^{1}H and ^{13}C NMR spectra were recorded by Agilent 600 MHz spectrometer. The mass spectra of all compounds were recorded using an Agilent 1260 infinity LC. 6210 HPLCTOF/MS spectrometer in electrospray mode.

2.2. General procedure for chalcones (1-5)

Substituted acetophenone (0.01 mol) and 4-formylbenzoic acid (0.02 mol) were dissolved in methanol (25 mL) and solid NaOH was added and then mixed at room temperature in a magnetic stirrer for 24 hours. The mixing process continued for 24 hours. After the completion of the reaction was determined by TLC, and extracted with dichloromethane. After extraction, the organic part was dried with $MgSO_4$. The mixture was filtered and removed from $MgSO_4$. The liquid organic phase was evaporated in the evaporator, and the solid was crystallized with the appropriate solvent to obtain a pure substance.[48]

2.3. *E*-4-(3-oxo-3-(4-pyrrolidin-1-yl)phenyl)prop-1-en-1-yl)benzoic acid (1)

Yellow solid, yield: 39.71 %, m.p: 191.4. °C. MS m/z: (321.37) 321.90 [M]+.

2.4. *E*-4-(3-oxo-3-(4-piperazin-1-yl)phenyl)prop-1-en-1-yl)benzoic acid (2)

Yellow solid, yield: 46.80 %, m.p: 178.5 °C. MS m/z: (336.38) 336.90 [M]+.

2.5.*E*-4-(3-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl) phenyl)-3-oxoprop-1-en-1-yl) benzoic acid (3)

Cream solid, yield: 68.00 %, m.p: 162.9 °C. MS m/z: (456.51) 456.80 [M]+.

2.6. *E*-4-(3-oxo-3-(4-trifluoromethyl)phenyl)prop-1-en-1-yl)benzoic acid (4)

Cream solid, yield: 50 %, m.p: 190.6 °C. MS m/z: (320.26) 320.80 [M]+.[49]

2.7. *E*-4-(3-(4-bromophenyl)-3-oxoprop-1-en-1- yl) benzoic acid (5)

Yellow solid**,** yield: 60 %, m.p: 166.6 °C. MS m/z: (331.16) 332.80 [M+H]+.[49]

2.8. Preparation of the Solution of the Compounds

The compounds and assay standards were dissolved in dimethyl sulfoxide (DMSO). The solutions of the synthesized chalcones **(1-5)** were prepared at four different concentrations i.e. 400, 200, 100, and 50 µM for the anticholinesterase and urease inhibition tests, and 400, 200, 100, and 50 mM for the tyrosinase inhibition test.

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Table 1. FTIR, ^{1}HNMR and ^{13}C NMR spectral data of chalcone **1-5**

Compound	FTIR ν_{max} (cm^{-1})	Elemental analysis		^{1}H NMR(δ) †	^{13}C NMR(δ) ††
		Anal. Calcd (%)	Found (%)		
1	2960, 2846 (aromatic CH), 2674, 2557 (aliphatic CH), 1679 (acid C=O), 1651 (ketone C=O), 1588, 1587, 1543, 1505 (C=C), 986 (trans C=C).	$C_{20}H_{19}NO_3$: C: 74.75 H: 5.96 N: 4.21	C: 74.50 H: 5.93 N: 4.21	1.95 (s, 4H, H_{15}), 3.36 (s, 4H, H_{14}), 6.47 (d, 2H, *J*=7.8 Hz, H_{12}), 7.65 (d, 1H, *J*=15.6 Hz, H_8), 7.95-8.05 (m, 5H, $H_{5,7,11}$), 8.11 (d, 2H, *J*=7.2 Hz, H_4), 13.27 (s, 1H, OH).	25.38, 47.76, 111.46, 125.09, 129.01, 130.00, 130.38, 131.48, 136.06, 139.31, 140.47, 151.35, 167.02, 193.48.
2	2923, 2851 (aromatic CH), 2742, 2508 (aliphatic CH), 1688 (acid C=O), 1660 (ketone C=O), 1593, 1505, 1455, 1407 (C=C), 973 (trans C=C).	$C_{20}H_{20}N_2O_3$: C: 71.41 H: 5.99 N: 8.33	C: 71.00 H: 5.83 N: 8.40	3.42 (s, 4H, H_{15}), 3.63 (s, 4H, H_{14}), 7.08 (d, 2H, *J*=8.40 Hz, H_{12}), 7.69 (d, 1H, *J*=15.60 Hz, H_8), 7.80-7.96 (m, 4H, $H_{11,5}$), 8.04 (d, 1H, *J*=15.60 Hz, H_7), 8.10 (d, 2H, *J*=7.80 Hz, H_4), 13.25 (s, 1H, OH).	42.65, 44.17, 114.31, 129.21, 130.01, 130.14, 130.38, 131.22, 132.21, 141.53, 153.99, 167.32, 186.94, 193.48.
3	3278 (urea NH), 3072 (aromatic CH), 2928, 2855 (aliphatic CH), 1668 (acid C=O), 1604 (ketone C=O), 1567, 1538, 1427 (C=C), 989 (trans C=C).	$C_{23}H_{24}N_2O_6S$: C: 60.51 H: 5.30 N: 6.14 S: 7.02	C: 61.00 H: 5.41 N: 6.10 S: 7.08	6.50 (s, 1H, H_{14}), 7.81 (d, 1H, *J*=15.6 Hz, H_8), 7.99-8.00 (m, 4H, $H_{4,5}$), 8.02 (d, 1H, *J*=15.6 Hz, H_7), 8.06 (d, 2H, *J*=7.80 Hz, H_{12}), 8.32 (d, 2H, *J*=7.80 Hz, H_{11}), 10.57 (s, 1H, H_{16}), 13.09 (s, 1H, OH)	24.65, 25.39, 32.68, 48.66, 124.44, 128.14, 129.53, 129.61, 129.67, 130.19, 132.99, 138.97, 141.11, 144.05, 150.83, 167.28, 189.00.
4	2951, 2828 (aromatic CH), 2642, 2547 (aliphatic CH), 1682 (acid C=O), 1661 (ketone C=O), 1607, 1567, 1505, 1426 (C=C), 1177 (C-F), 985 (trans C=C).	$C_{17}H_{11}FO_3$: C: 63.76 H: 3.46	C: 63.64 H: 3.49	7.81 (d, 1H, *J*=15.6 Hz, H_8), 7.93 (d, 2H, *J*=6.60 Hz, H_5), 7.99-8.01 (m, 4H, $H_{11,12}$), 8.05 (d, 1H, *J*=15.6 Hz, H_7), 8.33 (d, 2H, *J*=7.80 Hz, H_4), 13.17 (s, 1H, OH).	
5	2954, 2829 (aromatic CH), 2661, 2545 (aliphatic CH), 1682 (acid C=O), 1657 (ketone C=O), 1608, 1583, 1567, 1505 (C=C), 986 (trans C=C).	$C_{16}H_{11}BrO_3$: C: 58.03 H: 3.35	C: 58.70 H: 3.49	7.78-8.00 (m, 3H, $H_{8,5}$), 7.97-8.05 (m, 3H, $H_{7,12}$), 8.10-8.12 (m, 4H, $H_{4,11}$), 13.27 (s, 1H, OH).	124.26, 129.48, 130.00, 130.16, 130.38, 131.12, 132.36, 136.72, 143.48, 167.28, 188.39, 193.46.

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2.9. Enzyme Inhibition Assays

The all enzyme inhibition activity assays of chalcones **1-5** were tested at four µM concentrations (i.e. 400-200-100-50 µM for anticholinesterase and urease inhibition activity, 400-200-100-50 mM for tyrosinase inhibition activity) in triplicate measurements. The results of all enzyme inhibition activities were given as 50 % concentration (IC_{50}).

Anticholinesterase inhibition activity

The *in vitro* anticholinesterase inhibition activity against AChE and BChE of chalcones **1-5** was performed according to Ellman's method using 96 well microplate readers. For these assays were used AChE and BChE obtained from electric eel and horse serum, respectively. The acetylthiocholine iodide and butyrylthiocholine chloride were utilized as substrates in assays. DTNB (5,50-dithiobis(2-nitrobenzoic) acid was used as a coloring agent to measure the anticholinesterase inhibition activity.[50]

Tyrosinase inhibition activity

The spectrophotometric analysis of tyrosinase inhibition activity was performed according to the slightly modified literature procedures of Hearing.[51] DMSO with kojic acid and L-mimosine, respectively, was used for the control and tyrosinase standards for the determination of tyrosinase inhibition activity.

Urease inhibition activity

The spectrophotometric analysis of urease inhibition activity was performed by measuring ammonia production using the indophenol method according to procedures described in the literature as.[52] DMSO and thiourea were used as control and urease positive standards, respectively.

2.10. Absorption, Distribution, Metabolism and Excretion (ADME) properties

The basic parameters affecting drug metabolism such as the absorption, distribution, metabolism and excretion (ADME) properties of chalcones **1-5** in the body, were carried out with the web-based program SwissSimilarty (SwissADME) according to the rules of Lipinski and Veber.[53] The drug likeness model score properties of chalcone compounds **1-5** were performed using the Molsoft software program.[54]

3. RESULTS AND DISCUSSION

3.1. Chemistry

Benzoic acid hybridized chalcones were synthesized by Claisen-Schmidt condensation between a different ketone and 4-formylbenzoic acid in the presence of NaOH in methanol (Figure 1). Compounds **1-5** were crystallized in a hexane/DCM mixture. The yields were in the range of 39.71-60.00 %. The IR spectra of the chalcones (**1-5**) showed the aromatic CH stretching band at 2923-3278 cm^{-1}, the acidic C=O stretching band at 1668-1688 cm^{-1}, and the ketone C=O stretching band at 1604-1661 cm^{-1}.

The ^1H NMR spectra of compounds **1-5** showed that the Hα and H_β protons resonated as doublets at 7.65-7.98 ppm (j=14.4-15.6) and 7.95-8.08 ppm (j=15.6-17.4), respectively. Therefore, all compounds were in the trans structure.

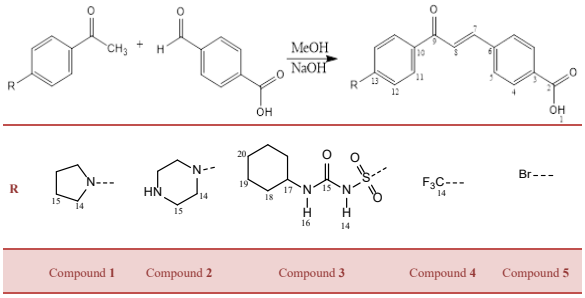

Figure 1. Synthetic route of target compounds (**1-5**)

3.2. Biological Activity

The anticholinesterase, tyrosinase, and urease inhibition activities of compounds **1-5** were determined at 100, 50, 25, and 5 µMi respectively. The IC_{50} values of the enzyme inhibition activities of compounds **1-5** were given in Table 2. The anticholinesterase inhibition activity of compounds **1-5**, compound **1** was determined to be the most active compound against each AChE enzyme.

Compounds **1** and **2** were found to be more active against BChE enzyme than galantamine, the standard of the assay. The IC_{50} values of the synthesized compounds against AChE were: Compound **2**> Compound **1**> Compound **3**> Compound **4** > Compound **5** > Galantamine, while against BChE were: Compound **2**> Compound **1**> Galantamine> Compound **3**> Compound **4** > Compound **5**.

In the tyrosinase inhibition activity of compounds **1-5**, compound **4** exhibited the best activity in the series. The IC_{50} values of tyrosinase inhibition activity of the synthesized compounds were: Kojic acid ~ L-mimosine> Compound **4**> Compound **5**> Compound **3**> Compound **1** > Compound **2**.

In the urease inhibition activity of compounds **1-5**, compound **3** displayed the best activity in this series. The IC_{50} value of urease inhibition activity of the synthesized compounds were: Compound **3**> Thiourea> Compound **2**> Compound **1**> Compound **4** > Compound **5**.

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Table 2. The IC_{50} values of enzyme inhibition activities of compounds **1-5**.

Compound	Anticholinesterase Inhibitory Activity		Tyrosinase Inhibitory Activity	Urease Inhibitory Activity
	AChE assay IC_{50} (µM)	BChE assay IC_{50} (µM)	Tyrosinase assay IC_{50} (mM)	Urease assay IC_{50} (µM)
1	47.09±0.73	47.10±0.51	47.01±0.46	31.77±0.58
2	40.21±0.67	40.32±0.28	56.82±0.54	28.30±0.91
3	53.05±0.49	62.17±0.36	38.22±0.77	20.18±0.51
4	69.20±0.12	78.44±0.69	21.73±0.24	43.07±0.22
5	75.65±0.85	83.50±0.19	30.42±0.16	59.64±0.86
Galantamine [b]	4.9±0.36	47.23±0.77	**NT**	**NT**
Kojic acid[b]	**NT**	**NT**	0.64±0.38	**NT**
L-mimosine[b]	**NT**	**NT**	0.75±0.14	**NT**
Thiourea[b]	**NT**	**NT**	**NT**	25.33±0.36

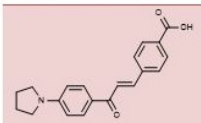
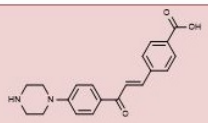
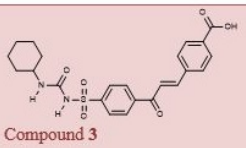
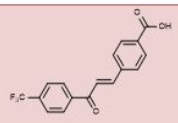
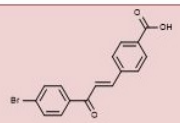
[a] Values expressed are means ± S.E.M. of three parallel measurements. $p< 0.05$, significantly different with the student's *t*-test. [b] Reference compounds. NT: Not tested.

3.3. Molecular properties, Lipinski rule, and ADME

The molecular weight of all compounds was between 321.37-456.51g (150 g/mol <MW<500 g/mol). The iLOGP values were in the range that should be between 2.20-2.70. All compounds, except **3**, passed the brain barrier. All compounds except compound **3** had a high gastrointestinal absorption value. The TPSA values of compounds **1**, **2**, **4** and **5** were in the range of 54.37-69.64 Å², while compound **3** was not in the required value range (20 Å²<TPSA<130 Å²) with a value of 138.02 Å².

The Brain or Intestine Predictive Permeability (BOILED-Egg) method was used to obtain a visual cue for the drug candidate of the synthesis molecules of the new compounds based on the oral absorption potential with respect to the polarity and lipophilicity of the small molecules. The visual estimates of gastrointestinal absorption and blood-brain barrier (BBB) penetration of chalcones **1-5** were shown in Table 3. According to the BOILED-Egg plot, chalcones (**1-5**) were located in the yellow circle (compounds **1**, **2**, **4**, and **5**) expressing good intestinal absorption and the gray area (compound **3**) representing poor intestinal absorption of BBB. Compound **2** was also found to be in the blue spot, indicating its good bioavailability. It appeared that this compound could be used as an alternative substrate for P-glycoprotein, and would decrease the absorption and penetration of this compound in the brain.[55,56]

Table 3. Drug-likeness properties of the synthesized benzoic acid hybridized chalcone derivatives (**1-5**).

	Compound				
	 Compound 1	 Compound 2	 Compound 3	 Compound 4	 Compound 5
Molecular Formula	$C_{20}H_{19}NO_3$	$C_{20}H_{20}N_2O_3$	$C_{23}H_{24}N_2O_6S$	$C_{17}H_{11}F_3O_3$	$C_{16}H_{11}BrO_3$
MW (g/mol)	321.37	336.38	456.51	320.26	331.16
iLOG P	2.70	2.69	2.20	2.21	2.48
BBB	Yes	Yes	No	Yes	Yes
GI	High	High	Low	High	High
TPSA Å²	57.61	69.64	138.02	54.37	54.37
Synthetic accessibility	2.56	2.76	3.49	2.60	2.51
Lipinski	Yes	Yes	Yes	Yes	Yes

*These parameters were determined with SwissSimilarity and Molsoft software

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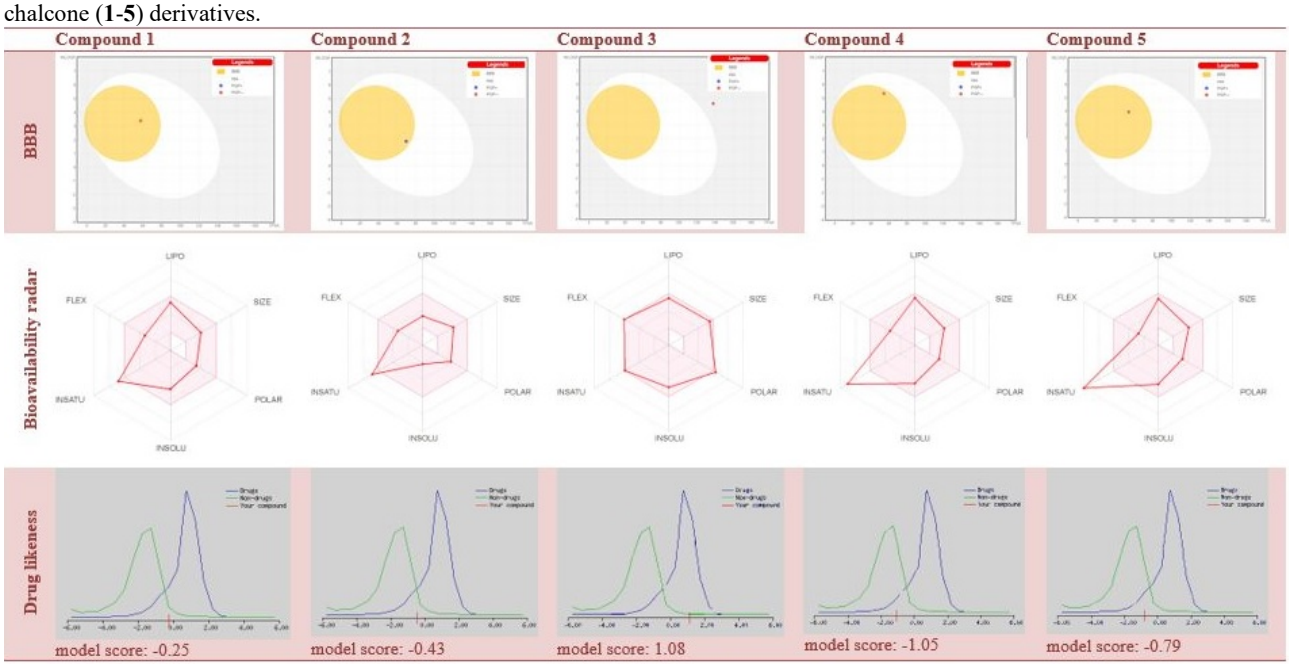
Table 4. Boiled-Egg, Bioavailability radar and Drug likeness model score properties of the synthesized benzoic acid hybridized chalcone (**1-5**) derivatives.



Bioavailability radar of the **1-5**. The pink area represents the optimal range for each properties (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. CONCLUSIONS

In this study, especially compound **3**, which showed the best activity in urease inhibition activity, can be developed as an agent that can also eliminate the symptoms that cause urease inhibition, as a result of the satisfactory results to be obtained from the further cytotoxic activity study. According to the other enzyme inhibition results, for anticholinesterase enzyme inhibition activity, AChE and BChE enzymes showed good inhibition activity against both enzymes, while compound **2** was the most active component in the tyrosinase enzyme inhibition activity. It can be concluded that the particularly compound **4** can be the potential candidate for the treatment of skin diseases and hyper-pigmentation caused by melanin.

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Conflict of interests

I declare that there is no conflict of interest with any person, institute, company, etc.

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