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SYNTHESIS AND ANTIOXIDANT ACTIVITY OF (*E*)-3-(3-(4-OXO-4*H*-CHROMEN-3-YL)ACRYLOYL) 2*H*-CHROMEN-2-ONE DERIVATIVES

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The aim is based on the results of the *in silico* prediction, to obtain and characterize a number of (*E*)-3-(3-(4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one derivatives, and also to study their antioxidant activity.

Materials and methods. The synthesis of the target compounds was carried out by condensation of substituted 3-formylchromones and 3-acetylcoumarins under the acid catalysis conditions. ^{1}H NMR spectra were recorded on the instruments of Bruker Avance-400 (400 MHz) and Bruker Avance-300 (300 MHz) in the solutions of $CDCl_3$ or DMSO-d_6. Mass spectra (ESI) were obtained on a Finnigan LCQ Advantage mass spectrometer (USA). The melting points of the compounds were determined on a PTP (M) instrument. Quantum-chemical calculations were carried out on the basis of a density functional theory using the Gaussian 09 program using the B3LYP/6-311G (d, p) method, as well as using the Way2Drug (PASS Online) online service. The antiradical activity of the compounds was studied by the DPPH test, and the chelating properties were assessed by the *o*-phenanthroline method.

Results. 15 derivatives of (*E*)-3-(3-(4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one have been obtained and characterized. The calculations based on the density functional theory showed that the highest occupied molecular orbital exhibiting electron-donating properties is localized on the propenone fragment, which confirms the likelihood of the manifestation of antiradical properties. According to the prediction of the probable spectrum of the biological activity, the obtained compounds are more likely to exhibit their direct antioxidant activity. According to the results of the *in vitro* study of the antioxidant activity, it was found out that compounds 1-15 are the most active in relation to the DPPH radical, which confirms the obtained prognostic data.

Conclusion. Thus, based on the *in silico* prediction data, 15 derivatives of (*E*)-3-(3-(4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one have been obtained and characterized, for which the method antioxidant activity has been studied *in vitro*. It was found out that compounds 1-15 exhibit the antiradical activity to a large extent.

Keywords: 3-formylchromone; 3-acetylcoumarin; chalcones; DFT calculations; antioxidant activity

Abbreviations: DFT – density functional theory; THF – tetrahydrofuran; DMF – dimethylformamide; HOMO – highest occupied molecular orbital; LUMO – lowest unoccupied molecular orbital; LPO – lipid peroxidation; TBA-AP – active products interacting with 2-thiobarbituric acid; ROS – reactive oxygen species.

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СИНТЕЗ И АНТИОКСИДАНТНАЯ АКТИВНОСТЬ ПРОИЗВОДНЫХ (*E*)-3-(3-(4-ОКСО-4*H*-ХРОМЕН-3-ИЛ) АКРИЛОИЛ)-2*H*-ХРОМЕН-2-ОНА

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Цель. На основе результатов прогноза *in silico* получить и охарактеризовать ряд производных (*E*)-3-(3-(4-оксо-4*H*-хромен-3-ил)акрилоил)-2*H*-хромен-2-она, а также изучить их антиоксидантную активность.
Материалы и методы. Синтез целевых соединений осуществляли конденсацией замещенных 3-формилхромонов и 3-ацетилкумаринов в условиях кислотного катализа. ЯМР^{1}Н спектры регистрировали на приборе Bruker Avance-400 (400 МГц) и Bruker Avance-300 (300 МГц) в растворах в дейтерированном хлороформе ($CDCl_3$) или дейтерированном диметилсульфоксиде (DMSO-d_6). Масс-спектры (ESI) были получены на масс-спектрометре Finnigan LCQ Advantage (США). Температуры плавления соединений определяли на приборе ПТП (М). Квантово-химические расчеты проводили на основе теории функционала плотности с помощью программы Gaussian 09 методом B3LYP/6-311G (d,p), а также с помощью онлайн-сервиса Way2Drug PASS Online. Антирадикальная активность соединений изучена методом DPPH-теста, а хелатирующие свойства оценены *o*-фенантролиновым методом.
Результаты. Получено и охарактеризовано 15 производных (*E*)-3-(3-(4-оксо-4*H*-хромен-3-ил)акрилоил)-2*H*-хромен-2-она. Расчеты на основе теории функционала плотности показали, что высшая занятая молекулярная орбиталь, проявляющая электронодонорные свойства, локализована на пропеноновом фрагменте, что подтверждает вероятность проявления антирадикальных свойств. По данным прогноза вероятного спектра биологической активности, полученные соединения с большей вероятностью могут проявлять прямую антиоксидантную активность. По результатам проведенного *in vitro* изучения антиоксидантной активности установлено, что соединения **1-15** проявляют наибольшую активность в отношение DPPH-радикала, что подтверждает полученные прогностические данные.
Заключение. Таким образом, на основании данных *in silico* прогноза получено и охарактеризовано 15 производных (*E*)-3-(3-(4-оксо-4*H*-хромен-3-ил)акрилоил)-2*H*-хромен-2-она, для которых методом *in vitro* изучена антиоксидантная активность. Установлено, что соединения 1-15 в значительной степени проявляют антирадикальную активность.
Ключевые слова: 3-формилхромон; 3-ацетилкумарин; халконы; DFT расчеты; антиоксидантная активность
Список сокращений: DFT – теория функционала плотности; ТГФ – тетрагидрофуран; ДМФА – диметилформамид; ВЗМО – высшая занятая молекулярная орбиталь; НСМО – низшая свободная молекулярная орбиталь; ПОЛ – перекисное окисление липидов; ТБК-АП – активные продукты, взаимодействующие с 2-тиобарбитуровой кислотой; АФК – активные формы кислорода.

INTRODUCTION

Currently, the relationship between the level of free radicals in the body and the development of a number of [1, 2], including malignant neoplasms [3], has been unambiguously established. These pathologies may be associated with the impaired DNA replication, as well as the normal functioning of membrane receptors, ion channels and membrane phospholipids [4].

Flavonoids are a wide class of natural polyphenolic compounds with a wide spectrum of a biological activity (including antioxidant) and a low toxicity [5–11]. Due to the antioxidant properties, the main types of the flavonoid activity are realized [12–15]. Flavonoids also include chalcones – compounds with an open pyran ring, in which two aromatic rings A and B which, in particular, exhibit the antimitotic activity, are linked by an α,β-unsaturated propenone fragment [16]. One of the possible mechanisms for the manifestation of the antiradical chalcones activity is the interaction of the vinylene group of the propenone fragment with reactive oxygen species. This mechanism occurs due to the transfer of electrons along the conjugation chain. From this point

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of view, a promising direction is the study of the effect of replacing one or both of the aromatic rings of chalcones with heterocyclic compounds.

In the article by Osipova et al. [17], chalcone analogs in which one of the rings was replaced by a 2*H*-chromen-2-one residue by the condensation of 3-acetylcoumarin and substituted benzaldehydes in butanol in the presence of acetic acid and piperidine, were synthesized. The obtained compounds showed a prolonged antioxidant activity on the systems of peroxidation of oleic acid and liver homogenate lipids.

THE AIM of the study is synthesis and an *in vitro* study of the antioxidant properties of chalcones analogs, in which one of the rings is replaced by a benz-γ-pyrone residue, and the second – by a benz-α-pyrone residue.

MATERIALS AND METHODS

Synthesis and determination of physical and chemical characteristics

The synthesis of the target compounds was carried out by condensation of substituted 3-formylchromones and 3-acetylcumarins under acid catalysis conditions. ^{1}H NMR spectra were recorded on a Bruker Avance-400 instrument (400 MHz) in the solutions of $CDCl_3$ or DMSO-d_6. Mass spectra at the atmospheric pressure with ionization by sputtering in an electric field (ESI) were obtained by full scanning of positive and negative ions on a dynamic tandem mass spectrometer Finnigan LCQ Advantage (USA). It was equipped with a mass analyzer with an ion trap MS Surveyor, an autosampler Surveyor, a generator nitrogen Schmidlin-Lab (Germany) and the information collection and the analysis system X Calibur (version 1.3, Finnigan) on a computer. The capillary temperature was 150°C, the field voltage between the needle and the counter electrode was 4.5 kV. The samples were injected into the ion source dissolved in acetonitrile using a syringe, through a 5 mL Reodyne injector at the carrier gas flow rate of 50 mL/min. The melting points of the compounds were determined in glass capillaries sealed from one end using a PTP (M) device.

General procedure for the preparation of *(E)*-3-(3-(4-oxo-4H-chromen-3-yl)acryloyl)-2H-chromen-2-one derivatives (1-15).

A mixture of 0.01 mol of the substituted 3-formylchromone and 0.01 mol of the corresponding 3-acetylcoumarin in 10 ml of AcOH was refluxed for 30 min in the presence of catalytic amounts of concentrated H_2SO_4. The precipitate obtained after cooling to room temperature, was filtered off and recrystallized from a THF-DMF mixture (7:3).

(*E*)-3-(3-(4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one (1)

Yield – 56%. MP 267–268°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.54 (s, 2H), 8.28 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 8.0 Hz, 2H), 7.82–7.75 (m, 2H), 7.65 (d, J = 8.5 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.38, 162.11, 161.83, 161.68, 161.25, 160.82, 156.51, 155.04, 152.14, 138.76, 136.64, 136.27, 131.19, 127.54, 126.66, 126.42, 123.23, 119.41, 118.98, 117.23, 113.21, 110.38. Anal. Calcd (%) for $C_{21}H_{12}O_5$ (344.32): Calculated: C, 73.3; H, 3.5; O, 23.2. Found: C, 73.21; H, 3.53; O, 23.26. ESI-MS (m/z) 344 $[M + H]^+$

(*E*)-6-methyl-8-nitro-3-(3-(4-oxo-4*H*-chromen-3-yl) acryloyl)-2*H*-chromen-2-one (2)

Yield – 55%. MP 254–256°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.63 (s, 1H), 8.31 (d, J = 15.8 Hz, 1H), 8.24–8.20 (m, 1H), 8.16 – 8.11 (m, 1H), 8.07 (s, 1H), 7.88 – 7.82 (m, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.60 – 7.52 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.40, 175.20, 161.70, 155.01, 145.84, 144.74, 137.30, 135.55, 134.67, 129.33, 126.53, 126.26, 125.51, 123.56, 120.17, 118.38, 19.87. Anal. Calcd. (%) for $C_{22}H_{13}O_7$ (403.34): Calculated: C, 65.5; H, 3.2; N, 3.5; O, 27.8. Found: C, 65.63; H, 3.42; N, 3.39; O, 27.56. ESI-MS (m/z) 403 $[M + H]^+$

(*E*)-6-bromo-8-methyl-3-(3-(4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one (3)

Yield – 54%. MP 264–266°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.56 (s, 1H), 8.32 (d, J = 16.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 7.84 (dd, J = 16.8, 9.5 Hz, 2H), 7.71 (d, J = 7.8 Hz, 1H), 7.61–7.50 (m, 2H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 188.18, 175.64, 162.03, 158.30, 155.46, 152.38, 146.41, 137.40, 135.10, 130.25, 128.44, 126.69, 126.54, 125.96, 124.01, 120.28, 119.03, 118.88, 116.39, 15.13. Anal. Calcd. (%) for $C_{22}H_{13}BrO_5$ (437.24): Calculated: C, 60.4; H, 3; Br, 18.3; O, 18.3. Found: C, 60.29; H, 3.12; Br, 18.45, O, 18.14. ESI-MS (m/z) 437 $[M + H]^+$

(*E*)-6-chloro-3-(3-(4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one (4)

Yield – 59%. MP 231–233°C. ^{1}H NMR (400 MHz, DMSO-d_6) **δ** 8.95 (s, 1H), 8.60 (s, 1H), 8.35 (d, J = 15.8 Hz, 1H), 8.18–8.13 (m, 1H), 8.08 (d, J = 2.5 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.80 – 7.71 (m, 2H), 7.60–7.52 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.64, 175.20, 161.63, 157.90, 155.01, 153.11, 145.71, 136.93, 134.65, 133.55, 129.22, 128.55, 126.68, 126.39, 126.25, 125.50, 123.57, 119.77, 118.58, 118.42, 118.25. Anal. Calcd. (%) for $C_{21}H_{11}ClO_5$ (378.76): Calculated: C, 66.6; H, 2.9; Cl, 9.4; O, 21.1. Found: C, 66.57; H, 3.07; Cl, 9.52, O, 20.84. ESI-MS (m/z) 378 $[M + H]^+$

(*E*)-3-(3-(6-methyl-4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one (5)

Yield – 52%. MP 235–237°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.53 (t, J = 7.8 Hz, 2H), 8.19 (d, J = 2.1 Hz, 1H), 8.04–8.00 (m, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.79 (d, J = 15.5 Hz, 1H), 7.67 (dd, J = 8.7, 2.1 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 2.56 (s, 3H), 2.53 (s, 3H). Anal. Calcd. (%) for $C_{22}H_{14}O_5$ (358.34): Calculated: C, 73.7; H, 3.9; O, 22.3. Found: C, 73.67; H, 3.87; O, 22.46. ESI-MS (m/z) 358 $[M + H]^+$

(*E*)-6-methyl-3-(3-(6-methyl-4-oxo-4*H*-chromen-3-yl)acryloyl)-8-nitro-2*H*-chromen-2-one (6)

Yield – 54%. MP 248–251°C. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.85 (s, 1H), 8.53 (t, J = 7.7 Hz, 2H), 8.19 (s, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 7.79 (d, J = 15.5 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 2.56 (s, 3H), 2.53 (s, 3H). Anal. Calcd. (%) for $C_{23}H_{15}O_7$ (417.37): Calculated: C, 66.2; H, 3.6; N, 3.4; O, 26.8. Found: C, 66.15; H, 3.57; N, 3.48; O, 26.8. ESI-MS (m/z) 417 $[M + H]^+$

(*E*)-6-bromo-8-methyl-3-(3-(6-methyl-4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one (7)

Yield – 57%. MP 256–258°C. ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.68 (s, 1H), 8.60–8.43 (m, 2H), 8.04 (s, 1H), 7.81–7.59 (m, 4H), 7.51 (d, J = 8.3 Hz, 1H), 2.52 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.27, 161.84, 161.40, 160.96, 150.65, 139.80, 138.86, 137.98, 137.35, 130.36, 129.02, 125.23, 119.42, 118.42, 115.62, 112.79, 109.97, 20.55, 14.26. Anal. Calcd. (%) for $C_{23}H_{15}BrO_5$ (451.27): Calculated: C, 61.2; H, 3.4; Br,17.7; O, 17.7. Found: C, 61.15; H, 3.38; Br, 17.58; O, 17.89. ESI-MS (m/z) 451 $[M + H]^+$

(*E*)-6-chloro-3-(3-(6-methyl-4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one (8)

Yield – 54%. MP 236–238°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.51 (d, J = 19.6 Hz, 2H), 8.04 (s, 1H), 7.82–7.63 (m, 4H), 7.52 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 2.52 (s, 3H). Anal. Calcd. (%) for $C_{22}H_{13}ClO_5$ (392.79): Calculated: C, 67.3; H, 3.3; Cl, 9; O, 20.4. Found: C, 67.23; H, 3.35; Cl, 8.89; O, 20.53. ESI-MS (m/z) 392 $[M + H]^+$

(*E*)-3-(3-(6-methyl-8-nitro-4-oxo-4*H*-chromen-3-yl) acryloyl)-2*H*-chromen-2-one (9)

Yield – 56%. MP 261–263°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.55 (d, J = 14.7 Hz, 2H), 8.41 (s, 1H), 8.29 (s, 1H), 7.84 – 7.67 (m, 3H), 7.55–7.44 (m, 2H), 2.61 (s, 3H). ^{13}C ЯМР (101 MHz, $CDCl_3$) δ 189.55, 176.52, 161.56, 161.13, 160.70, 160.09, 155.07, 151.63, 138.58, 137.57, 136.55, 136.33, 132.42, 132.04, 127.97, 126.42, 124.98, 123.64, 120.27, 118.55, 117.21, 115.93, 113.10, 20.91. Anal. Calcd. (%) for $C_{22}H_{13}NO_7$ (403.34): Calculated: C, 65.5; H, 3.2; N, 3.5; O, 27.8. Found: C, 65.44; H, 3.27; N, 3.24; O, 28.05. ESI-MS (m/z) 403 $[M + H]^+$

(*E*)-6-methyl-3-(3-(6-methyl-8-nitro-4-oxo-4*H*-chromen-3-yl)acryloyl)-8-nitro-2*H*-chromen-2-one (10)

Yield – 56%. MP 213–216°C. ^{1}H NMR (400 MHz, CDCl3) δ 8.83 (s, 1H), 8.57 (s, 1H), 8.52 (s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 7.91 (s, 1H), 7.75 (d, J = 15.5 Hz, 1H), 2.62 (s, 3H), 2.57 (s, 3H). Anal. Calcd. (%) for $C_{23}H_{14}N_2O_9$ (462.37): Calculated: C, 59.7; H, 3.1; N, 6.1; O, 31.1. Found: C, 59.63; H, 3.12; N, 6.18; O, 31.07. ESI-MS (m/z) 462 $[M + H]^+$

(*E*)-6-bromo-8-methyl-3-(3-(6-methyl-8-nitro-4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one (11)

Yield – 49%. MP 275–276°C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.57 (s, 1H), 8.52 (s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 7.91 (s, 1H), 7.75 (d, J = 15.5 Hz, 1H), 2.62 (s, 3H), 2.57 (s, 3H). Anal. Calcd. (%) for $C_{23}H_{14}BrNO_7$ (496.26): Calculated: C, 55.7; H, 2.8; Br, 16.1; N, 2.8; O, 22.6. Found: C, 55.68; H, 2.77; Br, 16.21; N, 2.83; O, 22.51. ESI-MS (m/z) 496 $[M + H]^+$

(*E*)-6-chloro-3-(3-(6-methyl-8-nitro-4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one (12)

Yield – 47%. MP 283–284°C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.57 (s, 2H), 8.52 (s, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 7.83 (s, 1H), 7.75 (d, J = 14.3 Hz, 2H), 7.44 (d, J = 8.9 Hz, 1H), 2.62 (s, 3H). Anal. Calcd. (%) for $C_{22}H_{12}ClNO_7$ (437.79): Calculated: C, 60.4; H, 2.8; Cl, 8.1; N, 3.2; O, 25.6. Found: C, 60.42; H, 2.74; Cl, 8.15; N, 3.13; O, 25.56. ESI-MS (m/z) 437 $[M + H]^+$

(*E*)-3-(3-(6-methyl-8-nitro-2-oxo-2*H*-chromen-3-yl)-3-oxoprop-1-en-1-yl)-4-oxo-4*H*- chromene-7-yl acetate (13)

Yield – 51%. MP 284–286°C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.62 (s, 1H), 8.28 (d, J = 15.8 Hz, 1H), 8.23 (s, 1H), 8.08 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 15.7 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 6.90 (s, 1H), 2.45 (s, 3H), 1.91 (s, 3H). Anal. Calcd. (%) for $C_{24}H_{15}NO_9$ (461.38): Calculated: C, 62.5; H, 3.3; N, 3; O, 31.2. Found: C, 62.52; H, 2.93; N, 3.11; O, 31.44. ESI-MS (m/z) 461 $[M + H]^+$

(*E*)-3-(3-(6-bromo-8-methyl-2-oxo-2*H*-chromen-3-yl)-3-oxoprop-1-en-1-yl)-4-oxo-4*H*- chromene-7-yl acetate (14)

Yield – 52%. MP 243–246°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.55 (s, 1H), 8.28 (d, J = 15.8 Hz, 1H), 8.03 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.82 (s, 1H), 7.52 (d, J = 15.7 Hz, 1H), 6.98 (d, J = 11.0 Hz, 1H), 6.90 (s, 1H), 2.39 (s, 3H). Anal. Calcd. (%) for $C_{24}H_{15}BrO_7$ (495.28): Calculated: C, 58.2; H, 3.1; Br, 16.1; O, 22.6. Found: C, 58.13; H, 3.12; Br, 16.18; O, 22.57. ESI-MS (m/z) 495 $[M + H]^+$

(*E*)-3-(3-(6-chloro-2-oxo-2*H*-chromen-3-yl)-3-oxoprop-1-en-1-yl)-4-oxo-4*H*-chromene-7-yl acetate (15)

Yield – 53%. MP 251–252°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.58 (s, 1H), 8.30 (d, J = 15.7 Hz, 1H), 8.07 (d, J = 2.5 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.94 (s, 1H), 7.77 (dd, J = 8.9, 2.6 Hz, 1H), 7.55 (s, 1H), 7.51 (d, J = 6.6 Hz, 1H), 6.98 (dd, J = 8.8, 2.2 Hz, 1H), 6.91 (s, 1H), 2.88 (s, 3H). Anal. Calcd. (%) for $C_{23}H_{13}ClO_7$ (436.79): Calculated: C, 63.2; H, 3; Cl, 8.1; O, 25.6. Found: C, 63.15; H, 3.06; Cl, 7.96; O, 25.83. ESI-MS (m/z) 436 $[M + H]^+$

In vitro study of antioxidant activity

The DPPH free radical scavenging capacity was measured according to [18]. To 0.05 ml of a 0.4 mM DPPH (Sigma-Aldrich) methanol solution, 0.1 ml of a solution of the test compound in DMSO with concentrations of 1000 μg/ml; 500 μg/ml; 250 μg/ml; 125 μg/ml and 62.5 μg/ml was added. The mixture was incubated at room temperature for 30 min. Trolox (Sigma-Aldrich) in similar concentrations was used as a reference substance. After a 30-min incubation, a spectrophotometric detection at the wavelength of 518 nm against pure methanol was performed. A solution of DPPH in methanol was taken as a positive control (A_0). The percentage of the inhibition of the DPPH radical formation was calculated using the formula:

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$$\% \ inh. = \frac{A_x}{A_0} \times 100,$$

where: A_x – absorbance of the extract sample; A_0 – absorbance of the positive control sample.

IC_{50} was calculated based on the concentration-inhibitory ability relationship by the probit analysis.

The study of the chelating properties of compounds **1-15** was carried out by the *o*-phenanthroline method [19]. The incubation medium consisted of 1 ml of a 0.05% methanol solution of *o*-phenanthroline, 2 ml of iron (II) chloride (200 μM), and 2 ml of various concentrations of the test substances. The resulting mixture was incubated for 10 min. at room temperature. The absorbance of the samples was measured at 510 nm. The incubation medium without the addition of the studied substances served as a positive control. The percentage of inhibition was calculated by the formula:

$$\% \ inh. = \frac{B_x}{B_0} \times 100,$$

where: B_x – absorbance of the sample; B_0 – absorbance of the positive control sample.

When studying Fe^{2+}-ascorbate-induced lipid peroxidation, the incubation medium consisted of 100 mM Tris HCl buffer, pH 7.4; 0.5 mM ascorbate, 12 μM iron (II) sulfate and 100 μl of a rat brain homogenate. The reaction was carried out in a water bath at 37°C for 45 min. To determine the intensity of lipid peroxidation, 0.5 ml of the suspension was taken at time zero and after 60 minutes of incubation, then it was mixed in the cold with 1 ml of a 30% trichloroacetic acid solution. The resulting mixture was centrifuged at 3000 rpm for 15 minutes. 0.1 ml of a 5 M HCl solution and 1 ml of a 0.6% 2-thiobarbituric acid solution were added to the supernatant and heated in a water bath at 100°C for 15 minutes. The amount of TBA-AP was calculated using the molar extinction coefficient of malonic dialdehyde –$1{,}56\times10^5 M^{-1}\ sm^{-1}$ [20].

RESULTS AND DISCUSSION

(*E*)-3-(3-(4-oxo-4*H*-chromene-3-yl)acryloyl)-2*H*-chromene-2-one derivatives are obtained by condensation of 3-formylchromone with 3-acetylcoumarin in alcohol using organic bases – N,N-dimethylaminopyridine [21] or piperidine [22]. For this reaction, the catalytic properties of Lewis acids had been studied under various conditions [23, 24]. However, in the authors' opinion, this synthetic approach cannot be applied when 3-formylchromone is introduced into the interaction due to the high reactivity of the C (2) position: in the presence of even weak nucleophiles, the pyrone ring opens with the formation of substituted phenols.

(*E*)-3-(3-(4-oxo-4*H*-chromene-3-yl)acryloyl)-2*H*-chromene-2-one derivatives **1-15** were synthesized by refluxing of equimolar amounts of the corresponding substituted 3-formylchromones and 3-acetylcoumarins in glacial acetic acid in the presence of catalytic amounts of concentrated sulfuric acid (Scheme 1).

$R^1 = R^2 = R^3 = R^4 = R^5 = H$ (**1**); $R^1 = R^2 = R^3 = H$, $R^4 = NO_2$, $R^5 = Me$ (**2**); $R^1 = R^2 = R^3 = H$, $R^4 = Me$, $R^5 = Br$ (**3**); $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = Cl$ (**4**); $R^1 = Me$; $R^2 = R^3 = R^4 = R^5 = H$ (**5**); $R^1 = R^5 = Me$, $R^2 = R^3 = H$, $R^4 = NO_2$ (**6**); $R^1 = R^4 = Me$, $R^2 = R^3 = H$, $R^5 = Br$ (**7**); $R^1 = Me$, $R^2 = R^3 = R^4 = H$, $R^5 = Cl$ (**8**); $R^1 = Me$; $R^3 = NO_2$, $R^2 = R^4 = R^5 = H$ (**9**); $R^1 = R^5 = Me$, $R^2 = H$, $R^3 = R^4 = NO_2$, (**10**); $R^1 = R^4 = Me$, $R^2 = H$, $R^3 = NO_2$, $R^5 = Br$ (**11**); $R^1 = Me$, $R^2 = R^4 = H$, $R^3 = NO_2$, $R^5 = Cl$ (**12**); $R^1 = R^3 = H$, $R^2 = OAc$, $R^4 = NO_2$, $R^5 = Me$ (**13**); $R^1 = R^3 = H$, $R^2 = OAc$, $R^4 = Me$, $R^5 = Br$ (**14**); $R^1 = R^3 = R^4 = H$, $R^2 = OAc$, $R^5 = Cl$ (**15**)

The information about some of the physicochemical parameters of compounds **1-15** is presented in Table 1.

At present, quantum-chemical calculation methods are actively used to predict the reactivity of compounds, one of the most promising of which is a density functional theory (DFT) calculation, which makes it possible to analyze the distribution of frontier molecular orbitals in a molecule. From the point of view of the search for new antioxidant agents, the use of this method is justified in view of the fact that the hydroxyl radical exhibiting electrophilic properties [25] will interact primarily with the highest occupied molecular orbital.

The distribution of the frontier molecular orbitals of compounds **1-15** was estimated on the basis of the structure analysis of the frontier orbitals. All necessary calculations were performed using the Gaussian 09 program based on the density functional theory (DFT) using the B3LYP / 6-311 G (d, p) basis set [26].

The parameters of the electron density distribution (the areas of the molecule where the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are concentrated) for compound **1,** are shown in Fig. 1. For the calculations, water was chosen as a solvent, since all biological processes occur in the aquatic environment of the body.

As can be seen from Fig. 1, the highest occupied molecular orbital is mainly concentrated on the benzγ-pyrone fragment and the propenone fragment. Compounds **2-15** have similar frontier orbital distribution parameters.

In addition, *in silico*, calculated the probable spectrum of pharmacological activity using the PASS Online online service [27]. From the obtained data set, we selected only those types of activity that characterize the antioxidant properties of molecules. The values obtained are shown in Table 2.

As can be seen from the Table, derivatives **1-15** can, to a greater extent, exhibit a direct antioxidant activity. Compounds **13** and **14**, containing acetoxy groups in the structure, are most likely to manifest this type of activity (Pa> 0.5).

The study of the antiradical properties of compounds **1-15,** was carried out by the DPPH test. The data obtained are presented in Table 3.

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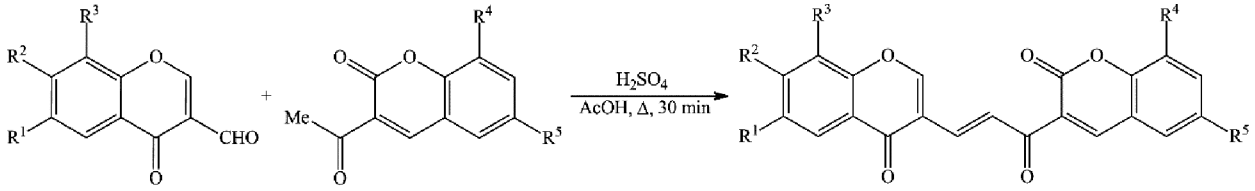
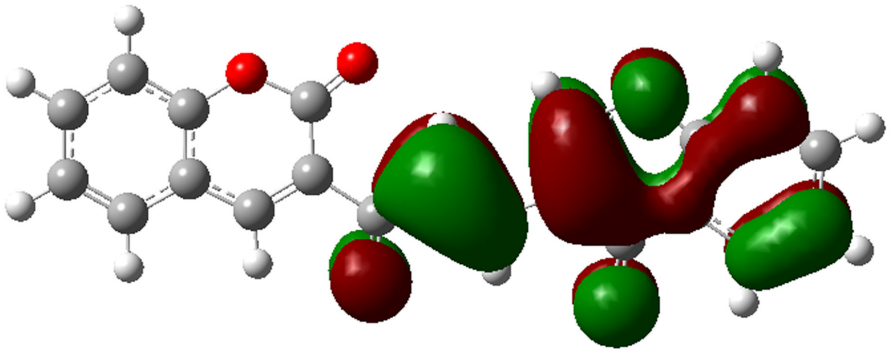
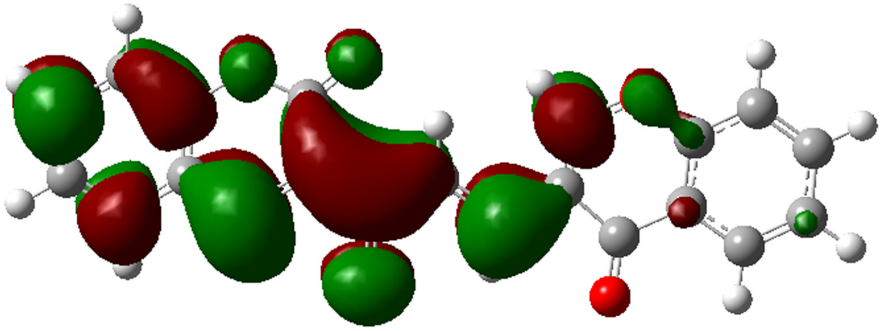


Scheme 1 – Synthesis of (*E*)-3-(3-(4-oxo-4H-chromene-3-yl)acryloyl)-2H-chromene-2-one derivatives



A



B

Figure 1 – Distribution of frontier orbitals in compound 1
Note: A – HOMO; B – LUMO

Table 1 – Physicochemical characteristics of *(E)*-3-(3-(4-oxo-4H-chromen-3-yl)acryloyl)-2H-chromen-2-one derivatives

Compound	Yield, %	MP (THF:DMF)	MW*	Molecular formula **
1	56	267–268 (lit. 270–272 [21])	344	$C_{21}H_{12}O_5$
2	55	257–259	403	$C_{22}H_{13}O_7$
3	54	258–260	437	$C_{22}H_{13}BrO_5$
4	59	231–233	378	$C_{21}H_{11}ClO_5$
5	52	235–237	358	$C_{22}H_{14}O_5$
6	54	248–251	417	$C_{23}H_{15}O_7$
7	57	256–258	451	$C_{23}H_{15}BrO_5$
8	54	236–238	392	$C_{22}H_{13}ClO_5$
9	56	261–263	403	$C_{22}H_{13}NO_7$
10	56	213–216	462	$C_{23}H_{14}N_2O_9$
11	49	275–276 (dif.)	496	$C_{23}H_{14}BrNO_7$
12	47	283–284 (dif.)	437	$C_{22}H_{12}ClNO_7$
13	51	284–286 (dif.)	461	$C_{24}H_{15}NO_9$
14	52	243–245	495	$C_{24}H_{15}BrO_7$
15	53	247–249	436	$C_{23}H_{13}ClO_7$

Note: * – according to the mass spectroscopy data (the obtained values correspond to the calculated ones); ** – the elemental analysis data are in agreement with the calculated values

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Table 2 – Prediction of the derivatives 1-15 antioxidant activity

Compound	Type of activity	
	Indirect antioxidant	Direct antioxidant
1	0.372	0.426
2	0.259	0.271
3	0.326	0.397
4	0.278	0.286
5	0.330	0.418
6	0.265	0.280
7	0.327	0.398
8	0.274	0.293
9	0.259	0.271
10	0.259	0.268
11	0.255	0.245
12	0.215	0.202
13	0.395	0.574
14	0.377	0.567
15	0.310	0.455

Table 3 – Antiradical activity of compounds 1-15

Compound	IC_{50}, mmol/ml	Compound	IC_{50}, mmol/ml	Compound	IC_{50}, mmol/ml
1	1.22±0.002	**6**	2.49±0.002	**11**	1.28±0.003
2	3.29±0.001	**7**	2.46±0.001	**12**	2.3±0.001
3	1.24±0.001	**8**	1.21±0.002	**13**	1.23±0.001
4	3.2±0.001	**9**	2.34±0.003	**14**	2.39±0.001
5	2.39±0.002	**10**	1.45±0.003	**15**	1.31±0.001
				Trolox	0.15±0.002

Table 4 – Chelating properties of compounds 1-15

Compound	IC_{50}, mmol/ml	Compound	IC_{50}, mmol/ml	Compound	IC_{50}, mmol/ml
1	2.9±0.161	**6**	3.03±0.183	**11**	3.05±0.069
2	2.11±0.224	**7**	3.15±0.089	**12**	3.36±0.128
3	2.47±0.235	**8**	3.55±0.26	**13**	3.64±0.185
4	2.86±0.13	**9**	2.73±0.168	**14**	3.16±0.13
5	3.58±0.202	**10**	3.26±0.098	**15**	4.98±0.097
				EDTA	1.52±0.014

Table 5 – IC_{50} values (mmol/ml) characterizing the ability of the studied compounds to affect Fe^{2+}-ascorbate-induced lipid peroxidation

Compound	IC_{50}, mmol/ml	Compound	IC_{50}, mmol/ml	Compound	IC_{50}, mmol/ml
1	9,88±0,197	**6**	7.16±0.145	**11**	9.6±0.058
2	8.73±0.183	**7**	7.76±0.137	**12**	7.34±0.158
3	9.84±0.07	**8**	7.32±0.199	**13**	7.03±0.091
4	8.27±0.047	**9**	9.8±0.125	**14**	8.19±0.122
5	8.8±0.091	**10**	9.78±0.101	**15**	9.42±0.073
				Trolox	2.3±0.003

Based on the data in Table 3, it can be assumed that compounds **1, 3, 11, 13** and **15** have the highest antiradical activity. Taking into account the peculiarity of the DPPH test, it can also be assumed that the studied substances have hydrogen-acceptor properties.

The data on the chelating properties of compounds **1-15** are presented in Table 4.

The most pronounced chelating properties in relation to Fe^{2+} are possessed by compounds **1-4**. This property is especially important in the processes of lipid peroxidation, induced by ions of divalent metals.

IC_{50} values (mmol/ml), characterizing the ability of the test compounds to affect Fe^{2+} -ascorbate-induced lipid peroxidation, are presented in Table 5.

Taking into account the high pathological role of Fe^{2+} – dependent oxidative processes in organs with a high metabolic activity, for example, the brain, the suppression of lipid peroxidation against the background of the studied substances, mainly **12** and **13**, can play a significant role in the survival of neurons and glial cells in case of brain damage of various etiologies.

An oxidative stress is an almost universal pathophysiological process that plays a role in the development and progression of a number of diseases, from atherosclerotic lesions of the vascular intima to a chronic obstructive pulmonary disease [28]. Modern concepts of the oxidative stress are based on two main postulates: damage to macromolecules is mediated by reactive oxygen species (ROS) or occurs because of the disruption of two-electron redox reactions of thiol chains. Herewith, the prevailing mechanism for the development of the oxidative stress is believed to be the oxidative modification of the cell structures under the influence of ROS in the presence of trace amounts of divalent metal ions, mainly Fe^{2+} known as lipid peroxidation (LPO). ROS are small molecules that have an unpaired electron and easily diffuse through the membrane lipid bilayer. ROS are very labile structures that spontaneously and without a significant energy expenditure, can undergo mutual transformations, which in most cases determines their pathogenetic significance in the development of diseases associated with an oxidative stress [29]. It has been established that ROS are more often of the intracellular origin and are generated in the processes of cellular respiration and metabolism. In the process of cellular respiration, during the sequential transfer of single electrons in the electron transport chain of mitochondria, intermediates with an odd number of electrons can “drop out” from the chain, forming ROS. At the same time, a large number of enzymes (xanthine oxidase, nitric oxide synthase, cytochrome, NADP-oxidase) produce ROS as a by-product of metabolism. It should be taken into consideration that ROS acquire cytotoxic properties only when the critical physiological concentration is exceeded or when antioxidant defense systems are dysfunctional [30].

A natural defense against ROS consists of ROS scavengers and antioxidant enzymes. Endogenous antioxidant defense enzymes are represented primarily by three superoxide dismutase isoenzymes, differing in the subcellular arrangement and catalyzing the dismutation of superoxide to oxygen and hydrogen peroxide. Catalase is also an important protective factor against ROS and degrades hydrogen peroxide to water. Thioredoxins, including several isoforms, make the reduction of oxidized proteins possible due to the thiol-disulfide exchange of cysteine. Glutathione peroxidases reduce lipid hydroperoxides to alcohols and hydrogen peroxide to water; Glutathione synthetase is responsible for the synthesis of the main cellular antioxidant glutathione and therefore plays an important role in the ROS detoxification. ROS scavengers are predominantly of the exogenous origin and are represented by active biomolecules such as tocopherol, ascorbic acid, carotenoids, uric acid, and polyphenols [31].

The main vector of the oxidative stress therapy is the use of substances with a direct antioxidant activity, both natural and synthetic. Thus, González et al., 2015 showed that propolis is an effective direct antioxidant [32]. Mai W, et al., 2020 showed that berberine, an isoquinoline’s alkaloid, significantly reduces the concentration of intracellular hydrogen peroxide due to the presence of radical-binding properties [33]. The most famous synthetic scavenger of ROS is N-acetylcysteine [34]. Direct antioxidant properties have also been established for some derivatives of chromone [35]. However, despite the presence of a fairly large number of compounds with the established antioxidant properties, expanding of the list of these substances, especially due to the targeted synthesis of effective antioxidants, is an urgent task of modern medicinal chemistry, as indicated by *Yang CS, et al., 2018.* [36]. In this regard, a study on the synthesis and on the antioxidant properties of (*E*)-3-(3-(4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one derivatives, was carried out. It showed that the analyzed compounds demonstrate a high level of a antiradical activity, which was confirmed by the data obtained during the DPPH test. It is also very important that the studied compounds have chelating properties with respect to Fe^{2+}, which can play a critical role in the termination of iron-induced lipid peroxidation and was confirmed in the course of this work. In addition, the toxicity analysis of related compounds suggests a low systemic toxicity of the analyzed compounds [37], which, together with a high antioxidant activity, makes a further study of these substances promising from the standpoint of drug development for a long-term systemic correction of the oxidative stress.

CONCLUSION

In this work, 15 derivatives of (*E*)-3-(3-(4-oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one have been synthesized and their structure has been confirmed by nuclear magnetic resonance, an elemental analysis , a

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mass spectrometry. According to *in silico* prediction data, the studied compounds are mainly characterized by a direct antioxidant activity. At the same time, the prediction data are generally consistent with the results of the *in vitro* studies of the antioxidant properties of the obtained compounds.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

Stanislav S. Shatokhin – search and analysis of literature, quantum-chemical calculations, synthesis and establishment of the obtained compounds structure, text of the manuscript writing; Vladislav A. Tuskaev – synthesis and establishment of the obtained compounds structure; Svetlana Ch. Gagieva – synthesis and establishment of the obtained compounds structure; Dmitry I. Pozdnyakov – conducting pharmacological studies and the obtained data interpretation; Eduard T. Oganesyan – search and analysis of literature, the obtained results interpretation, text of the manuscript writing.

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