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SYNTHESIS, STRUCTURE AND ANTI-RADICAL ACTIVITY OF 6-METHYL-4-OXO-4H-CHROMEN-3-ACYLHYDRAZONES

Abstract. This paper demonstrates data on synthesis of 6-methyl-4-oxo-4H-chromen-3-acylhydrazones with condensation of substituted 3-formylchromones and acylhydrazides. It is testifed to the fact that 4-oxo-4H-chromen-3-carboxaldehyde with hydrazides of isonicotinic and *o*- and *n*-hydroxybenzoic acids in isopropanol at boiling a reaction mixture for 2 h lead to the relevant chromen-containing hydrazones. Structures of the synthesized compounds were investigated with methods of ^{1}H and ^{13}C NMR spectroscopy, and data on two-dimensional (^{1}H-^{1}H) COSY and (^{1}H-^{13}C) HMQC spectra. Values of the chemical shifts, multiplicity and integrated intensity of ^{1}H and ^{13}C signals in one-dimensional NMR spectra were defined. Homo- and heteronuclear interactions confirming structure of the investigated compounds were determined with (^{1}H-^{1}H) COSY and (^{1}H-^{13}C) HMQC spectra. Data on an antiradical activity of synthesized 6-methyl-4-oxo-4H-chromen-3-acylhydrazones were showed. It was shown that the above compounds in the final concentration of 50 μM reduce the optical density of the initial solution of the DPPG radical by 27.5%, 25.2% and 8.8%, respectively, therefore, do not show pronounced antiradical activity under the conditions of this test system.

Key words: acylhydrazides, condensation, 4-oxo-4H-chromen-3-carboxaldehyde, ^{1}H and ^{13}C NMR spectra, two-dimensional (^{1}H-^{1}H) COSY and (^{1}H-^{13}C) HMQC spectra, antiradical activity.

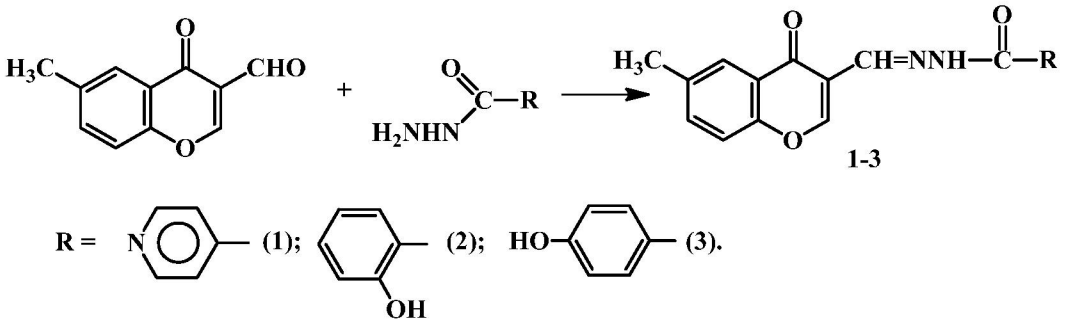
Introduction

Chromone (4H-1-benzopyran-4-one) is a parent of the class of oxygen-containing heterocyclic compounds – flavonoids widespread in flora. The flavonoids and chromone derivatives isolated from plants and fungi possess various types of the biological activity such as antitumoral, antifungal, antioxidant, P-vitamin, etc. [1-5]. Chromone cyclic system takes an important position among oxygen-containing heterocyclic systems. Some of the synthetic chromone products show a wide range of the biological activities such as antifungal, anticancer, antimicrobial and inhibit human immunodeficiency virus and mushroom tyrosinase virus [6-8]. It is natural that the chromen-containing derivatives are the valuable intermediate products in synthesis of new biologically active compounds including the pharmaceutical products. It should be noted that a chromone system is a part of flavonoids (quercetin, dihydroquercetin, etc.) belonging to group of antioxidant substances [1]. By reason of low toxicity for mammals and essential solubility, a chromone fragment is one of the exclusive structural blocks to develop the pharmacological important substances [9-20].

Experimental part

Referring to a large scientific interest to flavonoid compounds and their prospects in the applied relation and search the new antioxidant products, the synthesis of 6-methyl-4-oxo-4H-chromen-3-acylhydrazones **(1-3)** was performed by correlation of 6-methyl-4-oxo-4H-chromen-3- carboxaldehyde with hydrazides of isonicotinic and *o*- and *p*-hydroxybenzoic acids. It is demonstrated that at boiling in

isopropanol for 2 h the reaction proceeds smoothly and leads to the corresponding chromen-containing hydrazones with high yields.

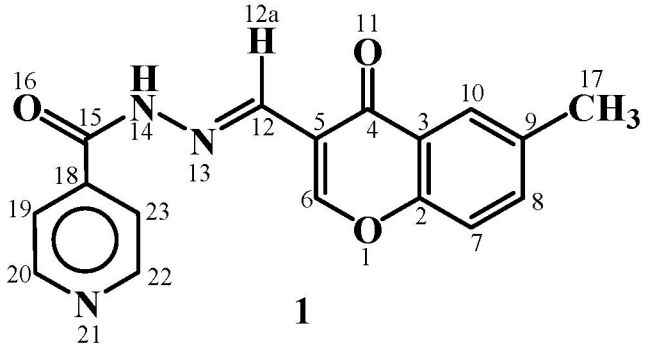


Reaction products of **1-3** are the light yellow powders soluble in many organic solvents, and a yield of compounds makes 63-98%.

Results and discussion

The structure of compounds **1-3** was confirmed with data of ^{1}H and ^{13}C NMR spectroscopy, and two-dimensional (^{1}H-^{1}H) COSY and (^{1}H-^{13}C) HMQC spectra.

NMR spectrum of compound **1** was studied in detail. ^{1}H NMR spectrum of compound **1** is characterized with strong pole area at 2:41 ppm of a singlet signal with intensity 3H belonging to protons H^{17} of a methyl substituting group. A multiplet signal with intensity 6H belonging to two symmetric protons $H^{8, 10}$ of a methyl substituting group of an aromatic system, to proton H^{7} of this aromatic nucleus, two symmetric protons $H^{19, 23}$ of a pyridine cycle, and to proton H^{12} at sp^{2}-hybridized carbon atom were observed in aromatic area of a spectrum at 7.61-7.88 ppm. The unscreened protons $H^{20, 22}$ of a pyridine cycle and protons H^{6} close by oxygen atom were shown as a multiplet at 8-48-9.80 ppm with integrated intensity 3H. Protons H^{14} of a hydrazine fragment of a molecule were observed as a broadened singlet with integrated intensity 1H in the lowest pole area of spectrum at 142.11 ppm.



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In ^{13}C NMR spectrum of the compound **1** the methyl carbon signals were found at 20.97(C^{17}) ppm. Carbon signals of an aromatic nucleus were shown at 118.37 (C^{3}), 119.02 (C^{7}), 124.93 (C^{10}), 136.25 (C^{9}), 136.34 (C^{8}) and 154.56 (C^{2}) ppm. Carbon atom C^{5} condensed with an aromatic nucleus of the heterocyclic oxygen-containing cycle not connected with oxygen atoms was observed at 123.48 ppm. Because of the shift of electronic density on carbon atoms as a result of correlation with electronegative oxygen the signals of C^{6} and C^{4} atoms passed into a low pole area of spectrum and were at 155.18 and 175.43 ppm respectively. Equivalent couple of atoms of pyridine fragment $C^{19,23}$ with low shift of the electronic density on carbon nucleus was found at 122.02 ppm. Whereas other couple of pyridine carbons $C^{22, 22}$ with low screening of carbon nucleus was observed in lowest pole area at 150.26 ppm. Carbon atom C^{18} of pyridine nucleus resonated at 140.67 ppm. The signal with a chemical shift at 142.32 ppm belongs to a carbon atom connected with double bond with nitrogen atom. In low pole area at 161.86 ppm the signal of carbonyl atom C^{15} was observed.

The structure of compound **1** was confirmed with methods of two-dimensional NMR spectroscopy, (^{1}H-^{1}H) COSY and (^{1}H-^{13}C) HMQC to establish the homo- and heteronuclear spin-spin interactions (Fig. 1 and 2).

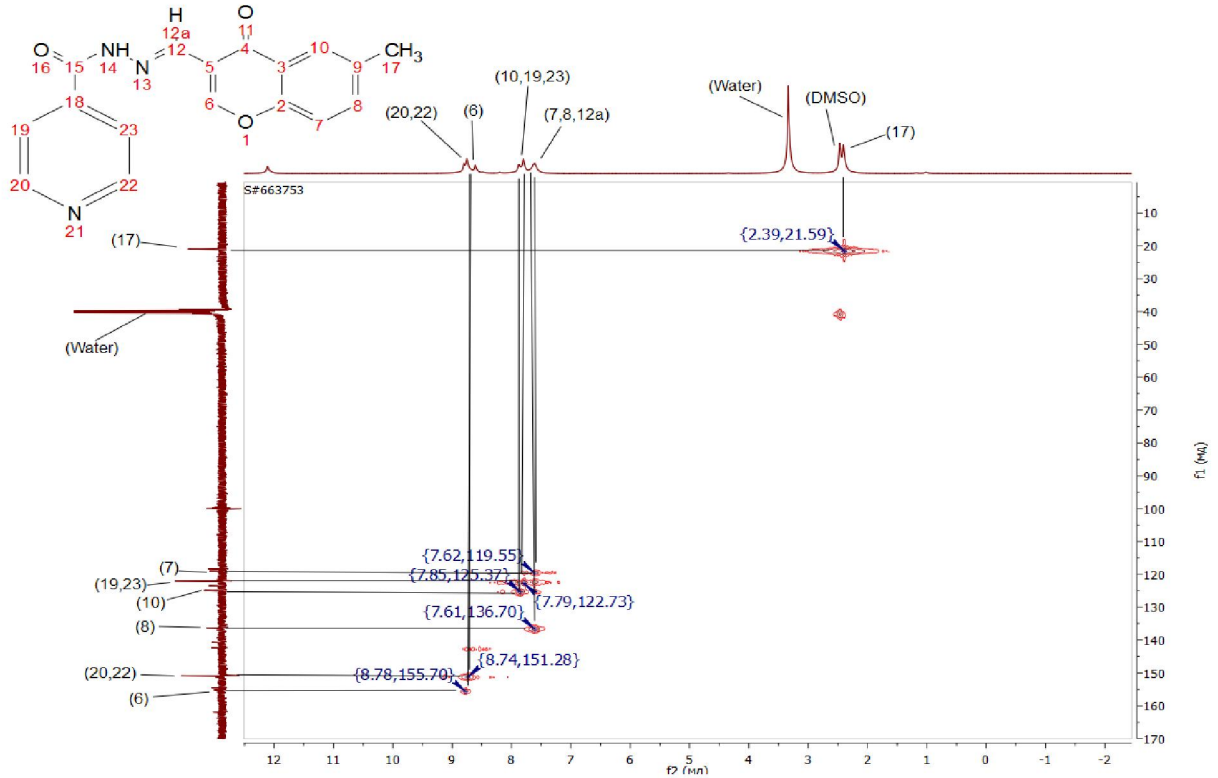

Figure 1 – Recording of HMQC spectrum of compound **1**

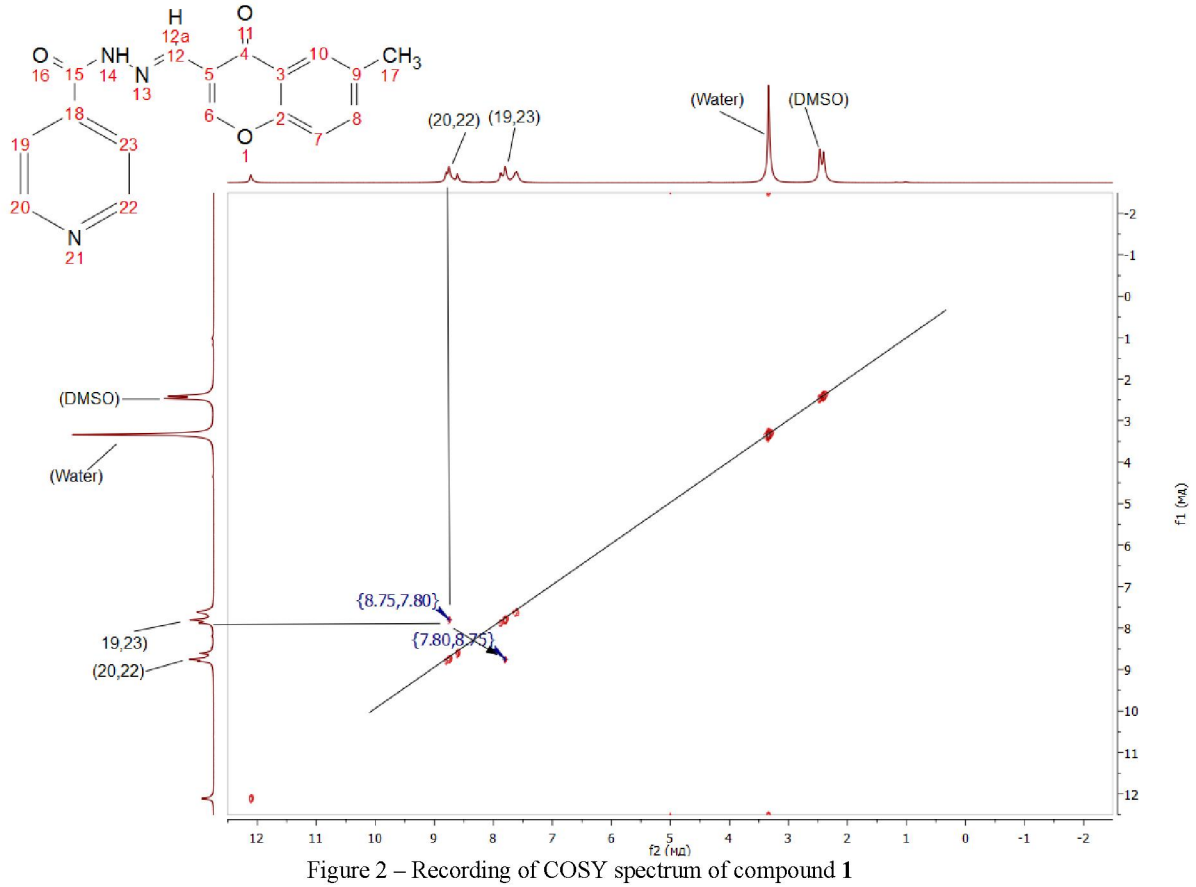

Figure 2 – Recording of COSY spectrum of compound **1**

The observed correlations in a molecule are presented on the scheme. Spectra of ^{1}H-^{1}H COSY of compound demonstrate the spin-spin correlations through three proton bonds of next methine groups $H^{19, 23}$-$H^{20, 22}$ of a pyridine ring with cross-peaks at 8.75, 7.80 and 7.78, 8.75.

The heteronuclear interactions of protons with carbon atoms through one bond were determined with ^{1}H-^{13}C HMQC spectroscopy for all couples of compounds: H^{17}-C^{17} (2.39, 21.59), H^{7}-C^{7} (7.62, 19.55), H^{8}-C^{8} (7.61, 136.70), H^{12}-C^{12} (7.62, 142.30), $H^{19, 23}$-$C^{19, 23}$ (7.79, 122.73), H^{10}-C^{10} (7.85, 125.37), $H^{20, 22}$-$C^{20, 22}$ (8.74, 151.28) and H^{6}-C^{6} (8.78, 155.70).

One - and two-dimensional NMR spectra of molecule **2** – isomer of compound **3** in size of the chemical shifts ^{1}H and ^{13}C NMR have big analogy. However change of a hydroxyl group position in an aromatic ring from the symmetric position in the asymmetrical corresponding to compound **2** slightly changed the size of the electronic density on the studied nucleus ^{1}H. As a result of it some signals of NMR protons, earlier presented as doublet, passed into areas of other spectra and were as multiplets. So, ^{1}H NMR spectrum of compound **2**, δ, ppm: 2.34 s (3H, H^{17}), 6.74-7.92 m (8H, $H^{7,8,10,12,20-23}$), 8.48-8.80 m (3H, $H^{6,20,22}$), 8.58 s (1H, H^{6}), 11.84 s (1H, NH). ^{13}C NMR spectra of the studied isomers were very identical. This result was predicted. So, the studied molecules have two aromatic cycles which signals of protons are very similar and thus there is a high probability of their superposition at each other. The general integrated intensity of protons of the studied isomers did not change.

Possibility to identify isomers on position of a hydroxyl group in an aromatic nucleus was shown with a homonuclear correlation of COSY (^{1}H-^{1}H) NMR spectroscopy. The spin-spin correlations through three proton bonds of next methine groups H^{20}-H^{21} (7.39, 6.90; 6.91, 7.37) and H^{22}-H^{23} (7.83, 6.87; 6.88, 7.81) were observed in isomer **2** in an aromatic fragment (Fig. 3). Such homonuclear correlation of NMR spectroscopy corresponds to isomer compound **2**.

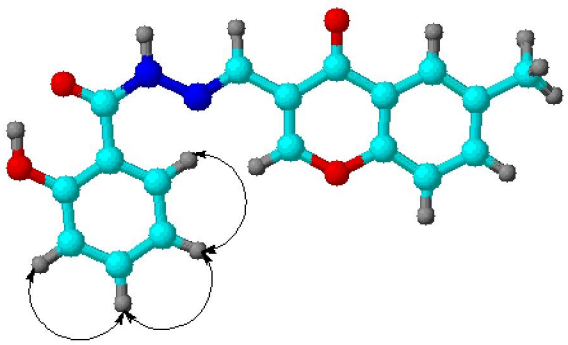

Figure 3 – Correlation scheme in COSY spectra of compound **2**

In order to investigate the pharmacological activity of the synthesized compounds **1-3** the screening of antiradical activity based on interaction of compounds with stable chromogen-radical 2,2- diphenyl-1-picrylhydrazil (DPPH) was performed. The methanol solution DPPH (100 μM) was used to evaluate primary the antiradical activity of the studied samples in test with the DPPH –radical. In order to select substances with the antiradical activity, 2 ml of the DPPH methanol solution (100 μM) was mixed with 20 μL of the studied object dissolved in DMSO in concentration 5 mM. Thus, the final concentration of the studied substance in reactionary mixture made 50 μM. The reduction in optical density at 515 nm was measured in 10 min after addition of the studied substance solution to the DPPH radical solution. The substances, which are able to reduce optical density more 30%, were tested for interaction with the DPPH radical in the final concentration of the studied substances (100, 75, 50, 25, 20, 10 and 5 μM). Then concentration of the studied substance reducing an optical density by 50% - IC_{50}(DPPH) was determined. In control 20μL solvent (DMSO) was added in 100 μM DPPH solution. Research results of biological activity of compounds **1-3** are presented in the table.

This table demonstrates that compounds **1, 2** and **3** in final concentration 50 μM reduce the optical density of the initial DPPH radical solution by 27.5%, 25.2% and 8.8%, respectively. Thus they do not show the expressed antiradical activity in the conditions of this test system.

Table – The optical density values of the DPPH radical solution (100 μM) after 10 min incubation with the studied substance in final concentration 50 μM

Comp.No.	Name of compound	Optical density	Value of decrease in optical density of initial solution DPPH-radical, in % from control
1	N'-((6-methyl -4-oxo-4H- chromen-3-il) methylene) isonicotinohydrazide	0.814	27.5
2	2-hydroxy-N'-((6-methyl-4-oxo-4H-chromen-3-il) methylene)benzohydrazide	0.839	25.2
3	4- hydroxy-N'-((6- methyl-4-oxo-4H- chromen-3-il) methylene) benzohydrazide	1.023	8.8
4	Control (DPPH solution without the studied substance)	1.122	-

Experimental part

^{1}H and ^{13}C NMR spectra were recorded on JNM-ECA Jeol 400 spectrometer (frequency 399.78 and 100.53 MHz respectively) with using of DMSO-d_6 solvent. The chemical shifts were measured concerning signals of residual protons or carbon atoms of dimethyl sulfoxide-d_6. The control of the reaction and purity of the received compounds was performed by Thin Layer Chromatography method on Silufol UV-254 plates in isopropyl alcohol-benzene-ammonia system (10:5:2). Plates were processed with iodine vapour.

N'-((6-Methyl-4-oxo-4H-chromen-3-il)methylene) isonicotinohydrazide (1). To 0.5g (0.0027 mol) of 6-methyl-4-oxo-4H-chromen-3-carboxaldehyde in 10 ml of ethanol at stirring was added 0.36 g (0.0027 mol) of hydrazide of isonicotinic acid in 5 ml of ethanol (hot). The reactionary mixture was boiled for 1 h. The yellow residue dropped out, was cooled, filtered and recrystallized from ethanol. The yield of the product was 0.8 g (96% from theor.), m.p. 210-211°C. ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, H^{17}), 7.61-7.88 m (6H, $H^{7,8,10,12,19,23}$), 8.48-8.80 m (3H, $H^{6,20,22}$), 12.11 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.97 (C^{17}), 118.37 (C^{3}), 119.02 (C^{7}), 122.02 ($C^{19,23}$), 124.93 (C^{10}), 136.25 (C^{9}), 140.67 (C^{18}), 142.32 (C^{12}), 150.86 ($C^{20,22}$), 155.18 (C^{6}), 161.86 (C^{15}), 175.43 (C^{4}).

2-hydroxy-N'-((6-methyl-4-oxo-4H-chromen-3-il)methylene) benzohydrazide (2) was received similarly to compound **1.** The yield of the product **2** was 77%, m.p. 206-207°C. ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, H^{17}), 6.74-7.92 m (8H, $H^{7,8,10,12,20-23}$), 8.48-8.80 m (3H, $H^{6,20,22}$), 8.58 s (1H, H^{6}), 11.84 s (1H, NH).

4-hydroxy-N'-((6-methyl-4-oxo-4H-chromen-3-il)methylene) benzohydrazide (3) was received similarly to compound **1.** The yield of the product **3** was 83%, m.p. >350°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.39 s (3H, H^{17}), 6.80 d (2H, $H^{20,22}$, ^{3}J 5.5), 7.59 d (1H, $H^{7,8}$, ^{3}J 10.4 Hz), 7.77 d (2H, $H^{19,23}$, ^{3}J 6.0 Hz), 7.86 s (1H, H^{10}), 8.55 s (1H, H^{12}), 8.72 s (1H. H^{6}), 10.10 s (1H, OH), 11.69 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 21.00 (C^{17}), 115.54 ($C^{20,22}$), 118.83 (C^{3}), 119.04 (C^{7}), 123.54 (C^{5}), 124.12 (C^{18}), 124.96 (C^{10}), 130.23 ($C^{19,23}$), 136.21 (C^{9}), 136.25 (C^{8}), 136.94 (C^{12}), 154.64 (C^{6}), 161.26 ($C^{2,21}$), 163.06 (C^{15}) and 175.56 (C^{4}).

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6-МЕТИЛ-4-ОКСО-4Н-ХРОМЕН-3-АЦИЛГИДРАЗОНДАРДЫҢ СИНТЕЗІ, ҚҰРЫЛЫСЫ МЕН РАДИКАЛДАРҒА ҚАРСЫ БЕЛСЕНДІЛІГІ

Аннотация. Жұмыста 6-метил-4-оксо-4Н-хромен-3-ацилгидразондарды функционалды ауысқан 3-формилхромендер мен ацилгидразидтердің конденсациясы арқылы синтездеу нәтижелері келтірілген. 6-метил-4-оксо-4Н-хромен-3-карбоксальдегидінің изоникотин және *о*- мен *п*-гидроксибензой гидразидтерімен

реакциялық қоспасын изопропанол еріткішінде 2 сағат бойы қайнату олардың сәйкес хроменқұрамды гидразондарының түзілуіне әкелетіні көрсетілген. Синтезделініп алынған заттардың құрылыстары ЯМР ^{1}H пен ^{13}C спектроскопия, сондай-ақ COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C)-дың екі өлшемді спектрлерімен зерттелген. ЯМР бірөлшемді спектрлеріндегі ^{1}H және ^{13}C атомдарының химиялық жылжымаларының, мультиплеттілік және интегралды сигналдарының мәндері анықталған. COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C) форматындағы спектрлер бойынша зерттелуші заттардың құрылысын дәлелдейтін гомо- мен гетероядролық әрекеттесулер анықталған. Синтезделініп алынған 6-метил-4-оксо-4Н-хромен-3-ацилгидразондардың радикалдарға қарсы белсенділіктері туралы деректер келтірілген. Осы жоғарыда айтылған заттар 50 μМ ең төмен концентрациясында бастапқы ДФПГ-радикалының ерітіндісінің оптикалық тығыздығын 27,5%, 25,2% және 8,8%-ға төмендетеді, сол себепті, олар осы тестік жүйе жағдайында айқын радикалдарға қарсы белсенділіктерді көрсетпейді.

Түйін сөздер: ацилгидразидтер, конденсация, 4-оксо-4Н-хромен-3-карбоксальдегид, ЯМР ^{1}Н- пен ^{13}С-спектрлер, екіөлшемді COSY (^{1}H-^{1}H) мен HMQC (^{1}H-^{13}C) спектрлері, радикалдарға қарсы белсенділіктер.

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СИНТЕЗ, СТРОЕНИЕ И АНТИРАДИКАЛЬНАЯ АКТИВНОСТЬ 6-МЕТИЛ-4-ОКСО-4Н-ХРОМЕН-3-АЦИЛГИДРАЗОНОВ

Аннотация. В работе приведены данные по синтезу 6-метил-4-оксо-4Н-хромен-3-ацилгидразонов конденсацией функционально замещенных 3-формилхромонов и ацилгидразидов. Показано, что реакции 4-оксо-4Н-хромен-3-карбоксальдегида с гидразидами изоникотиновой и *о*- и *п*-гидроксибензойной кислотами в изопропаноле при кипячении реакционной смеси в течение 2 ч приводит к образованию соответствующих хроменсодержащих гидразонов. Исследованы строения синтезированных соединений методами ЯМР ^{1}Н и ^{13}С спектроскопии, а также данными двумерных спектров COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C). Определены значения химических сдвигов, мультиплетность и интегральная интенсивность сигналов ^{1}Н и ^{13}С в одномерных спектрах ЯМР. С помощью спектров в форматах COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) установлены гомо- и гетероядерные взаимодействия, подтверждающие структуру исследуемых соединений. Приведены данные по антирадикальной активности синтезированных 6-метил-4-оксо-4Н-хромен-3-ацилгидразонов. Показано, что вышеуказанные соединения в финальной концентрации 50 μМ снижают оптическую плотность исходного раствора ДФПГ-радикала на 27,5%, 25,2% и 8,8%, соответственно, следовательно, не проявляют выраженной антирадикальной активности в условиях данной тест-системы.

Ключевые слова: ацилгидразиды, конденсация, 4-оксо-4Н-хромен-3-карбоксальдегид, ЯМР ^{1}Н- и ^{13}С-спектры, двумерные спектры COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C), антирадикальная активность.

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