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Synthesis and Antibacterial Activity of Hydrazones of Isonicotinic and Salicylic Acids Based on Acetyl Derivatives of Coumarin and Benzo[g][1,3,5]Oxadiazocine

In recent decades, the efforts of many researchers in the sphere of organic chemistry, physics and pharmacology have been focused on the search for new agents with pronounced antibacterial and especially antifungal activity. This is due to the widespread increase in the resistance of many bacterial strains and fungi to antibiotics and antifungal drugs available in medical practice. In this regard, the number of works related to the synthesis of new potential antibiotics from the most diverse class of organic derivatives, which either include known pharmacophore groups or represent a new structural class of compounds with unknown and unexplored activity, is increasing in the scientific literature. In this work, new previously undescribed hydrazones derivatives were obtained on the basis of physiologically active isonicotinic and salicylic acid hydroxides and laboratory-available acetyl-substituted heterocycles, namely 3-acetyl-2H-chromen-2-one 3,2-acetyl-3H-benzo[f]chromen-3-one 4 and 2,6-methanobenzo[g][1,3,5]oxadiazocine 5. The obtained hydrazones structure is explicitly proved by IR and ^{1}H, ^{13}C NMR spectroscopy data. The synthesized six new hydrazones underwent biological screening for antibacterial and antifungal activity on strains of microorganisms, namely gram-positive bacterium Staphylococcus aureus 209P, gram-negative bacterium Pectobacterium carotovorum VKM-B1247, and yeast-like fungus Candida albicans ATCC 10231. Screening revealed three compounds with antimicrobial activity and one promising compound — (E)-2-hydroxy-N'-(1-(2-oxochroman-3-yl)ethylidene)benzohydrazide 9, which also exhibits antifungal activity along with antimicrobial activity.

Keywords: hydrazides, isoniazid, salicylic acid hydrazide, coumarins, 3-acetyl-2H-chromen-2-one, 2-acetyl-3H-benzo[f]chromen-3-one, 2,6-methanobenzo[g][1,3,5]oxadiazocine, hydrazones, antimicrobial activity.

Introduction

Over the years the attention of many researchers in the field of medicinal chemistry has been focused on the search and development of new antibacterial drugs. Due to the widespread uncontrolled use of various antibiotics in recent decades, there has been a significant increase in antimicrobial resistance against many viruses, bacteria and fungi [1–3].

According to the World Health Organization (WHO) antimicrobial resistance is among the ten major public health problems that are progressing worldwide [4, 5]. Antibiotics, antiviral, antifungal and antiparasitic agents are combined into one class of compounds called antimicrobials. The devastating consequences related to resistance are much more global than it seems. Threats to human health caused by both gram-negative and gram-positive resistant strains of bacteria force scientists to investigate new classes of compounds exhibiting antibacterial biological effects and new approaches to solving the antimicrobial resistance problem [6, 7].

It is known that hydrazides and their various derivatives, including hydrazones, have a wide range of biological activity [8–12]. Anti-tuberculosis drugs such as isoniazid (isonicotinic acid hydrazide) and ftivazid (vanillin isonicotinoyl hydrazone) are well known among this class of compounds [13]. Moreover hydrazones are worth noticing due to the presence of antibacterial and analgesic properties [14–16].

Isonicotinic acid hydrazide (tubazid, isoniazid) is especially noteworthy among them, which despite the presence of a huge number of new drugs used in the tuberculosis treatment practice [17], currently holds a leading place in the treatment of various forms of tuberculosis as a new dosage form ("Isonicotinoyl Hydrazine iron sulfate" or the trade name "*Fenazid*"), i.e. its complex with iron (II) sulfate [18]. Modification of

isoniazid in particular its hydrazone with vanillin ("*Ftivazid*") (Fig. 1) led not only to a decrease in toxicity, but also to a better individual tolerance of the drug [19].

Salicylic acid hydrazide should also be noted among other hydrazides. Its derivatives such as *Diflunisal* [20] and *Salsalate* [21, 22] are used as antipyretic and anti-inflammatory agents [23]. In the case of *Salsalate* scientists investigated the possibility of its application in the treatment of diabetes [24, 25].

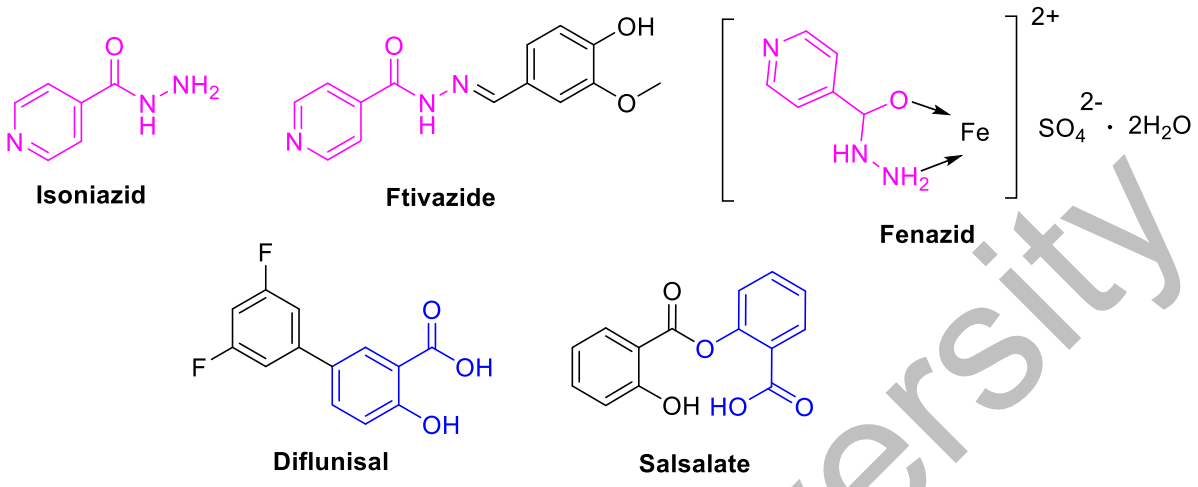


Figure 1. Derivatives of isonicotinic and salicylic acid used as pharmaceuticals

Thus, we took well-known pharmacophores, namely hydrazides of isonicotinic and salicylic acids as the chemical modification basis in order to obtain new hydrazones with potential antimicrobial activity.

Experimental

Materials and Methods

FTIR spectra were obtained with an Agilent Cary 630 spectrophotometer in a thin sample layer on a crystal attachment. ^{1}H and ^{13}C NMR spectra were recorded on a JNN-ECA Jeol 400 (400 and 100 MHz, respectively) and Magritek spinsolve 80 carbon ultra (81 and 20 MHz, respectively) instruments using DMSO-d_6, the internal standard was residual solvent signals (2.49 and 39.9 ppm for ^{1}H and ^{13}C nuclei in DMSO-d_6).

The reactions progress and the products purity were monitored by TLC on Sorbfil plates and visualized using iodine vapor or UV light.

Synthetic procedures

(*E*)-N'-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)isonicotinohydrazide (8). The solution of **3** (1.88 g, 10 mmol) and hydrazide **6** (1.37 g, 10 mmol) in 2-PrOH was heated at reflux for 10 h. The resulting yellow precipitate was filtered off. The yield was 60 %. Recrystallization from 2-PrOH gave yellow crystals, mp 237–240 °C.

^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.33 s (3 H, CH_3), 7.35–7.44 m (3 H, H-6, H-7, H-8), 7.63 d (1H, *J* = 7.1, H-5), 7.75 d (2H, *J* = 2.2, H-3', H-5', Py), 7.82 s (1H, H-4), 8.73 d (2H, *J* = 2.7, H-2', H-6', Py), 11.02 br. s (1H, NH).

(*E*)-2-hydroxy-N'-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)benzohydrazide (9). The solution of **3** (1.50 g, 8.0 mmol) and hydrazide **7** (1.22 g, 8.0 mmol) in 2-PrOH was heated at reflux for 10 h. The resulting orange precipitate was filtered off. The yield was 78 %. Recrystallization from 2-PrOH gave orange crystals, mp 230–233 °C.

^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.28 s (3 H, CH_3), 6.98 t (1 H, *J* = 7.3 Hz, H-5'), 7.03 d (1 H, *J* = 7.8 Hz, H-3'), 7.38–7.46 m (3H, H6, H-8, H-4'), 7.66 t (1H, *J* = 8.0 Hz, H-7), 7.89 d (1H, *J* = 7.8 Hz, H-5), 7.98 d (1H, *J* = 7.3 Hz, H-6'), 8.27 s (1H, H-4), 11.38 br. s (1H, NH), 11.74 br. s (1H, OH).

(*E*)-2-hydroxy-N'-(1-(2-oxo-3,4-dihydro-2*H*-benzo[h]chromen-3-yl)ethylidene)isonicotinohydrazide (10). The solution of **4** (0.48 g, 2 mmol) and hydrazide **6** (0.27 g, 2 mmol) in 2-PrOH was heated at reflux for 10 h. The resulting dark orange precipitate was filtered off. The yield was 65 %. Recrystallization from 2-PrOH gave orange crystals, mp 224–225 °C.

^{1}H NMR (80 MHz, DMSO-d_6), δ, ppm: 2.40 s (3H, CH_3), 7.47 br. s (1H, H-5), 7.58 br. s (1H, H-6), 7.67 br. s (1H, H-9), 7.75 br. t (1H, *J* = 7.5, H-8), 7.82 br. s (2H, H-3', H-5', Py), 8.21 d (1H, *J* = 8.7 Hz, H-7), 8.56 d (1H, *J* = 8.2, H-10), 8.72 br. s (2H, H-2', H-6', Py), 8.93 s (1 H, H-1), 11.11 br. s (1H, NH).

(*E*)-2-hydroxy-N'-(1-(2-oxo-3,4-dihydro-2*H*-benzo[h]chromen-3-yl)ethylidene)benzohydrazide (11). The solution of **4** (0.48 g, 2 mmol) and hydrazide **7** (0.30 g, 2 mmol) in 2-PrOH was heated at reflux for 10 h. The resulting orange precipitate was filtered off. The yield was 80 %. Recrystallization from 2-PrOH gave orange crystals, mp 266–267 °C.

^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.34 s (3H, CH_3), 6.99 t (1H, *J* = 7.1 Hz, H-5'), 7.04 d (1 H, *J* = 8.2 Hz, H-3'), 7.43 t (1H, *J* = 7.1 Hz, H-4'), 7.57 d (1H, *J* = 7.8, H-5), 7.64 d (1H, *J* = 7.8, H-6), 7.73 t (1H, *J* = 7.8, H-9), 7.75 t (1H, *J* = 7.8, H-8), 8.01 d (1H, *J* = 7.3 Hz, H-6'), 8.21 d (1H, *J* = 8.7 Hz, H-7), 8.57 d (1H, *J* = 8.2 Hz, H-10), 8.91 s (1 H, H-1), 11.44 br. s (1H, NH), 11.76 br. s (1H, OH).

(*E*)-N'-[(1)-1-(2-methyl-4-thioxo-3,4,5,6-tetrahydro-2*H*-2,6-methanobenzo[g][1,3,5]oxadiazocin-11-yl)ethylidene]isonicotinohydrazide (12). The solution of 5 (0.48 g, 2 mmol) and hydrazide 6 (0.30 g, 2 mmol) in 2-PrOH was heated at reflux for 24 h. The resulting white precipitate was filtered off and washed with water. The yield was 82 %. Recrystallization from 2-PrOH with 1,4-dioxane gave white crystals, mp 248–250 °C.

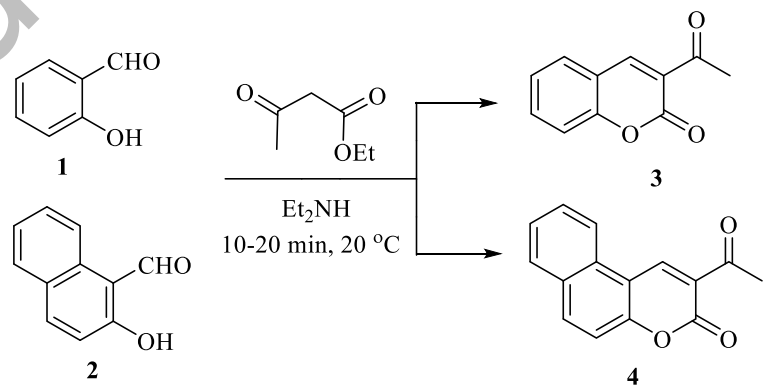
^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.83 s (3H, CH_3), 2.05 s (3H, N=C–CH_3), 3.17 br. s (1H, H-11), 4.49 br. s (1 H, H-6), 6.83 d (1H, *J* = 8.2, H-10), 6.93 t (1H, *J* = 7.3, H-9), 7.17–7.24 m (2H, H-7, H-8), 7.72 d (2H, *J* = 2.2, H-3', H-5', Py), 8.73 br. s (2H, H-2', H-6', Py), 9.03 br. s (1H, 3-NH), 9.10 br. d (1H, *J* = 10.5 Hz, 5-NH), 10.97 br. s (1H, NH).

(*E*)-2-hydroxy-N'-[(1)-1-(2-methyl-4-thioxo-3,4,5,6-tetrahydro-2*H*-2,6-methanobenzo[g][1,3,5]oxadiazocin-11-yl)ethylidene]benzohydrazide (13). The solution of **5** (0.26 g, 1 mmol) and hydrazide **7** (0.20 g, 1 mmol) in 2-PrOH was heated at reflux for 24 h. The resulting white precipitate was filtered off and washed with water. The yield was 73 %. Recrystallization from 2-PrOH gave white crystals, mp 230-232 °C.

^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.80 s (3H, CH_3), 2.02 s (3H, N=C-CH_3), 3.16 br. s (1H, H-11), 4.48 d (1 H, *J* = 3.2 Hz, H-6), 6.84 d (1H, *J* = 8.2, H-10), 6.91-6.97 m (2H, H-9, H-5'), 7.00 d (1 H, *J* = 8.2 Hz, H-3'), 7.18–7.23 m (2H, H-7, H-8), 7.40 t (1H, *J* = 7.3 Hz, H-4'), 7.94 d (1H, *J* = 7.3 Hz, H-6'), 9.08 br. d (1H, *J* = 4.6 Hz, 5-NH), 9.14 br. s (1H, 3-NH), 11.14 br. s (1H, NH), 11.76 br.s (1H, OH).

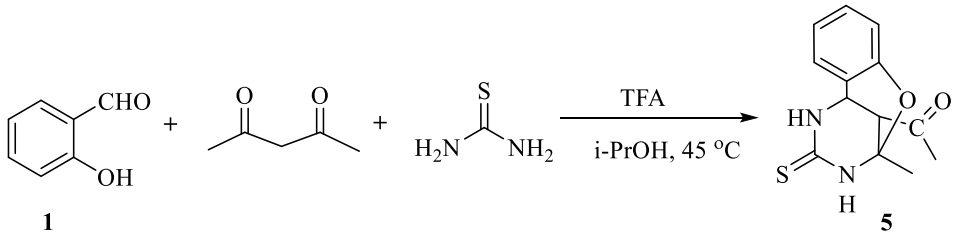
Results and Discussion

Based on the initial aim and the literature review data, it was of great interest to combine several pharmacophore groups in one molecule, namely isonicotinic and salicylic acid hydrazide and laboratory available acetyl-substituted heterocycles such as acetyl derivatives of coumarin **3, 4** (Scheme 1) and 2,6-methanobenzo[g][1,3,5]oxadiazocine **5** (Scheme 2). The choice was also based on the absence of such derivatives in chemical databases. The Perkin reaction is the main method of synthesis of coumarins and their derivatives, in which 2-hydroxyaromatic aldehydes are used as initial compounds. 3-Acetyl-2*H*-chromen-2-one **3** and 2-acetyl-3*H*-benzo[f]chromen-3-one **4** [26] were obtained with high yields by the reaction of acetoacetic ester with the corresponding salicylic and 2-hydroxynaphthaldehyde and diethylamine as a catalyst (Scheme 1).



Scheme 1

The obtained acetylcoumarins **3, 4** were identified by comparing their literature data on melting points and the ^{1}H NMR spectra. The Biginelli reaction product, namely 2,6-methanobenzo[g][1,3,5]oxadiazocine **5** was synthesized according to the method specified in the article [27] (Scheme 2).



1 **5**

Scheme 2

The structure of compound **5** was also identified by a comparative analysis of the melting point and ^{1}H NMR spectrum [27].

Listed acetyl-substituted heterocycles were chosen because many natural coumarins are biologically active compounds (Fig. 2) with different effects on the organism, namely hepatoprotective, diuretic, analgesic, anti-microbial (*Scoparone*) [28]; antitumor, cardioprotective, neuroprotective (*Isofraxidin*) [29, 30], antidepressant [31], hepatoprotective [32] and antioxidant [33] (*Scopoletin*) ones; and also show photosensitizing and antitumor activity [34–37].

Many researchers refer derivatives of 2,6-methanobenzo[g][1,3,5]oxadiazocine to the analogues of the anti-cancer drug *monastrol*, which has the structure of pyrimidinethione [38] (Fig. 2), but with an oxygen linkage. *Monastrol* has revealed a completely new mechanism of anticancer effects due to its specific effect on mitosis, which makes it a unique precursor in the synthesis of a wide range of biologically active compounds, in particular, pharmaceuticals.

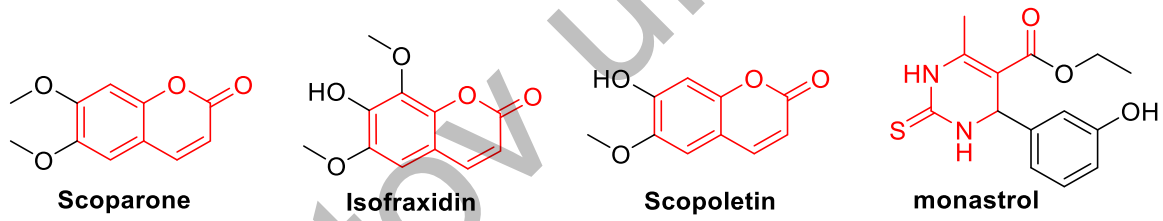


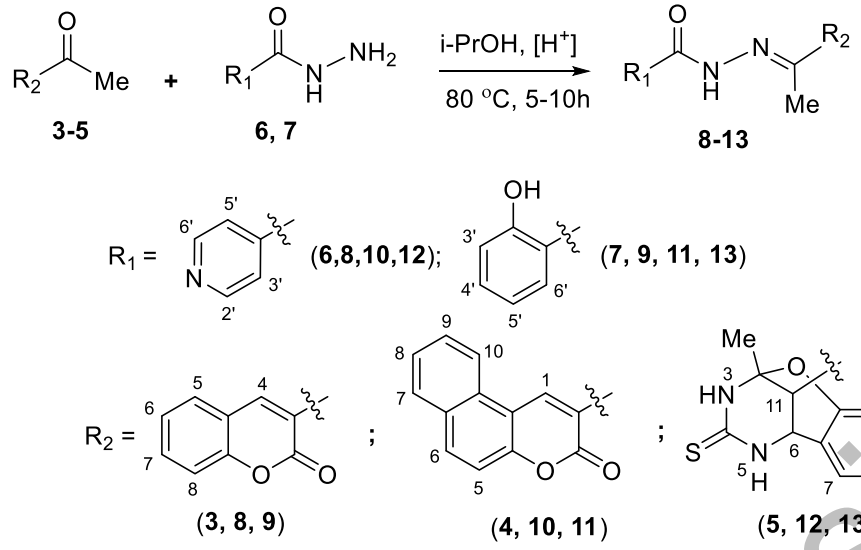
Figure 2. Chemical structure of biologically active derivatives of coumarin and monastrol

The incorporation of another active pharmacophore group into the structure of a physiologically active substance is a widely used method for obtaining new biologically active compounds in medicinal chemistry. The combination of two or more pharmacophore groups in one molecule increases the likelihood of the synthesized substance showing not only high biological activity, but also the presence of a new therapeutic potential.

Therefore, the introduction of pharmacophore groups into the structure of biologically active hydrazones can result in potentially increased biological activity. And in turn, the synthesis of coumarin derivatives is also an urgent task for the researchers in terms of finding new compounds with a diverse effect on the human organism.

The synthesis of hydrazones was carried out by boiling the initial hydrazides **6, 7** with acetyl derivatives **3-5** in 2-PrOH in the presence of catalytic amounts of formic acid (Scheme 3).

The obtained hydrazones **8-13** are yellowish crystals that are difficult to dissolve in common organic solvents. The structure of compounds **8-13** was confirmed by IR and NMR spectroscopy data. Thus, in the ^{1}H NMR spectrum of compound **9**, methyl group protons were registered by a singlet at 2.28 ppm. There were also singlets of the OH-group proton at 11.74 ppm and NH-group proton at 11.38 ppm.



Scheme 3

Biological studies

All the biological tests were carried out in the Laboratory of Antimicrobial Resistance, Institute of Environmental and Agricultural Biology (X-BIO) of University of Tyumen.

Taking into account the enlisted data in the literature review on the potential antibacterial activity of hydrazone derivatives, we carried out some biological studies of the compounds **8–13**. The antimicrobial activity of the synthesized samples was evaluated by diffusion into agar using the following strains of microorganisms: gram-positive bacterium — *Staphylococcus aureus* 209P, gram-negative bacterium — *Pectobacterium carotovorum* VKM-B1247 — (antibacterial activity) and yeast-like fungus — *Candida albicans* ATCC 10231 — (antifungal activity).

Microorganisms *Staphylococcus aureus* 209 P and *Pectobacterium carotovorum* VKM-B 1247 were cultivated on a liquid nutrient solution Luria–Bertani (LB) containing: trypton — 10 g/l ("Diaem", Russia), yeast extract ultrafiltered powder — 5 g/l ("Diaem", Russia), sodium chloride ("Diaem", Russia) — 5 g/l. *Staphylococcus aureus* 209 P and *Pectobacterium carotovorum* VKM-B 1247 were grown at 37 °C (pressure index: 150 rpm) and 28 °C (pressure index: 150 rpm), respectively. Yeast-like fungus *Candida albicans* ATTC 10231 was cultivated on a liquid nutrient solution YPD: peptone — 20 g/l ("Diaem", Russia), yeast extract — 10 g/l ("Diaem", Russia), glucose — 20 g/l ("Diaem", Russia). *Candida albicans* ATCC 10231 was grown at 37 °C (pressure index: 150 rpm).

Samples with a volume of 10 mql (at a concentration of 10 mg/ml, 5 mg/ml, 1 mg/ml) were applied to the surface of a nutrient solution (0.75 % LB) inoculated with the corresponding test strain. Petri dishes were incubated for 24 h, namely *Staphylococcus aureus 209P* and *Candida albicans ATCC 10231* at 37 °C, *Pectobacterium carotovorum VKM-B1247* at 28 °C. On the next day, the diameter of the microbial growth suppression zones was measured. Screening results of the compounds **8-13** for antimicrobial activity are shown in Table 1.

Table 1

Zones diameter of microorganisms' growth suppression by compounds 8-13

Compound	*Staphylococcus aureus*			*Pectobacterium carotovorum*			*Candida albicans*		
	10 mg/ml	5 mg/ml	1 mg/ml	10 mg/ml	5 mg/ml	1 mg/ml	10 mg/ml	5 mg/ml	1 mg/ml
8	5 мм / +/–	–	–	–	–	–	–	–	–
9	11 mm / ++	9 mm/ ++	–	5 mm/ +/–	–	–	4 mm/ +/–	–	–
10	–	–	–	–	–	–	–	–	–
11	–	–	–	–	–	–	–	–	–
12	5 mm / +/–	4 mm/ +/–	–	–	–	–	–	–	–
13	–	–	–	–	–	–	–	–	–
Antimicrobial effect: ++ pronounced antimicrobial activity; +/– very weak antimicrobial activity; — no activity									

Compound **9** exhibits the highest antimicrobial activity against a gram-positive microorganism — *Staphylococcus aureus* 209P at a concentration of 10 mg/ml. Compounds **8** and **12** showed a weak bacteriostatic effect at a concentration of 10 mg/ml. A low bacteriostatic effect against a gram-negative microorganism — *Pectobacterium carotovorum* VKM-B1247 and a yeast-free fungus — *Candida albicans* ATCC 10231 was demonstrated by the compound **9** at a concentration of 10 mg/ml.

Conclusions

Thus, new derivatives of hydrazones, which had not been described in the literature before, were obtained based on physiologically active hydrazides of isonicotinic and salicylic acids and acetyl-substituted heterocycles, namely 3-acetyl-2*H*-chromen-2-one **3**, 2-acetyl-3*H*-benzo[f]chromen-3-one **4** and 2,6-methanobenzo[g][1,3,5]oxadiazocine **5**. Obtained hydrazones structure was explicitly proved by IR and ^{1}H, ^{13}C NMR spectroscopy data. As a result of the carried out biological antibacterial and antifungal studies on strains of microorganisms, namely gram-positive bacterium — *Staphylococcus aureus* 209P, gram-negative bacterium — *Pectobacterium carotovorum* VKM-B1247, yeast-like fungus — *Candida albicans* ATCC 10231, three compounds demonstrated antimicrobial activity and compound **9** was also a promising agent since it exhibited anti-fungal effect along with antimicrobial activity.

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Кумарин мен бензо[g][1,3,5]оксадиазоцин ацетил туындылары негізінде изоникотин және салицил қышқылдары гидразондарының синтезі және бактерияғақарсы белсенділігі

Соңғы онжылдықтарда көптеген органик-химиктер, дәрігерлер мен фармакологтардың көптеген зерттеушілерінің назары айқын бактерияғақарсы және әсіресе зеңгеқарсы белсенділігі бар жаңа заттарды табуға бағытталған. Бұл көптеген бактериялық штамдар мен саңырауқұлақтардың медициналық тәжірибеде бар антибиотиктер мен зеңгеқарсы препараттарға төзімділігінің кең таралуына байланысты. Осыған байланысты ғылыми әдебиеттерде белгілі фармакофорлық топтарды қамтитын немесе белгісіз және зерттелмеген белсенділігі бар қосылыстардың жаңа құрылымдық тобы болып табылатын органикалық туындылардың әр түрлі тобынан жаңа потенциалды антибиотиктерді синтездеуге байланысты жұмыстар саны артып келеді. Осы жұмыста изоникотин мен салицил қышқылдарының физиологиялық белсенді гидразидтері және зертханалық қолжетімді ацетилмен орынбасылған гетероциклдар негізінде әдебиетте сипатталмаған гидразондардың жаңа туындылары — 3-ацетил-2*H*-хромен-2-он 3, 2-ацетил-3*H*-бензо[f]хромен-3-он 4 және 2,6-метанобензо[g][1,3,5]-оксадиазоцин 5 алынды. Алынған гидразондардың құрылымы ИҚ- және ЯМР ^{1}H, ^{13}C-спектроскопия деректерімен дәлелденді. Синтезделген жаңа 6 гидразон грамоң бактериялар *Staphylococcus aureus* 209P, грамтеріс бактериялар *Pectobacterium carotovorum* VKM-B1247, ашытқы тәрізді саңырауқұлақтар *Candida albicans* ATCC 10231 микроорганизмдер штамдарында бактерияғақарсы және зеңгеқарсы белсенділікке биологиялық скринингтен өтті. Скрининг нәтижесінде микробқақарсы белсенділігі бар 3 қосылыс және бір перспективалы қосылыс — (E)-2-гидрокси-N'-(1-(2-оксохроман-3-ил)этилиден)бензогидразид 9 анықталды, ол микробқақарсы белсенділікпен қатар, зеңге қарсы белсенділікті де көрсетті.

Кілт сөздер: гидразидтер, изониазид, салицил қышқылы гидразиді, кумариндер, 3-ацетил-2Н-хромен-2-он, 2-ацетил-3Н-бензо[f]хромен-3-он, 2,6-метанобензо[g][1,3,5]оксадиазоцин, гидразондар, микробқақарсы белсенділік.

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Синтез и антибактериальная активность гидразонов изоникотиновой и салициловой кислот на основе ацетилпроизводных кумарина и бензо[g][1,3,5]оксадиазоцина

В последние десятилетия усилия многих исследователей химиков-органиков, медиков и фармакологов сосредоточены на поиске новых средств с выраженной антибактериальной и, особенно, противогрибковой активностью. Это связано с повсеместным ростом резистентности многих бактериальных штаммов и грибков к имеющимся в медицинской практике антибиотикам и противогрибковым препаратам. В связи с этим в научной литературе увеличивается число работ, связанных с синтезом новых потенциальных антибиотиков из самого разнообразного класса органических производных, которые либо включают известные фармакофорные группы, либо представляют собой новый структурный класс соединений с неизвестной и неизученной активностью. В настоящей работе нами показано, что на основе физиологически активных гидразидов изоникотиновой и салициловой кислот и лабораторно доступных ацетилзамещенных гетероциклов — 3-ацетил-2*H*-хромен-2-он 3,2-ацетил-3*H*-бензо[f]хромен-3-он 4 и 2,6-метанобензо[g][1,3,5]оксадиазоцин 5 были получены новые неописанные в литературе производные гидразонов. Структура полученных гидразонов однозначно доказана данными ИК- и ЯМР ^{1}H, ^{13}C- спектроскопией. Синтезированные новые шесть гидразонов прошли биологический скрининг на антибактериальную и противогрибковую активность на штаммах микроорганизмов: грамположительной бактерии *Staphylococcus aureus* 209P, грамотрицательной бактерии *Pectobacterium carotovorum* VKM–B1247, дрожжеподобного гриба *Candida albicans* ATCC 10231. В результате скрининга было выявлено три соединения, обладающих антимикробной активностью, и одно перспективное соединение — (*E*)-2-гидрокси-N'-(1-(2-оксохроман-3-ил)этилиден)бензогидразид 9, которое, наряду с антимикробной активностью, также проявляет и противогрибковую.

Ключевые слова: гидразиды, изониазид, гидразид салициловой кислоты, кумарины, 3-ацетил-2*H*-хромен-2-он, 2-ацетил-3*H*-бензо[f]хромен-3-он, 2,6-метанобензо[g][1,3,5]оксадиазоцин, гидразоны, антимикробная активность.

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