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2-([1,2,4]triazolo[1,5-*c*]quinazolin-2-yl-)alkyl-(alkaryl-, aryl-)-amines and their derivatives. (3*H*-quinazolin-4-yliden)hydrazides (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)alkyl-(alkaryl-, aryl-)carboxylic acids: features of synthesis, modification and antibacterial activity of synthesized compounds

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Key words: *Aminoacids, (1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)alkyl-(alkaryl-, aryl-)carboxylic acids, (3H-quinazolin-4-yliden) hydrazides, 2-substituted [1,2,4]triazolo[1,5-c]quinazolines, Antimicrobial And Antifungal Activity.*

The combination of different "pharmacophore" components in one structure connected *via* "linker" functional groups is one of the major and justified approaches for the synthesis of new biologically active substances. In this area (3*H*-quinazoline-4-yliden)hydrazides (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl-)alkyl-(aralkyl-, aryl-)carboxylic acids are the most interesting compounds. They contain quinazoline and isoindole fragments united through alkyl, alkaryl and aryl groups and furthermore can be used for the synthesis of new heterocycles.

Aim. The purpose of this work is to find antimicrobial and antifungal agents among (3*H*-quinazolin-4-ylidene)hydrazides (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl-)alkyl-(alkaryl-, aryl-)carboxylic acids and their fused derivatives and to establish physical-chemical properties of these compounds and to correlate "structure – activity relationship" for structure optimization.

Methods and results. The study of microbiological activity was conducted by disco-diffusion method on Mueller–Hinton agar on the following strains of microorganisms: gram-positive cocci (*Staphylococcus aureus* ATCC 25923, *Enterococcus aeruginosa*, *E. faecalis* ATCC 29212), gram-negative bacteria (*Pseudomonas aeruginosa* PSS27853, *Escherichia coli* ATCC 25922), facultative anaerobic gram-negative bacteria (*Klebsiella pneumoniae*) and fungi (*Candida albicans* ATCC 885653).

Conclusion. The protected aminoacids were used to synthesize unknown (3*H*-quinazolin-4-ylidene)hydrazides (1,3-dioxo-1,3-dihydroisoindolo-2-yl-)alkyl-(alkaryl-, aryl-)carboxylic acids in the reactions of nucleophilic substitution for the first time. While new [1,2,4] triazolo[1,5-*c*]quinazolin-2-yl-)alkyl-(alkaryl-, aryl-)isoindol-1,3(2*H*)-diones were received by heterocyclization of the last. Structure and identity have been confirmed by elemental analysis, physical and chemical methods (^{1}H NMR spectroscopy, mass-spectrometry). Analysis of the results of microbiological study shows, that the synthesized compounds have never been active against *St. aureus, E. aerogenes, P. aeruginosa, E. coli, K. pneumoniae* (growth inhibition zone 6 mm). However, compounds **2.1, 2.2** are found among the (3*H*-quinazoline-4-ylidene)hydrazides (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl-)alkyl-(aralkyl-, aryl-)carboxylic acids (**2.1–2.9**) and inhibit the growth of *E. faecalis* zone 7 mm. Conducted cyclocondensation of **2.1–2.9** compounds does not lead to increase of antibacterial activity of corresponding [1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-alkyl-(alkaryl-, aryl-)-isoindol-1,3(2*H*)-diones (**3.1–3.9**) against *E. faecalis*. Thus, the antibacterial effect against *E. faecalis* is characteristic only for compounds **3.2, 3.3** and **3.4** (growth inhibition zone 7 mm) and is slightly lower than the corresponding activity of ampicillin.

2-([1,2,4]триазоло[1,5-*c*]хіназолін-2-іл-)алкіл-(алкарил-, арил-)-аміни та їхні похідні. (3*H*-хіназолін-4-іліден)гідразиди (1,3-діоксо-1,3-дигідро-2*H*-ізоіндол-2-іл-)алкіл(алкарил-, арил-)карбонових кислот: особливості синтезу, модифікація та антибактеріальна активність синтезованих сполук

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Комбінування в одній структурі різних «фармакофорних» компонентів, що сполучені через «лінкерні» функціональні групи, є одним із пріоритетних і виправданих підходів для одержання нових біологічно активних речовин. У цьому плані цікавими об'єктами виявились (3*H*-хіназолін-4-іліден)гідразиди (1,3-діоксо-1,3-дигідро-2*H*-ізоіндол-2-іл-)алкіл(аралкіл-, арил-)карбонових кислот, котрі вміщують у своїй структурі хіназоліновий та ізоіндольний фрагменти, сполучені через алкільні, алкарильні, арильні групи, та можуть використовуватися для синтезу нових гетероциклів.

Мета роботи – спрямований пошук протимікробних і протигрибкових агентів серед (3*H*-хіназолін-4-іліден)гідразидів (1,3-діоксо-1,3-дигідро-2*H*-ізоіндол-2-іл-)алкіл-(алкарил-, арил-)карбонових кислот та їхніх конденсованих похідних, дослідження фізико-хімічних властивостей, встановлення закономірностей «структура – активність» для оптимізації структури.

Матеріали та методи. Мікробіологічне дослідження здійснили диско-дифузійним методом на середовищі Мюллера–Хінтона на штамах мікроорганізмів: грампозитивні коки (*Staphylococcus aureus* ATCC 25923, *Enterococcus aeruginosa*, *E. faecalis* ATCC 29212), грамнегативні палички (*Pseudomonas aeruginosa* ПСС27853, *Escherichia coli* ATCC 25922), факультативно-анаеробні грамнегативні палички (*Klebsiella pneumoniae*) та гриби (*Candida albicans* ATCC 885653).

Результати. Встановили, що синтезовані сполуки проявляють помірну протимікробну дію до більшості досліджуваних штамів.

Висновки. У дослідженні вперше в реакціях нуклеофільного заміщення утилізовані захищені амінокислоти для синтезу невідомих (3*H*-хіназолін-4-іліден)гідразидів (1,3-діоксо-1,3-дигідроізоіндол-2-іл-)алкіл-(алкарил-, арил-)карбонових кислот, а шляхом гетероциклізації останніх отримані нові [1,2,4]триазоло[1,5-*c*]хіназолін-2-іл-алкіл-(алкарил-, арил-)ізоіндол-1,3(2*H*)-діони, будова та індивідуальність яких підтверджена за допомогою елементного аналізу та фізико-хімічних методів (^{1}Н ЯМР-спектроскопія, хромато-мас-спектрометрія). Аналіз результатів мікробіологічного дослідження показує, що синтезовані сполуки виявились не активними щодо *St. aureus, E. aerogenes, P. aeruginosa, E. coli*, *K. pneumoniae* (зона пригнічення росту 6 мм). Проте серед (3*H*-хіназолін-4-іліден) гідразидів (1,3-діоксо-1,3-дигідро-2*H*-ізоіндол-2-іл-)алкіл(аралкіл-, арил-)карбонових кислот (**2.1–2.9**) виявлені сполуки **2.1**, **2.2**, які пригнічують зони росту *E. faecalis* до 7 мм. Проведена циклоконденсація сполук **2.1–2.9** не призводить до посилення антибактеріальної активності відповідних [1,2,4]триазоло[1,5-*c*]хіназолін-2-іл-алкіл-(алкарил-, арил-)-ізоіндол-1,3(2*H*)-діонів (**3.1–3.9**) щодо *E. faecalis.* Так, антибактеріальна дія щодо *E. faecalis* характерна тільки для сполук **3.2, 3.3** та **3.4** (пригнічення зони росту до 7 мм), і вона дещо нижча за відповідну активність ампіциліну.

Ключові слова: *амінокислоти, (1,3-діоксо-1,3-дигідро-2H-ізоіндол-2-іл)алкіл(алкарил-, арил-)карбонові кислоти, (3H-хіназолін-4-іліден)гідразиди, 2-заміщені [1,2,4]триазол[1,5-c]хіназоліни, протимікробна та протигрибкова активність.*

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2-([1,2,4]триазоло[1,5-*c*]хиназолин-2-ил-)алкил-(алкарил-, арил-)-амины и их производные. (3*H*-хиназолин-4-илиден)-гидразиды (1,3-диоксо-1,3-дигидро-2*H*-изоиндол-2-ил-)алкил(алкарил-, арил-)карбоновых кислот: особенности синтеза, модификация и антибактериальная активность синтезированных соединений

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Объединение в общую структуру различных «фармакофорных» компонентов, соединённых через «линкерные» функциональные группы, является одним из приоритетных и оправданных подходов для получения новых биологически активных веществ. В этой связи интересными объектами оказались (3*H*-хиназолин-4-илиден)гидразиды (1,3-диоксо-1,3-дигидро-2*H*-изоиндол-2-ил)алкил-(алкарил-, арил-)карбоновых кислот, которые содержат в структуре хиназолиновый и изоиндольные фрагменты, соединённые через алкильные, алкарильные, арильные группы, и могут использоваться для синтеза новых гетероциклов.

Цель работы – направленный поиск противомикробных и противогрибковых агентов среди (3*H*-хиназолин-4-илиден)гидразидов (1,3-диоксо-1,3-дигидро-2*H*-изоиндол-2-ил)алкил- (алкарил-, арил)карбоновых кислот и их конденсированных производных, исследование физико-химических свойств, установление закономерностей «структура – активность» для дальнейшей оптимизации структуры.

Материалы и методы. Микробиологические исследования проведены диско-диффузионным методом на среде Мюллера–Хинтона на штаммах микроорганизмов: грамположительные кокки (*Staphylococcus aureus* ATCC 25923, *Enterococcus aeruginosa*, *E. faecalis* ATCC 29212), грамнегативные палочки (*Pseudomonas aeruginosa* ПСС27853, *Escherichia coli* ATCC 25922), факультативно-анаэробные грамнегативные палочки (*Klebsiella pneumoniae*) и грибы (*Candida albicans* ATCC 885653).

Результаты. Установлено, что синтезированные соединения проявляют умеренную противомикробную и противогрибковую активности к большинству исследуемых штаммов.

Выводы. В исследовании впервые в реакциях нуклеофильного замещения утилизированы защищённые аминокислоты для синтеза неизвестных (3*H*-хиназолин-4-илиден)гидразидов (1,3-диоксо-1,3-дигидроизоиндол-2-ил)алкил-(алкарил-, арил-)карбоновых кислот, а путём гетероциклизации последних получены новые [1,2,4]триазоло[1,5-*c*]хиназолин-2-ил-алкил-(алкарил-, арил-)изоиндол-1,3(2*H*)-дионы. Их строение и индивидуальность подтверждены с помощью элементного анализа и физико-химических методов (^{1}H ЯМР-спектроскопия, хромато-масс-спектрометрия). Анализ результатов микробиологического исследования показывает, что синтезированные соединения оказались не активными по отношению к *St. aureus, E. aerogenes*, *P. aeruginosa, E. coli, K. pneumonia*e (зона подавления роста 6 мм). Однако среди (3*H*-хиназолин-4-илиден) гидразидов (1,3-диоксо-1,3-дигидро-2*H*-изоиндол-2-ил)алкил(аралкил-, арил) карбоновых кислот (**2.1–2.9**) обнаружены соединения **2.1, 2.2,** которые подавляют зоны роста *E. faecalis* до 7 мм. Проведённая циклоконденсация соединений **2.1–2.9** не приводит к усилению антибактериальной активности соответствующих [1,2,4]триазоло[1,5-*c*] хиназолин-2-ил-алкил-(алкарил-, арил-)изоиндол-1,3(2*H*)-дионов (**3.1-3.9**) по отношению к *E. faecalis*. Так, антибактериальное действие по отношению к *E. faecalis* характерно только для соединений **3.2, 3.3** и **3.4** (угнетение зоны роста до 7 мм), и она несколько ниже, чем соответствующая активность ампициллина.

Ключевые слова: *аминокислоты, (1,3-диоксо-1,3-дигидро-2Н-изоиндол-2-ил)алкил-(алкарил-, арил-)карбоновые кислоты, (3Н-хиназолин-4-илиден)гидразиды, 2-замещённые [1,2,4]триазол[1,5-с]хиназолины, противомикробная и противогрибковая активность.*

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Quinazoline derivatives are an effective class of organic compounds with diverse biological activity. Now it is actively studied and used in medicine as antitumor, antimalarial, antibacterial, anti-inflammatory, anticonvulsant, antihypertensive and antidiabetic drugs [1–14]. Modern strategy of directed synthesis of potential drugs provides a choice of basic building blocks ("Matrix") to search highly active molecules. (3*H*-Quinazoline-4-ylidene)hydrazides of carboxylic acids turned to be the most interesting ones in this area [5,10,11,15,16]. The modification of hydrazide moiety by introducing aminoacid residues is an appropriate way to find potential biologically active compounds. Moreover, aminoacids are actively involved in metabolic processes and are the precursors of bioregulators and have a significant amount of binding centers in organism [17]. In addition, (3*H*-quinazoline-4-ylidene)hydrazide aminocarbonic acids can serve as an effective reagents for the construction of new functionally substituted heterocycles such as 2-aminosubstituted [1,2,4]triazine[1,5-*c*]quinazolines [5,10,11,18]. Thus, combination of different "pharmacophore" components in one structure connected *via* "linker" functional groups is a major and a reasonable approach to obtain new biologically active substances.

The aim of this work is directed to find antimicrobial and antifungal agents among (3*H*-quinazoline-4-ylidene)hydrazides (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl-)alkyl-(alkaryl-, aryl-)carboxylic acids and their fused derivatives and to establish physical-chemical properties of these compounds and to correlate "structure–activity" relationship for the structure optimization.

Materials and methods

Experimental chemical part. The melting point of compounds was determined by capillary method on the Stuart Scientific SMP-30. Elemental analysis of the newly synthesized compounds was carried out on "ELEMENTAR vario EL cube" analyzer. The ^{1}H NMR spectra were recorded on Mercury 400 spectrometer using TMS as the internal standard in DMSO-d_6. Mass-spectra analysis were determined on the high performance liquid chromatograph Agilent 1260 Series, equipped with a diode-array and mass selective detector Agilent LC/MSD SL. Ionization method was a chemical ionization at atmospheric pressure (APCI). Ionization mode was a concurrent scanning of positive and negative ions in the mass range 80–1000 m/z.

Synthetic studies were conducted according to the general approach of finding potential biologically active substances using reagents of companies "Sigma-Aldrich" (Missouri, USA), "Sinbias" (Donetsk, Ukraine) and "Enamine" (Kyiv, Ukraine).

(*1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl-)alkyl-(alkaryl-, aryl-)carboxylic acid (1.0) and 4-hydrazinoquinazoline* (**2.0**) were synthesized in accordance with known methods and constants corresponding to the literature [4,5,19].

General procedure for the synthesis of (3*H*-quinazoline-4-ylidene)hydrazides (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl-)alkyl-(aralkil-, aryl-)carboxylic acids (**2.1–2.9).** 1.62 g (0.01 mol) of *N,N'*- carbonyldiimidazole is added to a suspension

of 0.01 mol of corresponding acids **1.0** in 30 ml of dioxane. The mixture is kept at a temperature of 60–70 °C for 50–60 minutes to release completely all carbon dioxide. After addition of 1.6 g (0.01 mol) 4-hydrazinoquinazoline (**2.0**) the mixture is boiled for 1.5 hours. In the case of forming the residue, the solid product is filtered. In the case of a solution, dioxane is distilled. The precipitate is washed with dioxane or methanol. If it necessary the products are crystallized.

2-(1,3-Dioxo-1,3-dihydro-2H-isoindoline-2-yl)-N'-(quinazoline-4(3H)-yliden)acetohydrazide (2.1): Yield: 66.0 %; Mp 251–252 °C; LC–MC (APCI): m/z=348 $(MH)^+$, 349 $(MH+1)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 11.56 (s, 1H, 3-NH), 9.80 (s, 1H, NHCO), 7.95 (d, *J*=7.7 Hz, 1H, H, H-5), 7.93–7.81 (m, 5H. H-2, phthalimide H-4,5,6,7), 7.42 (t, *J*=7.6 Hz, 1H, H-7), 7.23 (t, *J*=7.6 Hz, 1H, H-6), 7.16 (d, *J*=7.7Hz, 1H, H-8), 4.78 (s, 2H, CH_2); Anal. Calcd. for $C_{18}H_{13}N_5O_3$: C, 62.25; H, 3.77; N, 20.16. Found: C, 62.12; H, 3.61; N, 20.04.

3-(1,3-Dioxo-1,3-dihydro-2H-isoindoline-2-yl)-N'-(quinazoline-4(3H)-yliden)propanhydrazide (2.2): Yield: 79.4 %; Mp 214–217 °C; LC–MC (APCI): m/z=362 $(MH)^+$, 364 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 11.34 (s, 1H, 3-NH), 10.11/9.55 (s, 1H, NHCO), 7.93–7.58 (m, 6H, H-2,5, phthalimide H-4,5,6,7), 7.35 (t, *J*=7.5 Hz, 1H, H-7), 7.16 (t, *J*=7.5 Hz, 1H, H-6), 7.05 (d, *J* =7.4 Hz, 1H, H-8), 3.94 (t, 2H, *J*=7.0 Hz, $COCH_2CH_2N$), 2.95 (t, 2H, *J*=7.0 Hz, $COCH_2CH_2N$); Anal. Calcd. for $C_{19}H_{15}N_5O_3$: C, 63.15; H, 4.18; N, 19.38. Found: C. 63,08; H, 4.04; N. 19,28.

4-(1,3-Dioxo-1,3-dihydro-2H-isoindoline-2-yl)-N'-(quinazoline-4(3H)-yliden)butanhydrazide (2.3): Yield: 84.5 %; Mp 206–209 °C; LC–MC (APCI): m/z=376 $(MH)^+$, 378 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 11.36 (bs, 1H, 3-NH), 9.96/9.45 (bs, 1H, CONH), 7.93–7.64 (m, 6H, H-2,5, phthalimide H-4,5,6,7), 7.34 (t, *J*=7.8 Hz, 1H, H-7), 7.23–6.94 (m, 2H, H-6,8), 3.72 (d, *J*=6.7 Hz, 2H, $COCH_2CH_2CH_2N$), 2.70/2.33 (t, *J*=6.8 Hz, 2H, $COCH_2CH_2CH_2N$), 1.98 (t, *J*=6.9 Hz, 2H, $COCH_2CH_2CH_2N$); Anal. Calcd. for $C_{20}H_{17}N_5O_3$: C, 63.99; H, 4.56; N, 18.66. Found: C, 63.83; H, 4.43; N, 18.58.

2-(1,3-Dioxo-1,3-dihydro-2H-isoindoline-2-yl)-N'-quinazoline-4(3H)-yliden)propanhydrazide (2.4): Yield: 66.4 %; Mp 170–175 °C; LC–MC (APCI): m/z=362 $(MH)^+$, 363 $(MH+1)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 11.44 (bs, 1H, 3-NH), 10.29/9.62 (bs, 1H, NHCO), 7.98–7.72 (m, 4H, phthalimide H-4,5,6,7), 7.69 (d, *J*=7.6 Hz, 1H, H-5), 7.55 (s, 1H, H-2), 7.34 (t, *J*=7.6 Hz, 1H, H-7), 7.15 (t, *J*=7.6 Hz, 1H, H-6), 7.06 (d, *J*=7.8 Hz, 1H, H-8), 5.36/5.00 (dd, *J*=12.7 Hz, 5.8 Hz, 1H, $CHCH_3$), 1.72 (t, *J*=5.8 Hz, 3H, CH_3); Anal. Calcd. for $C_{19}H_{15}N_5O_3$: C, 63.15; H, 4.18; N, 19.38. Found: C, 63.08; H, 4.03; N, 19.63.

2-(1,3-Dioxo-1,3-dihydro-2H-isoindoline-2-yl)-3-methyl-N'-(quinazoline-4(3H)-yliden)butanhydrazide (2.5): Yield: 85.8 %; Mp 142–145 °C; LC–MC (APCI): m/z=390 $(MH)^+$, 392 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 11.42 (bs, 1H, 3-NH), 10.52/9.57 (bs, 1H, CONH), 7.98–7.68 (m, 5H, H-2, phthalimide H-4,5,6,7), 7.64 (d, *J*=7.8 Hz, 1H, H-5), 7.30 (t, *J*=7.8 Hz, 1H, H-7), 7.14 (t, *J*=7.8 Hz, 1H, H-6), 7.02 (d, *J*=7.7 Hz, 1H, H-8), 4.95 (d, *J*=8.4 Hz, 1H, $\underline{CH}CH(CH_3)_2$), 2.81–2.64 (m, 1H, $CH\underline{CH}(CH_3)_2$), 1.11/0.91 (d, *J*=7.0 Hz, 6H, $CHCH(\underline{CH_3})_2$); Anal. Calcd. for $C_{21}H_{19}N_5O_3$: C, 64.77; H, 4.92; N, 17.98. Found: C, 64.60; H, 4.87; N, 18.03.

2-(1,3-Dioxo-1,3-dihydro-2H-isoindoline-2-yl)-4methyl-N'-(quinazoline-4(3H)-yliden)-penthahydrazide (2.6): Yield: 83.6 %; Mp- oil; LC–MC (APCI): m/z=404 $(MH)^+$, 406 $(MH+2)^+$; Anal. Calcd. for $C_{22}H_{21}N_5O_3$: C, 65.50; H, 5.25; N, 17.36. Found: C, 65.57; H, 5.28; N, 17.39.

4-(1,3-Dioxo-1,3-dihydro-2H-isoindoline-2-yl)-N'-(quinazoline-4(3H)-yliden)benzohydrazide (2.7): Yield: 89.0 %; Mp 334–338 °C; LC-MC (APCI): m/z=410 $(MH)^+$, 412 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 10.71 (s, 1H, 3-NH), 8.05–7.95 (m, 3H, H-5; 1,4-phenylene H-2,6), 7.94–7.89 (m, 4H, phthalimide H-4,5,6,7), 7.83 (s, 1H, H-2), 7.66–7.44 (m, 2H, H-6,7), 6.98 (d, *J*=7.7 Hz, 1H, H-8), 6.93 (d, *J*=7.7 Hz, 2H, 1,4-phenylene H-3,5); Anal. Calcd. for $C_{23}H_{15}N_5O_3$: C, 67.48; H, 3.69; N, 17.11. Found: C, 67.52; H, 4.78; N, 17.22.

3-(1,3-Dioxo-1,3-dihydro-2H-isoindoline-2-yl)-N'-(quinazoline-4(3H)-yliden)benzohydrazide (2.8): Yield: 75.0 %; Mp 318–322 °C; LC–MC (APCI): m/z=410 $(MH)^+$, 412 $(MH+2)^+$; Anal. Calcd. for $C_{23}H_{15}N_5O_3$: C, 67.48; H, 3.69; N, 17.11. Found: C, 67.53; H, 3.73; N, 17.19.

4-((1,3-Dioxo-1,3-dihydro-2H-isoindoline-2-yl)methyl)-N'-(quinazoline-4(3H)-yliden)benzohydrazide (2.9): Yield: 90.2 %; Mp 283–286 °C; LC–MC (APCI): m/z=424 $(MH)^+$, 426 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 10.56 (s, 1H, 3-NH), 8.20 (d, *J*=7.7 Hz, 1H, H, H-5), 8.02 (s, 1H, H-2), 7.96–7.77 (m, 6H, phthalimide H-4,5,6,7, 1,4-phenylene H-2,6), 7.62 (t, *J*=7.6 Hz, 1H, H-7), 7.47 (d, *J*=7.7 Hz, 2H, 1,4-phenylene H-3,5), 7.39 (d, *J*=7.7 Hz, 1H, H-8), 4.87 (s, 2H, CH_2); Anal. Calcd. for $C_{24}H_{17}N_5O_3$: C, 68.08; H, 4.05; N, 16.54. Found: C, 68.12; H, 4.08; N, 16.59.

The synthesized compound are white (**2.8**), yellow (**2.1**–**2.4, 2.9**), yellow-burning (**2.6, 2.7**) or orange-yellow oils (**2.5**), which are soluble in DMFA, DMSO, slightly soluble in alcohol, insoluble in water, dioxane (except compound **2.5**).

General procedure for the synthesis of 2-([1,2,4]triazolo[1,5-c]quinazoline-2-yl-)alkyl-(alkaryl-, aryl-)-isoindol-1,3(2H)-diones ***(3.1–3.9).*** 0.01 mole of corresponding hydrazide (**2.1–2.9**) is dissolved in 25 ml of glacial acetic acid and is boiled for 6 hours. The mixture is cooled. In case of forming residue, it is filtered. In the case of a solution, acetic acid is distilled under vacuum. The resulting precipitate is stirred with mixture of methanol and water and it is filtered. If it necessary the precipitate can be crystallized.

2-(2-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)methyl)isoindoline-1,3(2H)-dion (3.1): Yield: 93.1 %; Mp 311–313 °C; LC–MC (APCI): m/z=330 $(MH)^+$, 332 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 9.39 (s, 1H, H-5), 8.45 (d, *J*=8.3 Hz, 1H, H-10), 8.05 (t, 1H, H-8), 7.99–7.93 (m, 2H, H-3,6 phtalimide), 7.91–7.84 (m, 3H, H-7, H-4,5 phtalimide), 7.77 (t, 1H, H-9), 5.14 (s, 2H, CH_2); Anal. Calcd. for $C_{18}H_{11}N_5O_2$: C, 65.65; H, 3.37; N, 21.27. Found: C, 65.61; H, 3.33; N, 21.21.

2-(2-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)ethyl)isoindoline-1,3(2H)-dion (3.2): Yield: 82.4 %; Mp 227–232°C; LC–MC (APCI): m/z=344 $(MH)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 9.36 (s, 1H, H-5), 8.35 (d, *J*=7.9 Hz, 1H, H-10), 8.03 (d, *J*=7.8 Hz, 1H, H-7), 7.95–7.79 (m, 6H, H-8, phthalimide H-4,5,6,7), 7.76 (t, *J*=8.0 Hz, 1H, H-9), 4.12 (t, *J*=7.0 Hz, 1H, $COCH_2CH_2N$), 3.29 (t, *J*=6.9 Hz, 1H, $COCH_2CH_2N$); Anal. Calcd. for $C_{19}H_{13}N_5O_2$: C, 66.47; H, 3.82; N, 20.40. Found: C, 66.51; H, 3.93; N, 20.48.

2-(3-([1,2,4]triazolo[1,5-c]quinazoline-2-yl)propyl)isoindoline-1,3(2H)-dion (3.3): Yield: 79.4 %; Mp 212–215 °C; LC–MC (APCI): m/z=358 $(MH)^+$, 360 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 9.27 (s, 1H, H-5), 8.34 (d, *J*=7.7 Hz, 1H, H-10), 8.00 (d, *J*=7.7 Hz, 1H, H-7), 7.86 (t, *J*=7.7 Hz, 1H, H-8), 7.81–7.63 (m, 5H, H-9, phthalimide H-4,5,6,7), 3.82 (t, *J*=6.0 Hz, 2H, $COCH_2CH_2CH_2N$), 3.03 (t, *J*=6.0 Hz, 2H, $COCH_2CH_2CH_2N$), 2.27(t, *J*=6.0 Hz, 2H, $COCH_2CH_2CH_2N$); Anal. Calcd. for $C_{20}H_{15}N_5O_2$: C, 67.22; H, 4.23; N, 19.60. Found: C, 67.31; H, 4.29; N, 19.68.

2-(1-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)ethyl)isoindoline-1,3(2H)-dion (3.4): Yield: 68.5 %; Mp 220–224 °C; LC–MC (APCI): m/z=344 $(MH)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 9.41 (s, 1H, H-5), 8.43 (d, *J*=7.9 Hz, 1H, H-10), 8.03 (d, *J*=8.2 Hz, 1H, H-7), 7.96–7.81 (m, 5H, H-8, phthalimide H-4,5,6,7), 7.74 (t, *J*=7.4 Hz, 1H, H-9), 5.72 (d, *J*=13.1 Hz, 7.1 Hz, 1H, $CHCH_3$), 2.04 (d, *J*=7.1 Hz, 3H, $CHCH_3$); Anal. Calcd. for $C_{19}H_{13}N_5O_2$: C, 66.47; H, 3.82; N, 20.40. Found: C, 66.53; H, 3.91; N, 20.48.

2-(1-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)-2-methylpropyl)isoindoline-1,3(2H)-dion (3.5): Yield: 69.8 %; Mp 195–198 °C; LC–MC (APCI): m/z=372 $(MH)^+$, 374 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 9.44 (s, 1H, H-5), 8.45 (d, *J*=7.8 Hz, 1H, H-10), 8.03 (d, *J*=8.0 Hz, 1H, H-7), 7.95–7.79 (m, 5H, H-8, phthalimide H-4,5,6,7), 7.74 (t, *J*=7.6 Hz, 1H, H-9), 5.23 (d, *J*=9.7 Hz, 1H, $CHCH(CH_3)_2$), 3.23 (dt, *J*=14.7 Hz, 6.6 Hz, 1H, $CHCH(CH_3)_2$), 1.29/1.05 (d, *J*=6.1 Hz, 6H, $CHCH(CH_3)_2$); Anal. Calcd. for $C_{21}H_{17}N_5O_2$: C, 67.91; H, 4.61; N, 18.86. Found: C, 67.95; H, 4.69; N, 18.88.

2-(1-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)-3-methylbuthyl)isoindoline-1,3(2H)-dion (3.6): Yield: 37.1 %; Mp 159–161°C; LC–MC (APCI): m/z=386 $(MH)^+$, 388 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 9.38 (s, 1H, H-5), 8.43 (d, *J*=7.8 Hz, 1H, H-10), 8.02 (d, *J*=7.9 Hz, 1H, H-7), 7.947.82 (m, 5H, H-8, phthalimide H-4,5,6,7), 7.74 (t, *J*=7.8 Hz, 1H, H-9), 5.65 (d, *J*=11.2 Hz, $CHCH_2CH(CH_3)_2$), 2.60/2.36 (t, *J*=11.8 Hz, 2H,$CHCH_2CH(CH_3)_2$), 1.07 (m, 7H, $CHCH_2CH(CH_3)_2$); Anal. Calcd. for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.62; H, 4.99; N, 18.18.

2-(4-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)phenyl)isoindoline-1,3(2H)-dion (3.7): Yield: 57.5 %; Mp 332–336 °C; LC-MC (APCI): m/z=392 $(MH)^+$, 393 $(MH+1)^+$, 394 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 9.30 (s, 1H, H-5), 8.59 (d, *J*=7.5 Hz, 1H, H-10), 8.48 (d, *J*=7.6 Hz, 1H, H-7), 8.20 (d, *J*=8.1 Hz, 2H, 1,4-phenylene H-2,6), 8.08-7.96 (m, 2H, phthalimide H-4,7), 7.96–7.90 (m, 1H , phthalimide H-5,6), 7.86 (t, *J*=7.6 Hz, 1H, H-8), 7.76 (d, *J*=7.9 Hz, 2H, 1,4-phenylene H-3,5), 7.66 (t, *J*=7.6 Hz, 1H, H-9); Anal. Calcd. for $C_{23}H_{13}N_5O_2$: C, 70.58; H, 3.35; N, 17.89/ Found: C, 70.65; H, 3.39; N, 17.93.

2-(3-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)phenyl)isoindoline-1,3(2H)-dion (3.8): Yield: 79.6 %; Mp 327–329 °C; LC–MC (APCI): m/z= 392 $(MH)^+$, 394 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso-d_6) δ: 9.54 (s, 1H, H-5), 8.58 (d, 1H, H-10), 8.50–8.33 (m, 2H, 2-phenyl H-2,4), 8.09 (d, *J*=8.8 Hz, 1H, 2-Ph H-6), 8.05–7.97 (m, 2H, H-3,6 phtalimide), 7.97-7.87 (m, 3H, H-7, H-4,5 phtalimide), 7.83 (d, 1H, H-7), 7.73 (t, 1H, H-9), 7.63 (t, 1H, 2-phenyl H-5); Anal. Calcd. for $C_{23}H_{13}N_5O_2$: C, 70.58; H, 3.35; N, 17.89. Found: C, 70.55; H, 3.39; N, 17.78.

2-(4-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)benzene)isoindoline-1,3(2H)-dion (3.9): Yield: 79.7 %; Mp 270–276 °C; LC–MC (APCI): m/z=406 $(MH)^+$, 408 $(MH+2)^+$; ^{1}H NMR (400 MHz, dmso_d_6+ccl_4) δ: 9.48 (s, 1H, H-5), 8.56 (d, *J*=7.8 Hz, 1H, H-10), 8.27 (d, *J*=7.4 Hz, 2H, 1,4-phenylene H-2,6), 8.06 (d, *J*=7.6 Hz, 1H, H-5), 7.96-7.76 (m, 6H, H-8,9, phthalimide H-4,5,6,7), 7.54 (d, *J*=7.4 Hz, 2H, 1,4-phenylene H-3,5), 4.88 (s, 2H, CH_2); Anal. Calcd. for $C_{21}H_{17}N_5O_2$: C, 71.10; H, 3.73; N, 17.27. Found: C, 71.15; H, 3.79; N, 17.32.

The synthesized compounds are white (**3.1–3.4, 3.6–3.9**), yellow substances (**3.5**), soluble in DMFA, DMSO, slightly soluble in alcohol, insoluble in water and dioxane.

Experimental microbiological part. The study of antimicrobial and antifungal activity was conducted in bacteriological laboratory of Zaporizhzhia Regional Hospital. Disco-diffusion method was used (DDM) [21] on Mueller–Hinton agar on these strains of microorganisms: gram-positive cocci (*Staphylococcus aureus ATCC 25923, Enterococcus aeruginosa, Enterococcus faecalis ATCC 29212*), gram-negative rods (*Pseudomonas aeruginosa PSS27853, Escherichia coli ATCC 25922*), facultative anaerobic gram-negative rods (*Klebsiella pneumoniae*) and fungi (*Candida albicans ATCC 885653*). In determining the sensitivity the standard inoculum was used, corresponding to 0.5 standard Mac–Farland, that is it about 1,5×108 CFU/cm^3. The standard pipette inoculum was put on to the surface of a Petri dish with nutrient agar in a volume of 1.2 cm^3 and was evenly distributed over the surface. Inoculum excess was removed by pipette. Sterilized paper discs (6 mm diameter) were applied on agar, which was impregnated with a solution of synthesized compounds in DMSO (100 mg/disc). The duration of incubation was 24 hours at the temperature of 35 ºC for bacteria, and 48–72 hours for fungi at 28–30 ºC. The diameter of zones of growth retardation was measured to within 1 mm. Only DMSO disk did not cause growth inhibition of these microorganisms. Known antibacterial agents were used to compare the activity of synthesized compounds, namely: fluconazole, clotrimazole and ampicillin.

Results and Discussion

Methods of introduction of amino acids to other molecules are known and include a number of approaches. The first step is to protect the amino group, to prevent the formation of intermolecular products, then to activate the carboxylic group to enhance its reactivity, and finally to use them in reactions with substrates [17]. Thus, the protection of amino group with the help of phthalic anhydride was carried out during the first phase. And synthesized (1,3-dioxo-1,3-dihydroisoindolo-2-yl-) alkyl-(alkaryl-, aryl-)carboxylic acid (**1.0**), were used *in situ* reaction with *N,N'*-carbonyldiimidazole to obtain proper imidazolides (**1.1**, *Fig.1*). The last (**1.1**) interacted with 4-hydrazinoquinazoline (**2.0**) and formed individual compounds (**2.1–2.9**). It should be noted, that possible formation of mixtures of isomers is determined by the site of initial nucleophilic attack, which may be the final nitrogen of hydrazine residue or endocyclic atoms *N(1)* and *N(3)* quinazoline. However, mass-spectrometry data showed that the products of reactions are hydrazides (**2.1–2.9**), and the reaction is going through by the nucleophilic nitrogen atom of hydrazine group. Thus, the individual peaks spectra of quasimolecular ions $(MH)^+$ and $(MH+2)^+$ are recorded in spectra.

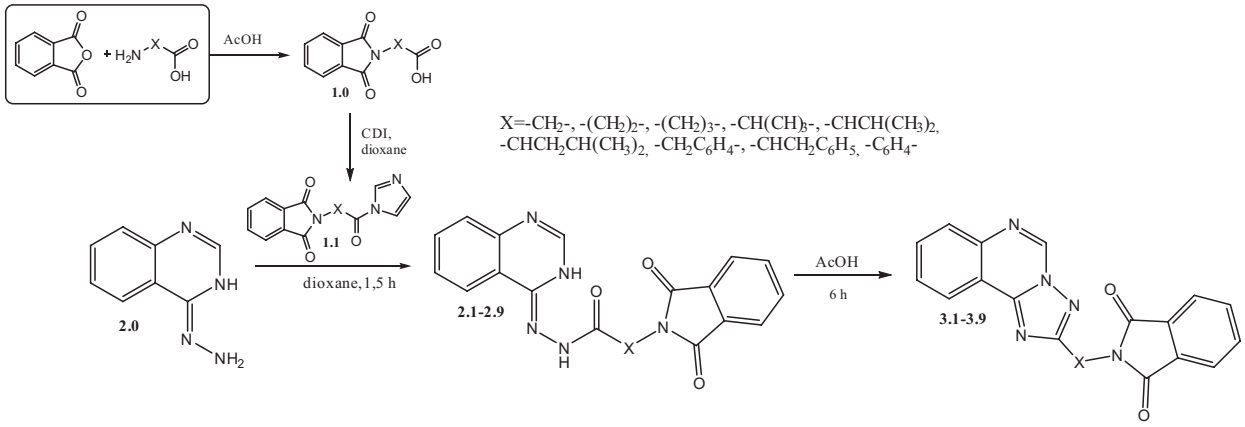

Fig. 1. Approaches to synthesize (3*H*-quinazoline-4-ylidene)hydrazides(1,3-dioxo-1,3-dihydroisoindolo-2-yl-)-alkyl-(alkaryl-, aryl-)carboxylic acid and 2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-)alkyl(alkaryl-, aryl-)isoindol-1,3(2*H*)-diones.

They have high intensity, confirming the structure and identity (chromatographic purity) of synthesized compounds.

Protons of position 3 of quinazoline cycle are recorded as enlarged singlets in a weak field, namely at 11.61–11.36 ppm, while NH-group and hydrazine residue at 10.71–9.45 ppm in the ^{1}H NMR spectra of synthesized compounds (**2.1–2.9)**. The latter has the ability of doubling signal (compounds **2.2–2.6**) due to the prototropic tautomerism (hydrazine-hydrazone) [5,11]. Protons of isoindolo and quinazoline cycles of compounds **2.1–2.9** were registered as broad multiplets in the "aromatic" part of spectra. Thus, multiple protons H-4, H-5, H-6 and H-7 of isoindol cycle at 7.98–7.58 ppm resonate together with protons H-2 and H-5 of quinazoline cycle. While signals of protons H-6, H-7 and H-8 quinazoline are informative for compounds **2.1–2.9**, that resonate in the form of two consecutive triplets and doublet (*Fig. 2*) [5,11]. Aromatic protons of "linker" phenilen substituent of compound (**2.7**) were found as A_2B_2-system, in which signals of protons H-3 and H-5 were found as doublets and signals of protons H-2 and H-6 as a multiplet together with H-5 quinazoline cycle.

There are also informative signals of protons of aliphatic groups in the spectra of ^{1}H NMR for **2.1–2.9** compounds.

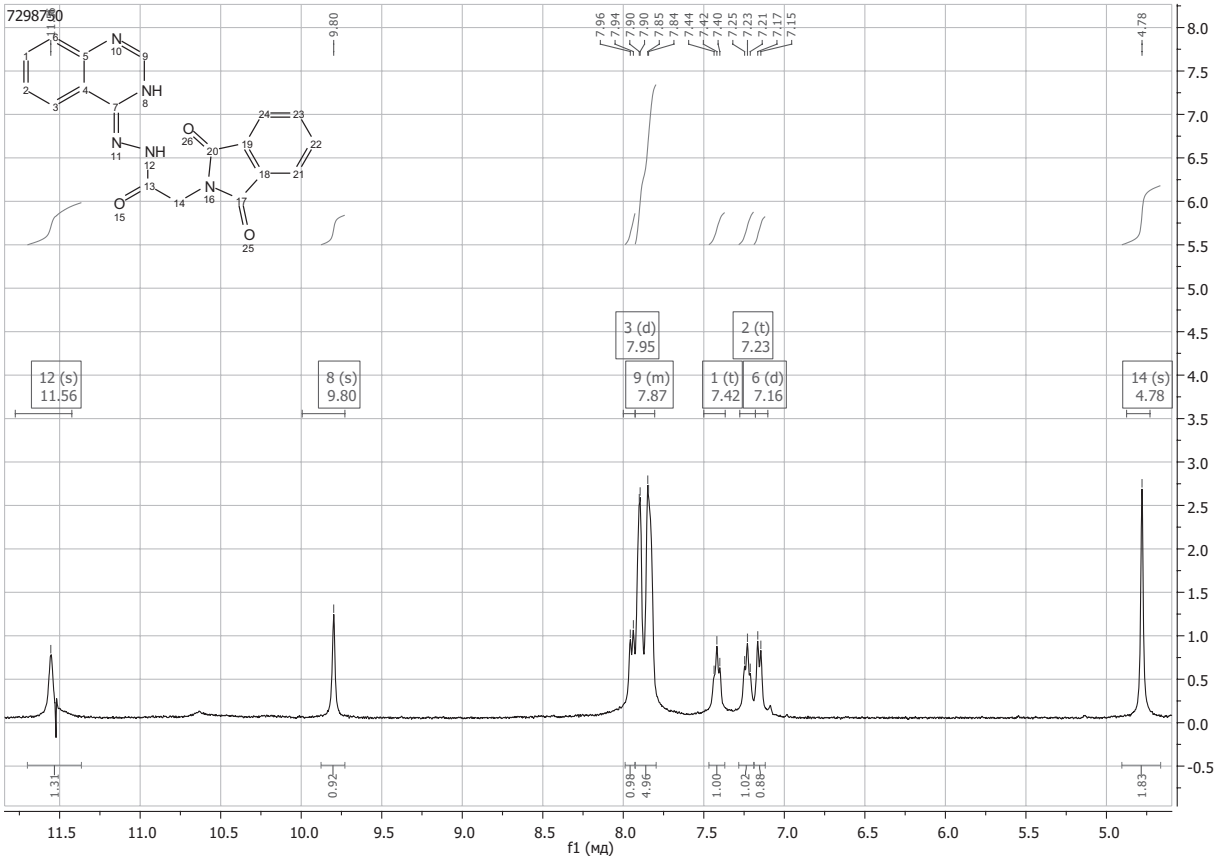

Fig. 2. Fragment of ^{1}H NMR spectrum (400 MHz, dmso d_6+ccl_4) 2-(1,3-dioxo-1,3-dyhidro-2*H*-isoindoline-2-yl)-*N'*-(quinazoline-4(3*H*)-yliden)acetohydrazide (**2.1**).

The multiplicity of these compounds is determined by proton environment. Thus, the signals of protons of methylene group are characterized by singlet in case of compounds **2.1, 2.9** at 5.24–4.37 ppm. Their chemical shift is characterized by the acceptor substituent properties. Extension (compound **2.2, 2.3**) or branching (**2.4, 2.6**) of aliphatic residue lead to change of multiplicity of protons and displace of the signal in the weak magnetic field (4.95–0.91 ppm). And in the case of branched aliphatic residue protons act as a doublet of doublets at 5.36 ppm (*J*=12.7 Hz, 5.8 Hz) and triplet at 1.72 ppm (*J*=5.8 Hz, compound **2.4**).

Cyclocondensation of **2.1–2.9** compounds under conditions of acid catalysis was conducted in the second phase of experiment. So, boiling of hydrazides (**2.1–2.9**) in glacial acetic acid leads to the formation of the corresponding 2-([1,2,4] triazolo[1,5-*c*] quinazoline-2-yl)-alkyl-(alkaryl-, aryl-)isoindol-1,3(2*H*)-diones (**3.1–3.10**) (*Fig.1*). ^{1}H NMR spectra show the formation of structures **3.1–3.9** which is characterized by the signal of proton H-5, which is observed as a singlet in 9.50–9.27 ppm [5,10,11,18]. In this case after the reaction of intramolecular heterocyclization of [1,2,4]triazolo[4,3-*c*] quinazoline, the last turn into corresponding [1,5-*c*]-series due to recyclization isomerization according to the Dimroth's rearrangement type [20]. It is important to note, that irrespective of the structure of the alkyl, aryl or alkaryl residue (branching, extension or saturation) there are no steric complications in the implementation of this transformation. Other proton signals of heterocycle of compounds **3.1–3.9** appear at 8.59–7.63 ppm in the form of consecutive doublets H-10, H-7 and H-8 triplets and H-9, as ABCD-system (*Fig. 3*). It is important, that the triazine[1,5-*c*]-quinazoline proton signal H-10 also undergo significant deshielded impact and appear at 8.59–8.34 ppm, which also show the formation of the corresponding heterosystems [5,11,18].

In addition, compounds **3.1–3.9** can be characterized by the signals of isoindol cycle protons in position 2, which are also experiencing the deshielded impact of heterocycle and resonate in a weak field, with a multiplicity similar to compounds **2.1–2.9**. The picture of aliphatic proton signals of compounds is similar to the spectra of compounds **3.1–3.9, 2.1–2.9** and is characterized by multiplicity appropriate with the small chemical shift in a weak magnetic field.

Compounds **3.1–3.10** as the previous ones were characterized using chromato-mass spectras in a "soft" ionization (chemical ionization). This method allowed to register in each case quasi ion peak $(MH)^+$ and $(MH+2)^+$, confirming the structure as well as personality (chromatographic purity) of synthesized compounds.

Thus, the reaction of cyclocondensation (3*H*-quinazoline-4-ylidene)hydrazides(1,3-dioxo-1,3-dihydroisoindolo-2-yl-) alkyl(aralkyl-, aryl-)carboxylic acids in acetic acid by heating is accompanied by recyclization isomerization to the type of Dimrot's rearrangement. It leads to form the corresponding 2-substituted [1,2,4]triazolo[1,5-*c*]quinazoline.

Analysis of the results of microbiological study shows, that the synthesized compounds have never been active against *St. aureus, E. aerogenes, P. aeruginosa, E. coli, K. pneumoniae* (growth

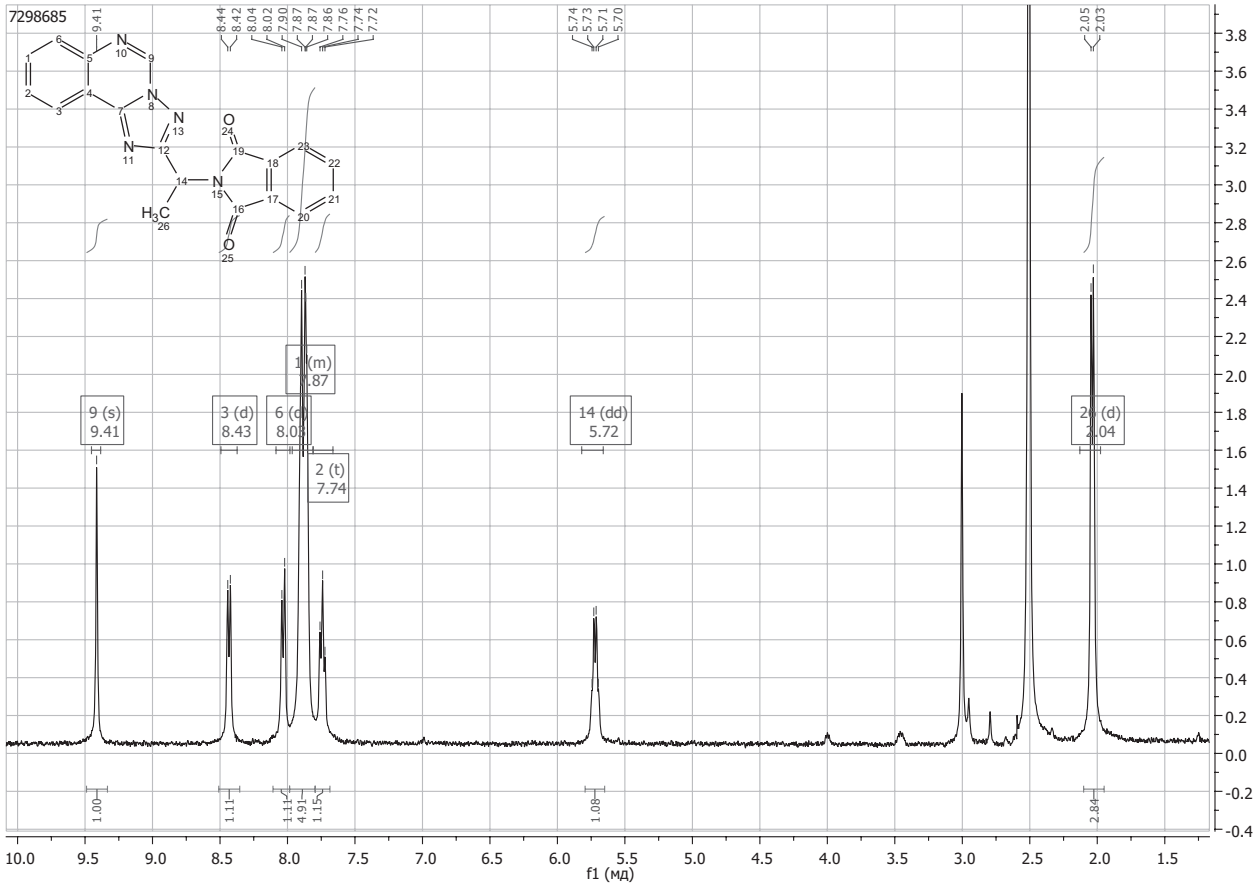

Fig. 3. Fragment of ^{1}H NMR spectrum (400 MHz, dmso d_6+ccl_4) 2-(1-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl)ethyl)isoindoline-1,3(2*H*)-dion (**3.4**).

inhibition zone 6 mm). However, compounds **2.1, 2.2** are found among the (3*H*-quinazoline-4-ylidene)hydrazides (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl-)alkyl-(aralkyl-, aryl-)carboxylic acids (**2.1–2.9**) and inhibit the growth of *E. faecalis* zone 7 mm (*Table 1*). Conducted cyclocondensation of **2.1–2.9** compounds does not lead to increase of antibacterial activity of corresponding [1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-alkyl-(alkaryl-, aryl-)-isoindol-1,3(2*H*)-diones (**3.1–3.9**) against *E. faecalis*. Thus, the antibacterial effect against *E. faecalis* is characteristic only for compounds **3.2, 3.3** and **3.4** (growth inhibition zone 7 mm) and is slightly lower than the corresponding activity of ampicillin. It is important, that neither lengthening of alkyl chains (compounds **3.2, 3.3**) nor its branching (**3.4**) in the "linker" group does not change the strength of antimicrobial action.

Table 1

Antimicrobial activity of the synthesized compounds against *E. faecalis*

№ of compound	Zone growth retardation, mm
2.1	7
2.2	7
3.2	7
3.3	7
3.4	7
Ampicillin	15

However, further chemical modification of obtained structures is rational in terms of finding new compounds with highly efficient antimicrobial action. Thus, the possible directions of further modifications of *s*-triazolo[1,5-*c*] quinazoline system to display and enhance the antibacterial activity can be: firstly, functionalization of position 2, including the introduction of various heterocycles *via* "linker" group. Secondly, it is the modification of the "linker" group. Thirdly, it is the introduction of substituents in position 7, 8, 9 and 10 of the heterocycle.

General conclusions

1. The protected aminoacids were utilized for further synthesis of unknown (3*H*-quinoline-4-ylidene)hydrazides (1,3-dioxo-1,3-dihydroisoindolo-2-yl-)alkyl-(alkaryl-, aryl-)carboxylic acids in the reactions of nucleophilic substitution for the first time. The new ones 2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl) alkyl-(alkaryl-, aryl-)isoindol-1,3(2*H*)-diones were received by heterocyclization of the last compounds.

2. Structure and individuality of synthesized compounds were confirmed by elemental analysis, physical and chemical methods (^{1}H NMR spectroscopy, chromatomass spektrometry).

3. A primary evaluation of antimicrobial and antifungal activity of synthesized compounds was made by disco diffusion method and it is shown that they have moderate antibacterial effect against *E. faecalis*.

Conflicts of Interest: authors have no conflict of interest to declare.

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